20

Antiarrhythmic therapies

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Introduction

Optimal cardiac function is achieved by a coordinated pattern of cardiac contraction and relaxation that is regulated by electrical activity within the heart (see Chapter 16). Severe arrhythmias (or the development of an arrhythmia in a patient with already compromised cardiac function) may result in impaired cardiac output, increased filling pressures and increased myocardial work (haemodynamic instability). Less severe arrhythmias may not cause haemodynamic instability; however, some can be a premonitory sign of a more severe arrhythmia or sudden death (electrical instability).

Haemodynamic or electrical instability may cause one or more adverse clinical sequelae:

- Signs of haemodynamic compromise
- Progression of concurrent cardiac disease
- Sudden cardiac death.

From this, *treatment of arrhythmias appears desirable.*

Antiarrhythmic therapies can come in many forms. The simplest and most effective therapy is treatment of the underlying condition causing the arrhythmia (e.g. gastric dilatation–volvulus, sepsis, heart failure). When this is not possible or effective, specific antiarrhythmic interventions may be necessary. These include antiarrhythmic drugs and electrical therapies (e.g. synchronized DC cardioversion, defibrillation, pacemaker therapy). All antiarrhythmic therapies have limitations, the most important of which is the potential to worsen the arrhythmia or the clinical status of the patient.

Antiarrhythmic drugs are fairly non-selective in action, possessing not only beneficial effects for suppressing arrhythmias in diseased areas of cardiac tissue, but also adverse effects that may potentiate arrhythmias in other areas of the heart (proarrhythmia). Some drugs adversely affect cardiac function or cause adverse non-cardiac effects. External electrical stimulation is inherently painful and therefore limited to patients under general anaesthesia (e.g. transthoracic pacing during pacemaker implantation) or for the treatment of acute, life-threatening arrhythmias (e.g. defibrillation during cardiac resuscitation). Internal pacemaker therapy in small animal cardiology is currently reserved for the treatment of bradyarrhythmias that result in clinical signs and carries a variety of risks, including intraoperative death, lead dislodgement and infection. When used inappropriately any antiarrhythmic therapy has the potential to cause harm, including death. Therefore, *antiarrhythmic therapy should not be considered completely benign.*

This apparent contradiction between the desire to treat an arrhythmia and to 'first do no harm' results in a therapeutic challenge for any clinician faced with managing a patient with an arrhythmia. Critical decision making is the key to appropriate management. Answering a few simple questions can help to determine the most appropriate treatment for any patient with an arrhythmia:

1. Is there a treatable underlying condition?
2. What are the potential adverse effects of the arrhythmia?
3. What are the potential effects (beneficial and adverse) of antiarrhythmic therapy?

Is there a treatable underlying condition?

Conditions that cause arrhythmias do so by altering myocardial structure, intra- or extracellular fluid composition, or neural control and include:

- Structural cardiac disease
- Cardiac trauma
- Autonomic imbalance
- Myocardial hypoxia
- Metabolic abnormalities
- Inflammation
- Drugs/toxins
- Extremes of temperature.

It is extremely important to identify any underlying disease that may cause an arrhythmia, as the most effective antiarrhythmic therapy is to abolish the cause (see Chapter 16). Treatment of the underlying disease alone may be sufficient to resolve the arrhythmia in some cases (e.g. oxygen supplementation in hypoxaemia). In other cases, a concurrent condition may be an important reason for failure of an antiarrhythmic therapy (e.g. hypokalaemia with ventricular tachycardia). It is also important to identify conditions that are not easily treatable and carry a poor prognosis for recovery, such as cardiac

neoplasia and end-stage organ failure. Antiarrhythmic therapy may be less effective in these patients.

For patients with arrhythmias secondary to critical systemic disease, it is important to ensure adequate oxygen supplementation and analgesia (if required) and to correct any fluid or electrolyte abnormalities.

What are the potential adverse effects of the arrhythmia?

The potential adverse effects of arrhythmias are the development of signs of haemodynamic compromise, progression of concurrent cardiac disease and sudden cardiac death. These can develop as a consequence of haemodynamic instability, electrical instability, or a combination of both.

Haemodynamic instability

Haemodynamically unstable arrhythmias are those that compromise cardiac function sufficiently to result in poor cardiac output or congestive heart failure (CHF). Poor cardiac output results in clinical signs of hypoperfusion, including:

- Lethargy
- Depressed mentation
- Weakness
- Collapse
- Pallor
- Poor pulse quality
- Cold extremities
- Hypothermia.

Unless concurrent myocardial failure is present, these signs usually only accompany sustained arrhythmias at very rapid rates (e.g. supraventricular tachycardia, ventricular tachycardia) or very slow rates (e.g. third-degree atrioventricular (AV) block). Patients are frequently hypotensive, although some are normotensive with signs of intermittent hypoperfusion. These patients may have no signs of hypoperfusion on examination, but instead have a history of exercise intolerance, episodic weakness or syncope, which develop when there is an increase in metabolic demand (e.g. during exercise) and/or from a transient worsening of the arrhythmia. This can be difficult to identify in animals with a sedentary lifestyle, such as cats and some dog breeds.

If an arrhythmia is suspected to be the cause of episodic collapse, it is important to rule out other conditions that resemble syncope (see Chapter 3). Obtaining a good description of the pattern of signs from the owner is essential. A video recording of collapse episodes may also help to differentiate syncope from seizure or muscular weakness. It is important to make attempts to document the actual cause of collapse in patients with known arrhythmias. Reports of bradyarrhythmia-related syncope in some Dobermanns and Boxers with concurrent ventricular arrhythmias highlight the fact that inappropriate presumptive therapy may be ineffective or even worsen clinical signs (Calvert *et al.*, 1996a; Thomason *et al.*, 2008). To this end, ambulatory (Holter) electrocardiogram (ECG) monitoring, exercise testing with ECG telemetry, or event monitoring with loop recording devices can be useful (see Chapter 9).

CHF tends to occur in patients with sustained tachy- or bradyarrhythmias. When CHF develops in patients without concurrent structural cardiac disease, it is more likely to be right-sided, since oedema develops at lower pressures in the systemic venous system than it does in the pulmonary system (see Chapter 15). Arrhythmias that cause both an abnormal heart rate and absent or asynchronous contractions are particularly likely to cause CHF, since both abnormalities elevate venous pressures independently. Examples include atrial fibrillation (AF) with a rapid ventricular rate, and third-degree AV block. A haemodynamically unstable arrhythmia almost invariably requires treatment. Therefore, a detailed history and thorough physical examination, including evaluation of mentation, inspection of veins, palpation of arterial pulses and assessment for effusions are vital for any animal with an arrhythmia.

Electrical instability

Electrically unstable arrhythmias are those that may result in sudden cardiac death due to the development of a life-threatening arrhythmia, such as pulseless ventricular tachycardia, ventricular fibrillation or asystole (see Chapter 16).

There is no consensus on which criteria are reliable indicators of electrical instability in small animals, and most are based on personal experience or evidence extrapolated from human studies. Most cardiologists agree that rapid, sustained ventricular tachycardia, third-degree or high-grade second-degree AV block (particularly with a ventricular rate <40 beats/minute or periods of ventricular standstill due to an unstable escape rhythm) and hyperkalaemic atrial standstill are potentially unstable arrhythmias, both electrically and haemodynamically. There is also general consensus that infrequent, isolated ventricular ectopy, low-grade AV block and short periods of sinus arrest do not require therapy in a patient without clinical signs, as these arrhythmias rarely result in haemodynamic compromise or electrical instability. Furthermore, supraventricular tachyarrhythmias rarely confer electrical instability and are therefore usually treated based on the presence of haemodynamic compromise or risk of myocardial failure due to tachycardia-mediated cardiomyopathy (see Chronic effects below).

The arrhythmias that present the most difficult therapeutic decisions for the clinician are complex or frequent ventricular arrhythmias that do not result in signs of haemodynamic compromise. Such arrhythmias include non-sustained ventricular tachycardia, ventricular runs, R-on-T phenomenon, polymorphic ventricular premature complexes, couplets, triplets and frequent ventricular premature complexes. It is possible that some or all of these arrhythmias are electrically unstable. From the experiences of human cardiology, couplets, triplets and non-sustained ventricular tachycardia do not confer an increased risk of sudden death in healthy individuals, but do in the

presence of myocardial disease, particularly if systolic dysfunction is present (Goldberger *et al.*, 2008). However, it is not known whether the arrhythmias themselves increase risk of sudden death, as their prevention with antiarrhythmic therapy may not necessarily result in improved survival. This has been shown in several studies in humans, in which reduction of arrhythmias and even arrhythmic death was not associated with a reduction in overall mortality (CAST Investigators, 1989). Although there are obvious limitations in direct extrapolation from human studies, this highlights the need to treat the patient rather than simply the arrhythmia. For example, in certain myocardial diseases, even isolated ventricular premature complexes are a marker for more severe, potentially life-threatening arrhythmias. This should always be considered if ventricular arrhythmias are detected in breeds prone to cardiomyopathy with an increased risk of sudden death (such as Boxers and Dobermanns).

Cardiac arrest rhythms

Cardiac arrest rhythms are those that result in no discernable cardiac output. Irrespective of the underlying cause, immediate intervention is essential as death will rapidly ensue. Treatment involves basic cardiac life support (airway, breathing, circulation), followed by advanced cardiac life support (drugs, intravenous fluids, DC cardioversion/defibrillation) as appropriate. For further details, see texts describing cardiopulmonary–cerebral resuscitation (*BSAVA Manual of Canine and Feline Emergency and Critical Care*).

Chronic effects

As well as acute effects, some arrhythmias can have adverse effects in the medium and long term. These are usually seen in patients with sustained tachyarrhythmias or bradyarrhythmias, and treatment should therefore be considered in such cases. *Myocardial failure is an inevitable consequence of a sustained tachyarrhythmia over time* (tachycardia-mediated cardiomyopathy). This typically occurs with supraventricular tachycardias and has been demonstrated in various canine models. For example, rapid ventricular pacing at >240 beats/ minute for 2–3 weeks can cause myocardial failure in a previously healthy canine heart (Wilson *et al.*, 1987). As discussed above, these arrhythmias can also precipitate or potentiate CHF.

Intra-atrial thrombus formation is a potential complication of disease associated with atrial dilatation in cats. Arrhythmias that result in poor or absent atrial contraction are further risk factors for thrombus formation, particularly AF. Low-velocity atrial blood flow predisposes to platelet aggregation.

What are the potential effects of antiarrhythmic therapy?

Pharmacological antiarrhythmic therapies

The most widely used antiarrhythmic therapies in veterinary medicine are drugs. Antiarrhythmic drugs do not act simply to suppress arrhythmias, but instead act by altering the shape of action potentials in cardiac tissue, with the aim of making arrhythmogenesis less likely. Knowledge of the mechanisms behind generation of action potentials in different parts of the heart helps in understanding how different classes of antiarrhythmic agents act, but is not essential for most clinical scenarios.

Cardiac action potentials

The majority of cardiac tissue comprises cardiac myocytes. All myocytes are excitable cells, each with one or more additional functions, such as impulse generation and conduction, cellular contraction and relaxation. Cells with similar functions tend to have similar electrophysiological properties. On this basis, myocytes can be divided into three types of cell: nodal cells; His–Purkinje cells; and working myocardial cells. These three types of cell differ in their ability to generate and conduct an electrical impulse. This is reflected in the shape of their action potential.

