ARTICLE TITLE

# Brady-Arrhythmias: Clinical Presentation, Diagnosis and Management


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The author has nothing to disclose


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Bradyarrhythmia, sinus node dysfunction, atrioventricular block, tachycardia-bradycardia syndrome, sinus arrest


## KEY POINTS

- Brady-Arrhythmias can reflect normal physiologic responses, like sleeping, or reveal a number of rhythm disorders, including sinus node dysfunction and atrioventricular conduction disturbances.
- In patients with confirmed or suspected bradycardia, a thorough history-taking and physical examination should include associated signs/symptoms, precipitating factors, medications (including nasal and ophthalmic routes), a personal and family history of coronary artery disease, cardiac arrhythmia, and sudden death.
- Management of bradycardia is based on the severity of symptoms, the underlying causes, presence of potentially reversible causes, presence of adverse signs, and risk of progression to asystole.

## SYNOPSIS

Bradyarrhythmias are common clinical findings and they consist of various physiologic and pathologic conditions (sinus node dysfunction and

atrioventricular conduction disturbances). Bradyarrhythmias can be benign requiring no treatment; however, acute unstable bradycardia can lead to cardiac arrest. In patients with confirmed or suspected bradycardia, a thorough history-taking and physical examination should include possible causes of sinoatrial (SA) node dysfunction or atrioventricular (AV) block. Management of bradycardia is based on the severity of symptoms, the underlying causes, presence of potentially reversible causes, presence of adverse signs, and risk of progression to asystole. Pharmacologic therapy and/or pacing are used to manage unstable or symptomatic bradyarrhythmias.

## INTRODUCTION

Bradycardia, also known as bradyarrhythmia, is a common finding for both healthy individuals and those who are ill. This paper provides an overview on types and causes of bradyarrhythmia, the clinical presentation, diagnosis, and management.

## DEFINITION OF BRADYCARDIA

In adults, bradycardia has traditionally been defined by consensus as a slow heart rate (HR) of fewer than 60 beats per minute (bpm) [1]. This easily-remembered HR threshold of 60 bpm for bradycardia has been challenged as it over-diagnoses bradycardia and is not consistent with published age and gender specific norms [2-4]. However, resting HR among the healthy, asymptomatic population varied greatly. A slow HR may be physiologically normal for some individuals but may be inadequate for others. Classic work from Jose and Collison (1970) showed that HR decreases with age [5]. There is also a circadian cycle of HR, with fastest rates occurring between 1400-1700 hours and the slowest rates occurring between 0400-0600 hours [6]. During sleep, HR decreases by an average of 24 bpm in young adults [7,8] and by 14 bpm in those over 80 years of age [6]. Women have faster HR than men during both waking and sleeping periods, by an average of 10 bpm in young adults [7,8]. Spodick and colleagues reported that the “normal” range of HRs in the afternoon was 46 to 93 bpm for men and 51 to 95 bpm for women; [9] thus, they proposed a HR of 50 bpm to be an appropriate level for defining bradycardia in adults [9-11].

## BRIEF OVERVIEW OF THE SINOATRIAL NODAL CONDUCTION SYSTEM

Cardiac rhythm is initiated and controlled by the sinoatrial (SA) node, the primary pacemaker of the heart. Current scientific knowledge indicates that the SA node structure consists of clusters of specialized cardiomyocytes enmeshed within strands of connective tissue or fibrosis [12]. In addition, there are also distinct SA conduction pathways that electrically connect the SA node to the right atrium. These SA conduction pathways play an important role in regulating the SA node

automaticity, thus the maintenance of the HR [12]. Autonomic stimulation, ischemia and/or structural remodeling can compromise the SA node pacemaker function and inhibit the impulse through the SA nodal conduction pathways (exit block) [12]. The SA node exit block allows the impulse to originate from subsidiary pacemakers, such as the atrioventricular (AV) node and the specialized ventricular conduction system.

The heart rate is modulated by several factors, including the autonomic nervous system (the dynamic balance between sympathetic and parasympathetic nervous systems), the baroreceptors, the Bainbridge reflex, the intrinsic heart rate, etc [13]. The autonomic nervous system is reported to be more densely innervated in the cardiac conduction system than in the myocardium in other parts of the heart, with the SA node being the most densely innervated region of the conduction system [14]. This supports the central role of the autonomic nervous system in initiating and regulating the cardiac impulse. Sympathetic and parasympathetic nervous systems interact with adrenergic (α- and β-) and muscarinic receptors. In general, stimulation of β-adrenoceptors increases HR while stimulation of muscarinic receptors decreases HR [15].

