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Parahisian and Left Bundle Pacing

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III List of Abbreviations

AF	Atrial Fibrillation/Flutter (with Bradycardia)
AHA	American Heart Association
ATP	Adenosinetriphosphate
AV-Block (AVB)	Block (Delayed or complete blockage) of the conduction around the atrioventricular node.
AV-Node	Atrioventricular node
BiV	Bi-Ventricular
BVP	Bi-Ventricular Pacing
CI	Confidence Intervall
CRT	Cardiac Resynchronization Therapy
ECG	Electrocardiogram
EF	Ejection Fraction
ESC	European Society of Cardiology
HBAP	His- Bundle-Area-Pacing
HBP	His-Bundle-Pacing (synonymous to HBAP)
HFH	Hospitalization due to Heart Failure
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Hart Failure with reduced Ejection Fraction
HPSP	HIS-Purkinje-System-Pacing
I2 (I-Square)	I-Sqaure: Statistical Measure of Overall Variability explained by heterogeneity between studies and not by chance.
LAD	Left Anterior Descending Artery
LBBAP	Left Bundle Branch Area Pacing

LBB	Left Bundle Branch
LBBB	Left Bundle Branch Block
LVAT	Left Ventricular Activation Time
LVEDD	Left Ventricular End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
M	Mortality (Here: “all-cause mortality”)
MS	Milliseconds
N.A.	Not applicable
N.R.	Not reported (missing data)
NYHA	New York Heart Association
PHP	Parahisian Pacing
RCT	Randomized Controlled Trial
RVP	Right Ventricular Pacing
STIM-LVAT	Stimulation to Left Ventricular Activation Time
TAVI	Transcatheter Aortic Valve Implantation
WHO	World Health Organization

IV Summary

As cardiac conduction abnormalities and heart failure prevalence rise globally, optimizing resynchronization becomes increasingly important. In the context of cardiac resynchronization therapy (CRT), this thesis explores two physiological pacing methods- parahisian pacing (PHP, Syn: his -bundle area pacing HBAP) and left bundle branch area pacing (LBBAP). Both parahisian pacing and left bundle pacing are intended to enable a (more) physiological activation of the ventricles, with the aim of synchronized action of both heart chambers. However: The techniques aim at different anatomical areas and different parts of the physiological conduction system, respectively. Despite different placement sites certain medical indications are eligible for the potential use of both techniques.

The aim of this thesis is to evaluate and compare the benefits and disadvantages of PHP and LBBAP in cardiac resynchronization. A systematic literature review is conducted using PubMed, MedRxiv, and Cochrane databases. Studies are selected based on predefined criteria, including randomized controlled trials, observational studies, and systematic reviews. Analysis is performed in an extended narrative manner, incorporating descriptive and semi-quantitative analysis.

Keywords: Cardiac resynchronization therapy (CRT), parahisian pacing, his-bundle area pacing (HBAP), left bundle branch area pacing (LBBAP), physiological pacing, AV block, heart failure.

1 Introduction

The worldwide burden of cardiac diseases is continuously increasing. Various etiological factors such as genetic predisposition, lifestyle influences (particularly in western societies), an overall rise in life expectancy, and improved survival following acute cardiac events act in concert to drive the growing need for long-term interventions. (Masaebi et al., 2021; Salari et al., 2023) The variety of cardiac diseases and their underlying pathophysiological mechanisms is broad. (AMBOSS, 2024e; McDonagh et al., 2021)

Regardless of the exact etiology, sufficient electrical conductivity is paramount for proper cardiac function (Klinke et al., 2003). Often in cardiac diseases, the conduction system is affected, or a primary conduction system disorder itself constitutes the cardiac disease. Therefore, conduction disorders -whether cause or consequence of heart failure- significantly contribute to both morbidity and mortality. (Olausson et al., 2023)

In particular, asynchronous conduction is associated with disease progression and worse prognosis. As the burden of cardiac diseases rises, so too does the need for cardiac resynchronization therapy. (Chen & Upadhyay, 2021; Chung et al., 2023)

While traditional biventricular pacing remains widely used, it has notable limitations, particularly in achieving physiological ventricular activation. Recent advancements in conduction system pacing, particularly parahisian pacing (PHP) and left bundle branch area pacing (LBBAP), offer promising alternatives. Both techniques aim to preserve or restore physiological ventricular activation by stimulating the his-purkinje system. Although targeting different anatomical regions, they are often considered in overlapping clinical scenarios, such as high-degree atrioventricular (AV) block or other common CRT indications. (Glikson et al., 2021)

In light of the aim not only to support survival following acute cardiac events but also to reduce the costs and consequences of heart failure, and to enhance quality of life and long-term prognosis, a closer evaluation of alternative pacing strategies to traditional biventricular pacing is justified.

"What are the benefits and disadvantages of parahisian pacing compared to left bundle branch area pacing in cardiac resynchronization?"

Under the above-mentioned research question, this thesis aims to clarify the applicability of both methods as potential alternatives to traditional biventricular pacing and to explore whether one method may be considered superior.

To address the research question, a systematic review was performed using the Cochrane, PubMed, and MedRxiv databases. Prior to outlining the methods of this systematic review, this thesis begins with a short focus on epidemiology, providing the background to highlight the urgent need for research in cardiac resynchronization therapy.

The epidemiological section is followed by anatomical and physiological considerations to illustrate normal cardiac and conduction system function. Subsequently, foundational pathophysiological mechanisms are discussed. At the end of the theoretical framework, pacing methods are introduced and a rationale for pacing is provided.

This thesis examines the technical feasibility, advantages, and limitations of each method based on clinical evidence. Furthermore, it identifies research gaps and proposes directions for future investigation.

Preliminary findings reveal a scarcity of studies directly comparing PHP and LBBAP, particularly randomized controlled trials. However, LBBAP appears more extensively studied and shows promise in overcoming some limitations inherent to his-bundle area pacing.

The thesis also analyzes complications, indications, contraindications, and technical challenges associated with both pacing strategies.

Chapter three provides transparency regarding the methodological approach. Chapter four presents the results of the included literature. The discussion section offers a critical synthesis of the available evidence and proposes areas for further research and clinical consideration.

Finally, a concise conclusion summarizes the findings and directly answers the research question.

2 Theoretical Background, Conduction Disorders and Pacing Strategies.

To implement a basic understanding of how the heart is built, how it works, and which physiological processes are constituting a well-functioning heart, this chapter outlines anatomical and physiological functioning of the heart. Before the background of normal anatomy and physiology, the pathophysiological processes will be explained. The interaction between heart disease and cardiac conductivity is crucial to understand how pacing allows restore cardiac function and why pacing is a thought-out therapy approach to several cardiac diseases such as heart failure and associated electrophysiological pathologies such as atrial fibrillation (AF) with bradicardia, AV-block (AVB), blocks of the bundle branches and further indications. (Chung et al., 2023; Glikson et al., 2021; Jameson, J.L. et al., 2020a)

This is because changes in conductivity may lead to mechanical malfunction and cardiac remodeling. (Jiang et al., 2023) On the long haul further negative effects on the conduction system are the consequence of maladaptive processes. A worsening condition might constitute heart failure. (Jiang et al., 2023) Vice versa, changes that do not directly affect the common conduction pathways but primarily cardiac muscle cells, are also leading to impaired conductivity. So cardiac disease and conduction are to be regarded as part of the same process. Important for the heart is a working interplay of electro-mechanical synchrony. (Chan et al., 2023; Huang, 2025; Huang et al., 2020)

The theoretical backgrounds to this insight will be outlined during this chapter to enable the understanding why CRT is required and how it is sought to improve the diagnosis and prognosis for patients suffering from different heart diseases. Signs and symptoms of heart diseases restrict personal life to a broad extent. Commonly the New York Heart Association's (NYHA) score is used for grading. Patients suffering from heart failure experience restriction in everyday activities such as walk-distance, shortness of breath after physical activity and further more. These symptoms and their severity are evaluated by the NYHA scale. (Merck & Co, 2025b) The NYHA scale will be part of the outcome evaluation of this thesis.

Not only on the individual level cardiac diseases are impairing the quality of life. Cardiac diseases play a major role in the global burden of diseases, impaired quality of life, consecutive illnesses and individual but also socioeconomic costs and consequences. (Masaebi et al., 2021) To outline the epidemiological meaning of later explained pathophysiological processes, this chapter will start providing a brief insight to the epidemiological background underlining the need for research in functioning therapies, such as CRT.

2.1 Epidemiology of Heart Diseases

Cardiac diseases are on the rise globally. They still remain the leading cause of death in the European Region. (Shahim et al., 2023; World Health Organization, 2024) Factors such as aging populations, sedentary lifestyles, and improved survival from acute cardiac conditions all contribute to the growing incidence and prevalence of cardiac diseases and associated conduction disorders. (Borlaug et al., 2023)

Roth et al. (2020) investigated in the course of cardiac diseases over the decade of 2009 to 2019. Their findings demonstrate the increase and devastating consequences of cardiac diseases, thus not only as a major cause of mortality but also as a socioeconomic factor causing disability and reduced quality of life:

> "The global trends for disability-adjusted life years (DALYs) and years of life lost also increased significantly, and years lived with disability doubled from 17.7 million (95% UI: 12.9 to 22.5 million) to 34.4 million (95% UI:24.9 to 43.6 million) over that period." (Roth et al., 2020)

Subsequently the need for long-term cardiac interventions allowing for sustained and working conductivity also continues to grow. The following sections will now introduce cardiac anatomy and function. On this basis later sections will demonstrate which pathophysiological processes are associated with the rising burden of cardiac disease.

2.2 Cardiac Anatomy, Function and Basic Physiology

The heart is the central organ of the circulatory system. Its main duty is to keep the circuit of oxygen and nutrient rich arterial blood flowing to the tissues of the human organism and to ensure the transport of waist products and poor oxygen blood back from the capillaries of the peripheral tissues. (Faller et al., 2004; Klinke et al., 2003)

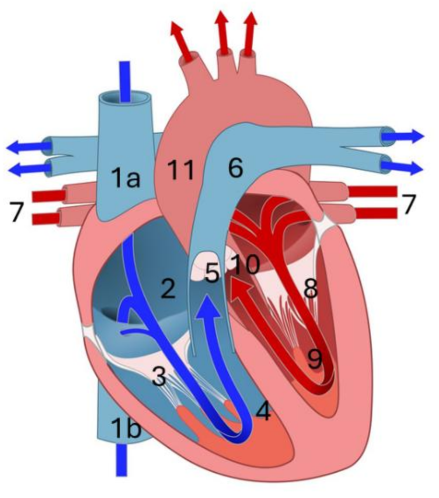

Figure 1: Blood flow through the Heart. Adapted from AMBOSS,2024b

Furthermore, the heart enables circulation within the lungs. This is crucial since oxygenation of venous blood takes place in the lungs. As shown in figure one the circuit of the blood flow that is promoted by cardiac function can be described as follows:

Venous blood returns via the superior (1a) and inferior (1b) vena cava from the peripheral circulation to the right atrium (2). It then flows through the tricuspid valve (3) into the right heart ventricle (4). Once the tricuspid valve closes the accumulated venous blood in the right ventricle is pumped forward through the pulmonary valve (5) into the pulmonary arteries (6). Here the venous blood is enriched with oxygen. The oxygen rich blood returns to the heart via pulmonary veins (7) into the left atrium. The mitral valve (8) regulates the influx of blood from the left atrium into the left chamber (9). From the left chamber the oxygen rich blood is pumped via the aortic valve (10) into the ascending aortic arch (11). From here it flows into the systemic circulation. (AMBOSS, 2024f; Fritsch & Kühnel, 2015)

In addition, a functioning heart enables the circulation of blood both to and from its own tissues. Thus, the blood flow generated by the heart is essential for the proper functioning of all organs, including the heart itself. This point is particularly important, as a properly functioning conduction system relies on an adequate blood supply to cardiomyocytes. Restriction of this supply - caused by various pathophysiological conditions - constitutes a major contributor to heart disease. (Borlaug et al., 2023)

This aspect will be discussed in greater detail later. For now, the thesis proceeds with a description of normal cardiac function.

The heart can be anatomically divided into four compartments:

- Left atrium and right atrium
- Left ventricle and right ventricle

These hollow structures are separated by cardiac valves. (Fritsch & Kühnel, 2015) Functioning valves regulate blood flow into and out of each anatomical subdivision. Blood flow through the cardiac compartments occurs in two consecutive phases: (Schünke, 2005)

- Filling phase (diastole)
- Output phase (systole)

During the filling phase (diastole), the atrioventricular (AV) valves - tricuspid valve on the right side and mitral valve on the left side - open, allowing blood to flow from the atria into the respective ventricles. Simultaneously, the pulmonary and aortic valves remain closed, preventing blood from flowing into the great vessels. This mechanical closure ensures that blood is directed into the ventricles rather than prematurely entering the pulmonary artery or aorta. (Klinke et al., 2003) As long as the aortic and pulmonary valves are closed, the inflowing blood increases pressure against the walls of the relaxed ventricles. Once ventricular filling is complete, the walls contract, initiating systole. Contraction forces the aortic and pulmonary valves open, allowing blood to be ejected (Fritsch & Kühnel, 2015):

- From the right ventricle into the pulmonary circulation

- From the left ventricle into the systemic circulation via the aortic arch

During the systole, the tricuspid and mitral valves close to prevent backflow from the ventricles into the atria. Preventing regurgitation is critical for efficient cardiac function. (Sarraj-Asil & Diez-Villanueva, 2021)

The volume that the heart pumps with each contraction or heartbeat into the peripheral and pulmonary circulation comprises a volume of about ~80-100 ml per stroke (systolic contraction). Considering a normal frequency of about 60-90 beats per minute (bpm), the circulating volume that is pumped by the heart for each passing minute is ~ 6-8 l/min. Under desirable conditions this performance is kept over the entire life span. (Lapp & Krakau, 2014)

To maintain efficient circulation, the hearts contraction is as decisive as its potential to relax. The chamber must fill first to afterwards pump out the blood against the peripheral resistance. Under normal conditions filling and outflow should be achieved in an isovolumetric manner. (Schünke, 2005; Waschke et al., 2019)

