

Cardiac Arrhythmia

What is cardiac arrhythmia?

Arrhythmias are disturbances to the natural rhythm of the heart. The heart has a 'pacemaker', called the sinus node, in the atrium of the right hand side of the heart that generates electrical impulses. These are transmitted through specialised conductive tissues to the muscles of the right and left ventricles, where they cause the muscular contractions that pump blood around the body.

The normal beating of the heart ranges between 60 and 100 beats per minute under resting conditions. Arrhythmias take the form of a speeding up (tachycardia) or slowing down (bradycardia) of the rate outside these limits, or of the insertion or deletion of beats from the normal pattern. An arrhythmia may be 'supraventricular' - caused by a process occurring in the atrium - or 'ventricular'.

Some cardiac arrhythmias are medically of little significance. The most common arrhythmia, premature beats—which affect mainly older people—are generally benign. Caffeine and stress may increase the occurrence of premature beats. Sometimes, people will have experienced occasional extra beats or palpitations, but these do not usually require therapy, while others (e.g. ventricular fibrillation) may be rapidly fatal if not treated at once. Some are of clinical significance, but are treated by surgery or the implantation of an artificial pacemaker.

Atrial fibrillation (AF) is the most common type of medically treated chronic arrhythmia. In itself, it is not a major cause of death, but it is linked to an increased risk of heart failure and stroke. AF develops when a disturbance in the electrical signals causes the atrial chambers of the heart to quiver rather than pump correctly. When this quivering occurs, blood pools inside the atrium and sometimes clots. Blood clots can cause a stroke if they break off, travel through the body, and block flow to the brain.

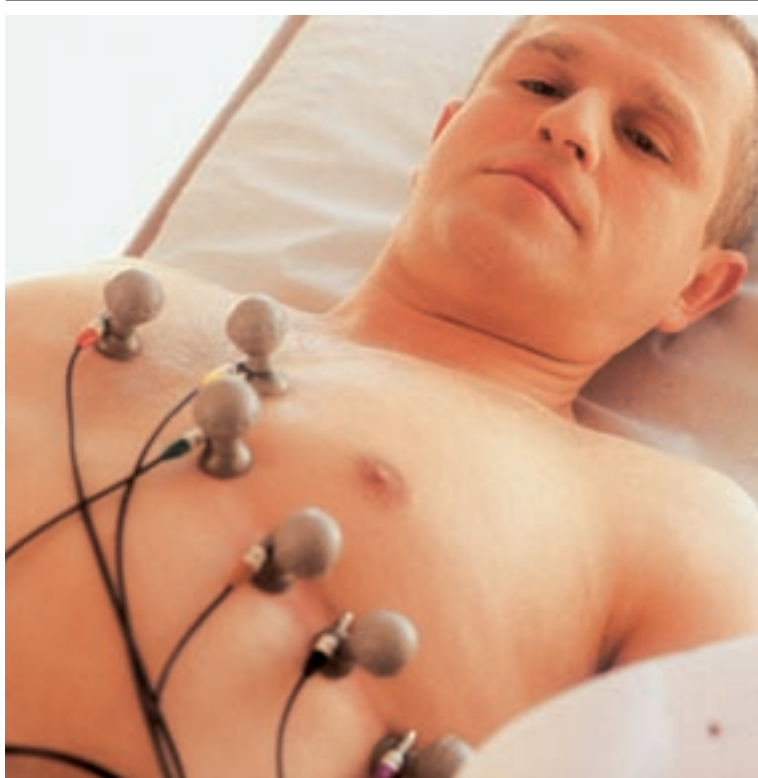
Clinically, AF is associated with coronary heart disease, hypertension, rheumatic heart disease or hyperthyroidism, and requires treatment alongside these conditions. AF may occur as recurrent episodes that resolve spontaneously (paroxysmal), as episodes that persist for more than seven days and do not clear up (persistent) or as an established pattern (permanent).

Who does arrhythmia affect?

From health surveys in EU member states it can be derived that some 2.5 per cent of adult respondents had experienced abnormal heart rhythm during the previous 12 months and about five per cent had experienced it at some stage in their lives.

The rate of recently experienced arrhythmia increased from 0.5-0.8 per cent in the 16-24 age group to 5-7 per cent in those aged 75+, with no significant difference between men and women.

Cardiac arrhythmias are changes to the natural rhythm of the heart. They can be medically insignificant or rapidly fatal. Cardiac arrhythmia becomes more common as people get older. There are medicines to treat it, but not all of them are well tolerated. Further compounds are being studied to help people who develop this condition.



Present treatments:

Medications used to treat arrhythmias have been grouped into four main classes, according to the internationally accepted Vaughan Williams classification. Those in class 1 (subdivided into three sub-classes, according to their electrophysiological effects) are sodium channel blockers, class 2 are the beta-blockers, class 3 drugs are potassium channel blockers and class 4 anti-arrhythmics are calcium channel blockers.