The thought that the impulse originates from a very focal region in the SA node has been challenged. Boineau and associates [16] demonstrated that humans have a widely distributed physiologic pacemaker complex extending across a significantly larger area of atrial tissue. The concept of an “atrial pacemaker complex,” including the SA node, SA nodal conduction pathways, and the surrounding atrial myocardium is proposed to initiate normal atrial or sinus rhythm [16].

## TYPES OF BRADYARRHYTHMIAS

Bradyarrhymias can reflect normal physiologic responses, as in sleeping, or reveal a number of rhythm disorders, including sinus node dysfunction and AV conduction disturbances [17]. Sinus node dysfunction is caused by a depressed automaticity or an impaired SA node and atrial impulse formation and/or propagation. Sinus node dysfunction, sometimes used interchangeably with “sick

sinus syndrome" [18,19], refers to a spectrum of heart rhythm disturbances, including sinus bradycardia (Figure 1), sinus arrest, sinus exit block, and tachycardia-bradycardia syndrome [18]. Of note, the bedside monitor is sensitive to artifactual noise in the ECG signal so that artifact can generate a false positive bardycardiac alarm (Figure 2). Chronotropic incompetence, defined as the inadequate HR response to increased activity or demand, without identifiable causes, is also considered sinus node dysfunction (Table 1A) [20].

AV conduction disturbances include first-, second-, high- and third-degree (or complete) AV blocks. First-degree AV block is defined as a PR interval over 0.2 seconds with a 1:1 AV conduction ratio on the electrocardiogram (ECG). There are two types of second-degree AV block: Mobitz Type I and II, categorized by intermittently dropped ventricular beats. Mobitz Type I block, also known as Wenckebach, is defined as a progressive increase in the PR interval until a P wave fails to conduct to the ventricle. Mobitz Type II block is a periodic AV block with constant PR intervals in the conducted beats. Advanced or high-degree AV block consists of multiple P waves that are blocked but without third-degree AV block present. Third-degree AV block occurs when atrial and ventricular activities are independent of each other (AV dissociation) and AV conduction is absent. Bradycardia is often associated with second- or third-degree AV block.

## CAUSES OF BRADYARRHYTHMIAS

Multiple physiological and pathophysiological causes can produce bradyarrhythmias (Table 2). A selected discussion of these factors is summarized below.

**Athletes:** In endurance athletes, sinus bradycardia with HR below 40 bpm is common and sinus pauses lasting more than two seconds were found in 37% of athletes during sleep [21]. Recent research has shown that the type of sport influences the level and mechanisms of resting bradycardia [22]. For example, resting bradycardia in runners depends on higher vagal tone while resting bradycardia in cyclists is probably associated with cardiac hypertrophy.

**Aging:** An explanation for the slower HR as an individual grows older is the sympathetic dominance of the cardiac conduction system in infancy and gradual transition into a sympathetic and parasympathetic co-dominance in adulthood [23]. Sinus node dysfunction is primarily a disease of the elderly. Recent work has shown that an age-induced increase of SA node fibrosis is strongly correlated with slowed intrinsic HR and slowed SA node conduction [24].

**Medications:** A number of pharmacologic agents, such as β-adrenergic blockers (metoprolol, nebivolol, etc.); non-dihydropyridine calcium-channel blockers (diltiazem, verapamil, etc,); antiarrhythmics, digoxin and other sympathomimic antihypertensives (clonidine, prazosin, etc.) are known to cause bradycardia. Importantly, topical ophthalmic medications, such as timolol maleate, used for treatment of glaucoma and ocular hypertension, are absorbed from the eye into the systemic circulation and can causes systemic adrenergic β-blocking, leading to AV block and bradycardia [25]. Bradycardia has also been reported with other non-cardiovascular pharmacologic agents in standard doses or overdoses. These include but are not limited to guanfacine extended release, corticosteroid, donepezil, narcotics, and anesthetics.