The force of contraction, their frequency, diastolic filling, and the amount of blood ejected per beat depend on various cardiac and peripheral influences. These include myocardial properties (stiffness vs. elasticity), metabolic function, ion homeostasis (Na^{+}, K^{+}, and Ca^{2+}), oxygenation, and neurohormonal regulation. Together, these shape the dynamic interplay between the heart and the organism. (Hall & Hall, 2021; Jameson, J.L. et al., 2020a, 2020b)

Regardless of the specific influence, maintaining sufficient circulatory flow under changing physiological demands is essential. This requires precisely coordinated activity of the two to three billion heart muscle cells found in the atria and ventricles, together with the valves. (Tirziu et al., 2010) Such synchrony depends on the effective propagation of electrical impulses that coordinate contraction and relaxation – a phenomenon known as electromechanical synchrony. Synchrony is one of the key factors for a healthy heart. (AMBOSS, 2024c) Therefore, cardiomyocytes, unlike skeletal muscle cells, exhibit special properties. Numerous gap junctions and intercalated discs, enabling enhanced and rapid exchange of ions in a sequential manner. (Padala et al., 2021)

Vice versa- if electromechanical synchrony is lost, the efficiency of the cardiac pump declines, potentially leading to reduced output and heart failure. Considering this, the conduction system is essential not only for rhythm generation but also for mechanical efficiency. Thus, synchronized contraction and relaxation of the cardiac chambers in a tightly regulated temporal sequence is crucial for physiological circulation. (Klinke et al., 2003)

This synchrony is governed by the cardiac conduction system, a specialized network of pacemaker cells and conductive pathways. Rather than a single pacemaker, the system comprises several hierarchical centers capable of autonomous action potential generation. These pacemaker regions are organized sequentially, ensuring redundancy: if a primary node fails, a subordinate center assumes control at a slower intrinsic rate. (Schünke, 2005; Schuster & Trappe, 2005)

Table 1 summarizes the structures of the conductions system, coordinating systole and diastole by rhythmically depolarizing and repolarizing the working myocardium. (AMBOSS, 2024f)

Depolarization begins in the sinoatrial (SA) node, which initiates an impulse that spreads through both atria. The signal reaches the atrioventricular (AV) node, located at the atrioventricular junction (Koch's triangle), where conduction is slowed to ensure atrial contraction precedes ventricular systole.(AMBOSS, 2024c, 2024f; Schuster & Trappe, 2005)

From the AV node, the impulse travels down the his-bundle, bifurcating into the left and right bundle branches and eventually reaching the Purkinje fibers. These structures ensure depolarization of the ventricular myocardium from apex to base, facilitating efficient ejection. (AMBOSS, 2024c; Jameson, J.L. et al., 2020b; Schünke, 2005)

Table 1: Sequence of natural pacing nodes. Based on (Hall & Hall, 2021; Klinke et al., 2003)

Sequence	Natural Pacemaker	Anatomical location	Pacing Frequency (beats per minute)
1	Sinoatrial node	Right atrium, close to the superior vena cava.	60-90
2	Atrioventricular node	Inter-atrial septum close to a thought border to the ventricles.	40-60
3	His-bundle	Proximal inter-ventricular septum	40-50
4	Bundle branches	Left bundle brach and right bundle branch of the anterior myocardium.	30-40
5	Purkinje fibers	Subendocardial ventricular myocardium.	20-30

The cardiac conduction system thus ensures a precisely timed and spatially organized depolarization cascade, along the pathways depicted in figure 2. Deviation can impair not only output but also coronary perfusion and ventricular filling. (AMBOSS, 2024d, 2024e, 2024a; Hall & Hall, 2021; Waschke et al., 2019)

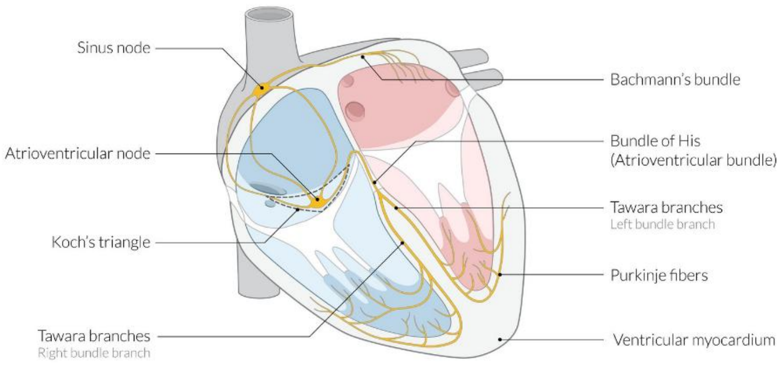

Figure 2: The Cardiac Conduction System. Source: AMBOSS, 2024b

Electrophysiological excitation is inherently metabolic. Ionic gradients across cell membranes (mainly Na^+, K^+, and Ca^{2+}) enable depolarization and repolarization. This requires continuous energy and oxygen supply. Consequently, the myocardium- especially pacemaker and conduction cells, is among the most oxygen-demanding tissues in the human body. (Jameson, J.L. et al., 2020b; Ramanathan & Skinner, 2005)

The heart is perfused via the coronary circulation (vasa privata), originating from the ascending aorta and draining into the right atrium via the coronary sinus. (Ramanathan & Skinner, 2005)

Figure 3 shows the coronary arteries originating from the aorta and branching into different areas of supply. Given the specialization of pacemaker and working myocytes, uninterrupted and sufficient perfusion is indispensable for myocardial excitation, contraction, and ultimately cardiac function. (Klinke et al., 2003; Mescher, 2024)

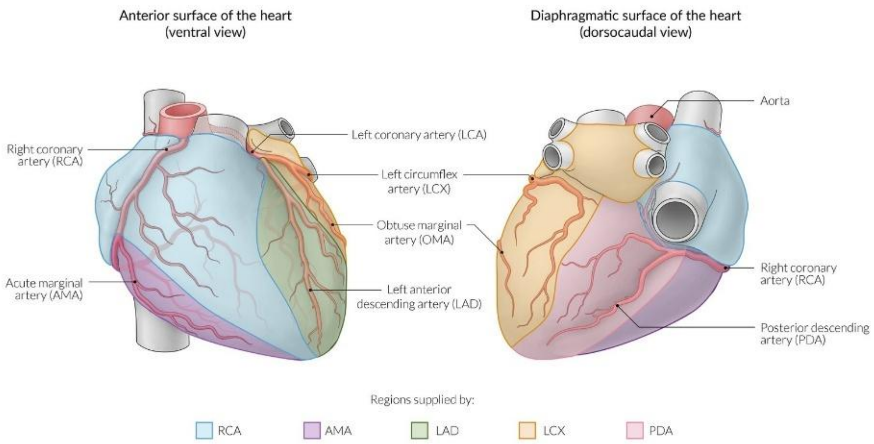

Figure 3: Coronary Arteries and Area of Supply. Source: AMBOSS, 2024b.

Notably (not depicted here), the venous system also serves as the anatomical route for transvenous pacemaker lead implantation. (Burri et al., 2021)

2.1 Heart Failure and Pathophysiology of the Conduction System

When myocardial oxygen demand exceeds supply, the function of pacemaker cells, as well as the conductive and contractile properties of the working myocardium, may be impaired. Ischemic heart disease is therefore one of the main causes of conduction disorders. (Severino et al., 2020; Shahim et al., 2023)

Ischemia is commonly caused by arterial stenosis, causing a narrowing of the vascular lumen due to atherosclerotic changes. A luminal narrowing of more than 70% can significantly reduce perfusion to downstream tissues, leading to oxygen and nutrient deprivation. (Neumann et al., 2019) Acute causes include thrombosis or embolism, resulting in sudden subtotal or total occlusion of one or more coronary arteries. This pathology is the mainstay of acute coronary syndrome. An acute infarction is one of the leading causes of death worldwide. (Salari et al., 2023)

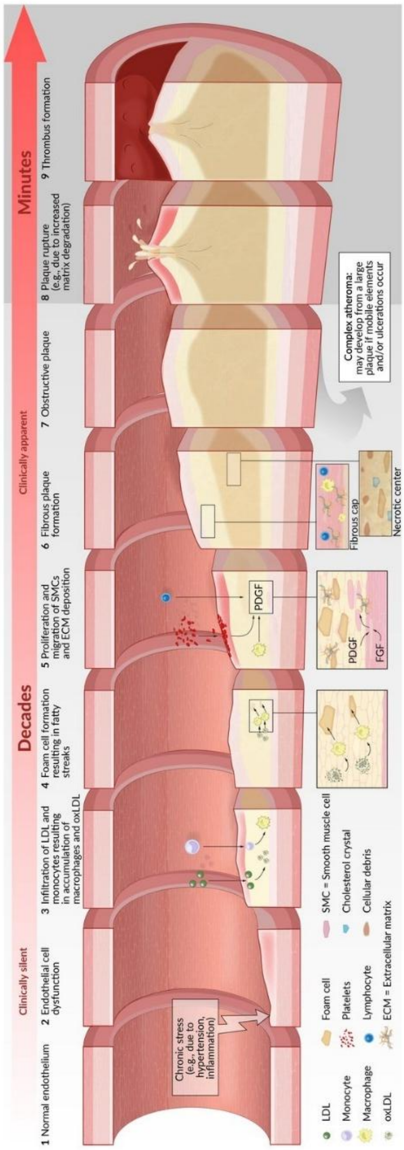

Figure 4: Athersoclerotic Plaque Formation.Source: AMBOSS, 2024a

Figure 5 illustrates that stenotic lesions often develop gradually and may initially be compensated for by collateral circulation. In contrast, acute occlusion, particularly if superimposed on chronic stenosis, poses an immediate ischemic threat to the supplied myocardium. Both acute infarction and chronic ischemia initiate compensatory mechanisms such as cardiac remodeling. However, ischemia may also result in cell death, followed by the formation of non-functional scar tissue in the affected region. (AMBOSS, 2024d; Levine et al., 2016)

Other etiologies of myocardial dysfunction and arrhythmias include congenital disorders, vasospasm, inflammation, and hypertrophic remodeling (often secondary to ischemia). (Slavich & Patel, 2016; Stern & Bayes De Luna, 2009)

This means, different etiologies, even extracardiac conditions such as peripheral atherosclerosis, can contribute to pressure overload, resulting in cardiac hypertrophy and eventual pacemaker or myocardial dysfunction. (Glikson et al., 2021)

Disturbances in conduction, propagation, or electrical synchrony may culminate in symptomatic arrhythmias, which are among the key indications for pacemaker therapy. (Glikson et al., 2021; Jameson, J.L. et al., 2020b, 2020a)

If oxygen supply is restored in time, hypoxic tissues may recover. Otherwise, cardiomyocytes undergo necrosis and are replaced by non-functional scar tissue. Such structural changes are irreversible, and therapy must then focus on compensating for lost function. (Ibanez et al., 2018; Levine et al., 2016; Roffi et al., 2016)

The extent of damage depends on both severity and cellular type affected. Ischemia may affect pacemaker cells or entire nodes. (Alboni et al., 1991; Alnsasra et al., 2018; Hall & Hall, 2021; Uyan et al., 2023)

2.1.1 Arrhythmias

If conduction fails, electrical impulses may not be generated or transmitted properly, leading to disorders such as atrioventricular block (AVB). In AVB, signals from the sinoatrial node are not propagated physiologically through the atrioventricular node. If the sinus node itself fails, sinus arrest or sick sinus syndrome (SSS) may occur. Excessive excitation, such as atrial fibrillation (AF), can also result from ischemia or other causes that impair the supply-demand balance of cardiomyocytes. (Alnsasra et al., 2018; Kosmidou et al., 2017; Rillig et al., 2021; Shi et al., 2024)

The most common pathophysiological denominator, as outlined in the previous section, is acute or chronic hypoxia, which impairs cellular energy homeostasis. The most important factor is that oxygen deprivation reduces the synthesis of ATP, the primary energy currency of the cell. ATP is crucial for maintaining ionic gradients intra- and extracellular compartments. Particularly of calcium, potassium, and sodium. Without ATP excitability cannot be maintained. This leads to conduction failure or inappropriate spontaneous depolarization. (AMBOSS, 2024a; Hall & Hall, 2021; Klinke et al., 2003; Li et al., 2022; Shi et al., 2024)

For the sake of completeness: Also non-hypoxic causes, such as genetic ion channelopathies, can lead to impaired calcium influx or sodium-potassium pump dysfunction. (Belletti et al., 2021; Jameson, J.L. et al., 2020b; Severino et al., 2020; Wiedmann et al., 2021)

In sum, ischemia, hypoxia, or genetic and structural abnormalities can disrupt action potential generation and propagation, causing pre-excitation (due to calcium overload), conduction delay (due to sodium channel dysfunction), inhomogeneous repolarization (potassium imbalance), or irreversible damage (fibrosis or necrosis). These processes manifest clinically as bradycardia, AV block, SSS, atrial flutter, or fibrillation (AF). (AMBOSS, 2024e; Chang & Li, 2022; Severino et al., 2020; Shi et al., 2024)

Chronically altered conduction increases myocardial wall stress and triggers progressive remodeling. The resulting breakdown of the electromechanical syncytium perpetuates a vicious cycle that ultimately leads to heart failure. Arrhythmias may therefore be both cause and consequence of cardiac decompensation. (Adamo et al., 2021; AMBOSS, 2024a, 2024e; Jameson, J.L. et al., 2020b; Thandavarayan et al., 2020)

2.1.2 Heart Failure

In a desynchronized myocardium, maintaining adequate cardiac output becomes increasingly difficult. A functioning syncytium ensures sufficient stroke volume and allows adaptation to variable demands, including exertion. In decompensated heart failure, even resting perfusion may be insufficient. (American Heart Association, 2025; Merck & Co, 2025b)

Thus- synchrony is essential to eject blood against vascular resistance into systemic and pulmonary circuits. Ejection fraction (EF), the proportion of blood expelled from the left ventricle per beat, is typically reduced in heart failure with reduced ejection fraction (HFrEF). EF must not be confused with blood pressure, which reflects arterial resistance.(McDonagh et al., 2021; Merck & Co, 2025a)

Heart failure may also occur with preserved (HFpEF) or mildly reduced EF (HFmrEF). In such cases, systolic function appears intact, but efficiency is compromised. Heart failure is not solely defined by EF; it represents a clinical syndrome caused by the interplay of mechanical and electrical desynchrony, diastolic dysfunction, and neurohormonal activation, especially of the renin-angiotensin-aldosterone system and sympathetic drive. (AMBOSS, 2024e; Merck & Co, 2025a)