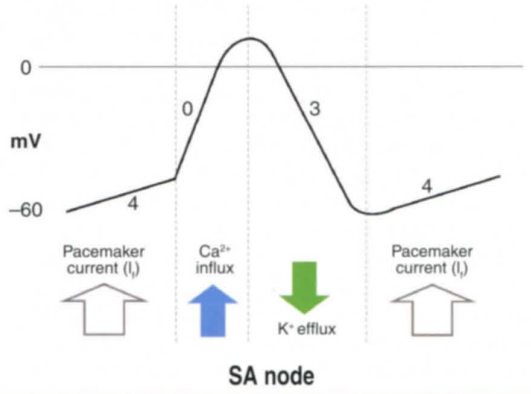
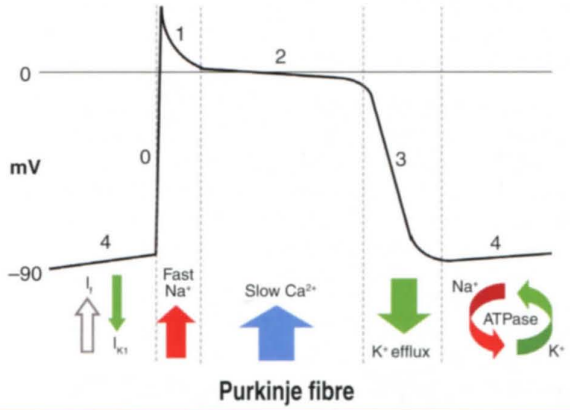
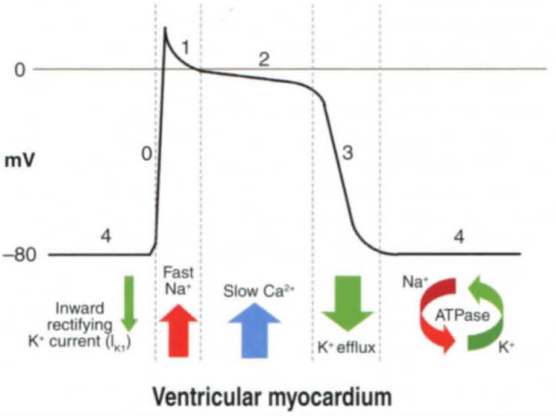
An action potential is a graphical representation of the change in potential difference (voltage) across the cell membrane over time. This change in membrane voltage is caused by the movement of ions across the cell membrane, primarily sodium, calcium, potassium and chloride. For the purposes of classification, the action potential is divided into five phases, referred to in chronological order as phases 0–4. For ease of understanding it is better to consider the action potential in three broader phases: threshold depolarization (phase 0); repolarization (phases 1–3); and resting phase (phase 4). Nodal cells, His–Purkinje cells and diseased myocardial cells may also undergo variable degrees of depolarization during phase 4. Figure 20.1 shows typical action potentials in cells of the sinoatrial (SA) node, ventricular myocardium and Purkinje fibres.

The rate of phase 0 depolarization determines the speed at which an electrical impulse traverses a cell. This is referred to as the *conduction velocity*. The rate of phase 4 depolarization is referred to as *automaticity*. The time taken for a cell to recover excitability is referred to as the *refractory period*. This is determined predominantly by the duration of repolarization (phases 1–3).

The differences in ion fluxes, automaticity, conduction velocity and refractory periods in different regions of the heart are important for understanding both the mechanisms of arrhythmogenesis and rationale for antiarrhythmic drug therapies.

Classification of antiarrhythmic drugs

In tachyarrhythmias, the aim of antiarrhythmic drug therapy is to reduce cardiac electrical activity. This is primarily achieved by slowing the rate of depolarization (phases 0 or 4), or prolonging repolarization (phases 1–3) within cells. Antiarrhythmic agents for tachyarrhythmias are broadly classified according to their mechanism of action. The most frequently used classification is the Vaughan Williams system (Vaughan Williams, 1984), which groups drugs into four classes based on their main electrophysiological effects (Figure 20.2). These effects are generally either an action on cardiac ion channels (e.g. sodium, calcium, potassium channels) or receptors (e.g. beta adrenergic receptors).

Cell type	Function	Location	Action potential
Nodal cells	Primary pacemakers	Sinoatrial (SA) node Atrioventricular (AV) node	
His–Purkinje cells	Rapidly conducting tissue	His bundle Bundle branches Purkinje fibre network	
Working myocardial cells	Mechanical work	Atrial myocardium Ventricular myocardium	

20.1 Cardiac action potentials.

Class	Mode of action	Examples	Main veterinary uses
I	Block sodium channels		
Ia	Depress phase 0 depolarization Prolong repolarization	Quinidine Procainamide Disopyramide	Refractory ventricular arrhythmias Supraventricular arrhythmias (including AVRT and AF conversion)
Ib	Depress phase 0 depolarization in abnormal tissue (little effect on normal tissue) Shorten repolarization	Lidocaine Mexiletine Tocainide Phenytoin	Ventricular arrhythmias May be useful in converting vagally mediated AF and some AVRT

20.2 Vaughan Williams classification of antiarrhythmic drugs. AF = Atrial fibrillation; ARVT = Atrioventricular reciprocating tachycardia (accessory pathway-mediated); AV = Atrioventricular; SVT = Supraventricular tachycardia. (continues) ▶

Class	Mode of action	Examples	Main veterinary uses
Ic	Markedly depress phase 0 depolarization Little effect on repolarization	Flecanide Encainide Propafenone	Little clinical experience in veterinary medicine Experimental efficacy in converting AF
II	Antiadrenergic drugs	Atenolol Propranolol Esmolol Metoprolol Carvedilol	Slow ventricular rate in atrial tachyarrhythmias (especially AF) SVT involving the AV node Ventricular arrhythmias
III	Prolong repolarization	Sotalol Amiodarone Bretylium Ibutilide	Ventricular arrhythmias Supraventricular arrhythmias (including SVT involving the AV node and AF conversion)
IV	Block calcium channels (not dihydropyridines)	Diltiazem Verapamil	Slow ventricular rate in atrial tachyarrhythmias (especially AF) SVT involving the AV node

20.2 (continued) Vaughan Williams classification of antiarrhythmic drugs. AF = Atrial fibrillation; ARVT = Atrioventricular reciprocating tachycardia (accessory pathway-mediated); AV = Atrioventricular; SVT = Supraventricular tachycardia.

- Class I antiarrhythmic agents block sodium channels in working myocardium and His–Purkinje tissue. This inhibits phase 0 depolarization and therefore slows impulse conduction.
- Class II agents are antiadrenergic drugs (mainly beta adrenergic receptor blockers). Catecholamines (via beta adrenergic receptors) cause arrhythmias by increasing myocardial work, activating pacemaker currents and stimulating calcium channels. Class II drugs antagonize these actions.
- Class III agents prolong repolarization in all parts of the heart. This occurs mainly via inhibition of repolarizing potassium currents. For an impulse to propagate from a cell, adjacent cells need to be fully repolarized before they are excitable. Therefore, by delaying repolarization, impulse conduction is slowed or blocked.
- Class IV agents are calcium-channel blockers. They exert their effects via inhibition of slow calcium channels, resulting in a decreased rate of depolarization in nodal cells. Class IV agents therefore slow both the SA nodal pacemaker and AV nodal conduction.

Class I agents are further subdivided according to slight differences in their action.

- Class Ia agents moderately slow conduction in working myocardium and His–Purkinje tissue. They also prolong repolarization (class III action), making them theoretically useful in the more rapid tachycardias.
- Class Ib agents preferentially slow conduction in abnormal (partially depolarized) myocardium. They have little effect on normal myocardium. This may result in a more targeted effect to inhibit depolarization in diseased tissue. They also shorten repolarization in diseased tissue, creating greater homogeneity of refractory periods between different areas of the heart.
- Class Ic agents are the most potent inhibitors of sodium channels. They markedly slow conduction in working myocardium and His–Purkinje tissue, but have minimal effect on repolarization.

There are two major limitations of the Vaughan Williams system. Firstly, it does not account for drugs with multiple classes of action (for example, class Ia agents also have class III actions, sotalol has classes II and III actions, amiodarone has classes I, II, III and IV actions). Secondly, other drugs with important antiarrhythmic actions are not included, such as digitalis glycosides, anticholinergic agents, sympathomimetic agents and magnesium salts. Figure 20.2 shows the main uses in veterinary medicine of antiarrhythmic drugs grouped according to the Vaughan Williams classification. The formulary in the Appendix has a more comprehensive list of antiarrhythmic agents, with suggested doses for dogs and cats.

Adverse effects of antiarrhythmic drugs

Since the actions of all antiarrhythmic drugs are relatively non-selective, they can have a variety of effects on cardiac and non-cardiac tissues, many of which are undesirable. Their effects are rarely targeted only to the area of arrhythmogenic tissue. Consequently, by affecting the electrophysiological properties of normal tissue, antiarrhythmic drugs can promote occurrence of an arrhythmia in one area of the heart, while trying to prevent an arrhythmia in another area (*proarrhythmia*).

Some antiarrhythmic drugs affect cardiac systolic and diastolic function. The negative inotropic effects of beta adrenergic receptor blockers and calcium-channel blockers are typical examples; both have a relative contraindication in patients with overt CHF or myocardial failure. Many antiarrhythmic drugs also have adverse non-cardiac effects. Typical examples of this are central nervous system (CNS) and gastrointestinal effects of many class I drugs. Amiodarone is worthy of specific mention: despite being a drug with classes I, II, III and IV antiarrhythmic effects, and therefore suitable for many ventricular and supraventricular tachyarrhythmias, it is also associated with a variety of adverse non-cardiac effects that limit its use (see below).

Overall, the development of adverse effects in individual patients is variable and unpredictable.

However, precautions to minimize adverse effects (such as administering mexiletine with food) should be followed.

Lidocaine

Lidocaine is a class Ib antiarrhythmic agent. It acts by inhibiting fast sodium channel opening, therefore slowing conduction in His–Purkinje and working myocardial cells. It has a preferential inhibition on cells with a less negative resting membrane potential, which results in a more targeted effect on diseased myocardium, and is effective in arrhythmias caused by all three main mechanisms (automaticity, triggered activity, re-entry). Lidocaine undergoes rapid first-pass hepatic metabolism, so is most effective when administered intravenously. It is mainly protein bound in the plasma.

The rapid onset of action, relative safety and efficacy make lidocaine *the ideal first-choice agent for treatment of ventricular tachyarrhythmias*. In dogs it can be administered at intravenous bolus doses of 2 mg/kg over about 1–2 minutes, up to a maximum of 6–8 mg/kg over 10 minutes. It is advisable to wait for 1–2 minutes between each bolus dose to observe for any resolution of the arrhythmia. Rapid bolus dosing or doses above 6–8 mg/kg should be avoided as they frequently result in neurological signs, ranging from involuntary muscle tremors to generalized seizures. If seizures occur, they can be treated with intravenous diazepam. Hypokalaemia should be corrected, as this is an important reason for a poor response to lidocaine.

The antiarrhythmic effects of lidocaine do not persist beyond 10–15 minutes after bolus therapy. Therefore, if continued therapeutic plasma concentrations are desired, a continuous rate infusion (CRI) at 25–100 µg/kg/minute should be started after bolus doses. The author usually starts at doses of ≥50 µg/kg/minute. Although lidocaine is rapidly metabolized by the liver, tapering may not be required when stopping a prolonged infusion. Active metabolites and distribution of the drug to peripheral tissues (e.g. adipose) lead to an elimination half-life of hours (Kowey *et al.*, 2000).

Although lidocaine has little effect on most supraventricular tachyarrhythmias, it may result in conversion to sinus rhythm in selected cases. These include patients with accessory pathway-mediated supraventricular tachycardia (SVT) (Johnson *et al.*, 2006) and acute-onset vagally mediated AF (Moïse *et al.*, 2005). However, lidocaine is not effective for the vast majority of patients with AF for whom disease of chronic duration is present associated with atrial dilatation and remodelling.

The main adverse effects of lidocaine are neurotoxicity (obtundation, anxiety, tremors, seizures) and gastrotoxicity (anorexia, nausea, vomiting, diarrhoea). There are few cardiac contraindications to the use of lidocaine, as adverse cardiac effects are rarely observed.

Lidocaine can be effective for treating urgent ventricular tachyarrhythmias in cats. However, this species is particularly prone to the adverse neurotoxic effects of the drug. Therefore, it should be administered at a much lower dose in cats (e.g. 0.5 mg/kg bolus, up to 2 mg/kg over 10 minutes).

