Comprehensive review of a common clinical finding

Bradyarrhythmias

Vanessa Weberndörfer, Ian Russi, Richard Kobza

Heart Centre Lucerne, Luzerner Kantonsspital, Lucerne, Switzerland

Summary

Pacemaker implantation is indicated when symptoms can clearly be attributed to bradyarrhythmias or in asymptomatic patients with type 2 second degree atrioventricular (AV) block or complete heart block.

First-degree AV block or Mobitz 1 second-degree AV block usually do not need any intervention unless there are signs of an infranodal AV block.

Biventricular pacemakers and implantable cardioverter defibrillators should be considered in patients with a pacing indication and reduced left ventricular ejection fraction.

Prior to pacemaker implantation reversible causes of bradyarrhythmias should be excluded.

Atropine should only be administered in intranodal AV block, as there is an elevated risk of causing asystole in infranodal block.

Key words: pacing; AV block; SA block; pacemaker; bradycardia; bradyarrhythmia; His-bundle pacing

Introduction

Bradyarrhythmias are a common clinical finding and can be physiological, as in athletes, or caused by a dysfunction in the cardiac conduction system at the level of the sinus node, the atrioventricular node or the His/Purkinje system. The most important prognostic factor is the location of the block and the underlying cardiomyopathy. Therefore, it is crucial to establish the correct diagnosis, as some bradyarrhythmias have an excellent prognosis and do not require treatment whereas others can be life threatening.

Clinical presentation

The clinical presentation of bradyarrhythmias depends on their duration (persistent vs intermittent), severity and the consequent reduction in cardiac output. Persistent bradycardia is associated with symptoms such as fatigue, inability to concentrate, cognitive impairment, dizziness, shortness of breath or exercise intolerance, whereas intermittent bradycardia presents more often with vertigo, blurred vision, light-headedness and syncope [1] caused by a sudden decrease in cerebral perfusion. Chest pain unrelated to effort might be due to cardiac hypoperfusion. Reduced exercise capacity can occur with normocardia in cases of chronotropic incompetence, which is defined as insufficient heart rate acceleration in response to physical or emotional triggers. Rarely, pacemaker-syndrome-like symptoms (pulsations in the head and neck) can be observed in patients suffering from first-degree atrioventricular (AV) block with very long AV conduction times (PQ >300 ms). The early diastolic atrial contraction is at the expense of early diastolic filling and diastolic mitral regurgitation may occur [2]. Adam-Stokes syndrome is a fainting spell caused by infranodal paroxysmal AV block and prolonged asystole due to suppression of impulse formation of subsidiary pacemakers leading to prolonged asystole. A second potential cause of Adam-Stokes syndrome in patients with complete AV block is runs of polymorphic ventricular tachycardia (torsade des pointes) elicited by ventricular premature beats with a long coupling interval occurring during the T-wave of the preceding ventricular depolarisation due to a very long QT interval (see fig. 1).

Intrinsic versus extrinsic causes of bradyarrhythmias

The number one primary cause of bradyarrhythmias is aging leading to fibrosis and degeneration of the conduction system and pacemaker cells. Hypertension, diabetes mellitus and chronic ischaemic heart disease are considered as risk factors [3]. Acute or chronic ischaemia in the territory of the right coronary artery may result in sinus bradycardia. Proximal occlusion of the left coronary artery or a dominant right circumflex artery is more likely to lead to subnodal conduction problems such as second-degree AV block or bundle-branch block, as well as transient third-degree AV block. A rare cause of sinus node disease is ion channel dysfunction. Mutations in the genes *SCN5A*, *HCN4*, and *MYH6* have been described [4]. The most common intrinsic and extrinsic causes of bradyarrhythmias are listed in table 1. The most common extrinsic cause of bradyarrhythmias are drugs (table 2). Athlete's heart may mimic sinus node disease or be associated with

conduction alterations as a consequence of increased vagal tone, a decrease in sympathetic tone and structural cardiac adaptations. These adaptations are usually seen in athletes engaged in high intensity endurance sports [5]. Carotid sinus hypersensitivity is an exaggerated response to stimulation of the carotid ar-

Table 1: Most common causes of bradycardia [2].