**Genetics:** There is a genetic component of bradyarrhythmias [26]. For example, familiar forms of primary sinus bradycardia have been associated with several genetic mutations; to name a few, the hyperpolarization-activated cyclic nucleotide–gated potassium channel 4 (HCN4) gene, the sodium channel voltage gated type V alpha subunit (SCN5A) gene, and the ankyrin 2, neuronal (ANK2) [27]. Genes affecting enzymes involved in medication metabolism and elimination can also contribute to bradyarrhythmias. For example, cytochrome P450 family 2 subfamily D polypeptide 6 (CYP2D6) is the main enzyme contributing to the metabolism of several beta-blockers. Several genetic polymorphisms of the CYP2D6 gene, such as CYP2D6 *4/*4, lead to no enzyme activity. Patients with these genetic defects, also called poor metabolizers of CYP2D6, are at increased risk of bradycardia [28].

**Acute myocardial ischemia/infarction:** Bradyarrhythmias can be due to myocardial ischemia/infarction involving the proximal right and/or circumflex

artery or the coronary artery supplying blood flow to the sinus node or to the AV node.

**Seizures:** Ictal bradycardia and asystole have been reported in 2% to 37% and in 1% to 16% of seizures, respectively [29]. The mechanism for seizure-related bradyarrhythmia is unclear. Since ictal bradyarrhythmias are frequently preceded by transitory tachycardia, the current thinking suggests that bradyarrhythmias may involve a reflex to counteract tachycardia by excessive activation of the vagal nerve [29].

**Gender:** Based on a large pacemaker implantation registry in Germany involving 17,826 patients, it was reported that women are more likely to have sick sinus syndrome but less likely to have AV block as a primary pacemaker indication [30]. The underlying mechanisms for these gender differences are unknown and require further investigation.

**Other conditions:** Other conditions that result in bradyarrhythmia may include Infection/febrile illnesses (encephalitis, dengue hemorrhagic fever, etc), endocrinologic abnormalities (hypothyroidism), anorexia nervosa, hypothermia, hypoglycemia, electrolyte disturbances (e.g, hyperkalemia), infiltrative disease, collagen vascular disease, trauma to the cardiac conduction system, hypoxia, and other complications [31].

## CLINICAL PRESENTATION

Cardiac output is determined by the left ventricular stroke volume multiplied by the HR. Patients with bradycardia may be asymptomatic if changes in stroke volume compensate for the decrease in HR. Symptoms of bradycardia can be diverse and related to reduce cardiac output, resulting in the hypoperfusion of vital organs. The symptoms can be nonspecific and chronic, including dyspnea on exertion, exercise intolerance, fatigue, and weakness. However, symptoms may be severe including syncope, lightheadedness/dizziness, palpitation, angina, or a change of mental status [17,32].

## EVALUATION/DIAGNOSIS OF BRADYARRHYTHMIAS

In asymptomatic individuals, bradycardia may be noted as an incidental finding during a routine check-up or on an ECG obtained for other purposes. In patients with confirmed or suspected bradycardia, a thorough history taking and physical examination should include documentation of associated signs/symptoms of hypoperfusion and precipitating factors, medications (including nasal and ophthalmic routes), personal and family history (coronary artery disease, cardiac arrhythmia, and sudden death), and possible causes of SA node dysfunction or AV block (Table 2).

**Diagnostic Testing**. Basic laboratory studies should include tests of electrolytes, glucose, toxicology screening for narcotics and digitalis level if the patient is on digoxin), and thyroid function. To establish the diagnosis of bradyarrhythmia, it is crucial to find a causal relationship between patient symptoms and abnormalities on the ECG [33]. A standard 12-lead ECG is used to determine the presence and type of bradyarrhythmia and/or presence of structural cardiac disease, such as prior or acute myocardial ischemia/infarction. Since bradyarrhythmia may be intermittent, prolonged cardiac monitoring should be considered if a 12-lead ECG does not yield a diagnosis. Selection of these modalities is based on symptom severity and frequency. A 24- to 48-hour Holter monitor is generally the first-line choice in patients with frequent symptoms. If suspicion of arrhythmia is high, but the Holter monitoring is non-diagnostic and the patient is experiencing intermittent symptoms, longer cardiac monitoring of 1 to 4 weeks using non-invasive mobile cardiovascular telemetry or event monitoring is the next step. Implantable loop recorders are available to provide continuous cardiac monitoring from any number of months to three years. These ambulatory cardiac monitoring devices and costs have been summarized [34]. In addition, invasive electrophysiologic studies may be used to evaluate sinus node dysfunction and AV blocks in patients with known or suspected bradyarrhythmias. For example, electrophysiologic studies are appropriate when sinus node dysfunction is suspected in symptomatic patients. During electrophysiologic studies, AV nodal and His–Purkinje conduction durations are

precisely measured on a His-bundle ECG so the site of the block is identified, but a causal relation between an arrhythmia and symptoms has not been established. [35].

