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## Editorial

Cardiac arrhythmias constitute the commonest cause of cardiogenic complaints, both in healthy people and in diseased from cardiac or other diseases. Besides the strong clinical and investigational interest, their treatment is frequently far from successful.

Contributions to this partial inefficiency are offered by the multiplicity of the pathogenetic mechanisms, the difficulty in their discrimination, the laborious diagnostic protocoles and the lack of a satisfactory success rate in the treatment, even with invasively directed regimens and interventions.

Antiarrhythmic drug treatments are not free of side effects, sometimes very dangerous. In the majority of the cases, drugs are prescribed on an empirical basis; however the understanding of their electrophysiological properties has permitted the more rewarding use of them during the latter 15 years.

The interventional methods have been developed in various technical degrees. They are destined in the treatment of life threatening or troublesome cardiac arrhythmias, not liable to successful drug treatment. Cardiology expects a lot from their further development.

It is favourable that in the majority of the cases, the diagnosis of a cardiac arrhythmia does not include a bad prognosis, because it is made on people not suffering from a major heart disease. The exclusion of the latter or the proper treatment, if such a disease does exist are among the main cares that a cardiologist has. The innocent prognostically arrhythmias do not deserve any particular treatment, except if they compromise remarkably the quality of life, since the current regimens are not innocent themselves.

The literature on the cardiac arrhythmias is already voluminous and rapidly growing up, because the questions emerging during investigation are more than the answers obtained. The investigation of the cardiac arrhythmias has already been extended into the field of the Molecular Biology.

The following papers cover the most important cardiac arrhythmias of the tachycardia type. They include a great deal of the matters on this subject, which are taught in the postgraduate teaching program of the 2nd Department of Cardiology, Aristotle's University of Thessaloniki, Hippokra- tion Territorial General Hospital, Thessaloniki, Greece.

The text has been divided into three parts. The 1 st one covers the pathogenesis of the commonest arrhythmias; the 2nd part focuses on the diagnostic approach of the individual pathogenetic mechanisms; the 3rd part, lastly, considers the treatment of the arrhythmias.

Assoc. Prof. Constantine L. Papadopoulos

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## Arrhythmogenic Substrate by

C.L. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Arrhythmogenic substrate is the existence of the appropriate electrophysiological conditions that favour the development of a higher class arrhythmia within the atria or the ventricles. As

higher class arrhythmias, the tachycardias, flutter and fibrillation are considered.

These arrhythmias are a result of the following mechanisms: 1) Abnormal automaticity: Rapid successive depolarizations occur after a focally enhancement of the inward diastolic cationic currents due to 3-adrenergic stimulation, myocardial distention and partial loss of resting potential. 2) Triggered activity, bradycardia-induced: After a long pause or during bradycardia, repolarization is delayed and may be inhibited either near the plateau level (phase 2), or at the downslope (phase 3); inhibition is followed by potential variations leading to early afterdepolarizations (afterpotentials) called early-early and late-early respectively. This kind of electrical instability is due to a "hesitation" and slowness in the development of the regular succession of repolarizing $K^+$ currents, whereas tail or window depolarizing currents do persist. Tachycardias, due to early-late afterpotentials take frequently the form of "Torsade de pointes". Myocardial distention and drugs with $I_A$ antiarrhythmic action, together with hypokalemia, induce or aggravate this phenomenon. 3) Triggered activity after $Ca^{2+}$ overload: This is usually the result of 3-adrenergic stimulation, digitalization or myocardial ischaemia and is favoured by hypokalaemia and rapid cardiac rates. Early in diastole, $Ca^{2+}$ from the overloaded sarcoplasmic reticulum leaks into sarcoplasm and it is extruded outside the cell interchanged with $Na^+$ in excess; a net depolarizing current thus created, which results in the late afterdepolarizations (afterpotentials). It has to be mentioned that both early and late afterpotentials, more frequently, induce simple extrasystoles that may secondarily create higher class arrhythmias. 4) Reentry: This is the most important mechanism, backing the majority of the higher class arrhythmias. In areas of unsafe conduction or long refractory period, the propagation of extrasystoles with low action potentials is blocked and the excitation, arriving slowly from distal areas, having been excited through side pathways, enters reciprocally; there, thanks to the delay, it creates a higher action potential able to be transmitted over the block area; from there it is conducted upstreamly and then comes down again through the side pathways, recirculating repetitively.

The main conditions which constitute the arrhythmogenic substrate are the following: 1) Chronic ischaemia or inflammation of the myocardium. They induce reentry because of the reduced resting potential, which favours unsafe propagation and the inhomogenous refractoriness. One or more programmed extrastimuli, properly delivered, may induce reentry arrhythmias. 2) Myocardial scarring or swelling. They favour reentry disclosed as above. 3) Acute myocardial distention, predisposing to abnormal or triggered automaticity. 4) Acute ischaemia in which several mechanisms of abnormal and triggered activity are involved together with reentry phenomena. 5} Prolonged repolarization either congenital or acquired. Its arrhythmogenic mechanisms are most controversial, so that the recent aspects deserve more extensive presentation.

Prolonged repolarization mainly occurs in the subendocardial network of Purkinje fibers and probably the intermediate layers of the ventricular myocardium, where action potentials are already the longest and the development of further inhibition of repolarization easier.

