Introduction to Antiarrhythmic Agents

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Anti Arrhythmic Agents

- Introduction to anti arrhythmic agents

    ➢ Mechanisms of arrhythmogenesis
    ➢ Management of arrhythmias
    ➢ Classification of antiarrhythmic agents

Introduction to Antiarrhythmic Agents

Mechanisms of Arrhythmogenesis

Arrhythmias result from **disorders of impulse generation**, **disorders of impulse conduction** or the combination of both. The trigger for a run of ventricular tachycardia, where the disorder is predominantly due to conduction abnormalities secondary to myocardial disease, may be a premature ventricular beat due to a disorder of impulse generation. There are two described types of disorders of impulse generation; **abnormal automaticity** and **triggered activity** (Fig 1).
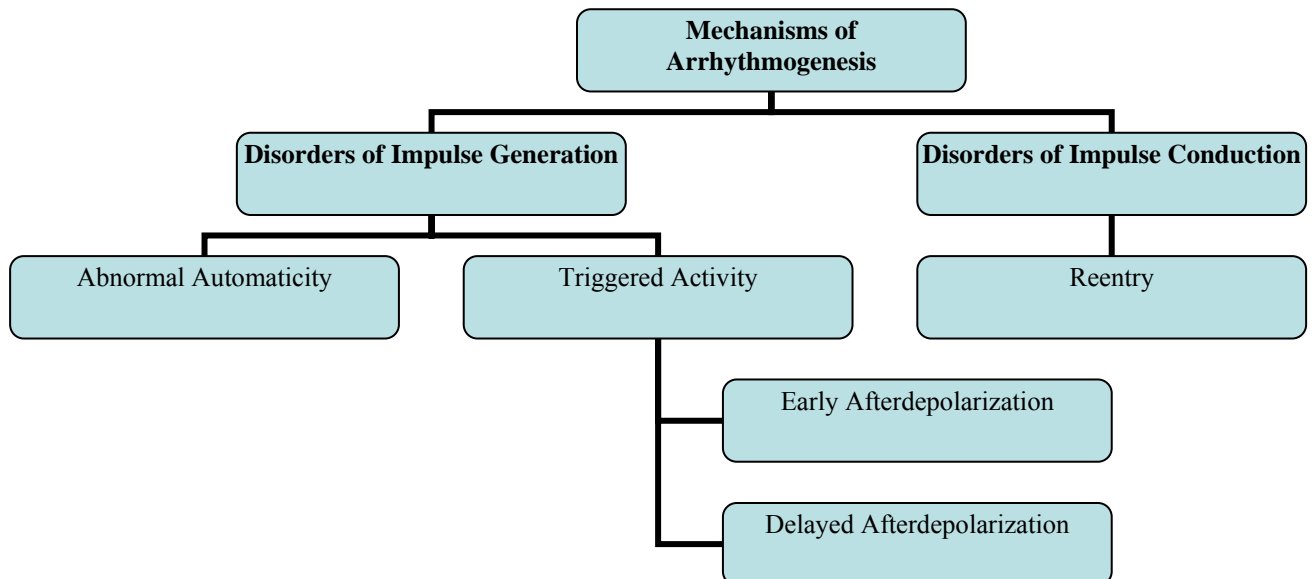

Fig 1. Mechanisms of arrhythmias

In abnormal automaticity, non-pacemaker cells begin to spontaneously and abnormally

initiate an impulse. Abnormal automaticity is believed to be the result of reduced (more positive) resting membrane potential bringing it closer to the threshold potential. Ischemia and electrolyte imbalances are two causes of reduced membrane potential that may result in abnormal automaticity.

Spontaneous depolarizations requiring a preceding impulse (a triggering beat) are called **afterdepolarizations (or triggered activity).** If afterdepolarizations originate during phase 2 or 3 of the monophasic action potential (MAP) they are classified as **early afterdepolarizations (EAD)** (Fig 2). Afterdepolarizations originating from phase 4 of the MAP are classified as **delayed afterdepolarization (DAD)** (Fig 3). An example of early afterdepolarization (EAD) is drug induced **torsade de pointe**, a polymorphic form of ventricular tachycardia that is a potentially lethal complication of anti arrhythmic and other drugs that prolong the QT-interval. The extrusion of potassium from myocardial cells allows the cell's membrane potential to go back to its resting potential. This process is called **repolarization,** and is carried via a potassium channel (I_K channel). The process involves bringing the transmembrane potential back to its resting value. The less negative the trans membrane potential, the less sodium channels are available to depolarize the cell making it **refractory** to any received impulse (unexcitable). The extrusion of potassium determines the duration of the action potential, the cell's refractory period and the length of the QT interval (the electrocardiographic equivalent of repolarization). Drugs that block this channel such as quinidine, procainamide, sotalol and dofetilide can result in torsade de pointe. Ventricular arrhythmias secondary to digoxin toxicity is an example of delayed afterdepolarization. Digoxin mediated increased intracellular Ca^{++} is believed to be the mechanism of this type of arrhythmia.
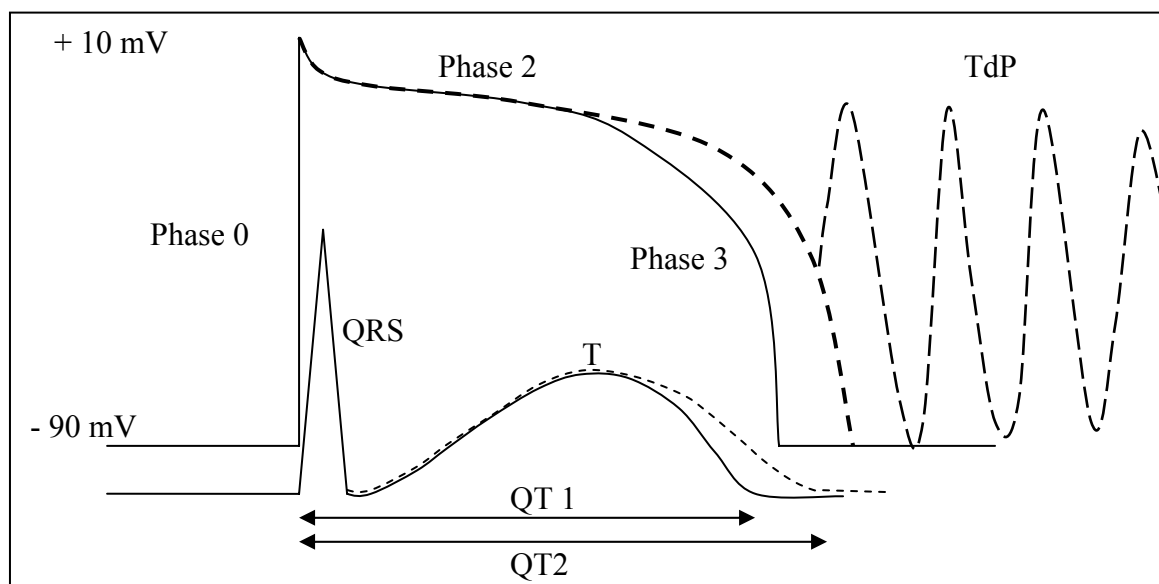

Fig 2. Prolongation of repolarization by inhibiting the potassium channels will result in lengthening of the QT interval (QT2). It may also precipitate early afterdepolarization, a form of triggered activity. Torsade de pointe (TdP), a potentially lethal polymorphic

ventricular arrhythmia, is an example of EAD, it may be precipitated by potassium channel blockers such as sotalol, quinidine, dofetilide and procainamide.
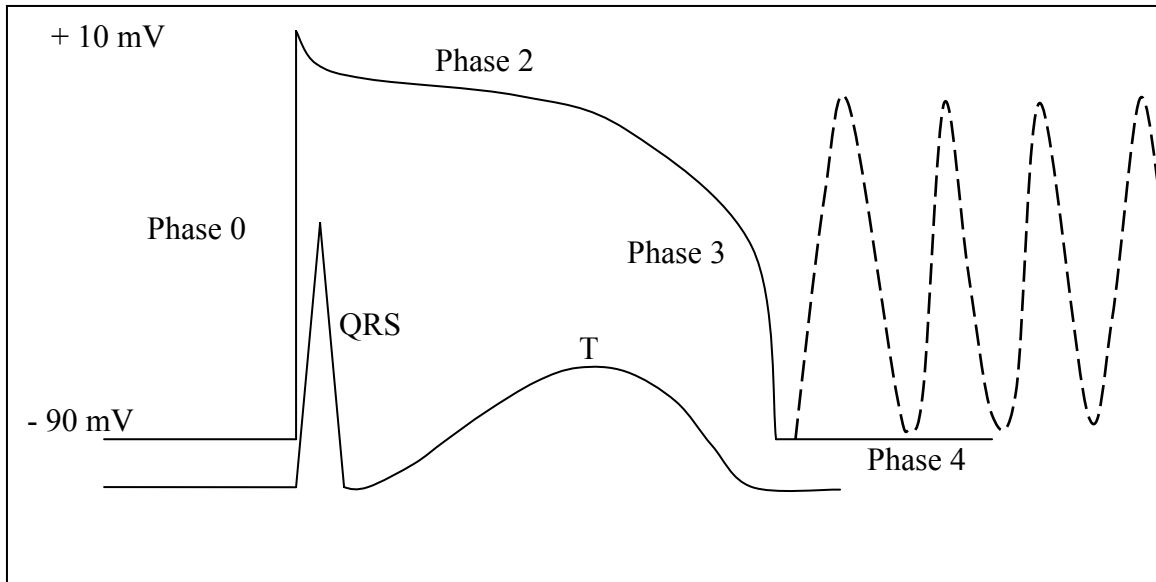

