Bradyarrhythmias

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Introduction

The definition of bradycardia differs globally with the National Institutes of Health defining bradycardia as a heart rate <60 bpm in adults other than well-trained athletes. Bradyarrhythmias are associated with advancing age, and thus, population studies frequently define bradycardia using a lower cutoff of 50 bpm, depending on one's age as well as gender. These heart rate cutoffs alone however do not define underlying pathology. Pathologic bradyarrhythmias typically present with a combination of an abnormal heart rate and symptoms suggesting inadequate cardiac output. These bradyarrhythmias result from either a reduction in the number of impulses generated by the pace-making cells of the heart or a failure of those impulses to conduct in a manner that stimulates ventricular contraction. Chronotropy refers to the number of impulses generated over a given time, while dronotropy describes how those impulses are conducted. The interplay between these two factors is critically important in maintaining physiologically sufficient heart rates that will satisfy metabolic demands. Bradycardia becomes clinically relevant once this relationship is no longer in balance, leading to symptoms such as fatigue, dizziness, lightheadedness, or syncope. Disease development and progression is intimately related to the underlying anatomy and embryological development of the conduction system, of which a fundamental understanding is integral in both assessing and treating clinical bradyarrhythmias.

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Embryology and Basic Physiology of the Cardiac Conduction System

The cardiac conduction system is differentiated relatively early during embryonic development with the sinoatrial node (SAN) serving the primary pacemaker role and the atrioventricular node (AVN) also having pacemaker functionality. The initial heart tube has automaticity provided by a caudal pacemaker producing a sinusoidal ECG pattern with associated slow conduction. Fairly rapidly, the heart tube continues to elongate with proliferation of the cells that will ultimately make up the atrial and ventricular tissues. Notably, the sinus venosus, atrioventricular canal (AVC), outflow tract, and inner curvatures continue to proliferate more slowly; these will ultimately be critical in formation of the pace-making and conductive structures of the heart. The SAN develops from the sinus venosus, while the AVN originates within the AV canal, which retains its slower mode of conduction [1].

The sinus node is located at the intersection of the superior vena cava and the right atrium, most commonly just inferior to the right atrial appendage [2]. The SAN itself is quite an extensive structure that is often cigar shaped and extends down the inferolateral aspect of the crista terminalis. On average, it is about 13.5 mm in length and is located subepicardially within the sulcus terminalis [3]. The specialized nodal tissue is surrounded by a fibrous matrix of connective tissue that helps to distinguish it histologically from the neighboring myocardium; however, the node is not insulated from the surrounding myocardial tissue [4]. Recent work utilizing optical mapping has demonstrated that action potentials originating within the sinus node exit in an anisotropic fashion, activating adjacent atrial myocardium by superior, inferior, and medial breakout sites [5].

Current research suggests that the AVN develops from the embryonic AVC. The AVN and SAN likely communicate via atrial myocardial tracts as opposed to intranodal pathways [6]. The AV node is anatomically located at the apex of the triangle of Koch, a region that is bounded by the septal leaflet of the tricuspid valve, the tendon of Todaro, and the ostium of the coronary sinus [6]. An action potential will enter the AV node via one of the two pathways, the fast pathway, which is located in the interatrial septum, or the slow pathway in the terminal crest [7]. The fast pathway is comprised of atrial transitional myocytes that are in continuity with the compact node. Conduction normally propagates through the fast pathway with the action potential generated in the sinus node and conducting through the interatrial septum to the compact node. The slow pathway extends through the septal isthmus (the area between the coronary sinus and the tricuspid valve that is directed toward the apex of the triangle of Koch) [8]. The AV node primarily functions as the gatekeeper between the atria and the ventricles, introducing a delay between atrial and ventricular contraction in order to ensure maximum ventricular filling during diastole. Furthermore, by blocking rapid atrial depolarizations, the AV node protects the ventricle from rapid excitation that can lead to lethal arrhythmias such as ventricular tachycardia or ventricular fibrillation [6]. Lastly, the AV node is capable of functioning as a backup pacemaker in the presence of sinus node dysfunction.

Depolarization of the sinus node and generation of action potentials is in large part regulated by the funny current (*If*). The funny current consists of an inward flux of

cations (potassium and sodium carried by HCN channels) that is activated when the membrane potential hyperpolarizes to −50 mV to −65 mV [9]. This inward current leads to depolarization of the membrane during phase 4 of the action potential and is integral in rate regulation of pacemaker cells. HCN channel activity is largely influenced by cyclic AMP, with beta-adrenergic activity leading to an increase in cAMP activity and consequently a rise in the *If* current, ultimately leading to an increase in heart rate. Conversely, muscarinic stimulation leads to the opposite effect and reduction in heart rate [6]. A second current (I-Na-Ca) governed by the release of calcium from the sarcoplasmic reticulum by the ryanodine receptor also functions to increase late diastolic depolarization and ultimately leads to activation of voltage-gated L-type calcium channels. In addition to the automaticity of the sinus node, pacemaker properties also exist in the more distal tissues, particularly the atria, AVN, and His-Purkinje System (HPS). However, based on the natural hierarchy of pacemaker function, these tissues remain latent due to the higher rate of depolarization of the sinus node.

Normal physiologic heart rates are generally considered to be in the 60–100 range with bradycardia existing at rates below 60 beats per minute. However, based on population experience, averages tend to be lower than these classically accepted values [10]. When evaluating a patient with a low heart rate, it is important to first understand whether or not the low heart rate is pathologic. There are numerous conditions that may lead to pathologically depressed heart rates (as discussed later); however, it has long been established that well-conditioned athletes may have resting heart rates in the 40–60 range, dropping as low as 30 beats per minute during sleep [11]. Rarely is this a cause for concern. The key factor in determining whether or not resting bradycardia is pathologic or simply functional is detailing the presence or absence of symptoms. Symptoms including fatigue, lightheadedness, and syncope are evidence of an inability to match metabolic demand and suggest chronotropic or dronotropic incompetence. While the mechanistic underpinnings leading to bradyarrhythmias are complex, the differential diagnosis can be divided neatly based on the anatomic location of the disease: commonly, this is either at the level of the sinus node or the AV node. The sinus node and AV node are both significantly affected by the autonomic nervous system with high parasympathetic tone potentially leading to bradycardia. Etiologies of sinus node dysfunction include idiopathic, inherited, heart failure, atrial tachyarrhythmias, diabetes, infiltrative diseases, and ischemia, among others [12]. AV nodal conduction may be similarly affected by ischemia and fibrosis but can also result from endocarditis and congenital block. These diagnoses will be discussed in more detail later in this chapter.

Sinus Node Dysfunction

Symptomatic sinus node dysfunction typically presents with symptoms of lightheadedness, dizziness, syncope, dyspnea, and activity intolerance. It is a disease that overwhelmingly affects the elderly. The incidence increases with decade of life with rate of pacemaker implantation for sinus node dysfunction near 0.3–0.5% in those older than 85 years old [13, 14]. Sinus node dysfunction and high-degree AV block are the most common indications for pacemaker implantation with sick sinus

syndrome (SSS) accounting for roughly 20–50% of initial implants worldwide and approximately 50% of implants in the United States [15, 16]. In 2012, there were an estimated 78,000 incident cases of SSS with a projected increase to 172,000 in 2060 in the United States alone [14].

