In the early 1900s Keith and Flack identified the sinus node as the region responsible for activation of the heart. Laslett first suggested sinus node dysfunction as a cause of bradycardia in 1909, and during the 1950s and 1960s Short, Ferrer, Lown, and others described the clinical spectrum of sinus node dysfunction that is commonly called the “sick sinus syndrome resting sinus bradycardia.” Sinus node dysfunction can have multiple electrocardiographic manifestations including sinus pauses, the bradycardia-tachycardia syndrome, and inappropriate sinus node response to exercise (chronotropic incompetence).

Epidemiology

It can be difficult to differentiate sinus node dysfunction from physiologic sinus bradycardia in a specific population. In a study of 50 young adult males, 24-hour ambulatory electrocardiographic monitoring revealed that 24% of the study group had transient heart rates less than 40 beats per minute (bpm), pauses up to 1.7 seconds while awake, and 2.1-second pauses while asleep. Similarly, in a study of 50 young adult women, pauses from 1.6 to 1.9 seconds were observed. In older asymptomatic individuals, transient heart rates less than 40 bpm and pauses of 1.5 to 2.0 seconds were observed in less than 2%. The decreased incidence of nocturnal bradycardia in this normal elderly population is probably due to the decrease in vagal tone that occurs with increasing age.

Sinus node dysfunction should be suspected when a patient describes symptoms of fatigue, syncope or presyncope, or exercise intolerance and is noted to have sinus bradycardia or pauses on the 12-lead ECG or during Holter monitoring. In general, symptomatic sinus node dysfunction increases with age, with the incidence doubling between the fifth and sixth decades of life. In one study of approximately 9000 patients visiting a regional cardiac center in Belgium, Kulbertus et al. estimated that the incidence of sinus node dysfunction is less than 5 per 3000 people older than 50 years of age. However, sinus node dysfunction is more commonly identified today because of an increased elderly population and increased physician awareness. In a 1997 survey, sinus node dysfunction accounted for approximately 50% of the 150,000 new pacemakers implanted in the United States and 20% to 30% of the 150,000 new pacemakers implanted in Europe.

Although more common in elderly patients, it is important to note that several specific younger patient groups can also have sinus node dysfunction. First, patients with congenital heart disease can have sinus node dysfunction. In 39 patients younger than 40 years of age who underwent pacemaker implant for sinus node dysfunction at the Mayo Clinic, 64% had associated congenital heart disease. The most common condition was transposition of the great arteries corrected by a
Mustard operation, since this procedure requires extensive atriotomies. Second, several familial forms of sinus node dysfunction have been identified and account for approximately 2% of patients who present with sinus node dysfunction. Bharati et al. described a family with congenital absence of sinus rhythm. Several other investigators have described different forms of sinus node dysfunction that appeared to be genetically transmitted. Finally, sinus node dysfunction is observed in approximately 4% of patients after cardiac transplant. Some, but not all, studies have found that a heart from a donor older than 40 years of age is associated with a higher incidence of sinus node dysfunction requiring permanent cardiac pacing.

Anatomy

The sinoatrial (SA) node is situated in the sulcus terminalis between the superior vena cava and the right atrial appendage in a somewhat curved fashion and extends from the hump of the atrial appendage, tapering toward the inferior vena cava (Fig. 12-1A). The SA node is a sizable structure, and although it is situated epicardially, some of the fibers may extend deep intramyocardially. At the gross level, the SA node cannot be dissected. It can be identified at the light microscopic level; it consists of small fusiform cells, distinctly smaller than the surrounding atrial myocardial cells, arranged to a considerable extent along the line of the sulcus terminalis but also serpiginously surrounding the SA nodal artery. The cytoplasm of the cells stain lighter than do the atrial myocardial cells (see Fig. 12-1B). The myofibrils are distinctly less prominent than the surrounding atrial myocardial cells, and the striations are scarce but do increase with age. There are no intercalated discs at the light microscopic level. The cells lie in a massive amount of thick collagenous and thinner elastic fibers.

BLOOD SUPPLY

The SA node is supplied by way of ramus ostii cavae superioris (SA nodal artery) and reinforced by other atrial branches, and branches from the bronchial arteries. In addition, Kugel's artery, a branch from the left coronary artery, also supplies the SA node. The ramus ostii cavae superioris originates in about 55% of cases from the right coronary artery and in 45% of cases from the left coronary artery. There are nerve cells and fibers evident in the periphery of the node. Nerve fibers are present in the midst of the head of the SA node.

PATHOLOGY

The anatomic base of supraventricular arrhythmias may lie in the SA node and its approaches, as well as in the atrial preferential pathways, the approaches to the atrioventricular (AV) node, and the AV node.
the moment there is no pathologic specificity for any one of the atrial arrhythmias, it would appear that the same type of pathology may be responsible for both bradyarrhythmias and tachyarrhythmias on different occasions. Rarely, sinus node dysfunction can be familial (Fig. 12-2).

**SICK SINUS SYNDROME IN THE YOUNG**

Although sick sinus syndrome is usually seen in the elderly, it may be seen in the young as well. Pathologically, a marked increase in connective tissue is found, with fat in the approaches to the SA node, the atrial preferential pathways, and approaches to the AV node. The penetrating AV bundle may be septated. In other cases an increased amount of fat in other parts of the atria, as well as around the SA and AV nodes, is seen.

**SICK SINUS SYNDROME IN THE ELDERLY-AGING**

In older patients with sick sinus syndrome, significant coronary artery disease is usually present; however, the basic pathology is variable. An abnormal formation of the atrial septum, resulting in fibrosis in the approaches to the SA and AV nodes and atrial preferential pathways, may be seen, or there may be similar findings within these structures along with fat. With advancing age, there may be loss of cells to a varying extent in the SA and AV nodes and their approaches and in the surrounding atrial myocardium, with replacement by fat and fibrosis, associated with varying degrees of focal hypertrophy or atrophy of myocardium (Fig. 12-3). In addition, arteriosclerosis, necrosis, or chronic inflammation may be present in the atria.

**SENILE AMYLOIDOSIS**

This is a type of primary amyloidosis seen in patients older than 80 years of age. It affects the atrial

**FIGURE 12-2** Histologic characteristics of the sinoatrial (SA) nodal area in a 72-year-old male member of a family with congenital absence of sinus rhythm and a tendency to develop atrial fibrillation at an early age who collapsed rising from a chair and could not be resuscitated. He had a history of atrial fibrillation, at first paroxysmal and later chronic for 18 years, but was only mildly incapacitated. Note the fragmented SA node. Weigert-van Gieson stain ×30. F, fat; M, atrial myocardium; R, remnant of SA node. (From Bharati S, Surawicz B, Vidaillet, HJ, Lev M: Familial congenital sinus rhythm anomalies, clinical and pathological correlations. Pacing Clin Electrophysiol 1993;15:1720-9).

**FIGURE 12-3** Fat accumulation around the SA node and replacement of SA node by fat with almost total separation of SA node from its approaches in an elderly patient with sick sinus syndrome. Weigert-van Gieson stain ×45. F, fat; N, SA node; RA, right atrium. Arrows point to the isolated SA node with marked fat in and around the node. (From Lev M, Bharati S: Age related changes in the cardiac conduction system. Intern Med 1981;2:19-21.)
myocardium including the SA node and its approaches, SA nodal artery, and the arterioles of the atria (Fig 12-4). Senile amyloidosis may be associated with sinus bradycardia, the bradycardia-tachycardia syndrome, and sinus echo phenomena. 

**TRANSIENT AND PERSISTENT ATRIAL STANDSTILL**

Here one may find arteriolosclerosis of the SA and AV nodes with fibrosis and fibroelastosis in the approaches to the AV node and within the AV node.

**IATROGENIC CONSIDERATIONS**

Sinus node dysfunction has been documented following cardiac surgery in both congenital and acquired heart disease. Radiation therapy for Hodgkin’s disease and blunt trauma to the chest wall may result in SA nodal dysfunction.

In summary, pathologic findings in and around the SA node, atria, approaches to the AV node, the AV node, the AV bundle and the ventricular myocardium are almost always present to varying degrees in chronic or permanent SA node dysfunction. However, isolated pathology of the SA node or the atria, or both, may be seen. Any pathologic state, such as myotonia dystrophica, Kearns-Sayre syndrome, primary or secondary tumor, primary or secondary amyloidosis, and numerous other diseases that affect the atria or SA node and its approaches and the AV node and its approaches may produce varying clinical forms of SA nodal dysfunction.

**BASIC ELECTROPHYSIOLOGY OF THE SINUS NODE**

The structural and functional organization of the sinus node is quite complex, and there are significant differences in the organization of the sinus node among species. The most extensive studies of the sinus node have been performed in rabbits. The node contains prototypical, small, structurally primitive pacemaker cells concentrated in the center, larger transitional latent pacemaker cells concentrated more peripherally; and intermingled, nonpacing atrial cells extending into the node from the atrial margins of the node in strands that are more prominent in the periphery. The cells within the node are relatively poorly coupled by gap junctions, and there is substantial interstitial tissue interspersed among the fascicles of nodal cells. The resultant relatively poor intercellular communication slows the propagation of the impulse from the central pacemaking regions toward the periphery of the node. In addition, the coupling of the transitional cells near the margins of the node with the atrial myocardial cells is not a smooth continuum but consists of irregular junctions of interweaving strands of transitional cells and atrial cells extending into the interior of the node. Mapping of electrograms in and around the node has disclosed an apparent “multicentric” initiation of activation that more likely represents irregular propagation to atrial myocardium than simultaneous generation of impulses at separated sites. The node preferentially connects to the atrium in the superior aspects of the crista terminalis, and there appears to be conduction block exiting the node in the direction of the atrial septum.

A dense representation of sympathetic and parasympathetic nerves and ganglia in the node ensures a sensitive autonomic responsiveness. With increasing vagal influence, the primary pacemaking site near the superior aspect of the node tends to migrate inferiorly, whereas an increasing adrenergic influence produces return to the primary dominant pacemaker sites in the superior region of the node. Detailed and sensitive analyses of P wave morphology, as well as mapping of the sinus node, indicate a dynamic shifting of pacemaker sites with changes in heart rate.

**Action Potentials**

Small, primitive pacemaker cells in the interior of the node generate the dominant pacemaker potentials...
and show the least polarized maximum diastolic potentials (−60 to −40 mV), the most rapid rates of diastolic depolarization with smooth transition from end-diastole to the upstroke, and the slowest upstroke velocities (=1-10 V/sec), as shown in Figure 12-5. Latent pacemakers are concentrated more peripherally in the node. These cells are more polarized, show less rapid diastolic depolarization, a more abrupt transition from diastole to upstroke, and more rapid upstrokes. There is a continuous gradation of the properties of transitional cells from the characteristics of primary pacemaker cells to the properties of highly polarized surrounding atrial cells with stable resting potentials close to −80 mV and upstroke velocities approaching 100 V/sec. This gradation of properties is conditioned by cell coupling and electrotonic interaction, as well as by the differing intrinsic properties of myocytes within the node. Due to the electrotonic influence of atrial cells, the pacemaker capabilities of transitional cells are muted, whereas the more remotely connected interior cells are shielded from the nonpacing atrial myocytes, allowing them to maintain pacemaker dominance. Separation of latent pacemaker cells near the atrial margins from the atrium and from the centrally located dominant pacemakers result in a faster intrinsic rate in latent pacemakers freed from the influence of the nonpacemaking atrial cells. Cells in other parts of the atrium can also act as backup pacemakers, especially in the inferior portions of the node near the coronary sinus. These pacemaker cells can respond appropriately to autonomic influence and under abnormal conditions can usurp control of the heart. The electrophysiological properties of these subsidiary pacemakers have not been as well characterized as those of the sinus node.

**Currents**

Sinus node pacemaker cells are relatively depolarized because of an absence of paucity of channels for the current $I_{K1}$. These channels are plentiful and open at negative membrane potentials in atrial and ventricular myocytes. They establish a dominance of $K^+$ permeability in the resting state, thereby determining a resting potential approximating the $K^+$ equilibrium potential ($\approx -90$ mV). The absence of these channels is most complete in the small, central pacemaker cells operating at diastolic potentials between −60 mV and −30 mV. In larger, more polarized transitional cells, $I_{K1}$ may be present but reduced to varying degrees. The low upstroke velocities of these cells are related to a lack of operating Na channels, those channels that transmit the intense excitatory Na current in atrial and ventricular cells. The absence or paucity of this excitatory current is due to a deficiency of the channels in individual myocytes and the depolarization of the myocytes during diastole to levels of membrane potential at which Na channels, if present, would be inactivated. The smallest cells may lack Na channels entirely. Larger transitional cells may contain Na channels and may operate at diastolic potentials at which Na channels can be activated to provide some excitatory Na current and more rapid upstrokes. The slow and diminutive upstrokes in the primary pacemaker cells are generated by the L-type Ca$^{2+}$ current ($I_{CaL}$), which serves as the trigger for release of Ca$^{2+}$ by the sarcoplasmic reticulum and therefore the trigger for contraction in all cardiac cells but is the primary excitatory current in depolarized sinus nodal cells. This current is slower and far less intense than the Na current, accounting for the poor upstrokes and slow conduction within the node. The currents producing diastolic depolarization, the fundamental pacemaker potential, comprise a multitude of candidates about which there is no uniform consensus. The “funny” current $I_{f}$ is a nonspecific cation current that is mainly an inward Na current activating relatively slowly at negative membrane potentials in the range of diastolic potentials. It becomes more intense at more negative membrane potentials. This current is well expressed in sinus nodal cells, responds appropriately to adrenergic and cholinergic stimulation, and thus is a plausible candidate as an important pacemaker current. However, some studies have shown activation at more negative levels than the diastolic potentials of the primary pacemakers (below −60 mV) and a greater representation in peripheral latent pacemakers. This has led some to suggest that $I_{f}$ is more active in latent pacemaker cells with a role to maintain pacemaker activity and counter the electrotonic influence of stable, well-polarized diastolic potentials of atrial cells. The $I_{f}$ current is activated by the second messenger adenylyl cyclase (cAMP), which shifts the voltage activation curve into a more positive range. It is argued that at physiologic levels of cAMP, the voltage activation curve is shifted into the range of the diastolic potentials of primary pacemaker cells.