Fig 3. Triggered activity originating from phase 4 of the MAP. This is known as delayed afterdepolarization (DAD)

Disorders of impulse conduction can result in conduction block and **reentry**, the most common mechanism of arrhythmias. For reentry to occur, myocardial tissue that is contiguous must have disparate electrophysiologic properties. A normally propagating impulse usually encounters electrophysiologically homogenous tissue. If the impulse blocks in some part of the tissue but not in others, while allowing retrograde conduction to occur, **unidirectional block** is said to have occurred. If a retrogradely conducting impulse encounters excitable tissue, reentry is set up. Electrophysiologic blocks may be anatomic (the annuli of the AV valves in AV reciprocating tachycardia), fibrosis due to a myocardial infarction or inflammation or altered electrophysiologic properties due to electrolyte imbalance or ischemia (fig 4).
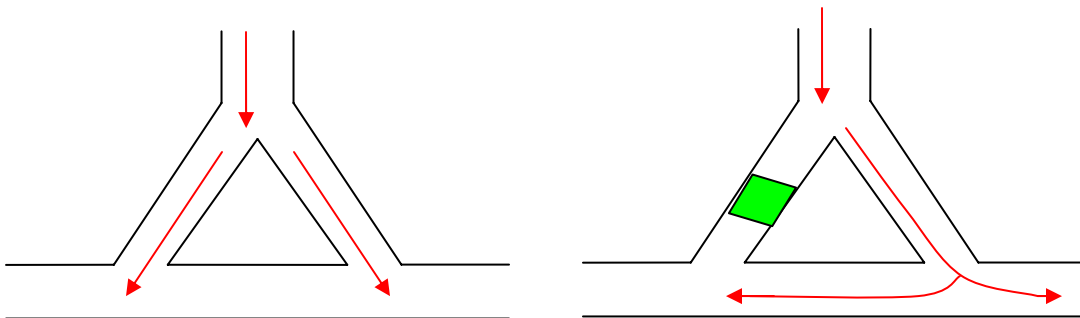
Fig 4. This schematic diagram displays a simplified model of reentry where on the left side, the two limbs of excitable tissue have similar electrophysiologic properties. If the electrophysiologic properties of one of the two limbs (the left limb of Fig 4 in this example) is altered, a premature impulse may block antegrade in that limb and conduct in the second (the right limb). The impulse will conduct distally to the insertion point of the left limb and if excitability has recovered in that left limb, conduct retrogradely and back to the proximal insertion point of both limbs and antegrade again setting up reentry.
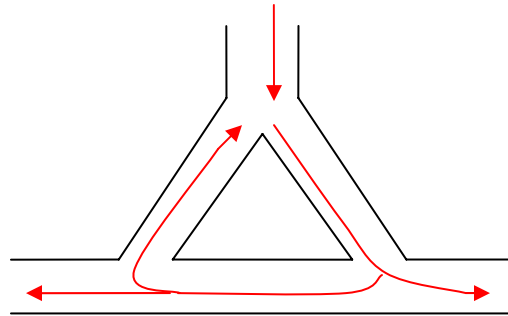
Reentry requires a critical mass of tissue, conduction velocity and refractoriness. The abnormal prolongation of the refractory period will allow block to occur and slowing of conduction will allow enough time for the blocked tissue to recover by the time the impulse has reached it, resuming excitability and allowing reentry. Lengthening of the refractory period and / or slowing of the velocity of conduction may help terminate reentry. Examples of reentrant arrhythmias include AV nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), atrial flutter, atrial fibrillation and ventricular tachycardia.

Management of Arrhythmias

Historically, medications used to be the only available method for managing arrhythmic disorders. Surgical procedures were subsequently developed for management of Wolff-Parkinson-White syndrome (accessory bypass tracts), ventricular tachyarrhythmias and more recently, atrial fibrillation (the Maze procedure developed in the late 80s by Cox and his colleagues). Three radical developments have reduced the role of anti arrhythmic agents to an ancillary and supportive role.

In the late 80's new and powerful sodium channel blockers were developed. Frequent premature ventricular beats were by then recognized as harbingers of sudden cardiac death in patients who suffered from myocardial infarction and had developed a cardiomyopathy. The CAST trial was designed to asses the impact suppression of these ventricular ectopic beats had in this high risk population (New England Journal of Medicine. 321(6):406-12, 1989 Aug 10, N Engl J Med 1991;324:781-788). Unexpectedly patients who received these powerful new anti arrhythmic agents had a 2.5 fold higher mortality than patients in the control arm of the trial forcing the premature termination of this trial. In 1990, Coplen et al reviewed six trials using quinidine to maintain sinus rhythm after cardioverting patients with atrial fibrillation to sinus rhythm (Circulation 1990;82:1106-1116). One year after converting patients with atrial fibrillation to sinus rhythm quinidine raised the percentage of patients maintained in sinus rhythm from 25% to 50% at the end of the first year. However mortality was three-fold higher in patients treated with quinidine. In these two landmark cases, it was postulated that antiarrhythmic

drugs, under special circumstances, can actually enhance the likelihood of developing a life-threatening arrhythmia hence the concept of **proarrhythmia**.

Potassium channel blocking drugs have long been recognized to result in a potentially fatal polymorphic ventricular tachycardia known as torsade de pointe. Delaying repolarization and lengthening of the monophasic action potential (MAP) is manifested electrocardiographically by lengthening of the QT-interval. Syncope was observed to occur in patients taking quinidine in the 1920s and was determined to be due to ventricular arrhythmias in 1964. In addition to potassium channel blocking anti arrhythmic agents, many unrelated drugs have been implicated in lengthening of the QT-interval, recurrent syncope and sudden death. Antibiotics (macrolides, fluoroquinolones, ketoconazole, trimethoprim-sulfamethoxazole) and anti psychotics (chlorpromazine, thioridazine, haloperidol, risperidone) comprise the largest number of drugs associated with QT-interval prolongation. In the late 1990s, two non-sedating antihistamines (terfenadine and astemizole) were taken off the market due to the risk of torsade de pointe.

In the management of patients who suffered from lethal ventricular arrhythmias, **implantable cardioverter-defibrillators (ICD)** were introduced in the early 1980s and approved by the FDA in 1985. Amiodarone, a Vaughan-William's class III anti arrhythmic drug, has been found to be safe when used in patients with ischemic cardiomyopathies. In the AVID (N Engl J Med 337:1576, 1997) and CASH (Am Heart J 127:1139-44, 1994) trials, when compared with amiodarone, survivors of cardiac arrest who had ICDs had lower cardiovascular and total mortality. Today, anti arrhythmic agents are used only to reduce the frequency of therapies delivered by ICDs in survivors of cardiac arrest or patients at risk of sudden cardiac arrest and who received ICDs prophylactically (primary prevention).

The ability to deliver pin point, circumscribed lesions to areas of the endocardium has revolutionized the management of arrhythmias. Catheters can now deliver radiofrequency energy to 4-10 mm tips creating well circumscribed lesions that can destroy focal areas or arrhythmogenesis (idiopathic ventricular tachycardia) or to limbs of macro (AV nodal reentrant tachycardia, AV reciprocating tachycardia, atrial flutter) or micro-reentrant tachycardia (ischemic ventricular tachycardia). **Radiofrequency catheter ablation (RFA)** has now become the treatment of choice for many of these arrhythmias. The procedure is relatively safe and provides for a long-lasting cure.