Chronotropic incompetence can be diagnosed by an incremental dynamic exercise testing when HR fails to reach an arbitrary percentage (≥ 80%) of the age-predicted maximal HR (usually 220-age). [36] Tilt-table testing may be used to diagnose neutrally mediated syncope (or vasovagal syncope) by eliciting syncopal symptoms during provocation of neutrally mediated hypotension and/or bradycardia [37].

## MANAGEMENT

Management of bradycardia is based on the severity of symptoms, the underlying causes, presence of potentially reversible causes, presence of adverse signs (Table 3), and risk of progression to asystole (Table 4)[38]. Some bradycardia may not require treatment or may involve correction of reversible causes for bradycardia. For example, bradycardia develops in patients with obstructive sleep apnea and hypoxia and appropriately treated sleep apnea may eliminate bradycardia. When a patient is unstable (Table 3), it is important to determine the cause of the patient's instability in order to direct treatment properly. For example, if a patient becomes hypotensive and develops a bradycardia due to respiratory failure and severe hypoxemia, treating the bradycardia without treating the hypoxemia is unlikely to improve the patient's instability. When adverse signs or high risk of progression to asystole are evident, immediate treatment for bradycardia should be initiated [39]. Patient assessment using a rapid evaluation tool such as the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach is recommended for acute unstable bradycardia (Table 3) [39].

### Pharmacologic Therapy

Initial treatments are pharmacological, with pacing being reserved for patients unresponsive to pharmacological treatments or with risk factors for asystole (Table 4).

- **Atropine Sulfate:** If bradycardia produces acute signs and symptoms of instability (Table 3), the first-line treatment is atropine sulfate [40]. Atropine is an anti-muscarinic medication which reverses cholinergic-mediated decreases in HR and AV conduction. Atropine improves heart rate and signs/symptoms associated with bradycardia [40]. The recommended initial atropine dose for bradycardia in adults is 0.5 mg intravenously, repeated if necessary every 3 to 5 minutes to a maximum total dose of 3 mg [40]. It is important to provide adequate doses of atropine as doses < 0.5 mg may result in paradoxical further slowing of the HR [41]. For adult patients who are morbidly obese, the dose of atropine should be calculated using lean body weight [42]. Atropine should be considered a temporary measure and should not delay implementation of a pacemaker for patients with symptomatic and/or unstable bradyarrhythmia or sinus arrest. Atropine should be used cautiously in patients with acute coronary syndrome as increased HR may worsen acute ischemia/infarction [41].
- **Alternative Medications:** Intravenous infusion of β-adrenergic agonists with HR accelerating effects (e.g., dopamine. epinephrine, isoproterenol) can be effective if the bradycardia is unresponsive to atropine [40]. Results from studies [43,44] have showed paradoxical slowing of the HR, AV block, and sinus arrest when atropine was administered to patients after cardiac transplantation. In these patients, β-adrenergic agonists as treatment measures are preferred over atropine [40]. For patients with Mobitz type II or third degree AV blocks with a wide-QRS complex, the location of a block is likely below the AV node, thus, the patient is unlikely to be responsive to atropine or β-adrenergic agonists. Alternative medications, such as glucagon, may also be appropriate in special circumstances if beta-blocker or calcium channel blocker overdose is suspected [41].

**Cardiac Pacing**

- **Temporary Pacing:** Temporary pacing should be initiated immediately in patients suffering from severe or clinically significant episodes of bradyarrhythmia and asystole [45], if there is no response to atropine or if

atropine is unlikely to be effective. It is an emergency measure to provide temporary ventricular rate support, thus cardiac output, for adequate perfusion of the vital organs until permanent pacing can be arranged. There are several forms of temporary pacing: transcutaneous, esophageal, epicardial or percutaneous transvenous. Transcutaneous pacing is done by applying adhesive pads to the chest in anterioposterior or anteroapical configuration. Esophageal pacing is rarely used. Traditionally, transvenous pacing is used to stabilize patients suffering from hemodynamic unstable bradyarrhythmia. This procedure is painful in conscious patients, thus requiring sedatives or anesthetics. Indications for pacemaker use and strategies to manipulate temporary pacemakers to optimize hemodynamics are of utmost importance [45].