Intrinsic causes	**Sinus node dysfunction**	**AV node dysfunction**
Ion channel dysfunction	+	
Ischaemic fibrosis	+	+
Heart failure	+	+
Infiltrative disease (amyloid heart disease, haemochromatosis, sarcoidosis)	+	+
Aging-related fibrosis of the sinoatrial node	+	+
Congenital		+
Post-radiation fibrosis		+
Inflammatory conditions (Chagas, Lyme disease, myocarditis, bacterial endocarditis, etc.)		+
Autonomic dysfunction	+	+
Extrinsic causes		
Drugs	+	+
Obstructive sleep apnoea	+	+
Intoxication	+	+
Hypothyroidism	+	+
Electrolyte abnormalities (e.g. hyperkalaemia hypocalcaemia) ,	+	+
Neurally mediated conditions	+	+
Heart surgery (heart transplantation, valve surgery)	+	+
Interventions (TAVI, RF ablation, TASH)		+
Intracranial hypertension	+	+

TAVI = transcatheter aortic valve implantation, RF = radiofrequency, TASH = transcoronary ablation of septal hypertrophy

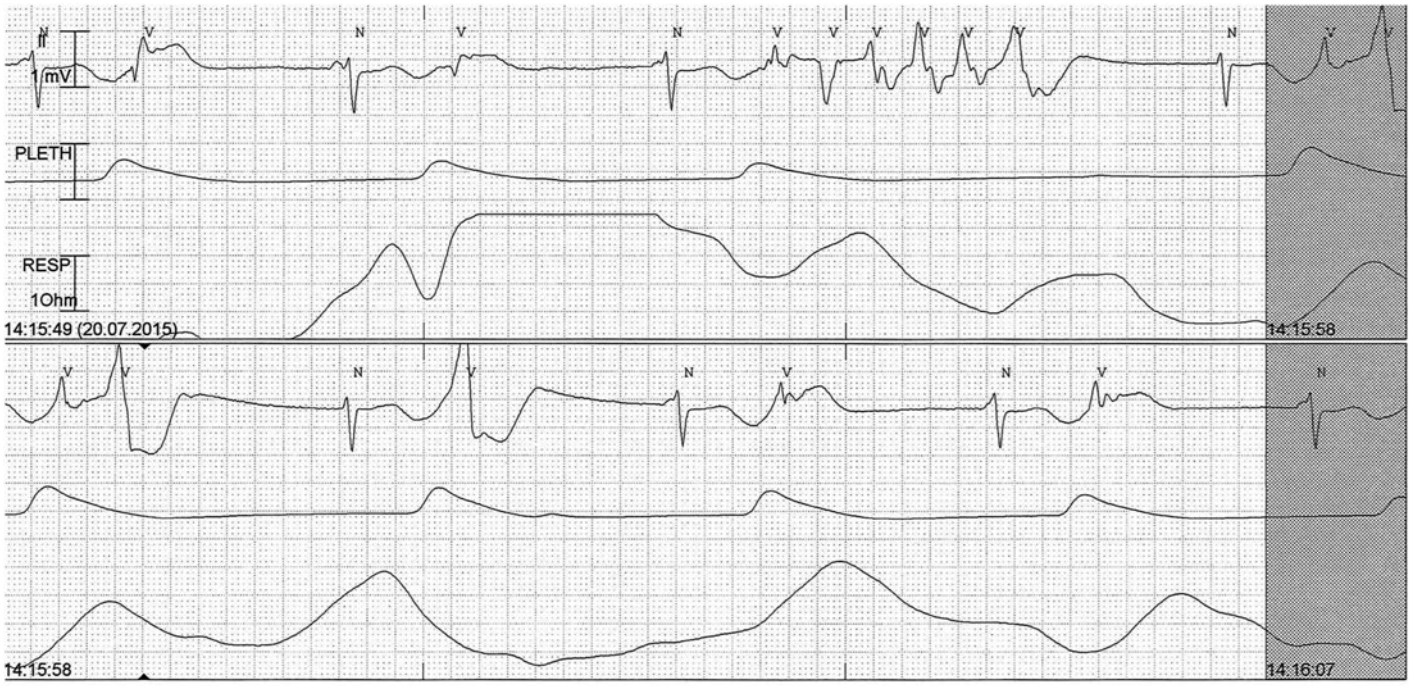

Figure 1: Patient with sinus node disease that was unmasked after cardioversion of atrial fibrillation. The ECG shows blocked P-waves in sinus bradycardia with idioventricular escape rhythm (N). The QT is prolonged and ventricular premature beats (V) with short coupling intervals are seen. One self-limiting polymorphic ventricular tachycardia over six beats. Shortly afterwards the patient developed ventricular fibrillation and was successfully resuscitated.