Classification of Anti Arrhythmic Agents

The widest employed classification of anti arrhythmic agents is the Vaughan-Williams classification. This classification suffers from major drawbacks but its ease of use has helped maintain its role. One major fault with this classification lies in it's over simplification of the effect of these drugs. The classification relies on the effect these agents have on normal tissue and under arbitrary conditions. The other problem is that the major effect an agent from one group has, overlaps with the effect agents from other groups have. An example is quinidine which is classified as a Vaughan-Williams group I

anti arrhythmic agent, i.e. sodium channel blockade. Quinidine also blocks the potassium channel (a class III effect) and may lead to torsade de pointe, the most serious consequence of its use. Amiodarone, classified as a group III anti arrhythmic has sodium channel blocking (class I), beta blocking (class II), potassium channel blocking (class III) and calcium channel (class IV) blocking properties. A more comprehensive classification of anti arrhythmic agents is available and has been called the "Sicilian Gambit".

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Table 1; The Sicilian Gambit attempts to classify antiarrhythmic agents to encompass as many of each agent's anti arrhythmic properties.

Anti arrhythmic agents work by blocking the sodium channel, the potassium channel, the calcium channel and or the adrenergic receptors. Sodium channel blockade reduces the rate of rise of phase 0 of the monophasic action potential (V_{max}) slowing conduction. Potassium channel blockers lengthen refractoriness. The principles of terminating reentrant arrhythmias include lengthening the refractory period (K^+ channel blockade) and slowing conduction (Na^+ channel blockade). The hope is that the lengthened refractory period (1) would preclude reentry in the limb of the reentrant model that displayed unidirectional block at the outset (Fig 5). By slowing conduction, the impulse traveling retrogradely may block (2), once again, breaking reentry.

Fig 5. Mechanisms of antiarrhythmic agents in terminating reentrant arrhythmias. By lengthening the refractory period at 1, the retrogradely traveling impulse would not encounter excitable tissue and reentry would be extinguished. If the reentrant impulse is slowed enough at 2 it would block and fail to travel up the second limb of the reentrant path.
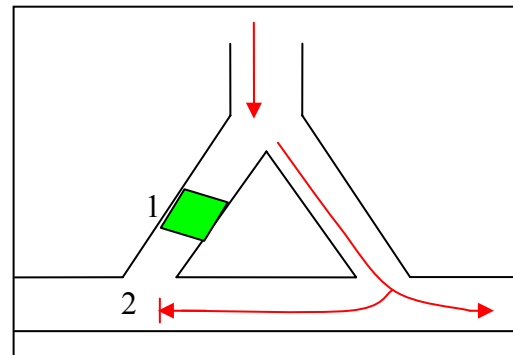
On the other hand, if the antegrade conducting wave front (impulse) is slowed down sufficiently enough for the unidirectional block to recover, reentry may actually be promoted. This may explain why powerful sodium channel blockers such as flecainide and propafenone may actually promote ventricular tachyarrhythmias, a potentially lethal form of proarrhythmia.

In the Vaughan-Williams classification; class I agents are sodium channel blockers, class II are beta blockers, class III are potassium channel blockers and class IV are calcium channel blockers. The class I agents are classified into class Ia (sodium and potassium channel blockage, kinetics of onset and offset of sodium channel blockade are intermediate in rapidity). This class includes **quinidine, procainamide** and **dispopyramide**. They slow the rate of rise of phase 0, lengthen the refractory period and the width of the monophasic action potential. The class 1b agents are pure sodium channel blockers, the do not slow the rate of rise of phase 0 of the MAP and shorten the

MAP duration and the kinetics of onset and offset of sodium channel blockade are rapid. This class includes **lidocaine, mexiletine** and **tocainide**. The class Ic agents are strong sodium channel blockers with slow onset and offset kinetics. This class comprises **flecainide, propafenone** and **moricizine**. The class III agents are drugs that block the potassium channel as their chief anti arrhythmic effect. The class include **sotalol, dofetilide, ibutilide, amiodarone** and **bretylium**. They exert their effect by prolonging the refractory period.

Ion channels are believed to exist in one of three states; **resting, active** and **inactive**. Sodium channel blockers have a greater propensity to bind to channels in the active state, the faster the rate, to more the binding and the drug's anti arrhythmic effect. This is called **use dependence**, a property of sodium channel blockers. On the other hand, many potassium channel blockers such as sotalol, bind to channels in the resting state. This property is called **reverse use dependence**. Potassium channel blockers display their proarrhythmia when the heart rate is slow, raising the risk of lethal arrhythmias such as torsade de pointe. The treatment of torsade de pointe includes pacing and isoproterenol in attempt to reduce pauses and increase heart rate, reducing the amount of time potassium channels spend in the resting state and reducing the arrhythmic effect of the agent.

Class I Anti Arrhythmic Agents

Quinidine, procainamide and dispopyramide have sodium and potassium channel blocking effects and are classified as IA. **Quinidine** is one of the oldest anti arrhythmic agents derived from the cinchona tree bark and has anti malarial, anti pyretic and anti arrhythmic effects. It is eliminated via hepatic and renal routes. The most common side effects are gastrointestinal; nausea, abdominal pain and diarrhea. Allergic reactions with rash, fever, hemolytic anemia, thrombocytopenia and hepatitis can occur. Cinchonism refers to quinidine's CNS side effects such as tinnitus, delirium, hearing and visual impairment. The most serious side effect is polymorphic ventricular tachycardia / torsade de pointe. The recurrent loss of consciousness once seen with this agent (quinidine syncope) is now believed to be due to non sustained forms of this arrhythmia.

Procainamide is predominantly excreted by the kidneys, its main metabolites, N-acetyl procainamide (NAPA) is a pure potassium channel blocker and is exclusively renally excreted. Patients with impaired renal function should have the dose adjusted. Procainamide is effective in treating supraventricular and ventricular arrhythmias. In patients with wide complex tachycardia, where differentiation of supraventricular arrhythmias from ventricular arrhythmias is difficult, procainamide can be used to terminate the arrhythmia if the patient is stable. Agranulocytosis is the most serious non-cardiac side effect. A lupus like syndrome with arthralgias, myalgias, pleuritis, pericarditis (polyserositis) and rash may occur. The development of positive anti nuclear antibodies is seen in 60%-70% of patients. Compared with systemic lupus erythematosis (SLE) the brain and kidneys are spared. Discontinuation of procainamide is followed by regression of these side effects.

Disopyramide has three important side effects. It is vagolytic causing urinary retention, constipation and dry mouth. Pyridostigmine, an acetylcholine esterase inhibitor, can be used to reverse disopyramide's vagolytic side-effects. This agent displays negative inotropy that is used in managing patients with hypertrophic cardiomyopathy and patients with neurocardiogenic (vaso vagal) syncope. Finally, disopyramide can cause torsade de pointe.

Lidocaine and **mexiletine** are class IB anti arrhythmic agents used only the management of ventricular tachyarrhythmias. Lidocaine can only be given intravenously and is metabolized in the liver. Dose should be adjusted in patients with liver disease and heart failure. Lidocaine toxicity manifests itself with CNS side effects; parasthesias, confusion and seizures. Mexiletine is used orally, its side effects are CNS; tremors, confusion, blurred vision and gastrointestinal; nausea and vomiting.

Flecainide and **propafenone** are class IC anti arrhythmic agents. They are used to treat ventricular and supraventricular tachyarrhythmias. They are contraindicated in patients with structural heart disease due to the risk of precipitating life-threatening ventricular arrhythmias (see CAST study above). These drugs can depress systolic function. They can suppress the sinus node in patients with sick sinus syndrome and impair AV and infra nodal conduction in patients with conduction disease. Propafenone has beta adrenergic receptor blocking effect.

Class III Anti Arrhythmic Agents

Sotalol is a non specific beta adrenergic receptor blocker with potassium channel blocking properties used in managing ventricular arrhythmias and atrial fibrillation. It is renally excreted and must be used with caution if at all in patients with impaired renal function. The most serious side effect is torsade de pointe, the corrected QT (QT_c) interval must be watched carefully for excess prolongation. Due to its beta adrenoreceptor blocking effect, patients with bronchospastic disease may experience an exacerbation of their pulmonary disease. **Ibutilide** is a short acting intravenous potassium channel blocker used only for the acute termination of atrial fibrillation or flutter. It can cause sustained ventricular arrhythmias and patients who receive this agent should be monitored electocardiographically, with resuscitative equipment readily available, for 8 hours. **Dofetilide** is a potassium channel blocker excreted by the kidneys. Dosage is determined by creatinine clearance and adjusted according to changes in the corrected QT (QT_c) interval. The use of this agent has been limited to physicians trained and certified in its use. It has been found safe in patients with advanced cardiomyopathy when used the dosage is adjusted individually and patients are monitored at the inception of therapy.

