UNIVERSITY OF NIŠ
The scientific journal **FACTA UNIVERSITATIS**
Series: **Medicine and Biology** Vol.6, No 1, 1999 pp. 1 –10
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http://ni.ac.yu/Facta

UC 616.71;616.12

ANTIARRHYTHMIC THERAPY FOR ATRIAL TACHYARRHYTHMIAS

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Summary. *Antiarrhythmic therapy can have a key role in prolonging the lives of patients with most common atrial tachyarrhythmias such as atrial flutter (AFL) or atrial fibrillation (AF). The optimal use of antiarrhytmic drug therapy depends in part on understanding the underlying mechanisms of AFL and AF and pharmacodynamis of each antiarrhythmic drug. Currently, there is a large body of experimental and clinical evidence that documents that AFL is associated with a macro-reentry mechanism associated with a largeaaa excitable gap in the right atrium and an area of slow conduction in the triangle of Koch. The common and uncommon types share the same mechanism on location. AF is a complex arrhythmia. Theories underlying the mechanism of AF are: the cirrcus movement, the multiple foci, the fractionate contactions, the unifocal theory, and the combination of theories. The mechanism of focal atrial tachycardia has been the subject of dabete, with abnormal automaticity, triggered activity, microreentry and all considered possibilities. Currently available antiarrhythmic drugs have limited efficacy for acute termination of AF and AFL, especially if the arrhythmia is not of recent onset. Intravenous Ibutilide given in repeated doses and i.v. procainamide hydrochloride have been recommended for acute termination of AF and AFL. Efficacy is highest in AFL and in AF with either a short arrhythmia duration or a normal left atrial size. For the prevention of AFL and AF, the following drugs have been recommended: disopyramide, quinidine, propafenone, flecainide, sotalol and amiodarone. Currently, catheter ablation using radiofrequency electrical energy is the preferred first therapy, when feasible for treatment of atrial tachyarrhytmisa, including ablation of ectopic atrial tachycardia, AFL. and AF (the Maze procedure). The surgical ablation (the corridor operation or the Maze operation for AF) has a limited role in the management of patients in whom catheter ablation has failed.*

Key words: *Atrial flutter, atrial fibrillation, antiarrhythmia agents, radiofrequency ablation, surgical ablation.*

Antiarrhythmic therapy can have a key role in prolonging the lives of patients with most common atrial tachyarrhythmias such as atrial flutter (AFL) or atrial fibrillation (AF). The optimal use of antiarrhytmic drug therapy depends in part on understanding the underlying mechanisms of AFL and AF and pharmacodynamics of each antiarrhythmic drug (1).

Classification shema

Attempts have been made to classify atrial tachyarrhythmias (AT). One classification schema is shown in Table 1. The majority of ATs appear to arise from the right atrium for uncertain reasons, and probably originate along the length of the crista terminalis from the SA node to the AV node (4). The P-wave acis may be useful for non-invasive localisation of the site of origin of AT. Positive P-waves in lead I on the surface ECG suggest a right atrial origin, and isoelectric or negative P-waves in lead I suggest a left sided focus (4).

Table 1.

I Sinus node dependent
* Sinus tachycardia
* Inappropriate sinus tachycardia
* Sinoatrial nodal re-entrant tachycardia
II Atrial myocardium dependent
* Focal atrial tachycardia
Re-entry
Triggered activity
Abnormal or enhanced automaticity
* Macroreentrant atrial tachycardia
Atrial tachycardia
Atrial flutter
* Atrial fibrillation
III Atrioventricultar junction dependent
* Atrioventricular nodal re-entry tachycardia
* Atrioventricular reciprocating tachycardia
* Atrioventricular junctional tachycardia
Paroxysmal
Nonparoxysmal

Theories underlying the mechanism

Sinus node re-entry

The results of experimental and clinical studies suggested the occurrence of the "functional" type of sinus node (SN) intranodal reentry (30). The findings of several investigators suggested a possible role of the SA-node in the genesis and perpetuation of *atrial fibrillation* (30). Pathological changes leading to prolonged sinoatrial conduction times may induce a sustained sinus re-entry. New fibrillation waves may represent spontaneous impulses arising from protected pacemaker fibers in the center of the SA node, which still demonstrated concealed automaticity, or based on sinus node echoes as a result of local sinoatrial entrance blok (20). New wavefronts could emerge along the entire crista terminalis and the septal side of the SA node region (30).