Sinus node dysfunction is related to either intrinsic (i.e., related to the node itself) or extrinsic (related to the impact of external factors on sinus node function) factors. The causes of intrinsic nodal dysfunction are multiple with the most common being idiopathic degeneration of the node. Additional etiologies include (but are not limited to) ischemic heart disease, atrial tachyarrhythmias, infiltrative diseases (e.g., amyloid, sarcoidosis, hemochromatosis, cancer), inflammatory diseases such as myocarditis, cardiomyopathy, inherited genetic mutations, congenital heart disease, surgical trauma, and collagen vascular diseases. Extrinsic factors include the effects of drugs/medications, autonomic regulation, electrolyte abnormalities (i.e., potassium), hypoxia, hypercapnea, hypothyroidism, and hypothermia, among others (Table 9.1).

Idiopathic sinus node dysfunction is a disease that disproportionately affects the elderly. There is age-associated increase in fibrosis of the sinus node that has been shown to correlate well with a decrease in the intrinsic rate of the node and a prolonged sinoatrial conduction time [16]. Furthermore, there is significant electrical remodeling within the atria and sinus node with aging that occurs as a result of decreased expression of key ion channels (e.g., Na 1,5) [12]. These observations provide the basis for the current understanding that idiopathic sinus node dysfunction results from both structural and molecular contributions.

Sick sinus syndrome is a subset of sinus node dysfunction that is characterized by symptomatic bradycardia. It can present as sinus bradycardia, sinoatrial block, sinus arrest, chronotropic incompetence and is often associated with atrial tachyarrhythmias ("tachy-brady syndrome"). Alternating tachycardia and bradycardia is classically identified by periods of tachycardia related to atrial tachyarrhythmias such as atrial fibrillation, atrial flutter, or atrial tachycardia followed by symptomatic pauses

Table 9.1 Etiologies of sinus node dysfunction

Intrinsic	Extrinsic
Idiopathic	Drugs
Ischemia	Antiarrhythmics (Class I-IV)
Hypertension	Ivabradine
Atrial tachycardias	Opioids
Cardiomyopathy	Clonidine
Inflammatory diseases	Acetyl-cholinesterase inhibitors
Infectious diseases (e.g., Lyme)	Digoxin
Infiltrative diseases (e.g., amyloid)	Antidepressants
Collagen vascular disease	Metabolic
Surgical trauma	Hypothermia
Congenital heart disease	Hyperkalemia
Inherited genetic mutations	Hypothyroid
Heart transplant	Hypercapnea
Neuromuscular disorders	Hypoxemia
	Autonomic influences
	Sleep apnea

or periods of sinus bradycardia [16]. The symptomatic pauses are due to overdrive suppression of the sinus node and secondary pacemaker function. This property is formally measured as the sinus node recovery time (SNRT) during an EP study (to be discussed later). It is believed that persistent atrial tachyarrhythmias lead to sinus node remodeling, shifting activation caudally, and altering expression of certain ion channels [16, 17]. However, most of these changes are likely reversible [18] as is clinically consistent with recovery of sinus node function in a patient after atrial fibrillation ablation.

Ischemic heart disease is also very common in patients with sinus node dysfunction. The sinus node receives its blood flow from the sinoatrial node artery, supplied by the right coronary artery in over 60% of patients [19]. While infarction of the sinoatrial node is possible (either due to proximal infarct in the right coronary artery or left circumflex artery), more commonly, sinus node dysfunction after myocardial infarction is transient and related to increased vagal tone.

Diagnostic Evaluation of Sinus Node Dysfunction

Initial evaluation of a patient with bradycardia is performed with a basic electrocardiogram. While a baseline ECG provides an important assessment, it will rarely yield a diagnosis of SND as many critical factors are not seen on a resting ECG. When concerned for chronotropic incompetence or activity-limiting bradycardia, it is often necessary to perform ambulatory monitoring, such as with a 24- or 48-hour Holter monitor. Exercise testing can also be valuable to assess heart rate response with physical activity. Lastly, invasive EP study can be performed if the initial workup is unrevealing in a symptomatic patient but is rarely necessary for diagnosis. For example, in the case of unexplained syncope, an EP study has generally low sensitivity but relatively high specificity. An EP study may provide additional information and is a particularly useful study in patients who have some degree of conduction abnormality at baseline to establish the level at which the conduction disease occurs. In patients with persistent but unexplained symptoms, an implantable loop recorder is also an option as it will provide over 2 years of continuous heart-rate-monitoring data.

Electrocardiographic features include sinus bradycardia (Fig. 9.1), sinus pauses (Fig. 9.2), and sinoatrial exit block (Figs. 9.3 and 9.4). As discussed previously,

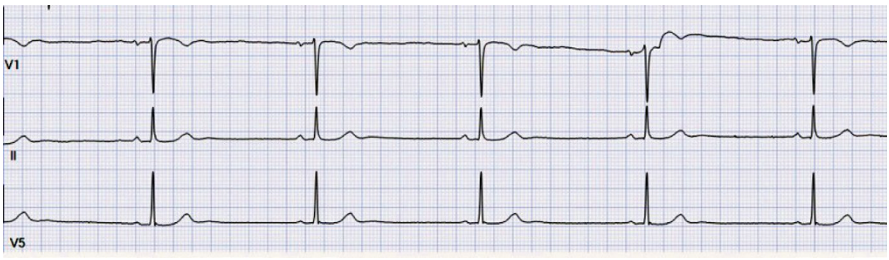

Fig. 9.1 Sinus bradycardia with heart rate of 34 BPM

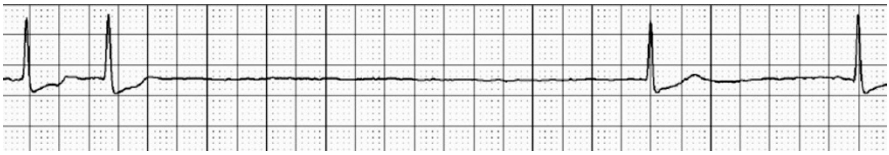

Fig. 9.2 Sinus pause. Post-conversion pause from atrial tachycardia of 3.6 seconds

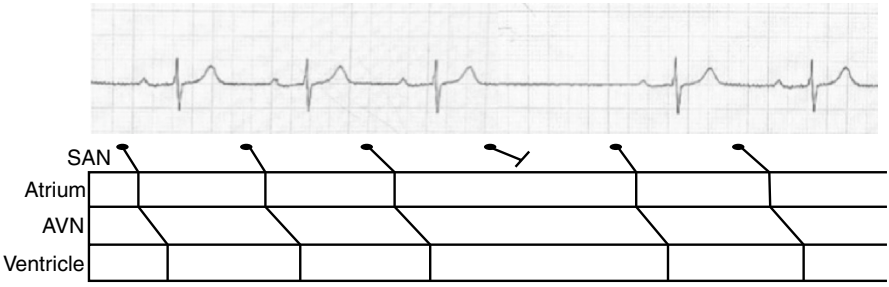

Fig. 9.3 Second-degree type 1 sinus exit block. Shortening of the P-P interval suggests conduction delay within the sinus node leading to delayed atrial activation. Furthermore, the resultant pause from failed conduction to the atrium is shorter than twice the shortest P-P interval