In the absence of $I_{K1}$, the delayed rectifier $K^+$ currents $I_{Kr}$ and $I_{Ko}$, which are activated during the action potential, can play a role in the attainment of the maximum diastolic potential by providing the $K^+$ permeability that would bring the transmembrane potential close to the $K^+$ equilibrium potential at the end of the action
potential when they are fully activated. As these currents deactivate in diastole, the membrane potential would drift positive toward the more positive equilibrium potentials of other major ions such as Na, Ca\textsuperscript{2+}, and Cl. It has been argued that one or another of the delayed rectifier currents is the major pacemaker current.\textsuperscript{41} However, although \(I_{\text{K}}\) has an appropriate autonomic sensitivity, \(I_{\text{K}}\) does not. \(I_{\text{K}}\) is not prominent in the sinus nodes of all species.

Ca\textsuperscript{2+} currents, both \(I_{\text{CaL}}\) and the T-type Ca\textsuperscript{2+} current \((I_{\text{CaT}})\), have also been implicated in pacemaker function. \(I_{\text{CaL}}\), which has an activation threshold more positive than \(-40\) mV in most cardiac cells, could be active toward the end of diastolic depolarization in the depolarized primary pacemaker cells whereas \(I_{\text{CaT}}\), with an activation threshold more negative, might be active in earlier phases of diastolic depolarization and in latent pacemaker cells. \(I_{\text{CaL}}\) responds to autonomic influence in a manner like the sinus node, and recent studies have suggested that the activation threshold may be more negative in sinus nodal cells. The role of \(I_{\text{CaT}}\) remains uncertain. Other currents that have been nominated include the NaCa\textsuperscript{2+} exchange current generating inward current as Ca\textsuperscript{2+} entering the cells during the action potential is extruded in diastole and a newly described sustained inward current. It is possible that multiple currents can be involved in pacemaking with different roles in primary versus latent pacemaker cells and under different conditions.

Pacemaker activity can be notably influenced by the acetylcholine-activated K\textsuperscript{+} current, \(I_{\text{K,ach}}\), which markedly increases K\textsuperscript{+} permeability throughout the cycle, speeding repolarization, hyperpolarizing the cell, and reducing the rate of diastolic depolarization.

This current appears to be less sensitive to acetylcholine than the \(I_{\text{f}}\) current in the sinus node. The complexities of pacemaker function remain to be fully clarified. Contemporary molecular biologic techniques will be powerful tools to clarify the location and function of channels in the SA node and their roles in SA nodal pacemaking.

### Etiology

Sinus node dysfunction results from various conditions that have in common the capability to depress automaticity in and electrical conduction from the sinus node and perinodal and atrial tissue. These conditions can be intrinsic, resulting from structural damage to the sinus node, or extrinsic, caused by medications or systemic illnesses. The manifestation of sinus node dysfunction is inappropriate sinus or atrial bradycardia.\textsuperscript{32-40} Some patients may also experience episodes of supraventricular tachycardias (tachycardia-bradycardia syndrome). Because the clinical manifestations of sinus node dysfunction can mimic normal physiologic conditions (bradycardia) or can be caused by diseases that do not affect the sinus node (supraventricular tachycardias), the assessment and management of patients with suspected sinus node dysfunction can be challenging.\textsuperscript{6,40-48}

### EXTRINSIC CAUSES OF SINUS NODE DYSFUNCTION

Sinus bradycardia can be caused by medications that suppress automaticity; these include \(\beta\)-blockers, some calcium channel blockers (diltiazem and verapamil), digoxin (especially in the presence of high vagal tone), class I and III antiarrhythmic medications, and sympathetic drugs such as clonidine. Sinus bradycardia in these cases is frequently transient and reversible once the offending agent is withdrawn.

Sinus bradycardias can also be a manifestation of systemic illnesses or other extrinsic conditions such as hypothyroidism; hypoxemia caused by sleep apnea; increased intracranial pressure; or increased vagal tone such as occurs during endotracheal suctioning, vomiting, and Valsalva’s maneuver. These conditions are important to diagnose, because their appropriate treatment often results in resumption of normal sinus node function.

### INTRINSIC CAUSES OF SINUS NODE DYSFUNCTION

Intrinsic sinus node dysfunction is usually caused by degenerative processes involving the sinus node and SA area. The syndrome is usually acquired but can rarely be familial.\textsuperscript{8} Sinus node dysfunction is present when inappropriate sinus bradycardia, pauses in sinus rhythm (sinus arrest), SA block, or a combination of these exist.\textsuperscript{44} The degenerative process and associated fibrosis may also involve the AV node and intraventricular conduction system; as many as 17% of patients with sick sinus syndrome have evidence of AV block and bundle branch block.\textsuperscript{30}

### NATURAL HISTORY

The natural history of sick sinus syndrome is one of spontaneous clinical improvement alternating with periods of clinical deterioration. Patients generally seek medical attention when they are symptomatic from bradycardia. In the majority of cases, the heart rate spontaneously increases, and symptoms diminish.\textsuperscript{31,32} However, the clinical course is not predictable. Even patients with more severe symptoms such as syncope may remain free of symptom recurrence for years, and slightly more than half do not experience another syncopal episode over a 4-year follow-up.\textsuperscript{38} There is no clear explanation for this erratic course of the syndrome. The autonomic nervous system may play an important role in the genesis of symptoms, especially in the trigger of syncope.\textsuperscript{35} The prevalence of abnormal responses to carotid sinus massage (pauses exceeding 5 seconds) and tilt table testing is significantly higher in patients who experience syncope than in those who do not, highlighting the contribution of abnormal neural reflexes in the pathophysiology (Fig. 12-6).\textsuperscript{35,34}

Although symptoms are common in patients with sick sinus syndrome, survival is usually not affected, even in patients who develop syncope.\textsuperscript{35} Death related directly to dysfunction of the sinus node occurs in less than 2%
of patients over 6 to 7 years of follow-up. However, patients with sick sinus syndrome often have comorbid conditions that can shorten their life span. Coronary atherosclerosis is the most prevalent among these conditions, although myocardial ischemia and infarction, congestive heart failure, and advanced age are also common. In one report, patients with sick sinus syndrome had a 4% to 5% excess annual mortality in the first 5 years of follow-up compared with an age and sex-matched population. However, the mortality in patients without other coexisting disease at the time of diagnosis of sinus node dysfunction did not differ significantly from that observed in controls. Thus, although medical intervention and permanent cardiac pacing may be required to improve symptoms, no data exist supporting that these management strategies improve survival.

**CLINICAL MANIFESTATIONS**

The clinical manifestations of sick sinus syndrome are due to both the bradycardia and tachycardia. In the bradycardia-tachycardia syndrome, patients experience paroxysmal episodes of supraventricular tachycardia, which can be atrial tachycardia, atrial flutter or fibrillation, or reentry tachycardia (Fig. 12-7). More than one type of tachycardia may occur in the same patient. Episodes of rapid heart rate can lead to palpitations, angina, and syncope. Conversely, slowing of the heart rate without a compensatory increase in stroke volume leads to a reduction in cardiac output resulting in fatigue, weakness, lightheadedness, and dizziness.

Failure of the heart rate to increase appropriately with exercise (chronotropic incompetence), is a manifestation of sinus node dysfunction. Proposed definitions for chronotropic incompetence include failure to reach 85% of age-predicted maximum heart rate at peak exercise, failure to achieve a heart rate above 100 bpm, or a maximal heart rate during exercise greater than two standard deviations below that of a control population. In patients with chronotropic incompetence, symptoms may be present only during activity.

In about 17% of patients with sick sinus syndrome, overt congestive heart failure may develop, which may be related or contributed to by the slow heart rate, loss of the atrial contribution to left ventricular filling in patients who develop atrial fibrillation, or loss of AV synchrony in patients with implanted ventricular pacing systems.

**Syncope or severe presyncope** is one of the classical manifestations of sick sinus syndrome and occurs in about 25% of patients. In one prospective trial, the actuarial rates of syncope were 16% and 31% after 1 and 4 years of follow-up, respectively. Syncope is usually due to excessive slowing of or transient pauses in sinus rhythm, or sinus exit block with an inadequate escape rhythm (Fig. 12-8). In patients with the bradycardia-tachycardia syndrome, overdrive suppression of the sinus node may occur when the tachycardia terminates, resulting in prolonged pauses and syncope. Use of antiarrhythmic medications in these patients, while successful in controlling the tachycardia, frequently leads to worsening of the bradycardia episodes with exacerbation of symptoms, and permanent cardiac pacing is required for rate support.

About one third to one half of patients with sick sinus syndrome experience episodes of supraventricular tachycardia. Published reports indicate that chronic atrial fibrillation occurs in about 11% of cases after a mean follow-up of 19 months, increases to 16% at 5 years, and to 28% at 10 years. Variables that have been associated with the development of chronic atrial fibrillation are age; left ventricular end-diastolic diameter; presence of valvular heart disease; and ventricular, rather
Chronic atrial fibrillation is also more common in patients with the tachycardia-bradycardia syndrome who have had paroxysmal atrial fibrillation. When atrial fibrillation develops, many patients previously symptomatic from bradyarrhythmia experience a substantial improvement, likely due to the increase in ventricular rate.

Thromboembolic events, which occur in 3% to 9% of patients, may be a manifestation of sick sinus syndrome. In patients with bradycardia-tachycardia syndrome, the incidence increases to 24%. Ventricular pacing (as opposed to atrial or dual-chamber pacing) and the presence of preexisting cerebrovascular disease are also associated with a higher thromboembolic event rate during follow-up. High-risk patients should be carefully identified and placed on long-term anticoagulation therapy. However, not all cerebrovascular accidents in these patients are due to embolic events. Elderly patients with atherosclerotic cerebrovascular disease...
may have transient ischemic attacks or frank cerebral infarction if bradyarrhythmia or the tachyarrhythmia is associated with a fall in cardiac output and reduction in cerebrovascular perfusion.

**ATRIOVENTRICULAR CONDUCTION IN SINUS NODE DYSFUNCTION**

At the time of diagnosis up to 17% of patients with sick sinus syndrome have evidence of AV conduction system disease, although high-degree AV block is unusual, reported in only 5% to 10% of cases. The presence of AV conduction disease will affect therapeutic decisions such as safety of concomitant antiarrhythmic drug use and pacemaker mode choice. Electrocardiographic and electrophysiological findings suggestive of significant AV conduction system involvement include a P–R interval greater than 240 milliseconds (ms), complete bundle branch block, development of type 1 second-degree block during atrial pacing at rates of 120 bpm or less, H–V interval prolongation, and second- or third-degree AV block. During follow-up, AV conduction in patients with sick sinus syndrome usually remains stable. In one literature survey of 28 studies of atrial pacing, an annual incidence of second- and third-degree AV block of 0.6% per year was reported. A similarly low incidence (4 of 110 patients) was reported in a prospective trial of atrial versus ventricular pacing in patients with sick sinus syndrome (included were those 70 years of age or younger with P–Q intervals ≤220 ms and those older than 70 years of age with P–Q intervals ≤260 ms); in addition, all patients had normal AV conduction at an atrial pacing rate of 100 bpm at pacemaker implantation.

**FIGURE 12-8**  Panel A, Sinus bradycardia in a young patient with primary electrical disease and syncope seen on a dual-channel Holter monitor recording. Panel B, Sinus pause in the same patient as in panel A with an escape low atrial or junctional rhythm on another dual-channel Holter recording conducted on a different occasion. Escape rhythms may have a rate slow enough to cause symptoms of cerebral hypoperfusion.
The progression of AV conduction disease is thus usually slow and can be detected by careful clinical and electrocardiographic monitoring of these patients. Extrinsic influences, such as exposure to antiarrhythmics or drugs that can block conduction in the AV node, are more frequently responsible for worsening of AV conduction than is progressive degeneration within the conduction system.56,74,75

**SINUS NODE DYSFUNCTION IN ACUTE MYOCARDIAL INFARCTION**

Sinus bradycardia occurs commonly in patients with acute myocardial infarction, especially those with inferior and posterior infarction.74,75 The bradycardia is usually due to stimulation of the afferent vagus nerve terminals, which are more common in the inferior and posterior ventricular walls. This vagal response can be potentiated by pain and by the use of vagotonic medications such as morphine sulfate and can be associated with a vasodepressor response resulting in systemic hypotension. Intravenous atropine usually reverses the vagal effects associated with myocardial infarction.

In addition to autonomic nervous system influences, sinus bradycardia may also be caused by ischemia of the sinus node or atrial tissue, although this diagnosis is rarely made clinically. Sinus node ischemia is also more common in inferior wall myocardial infarction, since the sinus node is usually supplied by the right coronary artery. The clinical manifestations are sinus bradycardia in the majority of cases; however, bradycardia alternating with episodes of supraventricular tachycardia has been reported in up to 35% of patients.76 In the majority of cases, the sinus node dysfunction is temporary and normal sinus rhythm returns during the hospitalization.76,77 Pacemaker implantation is rarely indicated. However, patients who experience alternation of bradycardia and tachycardia occasionally may require long-term antiarrhythmic therapy.76

Both noninvasive and invasive means of diagnosing sinus nodal dysfunction are available. Generally the noninvasive methods of electrocardiographic monitoring, exercise testing, and autonomic testing are used first. However, if symptoms are infrequent, invasive electrophysiological testing may be needed.