Amiodarone has a wide spectrum of electrophysiologic effects. Although classified as a class III agent, it displays use dependent sodium channel blockade, noncompetitive alpha and beta adrenoreceptor blockade and calcium channel blockade. Some of its electrophysiologic effect is by reducing the conversion of T_4 to T_3 and increasing rT_3. Amiodarone is also a vasodilator and was initially developed as an anti anginal agent.

Amiodarone is used in managing atrial fibrillation and recurrent ventricular arrhythmias in patients with cardiovascular disease.

It can be administered intravenously and orally. Amiodarone has a very long half-life (40-50 days). In order to achieve rapid therapeutic levels, the drug should be loaded. It is hepatically excreted with no renal excretion.

While it has a wide spectrum of side effects, some lethal, it rarely causes torsade de pointe and is safely used in patients with advanced cardiovascular disease. When compared with other anti arrhythmic agents, it has been shown to be superior in reducing the recurrence of ventricular arrhythmias and atrial fibrillation.

Amiodarone toxicity is influenced by the dosage employed and the duration of its use. Its most feared toxicity is pulmonary fibrosis which can be fatal in 10% of individuals treated for recurrent ventricular arrhythmias. One third of amiodarone is iodine by weight, this may interfere with biochemical assays of thyroid function and may lead to hypothyroidism or, less often, hyperthyroidism. Amiodarone accumulates in the liver and the skin, elevation of liver enzymes of up to three fold may be seen. A slate blue discoloration of the skin is seen in patients taking high doses of amiodarone chronically. Patients on amiodarone are advised to avoid sun exposure due to photosensitivity. While all patients receiving amiodarone will ultimately develop corneal deposits that are of negligible clinical significance, rarely optic neuritis has been reported. Optic neuritis can lead to blindness however a causal relationship with amiodarone therapy has not been established. Up to 25% of patients on this agent will have to discontinue it due to the development of a complication or side effect.

Classification of Anti Arrhythmic Drugs
(The Vaughan Williams Classification)

Drug	Primary Clearance	Half life (hrs)	Main adverse effects	Uses
Class I ; Sodium Channel Blockers				
Class IA agents; combined sodium and potassium channel blockade, intermediate kinetics of binding and dissociation				
Quinidine	Hepatic (CYP450 3A4)	6-8 hrs.	Diarrhea, nausea, rash, cinchonism. Serious; torsade de pointe, hepatotoxicity, myelosuppression	Ventricular arrhythmias and atrial fibrillation (oral)
Procainamide	Hepatic metabolism, renal excretion (main metabolite NAPA is a K channel blocker)	3-5 hrs.	Proarrhythmia; lethal ventricular arrhythmias and torsade de pointe. Positive anti nuclear antibodies (ANA) and lupus like syndrome. Blood dyscrasias; agranulocytosis, thrombocytopenia and anemia.	Ventricular arrhythmias and atrial fibrillation (oral or IV)
Disopyramide	Hepatic (P450 CYP 3A4) and	4-10 hrs.	Proarrhythmia, parasympatholytic (urinary	Ventricular arrhythmias and atrial fibrillation

	renal elimination		retention, blurred vision, constipation, dry mouth) and mild negative inotropy	(oral)
Class IB; Sodium channel blockade, rapid kinetics of binding and dissociation				
Lidocaine	Hepatic	1.5-2 hrs.	Tremors, seizures, parasthesias, confusion and delirium. Methemoglobinemia,	Ventricular arrhythmias (only IV)
Tocainide	Hepatic	11-23 hrs.	Blood dyscrasias, pulmonary fibrosis, GI and neurological symptoms	Ventricular arrhythmias (oral)
Mexiletine	Hepatic (P450 CYP2D6)	10-12 hrs.	Ataxia, dizziness, tremors, GI upset	Ventricular arrhythmias (oral)
Class IC; Sodium channel blockade, slow kinetics of binding and dissociation				
Flecainide	Hepatic (P450 CYP2D6)	20 hrs.	Proarrhythmias particularly in post MI patients. Heart failure, dizziness, headache, blurred vision	Contraindicated in patients with structural heart disease. Used in treatment of paroxysmal atrial fibrillation, WPW (oral)
Propafenone	Hepatic (P450)	2-10 hrs.	Proarrhythmias particularly in post MI patients. Nausea, vomiting, altered taste,	Contraindicated in patients with structural heart disease. Used in treatment of paroxysmal atrial fibrillation, WPW (oral)

Class II; Beta Adrenoceptor Blockers	
B1 Selective	
	Acebutolol (membrane stabilizing and ISI)
	Atenolol
	Bisoprolol
	Esmolol (IV only)
	Metoprolol
Non (β 1) selective	
	Nadolol
	Propranolol
Non B selective and α receptor blockers	
	Carvedilol (used in heart failure management)
	Labetalol (IV form is used in acute hypertensive crisis)

Class III; Potassium Channel Blockers				
Sotalol	Not metabolized, renal clearance	12 hrs.	Proarrhythmia; torsade de pointe. Fatigue, bradycardia, shortness of breath.	Atrial fibrillation ventricular arrhythmias. Contraindicated if creat. clearance < 40 or QTc > 450 msecs.
Dofetilide	Hepatic metabolism	10 hrs.	Proarrhythmia; torsade de pointe. Headache, chest pain.	Atrial fibrillation, contraindicated if

	(CYP3A4) renal excretion			creatinine clearance < 20, QTc > 440 msecs.
Ibutilide	Hepatic	6 hrs.	Proarrhythmia; polymorphic VT / torsade de pointe	Only used for the immediate, acute conversion of atrial flutter or fibrillation. Patient must be monitored no less than 4 hours for ventricular proarrhythmia.
Bretylium	Renal excretion	6-14 hrs.	Proarrhythmia, hypotension	Ventricular arrhythmias
Amiodarone	P450 CYP3A4 and CYP2C8	15-140 **days**	Pulmonary, neurologic, hepatic, dermatologic and ophthalmic side effects and complications	Used for ventricular arrhythmias and atrial fibrillation
Class IV; Calcium channel blockers				
Dihydropyridine; selective vasodilators acting on peripheral smooth muscles				
	Amlodipine			
	Felodipine			
	Isradipine			
	Nicardipine			
	Nifedipine			
Benzothiazepine; less selective vasodilator activity, depresses sinus node and AV node				
	Diltiazem			
Phenylalkylamine; less selective vasodilator activity, depresses sinus node and AV node				
	Verapamil			

General principles on the use of anti arrhythmic agents:

There has been a major evolution in the management of cardiac arrhythmias over the last fifteen years. The discovery that anti arrhythmic agents may predispose to ventricular arrhythmias has long been known but the impact was made clear with the premature termination and publication of the results of the CAST trial. Parallel to this decline in the role of anti arrhythmic agents has been the rise in the role played by implantable cardioverter defibrillators (ICD) and catheter based radiofrequency ablation (RFA) in managing life-threatening arrhythmias and supraventricular arrhythmias respectively. Anti arrhythmic drugs are being used less, with more care and often in conjunction with ICDs or catheter ablation. Anti arrhythmic drugs work by reducing automaticity of abnormal tissue, prolonging refractoriness or slowing conduction. Sodium channel blockers slow conduction by depressing the slope of rise of Vmax during phase 0 of the monophasic action potential (MAP) whereas potassium channel blockers prolong the cell's refractory period (phase 3 of the MAP).

Drugs that interact with their receptors more at faster heart rates are said to display **use dependence**. Sodium channel blockers display such characteristics depressing the rate of rise of Vmax more during rapid hear rates. It is postulated that these drugs interact more with their receptors when they are in the open or inactive state rather than in the resting state. Potassium channel blockers, on the other hand, interact more with the receptor in the resting state. This is termed **reverse use dependence**. An example of the latter is the greater risk of torsade de pointe following a pause or at slow heart rates, the management

of torsade de pointe includes pacing or the administration of isoproterenol to accelerate the heart rate and reduce the potential for torsade to recur.