Pacing-induced chronic AF induces sinus node dysfunction, prolongs intra-atrial conduction time, shortens atrial refractoriness, and perpetuates AF, changes that reverse gradually ofter termination of AE (34).

Atrial flutter and fibrillation

The following theories have been advanced to explain the underlying mechanism of AFL an AF: 1) theory of the *circus movement* travelling between the geart veins (AG Mayer, WE Garrey, GR Mines, Sir Th Lewis); 2) *unifocal* theory (CJ Rothberger, D Scherf I, M. Prinzmetal); 3) theory of *multiple atrial foci* (ThW Engelmann, H Winterberg I, HE Hering, B Kisch, D. Scherf II, GK Moe); 4) theory of *fractionate contractions* (DeBoer, CJ Wiggers), and 5) combination of theories.

Allessie MA (2) has developed the *leading circle* concept for AF, in which the re-entrant circuit is not dependent on an anatomic obstacle or an area of conduction block for maintenance of the arrhzthmia. On the other hand, Boineau (3) demonstrated experimentally that AFL was dependent on both fixed anatomic obstacles and functional nmonuniform repolarisation to maintain a large macro-re-entrant circuits.

Recently, experimental and clinical studies have revealed three basically different kinds of re-entrz: 1) circuits that are based on macroanatomic pathwazs, 2) functionally determined circuits in the syncitium of myocardia cells without the involvement of a gross anatomical obstacle (leading circle re-entry), and 3) re-entry in uniform or nonuniforme anisotropic tissue (14).

Atrial flutter

Atrial flutter (AFL) is a macroreentrant atrial tachycardia (AT), i.e. tachycardia using a circuit which involves a large portion of the atria (4). The rate of AFL is faster than that of AT (250-350 beats/min) in the absence of antiarrhythmic drugs therapy.

Type I or "*common*" AFL results from reentry within the right atrium. Intracardiac echocardiography was used to visualise the right atrial endocardium viewed anterior to posterior und enable the correlation of functional electrophysiologic properties with specific barriers to conduction during tipe I atrial flutter (the crista terminalis and Eustachian ridge) (19). The *onset* of the flutter wave is believed to be inferior or posterior to the coronary sinus ostium (CS os) where slow conduction is observed (20). and just anterior to the norrow isthmus of tissue between the inferior vena cava and the tricuspid annulus. In the frontal plane, the mapping has revealed a *counter-clokwise* re-entrant activation wavefront which proceeds caudocranially from the CS or along the right atrial septum and posterior wall and craniocaudally down the anterolateral right atrial free wall (16,19,53). The circuit completed along the isthmus between the interior vena cava ositum and tricuspid annulus (15). The electrocardiographic features are the characteristic atrial oscillations, very distinct in leads II, III, a VF, V_1 and V_2. The *common* type is characterised by inverted P waves in leads II, III, a VF, and V_6 and upright in V1(20) since the most of the right atrium and the entire left atrium are activated caudocranially (4).

Type II or "*uncommon*" AFL most ofen results from a reverse (*clockwise*) sequence of activation However, this type of AFL can also arise from macroreentry circuits anywhere in the right or left atria (4). More than one type of atypical AFL exists (16). In the uncommon type of AFL the P waves are upright in leads II, III, a VF, V_6 and inverted in V_1. Occasionally the direction of activation may be abruptly reversed.

Therapy

Antiarrhythmia drugs - theoretically can interrupt atrial flutter by abolishing the excitable gap through prolongation of the atrial refractory period or slowing isthmus conduction to a critical point bayond which propagation of the circulating impulse becomes impossible (52). *Medical therapy* - is often inffective for patients with flutter (72).

Cryoablation - is the current accepted rational to ablate the slow conducting isthmus between the inferior vena cava orifice and the tricuspid valve annulus at the base of the triangle of Koch (Fig. 1) (73) The RF catheter ablation is a safe and effective method (4) Success rate have varied from 56 to 100%. However, recurrence of typical AFL remains a significant problem (from 9 to 78%) (77). More worrying is the finding that up to 26% of patients experience atrial fibrillation. Predictors of AF after RF ablation of AFL include *prior occurrence* of AF and *structural* heart disease. Therefore, RF ablation should be reserved for symptomatic patients in whom AFL is the predominant clincal arrhythmia, but AF occurs rarely (77).