Even when EF is preserved, conduction disturbances may cause hemodynamic compromise and justify cardiac resynchronization therapy (CRT). In conditions like left bundle branch block, delayed ventricular activation leads to inefficient contraction patterns, visible as widened QRS complexes on the ECG. This prolongation (>120 ms) reflects mechanical dyssynchrony and correlates with reduced systolic performance. (Chung et al., 2023; Glikson et al., 2021)

If the sequence of excitation, contraction, and relaxation is disrupted, the vicious cycle of remodeling and dysfunction ensues. Heart failure symptoms typically present as right-sided or left-sided signs but often overlap in global heart failure. (AMBOSS, 2024e)

Left Heart Failure:

Symptoms:

- Symptoms of acute heart failure and cardiogenic shock such as chest pain, dyspnea, orthopnea with or without central cyanoses but more acute in supine position, weakness and fatigue might occur at any time,
- Symptoms of pulmonary congestion due to back stowed blood caused by a disenabled working capacity of the left ventricle. Orthopnea, dyspnea and even paroxysmal nocturnal events, such as sudden wake up periods accompanied by excessive coughing attacks, might occur. Causative is an increased venous return at night and the resorption of peripheral edemas. Increased pressure within the pulmonary system might further cause symptoms mimicking asthma. So called cardiac asthma is due to airway compression in consequence of pulmonary congestion. (AMBOSS, 2024e; Anderson et al., 2007; Fihn et al., 2012; Gulati et al., 2021, 2021; Jameson, J.L. et al., 2020b, 2020a)

Clinical Examination

- Reduced perfusion to the lower extremities in consequence of left ventricular failure. Extremities show signs of malperfusion such as clammy, cool skin and pallor.
- On auscultation bilateral rales or crackles might be found. These are signs of intravascular fluid being passively driven into the pulmonary interstitium, caused by back stowed blood and pulmonary hypertension. In worse and acute cases flash pulmonary edema might be present.
  (AMBOSS, 2024e; Anderson et al., 2007; Fihn et al., 2012; Gulati et al., 2021, 2021; Jameson, J.L. et al., 2020b, 2020a; McDonagh et al., 2021)

Right Heart Failure:

Symptoms:

- Symptoms of acute heart failure and cardiogenic shock might occur at any time,
- Abdominal pain is due to impaired outflow of the hepatic venous system, also known as congestive hepatopathy. Hepatomegaly occurs in

consequence to venous congestion, accompanied by increased pressure to the hepatic capsule, which elicits abdominal pain.
(AMBOSS, 2024a, 2024e)

Clinical Examination

- Peripheral edema hallmarks increased venous pressure and consecutive fluid loss to the extra vasal space.
- Signs of central venous distension, such as distended jugular veins (possibly including the Kussmaul sign)
- Liver congestion with increased lumen of the vena cava inferior on ultrasound. Might be accompanied by jaundice.
- Hepatojugular reflux
- Cardiac cirrhosis and ascites

(AMBOSS, 2024e; Anderson et al., 2007; Fihn et al., 2012; Gulati et al., 2021, 2021; Jameson, J.L. et al., 2020b, 2020a; McDonagh et al., 2021)

CRT does not reverse myocardial necrosis or fibrosis but may improve synchrony and enhance output. Its efficacy depends on patient-specific pathology. (McDonagh et al., 2021)

Selecting a pacing strategy requires consideration of anatomical, clinical, and pharmacological factors. (Anker et al., 2021; Chung et al., 2023; Glikson et al., 2021; Merck & Co, 2025b; Roffi et al., 2016; Tanabe et al., 2010) This thesis does not cover antiarrhythmic drugs or pacemaker technologies such as sensing modes and defibrillators.(AMBOSS, 2024b) Instead, the focus lies on CRT strategies, particularly HBAP and LBBAP, and their role in improving cardiac function.

2.2 Pacing: Therapy and Methodology

If cardiac disease is associated with failure in cardiac synchronicity, cardiac resynchronization therapy is a standard therapeutic approach aiming to re-establish a working conductive syncytium of the heart.

To improve cardiac conduction and consecutive synchronicity, several anatomical approaches for pacemaker placement are eligible. Over the past years biventricular pacing has become the most frequently used approach. (Chung et al., 2023)

HBAP and LBBAP evolved as alternative approaches to classical biventricular pacing. Yet, HBAP and LBBAP are not used as frequently, however they provide promising opportunities even though some implications remain. (Moore et al., 2023) This section introduces briefly into bi-ventricular pacing as the most frequently used pacing method. Studies often compare the here discussed HBAP and LBBAP before the background or in comparison to biventricular resynchronization therapy. This section will explain why and how pacing addresses the heart conditions mentioned, providing a foundation for later discussion of the studies. The anticipated positive outcomes as well as the implications of the demonstrated pacing methods will be discussed.

2.2.1 General Principles, Indications and Contraindications for CRT

Cardiac resynchronization therapy (CRT) is a proven treatment for heart failure patients. Commonly CRT is performed in an approach that stimulates both ventricles, called biventricular pacing (BiV pacing or BVP). Especially in cases of associated left bundle branch block and asynchronous left ventricular contractions, established CRT methods have demonstrated a high success rate. The major goal of CRT is to reestablish synchronous contraction of both ventricles to regain hemodynamic sufficiency and thereby to improve left ventricular function and enhance patient's prognosis. (Chung et al., 2023; Fihn et al., 2012; Glikson et al., 2021, 2021; Roffi et al., 2016)

In recent decades, LBBAP emerged as an additional strategy and HBP gained renewed attention within the scientific community. (Deshmukh et al., 2000; Huang et al., 2017)

To mitigate consequences of pathologic processes on the cellular level and improve (progression of) heart failure is a major advantage of cardiac resynchronization therapy. However- CRT is not indicated for all types of heart failure. (Ciesielski et al., 2022)

The most consented basic criteria for CRT indication, according to current guidelines of the leading European and American Societies comprise the following:

Symptomatic HFrEF (LVEF ≤ 35%) with QRS duration ≥ 130 ms and LBBB morphology. (Chung et al., 2023; Glikson et al., 2021)

Other indications might be given, especially in everyday clinical practice. The set of indications might not be handled similarly across different centers. As Normand et al. (2020) found out, the adherence to the European Society of Cardiology's (ESC) Guidelines seems to differ across regions. (Normand et al., 2020) The mentioned indications and contraindications should not be regarded as exhaustive

However, as described in table 2, the following contraindications are generally contradicting CRT if fulfilled.

Table 2: Common Contraindications to CRT. Based on Glikson et al., 2021)

Common contraindications	
No	Reason
1	Lack of access for lead placement, (e.g. venous obstruction)
2	Absence of electrical desynchrony, (no ↑ QRSd, no LBBB)
3	Advanced septal scarring, which especially applies to LBBAP
4	Desynchrony of mechanical nature might be a relative contraindication
5	Desynchrony caused by untreatable infections
LBBAP and HBP are also considered alternatives in patients with failed BiV CRT or anatomical limitations to biventricular pacing.	

After outlining the hearts anatomy and physiology the previous chapter went into deep with the pathological background for heart failure and general pathological processes arising from or leading to conduction disorders. After presenting the indications and contraindications for CRT according to the current guidelines, the following sections will introduce the particular pacing methods.

2.2.2 Traditional biventricular Pacing, HBAP and LBBAP

Traditional biventricular pacing (BVP) involves right ventricular (RV) and left ventricular (LV) stimulation. In this classical approach two pacer electrodes are implanted, one to the right ventricle close to the apex or in the area of the cardiac septum and a further electrode to the coronary sinus. (AMBOSS, 2024b) While it is supported by robust clinical trials, limitations include suboptimal lead placement and non-physiological LV activation. (Gardas et al., 2022) Especially the non-physiological stimulation bears the risk of pacer induced side effects such as cardiomyopathy. (Tanabe et al., 2010) The pacing threshold also remains a challenge in biventricular pacing since it is often high. Thus, favoring unphysiological stimulation. In addition, several observations report on loss of capture in biventricular pacing. About 1/3 of patients do not respond to BiV-CRT. (Glikson et al., 2021)

His- bundle pacing (HBP) seeks to recruit the native conduction system by placing and directly stimulating the his- bundle. The advantage is sought to be a in near-normal ventricular depolarization, often deflected by a near normal QRS duration if achieved sufficiently. (Cano et al., 2023) This is why HBAP is often framed as one method of the so-called physiological pacing approach. This is beneficial because it theoretically reduces the risk of several adverse pacing effects like pacer induced cardiomyopathy as compared to BiV-CRT. (Derndorfer et al., 2024; Vijayaraman et al., 2022)

Yet studies revealed that this potentially beneficial approach on the other hand often requires higher pacing thresholds. Additionally, HBAP appears to present technical challenges regarding the precise placement of the pacemaker. Loss of capture is therefore also a potential challenge in HBAP. Another limitation to HBAP is that not all types of LBBB are treatable by HBAP. This is because HBAP seeks to activate the his Bundle. While LBBB caused by a block proximal to the bundle are treatable via HBAP, more distal blocks remain challenging for HBAP but might be addressed by BiV pacing or LBBAP. The background is that viable but without pacing not sufficiently activated areas of the left bundle brunch are activated by the higher pacing stimulus applied to the HIS Bundle- if they are close to the area of pacer stimulation. In more distally located blocks the effect of the stimulus is already diminished and might not be sufficient enough to initiate propagation. This is why HBAP is considered beneficial in proximal LBBB but not eligible for all types of LBBB. (Bressi et al., 2023; Chung et al., 2023; Ezzeddine et al., 2023; Fu et al., 2022; Glikson et al., 2021)

Left bundle branch area pacing (LBBAP) aims to capture the proximal left bundle branch or surrounding septal myocardium with stable capture, low thresholds, and improved electrical synchrony, particularly beneficial in LBBB or high-degree AV block. LBBAP is considered technically easier or less challenging as HBAP. On the other hand, LBBAP bears some procedural risks, such as right ventricular capture instead of left ventricular capture and septum perforation. Furthermore, LBBAP has limited effect if transmural scar tissue formation is present. Therefore, it cannot be applied e.g. in patients with myocardial infarction of the left anterior descending artery (LAD) and evident scar formation. Due to LAD ischemia or due to chronic remodeling the cardiac septum might undergo vast fibrotic proliferation, disenabling a sufficient propagation of LBBAP stimuli. On the other hand, LBBAP has a broad spectrum of applications. It is eligible for LBBB as well AV-block, sick sinus syndrome and further more. (Glikson et al., 2021; Jastrzębski et al., 2022; Vijayaraman et al., 2021; Wang, 2024)

2.2.3 Therapeutic Rationale, Physiology and desired Outcomes of CRT

Under normal physiological conditions, cardiac conduction occurs in a sequential and highly coordinated manner. Once impaired, CRT doesn't just benefit individual cardiomyocytes but rather harmonizes activation across myocardial networks. Viable but depressed regions (stunned myocardium) regain coordinated contraction. This restores mechanical efficiency, enhances energy utilization, and reduces neurohormonal drive. (Glikson et al., 2021)

CRT employs implanted electrodes to deliver electrical stimulation to the myocardium, aiming to achieve resynchronization in an electrophysiological manner. Electrical stimulation creates a new pace that includes areas of slow or impaired conductivity. Delays in propagation, such as bundle branch blocks, are bypassed in a coordinated manner. Pacing initiates artificial depolarization. It induces a controlled electrical impulse exceeding the threshold for action potential initiation. In previously non-activated or dyssynchronous activated zones, CRT reintroduces synchronized depolarization and contraction. The Na+ influx (phase 0) rapidly depolarizes the cell, spreading through gap junctions. This creates an overspilling effect especially along the network of intercalated disks. In Phase 2 The Ca^{2+} influx (phase 2) triggers calcium-induced contractile activation. Afterwards repolarization (phase 3) ensures readiness for the next cycle. (Hall & Hall, 2021; Klinke et al., 2003) As clinical endpoints, a successful resynchronization will therefore be measurable in multiple ways. A shortened duration of the ventricular propagation will be depicted as shortening of the QRS duration in a simple electrocardiogram (ECG). The QRS-complex deflects the excitatory period of the ventricular myocardium. A delay in conduction usually forms broad QRS-complex-patterns with a duration of 120 ms, which are pathognomonic for e.g. bundle branch blocks. (Ganschow et al., 2010) Once the pacemaker takes over and effectively overrides impaired conduction and bypasses blocked areas of the propagation pathways, a shortened QRS duration is a useful surrogate for effective electrical resynchronization.(Tavolinejad et al., 2023)

Additional measurements such as the stimulation to left ventricular activation time (STIM-LVAT) derived from intracardiac electrograms (EGMs) and the left ventricular end-diastolic diameter (LVEDD) may enhance the evaluation of conduction system pacing. (Saini et al., 2019; Zhong et al., 2022) STIM-LVAT serves as a valuable marker to differentiate the type of myocardial capture. Short activation times (< 80 ms) typically indicate direct capture of the left bundle branch, whereas prolonged durations suggest septal or myocardial capture.(Arnold et al., 2020) This distinction is particularly relevant for verifying successful lead placement in LBBAP.(Zhu et al., 2022) LVEDD, on the other hand, reflects the diastolic compliance of the left ventricle and is useful for monitoring potential adverse effects of pacing therapy, such as pacing-induced cardiomyopathy. Reductions in LVEDD over time may indicate progressive cardiac remodeling.(Gui et al., 2022)

Together, these measurements allow the evaluation, of the cardiac response, effectiveness and long-term consequences of conduction system pacing approaches.