Anti arrhythmic use to manage life threatening ventricular arrhythmias is confined to intravenous hospital use (amiodarone, lidocaine) or in conjunction with an ICD (amiodarone, sotalol, mexiletine, quinidine). The use of anti arrhythmic agents in managing atrial fibrillation is guided by the presence (amiodarone, sotalol, dofetilide) or absence (flecainide, propafenone) of structural heart disease. Flecainide and propafenone are less useful in managing persistent atrial fibrillation than they are in managing paroxysmal AF. On the other hand, sotalol and dofetilide are more helpful in persistent than in paroxysmal atrial fibrillation.

Drugs that prolong the QT interval (potassium channel blockade; sotalol, dofetilide) should only be initiated on an inpatient basis where the patient is monitored for no less than three days. Drugs that delay conduction (sodium channel blockers particularly the group IC agents) should not be used if the patients has evidence of conduction disease (second degree AV block or higher, bundle branch block) unless the patient has a preexisting permanent pacemaker. Many of these drugs can suppress contractility (negative inotropes) and should be used carefully in patients with cardiomyopathy.

The potential for a potassium channel blocker to lengthen the QT interval is greater in some individuals than in others predisposing them to life threatening arrhythmias (torsade de pointe). A genetic basis for this predisposition is suspected. Many non cardiac drugs can interfere with the metabolism of these drugs enhancing the potential for these arrhythmias to occur. An example is the use of some macrolide and quinolone antibiotics with potassium channel blockers. Other drugs such as diuretics, increase the risk of proarrhythmia by decreasing serum potassium levels. Great care must be employed in using these drugs and preferably by physicians with experience in their use.

The Vaughan-Williams classification of anti arrhythmic agents has remained popular despite its inaccuracies. Antiarrhythmic agents each have overlapping effects making accurate classification difficult. Examples include classifying quinidine, a sodium and potassium channel blocker, as a class I (sodium channel blockers) agent. Sotalol is a potassium (class III) and beta blocking (class II) agent. Amiodarone has numerous receptor blocking effects in addition to blocking the conversion of thyroxine (T4) to triiodothyronine (T3) and they all account for its anti arrhythmic effect. The alternative to the Vaughan-Williams classification is the **Sicilian Gambit**. While the Sicilian Gambit displays the receptor blocking properties of anti arrhythmic agents more accurately, it is more complex and harder to memorize.

| Arrhythmia type	Primary option	Secondary option	Contraindicated or Ineffective
Drugs used for conversion of AF of < 7 days' duration to SR	Dofetilide, ibutilide (only IV), flecainide, propafenone	Amiodarone, quinidine, procainamide	Digoxin, sotalol
Drugs used for conversion of AF > 7 days' duration	Dofetilide	Amiodarone, ibutilide, flecainide,	Digoxin, sotalol

		propafenone, quinidine, procainamide	
Prevent recurrence of AF in the absence of any heart disease	Flecainide, propafenone, sotalol	Amiodarone, dofetilide	
Prevent recurrence of AF in the presence of hypertension without substantial left ventricular hypertrophy†	Flecainide, propafenone, sotalol	Amiodarone, dofetilide	
Prevent recurrence of AF in the presence of hypertension and substantial left ventricular hypertrophy	Amiodarone		Sotalol, flecainide, propafenone
Prevent recurrence of AF in the presence of coronary artery disease	Sotalol, dofetilide	amiodarone	Flecainide, propafenone
Prevent recurrence of AF in the presence of heart failure	Amiodarone, dofetilide		Flecainide, propafenone
Ventricular fibrillation / cardiac arrest*	Amiodarone (IV)	Lidocaine	
Sustained, hemodynamically stable, ventricular tachycardia*	Procainamide (IV), amiodarone (IV)	Lidocaine	Verapamil ¶, diltiazem ¶

† Defined as LV wall thickness of > 1.4 cm

* The management of ventricular fibrillation and hemodynamically unstable ventricular tachycardia (chest pain, shortness of breath, systolic BP < 90 mmHg) is by immediate defibrillation / cardioversion. Anti arrhythmic agents are only used in conjunction with cardioversion / defibrillation if defibrillation / cardioversion does not succeed in terminating the ventricular tachyarrhythmia or if it does, it is followed by recurrence of the arrhythmia and the agent is used to prevent future recurrence.

¶ These agents are absolutely contraindicated, they may convert a hemodynamically stable ventricular tachycardia into an unstable one by causing peripheral vasodilation and hypotension.

Electrocardiograms of Common Arrhythmias
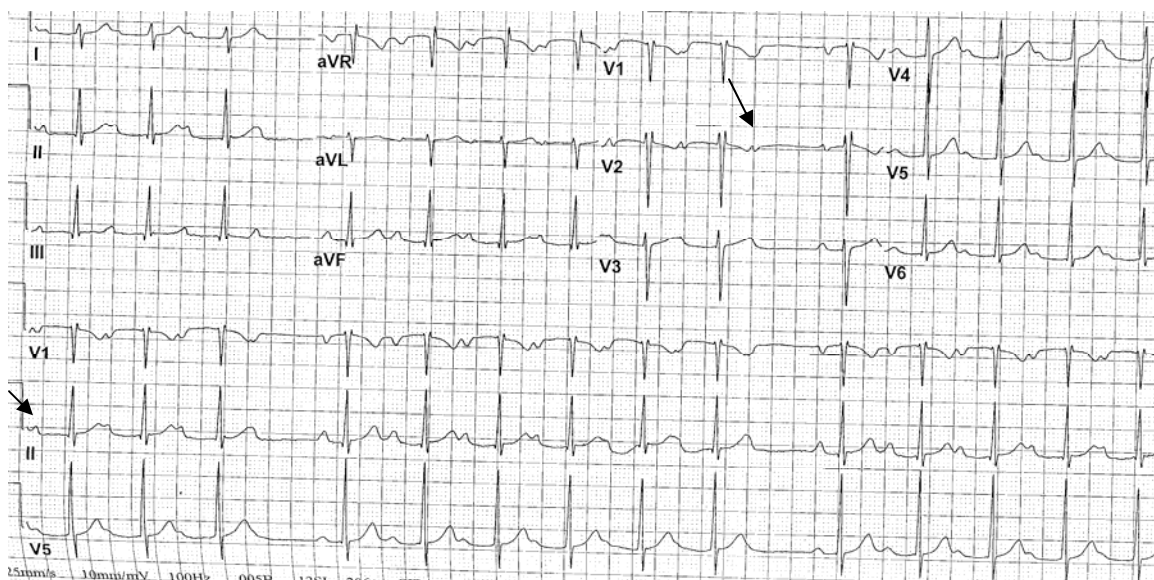
AV Wenckebach
Mobitz I 2º AV block

This electrocardiogram is arranged in a 12 lead format on top and three rhythm strips on the bottom. The underlying rhythm is sinus. There are regular P waves across this electrocardiogram best seen in lead II and V2. The first arrow points to the first P wave in lead II. One can see gradual lengthening of the PR interval before a P wave, by now buried in the T wave, fails to conduct leading to the pause seen. The P hidden in the T is best appreciated buried in the T wave preceding the next pause in lead V2 (the second arrow). The PR interval following the pause is shorter than the PR interval preceding the pause. This type of AV conduction disturbance is called Wenckebach or Mobitz I 2º AV block. The level of block is usually at the level of the AV node.