In the congenital form, ventricular tachyar-rhythmias are the result of a sympathetic overex-citation, leading to both 3 and a, myocardial receptor stimulation; 3-stimulation results in $Ca^{2+}$ overload, whereas the $a_t$ one favours the leakage from the sarcoplasmic reticulum and also inhibits repolarizing currents; thus a hybridic form of early and late afterdepolarizations is created. The unilateral left sympathetic stimulation may be an aggravating factor, since normaly the concommi- tant right one mitigates the excessive activity or the left sympathetic system by means of an inhibitory action.

The acquired form is considered as a result of latent dysfunction of $K^+$ channels that is aggravated by hypokalaemia, a loss of magnesium or administration of drugs with $I_A$ antiarrhythmic properties, all resulting in early afterpotentials.

The detection of the predisposition for higher

class arrhythmias is accomplished by several methods invasive or non invasive.

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## Supraventricular Tachycardias by P. Kotrides, C.L. Papadopoulos, N. Poulantzas

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

The Supraventricular Tachycardias are a result of disordered automaticity, conduction or both. They are classified in: a) sinus nodal, b) atrial tachycardias, c) atrial flutter, d) atrial fibrillation.

The treatment is individualized, the existence of organic cardiac substrate or any other disease being considered. The therapeutic measures range from manipulations for vagal stimulation, through several pharmaceutical regimens up to electrical or surgical interventional methods.

In particular, the treatment of atrial fibrillation comprises four targets:

a) Decrease of ventricular systoles during atrial fibrillation (digitalis, p-blockers, verapamil or diltiazem; only if preexcitation is present or suspected: antiarrhythmics Ic or III; AV node ablation plus pacemaker implantation if drugs unacceptable).

b) Restoration of sinus rhythm if the proper assumptions are fulfilled (antiarrhythmics $I_A$ after the pharmaceutical control of the ventricular rate or as a single drug if bradyarrhythmia exists; Ic or III as single drugs because they decrease AV conduction; synchronized d-c shock in emergency conditions).

c) Prevention of the recurrency (antiarrhythmics $I_A$, possibly with p-blockers in adrenergically induced atrial fibrillation; Ic; amiodarone; DDD cardiac pacemaker in sick sinus syndrome).

d) Prevention of embolic episodes, if needed, in chronic, recurrent or long lasting atrial fibrillation before cardioversion attempt (coumarine derivatives).

## Tachycardias due to Atrioventricular Nodal or Atrioventricular Reentry by P. Kotrides, N. Poulantzas, C. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Atrioventricular nodal tachycardias are very commong among the supraventricular ones and occur in people both with and without a cardiac disease.

Reentry, responsible for the 80 per cent of them, is attributed to longitudinal association of the AV node (atrioventricular nodal reentry), with slow orthodromic and fast antidromic propagation of the excitation (usual type) or fast orthodromic and slow antidromic propagation (unusual type). Reentry begins after an extrasystole, created at the proper place and time, so that the fast pathway with the long refractory period is still refractory from the previous normal systole, whereas the slow one has already been recovered. In the usual type, the triggering extrasystole is supraventricular; in the unusual type, extrasystole is ventricular. Parasympathetic stimulation, drugs with negative dromotropic effect on AV node (verapamil, p-blockers, adenosine, ATP, digitalis, propafenone, amiodarone) are used to treat this arrhythmia. Electrical methods, comprising synchronized dc shock, or right atrial overdrive or right atrial programmed premature systole, are sometimes very useful.

Atrioventricular tachycardias (accessory pathway associated) are due to the existence of a reentry circuit, involving both the AV node and an accessory pathway (atrioventricular reentry). They are classified as IA (orthodromic), IB (antidromic), II (intranodal reentry) and (II with more than one accessory pathways. Drugs prolonging the effective refractory period of both the normal and the accessory pathways are the most suitable in the treatment of these arrhythmias (propafenone, amiodarone, sotalol). Antiarrhythmic drugs of group U with anticholinergic effect may lead to

tachyarrhythmias should atrial fibrillation occur. Also digitalis and verapamil, shortening the refractory period of the accessory pathway may induce untolerable tachyarrhythmia, if tachycardia is converted to atrial fibrillation. Electrical methods are used in emergency conditions only.

To prevent recurrences, several antiarrhyth- mics of groups $I_A$, Ic or 111 may be useful. If drug are untolerable or ineffective, ablation of the accessory pathway should be attempted.

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## High Class Ventricular Arrhythmias in Coronary Artery Disease

by C.L. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

High class ventricular arrhythmias occur at all stages of coronary artery disease, due to mechanisms of either automaticity or reentry as following:

a) In acute ischaemia (2'-10'), automaticity from 3-and later OT-adrenergic stimulation or reentry may develop.

b) During early reperfusion, reentry of ventricular extra systoles, the latter been induced by a-i-stimulation is common.

c) The hyperacute phase of myocardial infarction is dominated by reentry phenomena.

d) The acute phase of myocardial infarction allows subendocardial automaticity, enhanced by p-adrenergic drive; it is followed by subepicardial reentry.

e) In late reperfusion, subendocardial automaticity occurs, related to the creation of free radicals.

f) The subacute phase is characterized by sub-endocardial reentry.

g) During chronic phase, in malignant arrhythmias reentry of extrasystoles dominates. The role of up regulation of P-receptors, due to sympathetic denervation of the myocardium, is very important in the creation of extrasystoles.

h) In acute ischaemia near an old scar, reentry may occur.