Mexiletine

Mexiletine is a class Ib antiarrhythmic agent. It therefore has electrophysiological properties, pharmacokinetics and adverse effects similar to those of lidocaine. The main difference is the less rapid hepatic metabolism and longer elimination half-life of mexiletine following oral administration.

Mexiletine is indicated for chronic therapy of ventricular tachyarrhythmias, particularly in patients with arrhythmias that have been successfully treated with lidocaine. Mexiletine can be administered orally at a dose of 4–8 mg/kg q8–12h. *It is important that it is administered with food* or on a full stomach to minimize the most common adverse effects of the drug (i.e. anorexia, nausea, vomiting). Neurological side effects are less common. A combination of mexiletine with a beta adrenergic blocker (e.g. atenolol) may increase efficacy and decrease adverse effects, by allowing administration of both drugs at a lower dose. A combination of mexiletine (5–8 mg/kg q8h) and atenolol (12.5 mg/dog q12h) has been shown to reduce the frequency of ventricular arrhythmias in Boxers with arrhythmogenic right ventricular cardiomyopathy (Meurs *et al.*, 2002). A combination of mexiletine and sotalol has also been used in Boxers with ventricular arrhythmias (Prošek *et al.*, 2006). Mexiletine can also be useful for chronic antiarrhythmic control in cases of accessory pathway-mediated SVT (Johnson *et al.*, 2006).

Class Ib agents can be very neurotoxic in cats. The author has no experience of using mexiletine in this species.

Beta adrenergic blockers

Beta adrenergic blockers (beta-blockers) are class II antiarrhythmic agents and inhibit the binding of potentially arrhythmogenic catecholamines to beta-1 adrenergic receptors on the heart. Catecholamines exert arrhythmogenic effects via increased concentrations of cyclic AMP (cAMP) within the cardiac myocyte. Excess cAMP causes increased cardiac work, increased pacemaker currents and increased calcium-dependent triggered activity. Beta-blockers inhibit all of these effects. There is probably little variation in the antiarrhythmic effect of any beta-blocker in terms of their action on beta-1 adrenergic receptors. Instead beta-blockers vary by their effects on other adrenergic receptors (e.g. atenolol is relatively beta-1 selective, propranolol affects beta-1 and beta-2 receptors), pharmacokinetics (e.g. esmolol has a half-life of minutes, atenolol has a half-life of hours) and additional properties (e.g. sotalol has additional class III effects).

Beta-blockers can be effective for the treatment of supraventricular tachyarrhythmias by inhibiting the initiation of atrial ectopy and slowing conduction via the AV node. The latter action is most useful to decrease the ventricular rate in AF. Beta-blockers are also useful in ventricular tachyarrhythmias, particular those associated with elevated catecholamines. In

humans, beta-blockers do not reliably decrease the frequency of ventricular premature complexes, but do decrease clinical signs and mortality as a result of ventricular arrhythmias.

As well as beneficial effects in reducing heart rate and excitability, beta-blockers have short-term adverse effects to reduce contractility and ventricular relaxation. These effects can acutely impair cardiac function in patients with myocardial failure. Consequently they should be used cautiously in patients with systolic dysfunction and generally avoided in patients with poorly controlled CHF. When used in patients with systolic dysfunction, they should be given in very low doses initially, with careful up-titration of the dose and frequency over several weeks to months, depending on the clinical response of the patient. Lethargy, collapse, bradycardia, hypotension and precipitation of signs of CHF are the most common adverse effects. The author usually performs echocardiography and/or radiography in patients with underlying cardiac disease to assess for risk of developing CHF before starting beta-blockers. Respiratory difficulties due to bronchoconstriction may occur with non-selective (beta-1 and beta-2) beta-blockers and high doses of selective (beta-1 specific) beta-blockers.

The most frequently used oral beta-blockers in small animal cardiology are atenolol (beta-1 specific), propranolol (beta-1 and beta-2), metoprolol (beta-1 specific) and carvedilol (beta-1, beta-2 and alpha-1). The author prefers to use atenolol at a dose of 0.2–1.5 mg/kg q12–24h in dogs and 0.5–3 mg/kg q12–24h in cats. Sotalol and amiodarone are considered separately because of their additional actions. Esmolol is an ultrashort-acting beta-1 selective adrenergic blocker that can be given at doses of 50–100 µg/kg intravenously over 5 minutes in both dogs and cats. Esmolol is rapidly converted in the blood to inactive metabolites, resulting in a half-life of minutes. If ongoing beta-blocking actions are required, a CRI (25–100 µg/kg/minute) can be administered after initial bolus therapy.

Sotalol

Sotalol is a class III antiarrhythmic agent with additional class II actions. Commercially available sotalol is a racemic mixture of D- and L-isomers (DL-sotalol), each isomer with differential class II (beta-blocking) and class III (repolarization prolonging) effects. The combined actions result in blockade of beta-1 and beta-2 receptors, and inhibition of repolarizing potassium currents (particularly I_{Kr}) causing prolonged action potentials in all parts of the heart. The beta-blocking effects appear to occur at lower doses than the class III effects. Sotalol is almost entirely unbound in the plasma and therefore has little interaction with other drugs, such as digoxin. It undergoes primarily renal excretion.

Sotalol is effective for both ventricular and supraventricular tachyarrhythmias. In humans, both oral and intravenous sotalol suppresses ventricular ectopy to a similar degree to class I agents, including some prevention of ventricular tachycardia and ventricular fibrillation. It can also be effective in terminating, slowing, or preventing paroxysmal SVT and AF, with a greater efficacy than beta-blockers. This is probably due to its class III effects that result in an increase in refractory periods in the atria, AV node and accessory pathways. In dogs, sotalol at doses of 1.5–3.5 mg/kg orally q12h appears effective in suppressing ventricular arrhythmias in Boxers, either alone (Meurs *et al.*, 2002), or in combination with mexiletine (Prošek *et al.*, 2006). Intravenous sotalol has anecdotal success in terminating SVT and ventricular tachycardia in dogs and cats; the author has given intravenous bolus doses of 1 mg/kg over 3–5 minutes, repeated as necessary, to either terminate or slow such arrhythmias. This is usually followed by oral sotalol. Doses in dogs can range from 0.5–5 mg/kg orally q12h and in cats from 10–30 mg/cat orally q12h. The author usually starts therapy at the low end of the range in cats.

The main adverse effects of sotalol in small animals are those of all beta-blockers (negative inotropy, negative chronotropy and bronchoconstriction, see above). Negative inotropy can result in exacerbation or precipitation of CHF in patients with advanced heart disease or systolic dysfunction. Administration of sotalol should be avoided in patients with poorly controlled CHF or at risk of developing CHF. Negative chronotropy can result in signs of bradycardia, lethargy and collapse, particularly in patients with concurrent bradyarrhythmias or neurally mediated syncope. QT prolongation is the biggest risk of sotalol use in humans, as this can precipitate sudden death from *torsades de pointes* (see Chapter 16). This complication does not appear to be common in dogs and cats, but consideration of this effect should be given to patients with pre-existing QT prolongation, hypokalaemia, hypomagnesaemia, and with concurrent use of drugs known to prolong the QT interval (e.g. class Ia antiarrhythmics).

Amiodarone

Amiodarone is a drug with classes I, II, III and IV actions according to the Vaughan Williams classification. It therefore has electrophysiological actions on all parts of the heart. Amiodarone is highly lipophilic and very highly protein bound in the plasma. It has poor oral bioavailability, a high volume of distribution to tissues and very long elimination half-life (several weeks) with predominantly hepatic metabolism. These properties result in a slow and variable onset of action after oral dosing, high frequency of non-cardiac effects and continued action for weeks after cessation of dosing. Consequently, most dosing regimens involve loading doses, and the relationship between effects and plasma levels in dogs is poorly defined.

Amiodarone is effective for both ventricular and supraventricular tachyarrhythmias. In humans it has similar efficacy to sotalol for ventricular arrhythmia suppression and treatment of SVT and AF, with a greater efficacy for maintaining sinus rhythm after AF conversion (Singh *et al.*, 2005). In dogs, a number of oral dosing regimens have been described. A loading dose of 10–15 mg/kg q24h for 7–14 days, followed by a maintenance dose of 5–7.5 mg/kg q24h may be effective for chemical cardioversion of AF (Saunders

et al., 2006), or to aid maintenance of sinus rhythm with electrical cardioversion (Bright and zumBrunnen, 2008). Similar doses may be effective for ventricular arrhythmias; a loading dose of 10 mg/kg q12h for 1–2 weeks followed by a maintenance dose of 5–10 mg/kg q24h has been described for treatment of ventricular tachycardia in Dobermanns (Calvert and Brown, 2004). Further adjustments may be required on an individual patient basis to achieve the lowest dose for arrhythmia suppression and minimal adverse effects. Given its very long half-life, it is recommended that the effect of any dose adjustment is assessed at least 4 weeks later. Amiodarone has been reported to be variably effective for AF cardioversion when given at doses of 4–8 mg/kg intravenously over 10–15 minutes, albeit with severe adverse effects (Oyama and Prošek, 2006).

Despite its efficacy for treatment of a variety of tachyarrhythmias, amiodarone use is limited by a large number of adverse non-cardiac effects. Toxicity associated with chronic oral administration in dogs includes appetite suppression, gastrointestinal disturbances, keratopathy and a positive Coombs' test (Calvert *et al.*, 2000). Amiodarone also increases serum digoxin concentrations, potentially causing signs of digitalis toxicity. Adverse effects associated with intravenous administration include pain at the injection site, hypotension, hypersalivation and hypersensitivity reactions (erythema, urticaria, swelling, agitation, pruritus); the latter may be a reaction to the carrier solvent (Cober *et al.*, 2009). Amiodarone has fewer negative inotropic effects and a lower risk of *torsades de pointes* than sotalol. The author prefers amiodarone for treatment of ventricular arrhythmias in dogs with systolic dysfunction and CHF, sometimes in combination with mexiletine. Monitoring of hepatic enzyme activities and thyroid function is recommended.

Diltiazem

Diltiazem is a benzothiazepine calcium-channel blocker or class IV agent according to the Vaughan Williams classification. Its main effects are dose-dependent slowing of the sinus rate and AV node conduction. It also has some arteriodilator actions, although less than dihydropyridine calcium-channel blockers, such as amlodipine. Diltiazem is mainly protein bound in the plasma, has high hepatic metabolism and a relatively short elimination half-life. The latter means that it needs to be administered frequently (q8h) unless sustained-release formulations are used.

Diltiazem is an *important agent for treatment of supraventricular tachyarrhythmias*. It can be given intravenously for treatment of SVT at a dose of 0.1–0.25 mg/kg over 1–2 minutes, up to a total dose of 0.75 mg/kg over 30 minutes. It can also be given orally for rate-control of AF or atrial tachycardias at a dose of 0.5–2 mg/kg q8h. Diltiazem can be given orally in a loading dose, initially 0.5 mg/kg, followed by 0.25 mg/kg every hour to effect or a 2 mg/kg total dose. Diltiazem is the author's preferred drug for treatment of supraventricular arrhythmias in cats with CHF, given orally at a dose of 7.5–15 mg/cat q8h.

At standard doses, diltiazem has few adverse effects. At toxic doses, signs related to decreased cardiac contractility and vasodilation, such as lethargy, obtundation and hypotension, may occur. Bradyarrhythmias such as sinus bradycardia and AV block are also possible. However, when given to cats at a dose of 60 mg/cat q24h, extended-release diltiazem can cause lethargy, gastrointestinal disturbances and weight loss (Wall *et al.*, 2005). Despite its negative inotropic effects, diltiazem is usually tolerated in patients with CHF or systolic dysfunction, but it should be used cautiously if signs of CHF are not well controlled.