**Diagnostic Evaluation**

**NONINVASIVE TESTING**

The diagnosis of sinus nodal dysfunction is rarely made from a random ECG. If symptoms suggestive of sinus node dysfunction are frequent, Holter monitoring may be useful.56,78,79 Documentation of symptoms by the patient in a diary, while wearing the Holter monitor, is essential for correlation of symptoms with the heart rhythm recorded at the time. In many cases, a Holter monitor can exclude sinus nodal dysfunction as the cause of symptoms if normal sinus rhythm is documented during dizziness, presyncope, or syncope. However, sinus bradycardia and sinus pauses may be recorded in asymptomatic individuals, reducing the specificity of these findings for the diagnosis.5,80,81

Event recorders are more useful than Holter monitors in patients with infrequent symptoms. Patient-activated models exist but are limited to patients who have symptoms prolonged enough to record the rhythm during an event. For patients with little to no warning, a loop recorder event monitor can be used. These recorders can be activated as soon as symptoms occur or after the fact, since the last 45 seconds of ECG recording are “frozen.” Newer models that can be automatically triggered by bradycardia or tachycardia are available and useful in some patients. When an ECG diagnosis cannot be recorded by less invasive means, implantable loop recorders are useful in patients with recurrent symptoms suggestive of a bradyarrhythmia.

Exercise testing is of limited value in diagnosing sinus node dysfunction.49 However, it is useful in differentiating patients with chronotropic incompetence from those with resting bradycardia who are able to demonstrate a normal heart rate increase with exercise. Patients with sinus nodal dysfunction and chronotropic incompetence exhibit abnormal heart rate responses to exercise. The increase in heart rate at each stage of exercise may be less than normal, with a plateau seen below the maximum age-predicted heart rate. Other patients may achieve an appropriate peak heart rate during exercise but have slow heart rate acceleration in the initial stage of exercise or a rapid deceleration of heart rate in the recovery stage. These abnormal chronotropic responses can help identify the cause of exercise intolerance in some patients with sinus nodal dysfunction and help determine their pacemaker prescription.82

Autonomic testing of the sinus node includes various pharmacologic interventions and maneuvers to test reflex responses. An abnormal response to carotid sinus massage (pause greater than 3 seconds) indicates carotid sinus hypersensitivity and may suggest the presence of carotid sinus syndrome. This response may also occur in asymptomatic elderly individuals.83 Heart rate response to Valsalva’s maneuver (normally decreased) or upright tilt (normally increased) can also be used to verify that the autonomic nervous system is itself intact.

The most commonly used pharmacologic intervention in the evaluation of sinus node dysfunction is the determination of the intrinsic heart rate.84

A low intrinsic heart rate is consistent with abnormal intrinsic sinus nodal function. A normal intrinsic heart rate in a patient with known clinical sinus nodal dysfunction suggests abnormal autonomic regulation.

**INVASIVE TESTING**

Sinus nodal function can be evaluated invasively with an electrophysiological study. This type of testing is usually reserved for symptomatic patients in whom sinus nodal dysfunction is suspected but cannot be documented in association with symptoms by noninvasive means. The pacing tests most commonly used are the sinus nodal recovery time and SA conduction time.

Pacing the atrium at rates faster than the inherent sinus rate is used to record the sinus node recovery time.
A delay in the return of spontaneous pacemaker activity (overdrive suppression) is a normal finding immediately after cessation of rapid atrial pacing. In patients with sinus nodal dysfunction, however, the sinus node generally takes longer to recover. A better measurement, however, is the corrected sinus nodal recovery time, which is obtained by subtracting the spontaneous sinus cycle length before pacing from the sinus nodal recovery time. Thus, a patient with an abnormally long sinus nodal recovery time could have a normal corrected sinus nodal recovery time if the resting heart rate is slow. The indirect measurement of the corrected sinus nodal recovery time reflects both SA conduction time and sinus automaticity and thus has some limitations. Indirect sinus nodal recovery time measurements can be confounded by sinus nodal entrance block during rapid atrial pacing with resultant shortening of the sinus nodal recovery time and by sinus nodal exit block post pacing, thereby prolonging the measured sinus nodal recovery time. An abnormal sinus nodal recovery time is not found in all patients with sinus nodal dysfunction, partly due to sinus nodal dysfunction not being a homogenous entity from a pathologic standpoint. Despite these limitations, the indirect corrected sinus nodal recovery time is employed frequently in the evaluation of sinus nodal function.

The SA conduction time, another commonly used invasive pacing test, is traditionally measured indirectly from the high right atrium. Several assumptions are used in the calculation, including sinus nodal automaticity not being affected by the premature beat, conduction in and out of the sinus node being equal, and the premature atrial beat not causing a shift in the principal pacemaker site. An additional limitation of the sinoatrial conduction time test is the need for a regular cycle length in sinus rhythm. Sinus arrhythmia may make calculation of the SA conduction time by this method impossible.

Clinical Electrophysiology

Electrophysiological testing for sinus node dysfunction is usually reserved for patients with significant symptoms suspicious for sinus node disease in whom a documented association between symptoms and sinus node abnormalities cannot be established by noninvasive testing. The three most common tests to assess sinus node dysfunction are sinus node recovery time, SA conduction time, and assessment of intrinsic heart rate. When used together, these tests have a sensitivity of 65% to 70% and a specificity of approximately 90%. A negative test result does not exclude sinus node dysfunction, whereas a positive test result strongly favors intrinsic sinus node disease.

Table 12-1

<table>
<thead>
<tr>
<th>Reference</th>
<th>SNRT (ms)</th>
<th>CSNRT (ms)</th>
<th>SACT (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breithardt</td>
<td>&lt;1480</td>
<td>&lt;508</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Mandel</td>
<td>1040 ± 56</td>
<td>&lt;525</td>
<td>45-125</td>
</tr>
<tr>
<td>Delius</td>
<td>&lt;1400</td>
<td>&lt;550</td>
<td>68-156</td>
</tr>
<tr>
<td>Josephson</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strauss</td>
<td>&lt;1500</td>
<td>&lt;550</td>
<td>&lt;125</td>
</tr>
</tbody>
</table>

SNRT, corrected sinus node recovery time; ms, milliseconds; CSNRT, corrected sinus node recovery time; SACT, sinoatrial conduction time; SNRT, sinus node recovery time.
However, patients with documented sinus node disease have a high incidence of falsely negative SNRTs during electrophysiological testing. Thus, the test has a low sensitivity but high specificity.

**Sinoatrial Conduction Time**

An indirect method to evaluate SA conduction is the response to induced atrial premature depolarizations (APDs, Figs. 12-10 and 12-11). This test assesses the effect of APDs on the timing and duration of the sinus cycle. The method, devised by Strauss, involves scanning the entire sinus cycle (A1A1) with programmed stimulation of single APDs delivered in the high right atrium near the sinus node. After approximately every eighth to tenth beat of a stable sinus rhythm, the premature beat is delivered with a gradual decrease in the coupling interval (A1A2), and the subsequent response of the next sinus return cycle (A2A3) is measured. The subsequent results are often plotted on a graph (see Fig. 12-10) comparing the timing of the atrial premature beat (A1A2) with the first sinus return cycle (A2A3). The response of the sinus node falls into four different zones (see Fig. 12-11): (1) collision; (2) reset; (3) entrance block or interpolation; and (4) reentry.

Zone 1 is referred to as the zone of collision, interference, or nonreset, since the mechanism of the response is due to a collision of the stimulated atrial impulse (A2) with the spontaneous sinus impulse (A1). In this zone, the return cycle intervals (A2A3) are fully compensatory with A1A2 plus A2A3 being equal to 2 times A1A1. This response usually occurs when APDs fall in the last 20% to 30% of the spontaneous cycle length. The sinus pacemaker is unaffected by A2, and the subsequent beat occurs “on time.”

Zone 2 is referred to as the reset zone, in which the spontaneous cycle length (A2A3) following the premature beat remains constant, producing a plateau in the curve. In this zone, the premature beat (A2) causes reset of the sinus pacemaker, resulting in a recovery cycle (A2A3) that exceeds the basic sinus cycle. However, the subsequent return cycle causes less than a compensatory pause with the sum of A1A2 and A2A3 being less than 2 times A1A1. Zone 2 typically occupies 40% to 50% of the cardiac cycle, and the plateau results from A2 entering the sinus node and resetting the pacemaker.
but having no effect on pacemaker automaticity. It has been assumed that conduction into and out of the sinus node is equal. The conduction from the sinus node to the atrium is the SA conduction time and is calculated as the A2A3 interval that results in reset minus the A1A1 interval divided by 2. However, isolated studies have shown that this assumption is not entirely correct and that conduction time out of the sinus node is greater than conduction time into the sinus node. This has also been confirmed by direct recording of the sinus node electrogram.

Despite this and other limitations, the SA conduction time is reasonably estimated by the introduction of APDs when a true plateau is present in Zone 2. The measurement of SA conduction time is considered normal if it is less than 125 ms. Errors in the measurement of SA conduction time may occur if sinus arrhythmia is present, a slow increase in the plateau due to a shift to slower sinus node pacemaker cells occurs, or there is an increase in conduction time into the sinus node due to refractoriness of the atrial tissue surrounding the node.

In Zone 3 (interpolation) and Zone 4 (reentry), the return cycle (A2A3) is shorter than the spontaneous sinus cycle (A1A1) in response to the premature beat (A2). The response in Zone 3 is due to interpolation and results from the premature beat encountering refractoriness of the tissue surrounding the sinus node, resulting in sinus node entrance block. SA conduction time is an insensitive indicator of sinus node disease, but a positive test can help establish sinus node dysfunction.

**Other Tests to Assess Sinus Node Dysfunction**

Direct recording of sinus node electrograms and the measurement of intrinsic sinus node function following autonomic blockade have both been reported for assessing patients with suspected sinus node dysfunction. Sinus node electrograms are recorded using catheters with 0.5 to 1.5 cm interelectrode distance positioned at the junction of the superior vena cava and right atrium in the region of the sinus node or a catheter looped in the right atrium, allowing firm contact in the region of the superior vena cava and junction with the atrium. Sinus node recordings can be obtained in 40% to 90% of patients studied but do take time and experience (Fig. 12-12). The high pass filter is usually between 0.1 and 0.6 Hz, the low pass filter between 20 and 50 Hz,
and the signal gained at a range of 50 to 100 microvolt/cm. Using this approach, Josephson reports obtaining stable sinus node electrograms in only 50% of an unselected population of patients. Studies of patients with sinus node dysfunction that compare both the indirect and direct methods show a good correlation between the directly measured SA conduction time and that made by indirect techniques using the introduction of APDs.

Autonomic blockade has been used to determine the intrinsic heart rate (IHR) using a combination of atropine and β-blockers. This testing assumes that autonomic blockade will remove the autonomic effects on sinus node function and unveil unmodulated sinus node activity. A pharmacologic denervation is achieved using propranolol, 0.2 mg/kg, and atropine, 0.04 mg/kg, to identify the IHR. The effects usually peak after 5 minutes, and the measurement of IHR is age dependent and defined by the regression equation:

$$IHR = 117.2 - (0.53 \times \text{age}) \text{ bpm}$$

The IHR helps to distinguish patients with true sinus node dysfunction from those with enhanced parasympathetic tone. Additional studies have demonstrated that the response to atropine provides as much information as the combined response to atropine plus β-blockade.

The direct electrogram used to record sinus node activity is difficult to obtain, and the technique is rarely used in the clinical electrophysiology laboratory. Similarly, measurement of IHR following autonomic blockade is infrequently used.

**EFFECTIVENESS OF DRUGS ON ASSESSMENT OF SINUS NODE FUNCTION**

Digoxin shortens the SNRT in patients with clinical sinus node dysfunction. This is possibly related to an increase in refractoriness in the atrial tissue surrounding the sinus node, creating SA entrance block. In this situation, fewer atrial-paced beats would enter the sinus node to suppress sinus node function. Propranolol has been demonstrated to increase the SNRT, possibly by decreasing sinus node automaticity. Verapamil and diltiazem have been shown to have minimal effects on sinus node function in normal persons. Antiarrhythmic drugs can adversely affect sinus node function in patients with evidence of sinus node disease but, in general, have minimal effects on sinus node function in normal persons. In general, electrophysiological assessment of sinus node function should not be performed in the presence of drugs known to affect sinus node activity, including digoxin, β-blockers, calcium channel antagonists, and antiarrhythmic drugs. Such drugs may exacerbate sinus node function in patients with sinus node disease and may also adversely influence sinus activity in otherwise normal patients.

**Management of patients with sinus node disease is most appropriately conducted using clinical, electrocardiographic, and long-term monitoring information. Electrophysiological testing of sinus node function infrequently adds important contributions to the care of patients with sinus node disease. A normal test result does not exclude the diagnosis of sinus node disease, and an abnormal test is not itself an indication for pacing in an asymptomatic patient. Drugs have an important effect on sinus node automaticity and atrial refractoriness and can exacerbate sinus node function in the presence of SA disease.**

**Evidence-Based Therapy**

During the past decade, the importance of making clinical decisions on the basis of evidence from clinical trials has been emphasized in clinical medicine. This section reviews the available information from clinical trials on the efficacy of pacing therapy and the effects of pacing mode selection in patients with sinus node dysfunction.
EFFECTIVENESS OF PACING THERAPY

There is only a single published study evaluating the effectiveness of pacing therapy versus no therapy or pharmacologic therapy for preventing symptoms in patients with sinus node dysfunction. In the THEOPACE study, 107 patients with presumed sinus node dysfunction (older than 45 years of age with a mean resting sinus rate < 50 bpm or intermittent sinoatrial block, or both, noted during a diurnal ECG on two separate occasions, and symptoms thought to be secondary to sinus node dysfunction) were randomized to no treatment, oral theophylline, or dual-chamber rate-adaptive pacing. Patients with severe sinus node dysfunction, defined as symptomatic heart rates less than 30 bpm or sinus pauses greater than 5 seconds, were excluded. After an average 18-month follow-up, syncope had occurred in 6% of patients who received pacing therapy and 17% and 23% in the theophylline and control arms, respectively. In all three groups the incidence of atrial tachycardias was similar (26% to 28%). THEOPACE demonstrates that pacing therapy provides symptomatic benefit in patients with sinus node dysfunction. However, it is unlikely that pacing therapy confers a survival benefit, since natural history studies suggest that sinus node dysfunction by itself does not appear to be associated with an increased risk of death.55