- **Permanent Pacing:** Permanent pacemaker implantation is the only effective treatment for symptomatic bradycardia [20] (Figure . The decision regarding the need for a pacemaker is influenced by the presence of symptoms directly attributable to bradycardia. For adults with SA node dysfunction, indications for permanent pacemaker implantation include frequent symptomatic sinus pauses, symptomatic chronotropic incompetence, and symptomatic sinus bradycardia that result from required drug therapy for medical conditions [20]. Recommendations for permanent pacemaker implantation for second-degree and third-degree AV block have also been summarized in the American College of Cardiology and American Heart Association guidelines [20]. In general, asymptomatic episodes of sinus bradycardia (with the HR as low as 40 bpm), sinus pauses of up to three seconds, first-degree and Mobitz type I AV block are not considered to be indications for permanent pacemaker implantation. It is crucial for clinicians to distinguish between physiological bradycardia due to autonomic conditions or athletic training effects and inappropriate bradycardia that requires permanent cardiac pacing. For example, in trained athletes, sinus bradycardia does not require permanent pacemaker implantation. Pacemaker placement is not necessary in patients

with anorexia nervosa because reversal of cardiac conduction disturbances occur with proper nutrition and weight normalization [46].

**SUMMARY**

Bradyarrhythmias are common clinical findings and they consist of various physiologic and pathological conditions (sinus node dysfunction and AV conduction disturbances). Bradyarrhythmias can be benign requiring no treatment; however, acute unstable bradycardia can lead to cardiac arrest. In patients with confirmed or suspected bradycardia, a thorough history taking and physical examination should include possible causes of SA node dysfunction or AV block. Management of bradycardia is based on the severity of symptoms, the underlying causes, the presence of potentially reversible causes, the presence of adverse signs, and the risk of progression to asystole. Pharmacologic therapy and/or pacing are used to manage unstable or symptomatic bradyarrhythmias [40].

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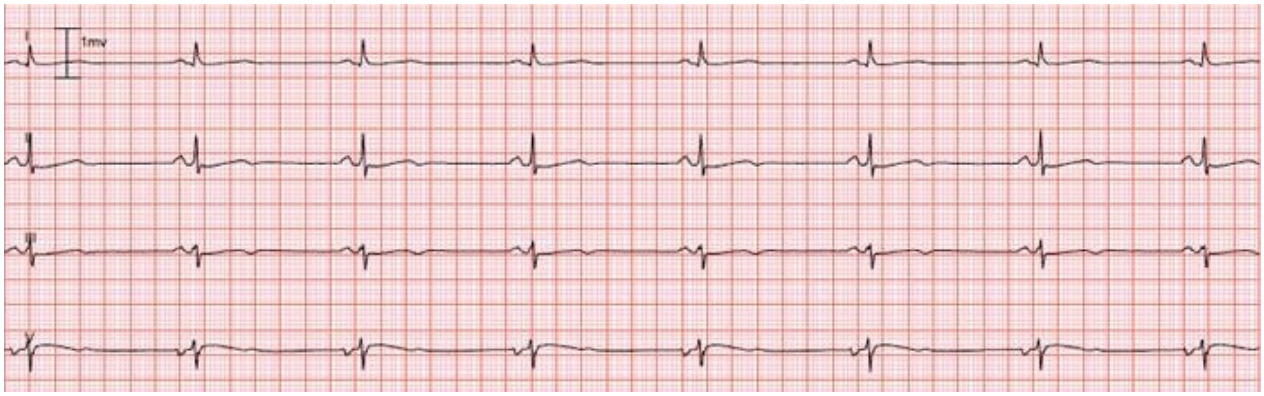
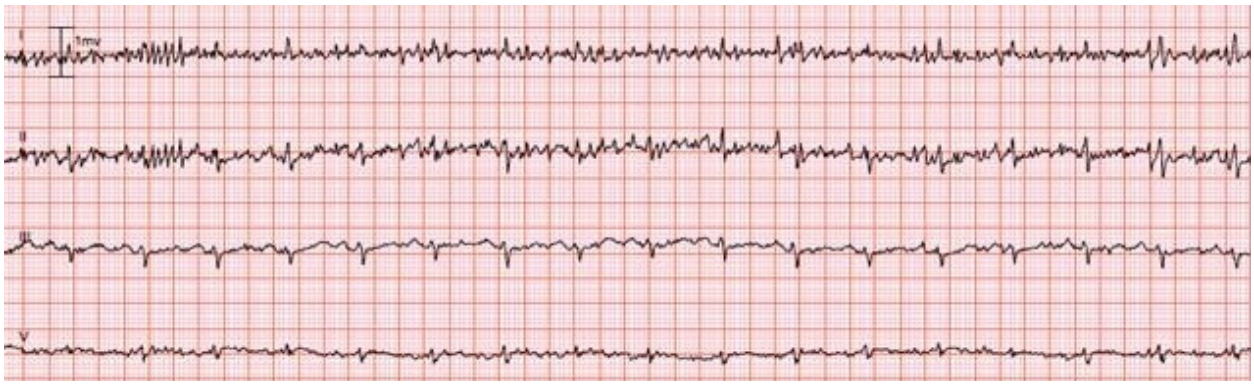
**Figure 1. Sinus Bradycardia**