Once a coordinated conduction is reestablished, mechanical resynchronization will follow in consequence. Cardiac resynchronization therefore means resynchronizing the electrophysiological propagation to resynchronize mechanical action in turn. The goal is to restore electromechanical synchrony. Once achieved, resynchronization reduces cardiac wall stress (Laplace's Law), improves stroke volume, and enables reverse remodeling, since a better perfusion of the myocardium itself is expected. CRT is capable of normalizing myocardial strain patterns, since resynchronized contraction also means resynchronized relaxation. This contributes to improved diastolic filling and even coronary perfusion by reducing end-diastolic pressure and enhancing the subendocardial perfusion gradient. (Abraham & Hayes, 2003; Federspiel et al., 2024; Glikson et al., 2021)

In turn the heart will regain strength to allow for an improved ejection fraction. In the end patients will recognize the effects of CRT via a reduction in symptoms. Often patients are already in high grade NYHA-Classification. An improved outflow will reestablish an enhanced relation of oxygen demand and supply. In a functional CRT, symptoms are expected to improve, possibly resulting in a lower NYHA classification grade for patients. Improved coordination of the heart's action may also enhance functional impairment related to mitral valve insufficiency. (Abraham & Hayes, 2003; Burri et al., 2021; Glikson et al., 2021, 2025)

After the principles of cardiac conduction have been demonstrated to ensure a clear understanding about the topic of this paper, the following chapter now outlines the methodology of the according literature search.

3 Methods

The cardiac conduction system and the relevant pathologies as well as general considerations for the different pacing approaches relevant for this research have been demonstrated in the previous chapter. A thorough literature review is essential to address this paper's research question. To emphasize transparency and reproducibility this chapter explains the established research methods being applied to this systematic review (Page et al., 2021, 2021; University of Leicester, o. J.) to sorrow answer the research question *"What are the benefits and disadvantages in cardiac resynchronization of parahisian pacing as compared to left bundle branch area pacing?"*.

3.1 Data Bases for Literature Research

To ensure that a sufficient amount of high yield and recent studies found and included, a comprehensive yet focused search was performed on three different data bases. In particular:

- NCBI PubMed, as the broadest medical data base
- MedRXiv, including preliminary papers and
- Cochrane Library as the primary database for systematic reviews

have been searched. For each data base boolean operators and filters (e.g., "Free Full Text", "English", "Human Studies", "Clinical Trial", etc.) were applied to refine the search and limit the inclusion to relevant and accessible studies. To generate comparable results a major search term addressing the research question was created as outlined in the following section. The search term was adapted to each database to ensure the comparability of all searches run during this review. (Higgins J. et al., 2024; MedRxiv, 2024; NIH PubMed, 2024a, 2024b)

3.2 Search Term

Based on the major search term, the search strategy for each platform was composed of five elements combined by Bboolean operators (AND/OR). As Outlined in table three it did not only focus on identifying literature involving CRT, but rather on studies comparing parahisian pacing and LBBAP, including outcomes such as procedural success, complications, and general clinical endpoints. To guarantee acceptable actuality of studies but also to restrict the results to human studies, accordingly filters have been applied. A preference for free full-text articles in English was set as well.

Table 3: Major Search Term with Boolean Operators. Source: Own Illustration.

Major Search Term	
Element of the Search Query combined by the Boolean operator "AND"	Requested Content
1	"Cardiac Resynchronization Therapy"
2 (AND)	"Left bundle branch pacing" OR "Left bundle branch area pacing" OR "LBBAP"
3 (AND)	"his bundle pacing" OR "Parahisian pacing"
4 (AND)	"comparison" OR "Clinical outcomes" OR complications OR success
Filters applied	Study Type: Human studies only Availability: Free full text Date Range: Last 10 years Language: English OR German

Due to the variation in terminology (e.g., *his-bundle pacing* vs. *parahisian pacing*), several synonymous terms were incorporated. Additionally, given the expected limited availability of direct comparison studies, the inclusion criteria were extended to studies focusing on each method individually, even technical studies, provided they discussed outcomes relevant to CRT. Furthermore, during a previous piloting of the available literature, it turned out that HBAP might be more difficult compared to LBBAP. Therefore, it is expected that technical studies are providing useful data to further clarify this question. Even though technical aspects are not the original scope of this thesis, it is part of a thought-out comparison to process data about factors influencing the success of each approach.

3.3 Study Selection and Selection Criteria

To safeguard a qualitative research procedure, general standards are followed during the screening and selection process. The process of study selection is performed in three phases according to the Preferred Reporting Items for Systematic Reviews and Metanalysis (Grobbee & Hoes, 2015; Page et al., 2021; PRISMA, 2020):

1. Title and abstract screening
2. Full-text review
3. Data extraction and quality assessment

After each query was run on PubMed, MedRxiv and Cochrane databases. All citations found have been saved and brought to CSV and RIS format to allow for transparent documentation of the studies that have been identified initially. The procedure is explained in section 3.3.3. It was based on the following In- and Exclusion criteria.

3.3.1 Inclusion Criteria

Final inclusion was only justified if all positive selection criteria had been met and none of the exclusion criteria was evident. If one exclusion criterion was met the study was excluded. As table 4 demonstrates, studies eligible for inclusion had to investigate in HBAP or LBBAP (synonymous terms have been accepted for inclusion too). In preliminary piloting for literature on the topic it was obvious that only a low amount of high-level evidence studies, such as RCT's or systematic reviews with meta analysis, would be available on the physiological pacing approaches of interest. It was challenging to ensure the inclusion of a sufficient number of articles while maintaining high-quality studies and avoiding overly stringent inclusion and exclusion criteria. The inclusion criteria have been led by the intention to gain quality and quantity within the framework of a low amount of high-level evidence on physiological pacing methods. This is why not only RCT's and metanalysis have been included, but also observational studies and even case series, given that a number of greater than ten cases was given, have been included. Thereby this paper follows the intention rather to include papers only of e.g. observational character than to exclude potential evidence. Nonexperimental evidence is not to be regarded as no evidence. In fact, observational findings provide important hints to direct further research, which is one of the core intentions of this paper. Still high yield studies were sought for retrieval to back up the results of this thesis. Tailored to the intended comparison between the physiological pacing approaches but taking the current amount of research available into account: The less restrictive inclusion of different study types enables to form a core of a few high yield studies and a corpus of lower level of evidence building a body and background to the center of this analysis. However, since per example case series are renowned to reflect on special and rare cases, a sufficient number of cases included was mandatory for this paper since the comparison between both approaches is intended to provide a rather general result and not to provide information on special situations. The third criterion for inclusion was "outcome specification". To assess LBAP and HBAP in a comparative manner, information about the clinical endpoints provided the necessary basis. The fourth criterion was the mode of publication. Peer reviewed journals was a prerequisite for inclusion to assure quality. Preprints have been included too in order to gain latest results on HBAP and LBBAP. The fifth criterion was publication language in English just to allow for suitable understanding of contents. The sixth criterion was set for the inclusion of studies that directly compared both physiological approaches of interest but also to include such studies that did not aim for comparison. The latter are providing the basis for the comparison of both approaches by this thesis in addition to the studies that already provide a comparison.

Table 4: Inclusion Criteria. Source: Own Illustration.

Inclusion Criteria	
#	Criterion
1	Topic: Studies reporting on left bundle branch area pacing (LBBAP) and/or his- bundle pacing (HBP)
2	Study Type: - Original research articles (overview-articles, RCTs, cohort studies, prospective or retrospective) OR - Overview articles of original research (systematic reviews, umbrella reviews with or without metanalysis)
3	Outcome Specification: Studies investigating cardiac resynchronization therapy (CRT) outcomes of LBBAP and/or HBAP. E.g.: complications, QRS duration, ejection fraction etc.
4	Published in peer-reviewed journals or available as preprints with sufficient methodological detail
5	Articles published in English.
6	Studies including either direct comparison (LBBAP vs HBP), comparison to other approaches or placebo-controlled studies or single-arm cohorts on one method.

As with the previous section the following section explains the chosen criteria for the exclusion of papers.

3.3.2 Exclusion Criteria

In addition to the inclusion criteria, the screening process also considered the exclusion criteria shown in Table 5. Exclusion criteria allow for transparency of the exclusion decision. Studies not eligible for the answer to the research question are ruled out in a systematic and comprehensible manner. (Higgins J. et al., 2024)

For this thesis technical barriers such as unavailability of full text or publications not available in English language, articles older than 10 years with threshold year being 2015 have been ruled out. Furthermore, animal studies have been ruled out as well as studies that did not focus on LBBAP and/ or HBP. In order to assure that publications reporting on single phenomena's rather than on recurrent aspects of LBBAP or HBAP are included, a threshold of minimum ten cases were set for case series studies. Case series that did not report on at least ten cases have been excluded. A further important exclusion criterion was if the studies failed to report endpoints or surrogates with clear written statements about their overall meaning. As mentioned in the inclusion section, outcome measurements are important to allow for comparison. However, also studies only providing a single outcome variable have been included, if there was clear and meaningful reflection on this variable providing information about advantages or disadvantages of the physiological pacing methods of interest.

Table 5: Exclusion Criteria. Source: Own Illustration.

Exklusion Criteria	
#	Criterion
1	Studies not involving LBBAP or HBP
2	Animal studies, in vitro studies, or simulations
3	Case reports or small case series (<10 patients)
4	Articles without accessible full texts
5	Non-English publications
6	Articles older than ten years (2015).

7	Studies without clinical or procedural outcomes relevant to CRT or pacing or not providing statements about the benefits or disadvantages of HBBAP or LBBAP.

After the criteria for in- and exclusion have been explained, the following sections concentrates on the process of selection and data extraction.

3.3.3 Selection Process and Data Extraction

The review of all articles identified was performed by the author of this thesis. There was no second reviewer. All citations found on Cochrane, MedRxiv and PubMed have been downloaded to a Zotero-Library. After all citations have been saved to Zotero-Citation-Program, the according citation files have been uploaded to a screening tool in the following step. The rayyan screening tool was used to rely on a well-renowned and established tool, free of charge. Rayyan allows for a simplified in- and exclusion approach for all parts of the selection process. (Ouzzani et al., 2016)

Whenever exclusion criteria have been identified during title, abstract or full text review, the according study was categorized as excluded. Studies meeting the inclusion without identified exclusion criteria have been qualified for the next step of the screening process. In particular: If the title did not show exclusion criteria, the study was qualified for the abstract screen. If the abstract screen did not demonstrate exclusion criteria, the study was qualified for full text screening. During the full-text screening each study had to fulfill all inclusion criteria and none of the outlined exclusion criteria must have been met. (Committee on Standards for Systematic Reviews of Comparative Effectiveness Research et al., 2011)

After the end of the title and abstract screening. Full text review was performed using Zotero. Studies have been tagged according to the in- and exclusion decisions. The according RIS- Files are found in the appendix to this thesis.

To improve quality, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed where applicable. The data were extracted using a standardized extraction sheet and categorized according to key thematic outcomes. (Page et al., 2021).

This section explained how the selection and extraction process will be carried out. The next section will provide information on the statistical analysis and visualization of the data retrieved.

3.3.4 Statistical Analysis and Visualization

Statistical data has been processed and visualized using Python 3.10 as well as Pandas and Matplotlib for visualization. (Hunter, 2007; *Pandas - Python Data Analysis Library*, 2024; The Matplotlib Development, 2025)

This chapter described the methods of data search, selection and final processing for description and interpretation. The following chapter will present the results of this review.

4 Results

Following the aforesaid methodological aspects the search on PubMed, MedRxiv and Cochrane data base was run. The results for the single steps of the selection process are depicted in the following PRISMA- flowchart. At all 192 Articles have been identified. Duplicate removal was performed on an automated basis, using Zotero and the Rayyan screening tool. At all 20 Duplicates have been removed from the identification process. With the remaining 172 publications, a title and abstract screening were performed. During this process 135 articles have been removed from further considerations. Main reason was a topic or outcome under study not relevant to the research question of this paper. Further reasons have been that exclusion criteria have already been identified during the title or abstract evaluation. Afterwards 37 reports remained eligible. A full text evaluation of all 37 studies was performed. Further 26 papers had to be excluded because exclusion criteria have been met. Main reasons, as depicted in the PRISMA-flowchart have been that no full text was available, even though according filters had been applied with each database search. Ten papers have been investigating interventions other than LBBAP and/or HBAP. Furter articles have not met inclusion criteria in a sufficient manner and/or exclusion criteria have been identified during full text analysis. Two studies have been investigating in pediatric populations only. Transposition of great vessels and other congenital defects special for childhood populations have been relevant to those investigations and therefore comparability to adult populations is not given. At all eleven papers have been included in this Review. Even though some publications rather focused on technical feasibility (N=7) they provided sufficient information about cardiac response to the according pacing approach and statements on perspectives for treatment that appeared useful for the answer of the research question. (Committee on Standards for Systematic Reviews of Comparative Effectiveness Research et al., 2011; Grobbee & Hoes, 2015; Higgins J. et al., 2024; Rothman et al., 2008)

4.1 PRISMA Statement

The PRISMA-flowchart in figure 6 depicts the above-described process of selection and the results of each step respectively.