Digoxin

Digoxin is a digitalis glycoside and the oldest antiarrhythmic agent. It has multiple cardiac and non-cardiac effects. The main effects of digoxin are inhibition of the sodium pump (sodium/potassium adenosine triphosphatase (ATPase) pump), improvement in baroreceptor sensitivity, activation of efferent parasympathetic (vagal) tone and inhibition of efferent sympathetic discharge. The neural effects of digoxin account for its antiarrhythmic actions as they result in slowing of the sinus rate and decreased AV nodal conduction. Digoxin inhibits the sodium pump by competing with potassium ions for their binding site. Sodium pump inhibition in the heart results in increased intracellular myocardial calcium concentrations, producing a slight positive inotropic effect, but also an increased risk of tachyarrhythmias, particularly from triggered activity. Sodium pump inhibition at the kidney decreases renin release and exerts a slight natriuretic effect. Digoxin has good oral bioavailability, a very long elimination half-life (1–1.5 days in the dog; 1–3 days in the cat), low protein binding and mainly renal excretion.

Digoxin is mainly used to slow the ventricular rate in persistent atrial tachyarrhythmias. It is the *antiarrhythmic agent of choice in dogs with AF and heart failure*. Digoxin should be given orally twice daily in dogs and dosed to lean bodyweight, so that the effect of obesity or large volume effusions are accounted for in the dose calculations. The most effective dose of digoxin in terms of clinical response and outcome is unknown in dogs. However, in humans, previous recommendations for dosing to achieve a 'therapeutic concentration' of 1.0–2.0 ng/ml have been superseded by recommendations to achieve a lower concentration of 0.5–1.0 ng/ml. This is based on convincing evidence of decreased mortality and hospitalizations for heart failure in human patients with low (<1.1 ng/ml) *versus* high (≥1.2 ng/ml) digoxin concentrations (Rathore *et al.*, 2003). Consequently the author uses a dose of 3–5 µg/kg q12h (0.1–0.15 mg/m^2 orally q12h) and aims for a trough (>8h) post-pill serum digoxin concentration of 0.6–1.1 ng/ml. Steady-state serum concentrations are often achieved within 5–7 days. The dose is decreased by 50% for patients with renal failure. There is rarely an indication for 'rapid digitalization', either with intravenous or oral loading doses. The author rarely uses digoxin in cats but, when given, uses a dose of 31.25 µg/cat orally q48h.

Drugs that increase serum digoxin concentrations include quinidine, flecainide, propafenone, amiodarone and verapamil. The effect of diltiazem on digoxin concentrations is usually negligible.

Digoxin has a very narrow therapeutic/toxic window. Most of the non-cardiac signs of digoxin toxicity result from its CNS and parasympathomimetic actions (e.g. depressed mentation, anorexia, vomiting, diarrhoea). Cardiac signs of digoxin toxicity include tacharryhthmias, particularly ventricular bigeminy and trigeminy, and excessively slow sinus rates or slow ventricular rates in AF. Clinical signs of digoxin toxicity can occur at any serum concentration, but are more likely to occur with high doses, hypokalaemia or renal insufficiency. Consequently monitoring of urea, creatinine and electrolytes is recommended in all patients receiving digoxin, particularly those concurrently receiving potassium-losing diuretics (e.g. furosemide, thiazides).

Electrical antiarrhythmic therapies

Electrical cardioversion and defibrillation

The principle behind electrical (DC) cardioversion and defibrillation is the termination of a tachycardia by the delivery of sufficient electrical energy to depolarize all excitable myocardial cells simultaneously. It is hoped that the subsequent uniform repolarization will allow restoration of normal sinus rhythm. Although the principle is the same, both are performed in a similar manner and both use the same equipment, electrical cardioversion and defibrillation are *not* the same.

- *Electrical cardioversion* is the delivery of energy to the myocardium that is *synchronized* to the R wave of the QRS complex.
- *Defibrillation* is the delivery of energy to the myocardium that is *not* synchronized to the underlying rhythm.

Defibrillation should not be performed on a patient with a stable ventricular rhythm, since inadvertent delivery of electrical energy to the myocardium during the T wave can precipitate ventricular fibrillation.

Both electrical cardioversion and defibrillation can be achieved with either monophasic or biphasic energy waveforms.

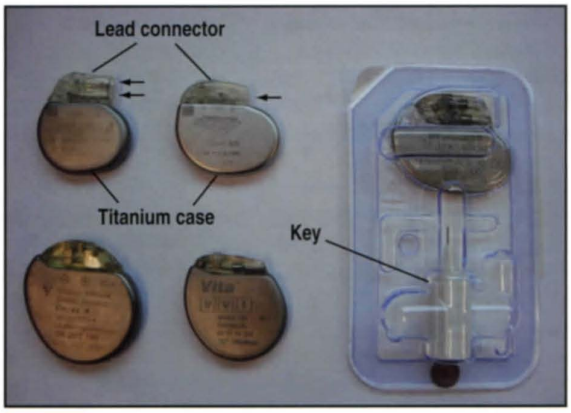
- *Monophasic* cardiovertor/defibrillators deliver a high-energy pulse across the chest in one direction.
- *Biphasic* cardiovertor/defibrillators alternate the direction of pulses across the chest, allowing a lower energy to be delivered.

Biphasic cardioversion is more effective and safer than monophasic, as it allows the generation of greater transmyocardial current for cardioversion/defibrillation with lower energy levels and therefore less soft tissue and myocardial injury to the patient.

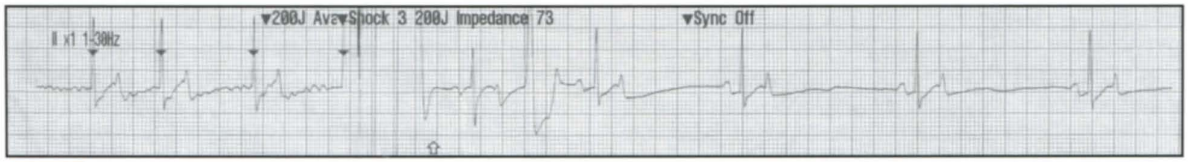
Defibrillation is used during cardiopulmonary–cerebral resuscitation for ventricular fibrillation and asystole. Electrical cardioversion (Figure 20.3) is performed in small animals for the conversion of supraventricular tachyarrhythmias and ventricular tachycardia to sinus rhythm.

Pacemaker therapy

The main indication for pacemaker therapy is a *bradyarrhythmia causing clinical signs of haemodynamic compromise* (see below). Since the vast majority of bradyarrhythmias of this type are permanent, most pacemaker therapy is also permanent. All pacemaker units comprise a pulse generator (battery, pacing circuits, telemetry coil and lead connector) and lead system (internal conducting wire, external insulation and electrodes). For permanent pacemaker implantation the pulse generator is a compact device with a titanium casing and a lithium-anode battery (often lithium–iodine), which has a lifespan of up to 10 years (Figure 20.4). New pulse generators and leads can be purchased from manufacturers. Second-hand equipment may be obtained



20.4 Pacemaker pulse generators of various sizes, makes and models. The pulse generator at the top left has two lead connectors (arrowed) to allow dual chamber pacing. The pulse generator on the right is in its sterile package, which includes the key to screw the lead into the lead connector.

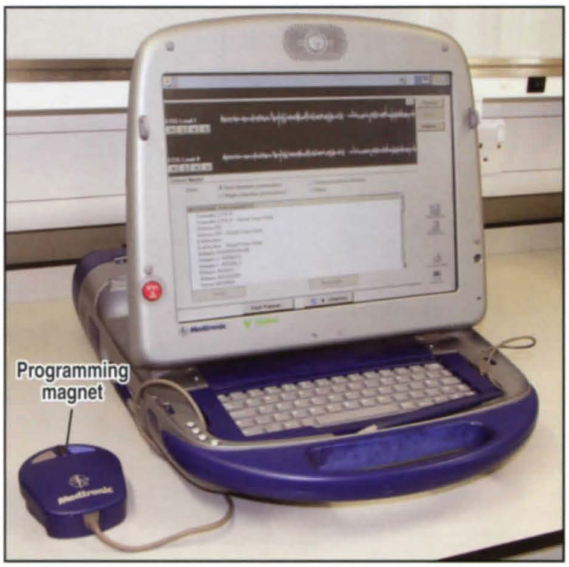


20.3 Electrical (DC) cardioversion in a Labrador Retriever with AF. The first four complexes have arrowheads above the QRS complexes, indicating that the device is correctly identifying the R waves. A shock is delivered synchronous with the R wave of the fourth complex. Sinus rhythm ensues, with a ventricular premature complex interpolated between the first and second sinus complex. Note that synchronous mode automatically turns off after the shock is delivered. Lead II shown. Paper speed 25 mm/s; gain 1 cm/mV. (Courtesy of A. Boswood.)

from human hospitals and should always be gas sterilized prior to use.

All pacing systems require two electrodes (cathode and anode) for an electrical circuit to be maintained and cardiac pacing to occur. The cathode is always located at the tip of the lead. The anode can be located either outside the heart (at the pulse generator) or within the heart (on the lead proximal to the cathode). The former is referred to as *unipolar* pacing and the latter *bipolar* pacing. Most modern pacing systems are bipolar, as there are many disadvantages of unipolar pacing, including: the need for continual contact between the pulse generator and body to maintain a circuit; a susceptibility to interference from normal skeletal muscle activity; and the potential for rhythmic stimulation of skeletal muscles at the site of pulse generator implantation (referred to as 'thumps').

Bipolar leads and pulse generators can be set for either unipolar or bipolar pacing, whereas unipolar systems can only be set for unipolar pacing. Therefore, if bipolar pacing is desired it is always recommended that leads and pulse generators are checked prior to use to ensure that they are compatible. This may require prior programming of the pulse generator. Pulse generator programming is performed by telemetry with a programmer device, which consists of a computer and programming magnet (Figure 20.5). When the magnet is positioned in close proximity to a pulse generator, the computer can be used to programme a number of settings depending upon the model and type of generator. These may include polarity, pacing mode, pacing rate, pulse amplitude (voltage), pulse duration, refractory period and sensitivity. Many devices will also provide information on previous use of the pulse generator and an estimation of remaining battery life.



20.5 Pacemaker programmer. A foldable screen and programming magnet are features of all models.

Pacing modes are referred to by a three- to five-letter coding system. Figure 20.6 provides a summary of the more common pacing modes used in veterinary species. For example, a pacemaker may be set to VVI mode at 80 beats/minute, indicating that the pacemaker only fires when the intrinsic heart rate falls below 80 beats/minute. This type of pacing is most useful for patients with clinical signs related to sinus arrest, for whom the heart rate is usually >80 beats/minute at other times. However, in patients with persistently low heart rates (e.g. third-degree AV block) this type of pacing does not account for changes in heart rate that are required in response to physiological needs. Consequently a preferred pacing mode for these patients is VVIR. This mode allows for pacing between a fixed lower and upper rate.

Changes in pacing rate can be based on one of a number of variables. These include movement, right ventricular pressure, or changes in physiological variables within the blood (e.g. oxygen saturation, pH, temperature). Dual chamber pacing can be achieved with an additional lead which is implanted into the right atrium. This provides a more physiological type of pacing in patients with AV block, as both sinus control of the heart rate and AV synchrony are maintained, but increases the potential for complications, particularly lead dislodgement. In an attempt to overcome this, use of a pacing system with a single ventricular lead and attached floating lead in the right atrium has been described in dogs (Bulmer *et al.*, 2006).

Permanent pacemakers can be implanted either transvenously or epicardially.

- Transvenous implantation is the most common route in dogs.
- Epicardial implantation is the most common route in cats.