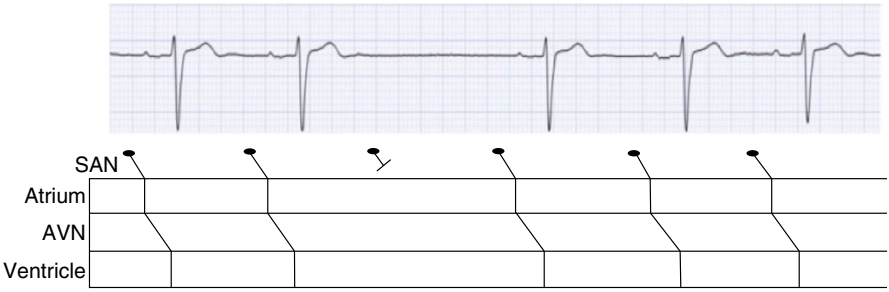

Fig. 9.4 Second-degree type 2 sinus exit block. Stable P-P interval with the dropped P wave occurring and resultant pause exactly twice the P-P interval

sinus bradycardia is generally considered to be pathologic if it is persistent and associated with symptoms. Well-conditioned athletes may have resting heart rates in the 40s that are not routinely considered pathologic in the absence of symptoms [11]. Sinus pauses of greater than 3 seconds are considered abnormal and often point to underlying sinus node dysfunction. These can occur spontaneously or commonly post conversion from an underlining atrial arrhythmia. Pauses of 1–2 seconds can be seen in normal individuals and are commonly observed in the athletic population, particularly during sleep [20].

Sinus exit block happens when an action potential generated within the sinus node does not conduct to the adjacent atrial tissue and therefore fails to propagate. It is often quite difficult to diagnose exit block on a surface ECG as it can be hard

to distinguish between sinus arrest and sinus arrhythmia. Much like atrioventricular block (AVB), sinus exit block is classified as first, second, or third degree. First-degree block cannot be diagnosed by surface ECG and can only be determined by invasive EP study. Third-degree sinus exit block also cannot be diagnosed on surface ECG and will appear the same as sinus arrest. Second-degree type 1 block can be diagnosed on surface ECG and is characterized by progressive shortening of the P-P interval prior to a nonconducted beat. Given that sinus node depolarization is not visible on the surface ECG, the progressive conduction delay within the sinus node leading to delayed atrial activation is manifested by shortening of the P-P interval for a given sinus cycle length. The P-P intervals follow the rules of decremental conduction where the increment in conduction delay for each subsequent impulse gets smaller until conduction failure to the atrial tissue finally occurs. The pause will be shorter than twice the shortest P-P interval. In type 2 exit block, there is no prolongation of the sinoatrial conduction time prior to a failed impulse conduction out of the sinus node. Therefore, there is no prolongation of the P-P interval prior to a pause. Type 2 exit block is suggested when the pause is a multiple of the P-P interval.

If ambulatory monitoring is nondiagnostic for chronotropic incompetence, treadmill exercise testing is a useful strategy to assess for heart rate response to increased physical demand. A patient with chronotropic incompetence will have a blunted heart rate response to exercise. While there is no exact definition of chronotropic incompetence, failure to achieve 70–85% of age-predicted maximal heart rate (as calculated by 220-age) or inability to achieve a heart rate greater than 100 beats per minute has historically been classified as abnormal. An additional value termed heart rate reserve has also been proposed as a metric to classify chronotropic response. This value is calculated as the change in heart rate from rest to peak exercise divided by the difference between the age-predicted maximal HR and resting heart rate. A heart rate reserve value of <0.8 is considered abnormal [21]. It is also possible for a patient to achieve a normal maximal heart rate but have abnormally slow acceleration in heart rate with stress or rapid decline in heart rate during recovery. Both of these patterns may also suggest sinus node dysfunction.

During an invasive EP study, one is able to measure the intrinsic heart rate (IHR), sinus node recovery time (SNRT), and sinoatrial conduction time (SACT). SNRT is an assessment of sinus node automaticity and is measured by overdrive pacing from the high right atrium at a site near the sinus node. Pacing is performed at multiple cycle lengths (CLs), decrementing each cycle to a minimum of 300 ms for 30–60 seconds at a time. SNRT is measured as the time between the last paced beat and the return of sinus rhythm and is measured for each CL (Fig. 9.5). The longest measured pause is the effective SNRT. Corrected SNRT is often commonly calculated. Corrected SNRT is equal to the SNRT minus the CL. Historically, a corrected SNRT of less than 525 ms has been considered normal [22]. Furthermore, a corrected SNRT of greater than or equal to 800 ms has been correlated with an increased risk of syncope and associated sinus node dysfunction [23]. Lastly, the ratio of SNRT to sinus CL can be calculated, with normal values typically less than 160%. SNRT is an important property in the pathophysiology of tachy-brady syndrome.

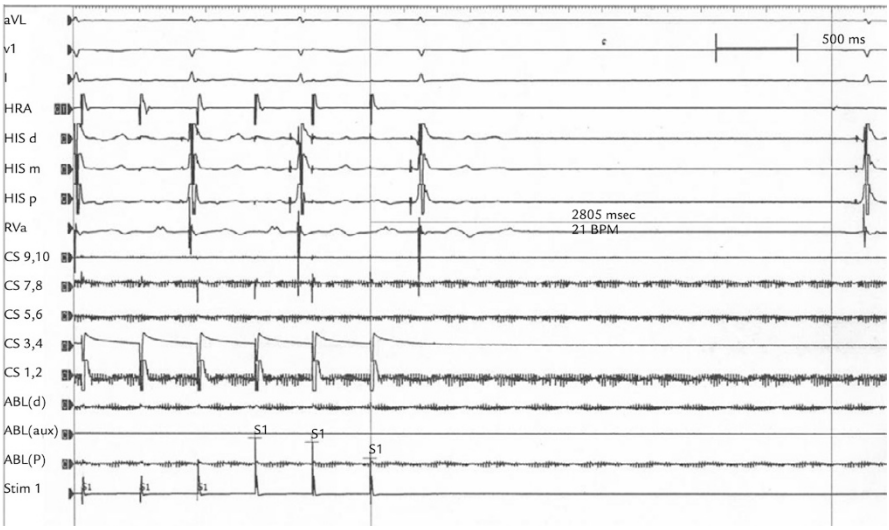

Fig. 9.5 Sinus node recovery time (SNRT). Overdrive pacing is performed from the high right atrium. SNRT is measured as the time between the last paced beat and the return of a sinus beat. In this example, SNRT measures 2.805 seconds. (Reprinted from Kuo et al. [24], with permission from Elsevier)

Sinoatrial conduction time (SACT) is another invasive measurement used to assess sinus node function. SACT is measured as the time between the local electrogram at the site of the sinus node and the earliest atrial deflection. Sinoatrial block is observed when the sinus node deflection fails to conduct to the atria. There are several methods for measuring SACT, but the general principle consists of introducing premature atrial stimulation during sinus rhythm and indirectly measuring the time of impulse conduction into and out of the sinoatrial node. SACT is a measure of sinoatrial conduction, whereas SNRT is a measure of sinus node automaticity. Clinically, SNRT tends to be the more useful measure. Lastly, pharmacologic interventions can also be used to assess for sinus node dysfunction. Intrinsic rate is measured after autonomic blockade with an infusion of atropine. A low intrinsic rate is suggestive of SND. Additional agents such as propranolol, isoproterenol, epinephrine, and calcium channel blockers may be given to study the effects on SNRT and SACT.