PACING MODE CHOICE

In patients with sinus node dysfunction, bradycardia can be prevented by single-chamber ventricular pacing (VVI mode), single-chamber atrial pacing (AAI mode), or dual-chamber pacing (DDD mode). Several randomized studies have evaluated the effects of pacing mode in patients with sinus node dysfunction. The first prospective study, initially published in 1994 with follow-up data presented in 1997 and 1998, evaluated 225 patients with sinus node dysfunction who were randomized to single-chamber atrial pacing or single-chamber ventricular pacing. After a mean follow-up of 3.3 years, atrial pacing was associated with a significant decrease in thromboembolic events (atrial pacing: 5.5%; ventricular pacing: 17.4%) and a nonsignificant reduction in atrial fibrillation (atrial pacing: 14%; ventricular pacing: 23%). In addition, progression of heart failure symptoms was observed in 9% of patients in the atrial pacing group and 31% of the ventricular pacing group. In the Pacemaker Selection in the Elderly (PASE) trial 407 elderly patients (mean age, 76 years) were randomized to either the VVIR or DDDR pacing mode with a mean follow-up of 30 months. In the 175 sinus node dysfunction patients enrolled, the DDDR pacing mode was associated with improved cardiovascular functional status and better quality-of-life scores in the role physical, role emotion, and social function categories of the SF-36 questionnaire. The DDDR pacing mode was associated with insignificant reductions in mortality (DDDR, 12%; VVIR, 20%) and incidence of atrial fibrillation (DDDR, 19%; VVIR, 28%). For the entire study group, 26% of patients crossed over from the VVIR pacing mode to the DDDR pacing mode because of symptoms related to pacemaker syndrome. The Canadian Trial of Physiologic Pacing (CTOPP) evaluated the effects of pacing mode choice in patients with symptomatic bradycardia. The 2568 patients were randomized to single-chamber ventricular pacing or a “physiologic” pacing mode that preserved AV synchrony (single-chamber atrial pacing or dual-chamber pacing). While no significant difference in the annual rate of stroke or death was detected (ventricular pacing, 5.5%; physiologic pacing, 4.9%), the annual rate of atrial fibrillation was significantly lower in the physiologic pacing group (ventricular pacing, 6.6%; physiologic pacing, 5.3%). The reduction in atrial fibrillation became more apparent 2 years after initial randomization. Details on the 40% of patients with sinus node disease not actually still in a physiologic pacing mode, and only 75% of patients randomized to physiologic pacing were actually still in a physiologic pacing mode. Finally, in the Mode Selection Trial (MOST), 2010 patients with sinus node dysfunction were randomized to dual-chamber pacing or single-chamber ventricular pacing. After a 5-year follow-up, no differences in mortality or stroke were detected, but there was a marked reduction in progression to atrial fibrillation, particularly in patients without a prior history of the arrhythmia; however, the crossover rate to dual chamber pacing was 31% due to symptoms of the pacemaker syndrome, and dual-chamber pacing was associated with improved quality of life.

Thus, available data suggest that pacing modes that preserve AV synchrony are associated with a reduced incidence of atrial fibrillation, particularly after several years. In addition, preservation of AV synchrony is associated with improved quality of life and a reduction in the incidence of pacemaker syndrome.

Management

The first step in the evaluation and management of patients with sinus node dysfunction is to exclude physiologic sinus bradycardia due to extrinsic conditions affecting the sinus node or sinoatrial tissue: β-blockers, some calcium channel blockers (verapamil and diltiazem), digoxin, and other medications having sympatholytic activity can result in sinus node dysfunction. It is therefore important to carefully review all medications taken by the patients, since withdrawal of offending agents usually results in restoration of normal sinus function. Other causes of extrinsic sinus node dysfunction should be investigated and excluded; these include hypothyroidism, sleep apnea, and other systemic diseases. The specific situation in which the bradycardia occurs should be analyzed in order to document bradycardia triggered by an increase in vagal tone, such as...
occurs during suctioning or vomiting. Whenever possible, treatment should be directed toward correcting the extrinsic condition causing bradycardia.

GUIDELINES FOR MANAGEMENT OF PATIENTS WITH INTRINSIC SINUS NODE DYSFUNCTION

When intrinsic sinus node dysfunction is suspected, it is important to attempt to correlate symptoms with documentation of the arrhythmia, since sinus node dysfunction is common, especially in elderly patients, and may not cause symptoms. The intermittency of symptoms and ECG features characteristic of the syndrome may result in difficulty in establishing a cause/effect relationship. A Holter monitor or event recorder may be useful to establish the diagnosis, but prolonged monitoring may be required. In selected cases, an implantable loop recorder that continuously acquires electrocardiographic signals can be used. Krahn et al. placed implantable loop recorders in 16 patients with syncope and negative electrophysiological and tilt table tests. Fifteen of the patients had recurrent syncope, and sinus arrest was documented in five patients. Invasive electrophysiological studies are usually not required to specifically evaluate sinus node function.

Therapy is aimed at improving symptoms. There is no evidence that medical therapy or pacemaker implantation improves survival; this is in part likely due to the low mortality rate related to the bradyarrhythmia per se.

INDICATIONS FOR PERMANENT PACING

Pharmacologic therapy for bradycardia due to sinus node dysfunction is generally ineffective; pacemaker implantation is therefore the optimum therapy. In the United States, sinus node dysfunction is the most common indication for pacemaker implantation. The benefit to be expected from permanent pacing depends largely on the appropriateness of the indication.

Guidelines for pacemaker implantation in sinus node dysfunction have been published. Indications for permanent pacing in sinus node disease are summarized in Table 12-2. The guidelines emphasize the importance of correlating symptoms and bradycardia whenever possible. The principal benefits of pacing therapy are prevention of syncope, improvement of symptoms due to poor tissue perfusion, and congestive heart failure due to decreased cardiac output caused by slow heart rates. In an observational series of severely symptomatic patients from the 1970s, pacemaker therapy improved symptoms of fatigue, lightheadedness, and near syncope. In a randomized trial from the 1990s conducted to assess the efficacy of pacemakers in patients with sick sinus syndrome, the occurrence of syncope was lower in the paced group over a mean follow-up duration of 18 months (6% versus 23% for controls; \( P = .02 \)). Heart failure also occurred less often in patients assigned to pacemaker therapy (3% versus 17%; \( P = .05 \)), whereas the incidence of sustained paroxysmal tachyarrhythmias, chronic atrial fibrillation, and thromboembolic events were not different between the groups. Compared with observational series and retrospective studies, pacemaker implantation in this randomized trial did not demonstrate different effects on “minor” symptoms such as fatigue, dizziness, palpitation, and New York Heart Association class compared with the “no-treatment” group; this was due to subjective improvement occurring in the placebo group as early as 3 months following randomization.

In some patients, the bradycardia may be iatrogenic and exacerbated by medications used to treat supraventricular tachycardias. If these medications constitute

<table>
<thead>
<tr>
<th>Class</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>Sinus node dysfunction with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. In some patients, bradycardia is iatrogenic and will occur as a consequence of essential long-term drug therapy of a type and dose for which there are no acceptable alternatives.</td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
<td>Sinus node dysfunction occurring spontaneously or as a result of necessary drug therapy with a heart rate &lt;40 bpm when a clear association between symptoms consistent with bradycardia and actual presence of bradycardia has not been documented.</td>
</tr>
<tr>
<td><strong>Class IIb</strong></td>
<td>Syncope of unexplained origin when major abnormalities of sinus node function are discovered or provoked in electrophysiological studies.</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>Minimally symptomatic patients, chronic heart rate &lt;40 bpm while awake. Sinus node dysfunction in asymptomatic patients, including those in whom substantial sinus bradycardia (heart rate &lt;40 bpm) is a consequence of long-term drug treatment. Sinus node dysfunction in patients with symptomatic bradycardia that are clearly documented as not associated with a slow heart rate. Sinus node dysfunction with symptomatic bradycardia due to nonessential drug therapy.</td>
</tr>
</tbody>
</table>

**Class I:** conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective.

**Class IIa:** conditions for which there is conflicting evidence or a divergence of opinion, or both, about the usefulness/efficacy of a procedure or treatment.

**Class IIb:** usefulness/efficacy is less well established by evidence/opinion.

**Class III:** conditions for which there is evidence or general agreement, or both, that a procedure/treatment is not useful/effective and, in some cases, may be harmful.

the only alternative for management of the tachycardia, and if the patients are symptomatic from the bradycardia, they should receive permanent pacing. However, if the bradycardia does not produce symptoms, the rhythm per se is not an indication for pacing.

The published guidelines also take into consideration the erratic course of the disease and the difficulty in establishing the cause-effect relationship between symptoms and arrhythmia. Accordingly, pacing is considered useful in patients with heart rates less than 40 bpm who have symptoms consistent with bradycardia, but in whom the correlation between the two cannot be clearly established. Pacing is not indicated in asymptomatic patients with bradycardia due to nonessential medical therapy, and when symptoms are clearly documented not to be caused by bradycardia.

Permanent pacing is indicated in patients with chronotropic incompetence who become symptomatic during activity because of inability to increase heart rate and cardiac output. These patients have an improvement in symptoms and exercise tolerance with rate-responsive pacing.9,96

PACING MODE SELECTION

Single-chamber atrial pacemakers, single-chamber ventricular pacemakers, and dual-chamber pacemakers will all prevent bradycardia in the patient with sinus node disease. Each pacemaker type is associated with inherent advantages and disadvantages. Single-chamber atrial pacemakers are simple, relatively inexpensive (approximately $3000 to $4000), and maintain AV synchrony. However, they will not prevent ventricular bradycardia if AV block develops. Up to 20% of patients will have abnormal AV conduction at the time of diagnosis of sinus node dysfunction; these patients are not candidates for single-chamber atrial pacing.50 In a prospective study of 225 patients with 1:1 conduction at heart rates less than 100, Andersen et al. found that AV conduction was unchanged from initial evaluation after a mean 5.5-year follow-up.69 The annual incidence of second- and third-degree AV block that required implantation of a dual-chamber pacing system was only 0.6% per year.69

Single-chamber ventricular pacemakers are also simple and inexpensive. They prevent bradycardia in the presence of AV block but do not maintain AV synchrony. Loss of AV synchrony is associated with a 20% to 30% decrease in cardiac output and is associated with “pacemaker syndrome.”108 Pacemaker syndrome is a constellation of symptoms that can include dizziness, chest pain, weakness, effort intolerance, presyncope, and syncope. The mechanism of pacemaker syndrome is complex but appears to be due to decreased cardiac output from loss of AV contraction and retrograde conduction through the His-Purkinje–AV node axis. Reduced cardiac output leads to reflex sympathetic activation. Atrial contraction when the mitral and tricuspid valves are closed also leads to an increase in atrial pressure and release of atrial natriuretic peptide and peripheral venous and arterial dilation. The reported incidence of pacemaker syndrome has varied widely among studies (1% to 80%), which probably reflects variability in definition rather than a true variability in incidence.107,106 In the large randomized trials such as PASE and MOST, crossover from single-chamber ventricular pacing to dual-chamber pacing due to pacemaker syndrome was approximately 25% to 30%.101,10,111

Dual-chamber pacemakers maintain AV synchrony and prevent bradycardia from all causes. However, dual-chamber pacemakers are more complex and relatively expensive ($5000 to $7000). In addition, since two intracardiac leads are required, the incidence of lead dislodgement is higher for dual-chamber systems (dual-chamber, 6%; single-chamber, 2%).

Currently available pacing systems have a rate-adaptation feature. When rate adaption is programmed “on,” the pacing system employs a sensor such as body motion, minute ventilation, Q–T interval changes, or combinations of these to estimate metabolic need. The pacemaker will change the pacing rate depending on input from the sensor. This feature is particularly useful for patients with sinus node dysfunction associated with chronotropic incompetence. Pacemakers have monitoring capabilities that allow the clinician to evaluate the range of heart rates a patient has over a specific interval of time. If a blunted range of atrial rates is recorded, the presence of chronotropic incompetence should be suspected.

Sinus Node Dysfunction in Specific Conditions

ACUTE MYOCARDIAL INFARCTION

Sinus bradycardia is common in acute myocardial infarction, especially in inferior and posterior wall infarction, where it is usually due to increased vagal tone or ischemia of the SA tissue.16,17 Increased vagal tone may also result in transient AV block and hypotension from peripheral vasodilatation. This arrhythmia usually does not require treatment unless the patient is symptomatic (hypotension, ischemia, or bradycardia-related ventricular arrhythmia). It usually responds well to intravenous atropine. In symptomatic patients who are unresponsive to atropine or who have recurrences requiring multiple doses of atropine, temporary transvenous pacing may be required. Pacing is usually performed at the right ventricular apex, but where it is important to maintain AV synchrony (such as refractory hypotension), an additional “J”-shaped electrode can be placed in the right atrial appendage for dual-chamber pacing. Alternatively, atrial pacing can be achieved using a temporary electrode positioned in the proximal coronary sinus. Sinus node dysfunction occurring during acute myocardial infarction is usually temporary, and permanent pacing is rarely required.76,77

CAROTID SINUS HYPERSENSITIVITY AND CAROTID SINUS SYNDROME

An abnormal response to carotid sinus massage (>3 seconds of asystole) may occur in asymptomatic patients
and does not constitute an indication for therapy; correlation with symptoms is essential. Up to 64% of patients with syncope caused by a hypersensitive carotid syndrome can remain asymptomatic during follow-up; therapy should be reserved for patients with recurrent presyncope or syncope. Drugs that can enhance the hypersensitive response to carotid sinus massage, such as digoxin and sympatholytics (clonidine, methyldopa), should be discontinued if possible.

The type and success of therapy (pacing versus pharmacologic) are based on the mechanism of syncope. Pacing is efficacious in the cardioinhibitory response to carotid sinus massage. In patients with a predominant vasodepressor response, neither pacing nor anti-cholinergic agents prevent the fall in blood pressure, since this is caused by inhibition of sympathetic vasocostrictor nerves as well as by activation of cholinergic sympathetic vasodilator fibers. Elastic support stockings and volume expansion with sodium-retaining drugs may be useful for ameliorating symptoms.