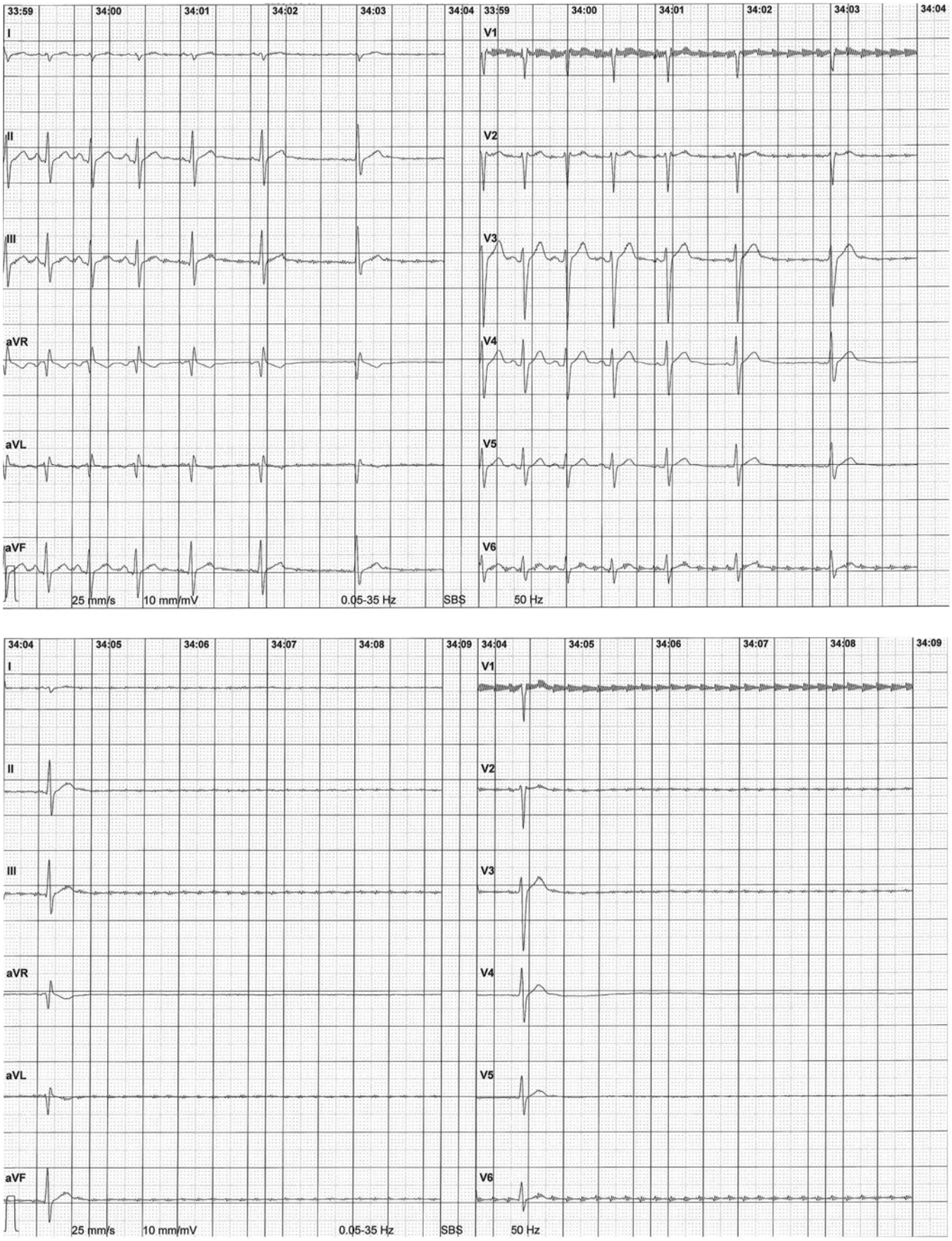

Figure 2: Sinus arrest after carotid sinus massage in a 31-year-old male with a history of fainting.

Table 2: Drugs frequently causing bradyarrhythmias.

Cardiac drugs causing bradyarrhythmia
Calcium-channel blocker (non-dihydropyridine type) e.g., verapamil, diltiazem
Class III antiarrhythmic drugs (amiodarone, dronedarone, sotalol)
Class Ic antiarrhythmic drugs (flecainide, propafenone)
Digoxin
Ivabradine
Beta-blockers
Non-cardiac drugs causing bradyarrhythmia
$5HT_3$-receptor antagonists – antiemetics
S1P-receptor-modulators (fingolimod) – multiple sclerosis
Mefloquine – malaria

tery baroreceptors. Vagal activation / sympathetic inhibition results in a higher than expected fall in heart rate and blood pressure and can lead to sinus bradycardia without structural alteration of the sinus node itself [6]. It tends to be observed predominantly in older males (see fig. 2).

Diagnosis

P wave morphology and its relation to the QRS complex, as well as the duration of the PR interval, are key to the diagnosis of any bradyarrhythmia, which can usually be made from a 12-lead ECG. Additional, autonomic testing can be useful to differentiate intranodal from infranodal type 2 AV block or when reflex syncope is suspected. The symptom–rhythm correlation is crucial to distinguish asymptomatic electrographic findings from symptomatic bradyarrhythmias requiring treatment. In cases of episodic symptoms, with or without ECG evidence of conduction disease, ambulatory Holter recordings are needed to establish the correct diagnosis. The required duration for rhythm monitoring is given by the frequency of the symptoms. In cases of daily recurrence, a 24-hour Holter may be sufficient. Symptoms with at least weakly occurrence should be detected on a 7-day recording [2]. In the case of less frequent symptoms, an implantable loop recorder may be helpful. Invasive electrophysiology testing is recommended in patients with unexplained syncope and previous myocardial infarction, sinus bradycardia, bundle-branch block or sudden brief undocumented palpitations [2]. Screening using a smartphone-based application (e.g., Kardia by AliveCor®) to obtain ECGs is not suitable for patients with syncope, but may be helpful in patients with intermittent dizziness.