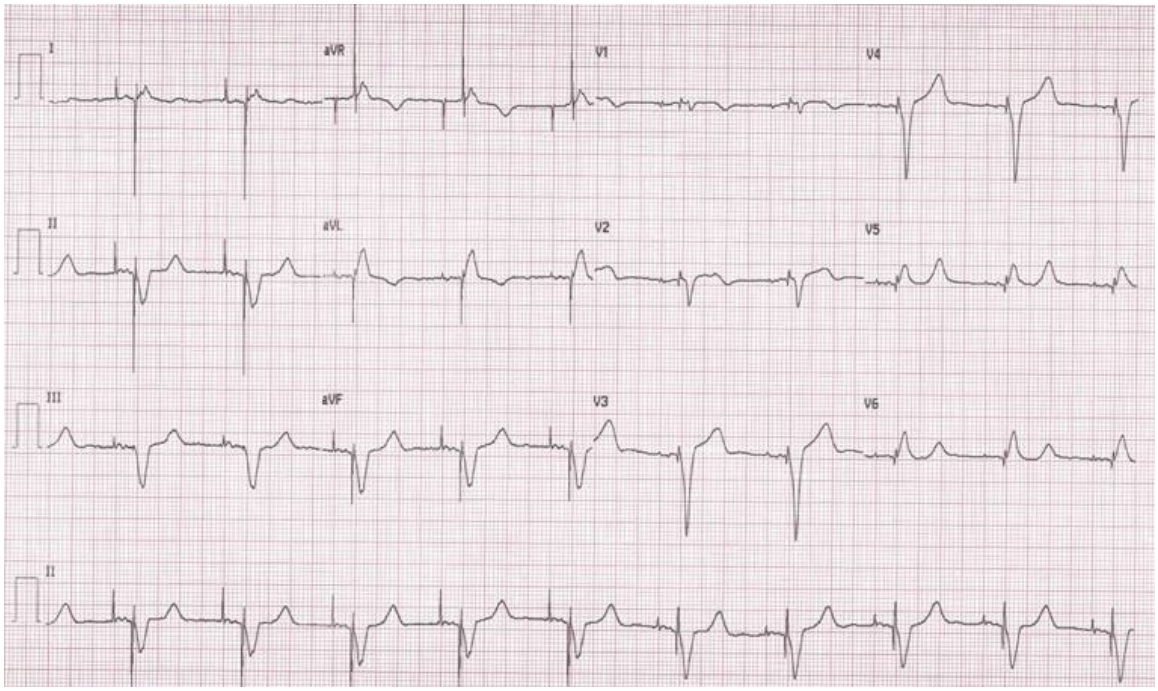
Sinus bradycardia is bradycardia in the presence of with normal sinus rhythm. The P wave is normally positive in leads I, II, III and biphasic in lead $V_1$. The PR is normal at less than 0.2 second. QRS is narrow. Since there are 34 small boxes between regular RR intervals, the heart rate calculation is 1500/34 = 44 beats per minute (bpm).

**Figure 2. False Interpretation of Bradycardia**



This is a false positive bradycardia alarm due to low amplitude QRS complexes and artifact interfering with the computer algorithm. The monitor reports a heart rate of 56 bpm but there are 15 small boxes between the regular RR interval; thus, the correct heart rate should be 1500/15 = 100 bpm. This demonstrates that a clinician's visual interpretation of cardiac rate is important in bradyarrhythmias determination.