AV Node Dysfunction (Table 9.2)

As with the sinus node, dysfunction in the AV node exists on a spectrum. AV node dysfunction may first be identified as prolongation of the P-R interval on the ECG, although this alone is not typically associated with bradycardia. There are numerable causes of AV nodal dysfunction with the most common being related to aging and age-related degeneration [25]. Congenital AVB is a condition that occurs in an estimated 1 in 22,000 live births. It is likely the result of either abnormal development

Table 9.2 Etiologies of AV node dysfunction

Inherited
Congenital AVB (associated with neonatal lupus)
Familial AVB (most common association with loss of function of SCN5A)
Inherited neuromyopathies (e.g., Erb's, Becker's, peroneal, myotonic dystrophy)
Long QT syndrome (e.g., LQT2, LQT3, LQT8, LQT9)
Acquired
Drugs (e.g., antiarrhythmics)
Ischemic heart disease
Infectious diseases (e.g., Lyme, Chagas)
Infiltrative diseases (e.g., amyloid, sarcoidosis)
Surgical/procedural complications (e.g., SAVR, TAVR, septal myectomy, right heart cath)
Athletic training

of or destruction of the conduction system. The condition is often associated with structural congenital abnormalities and is most commonly seen with congenitally corrected transposition of the great arteries, isomeric arrangement of the atrial appendages, and AV septal defects [26]. Studies have demonstrated a of lack of communication between the atrial musculature and the peripheral conduction system (atrial-axis discontinuity), interruption of the AV bundle (nodal-ventricular discontinuity), and inherent changes in an aberrant conduction system (intraventricular discontinuity) [27]. These young patients often have a relatively fast escape rhythm with a narrow QRS. Furthermore, congenital AVB is known to be associated with neonatal lupus and, in fact, anti-Ro/SSA-associated AVB may account for up to 20% of cases of idiopathic complete heart block in the adult population [28]. Familial forms of AVB are quite rare, with the majority of cases being related to a loss-of-function mutation of the SCN5A gene [29]. Most commonly, familial AVB is associated with bundle branch block and varying degrees of AVB. Progressive AVB can also be seen in inherited neuromyopathies such as Becker's muscular dystrophy, peroneal muscular dystrophy, Erb's dystrophy, and myotonic muscular dystrophy. Due to prolonged refractoriness of the ventricle, long QT syndrome (in particular LQT2, LQT3, LQT8, LQT9) can lead to functional block and consequent bradycardia [30].

Acquired etiologies of AVB are more common than inherited/congenital causes. In brief, this encompasses drugs (in particular, antiarrhythmics), ischemic heart disease, infiltrative diseases, infectious diseases, surgical/procedural complications, and intensive athletic training. High-degree AVB occurs in approximately 2–13% of patients with acute myocardial infarction with a two- to fourfold higher frequency observed in inferior MI as compared to anterior MI. Typically, AVB in this setting is transient and resolves within 2–3 days with only about 9% of patients ultimately requiring a pacemaker prior to hospital discharge [31]. This is particularly true in the case of inferior MI. In a majority of cases, transient AVB is likely secondary to increased vagal tone, which is exceptionally true in the setting of reperfusion. Persistent, or delayed, AVB may indicate hypoperfusion of the AVN, although true infarct or necrosis of the AVN is very rare. While high-degree AVB is associated with a worse prognosis, this is simply a reflection of a more extensive infarct and is not

directly related to the heart block itself. Moreover, chronic ischemic heart disease can lead to scarring and fibrosis within the myocardium that can ultimately progress to high-grade conduction disease. Infiltrative diseases such as sarcoidosis, hemochromatosis, amyloidosis, and tumors can all be associated with AVB [32]. In particular, approximately 25–30% of cases of cardiac sarcoidosis present with complete heart block, with first- and second-degree heart block also being common. Certain infections can also cause AVB. In particular, endocarditis associated with the aortic valve can affect the AV node and, ultimately, lead to high-degree AVB. Myocarditis, as seen with viral infections like mumps and measles, may affect the conduction system in a number of ways and has been associated with complete heart block. Parasitic and bacterial infections (e.g., Chagas disease and Lyme disease) are also potentially reversible causes of AVB of varying degrees. Potential iatrogenic causes of AVB include intracardiac catheter manipulation (e.g., a right heart catheterization in a patient with a left bundle branch block, leading to complete heart block), ablation in the vicinity of the AVN (e.g., AVNRT, AT), and cardiac surgery.

In the case of cardiac surgery, AVB is a result of ischemia or trauma to the conduction system during the procedure. As expected, the risk is higher for surgeries involving structures closer to the AVN. Roughly 4–5% of patients undergoing either aortic valve replacement or mitral valve replacement will require pacemaker implantation in the postoperative period. This rate increases with the number of valves being operated on as well as in the case of reoperation [33]. Septal myectomy and alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy also may lead to complete heart block with an incidence of approximately 3% and 12%, respectively [34].

An increasingly important and common cause of AVB is transcatheter aortic valve replacement (TAVR). Since its initial conception, TAVR has been associated with new-onset LBBB as well as high-degree AVB. As discussed previously, the aortic valve lies in very close proximity to the conduction system. The AVN exists within the right atrium, inside an anatomic region known as the triangle of Koch. The AVN then gives rise to the bundle of His, ultimately penetrating the membranous septum and then proceeding through the central fibrous body. The left side of conduction system exits below the membranous septum and forms the left bundle branch. Anatomically, the left bundle branch lies in very close proximity to the interleaflet triangle separating the right coronary and noncoronary cusps of the aortic valve. As one might expect, these anatomic relationships make not only the left bundle but also the bundle of His and, potentially, the AVN quite vulnerable during valve implantation. The presence of a pre-existing RBBB, porcelain aorta, increased age, prior conduction disease, elevated LV end-diastolic dimension, intraprocedural AVB, development of new LBBB, presence of bicuspid valve, increased ratio of prosthesis size to annulus diameter, and thickened interventricular septum have all been associated with need for pacemaker implantation after TAVR [35]. Furthermore, operator-specific influences that can lead to periprocedural trauma to the conduction system include the type/size of the valve chosen, the size of the balloon used for pre- and post-dilation, and the implantation technique (i.e., the depth of implantation) [36].

Reported rates of pacemaker implantation are quite variable with multiple sources citing a 19–42% risk for pacemaker implantation associated with the

Medtronic CoreValve Revalving System (Medtronic, Minneapolis, MN) and a 7–22% risk of pacemaker implantation for the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA). The PARTNER-3 trial that investigated the use of the Edwards Sapien 3 valve in a low-risk population found a 6.5% risk of pacemaker implantation at 30 days that increased to 7.3% at 1 year. The incidence of new LBBB was 22% at 30 days and 23.7% at 1 year. When compared to incidence of permanent pacemaker implantation in the patients receiving surgical aortic valve replacement (4% at 30 days and 5.4% at 1 year), there was no significant difference. By comparison, the Evolut Low Risk Trial found a 17.4% rate of permanent pacemaker implantation at 30 days and a 19.4% rate at 1 year in patients who underwent low-risk TAVR with the Medtronic CoreValve, Evolut R, or Evolut PRO. In this trial, the TAVR group did have a statistically significant increased rate of permanent pacemaker implantation as compared to the surgical group who had a rate of 6.1% at 30 days and 6.7% at 1 year. While historically it has been thought that most patients who develop high-grade AV block after TAVR develop it within the first few days following the procedure, there is a smaller subset who go on to develop delayed high-grade AVB. Observational data of a group of 150 patients undergoing TAVR (both with Sapien 3 or Evolut series) found a 12% incidence of high-grade AVB within 2 days of the procedure with an additional 12 cases (~10%) of delayed high-grade AVB identified with ambulatory event monitoring between postoperative day 2 and 30. In this prospective observational study, the presence of a RBBB was found to be the strongest risk factor associated with development of both immediate and delayed high-grade AVB, requiring placement of a pacemaker, although most events did occur within 24 hours of the TAVR procedure [35]. Notably, the self-expanding valve (Evolut series) was associated with an increased rate of high-grade AVB in the immediate period after TAVR (less than 2 days) but was not associated with an increased risk of delayed high-grade AVB.