Transvenous implantation is carried out under fluoroscopic guidance, via a jugular vein, with the lead implanted into the right ventricle and/or atrium, and the pulse generator usually implanted in either the subcutaneous tissues of the neck or in a tissue

First letter	Second letter	Third letter	Fourth letter
Chamber paced	***Chamber sensed***	***Response to sensing***	***Rate modulation/programmable functions***
V = ventricle	V = ventricle	T = triggers pacing	P = programmable (rate and/or output)
A = atrium	A = atrium	I = inhibits pacing	M = multiprogrammable (e.g. rate, output, sensitivity)
D = dual (A+V)	D = dual (A+V)	D = dual (T+I)	C = communicating functions (e.g. telemetry)
O = none	O = none	O = none	R = rate modulation

20.6 Pacing modes.

pocket beneath the omotransversarius muscle. Many cardiologists prefer to implant via the right jugular vein, as this minimizes the risk of inadvertent placement via a persistent left cranial vena cava.

- Endocardial leads maintain contact with the myocardium by either passive or active fixation.
  - Passive fixation leads have tined tips that are designed to hook within the trabeculae of the right ventricle.
  - Active fixation leads have helical tips that screw into the myocardium.
- Epicardial leads require active fixation using a screw-in type of lead. These leads are usually implanted via a transdiaphragmatic approach, with the pulse generator implanted in a pocket within the abdominal muscle wall.

Complications of pacemaker implantation include lead dislodgement, seroma formation, intraoperative mortality, pulse generator or lead failure, and infection. Lead dislodgement is the most frequently encountered major complication, irrespective of the type of lead system used (Oyama *et al.*, 2001; Wess *et al.*, 2006). This usually occurs within the first few days of pacemaker implantation. Complication rates can be quite high, with reported rates ranging from 20% to 60%, and an inverse correlation between complication rate and experience of the operator (Oyama *et al.*, 2001). Therefore, it is preferable that pacemaker implantation is performed by trained and experienced personnel.

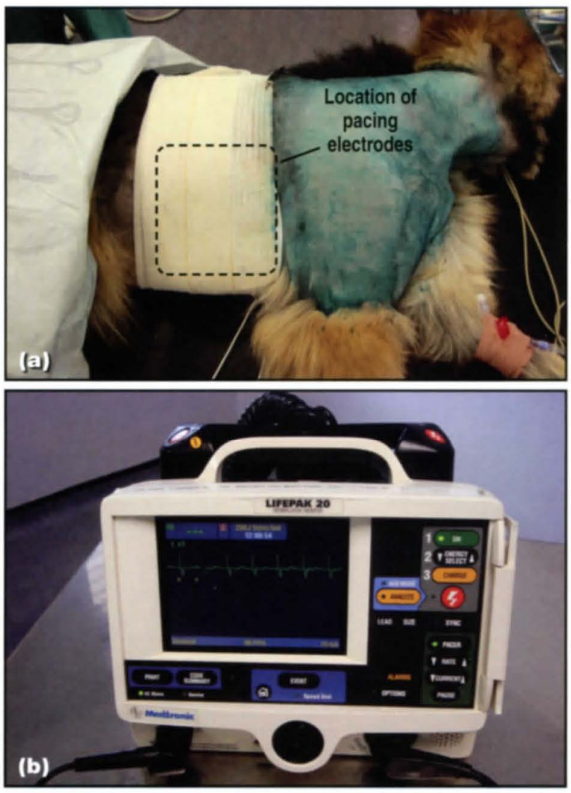
Pacemaker implantation requires more than just a skilled operator, pacing equipment and programmer. It also requires a sterile operating room, fluoroscopy unit and a skilled anaesthesia team. Patients requiring pacemakers often develop a more severe bradyarrhythmia or ventricular arrhythmias during induction and maintenance of anaesthesia. These arrhythmias may precipitate cardiac arrest from asystole or ventricular fibrillation. Such arrhythmias may be reduced by the use of temporary pacing, which can be accomplished by either transthoracic or transvenous methods.

Temporary pacing

Temporary transthoracic pacing uses electrode pads attached to clipped areas of skin on either side of the thoracic wall (Figure 20.7). This type of pacing is painful, as it results in skeletal muscle stimulation, and therefore requires anaesthesia to be induced first. Use of skeletal muscle relaxants during anaesthesia reduces the degree of skeletal muscle stimulation and therefore patient movement during subsequent permanent pacemaker implantation. However, this necessitates mechanical ventilation due to relaxation of the intercostal muscles and diaphragm.

Temporary transvenous pacing is usually achieved using a temporary pacing lead implanted into the right ventricle under fluoroscopic guidance via a femoral vein. The pacing lead is passed aseptically via a vascular introducer that is inserted into the vein via a Seldinger technique. This technique can be performed in well restrained patients prior to induction of general anaesthesia, but it is more technically demanding and time-consuming, requires additional radiation exposure and is difficult to perform in poorly cooperative patients without chemical restraint.

Other uses for temporary pacing include general anaesthesia for procedures other than permanent pacemaker implantation in a patient with a less severe bradyarrhythmia, and in patients with unstable bradyarrhythmias associated with a potentially reversible condition (e.g. endocarditis, drug toxicity).



20.7 Temporary transthoracic pacing in a German Shepherd Dog with third-degree AV block, undergoing general anaesthesia for permanent pacemaker implantation. **(a)** Pacing electrodes (adhesive pads) are placed on either side of the thoracic wall, over the heart. Cables attached to the pads run to a cardioverter/defibrillator unit **(b)**.

Management of patients following pacemaker implantation involves minimizing the risk of lead dislodgement in the short term and avoiding damage to the lead and pulse generator in the neck. Exercise restriction is recommended during the first month following implantation, to avoid lead dislodgement. To avoid damage to the lead, blood sampling should not be performed via the jugular vein and the owner should be informed that the dog should never be allowed to wear a collar. Either could result in catastrophic damage to the lead resulting from lead fracture or insulation failure. It is also important to avoid

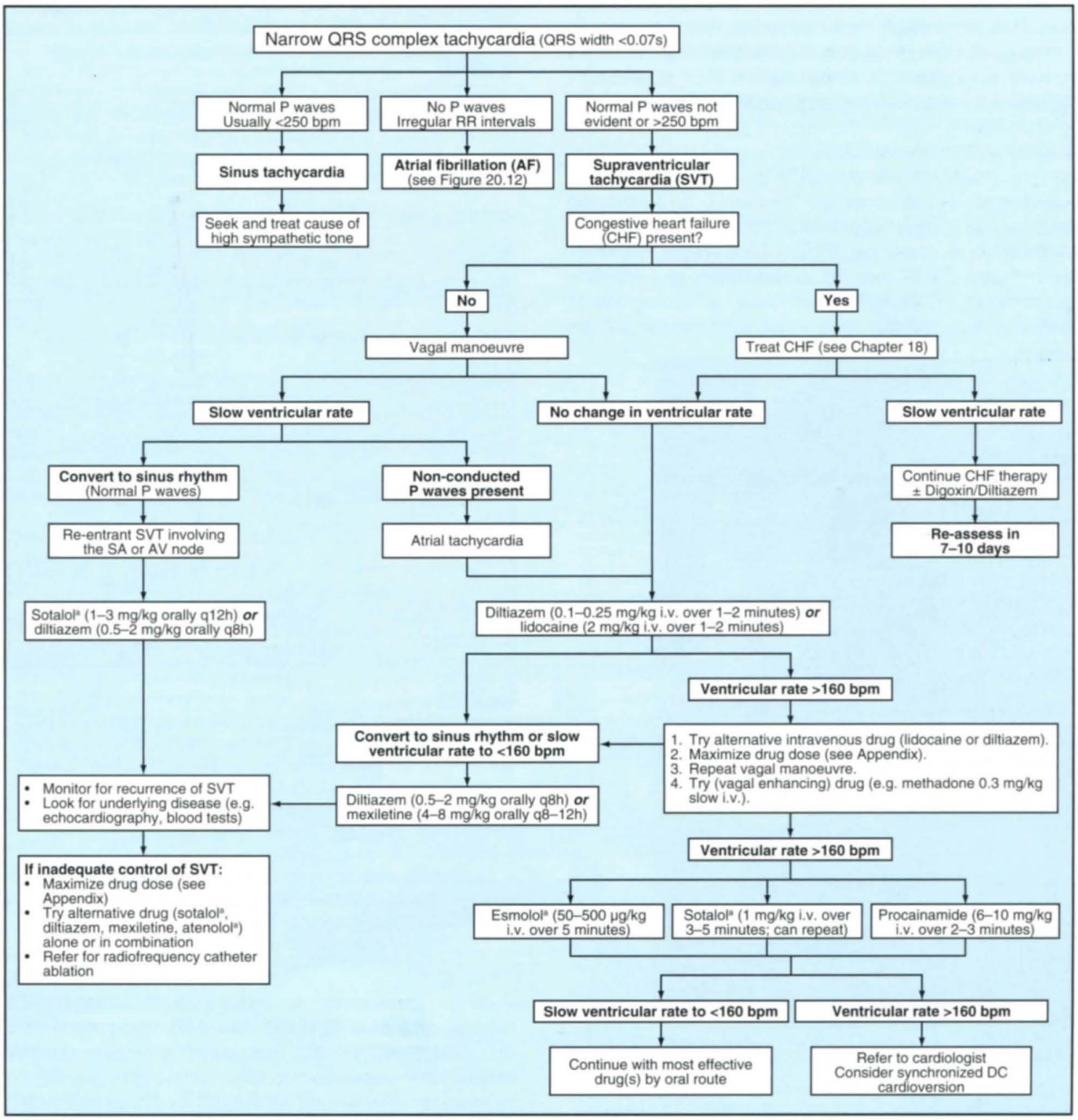
blood sampling from the jugular veins of any dog that may be in imminent need of a pacemaker, since a patent jugular vein is an important prerequisite for pacemaker implantation. In the event of death, the pulse generator should always be removed prior to cremation otherwise the battery will explode!

Therapy for specific arrhythmias

Flowcharts in the following sections show suggested approaches to narrow QRS complex tachycardia (SVT, Figure 20.8), AF (see Figure 20.12), wide QRS complex tachycardia (usually ventricular tachycardia, see Figure 20.13) and bradyarrhythmias (see Figure 20.15).

Supraventricular arrhythmias

Supraventricular arrhythmias usually occur secondary to structural heart disease, most commonly those resulting in atrial dilatation (e.g. AV regurgitation, myocardial disease, patent ductus arteriosus). Some patients will present with concurrent CHF. In this circumstance, treatment of CHF may be effective in reducing the rate, or occasionally result in conversion to sinus rhythm by decreasing circulating catecholamines and reducing atrial pressures. This alone may be sufficient to treat some supraventricular arrhythmias effectively and should therefore be the first therapeutic step. If CHF is not present or therapy is not effective, specific antiarrhythmic therapy should be considered if the arrhythmia is rapid enough to result in haemodynamic compromise in the short term, or is



20.8 Approach to narrow QRS complex tachycardia in the dog. [a] Use with caution in cases with systolic dysfunction; avoid use in cases with CHF; do not give together. AV = Atrioventricular; SA = Sinoatrial.

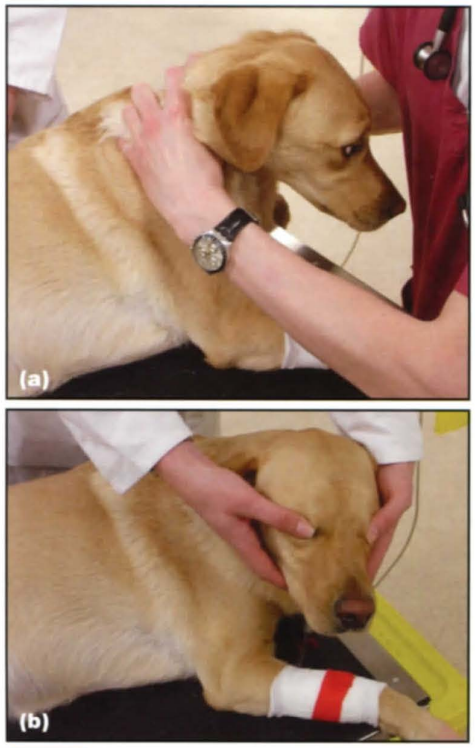
sufficiently rapid and sustained to cause myocardial failure in the long term. Unlike ventricular arrhythmias, supraventricular arrhythmias rarely result in death from electrical instability. However, they can precipitate death in patients with advanced cardiac disease.