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## Arrhythmias During Myocardial Ischaemia

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I. Papayiannis, C. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Various metabolic disturbances which take place during ischaemia are directly related to the appearance of ventricular arrhythmias. Such metabolic disturbances are: a) the surplus of potassium in the extracellular space. Arrhythmogenic factor is mainly the early (within the 1st minute) Joss of cellular $K^+$; it causes a decrease in the resting and action potentials, and a slow and unsafe conduction and undirectional block leading to reentry. Local potential differences, decrease of resting potential and catecholamine release stimulate abnormal automaticity with slow response action potentials. Intracellular $K^+$ loss is due mainly to intracellular acidosis and extrusion of lactate and phosphate anions; ATP dependent $K^+$ channel opening and cations pumps inhibition cooperate, b) The release of catecholamines. Noradrenaline is released by exocytosis following sympathetic terminal depolarization. Nonexocytotic release is the result of $Na^+$ enrichment after intracellular acidosis within the nerve terminals, and represents the most important source of catecholamines. Initially, the electrophysiological effects are due to 3 receptor stimulation {abnormal automaticity, late afterpotentials, effects on action potential and conduction); later OT receptor stimulation predominate (repolarization delay, early afterpotentials), c) The rise of tissue CAMP values. CAMP increase is the result of p adrenergic receptor stimulation and mediates its effects, d) Intracellular $Ca^{2+}$ alternations; they occur within the ischaemic myocar

dium or the marginal zone between the normal and ischaemic myocardium and strongly predispose to ventricular fibrillation, e) The accumulation of long chain acylcarnitine and lysophospha- tidylcholine within the sarcolemma favouring $Ca^{2+}$ entry, inhibition of $Na^{+}/K^{+}$ pump and uncovering of Oi adrenergic receptors. The result is arrhythmiogenesis from $Ca^{2+}$ overload and repolarization delay, leading to afterpotentials and intramyocardial conduction disorders.

## Reperfusion Arrhythmias by I. Kanonidis, C.L. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Reperfusion arrhythmias were familial to cardiologists since as early as mid thirties of this century. Although these arrhythmias occur in the same clinical setting and share the same pathophysiologic substrate with ischaemic arrhythmias, they have long remained out of the interest of the practicing cardiologists, mainly because they were thought to be "Laboratory" entities devoid of any clinical implication. Recent advances in clinical research have shed a new light on the pathophysiology of ischaemic heart disease revealing that reperfusion is a very common phenomenon underlying most of the ischaemic events encountered clinically.

The severity and duration of reperfusion arrhythmia is highly dependent on the preceding period of ischaemia. The duration of the ischaemic period is a major deteminant. This duration must exceed a certain period of time under which no reperfusion arrhythmia is induced. Beyond this time limit, arrhythmias are induced on reperfusion, whose number and severity progressively increases up to a second time limit at which point the maximum of arrhythmias is encountered on reperfusion. For longer periods of ischaemia the number and severity of arrhythmias start declin ing progressively up to a new time limit'beyond which no arrhythmia is any longer induced on reperfusion. These time limits mark important pathophysiologic points in the process of necrosis which takes place within the ischaemic region.

Other important determining factors include the degree of ischaemic and the rate of reperfusion.

The pathophysiologic process of necrosis creates the suitable electrophysiologic substrate for these arrhythmias to develop. That includes the interplay of two mechanisms namely triggered activity and reentry. Although the part played by each one of the above mentioned mechanisms differs according to the experimental model that is studied, it can be generally said that the arrhythmia is initiated by triggered activity and maintained by reentry.

Reentry is the result of inhomogeneity of both ischaemia and reperfusion. Both phenomena affect differently the different parts of the ischaemic myocardium, that is the degree of ischaemia, induced in two nearby myocytes, is not the same and consequently the necrotic process is also evolving differently. The same goes for reperfusion which is pathophysiologically the inverse of necrosis.

Triggered activity is the clinical result of afterdepolarizations taking place at the cellular level. These afterdepoiarizations are mainly the result of accumulation of cytosolic calcium that takes place during ischaemia and increases further during reperfusion.

Factors that contribute to this $Ca^{2+}$ accumulation include:

a) Inhibition at ionic pumps.
b) Free radicals formation.
c) a-receptor activation.
d) Electrolytic disturbances.

Drugs are mostly ineffective in reducing reperfusion arrhythmias. All classes of antiarrhythmic or antiischaemic drugs have been extensively tested on the clinical or the experimental setting in their ability to reduce these arrhythmias. Some drugs have shown an antiarrhythmic effect but only when they are given very early, before the

induction of ischaemia. When given at the time of reperfusion almost ail of them are ineffective. The only exception to this rule is the a-blockers which have shown an appreciable antiarrhythmic effect, when given at the time of reperfusion, and it is related to their pathophysiologic effect.

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## Cardiomyopathies and Cardiac Arrhythmias

by
C. Gitsios, S. Savatis

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

The cardiomyopathies (CM) are considered as idiopathic heart muscle disorders, which are classified in three categories: the hypertrophic cardiomyopathy (HDC), the dilated cardiomyopathy (DC) and the restrictive cardiomyopathy.

A frequent finding in hypertrophic CM is ventricular tachycardia (VT) occurring in 20-30% of the cases. Atrial fibrillation is found in 7-14% of the cases, whereas sudden death occurred in 5.9% mainly in young individuals with positive familial history and episodes of syncopic attacks. The use of 3-blocker improves the symptoms, but it does not reduce the incidence of ventricular arrhythmia.