Diagnostic Evaluation of AV Node Dysfunction

Initial evaluation for suspected AVN dysfunction begins with a surface electrocardiogram. While varying degrees of AVB are often transient and may not be demonstrated on a single ECG, this test is still highly valuable in providing relevant data such as PR interval, QRS duration/morphology, and ventricular rate. Presence of bundle branch blocks, interventricular conduction delay, or excessively prolonged PR interval may suggest higher-level conduction disease. Longer-term monitoring with a 24-hour Holter monitor can be helpful but also may be limited in a patient with more infrequent symptoms. In these patients, implantable loop recorders (ILRs) are useful in that they provide over 2 years of data and are implanted entirely subcutaneously. Recent studies have found that nearly 50% of patients have had a change in management due to the results of an ILR, a number that is higher than previously reported for Holter monitors [37, 38].

Exercise testing can be valuable not only in correlating exertional symptoms with the presence or absence of conduction disease, but also in establishing the level of disease in a patient already suspected of having AV node dysfunction. The

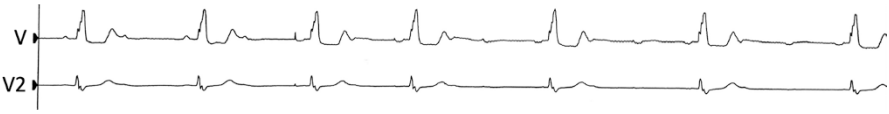

Fig. 9.6 Worsening AV conduction ratio with faster atrial rate. Initial 2:1 AV block that changes to 3:1 with faster atrial rate, suggesting the presence of intra- or infra-Hisian disease

physiologic response to exercise includes increased sympathetic tone and decreased vagal tone, both of which improve conduction through the AVN. Corresponding surface ECG will demonstrate an increased sinus rate as well as shortening of the PR interval. Invasive experimental work has confirmed this relationship by utilizing implanted devices to measure AV interval and AV block cycle length, both of which shorten with exercise [39]. Therefore, patients with first-degree AVB and second-degree type I AVB are expected to have an improvement in conduction with exercise; that is, PR interval may shorten and AV conduction ratios will increase. However, if intra- or infra-Hisian disease is present, AV conduction ratios may actually decrease with exercise (e.g., 2:1 to 3:1) due to the prolonged refractory period of the HPS (Fig. 9.6). For this reason, exercise testing is particularly useful in cases of 2:1 AVB where the level of block is uncertain.

Due to the fact that conduction through the AVN is highly influenced by the autonomic nervous system, it is also very sensitive to maneuvers that increase vagal tone (e.g., carotid massage) as well as parasympatholytics such as atropine. Conversely, conduction through the HPS is much less sensitive to these influences. Much like exercise, atropine will improve AVN conduction but will worsen infranodal block. Carotid massage will slow AVN conduction but may improve infranodal conduction by indirectly prolonging the recovery period secondary to a slowed sinus rate. Rarely is an invasive EP study required to diagnose AV node dysfunction, but can be helpful in select patients. This list includes concern for concealed junctional extrasystoles, second-degree AVB with bundle branch block, type II AVB with a narrow QRS, concern for phase 4 block, third-degree AVB with fast ventricular rate, and progression of conduction disease due to neuromuscular disorders [40]. AV conduction can be assessed by measuring A-H, H-V, P-R, and QRS intervals. For example, an H-V interval of >100 ms is highly predictive but insensitive of high-grade atrioventricular block, whereas an H-V interval >70 ms is nonspecific but more sensitive. Lastly, pharmacologic challenge with procainamide (a class I antiarrhythmic that is known to impair conduction in the HPS) can be useful to study HPS reserve and assess risk for spontaneous infra-Hisian block. In most individuals, procainamide will increase the H-V interval by 10–20%; however, a more significant increase (i.e., doubling of the H-V interval, H-V interval lengthening to >100 ms, or development of intra- or infra-Hisian block) suggests a higher likelihood of conduction disease [40].

Categorization of AV Block

First-degree AVB is relatively common in the general population with a prevalence of 1–2% in healthy young adults that increases to 3–4% in those over the age of

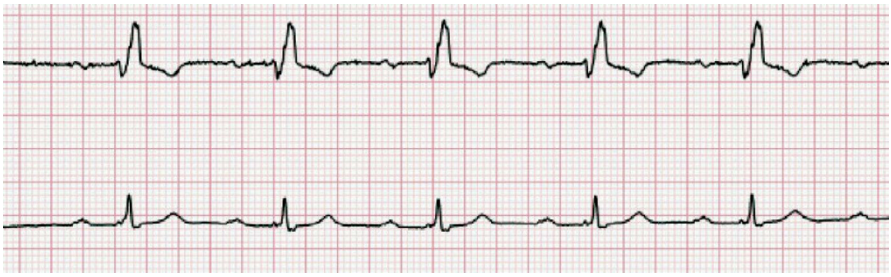

Fig. 9.7 First-degree AV block. PR interval is approximately 300 ms

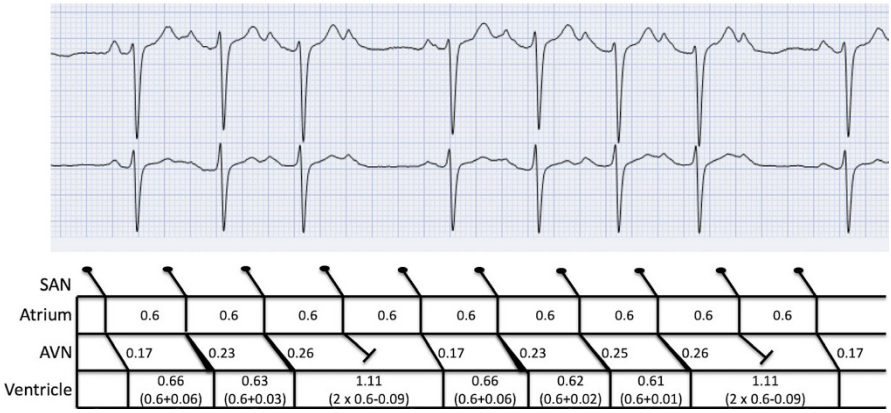

Fig. 9.8 Second-degree type I AVB (Wenckebach). Successive prolongation of the PR interval prior to the nonconducted beat. Note the slight prolongation in conduction through the AVN eventually resulting in a dropped beat. Intervals are presented in seconds

60 (Fig. 9.7) [41]. However, it has long been hypothesized that a markedly prolonged PR interval can lead to AV dyssynchrony and ultimately may present with symptoms similar to pacemaker syndrome and hence has been termed "pseudo-pacemaker syndrome" [42]. Furthermore, first-degree AVB may lead to diastolic mitral regurgitation and can confer an increased risk of developing atrial fibrillation [43, 44]. First-degree AVB has also been associated with adverse events in select patient populations such as increased risk of mortality and hospitalization in those with cardiac resynchronization therapy or heart failure [41]. For these reasons, the most recent bradycardia guidelines do support the use of dual chamber pacing in symptomatic patients with profound first-degree AVB, although this is a very rare indication for pacemaker implantation [45].