Recent data suggest that unexplained falls in the elderly might be due to carotid sinus hypersensitivity, and that in some cases pacing therapy may be beneficial. A selected group of 175 patients with a history of nonaccidental falls and significant bradycardia (asystole >3 seconds) in response to carotid sinus massage were randomized into pacing-therapy and no-pacing-therapy groups; after a 1 year follow-up, injurious events were reduced by 70% in the pacing-therapy group.

The indications for permanent pacing in the carotid sinus syndrome are summarized in Table 12-3. Single-chamber atrial pacing is contraindicated, since vagal activation frequently results in AV block and absence of a ventricular escape rhythm. Although single-chamber ventricular pacing prevents bradycardia, it can potentially exacerbate symptoms due to the neurohormonal effects associated with the pacemaker syndrome. Dual-chamber pacing is therefore preferred, since it maintains AV synchrony regardless of the cause of bradycardia. In addition, the current generation of dual-chamber pacing systems allows programming of different heart rates after sensed and paced ventricular beats (hysteresis). By programming a pacemaker to pace at a relatively fast rate on initiation of pacing, symptoms associated with carotid sinus syndrome can be ameliorated even in the presence of a significant vasodepressor response.

### TABLE 12-3 Indications for Permanent Pacing In Hypersensitive Carotid Syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of &gt;3 sec duration in the absence of any medication that depresses the sinus node or atrioventricular conduction</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Significantly symptomatic and recurrent neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt table testing</td>
</tr>
<tr>
<td>Class III</td>
<td>None</td>
</tr>
</tbody>
</table>

**Class I:** conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective.  
**Class II:** conditions for which there is conflicting evidence or a divergence of opinion, or both, about the usefulness/efficacy of a procedure or treatment.  
**Class III:** usefulness/efficacy is less well established by evidence/opinion.  
**Class IIb:** weight of evidence/opinion is in favor of usefulness/efficacy.  
**Class III:** conditions for which there is evidence or general agreement, or both, that a procedure/treatment is not useful/effective and, in some cases, may be harmful.


**VASOVAGAL SYNCOPE**

Vasovagal syncope is the most common cause of syncope in young people. Lewis, in 1932, used the phrase “vasovagal” to emphasize the combination of arterial vasodilation and bradycardia associated with this syndrome. While the exact mechanism of vasovagal syncope is not known, it does appear that activation of cardiac mechanoreceptors leads to activation of higher neural centers and reflex withdrawal of sympathetic tone and increased vagal tone.

The most common cause for bradycardia in vasovagal syncope is sinus bradycardia or sinus arrest. For this reason, although they do not affect the vasodepressor component of this syndrome, pacemakers have been used to treat the subset of patients that has particularly severe symptoms unresponsive to drug therapy. Two relatively large randomized studies have evaluated the efficacy of pacing therapy for the treatment of vasovagal syncope. In the North American Vasovagal Pacemaker Study (VPS-I), 54 patients with severe vasovagal syncope and relative bradycardia (trough heart rate <60 bpm during tilt table testing) were randomized to pacing or no pacing. The study was terminated after 2 years when analysis showed that pacing was associated with an 85% decrease in syncopal episodes. Similarly, in the Vasovagal Syncope International Study (VASIS-I), 42 patients with severe drug refractory vasovagal syncope were randomized to pacing or no pacing. Only one patient in the pacing group had syncope, while 14 patients in the no-pacing group had syncope during a mean 3.7-year follow-up. More recently, VPS-II found...
a 30% risk reduction in time to syncope with DDD pacing (P = .14), which was considerably lower than in previous studies. Patients who require pacing therapy for drug-resistant vasovagal syncope should receive a dual-chamber pacemaker, because transient AV block can be observed during bradycardia episodes. Special programming features that provide an initial higher pacing rate when pacing is initiated have been developed to optimize pacing therapy for patients with vasovagal syncope. More recent studies such as VASIS-II are under way to evaluate the effectiveness of these features.

REFERENCES

34. Shibata EF, Giles WR: Ionic currents that generate the spontaneous diastolic depolarization in individual cardiac pacemaker cells. Proc Natl Acad Sci USA 1985;82:7796-7800.


113. Richardson DA, Bexton RS, Shaw FE, Kenny RA: Prevalence of cardioinhibitory carotid sinus hypersensitivity in patients 50 years or over presenting to the accident and emergency department with "unexplained" or "recurrent" falls. Pacing Clin Electrophysiol 1997;20:820-3.


In 1852, Stannius noted that placing a ligature between the atria and ventricles could cause bradycardia in a frog’s heart. In the late 1800s Tawara and His identified the atrioventricular (AV) node and His bundle as the normal conduction axis between the atria and ventricles in humans, and Wenckebach suggested blocked AV conduction as a cause for slow and irregular pulses.

Epidemiology of Atrioventricular Block

Transient AV block can be observed in children and young adults during sleep; persistent AV block is unusual. This AV block is usually due to increased vagal tone and is often a normal finding. In a continuous monitoring study of 100 healthy teenaged boys, transient first-degree AV block was observed in 12% and second-degree AV block in 11% of the population. In young adults the incidence of transient AV block decreases to about 4% in women and 6% in men. In the normal elderly population, transient type I (Wenckebach) second-degree AV block is seen only rarely (1%), and higher-grade AV block is not observed.

Persistent first-degree AV block is rarely seen in young adults. Review of more than 70,000 ECGs from young men entering the Canadian and U.S. military demonstrated a prevalence of first-degree AV block of less than 1%. Electrocardiographic studies have shown increased P–R intervals and an increased incidence of first-degree AV block with aging. While approximately 2% of adults older than 20 years of age have first-degree AV block, the incidence increases to more than 5% in people older than 50 years of age. With increasing age, the development of AV conduction disorders is more common; in one epidemiologic study of 1500 patients older than 65 years of age, AV conduction and intraventricular conduction defects were identified in 30% of patients. Using high-resolution ECG techniques, the increased P–R interval associated with aging is due to delay in conduction in the AV node or the proximal portion of the His bundle. It is uncommon (4%) for persistent first-degree AV block to progress to second-degree or higher-grade AV block in the absence of associated disease in people younger than 60 years of age.

Acquired persistent second-degree and third-degree AV blocks are almost never observed in normal populations regardless of age. The incidence of symptomatic high-grade AV block is currently estimated to be 200/million per year.

Isolated congenital complete (third-degree) AV block is a well-described problem that occurs in approximately 1 in every 20,000 live births. Congenital complete AV block is the most common manifestation of neonatal lupus erythematosus and appears to be associated with the development of autoantibodies in the maternal circulation. Other hereditary conditions associated with AV block are the Kearns-Sayre syndrome (ophthalmoplegia, retinitis pigmentosa) and myotonic dystrophy.

Anatomy of the Atrioventricular Bundle

The anatomy of the AV node, bundle of His, and the atrioventricular connections have been substantially redefined. In early studies Truex and Smythe described extensions of the compact AV node that connected to atria, the most prominent of which was directed to the coronary sinus ostium. Anderson and colleagues
described zones of cellular aggregation at the atrium-AV nodal transition region as superficial, deep, and posterior (Fig. 13-1). Racker described superior, medial, and posterior atrionodal bundles that converged into the compact node. The properties of these atrionodal bundles differed from working atrial myocardium. For a more detailed discussion of this subject, see Chapter 14.

Pathology of Atrioventricular Block

Complete AV block may be viewed from an etiologic standpoint as falling into two major categories: congenital and acquired. On the other hand, from an electrophysiologic standpoint, AV block may be classified according to the location of the block with reference to the AV bundle. Thus, AV block may occur proximal to the bundle of His recording site, within the bundle of His (intra-Hisian), or distal to the bundle of His recording site. Pathologically, AV block can be considered as being due to or occurring in association with various disease states: (1) congenital heart disease; (2) coronary artery disease; (3) hypertensive heart disease; (4) sclerosis of the left side of the cardiac skeleton (i.e., idiopathic or primary AV block); (5) aortic valve disease; (6) collagen diseases; (7) myocarditis; (8) infective endocarditis; (9) iatrogenic; (10) tumors of the heart; and (11) miscellaneous diseases and altered physiologic states (Table 13-1).19-25

### CONGENITAL ATRIOVENTRICULAR BLOCK

Congenital AV block may occur in any type of a congenital heart disease or it may occur in an otherwise normal heart.19-25 Pathologically, there are four types of congenital AV block: lack of connection between the atria and the peripheral conduction system; interruption of the AV bundle; bundle branch disease; and abnormal formation and interruption of the AV bundle.

### LACK OF CONNECTION BETWEEN THE ATRIA AND THE PERIPHERAL CONDUCTION SYSTEM

This is the most common type of congenital AV block that is seen either with or without an associated congenital cardiac anomaly.19-25 In this type of block, the

### TABLE 13-1 Causes of Complete Heart Block

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
<th>Degenerative</th>
<th>Fibrosis and calcification</th>
<th>Ischemia and infarction</th>
<th>Medications</th>
<th>β-Blockers</th>
<th>Calcium channel blockers</th>
<th>Clonidine</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
<td>Degenerative</td>
<td>Fibrosis and calcification</td>
<td>Ischemia and infarction</td>
<td>Medications</td>
<td>β-Blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
<td>Lithium</td>
</tr>
</tbody>
</table>

### FIGURE 13-1 Schematic diagram of the atrionodal junctional region and the atrioventricular node and surrounding anatomic structures in the human heart. LBB, left bundle branch; RBB, right bundle branch. (Reproduced from Anderson et al: The human atrioventricular junctional area: A morphological study of the AV node and the bundle. Eur J Cardiol 1975;3:11.)
myocardium in the distal part of the atria is absent either completely or in part and is replaced by fat, vascular channels, calcification at times, and mononuclear cells with fibrosis (Fig. 13-2). The AV node is usually deficient or abnormally formed and has no continuity with the surrounding atrial myocardium. In extreme forms, the AV node may be totally absent. In still other forms, there may be remnants of nodal cells within the central fibrous body. In some cases, the penetrating AV bundle may be deficient as well. The block is thus proximal to the bundle of His recording site. The remainder of the conduction system is usually normal. Congenital AV block in an otherwise normally developed heart may permit survival to the fourth or fifth decade of life.\textsuperscript{19-25}

\textbf{INTERRUPTION OF THE BEGINNING OF THE BUNDLE BRANCHES}

This may be a familial form of AV block with beginning of the bundle branches replaced by empty spaces, fat and fibrous tissue. This is a rare type of a bundle branch disease resulting in complete AV block.\textsuperscript{19-21,23,24}

\textbf{ABNORMAL FORMATION AND INTERRUPTION OF ATROVENTRICULAR BUNDLE}

Interruption in an aberrant conduction system is seen in corrected transposition of the heart (mixed levocardia with ventricular inversion), in which the atria are situated more or less normally. This may be associated with congenital AV block. The block may be due to either deficiency or absence of the AV node and the surrounding myocardium or interruption within the penetrating or branching bundle, or both. In corrected transposition, in most cases, the AV bundle is situated anterosuperiorly in the morphologically left ventricle in an abnormal location, making it vulnerable to hemodynamic stresses, thereby resulting in interruption.\textsuperscript{19-21,23,24}

Congenital AV block may occur in any type of congenital heart disease; however, in corrected transposition there is an increased incidence for its development. Usually, there is absence of the AV node and the surrounding atrial myocardium, with infiltration of mononuclear cells, calcification, fibrosis, and fat.\textsuperscript{19,24}

\textbf{ACUTE MYOCARDIAL INFARCTION—CORONARY ARTERY DISEASE}

Complete AV block may occur in association with acute or chronic coronary artery disease. In acute myocardial infarction, a distinction must be made between anterior and posterior wall infarction.\textsuperscript{19-25,26-29}

In posteroseptal wall myocardial infarction, there may be infarction of part of the sinoatrial node and its approaches, as well as the approaches to the AV node, with focal necrosis of the node and the bundle. In some cases there may not be any obvious pathologic change within the conduction system, whereas in others, there may or may not be changes in the AV bundle and the bundle branches.

In contrast to posteroseptal wall infarction, in infarction of the anteroseptal wall, the branching bundle and the bundle branches are usually affected by the necrotic process. The AV node and the penetrating part of the AV bundle may be involved in the infarction as well. The infarction is usually extensive in nature; however, if the patient recovers, the heart block usually resolves.

Chronic AV block after acute myocardial infarction is
decidedly uncommon. Thus, the site of infarction is more important than the site of coronary artery occlusion in producing lesions in the conduction system.

**CHRONIC CORONARY INSUFFICIENCY**

Chronic coronary insufficiency, with or without previous myocardial infarction, may affect various portions of the conduction system, predominantly the bundle branches that may, over time, progress to complete AV block. In chronic coronary insufficiency, in addition to an ischemic factor, there are aging changes in the conduction system in the form of sclerosis of the left side of the cardiac skeleton; there may be an abnormal formation of the AV bundle itself. In addition, there may be associated small vessel disease (arteriolosclerosis). Thus, in chronic coronary insufficiency, several mechanisms may play a role in the pathogenesis of AV block. In general, in chronic ischemia, the right bundle branch is replaced by fibrous tissue; the left bundle branch fibers are replaced by both the chronic ischemic process and other factors such as a degeneration. For example, calcific mass at the summit of the interventricular septum can impinge upon the branching AV bundle and the origin of the main left bundle branch (Fig. 13-3).