In dilated cardiomyopathy, a frequent finding is the presence of ventricular extrasystoles, but supraventricular arrhythmias are also frequent, particularly the atrial fibrillation, which predes- poses to thromboembolic episodes.

Amiodarone is the drug of choise, in cases with ventricular extra beats.

Arrhythmogenic right ventricular dysplasia, which is a form of cardiomyopathy, may present with ventricular tachycardia that generally has a LBBB contour, often with right axis deviation.

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## Ventricular Tachycardia with No Demonstrable Heart Disease (Idiopathic Ventricular Tachycardia)

by C.T. Gitsios, S.C. Savatis

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Sustained ventricular tachycardia (VT), occurring without demonstrable cardiac disease, is not usually a life threatening event, but presents a diagnostic'problem. Sudden cardiac death has been rarely reported in association with these arrhythmias.

Patients with idiopathic ventricular tachycardias have been classified, according to:

1) The anatomical site of origin of the tachycardia and the typical EKG appearance of the tachycardia in the 12-lead EKG.

2) The response to drug therapy or provocabil- ity with exercise or both.

3) The presence of associated non-sustained bursts of VT (repetitive monophormic VT).

Idiopathic sustained VT, originating in the left ventricle (LV), has a RBBB QRS morphological appearance and usually has a superior and leftward frontal plane axis. Without antiarrhythmic therapy, the surface QRS complex tends to be relatively narrow (less than 0.16"). Patients developing this arrhythmia tend to be significantly younger than those patients who experience VT associated with coronary artery disease.

Detailed mapping localizes the VT to the inferior aspect of the septum of the LV, approximately midway from the apex to base. The tachycardia tends to be very responsive to verapamil. A second unique type of VT, that occurs without the presence of structural disease, originates in the outflow tract region of the right ventricle (RV). The VT has a LBBB morphological appearance with an inferior forntal plane axis.

Most patients have predominantly nonsustained VT, which may occur with a frequent repetition, so that the episodes are interspersed

by only short periods of slow rhythm, hence the term repltitive ventricular tachycardia.

Emphasis should be placed on the monomorphic nature of the tachycardia. If multiple morphological configurations are present, one should be suspicious of the diagnosis of right ventricular dysplasia.

Most ventricular tachycardias, that originate from the right ventricular outflow tract when structural heart disease is not present, are responsive to a variety of antiarrhythmic drugs, including the type IA antiarrhythmic agents. The high responsiveness to ß-blocking drugs is unique to this arrhythmia.

Occasionally, verapamil prevents spontaneous development of the tachycardia.

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## Cardiac Arrhythmias Related to the Mitral Valve Prolapse Syndrom by C. Gitsios and S. Savatis

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

A good number of patients with mitral valve prolapse develop ventricular and superventricular arrhythmias. Several mechanisms of arrhythmogenesis have been proposed, such as reentry, phase 4 depolarization, excessive traction of the pupillary muscle or disorder of the autonomic system. Beta blockers are usually used for the management of these arrhythmias.

## Clinical Diagnosis of Cardiac Arrhythmias by D. Hatseras

Department of Cardiology, Democritus University, General Hospital of Alexandroupolis, Alexandroupolis, Greece

The diagnosis of arrhythmias is based on data from the following tests:

A. The history of the patients and the description of their symptoms:

- sensation of being hit on the anterior thoracic wall {ventricular ectopics)
- palpitations accompanied by tension, vertigo or fainting (tachycardia-bradycardia syndrome)
- sensation of fullness in the neck-polyuria
- angina or cardiac failure.

B. Objective findings

- Alterations of venous and arterial pulse.
- Auscultation of the heart.
- ECG studies-continuous monitoring (Holter).
- Electrophysiological studies.

The appearance of angina at the start of paroxysmal supraventricular tachycardia indicates the existence of subclinical coronary disease. Some patients show a small increase of enzymes, supporting the existence of subendocardial infarction.

## The Role of the Electrophysiological Study in the Diagnosis of Supraventricular Arrhythmias

by C. Papadopoulos, G. Sakadamis

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

For the best exploitation of the newer therapeutical possibilities, the accurate knowledge of the electrophysiological backround of the arrhythmias is neccessary.

The study of the electrophysiological properties (refractory periods, conduction times) of the several myocardial areas with the assistance of the programmed stimulation of the atria and ventricles, the observation during tachycardia paroxysms and the response to acute administration of antiarrhythmic drugs effective constitute diagnostic methods, conducted in the laboratory of electrophysiology.

A number of catheter-electrodes is introduced into the heart; pacing, programmed extrastimulus delivery and myocardium electrical signal recordings are performed with them. The most common sites to put intracavitary electrodes are: a) the upper right atrial wall, near sinus node b) the coronary sinus, with sensing ability from proximal and distal positions c) the interventricular septum through the tricupsid valve. Atrioventricular conduction is studied by means of atrial pacing at stepped increases in heart rate. The refractory periods of the various segments of the heart are measured by programmed extrastimuli at gradually decreased coupling intervals; the test is conducted at the basal and at preselected rates of intra-atrial pacing. The existence and the location of the pathways of the ventriculoatrial conduction, as well as the possibility to induce tachycardias attributed to atrioventricular reentry, need to be investigated with programmed ventricular extrastimuli too.

Several electrophysiologica! properties detected by the proper tests discriminate between automaticity and reentry; the atrioventricular and atrioventricular nodal reentry tachycardias are the most important, since ablation techniques are increasingly used in their treatment. Mapping within atria and coronary sinus around the atrioventricular ring discloses the location of culprit accessory pathways and directs their ablation.