Blood tests can help to exclude thyroid disorders or electrolyte imbalances. Once the diagnosis of symptomatic bradyarrhythmia is established, echocardiography is recommended to assess left ventricular function and to screen for signs of ischaemic heart disease, as this will influence the choice of pacemaker. Echocardiography is a good screening tool for infiltrative disorders. Cardiac magnetic resonance imaging is advised in patients aged <55 years to exclude cardiomyopathy [2].

Electrographic features of common bradyarrhythmias

Sinus node disease

The sinus node is situated near the junction of the right atrium and the superior vena cava. The sinus P wave is typically positive in II, III, aVF and biphasic in V1. Each P wave is followed by a QRS complex and all PP intervals are equal to the RR intervals. Sinus bradycardia is defined by a heart rate <60 bpm and is rarely a cause of haemodynamic instability. Most frequently it is diagnosed in the elderly or in athletes. Signs of severe sinus node dysfunction are persistent bradycardia <45 bpm without identifiable cause, chronotropic incompetence, and paroxysmal or persistent sinus arrest, which may occur in combination with atrial fibrillation or flutter (tachy-brady-syndrome) [7].

Sinus arrest

When the sinus node fails to generate an impulse the corresponding P wave as well as the following QRS complex and T wave are missing and a pause is generated. Usually the AV node or lower parts of the conduction system take the role of principal pacemaker and the pause is followed by a junctional rhythm or an idioventricular rhythm. If no escape rhythm occurs the pause leads to syncope and, in extreme situations, asystole and the patient needs immediate advanced cardiac life support. Sinus pauses <3 seconds are frequently seen in normal individuals.

Junctional rhythm

When the sinus node fails to generate an impulse the AV node may work as principal pacemaker. The atria and ventricles are excited simultaneously at a rate of about 40–60 bpm. The ECG deflection created by the ventricular depolarisation, the QRS complex, exceeds by far the P wave created by the atrial depolarisation. The P wave may be buried within the QRS complex or may occasionally follow the QRS complex. If a P wave precedes the QRS, the PR interval is typically shorter than in sinus rhythm (<110 msec) and the P wave is neg-

ative in II, III, aVF. Individuals with junctional escape rhythm are usually haemodynamically stable as long as they are not otherwise compromised.

Idioventricular rhythm

As in junctional rhythm, the principal pacemaker is not the sinus node but is now within the ventricles. The heart rate is lower (20–40 bpm) and the QRS complexes are usually wide as the ventricles are not depolarised via the conduction system. This rhythm may cause haemodynamic instability.

Atrioventricular blocks

First-degree AV block is a delay in the atrioventricular conduction with a PR interval >200 ms on the ECG. Most commonly the conduction slowing is at the level of the AV node, but some first-degree AV blocks with wide QRS complexes arise from an infranodal block. Since the level of the block has a prognostic impact and may therefore change the management of the patient, it is important to watch out for wide QRS complexes (see fig. 3). Second-degree AV block Mobitz type 1 is a progressive slowing of the atrioventricular conduction until an impulse fails to conduct to the ventricle (Wenckebach phenomenon). The PR interval prolongs at decreasing increments while the RR interval progressively shortens. The pause after the blocked P wave is less than two times the baseline RR interval. Again, wide QRS complexes may indicate an infranodal block.

Mobitz type 2 second-degree AV block appears as an abrupt blocking of a P wave with a fixed PR interval. There is no PR interval prolongation, and the RR interval surrounding the blocked P wave is two times the baseline RR interval. Mobitz type 2 is frequently associated with significant underlying electrical disorders such as bundle-branch block, and can progress to complete heart block. The conduction disturbance is in the