The fibrosis of the left bundle branch is probably related to both mechanical factors produced by the calcific impingement, as well as chronic coronary insufficiency. Clinically, there may be chronic right bundle branch block or left bundle branch block that may progress to chronic complete AV block. In some cases, small vessel disease within the ventricular septum in the absence of major coronary artery disease may cause destruction of the branching bundle and the bundle branches. Chronic coronary insufficiency is the most common cause of bilateral bundle branch block.19-21,23,24,26-29

**HYPERTENSIVE HEART DISEASE**

Arteriolosclerosis (small vessel disease) of the heart is frequently present in hypertensive patients, with consequent conduction disturbances in the form of arteriolosclerosis of the sinoatrial node, AV node, AV bundle, and bundle branches. The pathologic effects of hypertensive heart disease on the conduction system are related to the mechanical forces as well as the arteriolosclerosis process. Since the branching AV bundle is a subendocardial and superficial structure, it is vulnerable to the mechanical stress and strain on the fibrous skeleton of the heart produced by hypertensive heart disease. Since hypertensive heart disease affects the entire heart, the pathologic changes and arteriolosclerosis in the sinoatrial node, AV node, AV bundle, and the bundle branches will result in various types of arrhythmias, such as sinus node dysfunction and right or left bundle branch block or complete AV block.19-21,23,24,26-29

**AGING CHANGES IN THE SUMMIT OF THE VENTRICULAR SEPTUM**

With advancing age, the summit of the ventricular septum, the membranous part of the ventricular septum, central fibrous body, aortic-mitral annulus, mitral annulus, aortic valve base, and the aortic valve undergo degenerative changes. The pathologic changes include fibrosis, calcification, arteriolosclerosis, fatty infiltration, and loss of conduction fibers with replacement of fibrotic strands. This type of degenerative process is referred to as “sclerosis of the left side of the cardiac skeleton.” It occurs as a result of “stress and strain” in a high pressure system that may affect the adjacent AV bundle and the bundle branches. Frequently, the branching part of the AV bundle, the beginning of the right and left bundle branches, or the main left bundle branch are compressed by calcium and replaced by fibroelastic process, loss of cells, and space formation with or without fat. The main left bundle branch may be totally disrupted from the branching AV bundle. The second part of the right bundle branch may be completely replaced by fibroelastic process. These changes may result in complete AV block, left bundle branch block, or bilateral bundle branch block. Aging of the summit of the ventricular septum usually begins in the fourth decade of life and is accelerated by hypertensive heart disease, coronary artery disease, and diabetes mellitus. The branching and the bifurcating part

**FIGURE 13-3** Chronic coronary insufficiency with atrioventricular (AV) block demonstrating calcification in the summit of the ventricular septum compressing the branching AV bundle and the left bundle branch Weigert-van Gieson stain ×30. B, AV bundle showing fibrosis and loss of fibers; C, calcific mass; LBB, remnant of left bundle branch; V, calcified ventricular septum.
of the AV bundle, the beginning of the main left bundle branch, and the beginning of the right bundle branch are quite superficial subendocardial structures and as such are vulnerable to degenerative changes caused by aging.19-21,23,24,26-29

**COLLAGEN DISEASES**

Since there is a considerable amount of collagen connective tissue in the conduction system, varying types of collagen connective tissue disorders may affect the conduction system to varying degrees. Thus, AV block or bundle branch block may occur in lupus erythematosus, dermatomyositis, scleroderma, and other mixed types of connective tissue disorders. Depending on the site of involvement of the conduction system, there may be bundle branch block or complete AV block. For example, complete replacement of the AV node by granulation tissue in lupus, fibrotic disruption of bundle branches to varying degrees in dermatomyositis, and granulomas in various parts of the conduction system in rheumatoid arthritis may be seen histologically.19-21,23,24,30,31

**MYOCARDITIS**

Myocarditis of any type, whether acute or chronic, may cause complete AV block. If the patient survives, the heart block usually resolves; chronic AV block after myocarditis is rare. Pathologically, in the acute phase of the illness, the inflammatory changes in the ventricular myocardium predominate, affecting the distal part of the conduction system, such as the branching bundle and the bundle branches. Rarely, a part of the conduction system may be affected. In general, the conduction system and the surrounding myocardium are involved by the inflammatory process. In rare cases, the conduction system is involved more than the surrounding myocardium.19-21,23,24

**INFECTIVE ENDOCARDITIS**

 Infective endocarditis of the aortic or mitral valve, or both, may extend to the aortic-mitral annulus, the membranous part of the AV septum, and the summit of the ventricular septum and thereby affect the AV node and AV bundle to produce AV block.19-21,23,24

**TUMORS OF THE HEART**

Any type of tumor that metastasizes to the heart has the potential to affect various parts of the conduction system to a varying degree, resulting in AV block.19-21,23,24,32

One specific type of benign tumor, a mesothelioma or celothelioma of the AV node, has an affinity to affect only the AV node and its approaches (Fig. 13-4). Although rare, the tumor may totally replace the AV node and its approaches and produce complete AV block with a narrow QRS complex in the ECG. In general, this is a slow-growing tumor and may manifest clinically as AV block from birth to old age. The tumor consists of neoplastic cells of benign nature with no anaplasia and tends to form cysts. The tumor is generally seen in young women who may remain totally asymptomatic; sudden death may be the first manifestation.

It is of interest that mesothelioma, although a benign tumor pathologically, may cause sudden death in otherwise normal, young, healthy persons. It is also of interest that the site of heart block produced by the tumor is proximal to the AV bundle, with a narrow QRS complex in the ECG, which is generally considered to have a favorable clinical course.19-21,23,24,32

**SURGICAL ATROVENTRICULAR BLOCK**

Surgical injury to the AV bundle during repair of a ventricular septal defect and ostium primum defect rarely occurs today. On the other hand, AV block occurring during closure of defects in hearts with corrected transposition is seen frequently. Septation of a single-ventricle heart often results in postoperative AV block. In general, when the ventricles are inverted or are in a crisscross position, the AV bundle is situated anterosuperiorly, in a vulnerable position for surgical injury. On the other hand, a right-sided AV bundle in simple,
complete transposition of the great vessels or ventricular septal defect may get caught in surgical closure of the defect. The Mustard procedure for complete transposition, in which the atrial septum is removed and a baffle is placed, can lead to distortion of the atrial septum with fibrosis of the approaches to the AV node. This may result in AV block and sudden death. Further, in the Mustard procedure, the sinoatrial node may be affected to a varying degree, resulting in supraventricular arrhythmias.59-21,23,24,33-36

MISCELLANEOUS DISEASES AND ALTERED PHYSIOLOGIC STATES

AV block is known to occur in numerous diseases and altered physiologic or metabolic states. These include mitral valve prolapse, Marfan’s syndrome, Chagas’ disease, Reiter’s disease, Lyme disease, Kearns-Sayre syndrome, hemochromatosis, leukemia, alcoholism, radiation therapy, hypothermia, exercise testing, introduction of catheters, prolonged coughing, sleep apnea with or without obesity, scorpion bites, and posture changes.39

Basic Electrophysiology

It is generally accepted that the AV junction consists of the AV node with its atrial connections of transitional fibers and the bundle of His.38 In electrophysiological considerations of AV block, it is useful to define the AV junction more broadly, including the atrial connections to the AV node, the AV node, the bundle of His, and the proximal portions of the bundle branches that are insulated from ventricular myocardium by fibrous matrix. Heart block can occur from interruption of conduction in any of these components of the AV junction as defined broadly. In this array of components, there is great electrophysiological and histologic diversity (Fig. 13-5). The range of conduction velocities, resting and action potential (AP) amplitudes, AP durations, and intercellular conductivity observed within the AV junction is greater than in the remainder of the atrial and ventricular myocardium.

THE COMPACT ATRIOVENTRICULAR NODE

Within the central compact node are cells with distinct electrophysiological characteristics. These characteristics of the prototypical AV nodal cells manifested by intracellular recordings in multicellular preparations have been replicated in cells isolated from the AV node, allowing determination of the activities of specific currents, pumps, and exchangers.39,40 The amplitudes of resting potentials (−60 mV), APs (85 mV), and upstroke velocities (<10 V/sec) are reduced. These cells manifest diastolic depolarization, a high total transmembrane (input) resistance, and relative insensitivity to changes in extracellular K+. They have postrepolarization refractoriness: the absolute refractory period outlasts the AP. The relative refractory period, during which relatively diminished, slowly conducting APs are generated, is prolonged during diastole. The amplitudes and upstroke velocities of APs and conduction velocity are strongly modulated by autonomic activity, increasing with adrenergic (sympathetic) stimulation and decreasing with cholinergic (vagal) stimulation. The AV node is richly innervated with vagal and sympathetic fibers. These characteristics of the APs, in large part, account for the slow conduction and spontaneous automaticity of the compact AV node.

Important features of the transmembrane potentials can be explained by the array and activities of specific ionic currents. Like sinoatrial nodal cells, AV nodal cells lack the ionic current IkI. These potassium ion channels in atrial and ventricular cells are open at strongly negative membrane potentials, providing the dominant potassium ion permeability that maintains the transmembrane potential near the potassium ion equilibrium potential. The absence of these channels in AV nodal cells is responsible for the relatively reduced resting potential positive to the potassium ion equilibrium potential, the insensitivity to extracellular potassium ion concentration, and the high membrane resistance of these cells.

FIGURE 13-5 A representation of the right atrium and action potentials from the atrium and atrioventricular (AV) junction. A, atrial potential; AVN, AV node; BB, bundle branch potential; CS, coronary sinus; CT, crista terminalis; FO, fossa ovalis; FP, fast pathway and potential; SP, slow pathway and potential; Hb, His bundle and potential; IVC, inferior vena cava; MP, mid pathway and potential; N, central nodal potential; NH, distal nodal potential; TT, tendon of Todaro.
AV nodal cells, like sinoatrial nodal cells, lack sodium channels, which provide the excitatory current for atrial and ventricular cells; some cells may have channels that are inactivated at the low resting potentials. The excitatory current for AV nodal cells is $I_{CaL}$, a calcium current that generates a slow upstroke because it is slower and less intense than the Na$^+$ current. L-type calcium ion channels require a relatively long period to recover from inactivation, hence the postpolarization refractoriness of the AV node. The potent actions of autonomic stimulation on AV nodal conduction are largely due to the modulation of $I_{CaL}$ by adrenergic and cholinergic stimulation via specific receptors and transduction systems. This current is enhanced and its kinetics of activation, inactivation, and recovery are accelerated by adrenergic stimulation; it is conversely affected by cholinergic stimulation.

AV nodal cells contain the pacemaker current $I_p$, which may contribute to the automaticity of AV nodal cells. On the other hand, the current $I_{Ko}$, a rapidly activating and inactivating potassium current that produces the notch of the AP (phase 1) and is prominent in atrial cells, is sparse or absent in AV nodal cells. The repolarizing potassium current $I_K$ is present and probably a major factor in the repolarization of AV nodal cells. The repolarizing current $I_K$, a contributor to repolarization in atrial, ventricular, and His-Purkinje cells, appears to be absent in AV nodal cells.

The potassium ion current $I_{Kach, Ado}$ is prominent in sinoatrial nodal and atrial cells but not in ventricular cells. It is also present in AV nodal cells. Activation of this current by acetylcholine or adenosine drives the resting potential to more negative values, suppresses automaticity, and diminishes the AP, thus slowing AV conduction.

Gap junctions appear to be sparse and smaller in the central AV node than in atrial and ventricular myocardium. The gap junctions in the node are composed predominantly of connexin 40 rather than connexin 43, which is dominant in ventricular myocardium. The relatively poor intercellular communication in the AV node is probably the result of these gap junction properties plus a relative increase in the volume of extracellular space surrounding AV nodal cells compared with atrial and ventricular myocardium.

**THE TRANSITIONAL ATRIONODAL CONNECTIONS**

The transitional fibers connecting the atrium to the AV node aggregate in zones that are functionally relatively discrete, though not insulated from atrial myocardium. Recent observations indicate that anisotropy is a major determinant of directional conduction in these pathways. They extend from the node to and beyond the border of Koch’s triangle and connect to the node at relatively discrete sites along its margins.

These atrionodal connections have APs with characteristics that are intermediate between atrial cells and prototypical cells in the compact node. Like the AV node, these transitional connections may show decremental conduction and Wenckebach type of block. Until recently, functional definitions of these connections distinguished a “fast pathway” located at the anterior-superior aspect of the node and connecting to the atrium anterior to the fossa ovalis, and a “slow pathway” connecting to the node inferiorly and posteriorly and extending posterior to the isthmus region inferior to the coronary sinus os. The terms “fast” and “slow” do not necessarily represent different conduction velocities in these pathways but different conduction times determined by access and length of the pathways depending on the site of origin of global atrial activation. In man, the “fast” pathway is usually but not invariably considered to have a longer refractory period than the “slow” pathway.

Recent observations indicate that the atrial connections to the node are more complex. A mid pathway has been described with deep (in relation to the right endocardium) connections to the node in its superior aspect and connections to the atrium in the septum posterior to the fossa ovalis. Left-sided connections have been described in man. The functional interrelationships of the pathways in normal AV conduction are not fully elucidated. It is clear that these pathways, the atria, and the AV node can form various configurations of reentry circuits that cause AV nodal reentrant tachycardia. Interruption of the atrial connections to the AV node can produce AV block.

**THE BUNDLE OF HIS AND BUNDLE BRANCHES**

The bundle of His and bundle branches, which are insulated by fibrous matrix from ventricular myocardium, constitute the ventricular aspect of the AV conduction axis. They function to rapidly disseminate activation to the ventricular myocardium in a pattern that optimizes ejection of blood by a synchronized and coordinated apex to base contraction. Conduction in these tissues is the most rapid of all cardiac tissue, promoting synchronization of activation of distal sites. The architecture of the bundle branches and their proximal insulation promotes apex-to-base conduction in fiber to fiber and septal-free wall synchronization. The APs of these fibers in multicellular preparations manifest very rapid upstrokes, prolonged plateau with distal reentry, and automaticity.

Quantitative measurement of individual currents in isolated Purkinje cells has been relatively limited. Sodium current is abundant, accounting in part for the fast upstroke and the rapid conduction velocity. The ionic basis for the prolonged plateau has not been determined, but $I_K$, appears to be less active in Purkinje than in ventricular myocardial cells.

The basis for the automaticity of the His-Purkinje system is debated. Some favor the decay of a potassium current activated during the AP as the primary basis for automaticity, whereas others favor the current $I_{ach}$ as in the sinoatrial node and AV node, there may be multiple ionic determinants of automaticity. The automaticity of the His-Purkinje system is more prominent proximally than distally. Automatic firing of the distal Purkinje system is slow and erratic. As a result, heart block due to degeneration and fibrosis of the bundle branches is
more malignant than heart block caused by interruption of conduction in the AV junction proximal to the bundle of His.