Sirgical techniques - use resection, cryoablation, and exclusion, singly or in combination. *Resection* applies to right atrial freewall and right and left appendage locations (73) *Cryoablation* can be combined with resection, particularly convinien for septal locations (73). *Exclusion* is used essentially for the left atrial locations (73).

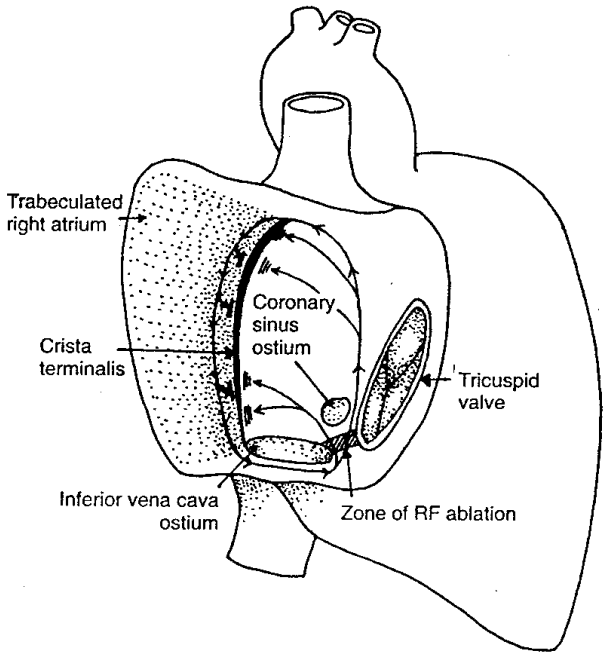

Fig. 1.

Atrial fibrillation

Mechanism

Patients with histories of AFL or AF have been shown to exhibit significant *intra-atrial* conduction delays during early premature impulses delivered at the *low right atrium* (18). These delays can be explained on the basis of *nonuniform atrial anisotropy* (18). If it were so, the nonuniform atrial anisotropy would lead to new treatment for AF: the radiofrequency ablation of the AV node (54,55) and the surgical tretment of atrial fibrillation (56).

The size of the atria

Atrial fibrillation is the most common arrhythmia todey. The atrial fibrillation is believed to occur secondary to enlargement of the atria due to the thinning and fibrosis of myocardial and conducting fibers, demonstrated in a pathological study (35). However, it does not explain the occurrence of af in patients with structurally normal hearts. (3% - 11% of the atrial fibrillation population). In humans atrial dilatation is an important risk factor for atrial fibrillation (12). It is konwn that in larger hearts atrial fibrillation is more stable and of longer duration. In addition to a proposed effect on impulse propagation by the atrial fiber geometry, other intracellular or intercellular factors might account for *nonuniforme anisotropic* conduction, which in turn may facilitate re-entry phenomena (18).

Stambler BS et al. (11) demonstrated that eighty-three percent of 266 patients had an enlarged left atrium, 55% had a depressed left ventricular ejection fraction, and 71% had valvular heart disease. On the other hand, Sanfilippo AJ, et al. (36) studied 15 patients who had no evidence of significant structural or functional cardiac abnormalities other than AF. They found that atrial enlargement can occur as a *consequence* of atrial fibrillation. Future studies are needed to address the role of atrial enlargement in atrial fibrillation.

The atrial activation during AF is the result of *multiple re-entrant wavelets* that propagate and become fractionate within the atrial tissue. The readiness of AF induction by *high right atrium* rather than the coronary sinus stimulation is due to the presence of site-specific conduction delays in the atrial myocardium (18). The others found AF to be more organised in the *lateral wall* than in other areas of the right atrium (37, 38). The atrial refractory period is shorter in the lateral and anterolateral wall than in other atrial sites (38). In atrial flutter and fibrillation, a critical wavelength is necessary to sustain each arrhythmia; AF requires a shorter wavelength than AFL (18). A prolongation of the wavelength may convert AF to atrial flutter.

The combination of right or left atrial enlargement and a history of atrial fibrillation is a strong predictor of subesquent occurrence of atrial fibrillation (16).

Electrical remodelling in atrial fibrillation

In the *recurrences* of AF, which are seen clinically during the first week after electrical or chemical defibrillation, the atrial refractory period *fails* to adapt to sudden slowing in heart rate by a prolongation of the refractory period (11). The atrial refractory period will be short. A duration of AF of only 7.6±1.1 min, the effective refractory periods (ERP) decreased by an average of 30 ms (33). This *shortening of refractory periods* termed *electrical remodelling* develops quickly, is progressive, and may be persistent (33). It opens the possibility to develop mechanism "atrial fibrillation begets atrial fibrillation" (13). It is suggested that atrial electrical remodelling is mediated by rate-induced *intracellular* calcium overload (33).