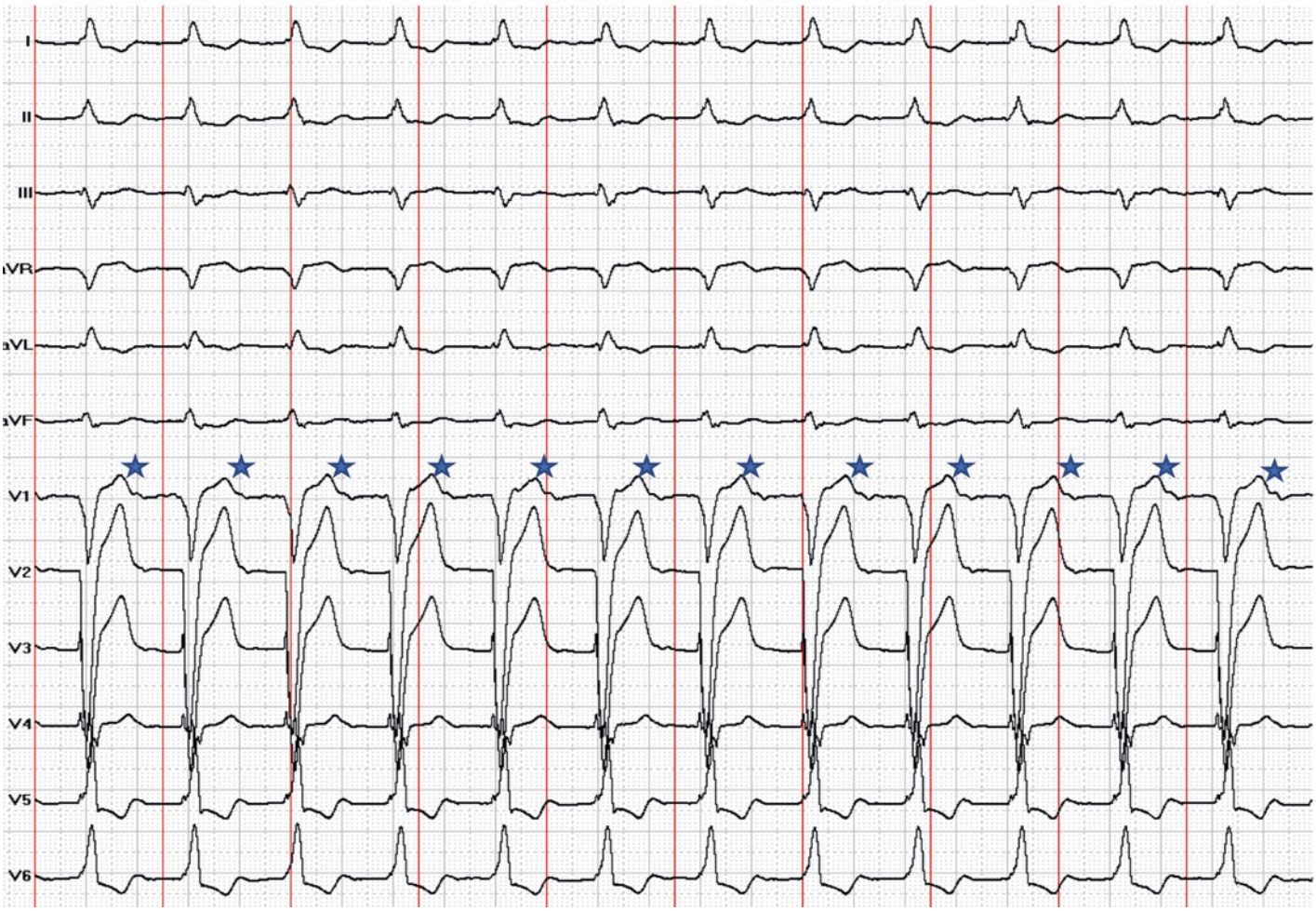

Figure 3: Patient with ischemic heart disease and reduced ejection fraction shows normocardic sinus rhythm with first degree AV block and left bundle branch block. P-waves are indicated by asterisks and best seen in lead V1.

His-Purkinje system. In electrophysiological studies, an H electrogram is recorded, but there is no subsequent ventricular activity in the blocked cycle.

A 2:1 AV block is a second-degree AV block in which every other P wave is blocked. Since the main electrocardiographic characteristic used to differentiate Mobitz 1 from Mobitz 2 is the variability of PR interval in Mobitz 1, it is impossible to categorise a second-degree AV block as either Mobitz 1 or Mobitz 2 when the conduction ratio is 2:1. The site of block can only be determined with an electrophysiological study. In prolonged or permanent 2:1 block pacemaker implantation is indicated in both situations, usually for symptomatic reasons. Features that suggest an AV nodal conduction disturbance are normal QRS duration, very long PR interval, concomitant type 1 block and worsening of the degree of the block with vagal manoeuvres. The opposite characteristics are seen in infranodal block.

In high-grade AV block two or more P waves are blocked. It may be associated with a junctional or ventricular escape rhythm (see fig. 4).

Third-degree AV block is a complete block of atrioventricular conduction and is frequently associated with haemodynamic instability. AV dissociation is indicated by an atrial rate faster than the ventricular rate. The rate of the escape rhythm depends on the site of block and can be junctional or idioventricular.

Red flags for immediate referral

Unstable patients with compromised haemodynamics including chest pain, confusion or hypotension require immediate referral to secondary care. Patients with severe bradycardia with ventricular rates <30 bpm are at risk for bradycardia-induced torsades des pointes and therefore need haemodynamic monitoring. Other reasons for hospitalisation might be ongoing syncope associated with bradycardia or syncope on exertion, signs of heart failure, family history of an inherited arrhythmia or sudden cardiac death.