**Figure 3. An example of a Dual-Chambered Pacemaker**




This is a standard 12-lead ECG recorded in a 79-year-old man with a dual-chamber pacemaker. The bottom tracing lead II is the simultaneous recording of rhythms above. In dual-chamber pacemakers, electrodes are inserted into both the right atrium and right ventricle. Atrial and ventricular pacemaker spikes are seen before each P wave and QRS, respectively, at a rate of 60 beats per minute. There is a programmable AV delay, interval between the atrial and ventricular pacemaker spikes, similar to PR interval seen in physiologic conduction.

**Table 1. Types of Bradyarrhythmias**

1A. **Sinus Node Dysfunction**

| Type | Definition |
|---|---|
| Sinus arrest | A pause in the sinus rhythm due to failure of the sinus node to depolarize (impulse formation) |
| Sinus exit block | A pause due to conduction failure from the sinus node to the surrounding atrium. The duration of this pause is a multiple of the sinus P-P interval. |
| Sinus bradycardia | Bradycardia in conjunction with normal sinus rhythm due to depressed automaticity of the sinus node |
| Tachycardia-Bradycardia syndrome | A combination of tachycardia (atrial fibrillation, atrial flutter, etc) and sinus bradycardia, also called sick sinus syndrome |
| Chronotropic Incompetence | Inadequate heart rate response to increased activity or demand, without identifiable causes |

1B. **Atrioventricular (AV) Conduction Disturbances**

| Type | Definition |
|---|---|
| First degree AV block | A PR interval over 0.2 seconds with a 1:1 AV conduction ratio |
| Second degree AV block | Categorized by intermittently dropped ventricular beat |
| Mobitz type I (Wenckebach) | A progressive increase in the PR interval until a P wave fails to conduct to the ventricle |
| Mobitz type II | Periodic AV block with constant PR intervals in the conducted beats |
| Advanced or high degree AV block | Multiple P waves that are blocked but without third-degree AV block present |
| Third degree AV block with junctional or ventricular escape rhythm | Complete dissociation of atrial and ventricular electrical conduction, thus, none of the signals generated above the AV node are conducted to the ventricles; thus, junctional or ventricular escape rhythms are approximately 30-50 beats per minute. |

**Table 2. Causes of Bradyarrhythmias**

Athlete

Aging

Medications Effects/Overdoses

- Beta Blockers, including eye drops for glaucoma (Timolol)
- Calcium channel blockers, non-dihydropyridine
- Antiarrhythmics (class I and III)
- Digoxin
- Other sympatholytic antihypertensive (clonidine, prazosin, etc.)
- Other (guanfacine extended release, corticosteroid, donepezil, narcotics, anesthetics, fingolimod, thiopentone sodium, etc,)

Genetics

Acute myocardial ischemia/infarction (right and/or circumflex artery)

Seizure

Other Conditions

- Myocarditis
- Infection and Febrile Illness (encephalitis, dengue hemorrhagic fever, etc)
- Endocrine (hypothyroidism, hypogonadotropic hypogonadism, etc)
- Anorexia nervosa
- Hypothermia, hypoglycemia
- Electrolyte disturbances (e.g., hyperkalemia, hypokalemia, hypocalcemia)
- Diving
- Infiltrative disorders
- Collagen vascular diseases
- Conduction system injuries (e.g., surgery)
- Altered autonomic influence (e.g., nausea/vomiting, neutrally mediated syncope [vasovagal syncope])
- Systemic hypoxia
- Sleep apnea

**Table 3 Adverse Signs Indicating Unstable Condition Related to Arrhythmia** [39]

| Adverse Signs | Signs and Symptoms of Instability |
|---|---|
| Shock | Pallor, sweating, cold and clammy extremities, impaired consciousness, hypotension (systolic blood pressure < 90 mmHg) |
| Syncope | Loss of consciousness |
| Heart failure | Pulmonary edema, hepatic engorgement |
| Myocardial ischemia | Angina, acute ischemia on electrocardiogram |

**Table 4. High Risk of Progression to Asystole** [39]

- Recent asystole
- Mobitz type II AV block
- Complete AV block with wide QRS
- Ventricular pause > 3 seconds