A brief episode of tachycardia or AF significantly *shortened* ERP. The shorter the tachycardia cycle length, the greater the decrease in atrial ERP (62). It might make the atrium more vulnerable to future AF. *Verapamil* infusion (0.15 mg/kg of body weight for a loading dose for 10 minutes and 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ for maintenance) can markedly blunt this effect, but not other antiarrhythmic drugs (class IA, IC, II, and III). These data suggested that *potassium* channels *might not play* a critical role in the change in ERP induced by AF of short duration (62).

Classification of atrial fibrillation

Wells et al. (28) distringuished four types of atrial fibrillation based on the morphology of a single bipolar atrial electrogram:

- *type I* – the electrogram with discrete complexes of variable morphology separated by a clear isoelectric baseline;
- *type II* – characterised by discrete atrial beat-to-beat complexes of variable morphology but differed from type I in that the baseline showed continuous perturbations of varying degrees;
- *type III* – fibrillation with highly fragmented atrial electrograms that showed no discrete complexes or

isoelectric intervals;

- *type IV* –fibrillation was characterised by alternation between type III and the other types.

During pacing-induced AF in humans, three types of right atrial activation (RA) were identified (29):

- *type I* – single broad wave fronts propagated *uniformly*, rapidly and without significant conduction delay across the RA, exhibiting only short arcs of conduction block (macro-reentry around one of the natural anatomic obstacles present in the atria). Type I fibrillation might be regarded as a case of type III atrial flutter;
- *type II* – was characterised by one or two *nonuniformly* conducting wavelets, showing a higher degree of delayed conduction and intra-atrial conduction block;
- *type III* – activation of RA was highly *fragmented* and showed three or more different wavelets that frequently changed their direction of propagation as a result of numerous arcs of functional conduction block. These various types of AF in humans appear to be characterised by different numbers and dimensions of the intra-atrial re-entrant circuits (29).

With the use of the surface ECG, AF has been divided clinically into "*coarse*" and "*fine*" fibrillation (31, 32). The "coarse" atrial fibrillation is associated with the activation patterns classified as type I fibrillation according to Konings' et al criteria (29). The "fine" atrial fibrillation, as present during vagal or cholinergic stimulation is associated with the activation classified as type III fibrillation (29). The different clinical manifestations of AF would be strongly related to the relative spatial organisation of activation sequences during AF (39). The sulf-terminating AF was determined by a larger tissue wavelength and tissue size (fewer wavelets) favouring termination, in contrast to chronic, sustained, nonterminating AF (39).

Therapy

Catheter ablation. – Swartz (78) and Haissaguerre (79) have opened the door to percutaneous catheter ablation of AF. The early RF catheter ablation procedure (78) is based on an anatomically guided surgical "Maze" developed by Cox et al. (80). Others include the "Coridor" for terminating AF (81). At the present time the Maze III procedure represents the state of the art in the nonpharmacologic treatment of AF (56, 82).

Supraventricular arrhythmias

Any form of tachyarrhytmia originating in the region above the His bundle or involving components of the atrium or atrioventricular node falls under the supraventricular arrhythmia (SVA). Of these disturbances, *atrial fibrillation* is the most common sustained arrhythmia, with an incidence of between 0.15 and 1% in the general population, and a preponderance in individuals over the age of 40.

Paroxysmal supraventricular tachycardia (PSVT) – is another major form of SVA. The prediction of mechanisms can often be accomplished with clinical and electrocardiographic observation (25).

The most common mechanism of PSVT appears to be A-V *nodal re-entrance* although other mechanism are not infrequent. Typical findings include a narrow QRS complex and a P wave simultaneous with the QRS complex. Associated organic hart disease is not uncommon (25). There are reports of an association between *atrioventricular nodal reentrant tachycardia* (AVNRT) and inducible *atrial flutter*, suggesting the possibility of a shared pathway around the tricuspid annulus to the anterior right atrium. PSVT was unrecognized oafter initial evaluation in 59 of 94 patients (55%), particulary in females (68% vs 40% of males, $p<0,01$) (71). Incorect initial diagnosis occurred in 50 patients, with symptoms attributed to panic, anxiety, or stress. The potential clinical overlap exists between PSVT and panic disorder.