Isolated supraventricular premature complexes (atrial or AV junctional) rarely require specific therapy as they do not usually cause measurable haemodynamic effects and do not affect the rate sufficiently to induce myocardial failure. However, they may be a marker for underlying cardiac disease or a precursor for a more sustained arrhythmia (e.g. AF).

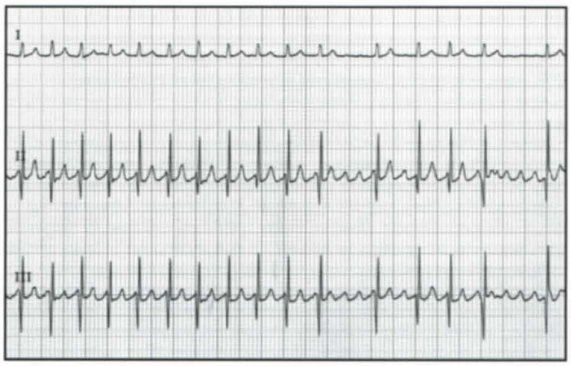
A sustained supraventricular arrhythmia usually requires antiarrhythmic drug therapy. *The aim is either conversion to sinus rhythm or to slow the ventricular rate.* Conversion to sinus rhythm is preferable, to optimize cardiac function. However, maintaining adequate rate control may be just as effective clinically. This has been illustrated in several large studies in humans with AF who have not demonstrated a benefit from conversion to sinus rhythm over pharmacological rate control (Wyse *et al.*, 2002).

Supraventricular tachycardia

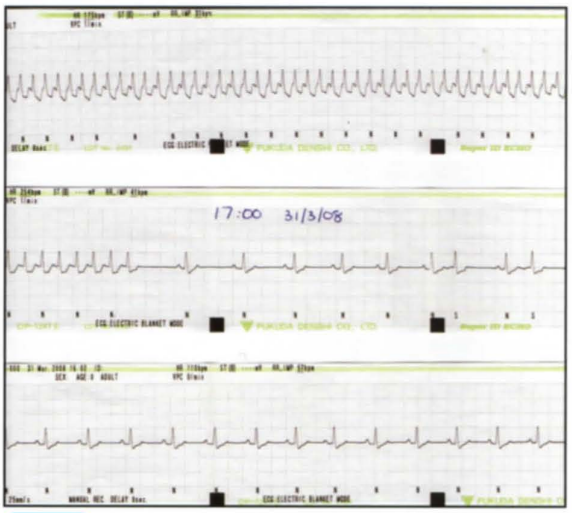
SVT is usually a narrow QRS complex tachycardia (QRS width <0.07 seconds in dogs). A suggested approach to the management of narrow QRS complex tachycardia is shown in Figure 20.8. Vagal manoeuvres (Figure 20.9) can be useful either to terminate some SVTs involving the AV node, or transiently to slow the ventricular rate in atrial tachycardia (Figure 20.10). The author finds that carotid massage is usually more effective than ocular pressure. However, in most cases, antiarrhythmic drug therapy (e.g. diltiazem, lidocaine, sotalol) is necessary to terminate the SVT or slow the ventricular rate (Figure 20.11).



20.9 Vagal manoeuvres. **(a)** Carotid sinus massage is achieved by applying continuous digital pressure to the region of the carotid sinuses, just caudal to the larynx, to stimulate carotid baroreceptors. **(b)** Ocular pressure is achieved by applying firm pressure over both globes for approximately 20 seconds.



20.10 Vagal manoeuvre in atrial tachycardia/flutter: carotid sinus massage in a 2-year-old Bulldog with SVT. Slowing of the ventricular rate after the ninth QRS complex revealed an atrial rate of about 450 beats/minute. By slowing the ventricular rate independently of the atrial rate, an atrial tachycardia was diagnosed. Leads I–III shown. Paper speed 25 mm/s; gain 1 cm/mV.



20.11 Pharmacological cardioversion of SVT: conversion of an SVT of >300 beats/minute in a 2-year-old Labrador Retriever following two doses of slow intravenous sotalol, each at a dose of 1 mg/kg given 5 minutes apart. Termination of the SVT and conversion to sinus rhythm occurred shortly after the second dose. Previous attempts at conversion with vagal manoeuvres, intravenous diltiazem, esmolol and lidocaine had been ineffective. The dog was subsequently maintained successfully on oral sotalol. An SVT at 350 beats/minute is seen on the top strip. Conversion to sinus rhythm occurs after the eighth complex in the middle strip. Sinus rhythm at 110 beats/minute is maintained on the lower strip. Lead II shown. Paper speed 25 mm/s; gain 0.5 cm/mV.

Once conversion to sinus rhythm or adequate control of the ventricular rate has been achieved, chronic therapy with the most effective drug(s) should be continued orally. Echocardiography to assess for concurrent structural or functional heart disease and laboratory tests for systemic disease can also be performed. Monitoring for arrhythmia

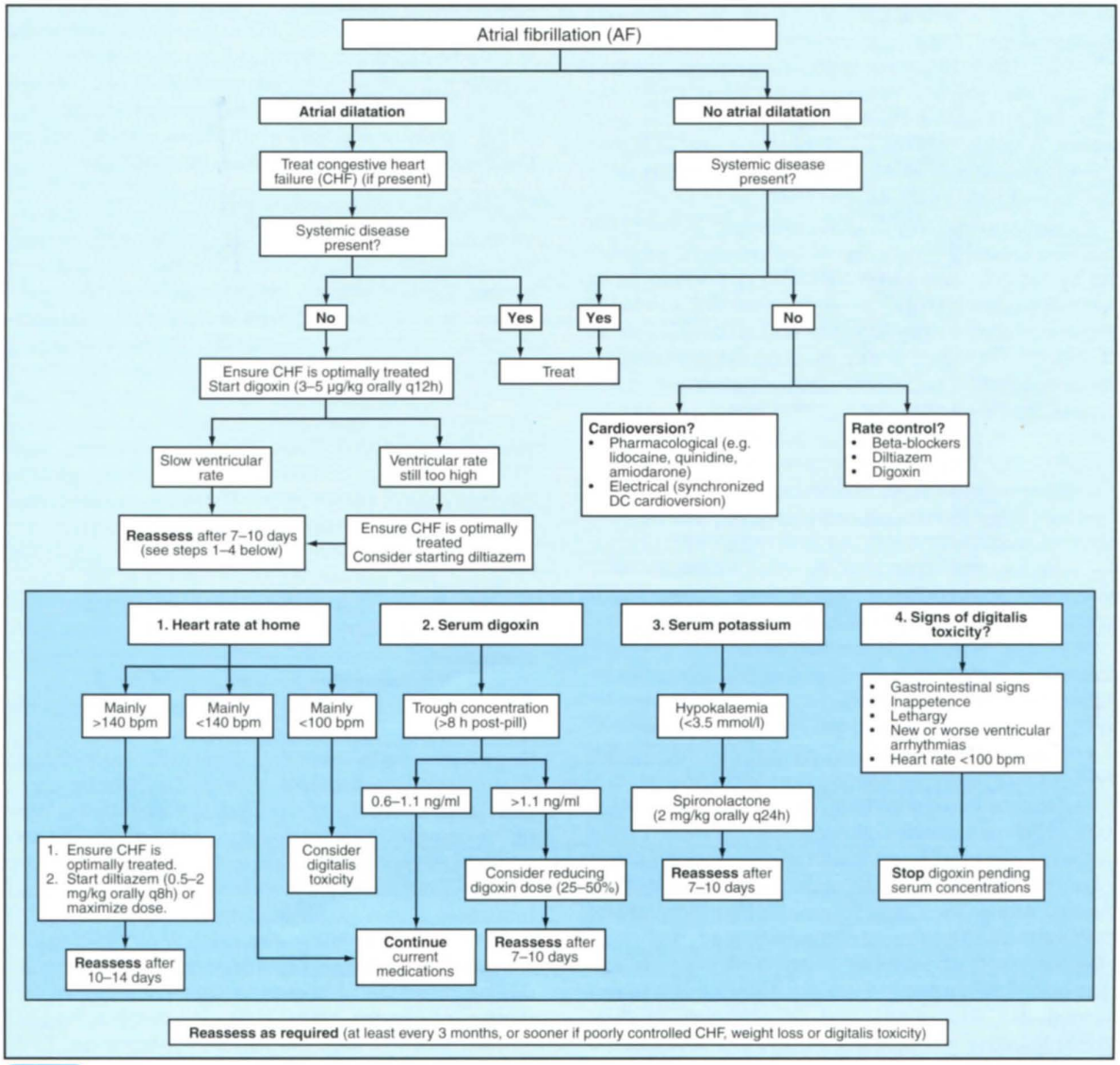
recurrence, ideally with ambulatory (Holter) ECG monitoring, is also important.

Animals with SVT that are refractory to pharmacological therapy may be candidates for electrical (synchronized DC) cardioversion (see above) or intracardiac electrophysiological mapping. The latter is a highly specialized technique that allows identification of a re-entrant pathway or ectopic atrial focus, and radiofrequency catheter ablation of a portion of the re-entrant circuit or arrhythmogenic focus. This technique can result in permanent resolution of AV reciprocating tachycardia or atrial tachycardia in dogs (Wright *et al.*, 2006). A further option in patients with incessant atrial tachycardia is AV node ablation and permanent pacemaker implantation.

Atrial fibrillation

A suggested approach to the management of AF is shown in Figure 20.12. AF is considered separately from other sustained supraventricular arrhythmias as it can differ in its underlying cause, treatment and outcome.

AF is the most common supraventricular arrhythmia. It is more likely to occur in larger atria and under conditions of enhanced autonomic tone; therefore, it is more frequently seen in animals with atrial dilatation secondary to structural heart disease. However, there is also an increased prevalence in giant-breed dogs in the absence of detectable underlying heart disease. The vast majority of cases of AF detected in small animals are persistent or permanent (see Chapter 16). This is in part because AF induces electrophysiological and pathological changes within the atrial myocardium that perpetuate the arrhythmia (Brundel *et al.*, 2005). Consequently *permanent restoration of sinus rhythm is not easily achievable*. The patients with the greatest chance for permanent conversion to sinus rhythm are those with acute-onset AF, particularly if iatrogenic (e.g. following intravenous opioid administration, during general anaesthesia, or



20.12 Approach to AF in the dog.

cardiac catheterization), and in patients without atrial dilatation. Options for cardioversion are either pharmacological (e.g. class I agents, amiodarone) or electrical (synchronized DC cardioversion). Permanent conversion to sinus rhythm is not achievable for most patients with AF. Therefore, the goal for the majority of cases is to control the ventricular rate in order to provide the most effective cardiac output and reduce clinical signs.

The 'ideal' rate is one that maximizes arterial pressure, while minimizing venous pressure and myocardial oxygen demand. Unfortunately the precise 'ideal' rate in the dog and cat is unknown. Furthermore, the rate obtained will vary depending upon temperament, the setting in which the heart rate is taken (in-clinic or at home), the method of heart rate measurement (ECG *versus* auscultation) and the presence or absence of CHF. One study assessing naturally occurring AF in dogs with CHF suggested that an at-home, owner-auscultated heart rate of 130–145 beats/minute (mean 138 beats/ minute) was optimal to allow both effective control of CHF (as measured by respiratory rate) and increased cardiac output (Hamlin, 1995). Since AF is most commonly present in dogs with cardiac disease resulting in CHF, this information is useful. On this basis, the author recommends a target rate of <140 beats/minute at home (owner-auscultated or Holter ECG) as a reasonable aim for most dogs with AF and CHF.