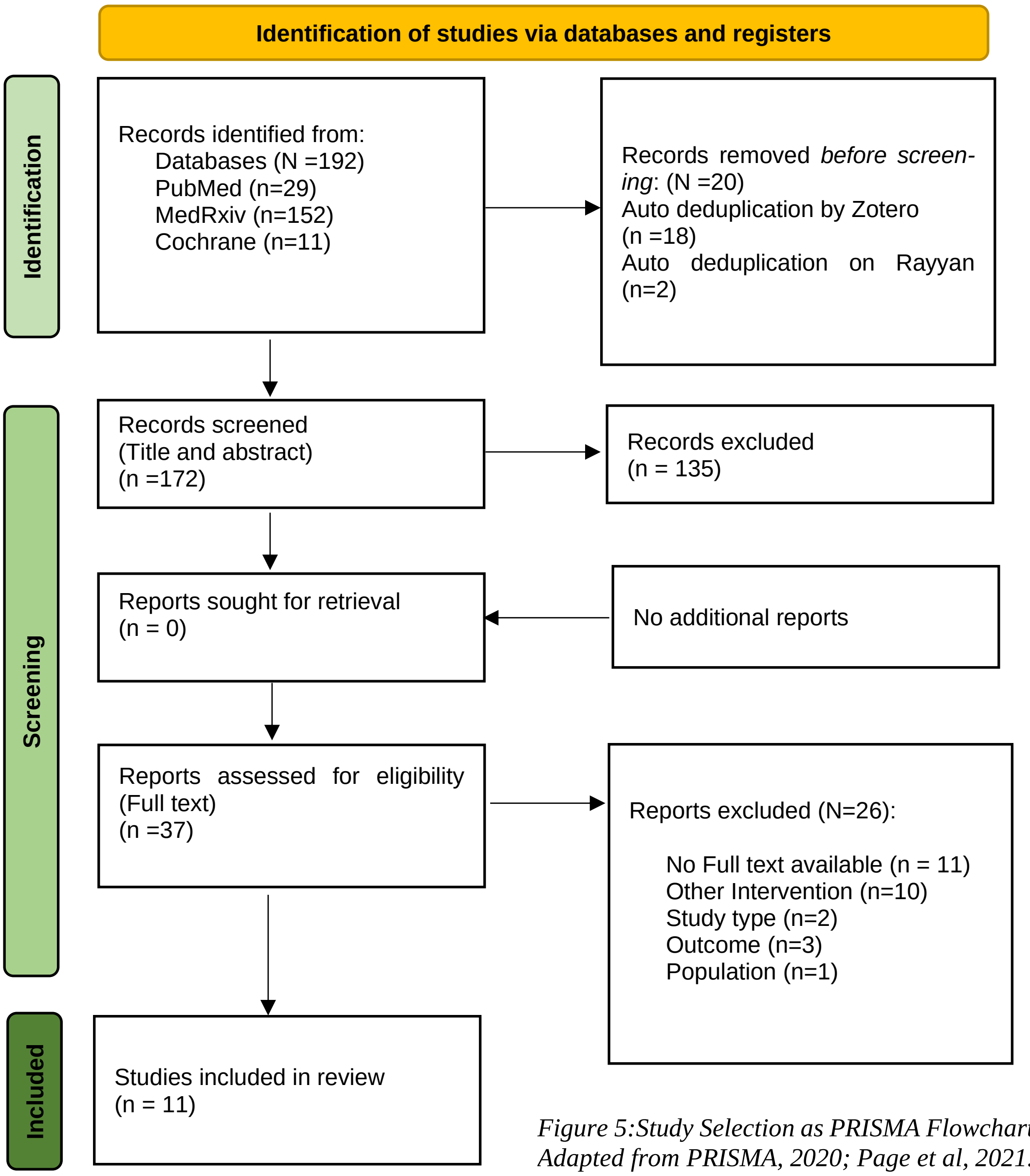

Figure 5:Study Selection as PRISMA Flowchart. Adapted from PRISMA, 2020; Page et al, 2021.

After the process of screening has been summarized the following sections will demonstrate the particular results extracted from the included studies.

4.2 Overview of Studies and their Characteristics

To comprehensively demonstrate the results, first this section will provide an overview of the study characteristics. The following section will then be concerned with the particular results important to the research question. Data extraction tables for crude data of study characteristics and outcome variables are depicted in section 4.2.1 (Table 6) and 4.4.5 (Tables 10 and 11) respectively.

Figure 7 provides an overview of the main characteristics as well as the intended outcome of all 11 studies included to this review. Some of those reviews investigated in more than one comparison, such as LBBAP vs. BVP as well as HBAP vs. BVP. If so the data of the according subsets have been extracted independently. Thus, in the overview table there will be 14 rows, since subset analysis was provided by 3 Studies. If no direct assessment of HBAP vs LBBAP was performed the comparisons of both approaches against a more established one like BVP or even RVP have been extracted separately to allow for comparison.

The following figures will visualize the distribution of the main characteristics.

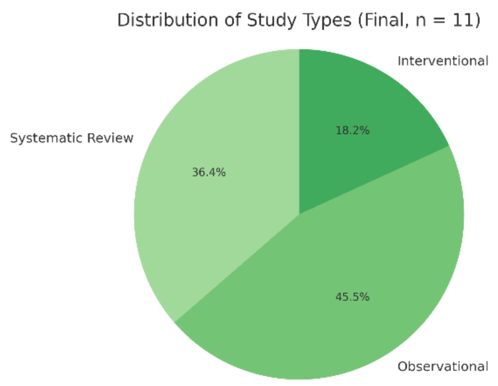

Figure 6: Study Types included. Source: Own Illustration.

Out of the eleven studies four systematic review, five observational studies and two interventional studies have been included. Two of the systematic reviews provided independent investigation into LBBAP and HBAP again BVP or RVP respectively. Those have been regarded separately. The same approach was chosen for one observational study also providing different subsets for LBBAP and HBAP.

All systematic reviews performed metanalysis (N=4), some with fixed and some with random effect models. The included metanalysis investigated in randomized controlled trials (RCT) as well as observational studies. The average number of studies included for the systematic reviews was 13,25.

Most of the observational studies (N=5) have performed retrospective analysis (N=3). One study labeled itself as cross-sectional, one as prospective but not interventional. There was one observational study performing analysis based on a multi-center approach. All others have been single-center Studies, or the setting was not reported. All observational studies have been from China (N=3) or the U.S. (N=2).

Interventional studies have been prospective in nature. Some of the two interventional studies found provided information on blinding procedures, however information on sampling procedures was not given. There was no randomized controlled trial included in this review. In one case from Europe, it was not reported if the study was based on a single or multicenter approach. The other study from China was a single center study.

According to the in- and exclusion criteria, preprint publications have been included too. Publication dates ranged from 2021 to 2024.

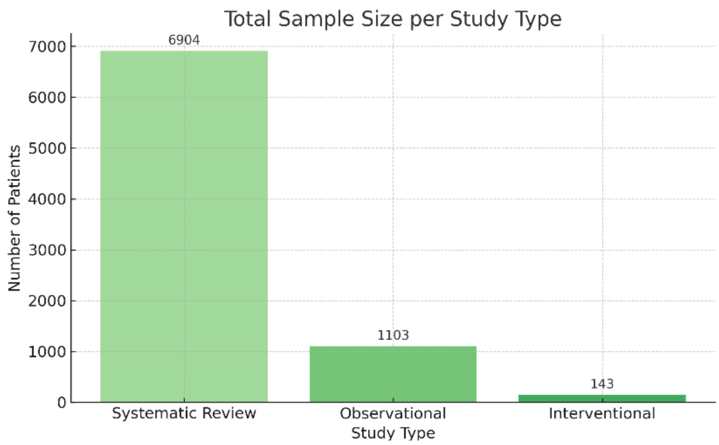

Figure 7: Total sample Size per Study. Source: Own Illustration.

Within the framework of the studies identified, data from a total of 8150 patients were retrieved. Most data and the largest sample sizes have been retrieved from the systematic reviews. As Figure 10 shows, observational and interventional studies had smaller sample sizes. Even though the samples investigated by the systematic review have been large in total, some reviews stated that the samples of the studies included in the reviews have been remarkably small. The high number of patients is predominantly achieved by the reviews from Leventopoulus et al. (2023) and Tokavanich et al. (2021). Especially loss of follow up and small samples have been observed in the review of Yu Gi et al (2023). In one interventional study, which was the preprint paper from Curila et al. (2023) the size of the sample was not clearly identifiable. Observational studies have been ranging from 21 patients (Ali, 2023) to 430 patients enrolled (Sarkar et al., 2024).

The mean follow up time, including the data of systematic reviews if an average follow up time was reported, was 22,19 months. In four studies follow up duration was not reported. Three of these papers have been preprint and one was a systematic review. (Ali, 2023; Curila et al., 2023; Shen et al., 2022; Tokavanich N, 2021).

The greatest follow up time was reported by Wang Y, et al. (2023) in the framework of their retrospective observational study, with 60 months. The lowest follow up time was 3 months reported by Su et al (2023).

Concerning the study population, the most frequent age span was > 70 years. However, five studies did not report on age distribution and one study had an average age above 60 years but lower than 70 years. If reported the distribution of gender was approximately equal between male and female participants. In seven out of the eleven papers included no information on gender distribution was found. Indications for CRT have been quite similar throughout all study populations. As demonstrated in Figure 10, the exact underlying pathology was not always specified. Most of the studies described conduction diseases, such as atrioventricular block (AVB), atrial flutter, fibrillation (AF) with bradycardia or sick sinus syndrome (SSS) as particular pathologies with CRT positive indication. Often these studies summarized additional indications such as heart diseases indicative for CR. One study did not report on the indication for CRT, Ali et al (2023) investigated rather in cardiac response and technical success of the Lead placement than in the clinical effort of CRT. Wang Y, et al (2023) investigated in CRT after transcatheter aortic valve implantation (TAVI). Further studies did not specify the CRT indication, 21,4% of the studies included were investigating in types of heart failure with unspecified CRT indication. To allow for a more structured analysis of the pacing approaches three study subsets of the eleven studies identified have been regarded individually. Subsets are counted in addition to the 11 studies identified (N=14). Overall, as shown in Figure 9, in 64,3 % of all 14 studies and subsets LBBAP was performed to mitigate the above-mentioned CRT – Indications. In 35,7% HBAP was chosen.

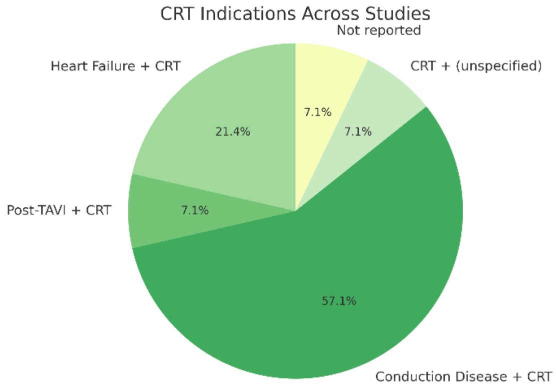

Figure 9: Indications for CRT identified in this Review. Source: Own Illustration.

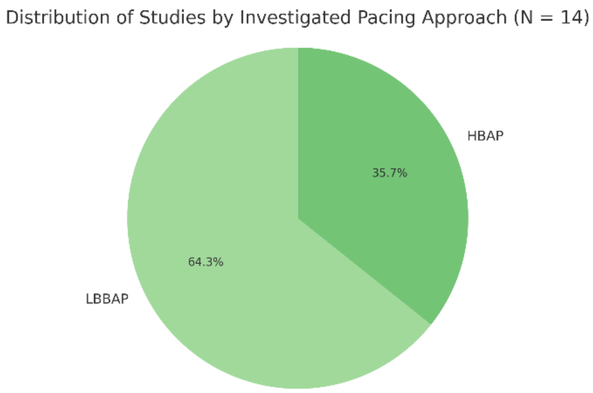

Figure 8: Percentage of Studies per LBBAP vs. HBAP. Source: Own Illustration.

4.2.1 Crude Data Table- Study Characteristics

Study ID	Comparison	Author (APA)	Year	Study Type	Design	Country	Setting	Studies (N)	Follow Up Time	Population (N)	Percentage M/F	Mean Age	CRT Indication	Exposure	Outcome of interest
INC01	No	Yu GI et al.	2023	Systematic Review	Meta-analysis	Multinational	Multi Center (16)	8	9.1	211 Patients	≈ equal distribution	> 60 Years	Heart Failure, CRT +	LBBAP	Efficacy of Treatment
INC02	LBBAP vs BVP	Hua J et al.	2022	Systematic Review	Meta-analysis	China / Multinational	n.r.	6	8.03	389 Patients	n.r.	n.r.	Heart Failure, CRT +	LBBAP (vs. BVP)	Efficacy of Treatment
INC02	HBAP vs BVP	Hua J et al.	2022	Systematic Review	Meta-analysis	China / Multinational	n.r.	6	8.03	see above	n.r.	n.r.	Heart Failure, CRT +	HBAP (vs. BVP)	Efficacy of Treatment
INC03	HBAP vs RVP	Wang Y et al.	2023	Observational	Retrospective	China	Multi Center(3)	n.a.	60	237 Patients	n.r.	> 70 Years	CRT + after TAVI	HBAP (vs. RVP)	Efficacy of Treatment
INC04	HBAP vs BVP	Tokavanich et al.	2021	Systematic Review	Meta-analysis	Multinational	n.r.	14	n.r.	2054 Patients	n.r.	n.r.	AVBlock, SSS, AFwB, CRT +	HBAP (vs. BVP)	Efficacy of Treatment
INC04	LBBAP vs BVP	Tokavanich et al.	2021	Systematic Review	Meta-analysis	Multinational	n.r.	14	n.r.	see above	n.r.	n.r.	AVBlock, SSS, AFwB, CRT +	LBBAP (vs. BVP)	Efficacy of Treatment
INC05	HBAP vs LBBAP	Sarkar et al.	2024	Observational	Retrospective	USA	Single-center	n.a.	28	430 Patients	n.r.	> 70 Years	AVBlock, SSS, AFwB, CRT +	HBAP (vs. LBBAP)	Cardiac Response
INC05	See above	Sarkar et al.	2024	Observational	Retrospective	USA	Single-center	n.a.	14	150 Patients	n.r.	> 70 Years	AVBlock, SSS, AFwB, CRT +	LBBAP (vs. HBAP)	Cardiac Response
INC06	No	Wang Y et al.	2024	Observational	Cross Sectional	China	Single-center	n.a.	36	320 Patients	≈ equal distribution	> 70 Years	AV Block, SSS, AFwB, CRT+	LBBAP	Cardiac Response
INC07	HBAP vs LBBAP	Curila et al.	2023	Interventional	Prospective	Europe	n.r.	n.a.	n.r.	unclear	n.r.	n.r.	CRT +	HBAP (vs. LBBAP)	Cariac Response
INC08	No	Su et al.	2023	Interventional	Prospective	China	Single-center	n.a.	3	143	n.r.	n.r.	AVBlock, SSS, AFwB, CRT +	LBBAP	Cardiac Response
INC09	No	Shen et al.	2022	Observational	Retrospective	China	Single-center	n.a.	n.r.	95	≈ equal distribution	> 70 Years	AVBlock, SSS, AFwB, CRT +	LBBAP	CardiacResponse
INC10	LBBAP vs RVP	Leventopoulos et al.	2023	Systematic Review	Meta-analysis	Greece	n.r.	25	11.2	4250 Patients	n.r.	> 70 Years	AVBlock, SSS, AFwB, CRT +	LBBAP (vs. RVP)	Efficacy of Treatment
INC11	No	Ali et al.	2023	Observational	Prospective	USA	n.r.	n.a.	n.r.	21 Patients	2/3 male ; 1/3 female	n.r.	n.r.	LBBAP	CardiacResponse

Table 6: Crude data extracted from the Studies included. Source: Own Illustration.