Mobitz II 2º AV Block

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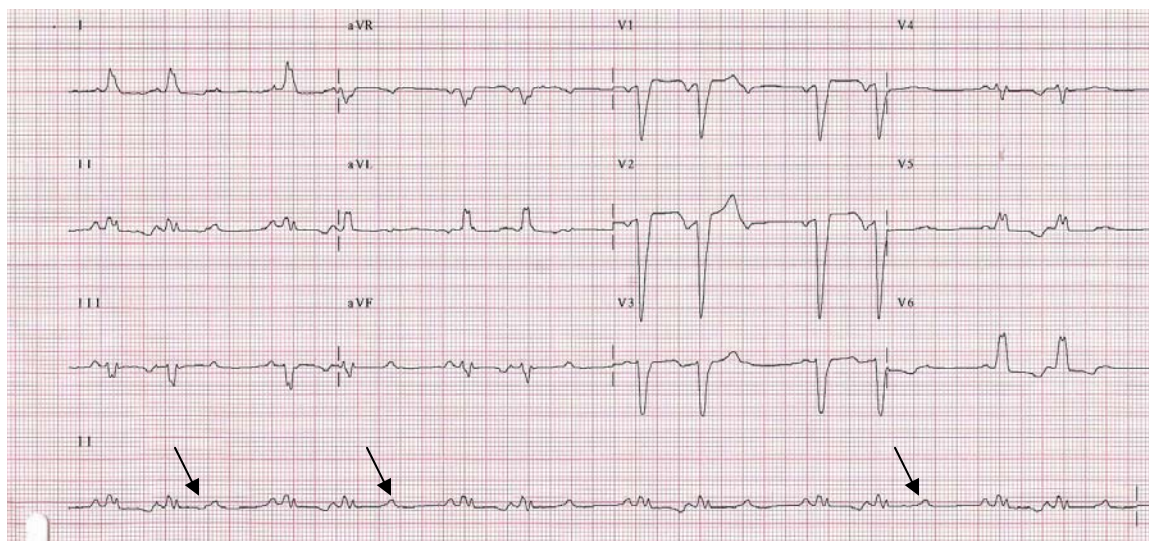
This 12 lead EKG shows sinus rhythm with P waves seen clearly in leads II, III, aVF, V1 and V2. The top three lines constitute the 12 lead EKG and the bottom strip, the rhythm strip, a continuous recording. On the rhythm strip, the first and second P waves conduct to the ventricle. The QRS is wide with a left bundle branch block morphology (LBBB). The 3rd, 6th, 12th and 15th P waves do not conduct to the ventricle. There is no prolongation of the PR interval before the non-conducted P waves or shortening of the PR interval after the block, signs of Mobitz I 2° AV block (Wenckeback). The PR intervals before and after the non-conducted P waves are identical. This type of block is termed Mobitz II 2° AV block. This type of block is much more serious than Mobitz I 2° AV block. The site of block is lower than the site of Mobitz I block, progression to complete heart block is sudden and the **escape rhythm** is slower, less reliable and has a wider QRS morphology due to its more inferior site of origin. Hence, this type of AV conduction disease mandates the immediate insertion of a permanent pacemaker.
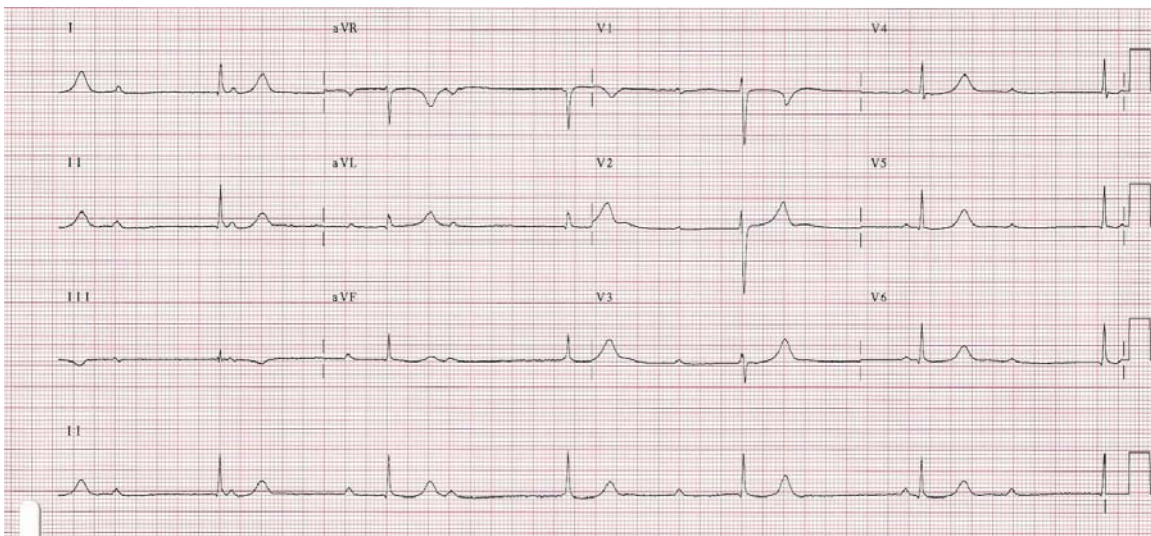

Third degree (complete) AV Block

The P waves do not conduct to the ventricle. The QRS complexes seen are regular and narrow have no relationship to the P waves. This narrow complex rhythm is described as an "escape". Auxiliary pacemaker cells endowed with automaticity, begin to fire at a rate usually slower than the sinus rate in an attempt to compensate for the slow ventricular rate caused by the AV conduction disease. The fact that the QRS complex is narrow and the rate between 40-60 bpm indicate that the site of origin is close to the AV node hence the term "junctional rhythm".
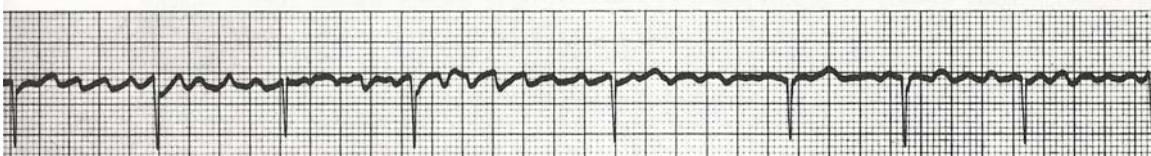

Atrial Fibrillation

The baseline is irregular, there are no discernible P waves. In atrial fibrillation the atrial "rate" is greater than 400 bpm which does not translate into any meaningful contractile function. The ensuing stagnation of blood predisposes to the formation of clot. This explains the high risk of thromboembolism in atrial fibrillation and the need to anticoagulate patients deemed at risk. The ventricular rate is usually rapid and irregular. A slowerer ventricular rate may represent atrioventricular conduction disease or the effect of rate controlling drugs such as beta blockers.
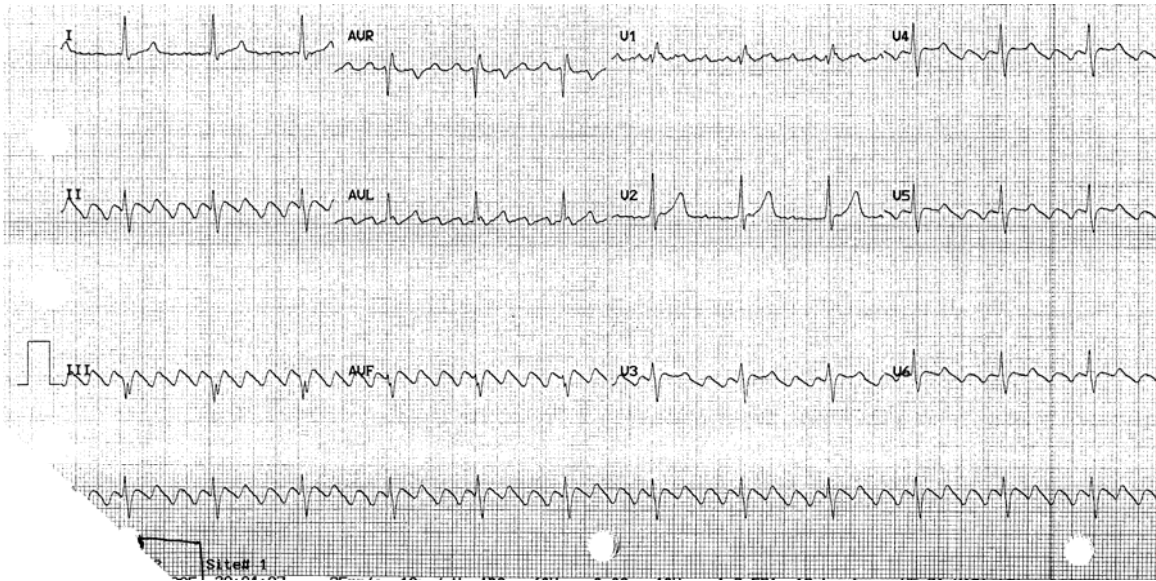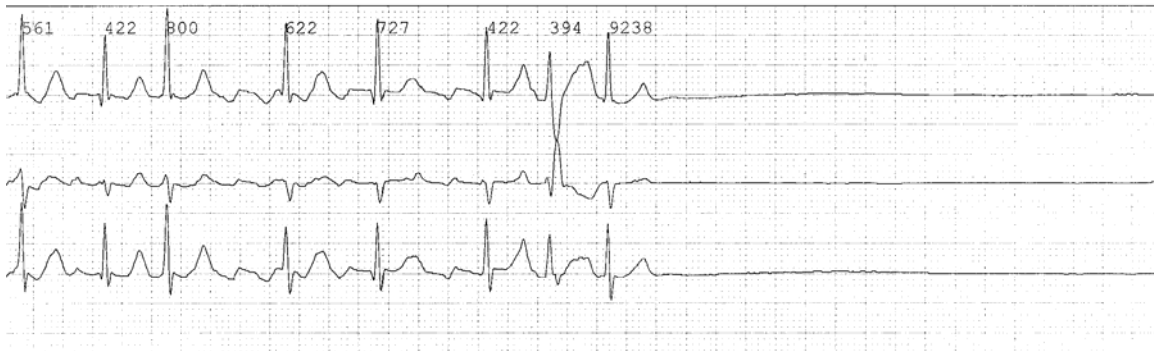

