Myocardial Repolarization and Drugs

Impossibility to predict the dominance of anti-arrythmic over pro-arrhythmic effects of drugs due to differential and ventricular electrical remodeling

Marc A. Vos, PhD, Harry J.G.M. Crijins, MD, PhD*
From the Departments of Cardiology, Academic Hospital Maastrich&Cardiovascular Research Institute Maastricht and *Academic Hospital Groningen, the Netherlands

It is known that application of anti-arrhythmic drugs for the acute treatment of arrhythmic can not only result in succesfull termination or prevention, but also can lead to unwanted pro- arrhythmic effects. On the basis of two arrhythmias, atrial fibrilation and Torsade de Pointes arrhythmias, we will highlight the relevance of differential atrial and ventricular electrical remodeling to explain the delicate and dynamic balance between anti- arrhythmic efficacy and pro- arrhythmogenic consequences of class III anti- arrhythmic drugs. *(Ana Kar Der, 2001; 1: 27-34)*

Introduction

Around 1970, Vaughan Williams suggested to list anti- arrhythmic drugs according to their pedominant action in 4 categories (1). Classification was primarily based on tests performed under physiological circumstances: i.e. assesment of the effect of the durg on ionic currents or receptors of normal cells, tissues or animals. From the currently, clinically available anti- arrhythmic drugs it is known that they all have the potential to generate Pro- arrhythmia, defined as worsening of the existing arrhythmia or the appearence of a new arrhythmia at a dose which is not considered toxic (2).

Anti- arrhythmic drugs that prolong repolarization belong to class III (1). They achieve their action by bloackade of repolarizing currents, although we are aware that (a) a number of class a drugs, like quinidine and procainamide, can also lengthen QT-time and (b) representatives of the class III group, such as amiodarone and sotalol, have a much broader action than just action potential duration (APD) lengthening. Still we refer to all these drugs as class III in the remainder of this text.

The development of improved anti- arrhythmic therapy depends in large on detailed understanding of the mechanisms for anti-and also pro- arrhythmic action. The search for new anti- arrhythmic in the late 80's was guided by the knowledge that multiple wave reentry plays an important role in the perpetuation of atrial fibrillation (and other (supra) ventricular tachycardias). Therefore much attention was given to drugs that could increase the wavelength, defined as the product of the conduction velocity and the refractory period (3) most particularly by increasing reporalization (class III action). However, more recent discoveries concerning time-dependent electrophysiologic and ultrastructural remodeling as a consequence of the arrhythmia (especially atrial fibrillation) were not considered. Indeed these pathophysiologic adaptations are not taken into account in the current designs of clinical drug trials.

To limit the size of this review, we will discuss two conditions to support our case: atrial fibrillation (AF), the most common clinically occuring arrhythmia, was selected in order to describe the efficacy of drugs as anti- arrhythmics. Acquired Torsade de Pointes arrhythmias (TdP) was chosen as a representative examble for clinical pro- arrhythmia of class III drugs, which can become life-threatening and severely limits the use of these drugs today (4). We will demonstrate new aspects concerning the delicate and dynamic balance between anti- arrhythmic efficacy and possible pro- arrhythmic consequences within these conditions and discuss experimental and clinical evidence to better understand the underlying mechanisms.

• G.Breitheradt ve A.Oto'nun editörlüğünü yaptıkları kitapta kısmen ve değişik olarak yayınlanacaktır.

Adress for correspondence: M.A. Vos, PhD Associate Proffessor Department of Cardiology Academic Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht m.vos@cardio.azm.nl

Anti- arrhythmic drugs and suppression of experimental atrial fibrillation

Large animal models of AF have been listed in table 1. With the development of chronic models, the potential role of the arrhythmia itself in the promotion, and contiunation of AF became clear (5,6). Also on the basis of the etiology, e.g. mitral regurgitation, different adaptation processes can be anticipated. Depending on the model therefore, different forms of contractile, structural and electrical remodeling have been described (5-7). In the "AF begets AF" goat model or in the "rapid pacing induced AF" canine model, electrical remodeling consists of long term shortening of the atrial effective refractory period (AERP) which is most pronounced at slower rhythms resulting in a flat or inverse frequency dependency of the atrial APD. Subsequently, atrial fibrillation becomes more stable and the duration