Indications for pacemaker therapy

Pacemaker implantation is the mainstay of bradyarrhythmia management. Any reversible cause of bradyarrhythmia should be corrected prior to pacemaker implantation. Patients with clinical or electrocardiographic signs of ischaemia should be treated prior to permanent pacemaker implantation as the bradycardia could potentially resolve. For AV block, the prognosis depends on the degree of block and its location. Complete heart block is the most common indication for permanent cardiac pacing. In second-degree AV block type 2, the risk of progression to complete heart block is high, therefore pacemaker implantation is clearly indicated [2]. In second-degree AV block type 1, a permanent pacemaker can be considered if the patient is symptomatic or the level of block is at

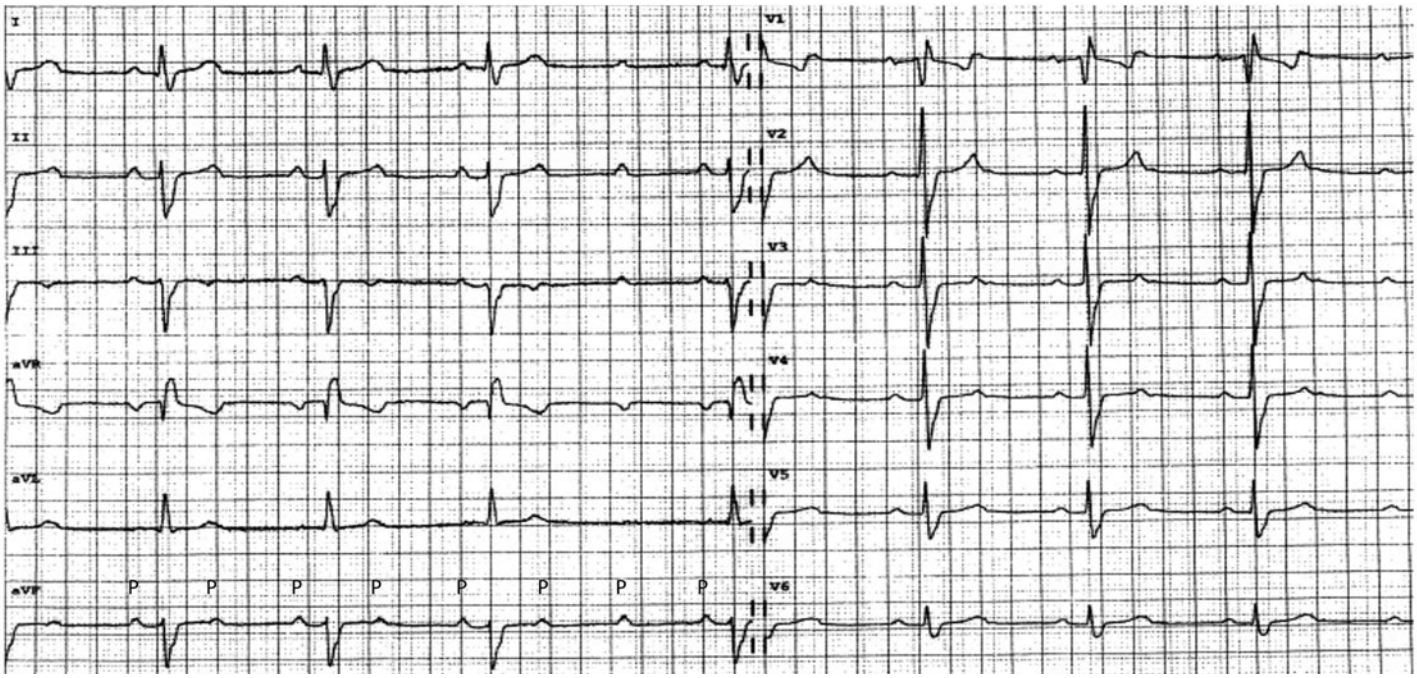

Figure 4: Sinus rhythm with 2:1 and 3:1 AV block in a patient with ischaemic heart disease and bifascicular block. P waves are marked with P.

intra- or infra-His levels [2]. Patients with 2:1 infranodal block should undergo pacemaker implantation. Sinus node disease is the second most common indication for permanent pacing. It is considered a safe rhythm and there is no evidence that cardiac pacing leads to a survival benefit in this patient cohort. Pacing is mostly performed to alleviate symptoms associated with sinus node disease (chronotropic incompetence, sinus pauses >3 seconds or sinus bradycardia <40/min) [2]. The current European Society of Cardiology (ESC) guidelines advise offering pacemaker implantation to patients with a history of syncope and asymptomatic sinus pauses >6 seconds as there is weak evidence that pacing may reduce syncopal events [2]. Determining if a patient has chronotropic incompetence can be challenging. If the heart rate rises to above 100 bpm in a treadmill test or ambulatory Holter recording, it is very unlikely that pacemaker implantation will improve the patient's symptoms. Table 3 lists indications for permanent pacing.