AVNRT *utilising a concealed extranodal pathway* – is typically associated with young age, absence of organic heart disease, relative fast rates, frequent occurrence of functional bundle branch block during tachycardia and P waves before the QRS complex (25).

Sinus or atrical reentrant tachycardia – is characterised by a large prevalence of organic heart disease, a narrow QRS complex and P waves before the QRS complex (25).

Automatic ectopic tachycardias or focal atrial tachycardias – tend to cluster in certain anatomic zones, such as along the crista terminalis in the right atrium, of from the ostia of the pulmonary veins in the left atrium (72). The crista contains cells that have very sparsely distributed transverse gap junction as well as cells with automatic properties. In a region of poor *cell-tocell coupling*, a less prominent electronic influence allows these cells to manifest their abnormal firing (72).

The criteria for diagnosis – a focal atrial tachycardia includes the following: 1) spontaneous onset of tachycardia not related to any initiating event, either critical rates or coupling intervals, 2) spontaneous tachycardia with the initiating beat being identical to subsequent beats of tachycardia, 3) inability to initiate and terminate the tachycardia with atrial and ventricular stimulations, 4) demonstration of ectopis focus recovery time after cessation of overdrive pacing, and 5) absence of dual A-V nodal pathways or concealed extranodal pathways (25).

Therapy

Medical therapy – is often ineffective for patients with atrial tachycardia or flutter. In the 16 years since first report of *catheter ablation* of the atrioventricular junction in humans, the role of catheter ablation in the management of cardiac arrhythmias has increased dramatically (74).

Radiofrequency catheter ablation – by severing corridors of slow conduction or abolishing foci of abnormal firing, can safely treat atrial arrhytmias in humans (72). The posterior approach to catheter ablation of AVNRT is now considered the procedure of choice because of the high incidence of success and lower incidence of AV block and arrhythmia recurrence (75). In 1991, oen of the first large studies looking at safety and efficacy of catheter ablation for accessory pathways mediated tachycardias (including those with WPW) reported the highest success rate of 99% with a 9% recurrence rate (76).

Surgical techniques – for AV nodal reentrant tachycardia are no longer used (73). In patients with ectopic atrial tachycardias, surgical techniques are indicated *only* after attempted catheter ablation (73).

Pharmacodynamics of antiarrhythmic drugs

The primary mechanism of antiarrhytmic drugs (AD) action is based on their effects on certain ion channels and receptors located on the mnyocardial cell membrane (1). According to the classification system developed by Vaughan Williams (5), drugs with class IA action prolong the repolarization and the refractoriness of isolated myocardial tissue in addition to blocking the rapid inward sodium current. Quinidine has also, to a lesser extend, class III effects (ie, it blocks potassium and sodium channels). Class IC drug (eg. *propafenone* hydrochloride) slows the conduction velocity but have little effect on repolarization. Class III drug *amiodarone* blocks the slowly activating component of delayed rectifier current (I_{ks}). In contrast, clas III agents like sotalod, and new clas III antiarrhythmia drugs such as ibutilide (11) and dofetilide (27, 51) specifically block the rapid component of delayed rectifier current (I_{kr}); ambasilide blocks both I_{kr} and I_{ks} currents – and facilitate slow sodium channel activation (1), and increased atrial effective refractory period (10). *Ibutilide* (the i.v. infusion 0.02 mg/kg over 10 minutes) is more effective in conversion of atrial flutter than are *propafenone* (the i.v. infusion 2 mg/kg over 10 minutes followed by 0.4 mg/min), and *amiodarone* (the i.v. infusion 10 mg/kg 10 minutes folowed by 30 mg/h) (52).

The coexisting ischemia, acidosis, electrolyte imbalance, or high catecholamine levels, may also affect the pharmacodynamics of an antiarrhythmic drug. A decreased hepatic blood flow, such as in patient with congrestive heart failure, may affects the elimination of hepatically metabolised drugs, such as propafenon and amiodarone (1). Quinidine, propafenone and particularly amiodarone *interact* with drugs that are hydroxylated in the liver. The serious interaction is the marked incrase in serum digoxin levels produced by quinidine.