Table 1: Animal models of AF

	Clinical Relevance	Sustained AF
1. Normal animals	-	-/+
2. Mitral regurgitation	+++	+
3. Sterile pericarditis	++	+
4. Vagal induced AF	+	+++
5. AF-induced AF	+++	+++
6. rapiad pacing induced AF	++	+++
7. CHF induced AF	+++	+++

of AF episodes increases progressively (5,6). A decrease in conduction velocity has not consistenly been described in "AF begets AF", but seems important in "rapid pacing induced AF" and is the sole contributor in "CHF induced AF" (5-7). The mechanisms underlying AF in the different models is therefore also quite different (table 2). In the "vagally induced AF", the shortening in AERP is physiological but not homogeneous causing an increase in spatial dispersion of repolarization and the possibility for numerous waves (8). As long as the cholinergic stimulation is maintained, atrial fibrillation will be present. Due to the very marked shortening in AERP (electrical remodeling), multiple very short waves can coexist in the "pacing induced AF" models (9). With time it becomes more difficult to terminate this fibrillation process. However, in "CHF induced AF" repolarization is normal ,but conduction has slowed and become non-uniform, i.e. there is excessive dispersion of conduction due to fibrosis. This results in AF consisting of a macro,Reentry circuit resembling atrial flutter (7). The different electrophysiological alterations in these models affect the (supposed) efficacy of drugs. The effects found in vagally-induced AF (8) may not translate to the other forms of AF. Recently, it has become clear that the response of the durg is indeed dependent on the substrate or underlying mechanism (10): dofetilide iv. Has been shown to be very effective against CHF induced AF (100%: dose 10-80 mg/kg), partly effective against cholinergic AF (42-50%, dose 80-160 mg/kg), and not effective aganist rapaid pacing induced AF (12.5%, 80 mg/kg).

Tablo 2: Mechanisms of AF

1 CHOLINERGIC INDUCED AF
- ↓ AERP
- İncreased spatial dispersion in AERP
- İnitation easiest at shortest AERPs
- Numerous waves
2 AF OR PACING INDUCED AF
- ↓ AERPS – electrical remodeling
- ↑ spatial electrophysiological heterogeneity
- (↓ conduction)
3 CHF INDUCED AF
- = AERP
- = electrical heterogeneity
- ↑ interstitial fibrosis – ↓ conduction
- macro-reentry (small number circuits) atrical flutter

Anti-arrhythmic efficacy for clinical atrial fibrillation

Numerous studies have evaluated the-anti-arrhythmic efficacy of drugs to terminate AF either intravenously or orally (11-15). In the most recent trials with new class III drugs (dofetilide or ibutilide), the efficacy against atrial flutter was higher than aganist atrial fibrillation (12,15), a finding which could sheed some light on the underlying mechanism when placed in the above context of the effects of dofetilide in the different animal models. In addition, the arrhythmia duration – and therefore time-dependent remodeling – is an important determinant of drug conversion (15): a long duratin (months) almost completely precludes drug conversion. Similarly, time-dependent reversed remodeling appears to be clinically important: drugs previously inffective may be applied successfully after (presumed) reversed remodeling was achieved (17). It must be kept in mind however that AF-induced electrical remodeling has not been proven yet in humans (18-21) and relies on postconversion reversal studies (22-25). At present it is not precisely known how conditions like atrial hypertrophy, dilatation, fibrosis or high atrial rate it-

self affect drug efficacy. In addition, these factors usually interact and their separate effects cannot be sorted out reliably in the cilincal situation. Therefore, acute conversion regimens tailored to these specific pathophysiologic conditions are not feasible yet.

Chronic prophylactic treatment is indicated for frequent paroxysmal as well as postcardioversion AF. Associated cardiac conditions, frequency of the attacks and duration all may affect drug efficacy. Especially in chronic AF time-dependent changes may affect success of postcardioversion drug pervention. Recently the types of postcardioversion AF have been further subdivided: (a) immediate postshock recurrence (IRAF), (b) subacute recurrence and (c) late-re-occurences. Presumably, a dynamic anti- arrhythmic approach is warranted depending on time after cardioversion (26).

Electrophysiologic and ultrastructural adaptations and anti-and pro-arrhythmic drug effects

The electrical in vivo adaptations have been the subject of recent experimental molecular and cellular studies. Concerning ionic channels, the reduction in atrial APD has been associated experimentally with reduced contribution of IcaL and Ito (27), whereas the conduction disturbance has been related to a decrease in Ina (28) but also (heterogeneous) down-regulation of connexins (29) and dispersion of conduction (7). In humans, similar observations have been made for IcaL and Ito (30,31). These observations are paralleled by a decrease in channel protein expressions (32).