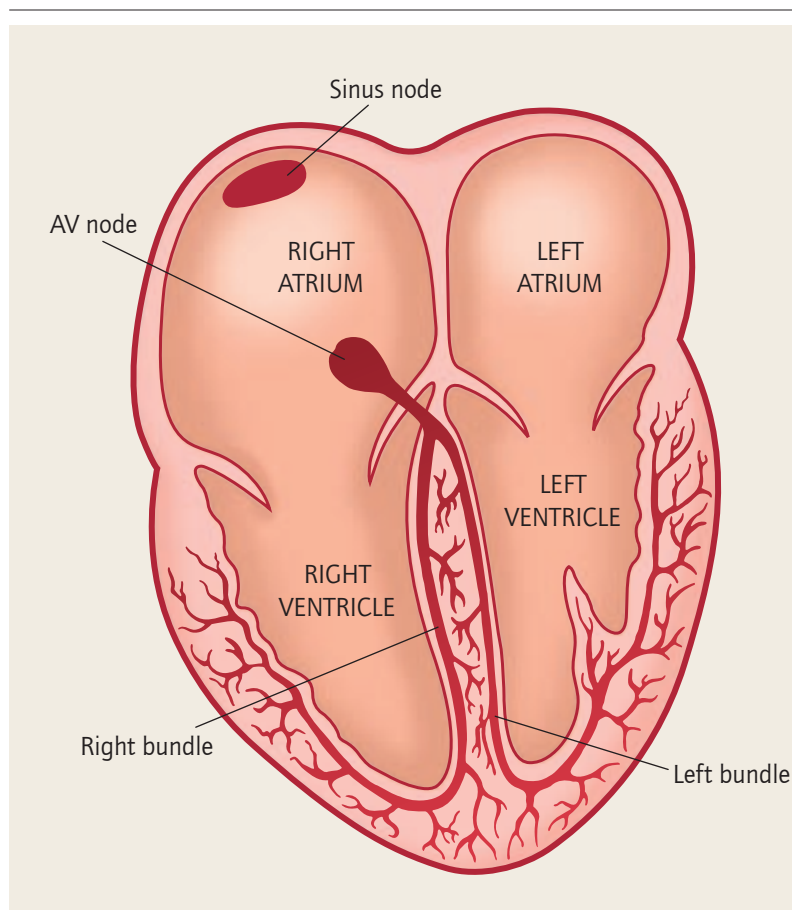


FIGURE 1: The conductive tissue of the heart

In paroxysmal AF, an attempt will usually be made to re-establish normal rhythm, either by electric shock or by treatment with medication. Once normal rhythm is re-established, other medication may be required to maintain an AF-free state.

Where AF has become established, or initial treatment has been unsuccessful, medication may instead be given to slow down excessively rapid heartbeat. Medicines in classes 1a, 1c, 2 and 3 are used to treat AF and, in addition, about 40 per cent of patients are prescribed anticoagulants because AF is associated with a much increased risk of stroke and thrombosis.

Unfortunately, not all of the existing anti-arrhythmic treatments are well tolerated. Gastrointestinal side effects (nausea, vomiting, diarrhoea, pain, etc) are common with some class 1 compounds. Visual disturbances and urinary retention may occur, as well as blood dyscrasias and moderate to severe skin rashes can develop with specific treatments.

Beta-blockers are generally well tolerated, but all anti-arrhythmic medicines must always be given with caution, as they may actually be pro-arrhythmic in certain situations:

a potentially life-threatening abnormal heart rhythm has been observed during their use. Antagonists of vitamin K are used in AF patients to prevent stroke-inducing blood clots. These compounds are effective anticoagulants as they interfere with the synthesis of several clotting factors in the liver.

What's in the development pipeline?

Three new anti-arrhythmic compounds have reached the Phase 3 stage. One has shown positive effects in earlier trials in preventing recurrence of atrial fibrillation and in the re-establishment of a normal heartbeat.

Another, a new class 3 anti-arrhythmic, is somewhat further advanced in Phase 3 studies in AF and paroxysmal supraventricular tachycardia (PSVT), a serious arrhythmia that is otherwise mainly treated by surgery. Thirdly, another class 3 potassium channel blocker is in advanced clinical development.

A further approach is a dual potassium + calcium channel blocker in Phase 2 trial. Compounds in this class are thought to have less risk of being pro-arrhythmic, which would make them valuable alternatives.

Also in Phase 2 trials are a 5HT₄ receptor antagonist, another class 3 compound and an indirect thrombin inhibitor, which is being evaluated for its ability to prevent stroke in patients with AF. Another ATP-dependent potassium channel blocker is in Phase 2 trial in ventricular arrhythmia. One research group has a selective adenosine A₁ receptor agonist in Phase 3 trial in PSVT and in Phase 2 trial for AF.

Blocking the angiotensin-2 type 1 receptor has been observed to reduce the incidence of episodes of AF in patients with paroxysmal disease and several of the medications of the angiotensin receptor blockers class already available for use to treat hypertension are now being explored for their possible use in AF.

Compounds are being studied in paroxysmal AF, for AF prevention and prevention of cardiac remodelling in those at risk of AF and for the reduction of recurrence in patients who have been treated for persistent atrial fibrillation.

At the Phase 2 stage, there are compounds in development as an alternative to existing anticoagulants for the prevention of stroke in AF. Also new at Phase 2 is a molecule which works by a process known as gap junction modulation and is the first potential anti-arrhythmic to use this approach.

The longer-term future:

Human embryonic stem (ES) cells may open another avenue in cardiac arrhythmia research. ES cells are pluripotent cells capable of developing into specific cell types of all three germ layers including heart muscle cells (cardiomyocytes).

Ongoing research is focused on optimising the differentiation of human ES cells into cardiomyocytes and characterisation of the resulting cardiomyocytes. Ultimately, these cells could have tremendous potential for cell-based therapies and could also provide useful cell culture models for a variety of basic research in cardiac arrhythmia.

Research in arrhythmias remains difficult and none of the compounds discussed above is likely to bring a radical shift in treatment. However, continuing incremental steps and improvements in effectiveness and tolerability are bringing worthwhile progress in the treatment of these difficult heart conditions.

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