Second-degree AVB is diagnosed when sinus P waves have an associated QRS complex, although not all P waves are followed by a QRS complex. There are two types of second-degree AVB, classified as Mobitz type I (Fig. 9.8) and Mobitz type II (Fig. 9.10). Mobitz type I AV block (Wenckebach) is diagnosed by progressive lengthening of the PR interval prior to the nonconducted beat. Like first-degree AVB, second-degree type I AVB can occur in normal individuals and

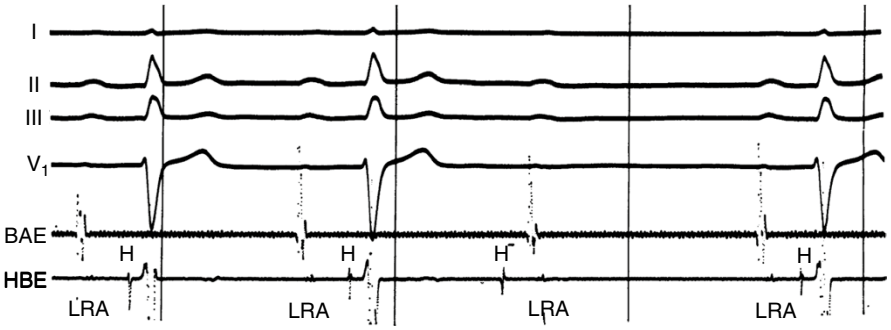

Fig. 9.9 Pseudo-AV Block due to concealed His extrasystoles. Note the retrograde activation of the His leading to blocking of the next sinus impulse. (Reprinted from Castellanos et al. [48], with permission from BMJ Publishing Group Ltd)

in fact has been reported in about 4–6% of normal healthy individuals during sleep [46]. Immediately following the nonconducted beat, the PR interval shortens. Furthermore, type I AV block will tend to display Wenckebach periodicity with grouped beating. In diagnosing Mobitz type I AV block, it is often easiest to compare the PR interval immediately following the dropped beat to the PR interval just before the nonconducted P wave. This will demonstrate the largest difference in PR interval. Pacing is rarely indicated for second-degree type I AVB, although may be considered for symptomatic bradycardia or in the setting of infra-Hisian disease. When type I AVB is seen in the setting of a wide QRS complex (e.g., bundle branch block), the likelihood of infra-Hisian block with Wenckebach periodicity increases. This can be further evaluated with an EP study and is diagnosed by demonstration of progressive prolongation of the H-V interval with stability of the A-H interval [47]. Pacemaker implantation is indicated in this case.

Second-degree type II AVB is characterized by a fixed P-R interval both before and after a dropped beat. Mobitz type I AVB is often due to disease within the AV node itself, whereas Mobitz type II AVB is more often intra-Hisian (at the level of the His) or infra-Hisian (level of the bundle branches). True type II AVB is unlikely to occur at the level of the AV node. In instances where this appears to be the case, it is more likely due to a different phenomenon such as concealed His extrasystoles that lead to retrograde activation of the His and ultimately block the sinus impulse (Fig. 9.9) [48].

Generally speaking, type II AVB can be diagnosed on a surface ECG alone; however, in rare instances, an EP study may be required for further evaluation. An EP study will demonstrate an abnormally long H-V interval (Fig. 9.10). Pacemaker implantation is indicated in patients with second-degree type II AVB given the risk of progression to complete heart block and asystole [45].

In the instance of 2:1 AVB, it is impossible to differentiate between Mobitz type I and type II based on the surface ECG alone (Fig. 9.11). However, type II block

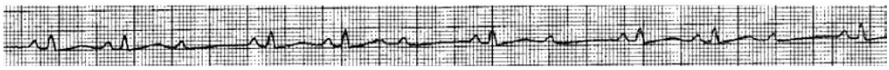

Fig. 9.10 Second-degree type II AV block. Note that the PR interval is constant prior to the non-conducted beat. (Reprinted from Barold and Padeletti [49], with permission from BMJ Publishing Group Ltd)

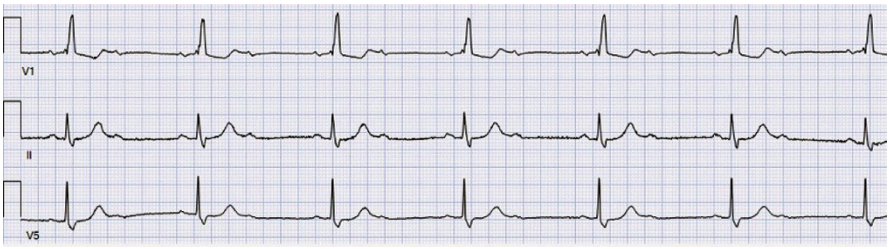

Fig. 9.11 2:1 AV block in a patient with underlying RBBB. Patient ultimately required placement of a permanent pacemaker

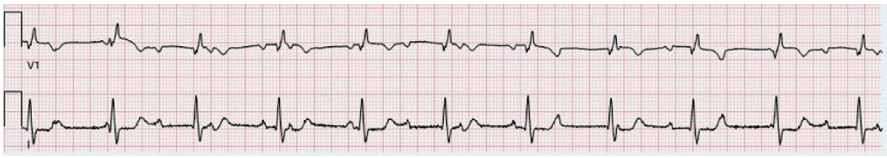

Fig. 9.12 Complete heart block with junctional escape rhythm. Note that sinus rate exceeds the rate of the junctional escape

may be more commonly observed in combination with intraventricular conduction delay such as bundle branch block given the effects on the distal conduction system, although intra-Hisian block is often seen with a normal QRS duration. Likewise, a PR interval of ≤160 ms is suggestive of intra- or infra-Hisian block as a longer PR interval typically indicates involvement of the AV node. Furthermore, improvement with atropine, or exercise, is suggestive of type I block, as type II block will tend to worsen with exercise. High-grade second-degree AVB is seen when there are multiple consecutive dropped beats. This should also be considered in the presence of prolonged pauses greater than 5 seconds during atrial fibrillation.

Third-degree AVB (or complete heart block) is present when there is complete dissociation between atrial and ventricular activities (Fig. 9.12). In the case of third-degree AVB, the sinus rate will often be faster than the ventricular or junctional escape rhythm.