A higher heart rate is often expected in the clinic due to increased production of catecholamines from the stress of a visit. Overestimation of the rate by at least 20 beats/minute for in-hospital ECG *versus* Holter monitoring was found in one study (Gelzer *et al.*, 2009). Therefore, a rate of <160 beats/minute in the hospital/clinic setting may be consistent with good control. Some owners can become adept at counting their animal's heart rate by thoracic palpation or auscultation, but this usually requires some degree of training and practice. As well as being more accurate, 24-hour Holter monitoring provides more information, such as maximum, minimum and mean heart rates, as well as rate response to exercise/excitement, which may be increased in dogs with AF. Some cardiologists advocate more stringent control, such as maintaining rates <120 beats/minute; this is more achievable in dogs without CHF. It is also important to remember that effective rate-control therapy in AF must be one that results in the greatest improvement in clinical signs, particularly control of CHF, rather than purely targeting a specific numerical end-point.

Adequate therapy of CHF is an essential component of AF rate control, since poorly controlled CHF results in elevated sympathetic and decreased vagal tone. Oral digoxin is usually given in addition to CHF therapy. Many dogs also require further rate-control therapy. Diltiazem is most commonly used, and often provides good rate-control in combination with digoxin and CHF therapy. Beta-blockers can be given instead, but should be used with caution as their potent negative inotropic action may impair adequate control of CHF. It is for this reason that diltiazem is preferred by the author.

Non-antiarrhythmic drugs that may be useful in AF include angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists (e.g. spironolactone) and omega-3 fatty acids. These drugs may help to reverse some of the structural atrial remodelling and pro-inflammatory cytokines that modulate arrhythmia perpetuation (Brundel *et al.*, 2005).

Supraventricular arrhythmias in cats

Cats with supraventricular arrhythmias almost invariably have underlying cardiac disease. They differ from dogs in that they are less likely to develop sustained supraventricular arrhythmias, presumably due to smaller atrial mass. Additionally, they are more susceptible to the toxic effects of digitalis glycosides. Fortunately, since cats develop cardiac disease with diastolic dysfunction (i.e. hypertrophic and restrictive cardiomyopathy) far more commonly than systolic dysfunction (i.e. dilated cardiomyopathy), the use of drugs with a negative inotropic effect (diltiazem or beta adrenergic blockers) to control ventricular rate is often most appropriate, in addition to optimal control of CHF. As with dogs, the author prefers diltiazem to beta-blockers for rate-control in cats with CHF. If a digitalis glycoside is to be used in a cat, digoxin should be given, but in much smaller doses (e.g. 31.25 µg/cat orally q48h). Digitoxin should not be used in cats due to its extremely long half-life.

Ventricular arrhythmias

Ventricular arrhythmias can result from both cardiac and systemic disease (see Chapter 16) and can range from occasional isolated monomorphic ventricular premature complexes to rapid sustained polymorphic ventricular tachycardia. Holter monitoring studies reveal that isolated ventricular premature complexes may occur infrequently (<24 ventricular premature complexes/day) in otherwise healthy dogs (Meurs *et al.*, 2001). Even when more frequent, ventricular premature complexes do not usually result in haemodynamic compromise. Therefore, isolated ventricular premature complexes by themselves are rarely an indication for antiarrhythmic therapy. However, their presence should prompt further investigation into an underlying disease process and ambulatory (Holter) ECG monitoring to assess for a more severe arrhythmia, particularly in patients with clinical signs of haemodynamic compromise.

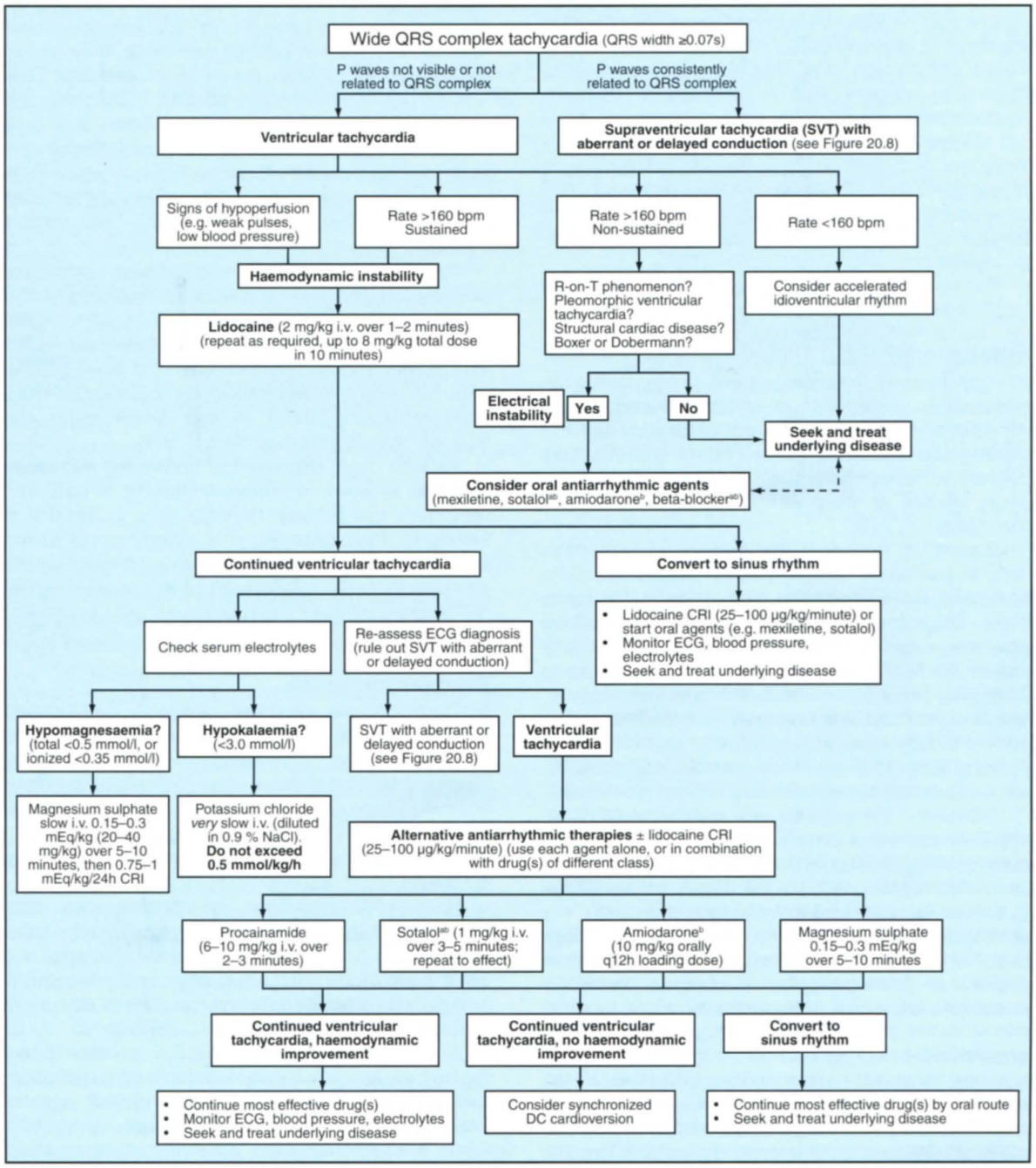
The electrical instability of a ventricular arrhythmia is roughly correlated to its frequency and complexity. Dogs with more complex ventricular arrhythmias (ventricular tachycardia, R-on-T phenomenon, polymorphic ventricular premature complexes) may be at greater risk of sudden cardiac death and therefore most likely to benefit from antiarrhythmic therapy, although there is at present no evidence that reduction in the frequency of ventricular ectopy or complexity of arrhythmia results in a reduced risk of sudden cardiac death. More important considerations are the presence of haemodynamic compromise and underlying cardiac disease likely to result in sudden cardiac death, such as cardiomyopathy or CHF. These patients are more likely to benefit from antiarrhythmic therapy.

Those with intermittent signs are managed with oral medications. Drugs that can be effective for the oral treatment of ventricular arrhythmias in dogs include class Ia and Ib agents, beta-blockers, sotalol and amiodarone. Mexiletine (class Ib) is generally now preferred over other class I agents (procainamide, quinidine, tocainide), which have tended to require more frequent dosing and result in greater toxicity (Calvert *et al.*, 1996b). There is also anecdotal evidence of greater efficacy for mexiletine in dogs (Lunney and Ettinger, 1991).

Antiarrhythmic medications may be given alone or in combination. Suitable combinations include a class I drug with either class II or III, or class Ia drug with a class Ib. There is evidence suggesting a benefit for such therapy in Boxers and Dobermanns with ventricular arrhythmias and episodic collapse (Meurs *et al.*, 2002; Calvert and Brown, 2004).

Ventricular tachycardia

Patients with sustained ventricular tachycardia typically present with a wide QRS complex tachycardia (QRS width ≥0.07 seconds). This is an urgent scenario and a suggested approach to wide QRS complex tachycardia is shown in Figure 20.13.



20.13 Approach to wide QRS complex tachycardia in the dog. [a] Use with caution in cases with systolic dysfunction; avoid use in cases with signs of CHF. [b] Do not give together.

Patients with a ventricular rate >160 beats/minute or clinical signs of hypoperfusion should be treated promptly and aggressively with intravenous lidocaine. Boluses of 2 mg/kg should be given to effect, or up to 8 mg/kg total dose in 10 minutes. Failure to convert warrants assessment and correction of electrolyte imbalances, re-evaluation of the ECG or use of an alternative antiarrhythmic agent. Concurrent hypokalaemia is an important reason for failure of lidocaine therapy. Choice of second-line agents is empirical and options include sotalol, procainamide, beta-blockers, magnesium sulphate and amiodarone (oral).

Patients with a ventricular rate <160 beats/minute and no signs of hypoperfusion may have an accelerated idioventricular rhythm (see Chapter 16). These arrhythmias most commonly occur following abdominal surgery and in critically ill patients. Aggressive treatment with antiarrhythmic drugs is not always necessary, as this tends to be a relatively stable rhythm and less likely to result in signs of hypoperfusion. Treatment of the underlying disease process is recommended, including the administration of analgesia, intravenous fluids and oxygen as necessary.

Failure to pharmacologically convert ventricular tachycardia to sinus rhythm confers a poor prognosis, but a reduction in rate and improvement in haemodynamic status following antiarrhythmic therapy are reasonable secondary end-points. In this circumstance, continuation of effective therapy either via CRI or orally is warranted while seeking and treating an underlying cause. Some patients may convert to sinus rhythm after several days if the acute effects of their arrhythmia are adequately managed.

Successful treatment of a ventricular arrhythmia with a parenteral antiarrhythmic usually warrants continued therapy with an oral drug of the same class. Chronic therapy with drugs or combinations that have class II effects is preferred, as this may reduce the likelihood of sudden cardiac death due to ventricular fibrillation. Sotalol, amiodarone, or mexiletine and atenolol are commonly used. The author prefers to use amiodarone for patients with systolic dysfunction or CHF, as these patients may not tolerate more potent beta-blockers.

Ultimately, the goal for any antiarrhythmic therapy is to provide a clinical benefit while minimizing adverse effects. Regular monitoring of patients that have started antiarrhythmic therapy is recommended to assess for continued arrhythmia suppression, any proarrhythmic effect and any other adverse effects. Resolution of both clinical signs and arrhythmia is desired. In those patients for whom a ventricular arrhythmia is present without clinical signs, a reduction in ventricular ectopic frequency of >80–85% on sequential 24-hour ambulatory (Holter) ECG recordings is necessary to provide evidence of an antiarrhythmic benefit. This degree of reduction is required since the day-to-day spontaneous variability in frequency of ventricular ectopy can be up to 80–85% in humans and dogs (Spier and Meurs, 2004).

Ventricular arrhythmias in cats

It is unusual for cats to develop ventricular arrhythmias that require urgent antiarrhythmic therapy. Most cats with ventricular arrhythmias have myocardial disease and, when present, arrhythmias tend to be of low grade.