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## Electrophysiologic Study in Patients with Suspected or Clinical Ventricular Tachycardia

by G. Sakadamis and C.L. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

The aim of electrophysiologic study (EPS) is a) to confirm the appearance of the above arrhythmia, b) to elucidate the starting mechanism and perpetuation of arrhythmias and c) to study the behaviour of arrhythmia after having induced electric stimuli or after having given antiarrhyth- mic drugs.

The patients who need EPS may be divided in three groups according to the type of the arrhythmia and the presence of organic heart disease. Group I includes patients who had recurrent episodes of sustained monomorphic Ventricular Tachycardia (VT) with organic heart disease, most often coronary artery disease with old myocardial infarction, cardiomyopathies of the dilated or hypertrophic type, and valvular heart disease. The other type of patients with VT is the one who is repeatedly admitted to the hospital for this arrhythmia without apparent heart disease {arrhythmogenic ventricular disease^The second group of patients (Group II) are the ones with aborted sudden death. These patients have a heart disease and the circulatory failure was induced by rapid VT or VF non documented at the moment of episode. In Group III are patients with syncope of unknown origin and heart disease which gives us reason to suspect that the etiology for the syncopal episode is a VT.

The EPS for VT comprises of programmed cardiac pacing of the apex and outflow tract of the Right and also the Left Ventricle with extrastimuli {and isoproterenol infusion) and simultaneous multiple endocarvitary and surface recordings in an attempt to initiate ventricular arrhythmias and to record evidences of the mechanisms or the areas of arrhythmia initiation. Also, by scanning the diastolic phase of the arrhythmia cycle length with extrastimuli, one is able to estimate the behaviour of the arrhythmia.

The EPS results are different in the above three groups of patients and have direct relationship with the underlying heart disease, the degree of ventricular dysfunction, and possibly the mechanism of arrhythmia initiation. The results of EPS depends upon the ventricular refractory period. The différencies between EPS protocols do not significantly influence the possibility of induction of sustained monomorphic VT. On the contrary, these différencies are important in the initiation of polymorphic VT or ventricular

fibrillation (VF).

Also the EPS results, are directly dependent on the patients' population under study and on the "agressiveness" of the stimulation protocol, although the induction of polymorphic sustained VT with an "agressive" EPS protocol is not a meaningless event.

In patients having myocardial infarction the EPS may reveal a potential reentry circuit with short refractory periods capable of serving as a substrate for sustained monomorphic VT after the patients recieve drugs that may prolong the refractoriness. This helps to avoid the use of such a drug in this group of patients. The initiation of sustained monomorphic VT in the above patients identifies a high risk group for arrhythmic events, while it is difficult to induce the above arrhythmia in a patient with normal myocardium. The induction of sustained ventricular tachyarrhythmia during the EPS suggests a high risk of arrhythmia appearance in patients with myocardial infarction. It is characteristic that the initiation of VF in the EPS does not predict the spontaneous appearance of this arrhythmia.

The response to programmed electrical stimulation reveals inducible VT and/or VF in 80 to 90% of patients suggesting a reentry mechanism for the arrhythmia.

Apart from any doubt, the EPS may be predictive of impending events of sudden death or sustained VT and any treatment based on EPS is pretty successful. For the above reasons the number of patients subjected in EPS is constantly increasing.

## Ventricular Tachyarrhythmias and Late Potentials

by C.T. Gitsios

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Ventricular tachyarrhythmias are frequent in cases of serious coronary artery disease (CAD). Most patients who develop sustained ventricular tachycardias (VT) have a history of extensive myocardial infarction (MI) resulting in a marked wall-motion abnormality, usually with aneurysm formation and significant left ventricular dysfunction.

Most VT's associated with CAD probably originate from a small area (less than 2 cm) with all or part of the presumed arrhythmias circuit located near the endocardial surface of the left ventricle.

For the evaluation of ventricular electrical instability there are three current approaches.

One approach is the categorization and stratification of spontaneous ventricular arrhythmias from standard surface ECG recordings including longterm abulatory ECG monitoring. A growing system of ventricular premature contractions (VPC's) was first suggested by Lawn. An obvious weakness of the concept of prognostic stratification of VPC's from standard ECG recordings is that, it does not take into consideration one crucial characteristic, namely the underlying electro- physiological mechanism.

Another approach is programmed electrical stimulation (PES), which has been utilized to induce ventricular tachyarrhytymias probably based on reentry. There are at least two major limitations of PES at the present time. First, there is no unanimity on the most sensitive and specific techniques for PS and, second, the technique is an invasive one and therefore less suitable for repeated follow-up evaluation.

The third approach for evaluation of ventricular electrical instability is direct recording of delayed depolarization potentials usually referred to as late potentials (LP).

The late potentials represent low amplitute and high frequency waveforms, which appear in the final part of the QRS complex but they are no evident in the conventional surface ECG.

The clinical significance of LP consists of the fact that they frequently represent electrical activity, which is generated from arrhythmogenic substrate responsible for the initiation and perpetuation of life threatening arrhythmias, particularly after myocardial infarction. In the recent years LP

were able to be recorded from the surface of the body with the technic known as Signal Averaging (SAECG). Various studies in the last decade showed that LP were present in 73-92% of the patients who had suffered sustained VT or VF and only 0-6% of the normal persons.

The clinical application of SAECG has been used in recent years in pts with syncope, in risk stratification of post myocardial infarction patients and in cases with potentially lethal arrhythmias, like non-sustained VT, in a variety of heart disease. There are other possible applications which are in the process of investigation.