In addition to electrophysiological changes, AF causes alterations in cellular ultrastructure and Ca-handling, which resemble the changes seen in hibernating myocardium (33), resulting in negative inotropy or complete absence of contractille function. Hibernation is compatible with the clinical observation that it takes some time before contractile function returns to normal when sinus rhythm is restored. How these alterations (an9d their reversal after restoration of sinus rhythm) affect drugs' actions is largely unknown at present.

These tachycardia-induced changes in ion channel functions affect anti- arrhythmic drug actions at the atrial level. The same holds however also for the ventricules. During chronic tachycardia electrical and ultrastructural ventricular adaptations also occur, either due to heart failure, hypertrophy or the tachycardia itself. The net effect is not always predictable: these conditions may reduce or enhance ventricular anti- arrhythmic drug effects or even produce TdP.

Clinical evidence of pro- arrhythmia

A classic description of the fact that a9nti- arrhythmic treatment may produce pro- arrhythmic complications was presented by Selzer and Wray in 1964 (34). At first classified as self-terminating ventricular fibrillation it became clear that it was a polymorph ventricular tachycardia in the presence of a prolonged QT-time, commonly referred to as TdP (35).

More detailed analysis from literature data revealed that TdP on the basis of anti- arrhythmic (drug induced prolongation of QT) occurs as a complication of anti- arrhythmic drug treatment in 1-5% of patients (12-15, 34,36-38). All class Ia (quinidine, procainamide) and class III drugs can cause TdP, both during (teh attempt of) pharmacological conversion as well as during oral treatment to maintain sinus rhythm. TdP may occur as an idiosyncratic response in susceptible patients but seems to be especially frequent in patients with heart failure. This suggests that patients developing heart failure (e.g. during the course of the disease which also caused AF) at the same time may develop the electrophysiologic conditions related to class III pro- arrhythmia (figure 1).

Experimental evidence for drug-induced pro-arrhythmia

Looking at data from animal models studying the sensitivity of class II drugs to induce TdP arrhythmias, we have to acknowledge the fact that ventricular electrical remodeling is an important pre-requisite for the occurence of TdP. This knowledge came forward from studies using dogs comparing acute (AAVB) versus chronic AV-block (CAVB). At first, studies were initiated to elucidate the mechanisms involved in drug induced polymorphic ventricular tachycardia (39-42). Because bradycardia is one of the predisposing clinical factors for acquired TdP (together with hypokalemia / hypomagnesemia), interventions were aimed at slowing the rhythm: vagal stimulation, sinus node crush and AV-block. The bradycardia induced at AAVB leads to frequency dependent lengthening of ventricular APD (hpysiological adaptation), increases in ventricular end-diastolic pressures, and a fall in cardiac output. Application of the class III agent d-sotalol (2 mg/kg), however, does not result in spontaneous or pacing induced TdP at this early time point (42). However, repetition of the same protocol 5 weeks later (CAVB) re-