Atrial Flutter

A reentrant supraventricular arrhythmia characterized by a "saw tooth" or "picket fence" looking baseline representing atrial flutter. The atrial rate is usually between 250 and 350 bpm, conduction to the ventricle is usually with 2:1 or 4:1 block. Hence, the ventricular rate is usually rapid and regular unless atrioventricular conduction is variable. This arrhythmia also carries a risk of thromboembolism. This arrhythmia is usually localized to the annulus of the tricuspid valve and a cure can be achieved by radiofrequency ablation of the isthmus between the tricuspid valve and the inferior vena cava.
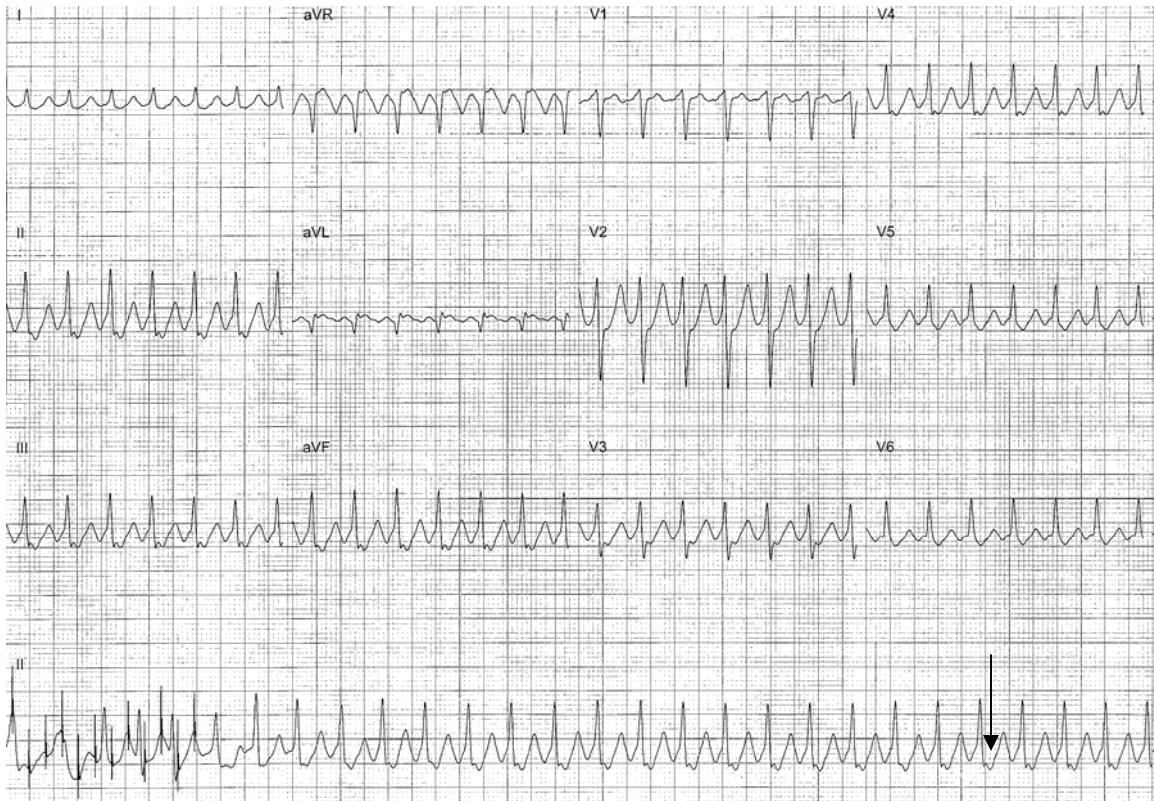
Supraventricular Tachycardia

This electrocardiogram shows the 12-leads in the first three lines a continuous rhythm strip below (lead II). This shows a narrow complex tachycardia. The differential diagnosis is **atrioventricular nodal tachycardia (AVNRT)**, **atrioventricular reentrant tachycardia (AVRT)** or **atrial tachycardia (AT)**. The vertical arrow points to a P wave. In the case of reentrant supraventricular tachycardias such as AVNRT or AVRT, these P waves are retrograde and are labeled P'. In AVNRT atrial cells with disparate electrophysiologic properties converge onto the AV node. Their properties set the stage for a reentrant supraventricular tachycardia, the most common type of paroxysmal supraventricular tachycardia. In AVRT, fibers traverse the annulus of the tricuspid valve on the right or the mitral valve on the left and can support another type of supraventricular tachycardia. When these fibers conduct antegradely in sinus rhythm, bypassing the AV node, the QRS becomes wide due to the premature stimulation of the ventricle creating a delta wave. These fibers are called "bypass tracts". Supraventricular tachycardias that occur suddenly and break suddenly are termed **Paroxysmal Supraventricular Tachycardia (PSVT)**

Tachy-Brady syndrome

The rhythm strip above shows a supraventricular tachyarrhythmia, probably atrial flutter, on the left. Upon termination of the arrhythmia, notice the flatness of the ensuing recording, no P waves are seen where a normally functioning intrinsic sinus node should have set in. This is a form of sinus node dysfunction (**Sick Sinus syndrome**). Sick sinus syndrome is usually seen in elderly individuals where atrial fibrillation is prevalent as well. The confluence of both, tachycardia when in atrial fibrillation, and bradycardia when atrial fibrillation terminates and the sinus rhythm is either slow or absent, gave rise to the term Tachy-Brady syndrome. Medications given to slow the rapid ventricular rate associated with atrial fibrillation or flutter, exacerbate the bradycardia associated with return of sinus rhythm. Treatment is with a permanent pacemaker.

Preexcitation

The underlying rhythm is sinus, observe the P waves. The PR interval is short and the QRS wide. These are the hallmarks of preexcitation. Abnormal myocardial fibers traverse the AV valves connecting the atrium to the ventricle, "bypassing" the AV node, the only electrical conduit between the atrium and the ventricle. Bypassing the AV node, conduction down these accessory fibers is rapid hence the short PR interval. Premature eccentric activation of the ventricle (preexcitation) via the bypass tract leads to the initial widening of the QRS complex termed the "delta wave", the hallmark of antegrade conducting bypass tracts. Accessory bypass tracts can lead to a supraventricular tachycardia known as atrioventricular reentrant tachycardia (AVRT). Other arrhythmias, rarely life-threatening, can occur. The confluence of preexcitation and arrhythmias is known as the **Wolff-Parkinson-White syndrome (WPW)**. If the bypass tract only