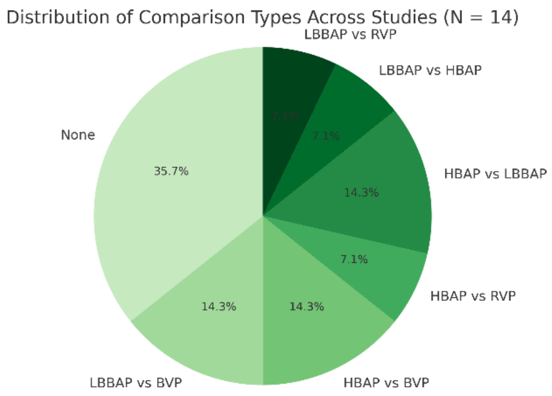

Figure 10: Comparisons investigated by papers included. Source: Own Illustration.

While 35,7% did not follow a comparative approach, all other papers included approached the study outcomes in a comparative manner. Of the 5 studies that did investigate a single pacing approach without comparison, all studies have been investigating in LBBAP only. In fact, there was only one study directly comparing LBAAP vs HBAP. Another study investigated LBBAP and HBAP against other methods, the subsets were extracted to approach a comparison of LBBAP and HBAP before the background of their performance. A direct comparison was not performed by this study. The subsets are included in the pie chart.

4.1 Study Outcomes

To distinguish between studies investigating rather in technical feasibility and cardiac response and studies investigating in clinical outcomes, all studies have been categorized into "cardiac response" and "efficacy of treatment". The background is that measurements vary, because the rationale of those studies differs. While cardiac response studies are aiming to answer the question if a particular pacing approach is working, which complications might be present, studies seeking efficacy of treatment outcomes are rather investigating in the clinical effect of the method. Both are of interest to this paper since technical feasibility is a prerequisite to effective treatment.

4.1.1 Primary Outcome Categories, Endpoints and Outcome Variables

Out of all Studies and subsets extracted 7 datasets investigated in treatment efficacy and 7 more investigated in cardiac response to the pacing approach. Endpoint variables and surrogates for the primary outcome categories varied, as visualized in Figure 12. Cardiac response studies provided endpoints informing over success ratios and pacing threshold and just in single cases information on left ventricular ejection fraction (LVEF) as well as QRS duration. Studies with interest in treatment efficacy provided surrogate information on threshold and success ratios too, however their endpoints focused more often on clinically more relevant variables such as LVEF, QRS Duration. Real endpoints like all-cause mortality, hospitalization due to heart failure during follow up (HFH) and NYHA score have only been reported by two studies.

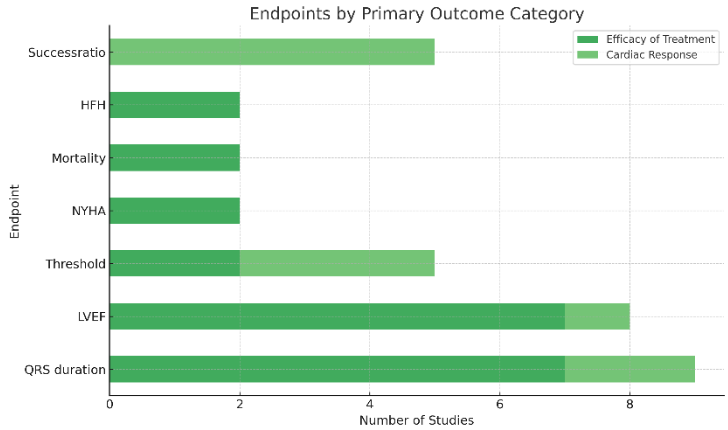

Figure 11:Endpoints in total numbers per Outcome Category (green). Source: Own Illustration.

All studies using QRS duration, LVEF, NYHA score included comparison of baseline and post intervention values. In the process of data extraction only the differences between the pacing approaches have been extracted for comparison studies. If no comparison was part of the study, baseline and post-intervention differences have been extracted.

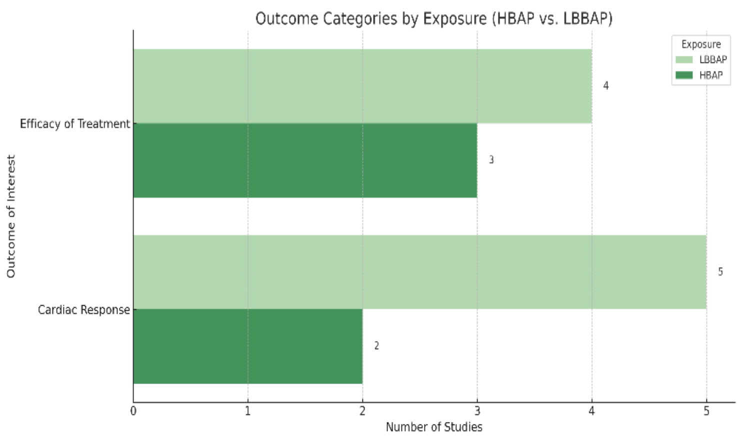

Figure 12: Pacing Approach distribution by Outcome Category. Source: Own Illustration.

As shown in Figure 13, out of the nine Studies (including study subsets) a total of five LBBAP studies investigated in cardiac response, while 4 LBBAP studies investigated in treatment efficacy. For the remaining five HBAP studies (also including study subsets) two studies investigated in cardiac response while three studies investigated in efficacy of treatment.

Before starting the analysis for the particular clusters first the overall success of implantation for HBAP and LBBAP respectively is observed in the following section.

4.1.2 Overall Succes Ratio and Complications in HBAP

Even though two of the HBAP studies have originally been investigating in cardiac response, data on success ratios have been reported in one study only. Sarkar et al. (2024) have been investigating in direct comparison of LBBAP vs. HBBAP. For HBAP a success ratio of 85% successfully implanted HBAP devices were described. In addition, the authors reported 60 cases of unsuccessful interventions and complications. Table 7 provides the extracted data for all HBAP studies on implant success and complications. In addition to the data shown in table 7, Sarkar et al. reported that 50 lead revisions had to be performed in the HBAP subset. This will be of interest in the discussions chapter. Out of the remaining four studies providing data on HBAP, no data on implant success and complications has been reported (n.r.).

Table 7: Data on Implant Success for HBAP. Source: Own Illustration.

Study ID	Author (APA)	Exposure	Implant Success	Complications
INC02	Hua J et al.	HBAP	n.r.	n.r.
INC03	Wang Y et al.	HBAP	n.r.	n.r.
INC04	Tokavanich et al.	HBAP	n.r.	n.r.
INC05	Sarkar et al.	HBAP	85%	60
INC07	Curila et al.	HBAP	n.r.	n.r.

One further study, not depicted here, since no crude data on HBAP was provided, investigated in cardiac response and compared LBBAP to HBAP. This study of Leventopoulos et. Al (2023) stated that there was no difference in total numbers of complications between HBAP and LBBAP. The success ratios and complications reported for LBBAP are depicted in table 8, in the following section.

4.1.3 Overall Success Ratio and Complications in LBBAP

For the success of LBBAP device implantation six out of nine studies reported implant success ratios. Table 8 provides an overview of the according data. Four out of the nine LBBAP datasets reported complications in total numbers. One paper did not provide ratios, percentages or crude numbers on complications. Ali et al (2023) therefore mentioned that the total numbers of complications did not vary between HBAP and LBBAP. The average success ratio of LBBAP is 94,1 % as computed from the studies which provided information on success ratios. The average number of complications

Table 8: Data on Implant Success for LBBAP. Source: Own Illustration.

Study ID	Author (APA)	Exposure	Implant Success	Complications
INC01	Yu GI et al.	LBBAP	91,30%	19
INC02	Hua J et al.	LBBAP	n.r.	n.r.
INC04	Tokavanich et al.	LBBAP	n.r.	n.r.
INC05	Sarkar et al.	LBBAP	97%	4
INC06	Wang Y et al.	LBBAP	93,40%	21
INC08	Su et al.	LBBAP	97,20%	n.r.
INC09	Shen et al.	LBBAP	92,60%	7
INC10	Leventopoulos et al.	LBBAP	93,60%	No Difference in total
INC11	Ali et al.	LBBAP	n.r.	n.r.

reported over all studies that provided this data is 12,75. These numbers do not take into account the proportionality against the total numbers of implantations. Furthermore, success ratios are not weighed by sample size. This will be part of the later discussion.

4.2 Comparison Clusters

Table 9: Clusters for Analysis. Source: Own Illustration.

Cluster Overview

Cluster A – LBBAP vs. HBAP (only Cardiac Response studies included)

Study	Comparison
INC05 – Sarkar et al.	
INC07 – Curila et al.	

Cluster B1 – LBBAP: Cardiac Response

Study	Comparison
INC06 – Wang Y et al.	No
INC08 – Su et al.	No
INC09 – Shen et al.	No
INC11 – Ali et al.	No

Cluster B2 – LBBAP: Efficacy of Treatment

Study	Comparison
INC02 – Hua J et al.	vs. BVP
INC04 – Tokavanich et al.	vs. BVP
INC10 – Leventopoulos et al.	vs. RVP
INC01 – Yu GI et al.	No

Cluster C1 – HBAP: Efficacy of Treatment

Study	Comparison
INC02 – Hua J et al.	vs. BVP
INC03 – Wang Y et al.	vs. RVP
INC04 – Tokavanich et al.	vs. BVP

To appropriately summarize and visualize the results of this thesis the data are stratified into three clusters. The clusters, as shown in table 9, are as follows: Cluster A incorporates studies of direct comparison between HBAAP and LBBAP. This cluster incorporates the studies of Curila et al. (2023) as well as Sarkar et al. (2024). There was no direct comparison between HBAP and LBBAP in studies seeking efficacy of treatment as primary outcome. So, by chance only more technical studies reporting on implant success and cardiac response have been included. Clusters B summarize cardiac response studies in LBBAP. None of the studies in cluster B1 were comparative. The following sections on cluster A and B1 will be held short. This is due to the low number of studies and especially due to missing data for cardiac response studies in HBAP only. The overall success ratios and complications in total numbers have already been reported in sections 4.3.2 and 4.3.3. Clusters A and B follow the intent of this paper to provide direct comparison.

4.2.1 Cluster A - Direct Comparison HBAP/LBBAP

In cluster A two studies directly comparing HBAP/LBBAP, the observational retrospective study from Sarkar et al. (2024) and the preprint of the interventional prospective study Curila et al (2023) have been included. The study from Curila et al. (2023) did neither report success ratios nor complications. Therefore, Figure 14 only illustrates implant success and reported complications based on data from Sarkar et al. (2024). In the two arms of the study 430 patients have been enrolled. 150 to the HBAP treatment regimen. Higher complications were reported for HBAP. It remained unclear how many patients indeed have been enrolled in the LBBAP arm of the study. A success ratio of 85% was reported for HBAP while a total of 60 complications were reported too. In 50 cases lead revision had to be performed in the HBAP arm. The success ratio for LBBAP was 97%. A total of 4 complications and no lead revisions have been reported. Sarkar et al stated that pacing threshold for capture was higher in the HBAP arm as compared to the LBBAP arm.

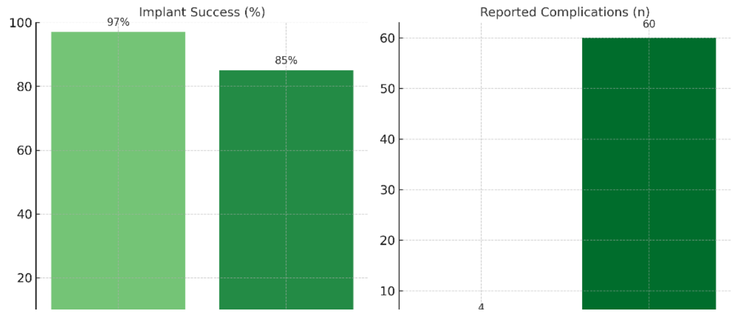

Figure 13: Cluste rA, Succes&Complications LBBAP vs HBAP Source: Own Illustration.

Curila et al observed an average QRSd of +10 ms (95% CI +7/+14) for the HBAP as compared to LBBAP arm that was statistically significant (p<0,001). However, the study reported further that QRSd for the individual measures have been shorter in the HBAP subset, while the average QRSd was shortest for LBBAP. In addition, the study stated that the capture-threshold for HBAP was higher as compared to LBBAP. According data was missing. These findings have been relatively equal to the results of Sarkar’s study.

Summary Cluster A:

In direct comparison of cardiac response to HBAP as compared to LBBAP the results of cluster A can be summarized as follows:

LBBAP provides lower pacing thresholds, shorter QRSd on average and is associated with higher success ratios but lower numbers of complications and lead revisions.

4.2.2 Cluster B1 - LBBAP- Cardiac Response

Cluster B1 involves studies focusing on cardiac response to LBBAP pacing interventions. Cardiac response was measured as implant success confirmed by capture of the generated impulses by the LBB and consecutive response of the myocardium. Within these studies different approaches of LBBAP have been investigated. As depicted in figure 15, there was a high success ratio.

The preprint paper of Ali et al. did not provide information on success ratios. Of the three remaining studies two studies reported complications in total numbers. One study reported seven complications (Shen et al (2022) 95 patients enrolled), another 21 complications. (Wang Y et al (2024): 320 Patients enrolled)

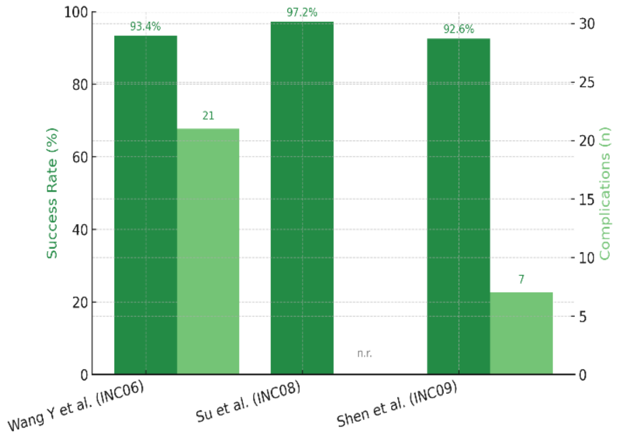

Figure 14: Cluster B1. Cardiac Response in LBBAP. Source: Own Illustration.