Gap junctions are abundant in the Purkinje strands of the bundle branches and their distal ramifications. They are uniformly distributed along the lengths and ends of the fibers promoting good intracellular communication throughout the margins of the cells and rapid conduction. However, the bundle of His fibers appear relatively poorly connected in the transverse dimension so that dissociation within the bundle of His has been observed in experimental animals and in man.49

Electrocardiography of Atrioventricular Block

The earliest diagnoses of AV block were made by clinicians using irregularities in the pulse rate or a pulse deficit and were later documented by peripheral pulse recordings by Wenckebach and other investigators. While the peripheral pulse and its irregularity, whether periodic or not, can provide the clinician with initial inkling that AV conduction has been compromised, the surface ECG has become the clinical mainstay to diagnose type and potential location of AV block. It is conceptually convenient to consider the three types of AV block as reflecting delayed conduction in the AV conduction system (first-degree AV block), intermittent conduction (second-degree AV block), or failure of conduction (third-degree or complete heart block). First-degree AV block is characterized by prolongation of the PQ or P–R interval beyond 200 milliseconds (ms) (Fig. 13-6). The site of delay may lie in the atrial, AV node, bundle of His, or His-Purkinje system conduction. The associated QRS complex provides insight into the sites of diseased conduction but is not proof of location of the AV block. There may be evidence of distal conduction disease as seen in Figure 13-6 in the form of bundle branch block. Alternatively, a narrow QRS complex would favor conduction delay in the AV node or much less commonly in the bundle of His. However, the latter diagnosis should be suspected in calcific mitral valve disease, typically seen in middle-aged women with syncope or near syncope. Second-degree AV block can be categorized as type 1 (Wenckebach or Mobitz type 1), characterized by gradual prolongation of the P–R interval followed by a nonconducted P wave (Fig. 13-7). The beat following this pause in conduction is characterized by a shorter P–R interval, which may prolong in subsequent beats. Importantly, the last few cycles before the nonconducted P wave may not show significant P–R prolongation, and if the early cycles are not seen, this diagnosis may be missed. This is occasionally referred to as atypical Wenckebach conduction. An important differential diagnosis is spontaneously alternating conduction in the slow and fast AV nodal pathways in patients with dual AV nodal conduction pathways (Fig. 13-8). This may masquerade as type 1 block on a cursory ECG examination. Furthermore, this may demonstrate grouped beating during tachycardias such as atrial fibrillation and flutter, further confusing the conduction pattern analysis. Mobitz type 2 second-degree block is characterized by a lack of P–R interval prolongation before the nonconducted P wave (Fig. 13-9). Importantly, the P–R interval of the subsequently conducted beat can be shorter than the subsequent stable P–R interval before the nonconducted P wave. This must be differentiated carefully from the atypical type 1 second-degree block. Type 2 second-degree block can be characterized by an occasional nonconducted P wave or a series of such P waves when it is referred to as paroxysmal high-degree AV block. This type of block is typically

FIGURE 13-6 First-degree atrioventricular block with P–R prolongation and a bundle branch block QRS pattern on surface ECG.

FIGURE 13-7 Second-degree type 1 atrioventricular block (Mobitz type 1 or Wenckebach type) showing gradual P–R prolongation before the nonconducted P wave.
seen in the distal or infra-His conduction system and is often associated with bundle branch block on the conducted beats on the surface ECG. This is suggestive of progressive bundle of His and bundle branch involvement in the pathologic process. Complete failure of conduction in third-degree AV block or complete heart block can be localized with some success based on the escape rhythm (Figs. 13-10 and 13-11). A narrow QRS escape rhythm suggests a nodal or bundle of His escape pacemaker and usually localizes the block to the AV node (much less often to intra-His locations). Narrow QRS complexes are typically seen in patients with congenital complete heart block, and a stable junctional pacemaker may be present for many years (see Fig. 13-10). More commonly, complete heart block is associated with a more distal disease process and an idioventricular escape rhythm at rates usually below 40 beats per minute (see Fig. 13-11). The site of AV block can be well directed by careful electrocardiographic analysis and confirmed by clinical electrophysiological investigation as indicated later in this chapter.

Diagnostic Techniques

Since the prognosis and treatment differ in AV block depending on whether block is within the AV node or infranodal, determining the site of block is important. In many cases this can be done noninvasively. The QRS duration, P–R intervals, and ventricular rate on the surface electrogram can provide important clues in localizing the level of block. Several noninvasive interventions may also prove helpful, such as vagal maneuvers, exercise, or administration of atropine. These methods take advantage of the differences in autonomic innervation of the AV node and His-Purkinje system. While the AV node is richly innervated and highly responsive to both sympathetic and vagal stimuli, the His-Purkinje system is influenced minimally by the autonomic nervous system. Carotid sinus massage increases vagal tone and worsens AV nodal block. Exercise or atropine improves AV nodal conduction due to sympathetic stimulation. In contrast, carotid sinus massage improves infranodal block, while exercise and atropine worsens infranodal block, due to the change in the rate of the impulses being conducted through the AV node.

Exercise testing is a useful tool to help confirm the level of block that is already suspected in second- or third-degree block with a narrow or wide QRS complex. Patients with presumed AV nodal block or congenital complete heart block and a normal QRS complex will usually increase their ventricular rate with exercise. However, patients with acquired complete heart block and a wide QRS complex usually show minimal or no increase in ventricular rate.

An electrophysiological study is indicated in a patient with suspected high-grade AV block as the cause of syncope or presyncope when documentation cannot be obtained noninvasively. In patients with coronary artery disease, it may be unclear whether symptoms are secondary to AV block or ventricular tachycardia, and
The electrophysiological study allows analysis of the bundle of His–electrogram, as well as atrial and ventricular pacing to look for conduction abnormalities and inducible ventricular tachycardia. The atrio–His (A–H) and His ventricle (H–V) intervals are measured from the bundle of His–electrogram. Atrial pacing techniques are used to help define the site of block and assess AV nodal and His-Purkinje conduction. During decremental atrial pacing, the A–H interval normally will gradually lengthen until AV nodal Wenckebach block is noted. The H–V interval will normally remain consistent despite different pacing rates. Abnormal AV nodal conduction is defined as Wenckebach block occurring at slower atrial-paced rates than what is normally seen (i.e., >500 ms). To determine whether AV nodal disease is truly present or just under the influence of excessive vagal tone, atropine alone or autonomic blockade with atropine and propranolol can be given to differentiate inherently abnormal AV nodal conduction from vagally mediated abnormalities. Infranodal block (Mobitz 2) is present when the atrial deflection is followed by the His electrogram, but no ventricular depolarization is seen. Block below the His is abnormal, unless associated with very short-paced cycle lengths (350 ms or less).

Clinical Electrophysiology

Intracardiac electrophysiological studies in patients with conduction system disease can provide information about the site of AV block, assess possible mechanisms of syncope in affected patients, and stress the conduction system by atrial pacing and pharmacologic

FIGURE 13-10 Congenital complete heart block in a young asymptomatic woman with excellent exercise response of the junctional pacemaker.
intervention to help determine the risk for developing heart block and the need for permanent pacing. Patients with conduction disease may present with cardiac syncope believed due to intermittent heart block. However, the conduction disease is often due to myocardial disease such as cardiomyopathy, but the syncope can be due to ventricular tachycardia. In this situation, both the conduction disease and propensity to malignant ventricular arrhythmia can be assessed to determine more appropriate therapy. During electrophysiological assessment of patients with significant conduction disease, the presence of intact ventriculoatrial conduction can be assessed to help determine the type of pacemaker to be used. Patients with intact ventriculoatrial conduction should have a dual-chamber pacemaker placed to avoid pacemaker syndrome or pacemaker-mediated tachycardia.

**FIRST-DEGREE ATRIOVENTRICULAR NODAL BLOCK**

The most common cause of P–R interval prolongation is delay in conduction through the AV node. This can be identified readily at the time of intracardiac study by measuring the A–H interval and assessing the response to pharmacologic testing. The A–H interval represents conduction through the AV node and is measured from onset of the atrial electrogram to onset of the bundle of His–electrogram as recorded by the bundle of His–catheter. The normal A–H interval should not exceed 130 ms (Table 13-2). Most commonly, a prolonged A–H interval is due to either residual drug effect (β-blocker, calcium channel blocker, digoxin, antiarrhythmic drugs) or enhanced vagal tone. Atropine can be administered to reverse vagal tone to help determine whether intrinsic AV nodal conduction disease is present in the absence of AV nodal–blocking drugs. A prolonged A–H interval with AV node Wenckebach during slow atrial pacing (<100 bpm) in the presence of vagal blockade with atropine implies intrinsic AV nodal conduction disease.

**SECOND-DEGREE ATRIOVENTRICULAR BLOCK**

Type 1 second-degree AV block (Wenckebach) usually occurs within the AV node. Type 2 second-degree AV block is usually infranodal in the His-Purkinje system. However, either type of block may occur within or below the node. The exact level of block can be assessed with electrophysiological testing (Figs. 13-12 and 13-13). Electrophysiological testing can further define if AV block is due to disease in the His-Purkinje system or delayed conduction within the AV node in patients who present with first-degree AV block on their resting ECG and have associated bundle branch block.

Patients with a 2:1 or higher degree of AV block can have the site of block in the AV node or His-Purkinje system. Block in the AV node is often treated by altering the patient’s medications, while block in the His-Purkinje system usually requires permanent pacing. The exact level of block in such patients can be determined at the time of electrophysiological testing and appropriate therapy initiated.

**HIS-PURKINJE DISEASE**

Abnormal conduction within the distal conduction system is referred to as infranodal or distal-to-His conduction disease. Conduction delay in the His-Purkinje system is clinically important because of the risk for progressing to complete heart block and need for permanent pacing. Usually, patients who will benefit from a permanent pacemaker can be identified clinically based on noninvasive ECG recording, either short or long term, and correlation of symptoms with ECG abnormalities. Conduction disease in the His-Purkinje system can be assessed by measuring the H–V interval. The H–V interval is determined as the conduction time between the onset of the His electrogram recorded by the His-bundle catheter and earliest ventricular activity recorded by either intracardiac or surface electrograms and usually consists of a sharp single deflection on the recording (see Fig. 13-12A). The normal H–V interval is between 35 and 55 ms (see Table 13-2). Shorter intervals are due to ventricular preexcitation or recording the right bundle electrogram instead of the His-bundle electrogram. First-degree intra-His block can be demonstrated by atrial extrastimuli during programmed stimulation (see Fig. 13-12B). Typically, split His potentials are seen (indicated as H1 and H2 on the figure). Type 1 second-degree block within the His-Purkinje system can occur and is demonstrated by progressive beat-to-beat increases in the H–V interval prior to infra His block (see Fig. 13-12C). This type of block is uncommon. Type 2 second-degree block within the His-Purkinje block is more common and is usually associated with bundle-branch block, a prolonged H–V interval at rest, and the development of either spontaneous or pacing induced infra His block during electrophysiological testing (Fig. 13-13). This constellation of abnormalities of the His-Purkinje system most often warrants permanent pacing. At times, intracardiac recordings may demonstrate a split His potential with the clear recording of two His deflections separated by approximately 15 to 25 ms. Block can occur between the two His potentials, and, although this problem is rare, it should be treated as second-degree infranodal block with permanent pacing.

### TABLE 13-2 Electrophysiological Intervals: Normal Values

<table>
<thead>
<tr>
<th>Reference</th>
<th>P–A (ms)</th>
<th>A–H (ms)</th>
<th>H–V (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhingra</td>
<td>9-45</td>
<td>54-130</td>
<td>31-55</td>
</tr>
<tr>
<td>Gallagher</td>
<td>24-45</td>
<td>60-140</td>
<td>30-55</td>
</tr>
<tr>
<td>Fisher</td>
<td>10-45</td>
<td>55-130</td>
<td>30-55</td>
</tr>
<tr>
<td>Josephson</td>
<td>—</td>
<td>60-125</td>
<td>35-55</td>
</tr>
<tr>
<td>Recommended</td>
<td>25-50</td>
<td>50-130</td>
<td>35-55</td>
</tr>
</tbody>
</table>

A–H, interval from the onset of the atrial electrogram to the onset of the His electrogram recorded by the His catheter; H–V, interval from the onset of the His electrogram to earliest ventricular activation; P–A, interval from the onset of atrial activity to the atrial electrogram recorded by the His catheter.
**BUNDLE BRANCH BLOCK**

The H–V interval reflects the shortest conduction time from the His bundle to the ventricle and is often used to assess the state of the remaining conducting fascicles in patients with chronic bundle branch block. For example, patients with chronic left bundle branch block who have a prolonged H–V interval have damage to the remaining right fascicle represented by the H–V interval prolongation. Typically, asymptomatic patients with an H–V interval of 55 to 70 ms have a 1% annual incidence of progression to spontaneous second-degree or third-degree infranodal block, and treatment with permanent pacing should be individualized. Asymptomatic patients with an H–V interval of 70 to 100 ms have a 4% annual incidence of complete heart block and probably should be paced, whereas asymptomatic patients with an H–V interval of greater than 100 ms have an 8% annual incidence of complete heart block and should undergo implantation of a permanent pacemaker. Patients with spontaneous pacing-induced distal-to-His block at slow rates have a high incidence of subsequent complete heart block and sudden death and should be paced.
The value of stressing the His-Purkinje conduction by using intravenous procainamide was assessed in a study by Girard and associates. Seventy-nine patients who underwent electrophysiological testing received intravenous procainamide. An abnormal response to procainamide (defined as an H–V interval >80 ms) was observed in only 3% of 37 patients with a normal baseline H–V interval of less than 55 ms, 48% of 27 patients with mild H–V prolongation (56 to 70 ms), and in all 15 patients with moderate H–V prolongation (>70 ms). Procainamide induced distal-to-His block in 14% of patients studied for syncope and in 2% of patients studied for ventricular tachycardia. Syncope as the indication for electrophysiological study and left bundle branch block on the ECG were the best predictors of subsequent distal-to-His AV block. There was a strong linear correlation between post drug and baseline H–V intervals. This linear response to procainamide and published prospective studies support pacing patients with syncope who have a baseline H–V interval of greater than 70 ms. This study concluded that procainamide infusion during electrophysiological study of patients with undifferentiated syncope should be reserved for those patients with mild H–V prolongation of 55 to 70 ms in duration. The exact sensitivity and specificity of atrial pacing and IV procainamide to stress His-Purkinje conduction for predicting long-term outcome remains unclear.