Quinidine

Quinidine suppresses the *rapidly* activating component of the cardiac delayed rectifier (I_{kr}), and in some patients markedly prolongs the QT interval and produces polymorphic ventricular tachycardia, the torsade de pointes syndrome (6). On the other hand, quinidine produces greater prolongation of action potential duration and induces, at low concentration, early afterdepolarization and triggered activity in M cells but not in endocardium or epicardium. The result is drug-induced polymorphic ventricular tachyarrhythmia (7). Clinicians must be vigilant to avoid clinical circumstances that are likely to increase the risk: serum $K^+ < 4$ mmol/l and administration to unstable patients. Quinidine is more effective than no suppressive antiarrhythmic therapy in keeping patients in sinus rhythm, but this effectiveness appears to be obtained at the cost of at least a 3% annual incidence of mortality related to sudden cardiac death (21).

Propafenone

Propafenone *prolongs the flutter cycle length* due to a predominant increase of activation time in the low right atrial isthmus (52). In this tudy, propafenone produced use-dependent decrease of conduction velocity in the isthmus and free wall and increased atrial refractory period by 15% to 29% (52) – blocking the transient outward, delayed recifier and inward rectifier potassium currents (58).

Two of the main metabolites of propafenone (50H propafenone and ND propyl propafenone) have type IC electrophysiologic effects. Clinical data suggest that clas IC drugs exert a direct effect on arrhythmogenic areas with enhanced abnormal automaticity. Propafenone was found to be effective in the management of supraventricular tachycardia caused by ectopic foci.

Propafenone or other class I antiarrhythmia drugs terminated atrial flutter primarily by *depressing conduction* to a critical point beyond which wave front propagation becomes impossible (52). The *excitable gap* of experimental canine AFL was *not* significantly changed by propafenone (61).

Amiodarone

Amiodarone is a paradoxical agent (8). The same drug can be at once so helpful and so toxic. Amiodarone may be effective due to, rather than despite, its pharmacologic complexity having many properties: sodium channel blocking, calcium channel blocking, non-specific sympathetic blocking, possessing anti-ischemic, antiarrhythmic and antifibrillatory properties (8). Its calcium channel blocking property may prevents early afterdepolarization induced abnormal replorization and triggered activity. Probably the most effective drug for paroxysmal atrial flutter is amiodarone (9) or ibutilide (11).

Amiodarone has the least effects on the atrial flutter circuit although it midly increases atrial effective

refractory period (52) by *inhibiting potassium channels* (57).

Class III drugs are thought to terminate re-entry in atrial flutter by prolonging the action potential and refractory period and eliminating the excitable gap. Short excitable gap circuits, such as AF or type II AFL, are more likely to terminate with potassium channel blockers (class III drugs), whereas long excitable gap circuits, such as typ I AFL, are more vulnerable to conduction block by sodium channel-blocking agents (class IA, quinidine and IC, propafenone) (11).

The Avram's R et al (17) *open, active clinical trial* confirms the previous findings in humans of the efficacy of amiodarone, quinidine and propafenon in terminating and preventing the reinduction of atrial fibrillation and flutter. Recently, Coplen et al. (21) summarised 6 quinidine studies and reported that 69%, 58% and 50% of patients maintained sinus rhythm for 3, 6 and 12 monts, respectively. A similar progressive pattern of relapses in the course of follow-up has been found for amiodarone (22, 23) and propafenone (24). Amiodarone was rather successful. Low dose amiodarone 204 ± 66 mg (mean $\pm$ SD) is effective for maintaining sinus rhythm. It may be used as a first choice drug in the prevention of recurrences of chronic atrial fibrillation and flutter (17). These findings are in contrast with the note of Estes who reported that a low-dose amiodarone may be appropriate in selected patients with more symptomatic, life-disordering or lifethreatening atrial fibrillation that is refractory to alternate pharmacologic therapy.

The mimpact of *prophylactic* antiarrhytmic drugs appears to be limited. Amiodarone should be avoided in patients with mitral stenosis or previous arrhythmia of long duration (17). In addition to this, the correct approach in a given case must be based on the characteristics of the individual patient, the short-term and long-term safety and costs of the various drugs.

It is impossible to draw conclusions concerning the prophylactic efficacy of these drugs because the study was not a randomised one, and there was no control group (17). However, preventin of AF and treatment of patients with AF and associated with other cardiovascular diagnosis may yield benefits in reduced mortality and stroke as well as reducing health care costs (40).