There are instances in which AV dissociation is present but does not suggest complete heart block. Examples include accelerated idioventricular rhythm or

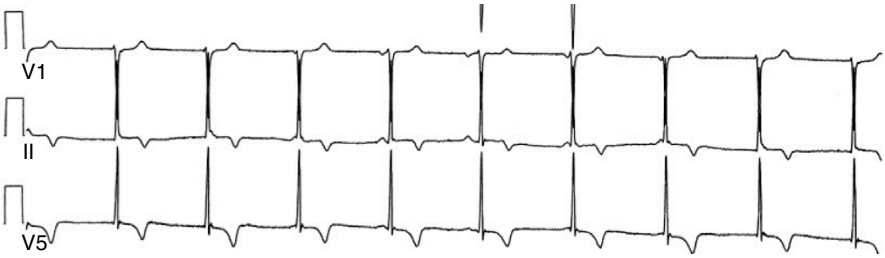

Fig. 9.13 Sinus rhythm with a competing junctional pacemaker. Sinus rate and junctional rate are very similar, but there is clear AV dissociation

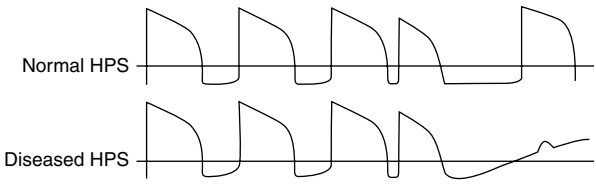

Fig. 9.14 Phase 4 depolarization in diseased myocardium. (Reprinted from Lee et al. [50], with permission from Elsevier)

accelerated junctional rhythms in which the ectopic lower focus is discharging at a faster rate than the sinus rate (Fig. 9.13). These rhythms are particularly common after cardiac surgery and alone do not indicate underlying conduction disease.

Other Causes of AV Block

Paroxysmal AV block is a rare cause of sudden complete AV block and asystole occurring in the setting of a diseased conduction system. This phenomenon is often secondary to a premature depolarization during the phase 4 of the action potential, leading to a compensatory pause and partial phase 4 depolarization in diseased myocardial cells (Fig. 9.14). While phase 4 depolarization is a normal occurrence in cells with automaticity such as the sinus or AV node, the presence of an enhanced partial phase 4 depolarization in diseased His-Purkinje cells leads to sodium channels inactivation when a subsequent impulse is encountered and resultant heart block. The membrane potential does not reset to the normal state unless a well-timed conducted sinus or escape beat results in full depolarization (Figs. 9.15, 9.16, and 9.17).

The incidence of paroxysmal AV block is not known; however, in patients with conduction system disease, it can be a significant cause of syncope as well as sudden cardiac death and, thus, when recognized permanent pacemaker insertion is warranted [51].

Given the unpredictable nature and rapid onset of AV block, paroxysmal AV block can be misinterpreted as other causes of episodic AV block such as enhanced

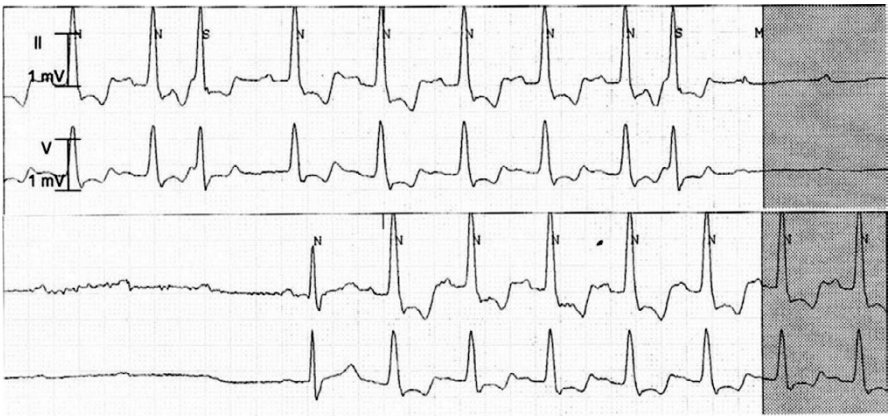

Fig. 9.15 Paroxysmal AV block secondary to phase 4 pause-dependent block caused by a premature atrial beat. The P-P interval slightly slows immediately before a capture beat and restoration of 1:1 AV conduction. The captured beat is narrow, suggesting temporary resolution of functional block in the His-Purkinje system

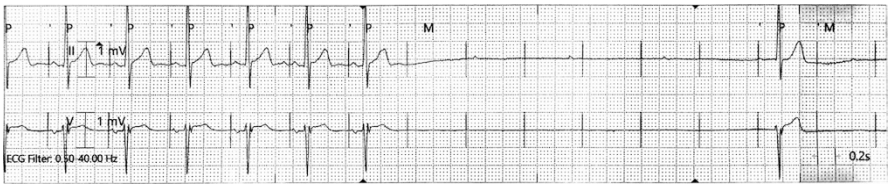

Fig. 9.16 Paroxysmal AV block secondary to phase 4 block due to loss of capture of atrial lead. AOO pacing with sudden loss of atrial capture results in a prolonged pause before sinus node recovery. The intrinsic sinus rate is much slower than the paced atrial rate, resulting in phase 4 block

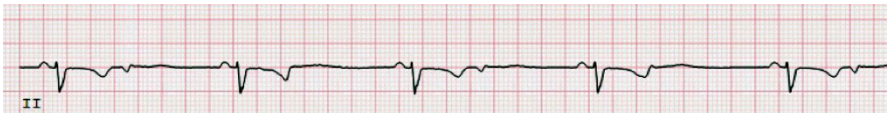

Fig. 9.17 Atrial bigeminy with blocked PACs. Block occurs at the level of the AV node and is initiated by a premature beat. Conduction resumes with a sinus beat

vagal tone or even at times blocked PACs (Table 9.3). While bradycardia caused by vagal events typically have concurrent sinus node slowing and PR prolongation suggesting dual-site pathology, in this case, a reversible trigger from global increased parasympathetic tone. Vagal-mediated events in general are associated with triggering vagal events commonly seen in ambulatory rhythm monitoring during sleep. While not diagnostic of sleep apnea, nocturnal bradycardia should prompt evaluation for underlying sleep disturbances. Pacemaker implantation for isolated AV block during vagal triggers is typically not warranted.

Table 9.3 Comparison of vagal versus paroxysmal AV block versus blocked PACs

	Vagal AV block	Paroxysmal AV block	Blocked PACs
Level of block	AV node	Infranodal	AV node
Initiated by premature beat	No	Yes	Yes
Tachycardia before initiation	No	May be seen	May be seen
Prolonged AV block	Often	Often	Rarely
Resumption of conduction	Sinus acceleration P-P shortening or withdrawal of vagal input	Escape or premature beat	Sinus beat
Initiation			
P-P lengthening	Present	Present but not mandatory	No
PR prolongation	Present	Typically, not present	No
Indication for pacemaker	Not commonly	Yes	Rarely

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References

1. Christoffels VM, et al. Development of the pacemaker tissues of the heart. Circ Res. 2010;106(2):240–54.
2. Anderson RH, et al. The anatomy of the cardiac conduction system. Clin Anat. 2009;22(1):99–113.
3. Ho SY, Sanchez-Quintana D. Anatomy and pathology of the sinus node. J Interv Card Electrophysiol. 2016;46(1):3–8.
4. Monfredi O, et al. The anatomy and physiology of the sinoatrial node--a contemporary review. Pacing Clin Electrophysiol. 2010;33(11):1392–406.
5. Fedorov VV, et al. Optical mapping of the isolated coronary-perfused human sinus node. J Am Coll Cardiol. 2010;56(17):1386–94.
6. Dobrzynski H, et al. Structure, function and clinical relevance of the cardiac conduction system, including the atrioventricular ring and outflow tract tissues. Pharmacol Ther. 2013;139(2):260–88.
7. Spach MS, et al. Collision of excitation waves in the dog Purkinje system. Extracellular identification. Circ Res. 1971;29(5):499–511.
8. Li J, et al. Computer three-dimensional reconstruction of the atrioventricular node. Circ Res. 2008;102(8):975–85.
9. Monfredi O, Maltsev VA, Lakatta EG. Modern concepts concerning the origin of the heartbeat. Physiology (Bethesda). 2013;28(2):74–92.
10. Spodick DH, et al. Operational definition of normal sinus heart rate. Am J Cardiol. 1992;69(14):1245–6.
11. Link MS, et al. Cardiac arrhythmias in the athlete. Cardiol Rev. 2001;9(1):21–30.