Table 3: Recommendations for pacemaker implantation according to reference [2].

Recommendations in sinus node disease	Class/level of evidence
Pacing is indicated when symptoms can clearly be attributed to bradycardia in sinus node disease.	IB
Pacing is indicated in patients affected by sinus node disease who have documentated symptomatic bradycardia due to sinus arrest or sinoatrial block.	IB
Sinus node dysfunction after cardiac surgery and heart transplantation. A period of clinical observation from 5 days to some weeks is indicated in order to assess if the rhythm disturbance resolves.	IC
Recommendations in AV conduction disorder	
Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptoms.	IC
Intermittent/paroxysmal AV block (including atrial fibrillation with slow ventricular conduction). Pacing is indicated in patients with intermittent/ paroxysmal intrinsic third- or second- degree AV block.	IC
Pacing is indicated in patients with alternating bundle-branch block with or without symptoms.	IC
Pacing is indicated in patients with syncope, bundle-branch block and positive electrophysiology studies defined as HV interval of ≥70 ms, or second- or third-degree His-Purkinje block demonstrated during incremental atrial pacing or with pharmacological challenge.	IB
High degree or complete AV block after cardiac surgery and transcatheter aortic valve implantation. A period of clinical observation up to 7 days is indicated in order to assess whether the rhythm disturbance is transient and resolves. In the case of complete AV block with low rate of escape rhythm this observation period can be shortened since resolution is unlikely.	IC
Pacing should be considered in patients with history of syncope and documentation of asymptomatic pauses >6 s due to sinus arrest, sinoatrial block or AV block.	IIaC
Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels in electrophysiology studies.	IIaC
Pacing should be considered in patients ≥40 years with syncope and documented symptomatic pause/s due to sinus arrest or AV block or the combination of the two.	IIaB

Complications of pacemaker therapy

Several complications related to the implantation procedure can occur and depend partly on the implantation technique. The occurrence of pneumothorax and haemothorax is related to the venous access technique most preferably if the subclavian vein is punctured [8]. In patients on antiplatelet and/or anticoagulant therapy, the risk for pocket haematoma is increased. Bridging with low-molecular weight heparin is contraindicated as it increases tremendously the risk of postoperative bleeding. Lead-related complications are cardiac perforation or tamponade, diaphragmatic stimulation, dislodgement or venous thrombosis [9].

Recent advances in therapy

Leadless pacemakers

Leadless pacemakers were designed to overcome typical complications of transvenous devices, such as lead problems, valve injuries, pocket erosion or infections. These miniaturised devices are inserted via the femoral vein and directly attached to the right ventricular myocardium with tines. The only system which is currently available is the Micra™ transcatheter pacing system manufactured by Medtronic, a VVI pacemaker (see fig. 5). Two prospective nonrandomised multicentre trials reported 99.6% implant success and a low rate of major complications (1.5–4%), including pericardial effusion, infection or dislocation, which was actually lower than with conventional transvenous pacing systems in the historical control group. During a follow-up period of up to 24 months, electrical performance was excellent and projected battery longevity was 12.1 years [10, 11]. Currently, leadless pacemakers, which can sense the atrium and pace the ventricle, are under development, as is a true dual chamber pacemaker with implants in the atrium and the ventricle that can communicate with each other to achieve true dual chamber pacing. An accelerometer-based atrial sensing algorithm in a single chamber ventricular leadless pacemaker is a potential technology to improve AV synchronicity in patients with AV block (VDD) [12].

Battery-less pacemakers

Generator changes are a potential source of complications such as pocket infections. Several battery-less pacemaker systems have been tested in animal models. Piezoelectric nanowires harvest energy from pulmonary motion [13]. Mechanical clockwork converts motion energy from right ventricular contractions into electrical energy [14] and intravascular turbines harvest energy from the blood flow [15]. Another sys-