Detailed information on the type and consequence of the complications was not available. Cluster B1 is a subset of the overall success ratio, discussed in Section 4.3.3. Results of the LBBAP only studies, comprised of one interventional and three observational studies are similar to the overall findings. A successful implantation was achieved in > 90% of procedures. Wang Y et al (2024) explicitly reported success for the particular CRT indications (AVB, AF with bradycardia, SSS). However, the success rates have not been quantified among subset distributions, by this preprint publication. In addition to success ratio, Sue et al. reported an overall improved LVEF as compared to baseline (Baseline: 41.3±14.7% Post intervention: 53.7±11.9). The increase in LVEF was statistically significant (p< 0,001). Further information have not been reported by the studies. All papers included in this cluster are preprint publications.

Summary Cluster B1

Based on the information available, LBBAP cardiac response studies can be summarized as follows:

LBBAP interventions are successfully achieved in > 90% of cases. Complications occur in relatively low to intermediate numbers. Cardiac response was also demonstrated by an increase in LVEF in one study.

4.2.3 Cluster B2 LBBAP- Efficacy of Therapy

Cluster B2 includes four studies of which three have been comparing LBBAP to established pacing approaches, while one study focused on LBBAP without comparison to another approach. Of the four studies in this cluster all have been systematic reviews providing meta-nalysis, partly with broad sample size. (Leventopoulus et al. (2023) N=4250; Tokavanich et al. (2021) N=2054)

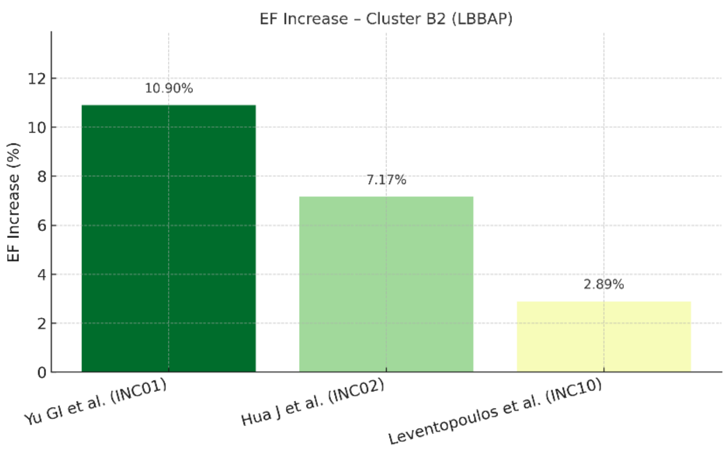

Figure 15: Cluster B2. EF Increase in LBBAP. Source: Own Illustration.

All studies reported an increase in LVEF for LBBAP. The systematic review of Tokavanich et al. (2021) provided data on comparison between the methods investigated (LBBAP, RVP, BVP, HBAP). The supplemental data table mentioned in this study, was sought to provide the crude data per pacing approach. This data table was not available before the end of this thesis. Furthermore Tokavanich et al. found no significant change in LVEF throughout comparison groups. For LBBAP as compared to BVP a statistical unsignificant increase of 5.5% (95% CI: +11% to +22%) was reported. Of the three further studies LBBAP demonstrated a post interventional increase in LVEF as compared to the other methods under investigation (RVP, BVP). This is shown in Figure 16. All studies with exception of Tokavanich et al. found a statistically significant increase in LVEF (Yu Gi et al.: LVEF +10,90%, 95% CI: +6,56 to +15,23, p < .001; Hua J et al.: LVEF +7.17 %, 95% CI: +4,31 to + 10,04, p < .05; Leventopoulos et al.: LVEF +2.89 %, 95% CI: + 1.70 to +4.07, I2=56%; p<0.001).

Besides LVEF increase all studies reported on QRS duration. Figure 17 visualizes the reduction of QRSd in LBBAP as compared to baseline. The most remarkable reduction in QRSd was observed by Yu Gi et al. (2023) in their non comparative metanalysis (QRSd -34,51, 95% CI: -09,10 to -60,00, p < .001), followed by Leventopoulus et al. (2023) observing a QRSd reduction of -32,20 (95% CI: -40.70 to -23.71, p < .001), Huaj et al. (2022): QRSd -27,40 (95% CI: -10,81 to -43,99, p < .05) and Tokavanich et al. (2021) observing QRSd of -27,00 (95% CI: -10,00 to -44,00, p: n.r.). Besides QRSd, further investigations to assess the clinical efficacy of LBBAP have been undertaken. Yu Gi et al aimed to compare NYHA status pre- to post intervention. A thought-out analysis was not possible since only one of the studies included to their metanalysis assessed for NYHA classification. In this single study a reduction of NYHA post LBBAP intervention was reported. However, no data was available to provide comparative analysis. In addition, the authors stated that many of the studies included have been of small sample size and low follow up duration. Loss of follow up was reported for > 50% in some studies. None of the other studies in this cluster reported NYHA scores to assess heart failure or heart failure severity. As further measurement Huaj et al assessed pacing threshold besides QRSd and LVEF. In a subset analysis they observed a lower threshold for LBBAP as compared to HBAP.

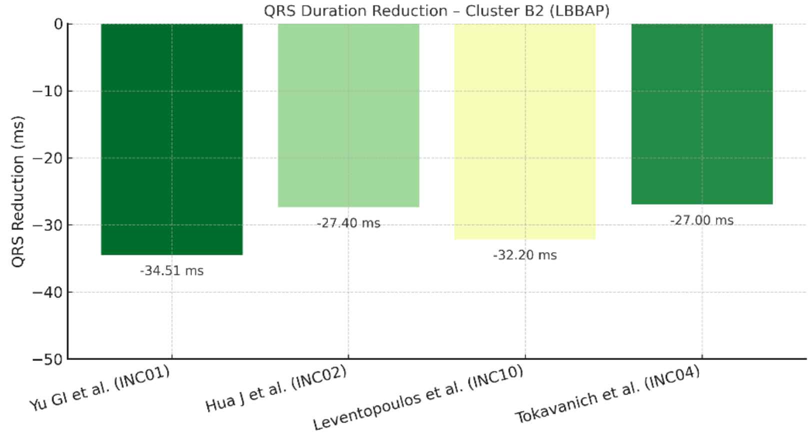

Figure 16: Cluster B2, QRSd Reduction (LBBAP). Source: Own Illustration.

Within the same study it was demonstrated that LBBAP as well as HBAP have been significantly superior to BVP. The subset for HBAP will be part of the analysis in the following section.

Leventopoulos et al. assessed for some additional endpoints. Their metanalysis was the only study in cluster B2 presenting results for hospitalization due to heart failure throughout the follow up period (HFH) and all-cause-mortality. The according risk ratio (RR) for HFH was significantly lower for patients who underwent LBBAP as compared to right ventricular pacing (RVP): HFH RR:0.33, CI 95%: 0.21 to 0.50; I2=0%; p < 0.001. All-cause mortality (M) risk ratios revealed a significantly lower risk for LBBAP as compared to RVP to die of any cause during follow up: M RR:0.52 CI 95%:0.34 to 0.80; I2=0%; p=0.003.

To enforce the assessment for electromechanical synchrony Leventopoulos et al. also assessed the time from stimulation to activation of the left ventricle. Treatment efficacy in terms of cardiac response was significantly higher in LBBAP as compared to RVP. The measured stimulation to left ventricular activation time (STIM L-VAT) was significantly lower in the LBBAP arm: STIM L-VAT: -24.40 msec, CI 95%: -36.32 to -12.48; I2=98%; p<0.001.

Within cluster 2B no further endpoints or surrogates of relevance to this paper have been reported.

<u>Summary Cluster B2:</u>

LBBAP was statistically significantly superior to more conventional pacing methods such as BVP and RVP, in terms of treatment efficacy measured as QRSd, LVEF, all-cause mortality, HFH and STIM- LVAT. The subset analysis which provided a direct comparison of LBBAP to HBAP did not show significant differences. Pacing threshold however seems to be lower in LBBAP.

4.2.4 Cluster C - HBAP- Efficacy of Therapy

All studies included to cluster C provided data on LVEF. The results are demonstrated in Figure 18 as mean difference (point) and according 95% CI (lines). All studies showed an increase in LVEF for HBAP. The highest increase was found in the paper of Wang Y et al. (2023) with 6,01 % (95% CI: 4.81 to 7.22, P < 0.001, I2 = 0%)

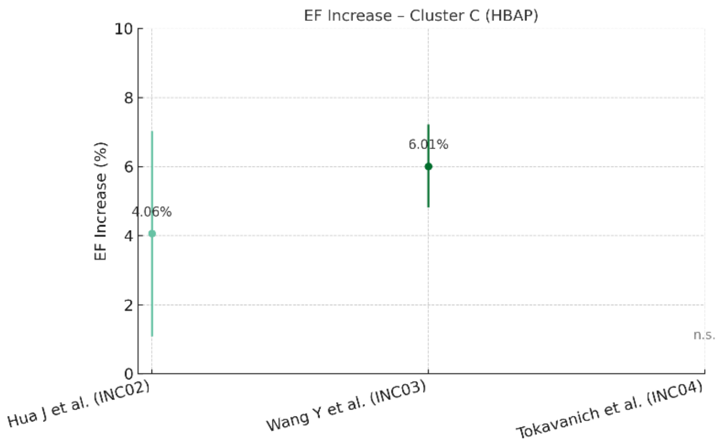

Figure 17: Cluster C- HBAP increase EF (+CI) . Source: Own Illustration.

comparing HBAP to BVP. Hua J et al. (2022) reported an increase of 4,06% (95% CI: +1,09 to +7,03, p < .05) also in comparison to BVP.

Tokavanich et al. reported a post interventional increase in LVEF for HBAP as compared to BVP. HBAP increase in LVEF was 3.3% (95% CI: +13% to +20%). However, same as with the LBBAP in cluster B2, the result remained statistically not significant (indicated as n.s.).

Besides the increase in LVEF all studies found a reduction in QRS duration for HBAP as compared to BVP. Figure 19 illustrates the mean reduction for each study. 95% confidence intervals are indicated as lines. The greatest reduction was reported in the systematic review of Tokavanich et al. (2021) with a mean of 33,00 ms (95% CI: -18,00 to -49,00), closely followed by Hua J et al. (2022) -31,58 (95 % CI: -12,75 to -50,40, p < .05) and Wang Y et al. (2023) -26,25ms (95% CI: -34.54 to -17.92, P < 0.001, I2 = 91%).

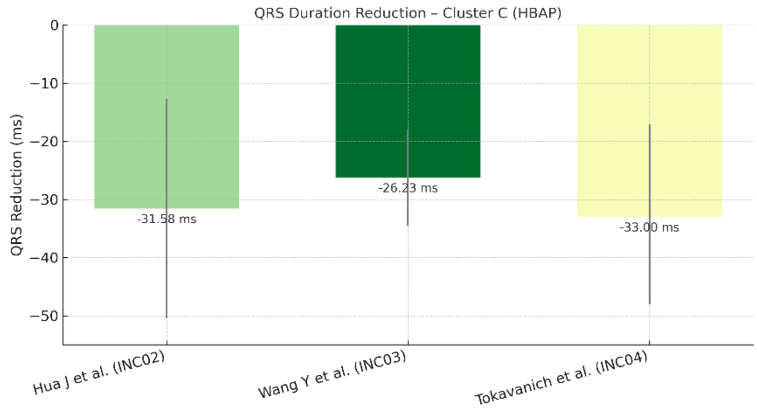

Figure 18: Cluster C. Reduction in QRSd (ms) with 95% CI. Source: Own Illustration.

Further Findings have been:

Wang Y et al. reported a consortium of further measures across their comparison between HBAP and BVP. It was found that HBAP provided higher odds for responses on echocardiography (Odds ratio (OR): 2.76, 95% CI: 1.74 to 4.39, P < 0.001, I2 = 0%), as well as higher odds for improved clinical outcomes (OR: 2.10, 95% CI: 1.16 to 3.80, P= 0.01, I2 = 0%) as compared to BVP. The hospitalization due to heart failure during follow up was lower (OR: 0.34, 95% CI: 0.22 to 0.51, P < 0.001, I2 = 0%), while no difference (OR: 0.68, 95% CI: 0.44 to 1.06, P= 0.09, I2 = 0%) in all-cause mortality was detectable for HBAP as compared with BVP.(Wang Y, 2023)

Both Wang et al. (2023) and Hua J. et al. (2022) reported a higher Pacing Threshold for HBAP.

Summary Cluster C:

HBAP demonstrates clear superiority in terms of clinically relevant endpoints against BVP. Significant reductions in QRSd and increases in LVEF have been reported. Again, HBAP was found to have a higher pacing threshold as compared to BVP. Even though only one study investigated further outcomes, in comparison to BVP, HBAP showed favorable odds for HFH, clinical response. Echocardiographic findings confirmed results.

4.2.5 Extracted Crude data (Outcome variables)

Table 11: Crude Data extracted for Endpoints. Part I. Source: Own Illustration.

Study ID	Author (APA)	Year	Exposure	Outcome of interest	Implant Success	Complications	Actual Outcome	Results EF Increase	95 % CI EF	p-value
INC01	Yu GI et al.	2023	LBBAP	Efficacy of Treatment	91,30%	19	QRS ↓, EF ↑, NYHA ↓	+10,90%	+6,56 to +15,23	p < .001
INC02	Hua J et al.	2022	LBBAP (vs. BVP)	Efficacy of Treatment	n.r.	n.r.	QRS ↓, EF ↑	+7.17 %	+4,31 to + 10,04	p < .05
INC02	Hua J et al.	2022	HBAP (vs. BVP)	Efficacy of Treatment	n.r.	n.r.	QRS ↓, EF ↑	+4,06%	+1,09 to +7,03	p < .05
INC03	Wang Y et al.	2023	HBAP (vs. RVP)	Efficacy of Treatment	n.r.	n.r.	QRS ↓, EF ↑, NYHA ↓, M =, HFH↓, Threshold ↑	not significant	not significant	not significant
INC04	Tokavanich e	2021	HBAP (vs. BVP)	Efficacy of Treatment	n.r.	n.r.	QRS ↓ EF ↑	↑ vs BVP, not significant vs LBAP		n.r.
INC04	Tokavanich e	2021	LBBAP (vs. BVP)	Efficacy of Treatment	n.r.	n.r.	QRS ↓ EF ↑	↑ vs BVP, not significant vs HBAP		n.r.
INC05	Sarkar et al.	2024	HBAP (vs. LBBAP)	Cardiac Response	85%	60	Threshold ↑/Success Ratio ↓	n.r.	n.r.	n.r.
INC05	Sarkar et al.	2024	LBBAP (vs. HBAP)	Cardiac Response	97%	4	Threshold ↓ /Succes Ratio ↑	n.r.	n.r.	n.r.
INC06	Wang Y et al.	2024	LBBAP	Cardiac Response	93,40%	21	V6-R Wave Peak Time, EGM.	n.r.	n.r.	n.r.
INC07	Curila et al.	2023	HBAP (vs. LBBAP)	Cariac Response	n.r.	n.r.	QRS ↓, Thershold ↑	n.r.	n.r.	n.r.
INC08	Su et al.	2023	LBBAP	Cardiac Response	97,20%	n.r.	Successratio, EF ↑	41.3	±14.7 SMD	p < .001
INC09	Shen et al.	2022	LBBAP	CardiacResponse	92,60%	7	Successratio	n.r.	n.r.	n.r.
INC10	Leventopoulc	2023	LBBAP (vs. RVP)	Efficacy of Treatment	93,60%	No Difference in total	QRS ↓,EF ↑, M ↓ , HFH ↓	+2.89 %	+ 1.70 to +4.07;	I2=56%; p<0.001
INC11	Ali et al.	2023	LBBAP	CardiacResponse	n.r.	n.r.	QRS ↓	n.r.	n.r.	n.a.