12. Choudhury M, Boyett MR, Morris GM. Biology of the sinus node and its disease. Arrhythmia Electrophysiol Rev. 2015;4(1):28–34.
13. Bradshaw PJ, et al. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. Open Heart. 2014;1(1):e000177.
14. Jensen PN, et al. Incidence of and risk factors for sick sinus syndrome in the general population. J Am Coll Cardiol. 2014;64(6):531–8.
15. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009--a World Society of Arrhythmia's project. Pacing Clin Electrophysiol. 2011;34(8):1013–27.
16. John RM, Kumar S. Sinus node and atrial arrhythmias. Circulation. 2016;133(19):1892–900.
17. Chang HY, et al. Sinus node dysfunction in atrial fibrillation patients: the evidence of regional atrial substrate remodelling. Europace. 2013;15(2):205–11.
18. Stiles MK, Brooks AG, Roberts-Thomson KC, Kuklik P, John B, Young GD, et al. High-density mapping of the sinus node in humans: role of preferential pathways and the effect of remodeling. J Cardiovasc Electrophysiol. 2010;21(5):532–9.
19. Pejković B, Krajnc I, Anderhuber F, Kosutić D. Anatomical aspects of the arterial blood supply to the sinoatrial and atrioventricular nodes of the human heart. J Int Med Res. 2008;36(4):691–8.
20. Senturk T, et al. Cardiac pauses in competitive athletes: a systematic review examining the basis of current practice recommendations. Europace. 2016;18(12):1873–9.
21. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation. 2011;123(9):1010–20.
22. Gann D, Tolentino A, Samet P. Electrophysiologic evaluation of elderly patients with sinus bradycardia: a long-term follow-up study. Ann Intern Med. 1979;90(1):24–9.
23. Menozzi C, Brignole M, Alboni P, Boni L, Paparella N, Gaggioli G, et al. The natural course of untreated sick sinus syndrome and identification of the variables predictive of unfavorable outcome. Am J Cardiol. 1998;82(10):1205–9.
24. Kuo FY, et al. Recurrent syncope due to carotid sinus hypersensitivity and sick sinus syndrome. J Chin Med Assoc. 2008;71(10):532–5.
25. Barra SN, et al. A review on advanced atrioventricular block in young or middle-aged adults. Pacing Clin Electrophysiol. 2012;35(11):1395–405.
26. Brugada J, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace. 2013;15(9):1337–82.
27. Kertesz NJ, Fenrich AL, Friedman RA. Congenital complete atrioventricular block. Tex Heart Inst J. 1997;24(4):301–7.
28. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Isolated atrioventricular block of unknown origin in adults and anti-Ro/SSA antibodies: clinical evidence, putative mechanisms, and therapeutic implications. Heart Rhythm. 2015;12(2):449–54.
29. Smits JP, Veldkamp MW, Wilde AA. Mechanisms of inherited cardiac conduction disease. Europace. 2005;7(2):122–37.
30. Sumitomo N. Clinical features of long QT syndrome in children. Circ J. 2016;80(3):598–600.
31. Gang UJ, et al. High-degree atrioventricular block complicating ST-segment elevation myocardial infarction in the era of primary percutaneous coronary intervention. Europace. 2012;14(11):1639–45.
32. Bejar D, et al. Infiltrative cardiomyopathies. Clin Med Insights Cardiol. 2015;9(Suppl 2):29–38.
33. Leyva F, Qiu T, McNulty D, Evison F, Marshall H, Gasparini M. Long-term requirement for pacemaker implantation after cardiac valve replacement surgery. Heart Rhythm. 2017;14(4):529–34.
34. Talreja DR, et al. Alcohol septal ablation versus surgical septal myectomy. J Am Coll Cardiol. 2004;44:2329–32.
35. Ream K, et al. Ambulatory rhythm monitoring to detect late high-grade atrioventricular block following transcatheter aortic valve replacement. J Am Coll Cardiol. 2019;73(20):2538–47.

36. Toggweiler S, Kobza R. Pacemaker implantation after transcatheter aortic valve: why is this still happening? J Thorac Dis. 2018;10(Suppl 30):S3614–9.
37. Hoefman E, Bindels PJE, van Weert HCPM. Efficacy of diagnostic tools for detecting cardiac arrhythmias: systematic literature search. Neth Heart J. 2010;18(11):543–51.
38. Padmanabhan D, et al. Diagnostic and therapeutic value of implantable loop recorder: a tertiary care center experience. Pacing Clin Electrophysiol. 2019;42(1):38–45.
39. Chicos AB, Kannankeril PJ, Kadish AH, Goldberger JJ. Parasympathetic effects on cardiac electrophysiology during exercise and recovery in patients with left ventricular dysfunction. Am J Physiol Heart Circ Physiol. 2009;297(2):H743–9.
40. Katritsis DG, Josephson ME. Electrophysiological testing for the investigation of bradycardias. Arrhythmia Electrophysiol Rev. 2017;6(1):24–8.
41. Nikolaidou T, Ghosh JM, Clark AL. Outcomes related to first-degree atrioventricular block and therapeutic implications in patients with heart failure. JACC Clin Electrophysiol. 2016;2(2):181–92.
42. Carroz P, Delay D, Girod G. Pseudo-pacemaker syndrome in a young woman with first-degree atrio-ventricular block. Europace. 2009;12(4):594–6.
43. Ishikawa T, et al. Diastolic mitral regurgitation in patients with first-degree atrioventricular block. Pacing Clin Electrophysiol. 1992;15(11 Pt 2):1927–31.
44. Nielsen JB, et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG study. Heart Rhythm. 2013;10(9):1249–56.
45. Kusumoto FM, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. J Am Coll Cardiol. 2019;74(7):932–87.
46. Adlakha A, Shepard JW Jr. Cardiac arrhythmias during normal sleep and in obstructive sleep apnea syndrome. Sleep Med Rev. 1998;2(1):45–60.
47. Antoniadis AP, et al. Infra-Hisian block as cause of Wenckebach's phenomenon in an asymptomatic middle-aged man. Europace. 2010;12(6):898–902.
48. Castellanos A, Befeler B, Myerburg RJ. Pseudo AV block produced by concealed extrasystoles arising below the bifurcation of the His bundle. Br Heart J. 1974;36(5):457–61.
49. Barold SS, Padeletti L. Mobitz type II second-degree atrioventricular block in athletes: true or false? Br J Sports Med. 2011;45:687–90.
50. Lee S, Wellens HJJ, Josephson ME. Paroxysmal atrioventricular block. Heart Rhythm. 2009;6(8):1229–34.
51. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. Circulation. 2001;104(17):2045–50.