Ibutilide

Ibutilide fumarate is a novel class III antiarrhytmia drug that prolongs the action potential duration and efective refractory period in both atria and ventricles (1, 52, 59) by *increasing* a slow inward plateau sodium current and *inhibiting* the outward repolarizing potassium current (6, 52, 60). It does not significantly decrease conduction velosity (52). The intravenous ibutilide singificantly ibcreased atrial effective refractory period in patinents with clinical atrial flutter by 24% to 31% (52).

Antiarrhythmic drugs for specific indications

Several recommendations are proposed for optimizing the use of antiarrhytmic drug therapy. One must take into consideration not only the pharmacological properties of a specific antiarrhytmic drug but also such factors as the patient's age, coexisting disease, and wether the patient takes other drugs or has an implantable cardioverter defibrillator (ICD) (1). One should individualize therapy whenever possible because each patient is unique. Table 2 lists some common arrhythmias and examples of drugs from the Vaughan Williams classification system (1).

Table 2.

Indication	Drug
Sinus tachycardia	Propranolol hydrochloride
Sinoatrial reentrant tachycardia	Propranolol hydrochloride Verapamil
AV nodal reentrant tachycardia and AV reciprocating tachycardia (orthodromic)	
Termination	I.V. verapamil I.V. diltiazem hydrochloride
Prevention	Verapamil Propranolol hydrochloride Flecainide acetate Sotalol hydrochloride
Atrial fibrillation or flutter	
Termination	I.V. procainamide hydrochloride I.V. ibutilide fumarate
Prevention	Disopyramide Quinidine Propafenone Flecainide Sotalol Amiodarone

Serial electrical cardioversion

The DC electrical cardioversion is an effective and safe method to obtain sinus rhythm in patients with *chronic atrial fibrillation*. Patients with chronic (>24 hours) atrial fibrillation received *warfarin* or a derivative at least 4 weeks prior electrical cardioversion. The target prothrombin time was an international normalized ratio of 2.4 to 4.8 (65). The increasing duration of atrial fibrillation inversly correlates with the chance of reinstitution of sinus rhythm (65). The tachycardia-induced changes (eg, electrical remodeling) are probably more easily reversible (13).

A few studies have shown that atrial thrombus and spontaneous echo contrast (SEC) occur in patients with atrial flutter (69). Irani et al (70) have demonstrated that 34% of male patients who presented for elective cardioversion of atrial flutter had atrial thrombus and/or SEC; 28% patients showed evidence of absent mechanical atrial activity immediately after restoration of sinuns thythm. These findings may be associated with inceased risk of thromboembolism. It is sugegested

that a large stuy may be warranted to reassess the need for anticoagulation in these patients (70).

After cardioversion (CV) of chronic AF to sinus rhythm, there is a *gradual increase* in *cardiac autput* over 4 weeks. Cardiac output decreases after CV of atrial fibrillation in more than a third of patients, abd the decrease may kast a week. Acute pulmonary edema after CVis uncommon; mortality is 18%. Half of the cases occur within 3 hours of CV, but it can occur as late as 4 days after CV. Anticoagulant therapy should be continued for a month or longer after CV (83).

Atrial fibrillation and stroke

In recent years, *nonhreumatic* atrial fibrillation (AF) has been identified as a most powerful independent risk factor *predisposing* to stroke. The incidence of stroke is increased nearly 5-fold in the presence of AF (40). Stroke rates are approximately 25% higher in women with AF ($p<0.05$) but only 10% higher in men (40). Female patients aged 75 to 89 years *with* AF were more likely to be admitted with stroke, compared with similarly aged women *without* AF.

Anticoagulation

Despite consensus that warfarin is strongly indicated in most patients with AF, past studies demonstrate that anticoagulation in AF is inadequately used (less than 40% of such parients) (41, 43, 63). There is a considerable inconsistency among physicians about the decision to use warfarin for stroke prophylaxis (84). Another study has suggested that more than 60% of patients with AF can safely undergo anticoagulation (64). The *oldest* patients (>80 years), in whom warfarin may have its greatest benefit, appear to have the lowest rates of anticoagulant use (19%) compared with younger patients (36%) (63). They are at relatively increased risk for major bleeding complications. Nevertheless, they appear to be at the highest risk for ischemic stroke if not treated and have the greatest absolute reduction in risk of ischemic stoke when treated (41, 63).

Among 1.066 patients with AF in the pooled analysis of 3 randomized clinical trials: the Stroke Prevention in Atrial Fibrillation (SPAF) (44), the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) study (45), and the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) (46) − independent clinical predictors of ischemic stroke in these patients were age, previous stroke or transient ischemic attack, history of diabetes, and history of heart failure (48).