**COMPLETE HEART BLOCK**

Electrophysiological testing has a minimal role in the assessment of patients with complete AV block, especially if they present with a slow escape rhythm and a wide QRS complex, indicating a ventricular escape focus. Such patients require pacing. Patients with complete heart block proximal to the His bundle usually have enhanced vagal tone, inferior myocardial infarction with ischemia of the AV node, or AV nodal block due to drugs such as β-blockers, calcium channel blockers, or digoxin. In these situations, electrophysiological testing is usually not required as the diagnosis and further management is handled clinically. Similarly, the role of electrophysiological testing in patients with congenital complete heart block has not been determined, and the test usually does not provide helpful information on which to base clinical management.

Electrophysiological studies usually do not make a significant contribution to the management of patients with documented AV block and associated symptoms of altered consciousness as the decision to implant a pacemaker is made clinically. However, in selected patients
with conduction disease, including bifascicular block, prognostic information can be gained from invasive electrophysiological testing to assess the integrity of the His-Purkinje system and the risk for developing complete heart block. In addition, assessment of the electrical properties of the AV conduction system and inducibility of ventricular arrhythmias in patients with syncope and heart disease can be extremely helpful in determining appropriate management.

**Evidence-Based Therapy**

While retrospective studies provide useful information that can often help in hypothesis generation, they frequently exaggerate the benefit of treatment. It is always preferable to base clinical decisions, if possible, on data from prospective randomized trials. However, no prospective randomized trials have evaluated the efficacy of pacing therapy in patients with AV block since there are no alternatives to pacing therapy for the patient with symptomatic AV block (not due to reversible causes). In addition, it is difficult to assemble large groups of asymptomatic patients with specific types of AV block. Recommendations for permanent pacemaker implantation are based on observational studies on the natural history of AV block. In general, permanent pacemakers are implanted in patients with symptomatic AV block and in patients with asymptomatic AV block due to His-Purkinje disease.65

**Pacing Mode Choice**

Prospective data on the effects of pacing mode choice in patients with AV block are limited. Both single-chamber ventricular pacing and dual-chamber pacing will prevent bradycardia in patients with AV block. However, only dual-chamber pacing maintains AV synchrony. Dual-chamber pacing also reduces the incidence of pacemaker syndrome. Despite these potential advantages, the importance of dual-chamber pacing in patients with AV block has not been well established, particularly in the elderly.

In the Pacemaker Selection in the Elderly (PASE) trial, 407 elderly patients (mean age 76 years) were randomized to either the rate-adaptive ventricular inhibited (VVIR) or rate-adaptive dual chamber (AV) inhibited/triggered (DDDR) pacing mode.66 In the 201 patients who had pacing systems implanted for AV block, no reduction in mortality, stroke, or atrial fibrillation was observed. In contrast to the patients with...
Management of Atrioventricular Block

When AV block is identified, management requires a search for reversible causes, an assessment of hemodynamic stability to determine whether temporary pacing is required, and, finally, a decision on whether permanent pacing will be necessary.

TEMPORARY PACING

In the hemodynamically unstable patient with AV block, the clinician must identify any rapidly reversible causes. Reversible causes include hyperkalemia, hypoxia, increased vagal tone, and ischemia. While treatment for reversible causes is initiated, it must be decided quickly whether temporary pacing will be required for the hemodynamically unstable patient. Temporary pacing is most quickly initiated by transcutaneous passage of current between two specially designed pads placed on the chest wall. Patch position is the most important factor for determining effectiveness of transcutaneous pacing. The cathode should be placed on the left chest over the cardiac apex, and the anode placed on the back between the spine and scapula or anteriorly just above the right nipple. Currents of 20 to 140 mA are usually required to capture and activate the ventricles. Using the correct technique, transcutaneous pacing is effective in more than 90% of cases and associated with very few complications. However, transcutaneous pacing cannot be used for prolonged periods because of patient discomfort and unreliability of capture due to impedance changes.

If temporary pacing must be used for more than 30 minutes, transvenous pacing should be initiated since it is far more stable and better tolerated. With transvenous pacing, intravascular access is obtained, usually through the right internal jugular vein, and a pacing catheter is positioned into the right ventricle. The pacing catheter is connected to a pulse generator; ventricular capture can usually be obtained with currents of 1 to 2 mA. Transvenous pacing can be used for long periods with minimal complications (<2% once venous access is achieved).

PERMANENT PACING

Once the patient is stabilized, the clinician must assess whether the AV block will be permanent. There are several conditions where persistent AV block will gradually resolve. In approximately 10% to 15% of patients with inferior and posterior wall myocardial infarctions, transient second-degree, advanced, or complete AV block will be observed. In almost all cases the AV block will resolve, and permanent pacing is not required. The use of fibrinolytic therapy has not altered the incidence of AV block in inferior wall myocardial infarction. Approximately 8% to 10% of patients with Lyme disease will have transient AV conduction abnormalities due to myocarditis involving the AV nodal region. AV block usually resolves within several weeks, and permanent pacing is almost never required. Acute rheumatic fever can also present with AV block that is expected to resolve after several weeks.

INDICATIONS FOR PERMANENT PACING

Indications for permanent pacing in acquired AV block have been published by a Joint Committee of the American College of Cardiology (ACC) and the American Heart Association (AHA) in 1984, 1991, 1998, and 2002.
THIRD-DEGREE ATRIOVENTRICULAR BLOCK

Symptomatic third-degree AV block is a class I indication for pacing therapy. For asymptomatic patients, the current guidelines use a rate cutoff, with escape ventricular rates less than 40 beats per minute designated as a class I indication and ventricular rates greater than 40 beats per minute designated as class IIa. Although this distinction may seem reasonable, one must confirm whether the patient is truly asymptomatic; in some cases symptoms associated with third-degree AV block are subtle. More importantly, prognosis depends on the stability of the escape rate pacemaker rather than the actual rate; escape rhythms from ventricular tissues (wide QRS complexes) are inherently unstable. In practice, acquired third-degree AV block not associated with any reversible causes is usually considered a class I indication for permanent pacing regardless of whether symptoms are present or absent.

SECOND-DEGREE ATRIOVENTRICULAR BLOCK

Symptomatic second-degree AV block is a class I indication for pacing regardless of type of block. The use of pacing therapy for asymptomatic patients with second-degree AV block is controversial and depends on the type (site) of AV block.

In general, type 1 second-degree AV block associated with a narrow QRS complex (<0.12 sec) is due to block in the AV node, and the current published guidelines do not recommend pacemaker implantation in the asymptomatic patient. In a study of 56 patients with documented chronic second-degree AV block due to AV nodal conduction delay, those without associated cardiac disease had a benign course while those with associated cardiac disease had a poor prognosis due to progression of underlying cardiac disease rather than to the development of sudden bradycardia.80 However, in another retrospective study of 214 patients with second-degree AV block, survival and requirement for pacing were not different among patients with type 1 and type 2 heart block, and the presence or absence of bundle branch block did not appear to aid in the prediction of survival.80 In view of these conflicting data, it is prudent to closely monitor patients with type 1 second-degree AV block and a narrow QRS complex for symptoms and for progression of conduction tissue disease (e.g., development of fascicular block or QRS widening). If type 1 second-degree AV block is associated with a wide QRS complex (>0.12 sec) AV block will be located in the AV node in 30% to 40% of patients and in the His-Purkinje system in 60% to 70% of cases.81,82 In these cases an invasive electrophysiological study is often required to identify the site of block. If intra-Hisian or infra-Hisian block is identified, a pacemaker should be implanted since these conditions usually progress to complete heart block within 5 years.83

Type 2 second-degree AV block probably always occurs in His-Purkinje tissue. Asymptomatic patients with type 2 AV block usually do develop symptoms and will require permanent pacing.84,85

In 2:1 second-degree AV block, every other P wave conducts, preventing comparison of consecutive P–R intervals. The QRS complex provides a clue as to the site of block: A narrow QRS complex is associated with His-Purkinje block 30% of the time, and a wide QRS complex is associated with His-Purkinje block approximately 80% of the time.85 In the asymptomatic patient with 2:1 block, maneuvers to alter the conduction ratio between the atria and ventricles (such as exercise, atropine, or continuous ECG monitoring) may allow localization of the site of block. However, in some cases electrophysiological evaluation to determine the site of block will be required.

FIRST-DEGREE ATRIOVENTRICULAR BLOCK

If first-degree AV block is severe, atrial activation and contraction can occur while the ventricles are contracting in response to the previous atrial contraction, which leads to an inappropriate rise in atrial pressures and

TABLE 13-3 Indications for Permanent Pacing in Atrioventricular Block

<table>
<thead>
<tr>
<th>Indication</th>
<th>Type of AV Block</th>
<th>Pacing Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>First-degree</td>
<td>Pacing not indicated</td>
<td></td>
</tr>
<tr>
<td>Second-degree</td>
<td>Pacing not indicated if type I second-degree AV block is present; Pacing if type II second-degree AV block is present</td>
<td></td>
</tr>
<tr>
<td>Third-degree</td>
<td>Pacing if type II second-degree AV block is present</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Pacing regardless of type</td>
<td></td>
</tr>
</tbody>
</table>

The ACC/AHA/NASPE 2002 guidelines use the standard three-group classification schema. Class I indications are conditions for which there is evidence or general agreement that a given procedure or treatment is beneficial, useful, and effective. Class II indications are conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class II has been further divided into class IIa, where the weight of evidence/opinion is in favor of usefulness/efficacy, and class IIb, where usefulness/efficacy is less well established by evidence/opinion. Class III indications are conditions for which there is evidence or general agreement that a procedure/treatment is not useful/effective and, in some cases, may be harmful. Despite some shortcomings,76 the ACC/AHA/NASPE guidelines provide a useful framework upon which management is based. The indications for permanent pacing in asymptomatic patients with second- or third-degree AV block are often straightforward (Table 13-3). Controversial indications involve mostly symptomatic patients.76,77 The decision to implant a pacemaker in asymptomatic patients is more difficult and requires knowledge of the pathophysiology and natural history of AV block. As a general rule, since escape rhythms from ventricular tissue are unreliable, a pacemaker should be implanted in asymptomatic patients if AV block occurs in His-Purkinje tissue.
symptoms similar to the pacemaker syndrome. In this situation symptoms can be significant even with exercise since the P–R interval does not shorten appropriately with adrenergic stimulation. The current guidelines classify symptomatic first-degree AV block as a class IIa indication for pacemaker implantation. Asymptomatic first-degree AV block is a class III indication for pacing. The one exception to this recommendation is the asymptomatic patient with first-degree AV block, abnormal QRS axis due to left anterior or left posterior fascicular block, and neuromuscular disease. Neuromuscular diseases such as myotonic dystrophy and Kearns-Sayre syndrome are associated with progressive AV block; since development of complete heart block can be unpredictable, a permanent pacemaker is justified.

**PACING MODE CHOICE**

Three pacing modes (DDD, VDD, and VVI) can be used to prevent bradycardia in patients with AV block (Fig. 13-14).

**VVI AND VVIR PACING**

In the VVI or VVIR pacing mode, bradycardia is prevented, and if rate adaptation is programmed “on,” the heart rate will increase with exercise. However, in neither of these pacing modes is AV synchrony present. The importance of AV synchrony is controversial in patients with AV block, since the main contribution to increased cardiac output with exercise is heart rate rather than AV synchrony, and the incidence of pacemaker syndrome is lower in patients with AV block compared with patients with sinus node dysfunction. However, it seems intuitively reasonable that in the presence of organized atrial activity, the VDD and DDD pacing modes are most appropriate. In fact, since the early 1990s the British Pacing and Electrophysiology Group guidelines have stated that the only indication for the VVI and VVIR pacing modes is atrial fibrillation/flutter with AV block or slow ventricular response. The VVI and VVIR pacing modes may also be appropriate in patients who are incapacitated and inactive, as well as those with other medical problems associated with a short life expectancy.

**DDD AND DDDR MODES**

The DDD pacing mode prevents bradycardia and provides AV synchrony in patients with AV block. Although less important for exercise-related increases in cardiac output, several studies have demonstrated that AV synchrony is associated with improved symptoms at baseline levels of activity. A large randomized study (UK-PACE) that compares the VVI and DDD pacing modes in elderly patients (older than 70 years old) with second-degree or third-degree AV block has been reported. Although the DDD pacing mode is the most complex, most guidelines recommend this pacing mode in patients with AV block since it maintains AV synchrony regardless of the cause of the bradycardia.

**VDD AND VDDR MODES**

Although the DDD pacing mode provides AV synchrony, its use requires the presence of a separate atrial lead. Recently, a single lead that has both ventricular and atrial electrodes has been developed; the ventricular electrodes are in direct contact with the right ventricular endocardium, while the atrial electrodes “float” in the right atrium. When used with a pacemaker in the VDD pacing mode, this lead allows sensing of atrial activity and ventricular pacing. In the presence of normal sinus rates, AV synchrony is maintained using a less complex system. However, if sinus bradycardia develops, AV synchrony is lost since the atria cannot be paced (see Fig. 13-14).

**FIGURE 13-14** Responses of various modes in a patient with complete atrioventricular (AV) block and a sinus pause. *First row,* Baseline rhythm strip before pacing shows complete heart block. In addition, there is a sinus pause. *Second row,* Same strip with a pacing system in the VVI pacing mode. Bradycardia is prevented, but AV synchrony is not present. *Third row,* In the VDD pacing mode, atrial activity is sensed by the pacemaker (*), which initiates the A–V interval and maintains AV synchrony. However, when a sinus pause occurs, since the atria are not paced, ventricular pacing occurs, and AV synchrony is lost. *Fourth row,* In the DDD pacing mode AV synchrony is maintained regardless of the cause of bradycardia. When a sinus pause occurs, an atrial stimulus (Ap) is provided.