Study ID	Author (APA)	Year	Study Type	Design	Exposure	Outcome of interest	Results QRS	CI QRS	Significance	Results NYHA	CI NYHA	Other Results	Measure Other
INC01	Yu GI et al.	2023	Systematic Review	Meta-analysis	LBBAP	Efficacy of Treatment	-34,51	-09,10 to -60,00	p < .001	↓ (only one Stuc	n.r.	n.r.	n.r.
INC02	Hua J et al.	2022	Systematic Review	Meta-analysis	LBBAP (vs. BVP)	Efficacy of Treatment	-27,4	-10,81 to -43,99	p < .05	n.r.	n.r.	Pacing threshold ↓	n.r.
INC02	Hua J et al.	2022	Systematic Review	Meta-analysis	HBAP (vs. BVP)	Efficacy of Treatment	-31,58	-12,75 to -50,40	p < .05	n.r.	n.r.	Pacing threshold ↑	n.r.
INC03	Wang Y et al.	2023	Observational	Retrospective	HBAP (vs. RVP)	Efficacy of Treatment	-29	n.r.	p < .001	Class III-IV RVP: 17%, LBBAP 8%	p=0,04	Adjusted HR HFH 2,:	95 % CI HR 1,01 to 5,08
INC04	Tokavanich et al.	2021	Systematic Review	Meta-analysis	HBAP (vs. BVP)	Efficacy of Treatment	-33	-18,00 to -49,00	n.r.	n.r.	n.r.	n.r.	n.r.
INC04	Tokavanich et al.	2021	Systematic Review	Meta-analysis	LBBAP (vs. BVP)	Efficacy of Treatment	-27	-10,00 to -44,00	n.r.	n.r.	n.r.	n.r.	n.r.
INC05	Sarkar et al.	2024	Observational	Retrospective	HBAP (vs. LBBAP)	Cardiac Response	n.r.	n.r.	n.r.	n.r.	n.r.	Lead Revisions	N= 50
INC05	Sarkar et al.	2024	Observational	Retrospective	LBBAP (vs. HBAP)	Cardiac Response	n.r.	n.r.	n.r.	n.r.	n.r.	Lead Revisions	N = 5
INC06	Wang Y et al.	2024	Observational	Cross Sectional	LBBAP	Cardiac Response	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
INC07	Curila et al.	2023	Interventional	Prospective	HBAP (vs. LBBAP)	Cariac Response	+10,00	+07,00 to + 14,00	p < .001	n.r.	n.r.	n.r.	n.r.
INC08	Su et al.	2023	Interventional	Prospective	LBBAP	Cardiac Response	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
INC09	Shen et al.	2022	Observational	Retrospective	LBBAP	CardiacResponse	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
INC10	Leventopoulos et al	2023	Systematic Review	Meta-analysis	LBBAP (vs. RVP)	Efficacy of Treatment	-32,20	-40.70 to -23.71	p < .001	n.r.	n.r.	HFH, M, Stim LVAT	HFH RR:0.33, CI 95%: 0.21 to 0.50; I2=0%; p < 0.001; M RR:0.52 CI 95%:0.34 to 0.80; I2=0%; p=0.003; STIM L-VAT: -24.40 msec, CI 95%: -36.32 to -12.48; I2=98%; p<0.001.
INC11	Ali et al.	2023	Observational	Prospective	LBBAP	CardiacResponse	n.a.	n.a.	n.a.	n.r.	n.a.	n.a.	n.a.

Table 10: Crude Data extracted for Endpoints. Part II.. Source: Own Illustration.

5 Discussion

The previous chapter presented the data and outlined the results extracted from the studies, organized into clusters by comparison, pacing approach, and primary outcome of interest. This chapter summarizes and interprets the key findings, discusses their implications and limitations, and provides recommendations for future clinical application and research. After this critical reflection, the subsequent chapter will directly address the research question of this thesis:

5.1 Key Findings

The primary focus of this thesis was to compare his-bundle area pacing (HBAP) and left bundle branch area pacing (LBBAP) to determine whether one approach is superior overall or in specific indications. A secondary objective was to evaluate whether either, or both, pacing approaches offer better results in terms of cardiac response and clinical efficacy compared to conventional methods such as biventricular pacing (BVP) or right ventricular pacing (RVP).

This thesis included studies assessing both clinical outcomes and cardiac response. Studies primarily investigating technical or immediate physiological outcomes were classified as "cardiac response" studies, whereas those with a broader clinical focus and longer follow-up durations were categorized as "efficacy of treatment" studies.

Among the fourteen studies and subsets included, seven focused on cardiac response, and seven assessed clinical efficacy. Based on the results presented in the previous chapter, the key findings are summarized as follows:

Measures of Cardiac Response and Technical Feasibility for LBBAP and HBAP:

- <u>Pacing Threshold:</u>
  Almost all studies reported lower pacing thresholds for LBBAP compared to HBAP.
- <u>Implant Success Ratios and Complications:</u>

  Implant success rates were higher for LBBAP, and overall complications were fewer compared to HBAP. However, it is important to note that only one study reported implant success and complication rates for HBAP, while six studies reported this data for LBBAP.
  The high number of complications (including fifty lead revisions) observed in the HBAP group in one study raises concerns regarding the technical feasibility of HBAP. However, due to the unclear reporting in that study, these findings should be

interpreted with caution. Another study found no significant difference in complication rates between LBBAP and HBAP.

Measures for the Efficacy of Treatment:

- LVEF and QRSd

  Improvements in left ventricular ejection fraction (LVEF) and reductions in QRS duration were slightly better with LBBAP. However, direct comparisons between LBBAP and HBAP, where available, showed no statistically significant differences
- NYHA Functional Class, Heart Failure Hospitalization and All-cause Mortality

Only one study reported NYHA functional class improvement for HBAP compared to BVP, demonstrating a reduction in heart failure severity. For LBBAP, a meta-analysis including 211 patients identified only one study reporting NYHA class improvements, which also showed positive results. HFH during follow-up was significantly lower for both HBAP (compared to BVP) and LBBAP (compared to RVP).

All-cause mortality during follow-up was significantly reduced for LBBAP compared to RVP, but no significant difference was found for HBAP compared to BVP.

Comparison of HBAP and LBBAP against BVP and RVP:

Whenever compared, both HBAP and LBBAP demonstrated better overall outcomes than conventional pacing methods. While considering the limitations of the available data, these results appeared consistent for both physiologic pacing strategies. As demonstrated in the cluster analysis in the previous chapter, physiological pacing approaches were consistently associated with favorable outcomes, particularly with regard to QRS duration shortening and LVEF improvement.

5.1.1 Interpretations

Regarding implant success and technical feasibility, the findings of this thesis are consistent with prior research, indicating that LBBAP appears technically easier to implement compared to HBAP. Reductions in QRS duration (QRSd) and increases in left ventricular ejection fraction (LVEF) respectively demonstrate better cardiac response to physiological pacing approaches. Moreover, QRSd and LVEF serve as surrogate markers for treatment efficacy.

The results demonstrate a higher likelihood of favorable clinical outcomes when compared to conventional pacing methods (BVP/RVP). When HBAP and LBBAP are viewed together as physiological pacing approaches, a consistent pattern of superiority emerges across the available data. This superiority is further supported by advanced measurements in some included studies. Beyond QRSd and LVEF, computed ratios for all-cause mortality, hospitalization rates, and advanced cardiac response parameters (e.g., Stimulation to left ventriculat activation time (STIM-LVAT), Left ventricular end-diastolic diameter LVEDD) corroborate the promising potential of physiological pacing.

Interestingly, the pacing indications were relatively similar across the included datasets. Although the overlapping indications of various pacing methods are already recognized, these observations reinforce the notion that LBBAP and HBAP may represent more sophisticated strategies compared to conventional approaches. However, a more detailed analysis of specific indications could have provided deeper insights into the relative advantages of each physiological pacing technique.

More direct comparative studies between HBAP and LBBAP are required to reveal the true benefits and limitations of each approach. Furthermore, despite the promising results favoring physiological pacing over conventional methods observed in this thesis, additional studies with complete datasets are necessary to substantiate these findings.

Nearly all authors limited the interpretation of their results due to missing data, unassessed competing risks, and potential confounders. This is consistent with the impression derived from this thesis and highlights a broader lack of sophisticated, especially randomized controlled trials clearly outlining all relevant variables.

5.1.2 Implications and Limitations

This thesis underscores the significant need for further research in the field of conduction system pacing. The findings suggest that physiological pacing methods potentially offer superior alternatives to conventional pacing, particularly regarding clinical efficacy and cardiac response.

However, the exploratory power of this thesis is limited due to the high proportion of missing data. In particular, the low number of direct comparisons between HBAP and LBBAP restricts comprehensive analysis. Furthermore, the data for LBBAP significantly outweigh the available data for HBAP, creating a potential bias.

Although it is possible that the strictness of the research terms contributed to the limited number of included studies, major medical databases (PubMed, Cochrane, MedRxiv) were thoroughly searched. Given that even large meta-analyses sometimes yielded fewer relevant studies, it seems more likely that relevant trials are simply lacking rather than missed by the search strategy.

This limitation in available evidence is itself an important finding of this thesis. Besides the direct effects of physiological pacing approaches outlined here, the identification of these research gaps forms an additional key contribution of this work.

5.1.3 Recommendations

Based on the findings of this thesis, further investigation of both LBBAP and HBAP, as well as direct comparisons between the two methods, is clearly recommended. Future studies should address not only technical feasibility and cardiac response but also long-term clinical outcomes.

In particular, studies should report comprehensively on LVEF, QRSd, NYHA functional class, all-cause mortality, and heart failure hospitalizations (HFH), providing reasonable endpoints for middle- and long-term effects. A minimum follow-up duration of one year post-intervention is recommended to detect potential adverse effects that may develop over time. Given that pacing interventions are designed to influence long-term cardiac function, short-term studies risk missing important outcomes.

Additional techniques such as STIM-LVAT measurement, EGM-based assessments and LVEDD evaluation -especially to assess for adverse effect, such as pace maker induced cardiomyopathy- should complement the standard clinical endpoints to provide a more comprehensive evaluation of pacing efficacy.

6 Conclusion

The scientific interest of this thesis followed the research question:

"What are the benefits and disadvantages of parahisian pacing compared to left bundle branch area pacing in cardiac resynchronization?"

This thesis aimed to clarify the use of both methods as potential alternatives to traditional biventricular pacing and to determine whether one approach may be considered superior.

6.1 Answer to the Research Question

Due to a lack of comparative studies, particularly randomized controlled trials, this thesis can only approximate an answer regarding the true advantages and disadvantages of HBAP compared to LBBAP.

Based on the available data, clinical outcomes appear broadly similar between the two approaches for comparable indications. Consequently, there is currently no clear evidence of superiority for one technique over the other. LBBAP may offer slightly higher technical feasibility and lower pacing thresholds; however, this finding cannot be confirmed robustly.

What has been clearly demonstrated is that both physiological approaches- HBAP and LBBAP- potentially offer superior outcomes compared to traditional pacing strategies such as BVP and RVP.

Further high-quality research, including direct comparisons between HBAP and LBBAP, is necessary to confirm these preliminary findings and to fully establish the benefits of physiological pacing over conventional methods.

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VI Appendix I Search summaries

2025_CRT_Cochrane_Screen.ris

2025_CRT_MedRxiv_Screen.ris

2025_CRT_PubMed_Screen.ris

2025_CRT_All Platforms_FullTextScre

2025_CRT_ExclusionFullText.ris

2025_CRT_Final Inclusion_FDW.ris

VII Appendix II- Data Extraction File (Included Full Text Publications)

2025_CRT_Thesis_HBAP_LBBAP_FDW_Extracti

VIII Appendix III- Warranty

Vilniaus universiteto studijuojančiojo, teikiančio baigiamąjį darbą,
GARANTIJA

Vardas, pavardė: Fabian David, Wedeleit

Padalinys: Medicine

Studijų programa: Parahisian & Lef Bundle Pacing

Darbo pavadinimas: Parahisian & Lef Bundle Pacing

Darbo tipas: Narrative

Garantuoju, kad mano baigiamasis darbas yra parengtas sąžiningai ir savarankiškai, kitų asmenų indėlio į parengtą darbą nėra. Jokių neteisėtų mokėjimų už šį darbą niekam nesu mokėjęs.

Šiame darbe tiesiogiai ar netiesiogiai panaudotos kitų šaltinių citatos yra pažymėtos literatūros nuorodose.

WARRANTY
of Vilnius University Student Thesis

Name, Surname: Fabian David, Wedeleit

Faculty: Medicine

Study programme: Medicine (Integrated)

Thesis topic: Parahisian & Lef Bundle Pacing

Thesis type: Narrative

I guarantee that my thesis is prepared in good faith and independently, there is no contribution to this work from other individuals. I have not made any illegal payments related to this work.

Quotes from other sources used in this thesis, directly or indirectly, are indicated in literature references.

Aš, Fabian David Wedeleit patvirtinu (pažymėti)
I, Fabian David Wedeleit , confirm [X]

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