The SAECG can identify a high risk subset of patients following acute myocardial infarction for whom more intensive diagnostic and/or therapeutic measures are indicated. On the other hand, the combined use of SAECG with other investigations, such as ventricular ejection fraction assessment or Holter monigoring, can lead to increased predictive accuracy of the method.

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## Pharmacological Treatment of Cardiac Arrhythmias

by
C. Papadopoulos[1] and B. Kokkas[2]

1. 2nd Department of Cardiology, and
2. Laboratory of Experimental Pharmacology, Aristotle's University, Thessaloniki, Greece

The treatment of cardiac arrhythmias is indirect and direct. The indirect is addressed against the underlying disease, whereas the direct one aims to the arrhythmia itself. The direct antiar- rhythmic treatment has the following targets:

1) Interruption of reentry circuit.

2) Abnormal automaticity elimination.

3) Elimination of extrasystoles which constitute the origin of reentry arrhythmias or disclose the existence of triggered activity.

4) Inhibition of facilitating factors, particularly p-adrenergic stimulation.

5) Correction of electrolyte disturbances or drug side effects.

The proper antiarrhythmic drugs are classified into 4 groups according to Vaughan Williams:

I) Sodium entry blockers. They bind the channels during action potential and unbind slowly during electrical diastole. Preventing the early reactivation of $Na^+$ channels, they prolong the effective refractory period well beyond the end of the action potential, that is beyond the time the arrhythmogenic mechanisms usually operate.

They are divided into three subgroups: a) L {quinidine, procainamide, disopyramide): They unbind slowly and additionaiy block, at diastole, potassium exit channels; thus, they favour early afterpotentials at low heart rates or hypokalae- mia. b) IB (lidocaine, mexiletine, diphenylhydan- toin): They unbind more easily, and also shorten the long action potentials, c) lc (encainide, flecai- nide, ajmaline, propafenone): They unbind very slowly and thus delay the intramyocardial conduction remarkably, favouring sometimes reentry arrhythmias.

II) Beta-adrenergic blockers. They prevent arrhythmias related to excess PT adrenergic activity as on exercise.

III) Potassium channel blockers. They prolong the action potential and accordingly the effective refractory period (amiodarone, sotalol, bretylium). Some of them favour arrhythmias related to early afterpotentials.

IV) Calcium entry blockers. They inhibit slow response action potentials and prevent arrhythmias related to the cardiac nodes or to $Ca^{2+}$ overload.

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## Amiodarone

by
B. Kokkas[1] and C. Papadopoulos[2]

1. Laboratory of Experimental Pharmacology and
2. 2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

Amiodarone is an iodinated benzofuran, which has a structural similarity to thyroxine.

It is mainly a potassium channel inhibitor, which prolongs repolarization and refractoriness and is qualified as a group II antiarrhythmic agent. Additionally, it possesses a variety of electrophysiological actions, such as sodium channel blockade, calcium channel blockade and non competitive inhibition of adrenergic receptors. There is also a tenable hypothesis that the long term effect of amiodarone may be mediated in part by a selective blockade of thyroid hormone action on cardiac muscle.

Amiodarone depresses sinus node automatic- ity, atrioventricular node conduction and prolongs the refractory period of all cardiac tissues. It is active on all cardiac arrhythmias, but its particular usefulness is against malignant ventricular tachyarrhythmias.

Amiodarone is an amphiphilic compound, slowly absorbed from the gastrointestinal system and extensively metabolized to desethylamioda- rone, a metabolite with antiarrhythmic potency equal to or greater than amiodarone. They both have very long elimination half times, Amiodarone is rapidly concentrated in the cardiac tissue, but it accumulates more slowly in the adipose one. Early recurrence of arrhythmias after discontinuation of therapy or rapid reduction of dosage may be due to a rapid redistribution of the substance out of the myocardium.

The use of amiodarone is limited by the risk of numerous and remarkable side effects, mainly extracardiac, which depend on dosage and duration of treatment (pulmonary fibrosis, disturbance in thyroid function, corneal microdeposits, liver toxicity, photosensitivity, slate-gray facid discoloration, neuropathy and muscle weakness. Pharmacokinetic interactions and potentiation of the electrophysiological effects of other drugs must be considered like with digoxin; reduction of digoxin dose, is necessary in such cases.

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## Peculiarities of Amiodarone with Clinical Relevance

by
C. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

The most dangerous higher class cardiac arrhythmias are created by reentry mechanisms; this applies particularly for arrhythmias generated within the scarred myocardium after a myocardial infarction. Reentry is interrupted by the prolongation of the effective refractory period. $Na^+$ channel blockers (antiarrhythmics I and 111) having bound these channels during action potential, unbind gradually during electrical diastole, thus prolonging refractoriness after the end of the action potential. The prolongation increases further should the drugs prolong action potential too, as group III does (amiodarone,[1] sotalol). A lesser effect on action potential prolongation is exerted by group U (quinidine, disopy- ramide, procainamide). All the drugs prolonging action potential block $K^+$ channels, after binding a percentage of them during electrical diastole; In contrast to the group U drugs, which are slowly released from $K^+$ channels during action potential, group III ones almost do not unblock these channels at all, so that they prolong repolarization even at low heart rates. The prolongation of repolarization after group U drug administration is responsible for multiform ventricular tachycardias due to early afterpotentials, occurring during slow cardiac rates and especially if hypokalaemia exists. Such arrhythmias are unusual with amiodarone, because its additional property of $Ca^{2+}$ channel blockade attenuates the depolarizing current at near plateau level and inhibits early-early afterpotentials.