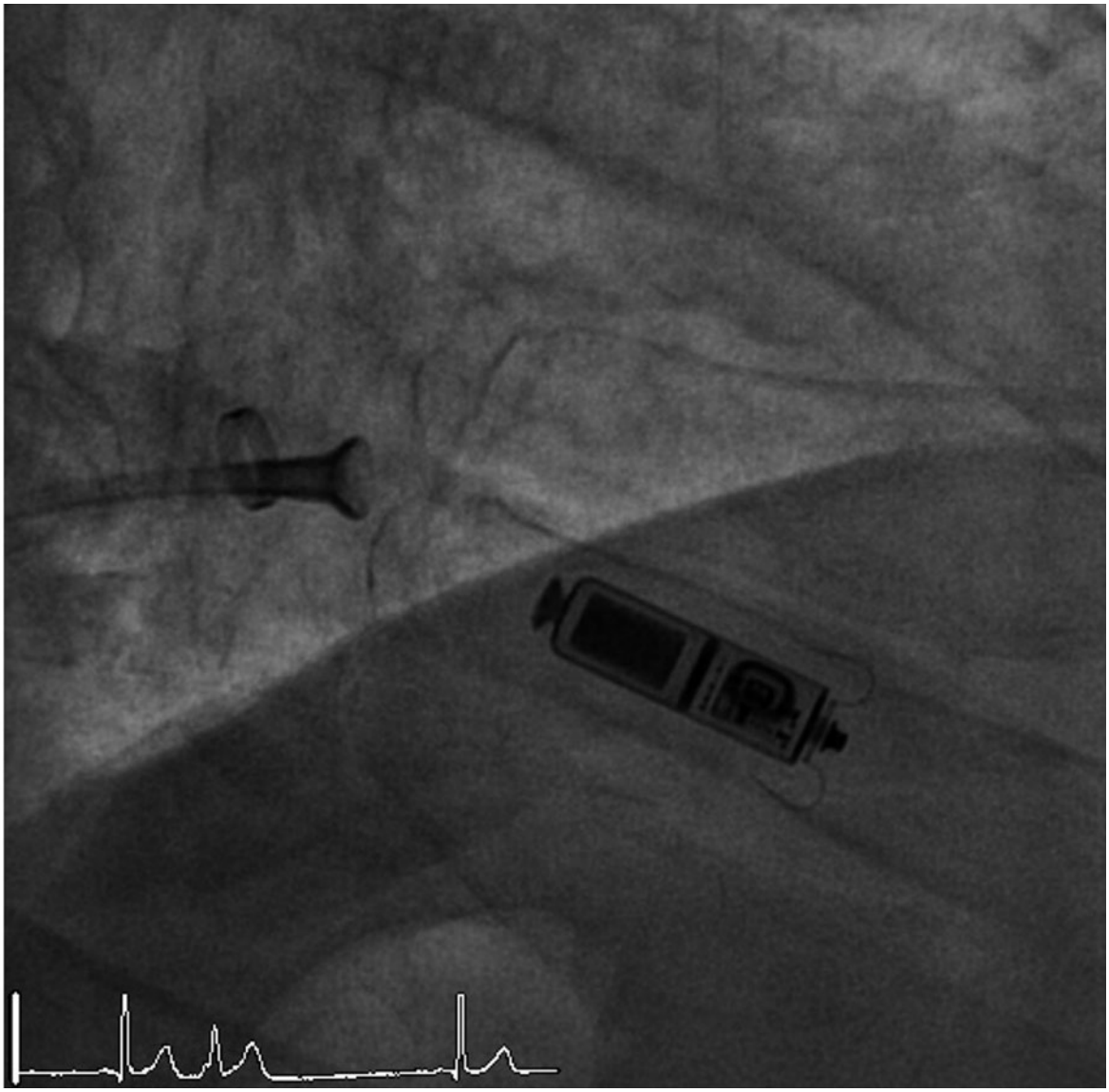

Figure 5: Deployment of a Micra™ pacemaker. The delivery catheter is pulled back after the pacemaker capsule has been positioned in the RV apex and the tines are fixed.

tem works with subcutaneously implanted solar cells [16]. An alternative to pacemaker devices are biological pacemakers. Non-pacemaker myocytes are modified into pacemaker cells providing automaticity by means of gene therapy [17]. Biological pacemakers have a potential for arrhythmia and are in the very early stages of development.

His bundle pacing

Right ventricular apical pacing induces dyssynchrony in the ventricle and is associated with an increased risk of heart failure [18–20]. Biventricular pacing is superior to right ventricular apical pacing in patients with reduced ejection fraction [21, 22] and reduces morbidity and mortality in heart failure patients [22]. However, biventricular pacing therapy has to cope with procedural complexity, nonresponders and complications of lead burden. His-bundle capture enables rapid activation of the ventricles via the intrinsic conduction system with a narrow QRS and was described for the first time in 2000 by Deshmukh et al. [23]. His bundle pacing has been performed in intact His-Purkinje system [23, 24], in bundle-branch block and complete nodal and infra-nodal AV block [25]. In selected patients, it was used for cardiac resynchronisation [26]. The largest single-centre series of His bundle pacing was recently published by Abdelrahman et al. and showed a signifi-

cant decrease in heart failure hospitalisations and a trend towards decrease in mortality [27]. So far, there have been no randomised controlled trials comparing permanent His bundle pacing and right ventricle pacing.

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Correspondence:
Vanessa Weberndörfer, MD
Heart Centre Lucerne, Cardiology
Spitalstrasse
CH-6000 Luzern
vanessa.weberndoerfer[at]luks.ch