Treatment options for cats with ventricular tachycardia are limited compared with those for dogs, since cats are far more susceptible to the adverse effects of class I drugs, particularly neurological and gastrointestinal effects. *Hypokalaemia should always be ruled out or treated when present.* Intravenous lidocaine can be given, but in lower doses (0.25–0.75 mg/kg bolus) and slowly (over 2–3 minutes). Beta-blockers are often preferred in cats with concurrent diastolic dysfunction but, as with dogs, they should be avoided in patients with poorly controlled CHF. Sotalol can also be given to cats, both orally and intravenously. In the author's experience this drug appears to be well tolerated in patients without systolic dysfunction or CHF. It can be given in intravenous boluses of 1 mg/kg over 3–5 minutes and repeated to effect. Another option is esmolol, 50–500 μg/kg i.v. over 5 minutes.

For chronic therapy in cats with ventricular arrhythmias, the author prefers atenolol (6.25–12.5 mg/cat orally q12–24h) or sotalol (10–20 mg/cat orally q12h, occasionally up to 30 mg/cat q12h). Procainamide and quinidine have also been used in cats, but recent limited availability, the need for more frequent dosing (three to four times daily) and frequent toxicity limit their clinical utility.

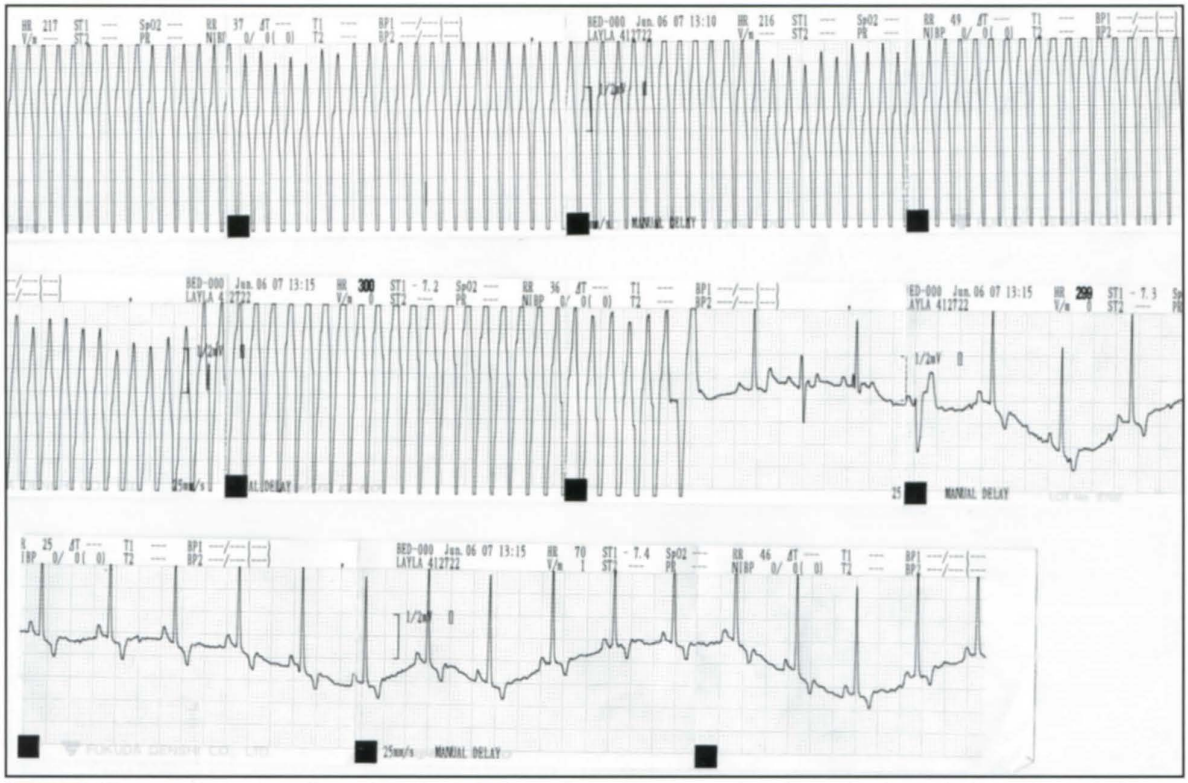
As with dogs, treatment of underlying cardiac or systemic disease is always preferable in cats with ventricular arrhythmias. Consequently, in addition to testing for hypokalaemia, *it is usually worth testing any middle-aged or older cat with a tachyarrhythmia for hyperthyroidism.* Figure 20.14 shows an example of pharmacological cardioversion of ventricular tachycardia in a cat.

Bradyarrhythmias

Bradyarrhythmias are most frequently encountered in small animals as a result of high vagal tone, general anaesthesia or sedation. These rarely require treatment beyond reversal of the underlying condition or drug. Those that require more specific treatment usually result from hyperkalaemia, inadvertent drug toxicity, or cardiac disease affecting the atria, SA or AV nodes.

Bradyarrhythmias can be divided into atrial standstill, sinus bradyarrhythmias (sinus bradycardia, sinus arrest) and AV block. *Sick sinus syndrome* and *sinus node dysfunction* are terms applied to patients with sinus bradyarrhythmias in the absence of disease causing high vagal tone.

Bradyarrhythmias that require treatment are those that are electrically unstable (may result in sudden cardiac death) or result in clinical signs of haemodynamic compromise (hypoperfusion, CHF). Sinus bradycardia, short durations of sinus arrest and low-grade second-degree AV block rarely result in clinical signs; consequently they do not require



20.14 Pharmacological cardioversion of ventricular tachycardia: conversion of sustained ventricular tachycardia in a 5-year-old Domestic Shorthaired cat following slow intravenous lidocaine at a dose of 0.5 mg/kg. Ventricular tachycardia at 380 beats/minute is seen on the top strip. Conversion to sinus rhythm occurs two-thirds of the way along the middle strip. Sinus rhythm is maintained on the lower strip. Hypertrophic cardiomyopathy with focal ventricular wall thickening was diagnosed on echocardiography. Oral therapy was continued with sotalol. Lead II shown. Paper speed 25 mm/s; gain 1 cm/mV.

treatment. Those that do require treatment include high-grade AV block, sinus node dysfunction and atrial standstill. If an underlying reversible condition is present (e.g. hyperkalaemia), then this should be treated first. Otherwise *the most effective therapy is permanent pacemaker implantation* (see above). Trial therapy with sympathomimetic agents (e.g. terbutaline), phosphodiesterase inhibitors (e.g. theophylline) and/or anticholinergic agents (e.g. propantheline) may be effective in reducing clinical signs in some patients. However, response is variable and adverse effects are common (e.g. gastrointestinal signs with anticholinergic agents, hyperexcitability with phosphodiesterase inhibitors). Figure 20.15 shows an approach to bradyarrhythmias.

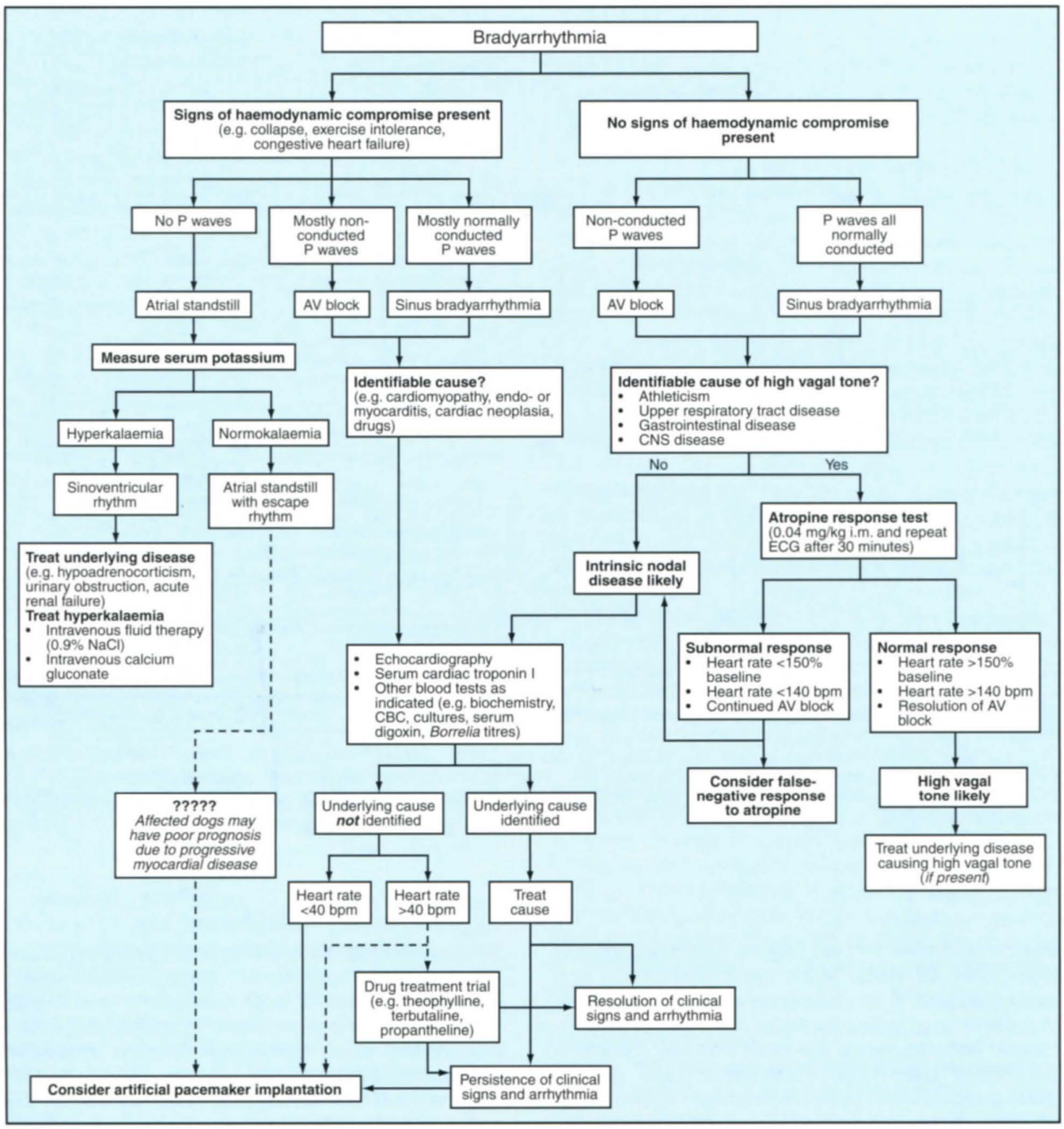
Bradyarrhythmias in cats

Cats with sinus bradyarrhythmias (sinus arrhythmia, sinus bradycardia, sinus arrest) usually have concurrent disease causing high vagal tone. Nasopharyngeal obstruction is a common example of this. These patients require treatment of their underlying non-cardiac disease.

Hyperkalaemic atrial standstill is the most common bradyarrhythmia in cats, with urinary obstruction the most common cause. High-grade AV block is the most common idiopathic bradyarrhythmia in cats and can cause signs of hypoperfusion and/or CHF. Third-degree AV block is more common in older cats and is often permanent. However, some cats present with sinus rhythm and syncope associated with transient third-degree AV block. These can be very difficult to distinguish from seizures, but arrhythmic episodes usually have a rapid recovery. Concurrent myocardial disease may be present, but often the disease is idiopathic.

Unlike dogs, cats may have stable and relatively fast escape rhythms (80–140 beats/minute) (Kellum and Stepien, 2006). As a consequence, some cats do not have clinical signs associated with their arrhythmia. *Often the only sign is a slow heart rate* detected during routine examination. Concurrent systemic disease (e.g. hyperthyroidism) may also be present. Normokalaemic atrial standstill rarely occurs in cats.

If clinical signs are present, permanent pacemaker implantation can be considered for cats with AV block or normokalaemic atrial standstill. This is usually performed via an epicardial approach, due to the technical difficulties of the transvenous route and a higher incidence of thromboembolic complications and obstruction to venous drainage.



20.15 Approach to bradyarrhythmias in the dog.

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