conducts retrogradely, it can support an AVRT but no preexcitation will be seen on the electrocardiogram. This is known as a **concealed bypass tract**.
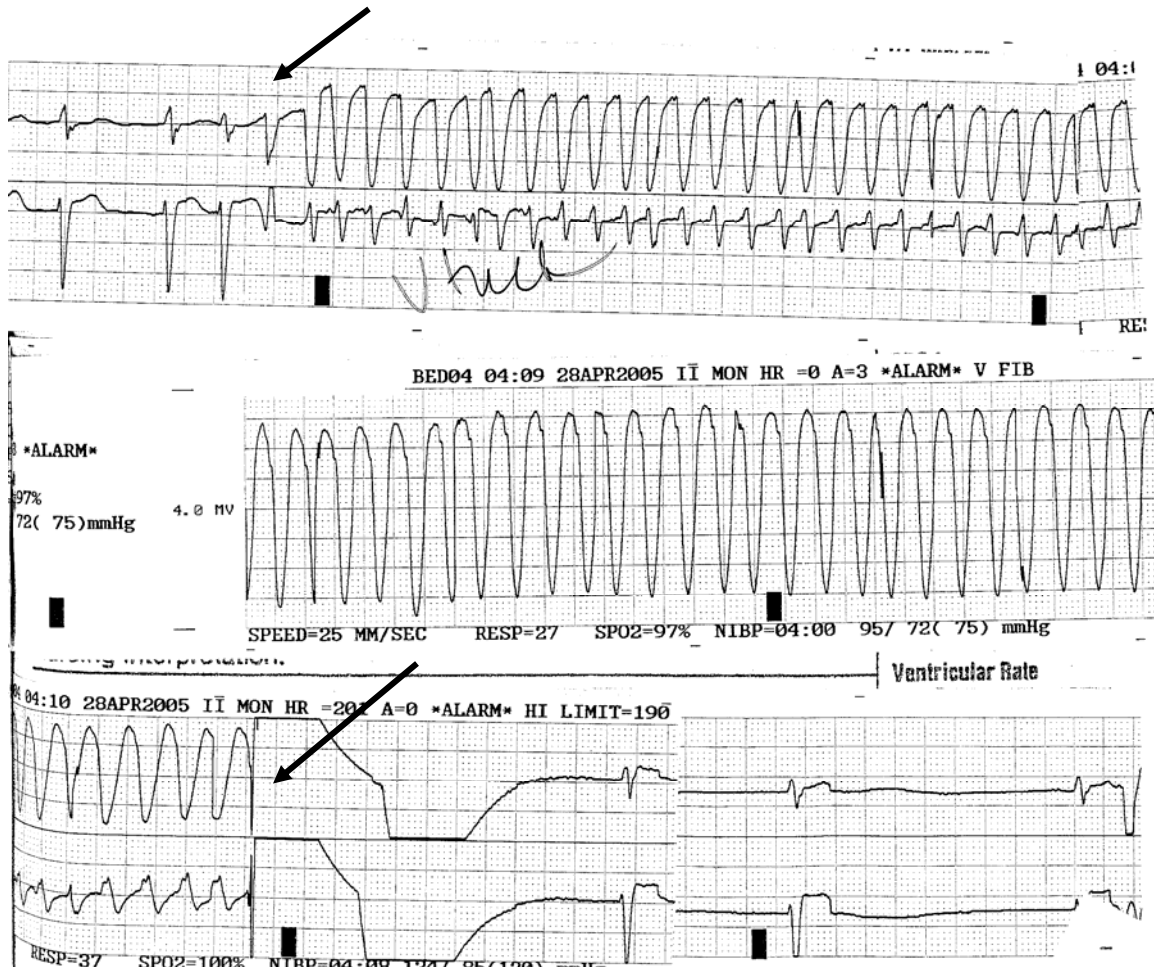
Sustained Ventricular Tachycardia

Three sequential rhythm strips from a monitor are shown above. To the left of the upper strip two supraventricular beats are seen followed by a premature atrial beat. A premature ventricular contraction (PVC; upper arrow) is followed by a wide complex tachycardia most probably ventricular tachycardia. These tachycardias originate from the ventricles, usually in the setting of structural heart disease (ischemic, valvular, idiopathic or others). The onset of ventricular tachycardia may be associated with palpitations, shortness of breath, chest pain, presyncope or syncope. Ventricular tachycardia that breaks spontaneously within 30 seconds and is not associated with hemodynamic compromise is termed **non-sustained ventricular tachycardia (NSVT).** Sustained ventricular tachycardia is VT that requires prompt termination due to hemodynamic compromise (hypotension, heart failure, chest pain, loss of consciousness). In the bottom strip the delivery of a DC shock can be seen at the arrow. This is followed three supraventricular beats similar to the ones preceding the onset of VT. Careful inspection also reveals

elevation of the ST-segment indicating that ischemia may have resulted from the run of VT.
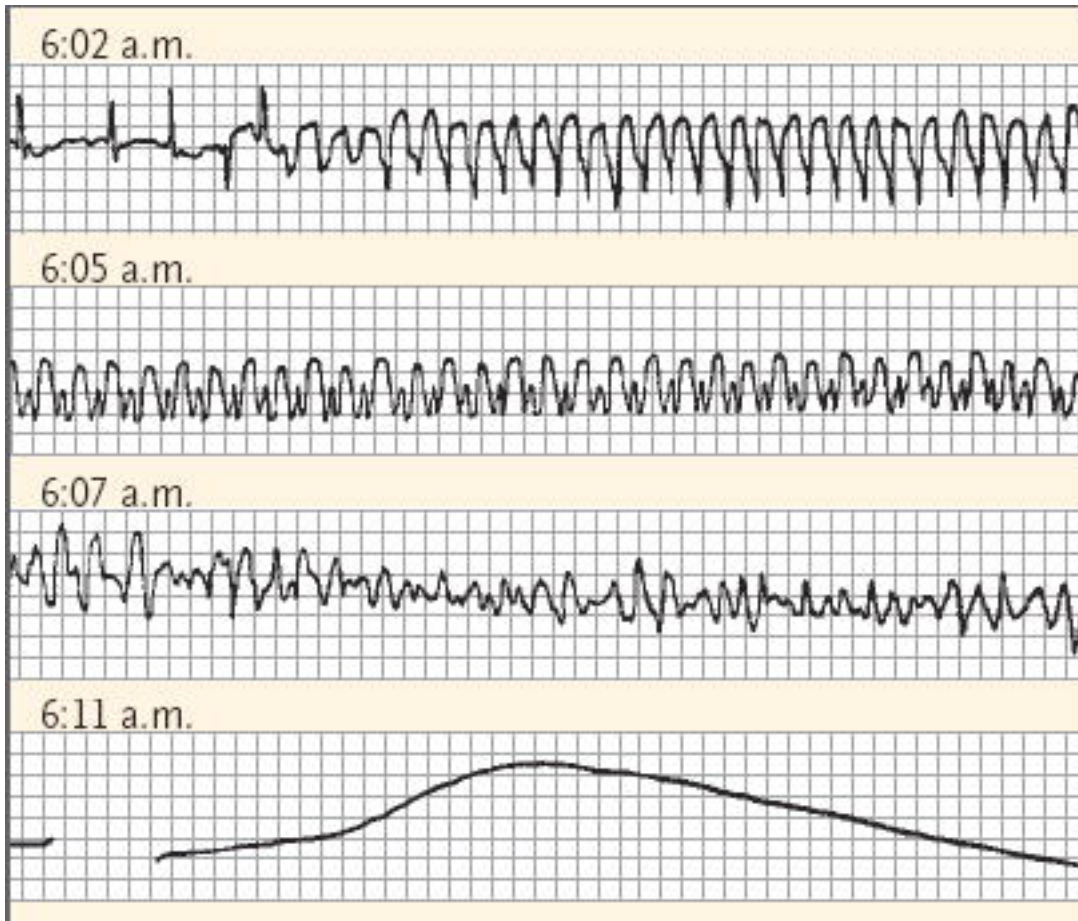
Ventricular Fibrillation

Ventricular fibrillation is not an arrhythmia compatible with life. Its inception is immediately followed by loss of consciousness secondary to precipitous drop in cardiac output and blood pressure. Ventricular fibrillation is the most common arrhythmia leading to sudden cardiac death (SCD). The example above shows sinus rhythm, ventricular tachycardia that degenerates into ventricular fibrillation and finally, asystole. As the example above shows, the arrhythmia recorded in patients who have succumbed to SCD is related to time. Ventricular tachycardia and fibrillation are commonly seen early and asystole, late. Resuscitation requires immediate defibrillation, once asystole has set in, successful resuscitation is very unlikely and the patient would have, by then, suffered irreversible brain damage. The understanding that ventricular tachycardia and fibrillation are the arrhythmias associated with SCD and respond well to immediate defibrillation coupled with the knowledge that any delay in resuscitation drastically reduces the chances of a meaningful recovery have led to the implementation of widespread community based measures to implement first response resuscitation. The value of

automatic external defibrillators (AED) in resuscitating victims of sudden cardiac death is now well established.

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How an AED is employed in an unconscious patient suspected of having succumbed to a ventricular tachyarrhythmia. Once the AED is connected to the patient, it analyzes the rhythm and if the AED determines the rhythm to be a ventricular tachyarrhythmia, it will prompt the operator to deliver the shock. The figure on the right shows a rhythm strip retrieved from an AED representing ventricular fibrillation.

From; Improving Survival from Sudden Cardiac Arrest. The Role of the Automated External Defibrillator. Marenco, JP et al. JAMA. 2001;285:1193-1200