Previous history of hypertension was shown to predict stroke (47), as well as the left atrial diameter (48). It was not predictive of stroke in patients with AF given *aspirin* in SPAF study (49). In the current analysis neither hypertension nor left atrial diameter and mitral regurgitation were significantly associated with stroke (50). The left ventricular dysfunction shown via 2-dimensional transthoracic echocardiography indpendently predicts risk of stroke in patients with atrial fibrillation (50).

Presently available data support the recommendation of adjusted-dose warfarin therapy (INR 2,0–3,0) for most patients with AF who *do not have contraindications* to anticoagulation therapy (84, 85). Patients with AF and a recent stroke or transient ischemic attack or multiple risk factors for stroke are at extremely high risk for stroke and are likely to benefit from anticoagulation therapy, even if they have relative contraindications to warfarin therapy (84).

The adition of *aspirin* to a low-dose warfarin sodium 1.25 mg/d (below an INR of 2.0) does not provide any significant benefits and should be avoided (84, 85). Therapy with *aspirin alone* is appropriate for specific subgroups of patients with AF who are at low risk for stroke based on the absence of clinical and electrocardiographic risk facotors (85).

Atrial fibrillation after coronary artery surgery

The incidence of AF after major nonthoracic procedures is reported to be ≈ 5% (66). The incidence of AF after CABG varies widely, with reported incidence of 5% to 40% (67). The continuous on line ECG monitoring and Holter monitoring and the increasing age of the patient population, increased fibrosis, and atrial dilatation are the major factors that have contributed to the higher incidence of AF in recent years (68). The advanced age (≥70 years) and *hypertension* are independent predictors of *postoperative* AF (67).

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ANTIRITMIČKA TERAPIJA PRETKOMORSKIH ARITMIJA

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Kratak sadržaj: *Antiaritmičko lečenje može da ima ključnu ulogu u produžavanju života bolesnika sa najčešćim pretkomorskim tahiaritmijama, kao što su lepršanje pretkomora (AFL) ili treperenje pretkomora (AF). Optimalna upotreba lekova sa antiaritmičkim dejstvom zavisi delimično od poznavanja mehanizama nastanka AFL i AF i farmakodinamike svakog pojedinačnog antiaritmičkog leka. Danas postoji velik broj eksperimentalnih i kliničkih dokaza da AFL nastaje širenjem aktivacije po velikom krugu sa velikim "ekscitabilnim međuprostorom" u desnoj pretkomori, a u predelu sa usporenim širenjem, koje se nalazi u Kochovom trouglu. U istom području, odvija se uobičajen i ređi tip AFL. AF nastaje složenim, pokatkad različitim mehanizmom. Teorije koje objašnjavaju mehanizam nastanka AF jesu: kružno širenje aktivacije, aktivacija iz većeg broja žarišta, frakcionirane kontrakcije, teorija o*

nastanku AF iz jednog žarišta negde u pretkomori, ili kombinacija više teorija. Antiaritmici koji su danas na raspolaganju nisu u potpunosti efikasni u zaustavljanuu akutno nastalih AFL i AF, a posebno u aritmijama koje duže traju. Za zaustavljanje akutnih AFL i AF, danas se preporučuje i.v. davanje Ibutilida u ponovljlenim dozama ili prokainamid hidrohlorida. Efikasnost je najveća u bolesnika sa AFL i AF bilo da ono traje kratko ili da je veličina leve pretkomore normalna. Za prevenciju AFL i AF, preporučuju se sledeći lekovi: disopiramid, hinidin, propafenon, flekainid, sotalol i amiodaron. Najnoviji rezultati izučavanja ukazuju da je ablacija kateterom korišćenjem eleketrične energije prvi izbor, ukoliko to omogućuje stanje bolesnika, u lečenju pretkomorskih tahiaritmija: AFL, FL (Maze postupak) i žarišnu pretkomorsku tahikardiju. Ablacija hirurškim putem (Corridor ili Maze operacija za F) imaju udeo u lečenju ovih tahiaritmija u bolesnika kod kojih ablacija sa kateterom nije uspela.

Ključe reči: *Lepršanje pretkomora, treperenje pretkomora, antiaritmici, ablacija sa kateterom i električnom strujom, ablacija hirurškim putem*

Received: September 7, 1998