Long term amiodarone administration leads to maximal prolongation of the action potential in those cells, that normaly display the shortest one (working myocardium), whereas the action- potential in the Purkinje fibers, where normaly it

is longest, is slightly shortened, since there the $Ca^{2+}$ blocking effect exceeds the $K^+$ blocking one; thus, the elimination of action potential duration differences prevents reentry arrhythmias. In contrast, other group III drugs {sotalol, clofilium, bretylium), as well as verapamil and quinidine may prolong action potential in Purkinje fibers. Myocardium in chronic ischaemia behaves like Purkinje fibers.

Unlike group Ic drugs (encainide, flecainide), which may induce ventricular arrhythmias from reentry due to maximal deterioration of conduction within scar myocardium, amiodarone does not slow intramyocardial conduction and, by prolonging refractoriness, prevents such arrhythmias.

Propafenone (Ic) shares with amiodarone the properties of slight 3- and $Ca^{2+}$ blocker and may be an imperfect substitute for the second one in some cases; especially, in bradycardia-induced atrial fibrillation, propafenone is completely ineffective, whereas amiodarone preserves at low heart rates the antiarrhythmic effect. In recurrent ventricular tachycardia or fibrillation, amiodarone is more effective than propafenone.

Amiodarone may successfully be combined with mexiletine (Ib) because the second one, abbreviating the longer action potential, helps amiodarone eliminate action potential inhomoge- neities and, thus, reentry.

Unlike other antiarrhythmics exerting a negative inotropism and especially the 3-blocking ones, amiodarone is suitable for patients with heart failure, since it is devoid of a negative inotropism and reduces afterload.

Finally, amiodarone prevents adrenergically induced arrhythmias, without aggravating heart failure.

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## Interventional Electrophysiological Treatment of Tachyarrhythmias by Means of Implantable Devices

by G. Sakadamis and C.L. Papadopoulos

2nd Department of Cardiology, Aristotle's University,

*a)Antitachydardia pacing (ATP):* It is used for the conversion of atrioventricular nodal and atrioventricular reentry tachycardias, atrial flutter, several atrial and many types of ventricular tachycardias (VT). This method is based on the implantation of an endocardial pacing device capable to recognise the arrhythmia and to deliver automatically programmed stimuli or rapid pacing bursts of extrastimuli at progressively shortened coupling interval. The used algorithms for arrhythmia detection are; a) rapid rate, b) sudden onset of arrhythmia, c) constancy of cycle length,
d) endocardial signal amplitude, slow rate, morphology, frequency content or sequence, e) probability density function, f) responses to extrastimuli. The above algorithms have their own limitations, but with a combination of these it is possible to descriminate an episode of SVT from an episode of very rapid atrial fibrillation or a high increase of sinus rate.

Although the rapid pacing modes are considered to be more successful, the major risk in this setting is the aggravation of arrhythmia to a lethal one, especially in the ventricular ATP.

The development of other techniques (catheter ablation) for controlling the supraventricular tachycardias has limited the use of ATP.

Most investigators reported long-term results with a continuing efficacy rate 60-80% at 5 years.

Recently the ATP is used mainly in ventricular level with a higher rate of success in the slow VTs. According to the last reports, 53% of patients with VT have a successful treatment, 18% a partially successful and 3% poor results with an undetermined result in 14% of the above patients. In the high rate VT, the antitachycardia pacing enables the risk of tachycardia acceleration or precipitation to VF. In this situation the implantation of an antitachycardia pacer with a back up implantable defibrillator, placed separately or in the same unit, is mandatory.

*b) Implantable Cardioverter/defibrillator, (ICD):* The updated clinical specific indications for the use of an ICD are: a) episodes of spontaneous VT or VF in patients where EPS and/or spontaneous ventricular arrhythmias cannot be used to

predict successful therapy by other methods; b) recurrent episodes of spontaneous sustained VT or VF in a patient under antiarrhythmic drug treatment; c) spontaneous sustained VT or VF in patients under intolerated or noncompliant medical antiarrhythmic therapy; d) persistent induction of clinically relevant sustained VT or VF at EPS in a patients with spontaneous episodes of VT or VF despite the best available drug treatment or after an invasive procedure (surgery, ablation); and e) syncopal attacks of undetermined origin in a patient with clinically relevant sustained VT of VF induced during EPS in whom antiarrhythmic drug therapy is limited by inefficacy, intolerance or noncompliance (in this indication consensus does not exist).

Currently approved ICD devices require thoracotomy with a wide spectrum of surgical approaches (subxiphoid or subcostal).

Recently a transvenous approach is used by means of a tripolar endocardial lead (Endotac C, CPI) alone or with a combination with a subcutaneous thoracic patch. The size of this lead permits the implantation through the subclavian route to the Right Ventricular apex for sensing and pacing. The proximal poles (coils) are used alone or in combination with the subcutaneous patch for defibrillation. This system was approved to be as successful as the epicardial one with low perioperative morbidity and mortality.

Adequate amplitude and signal duration for ventricular electrogramms during sinus rate and adequate pacing threshold for ICD rate sensing/-pacing leads are mandatory. All patients require intraoperative inductions of VF followed by shock delivery via the energy delivering electrodes to determine the lowest energy value which can reproducibly terminate VF.

In selected patients, epicardial sensing/pacing and energy delivering patches alone can be implanted at the time of another cardiac surgical procedure.

The mortality rate, depending upon the implantation technique, is between 1 -3 per cent. Major complications are mainly presented after using thoracotomy.

For saving energy in patients with slow VT, a combination of ATP with back up defibrillation capabilities is preferable. If the ATP failed to restore the arrhythmia or an arrhythmia aggravation occurs, a defibrillation shock is released. A limiting factor during this procedure is the deterioration of the patient's haemodynamic condition which is an impeding factor in arrhythmia restoration.

Prior to hospital discharge, EP testing is advisable in all patients to demonstrate efficacy of the ICD in recognising and terminating induced VF and VT, especially in patients receiving antiarrhythmic drugs which may alter the arrhythmia profile or the defibrillation threshold (e.g. Amiodarone).

Preliminary short-term data confirmed a significant survival advantage. An apparent reduction in sudden death rate from 20% to 5% in patients no controlable with antiarrhythmic therapy is indicative that an ICD implantation is the most successful treatment for these patients, especially with the use of transvenous systems.

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## Non Electrophysiological Interventional Treatment of Tachyarrhythmias

by G. Sakadamis and C.L. Papadopoulos

2nd Department of Cardiology, Aristotle's University, Thessaloniki, Greece

For the interventional non electrophysiological treatment of tachyarrhythmias the following methods are used:

a) *Transvenous electrical catheter ablation* of the arrhythmogenic area.

The aim of the method is to destroy a myocardial area by delivering electrical energy. High energy direct current (DC) shocks, or radiofrequency (RF) energy are delivered through electrodes of a catheter placed next to endocardial area related to the generation or the continuation of the arrhythmia. For the DC shock delivery, the intracardiac electrode can be the anode, with a metal plate or conducting adhesive pad on the

skin of the thorax as a cathode. Also, the DC shock delivery would be performed between two electrodes on the same or two separate catheters. The tissue destruction is due to barotrauma, electrolysis and the flow of current. General anesthesia for the patient is necessary.

Radiofrequency energy is derived from low-power.(15-60 V, 5-30 Watts), high frequency (30 KHz-300 MHz) alternating current. The energy is delivered between the distal pole of an endocardial catheter and an external patch electrode placed in the left infracapular area. Radiofrequency ablation destroys tissue by heat production. The heat level is controlled manualy or automatically by the use of a thermistor. The usual settings are 70°C for 20-30 secs. The application of RF current creates desication of the tissue with coagulation-necrosis. The method is rather painless and no anesthesia is necessary.

Catheter ablation is used to control: 1} Atrial flutter or fibrillation with no pharmacologically controllable ventricular rate. In this situation the creation of a degree of AV block is desirable. The energy is delivered at the site where the largest His bundle potential amplitude is recorded. This usually makes the patient pacemaker dependent and antibradycardia pacing is necessary. Catheter ablation can also eliminate atrial flutter, RF energy application is preferable.

2) AV Nodal reentry tachycardia (AVNRT). Successful elimination of AVNRT with selective ablation of the fast or slow pathway with preservation of AV conduction can be achieved in up to 90% of patients. The possibility of creating complete AV block is about 10%.

3) Tachycardias due to accessory pathways (AP). Ablation of the APs is performed mainly in patients with Wolf-Parkinson-White Syndrome with short AP refractory periods. Optimal localization of the AP is crucial. This is achieved by direct recording of AP potentials, and by maneuvering a steerable electrode catheter inside the coronary sinus and/or tricuspid *anullus* for the right-sided APs. Left-sided APs have been easier to localize and to ablate using the retrograde aortic approach and searching the mitral annulus.

There is a high success rate (>90%) of Left APs ablation. Less success rate (60-80%) has been reported for the right APs. The right posterior pathways are easy to ablate applying DC shocks near the os of coronary sinus. However, a high rate of complications, such as rupture of coronary sinus (5%) and complete AV block (2%), have been reported.

Radiofrequency ablation similarly achieves a high success rate *(up* to 99%), but with much lower severity and rate of complications (<2-3%). The use of extended fluoroscopy is a limiting factor.

4) Ventricular tachycardia (VT): Shocks have been delivered to sites where isolated middiastolic potentials and areas of slow conduction have been recorded. The success rate of VT ablation has been generally disajppointing with serious complications during the DC shock procedures. Experience with RF ablation is limited and its major limitation is the small lesions. In scarred endocardium it is questionable if an RF application can penetrate to the arrhythmogenic area. This method is much more successful in cases of bundle branch reentry VT or VT with a right ventricular outflow tract focus. Complications are very serious and the mortality rate is 7 per cent.

*a) Chemical ablation:* The arrhythmogenic area is destroyed by alcohol or phenol infusion within the local branch of coronary artery. Excessive myocardial necrosis is the major complication.

*b)Surgical dissection of the accessory pathway* in preexcitation syndrome is performed in those groups of patients where the other methods are ineficient or unsuccessful. The surgical technique consists of an open heart endocardial or a closed heart epicardial approach.

*c) Surgical treatment of malignant ventricular arrhythmias* achieved by endomyocardial resection, cryoablation, Laser-ablation or circular endomyocardiotomy. The etiology of the underlying heart disease influences the type of surgery performed. Preoperative and intraoperative ventricular mapping is necessary. Indirect surgical approaches, including coronary artery bypass, grafting and ventricular aneurysm or infarct resection are usually used.