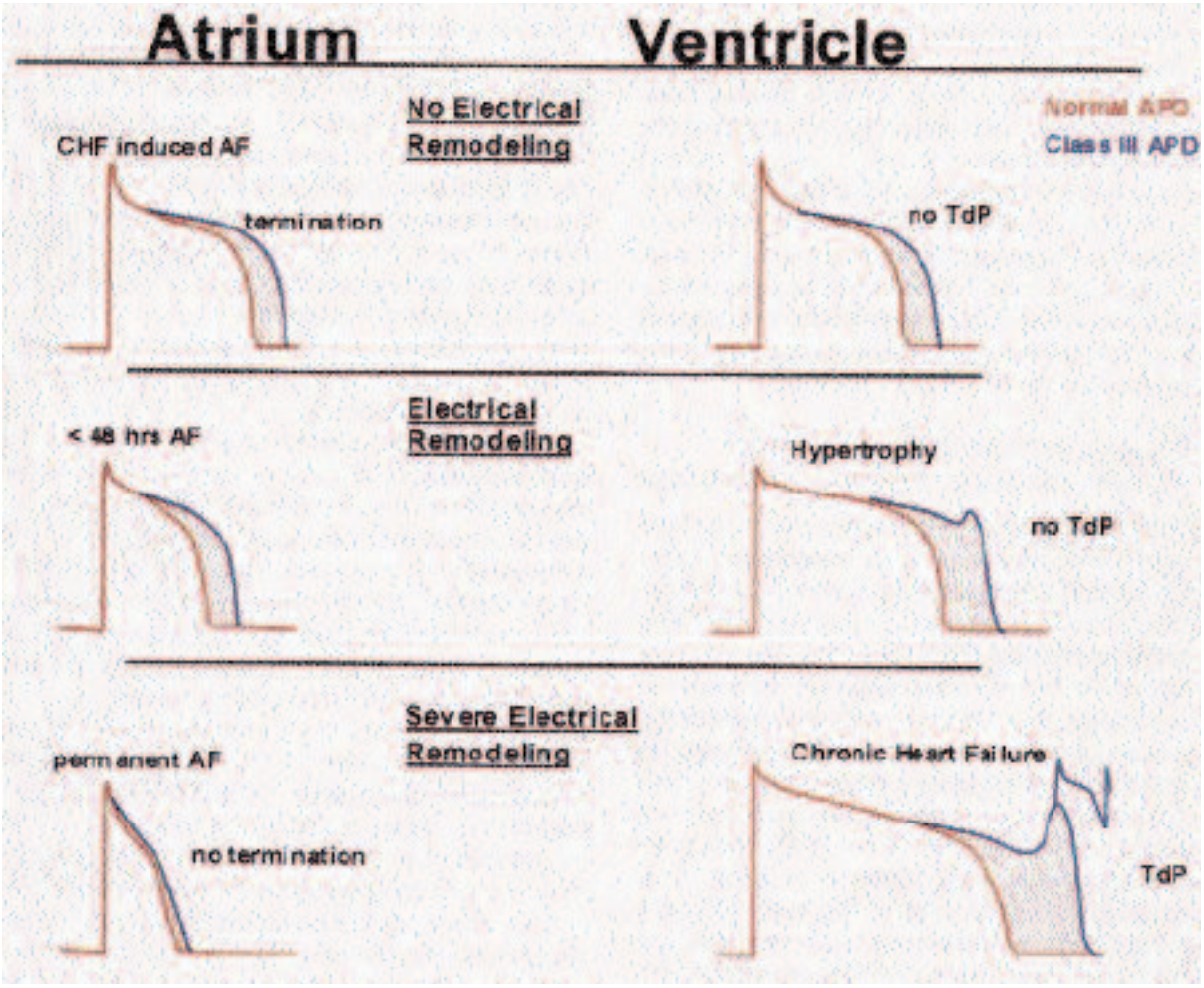

Figure 1: In this illustration 3 atrial (left part) and 3 ventricular action potentials are depicted representing 3 conditions of electrical remodeling: 1) no (upper part), moderate and severe electrical remodeling (lower part) before and after class III drug administration. Whereas the atria respond to AF with shortening of the APD (upper to lower left), ventricular electrical remodeling due to hypertrophy or heart failure is characterized by an increase in the repolarization times. The reverse use dependency of class III drugs is incorporated. Therefore pharmacological intervention to treat AF may lead to termination depending on the electrophysiologic atrial substrate. At the same moment, the lengthening in ventricular APD poses a risk for TdP arrhythmias. Especially in heart failure the anti-arrhythmic effect of a drug (termination of AF) may be accompanied by a pro- arrhythmic response (TdP).

sults in the induction of TdP in the majority of the dogs, alhough the severity of the bradycardia and/or the dose of d-sotalol are similar (42). Other studies have shown that to initate TdP in dogs with sinus rhythm or AAVB requires higher concentrations of drugs (up to 4 times the dose of CAVB) indicating that predisposing factors should be present in the chronic dog model. This enhanced susceptibility has been associated with ventricular remodeling, including (a) electrical romedoling: market non-homogeneous lengthening of the ventricular APD leading to more marked interventricular dispersion (40+35 ms at AAVB vs 70+30 ms at CAVB), and an altered electrophysiological response to d-sotalol (no increase in dispersion at AAVB, 45+30 ms, versus a further increase in APD dispersion at CAVB, 125+65 ms); (b) contractile remodeling: marked increase in contractility (dP/dt max + 100%), and return of the end-diastolic pressures to pre-AV-block levels with an increased incidence of triggered ectopic beats when the cardiac function is potentiated, and; (c) structural remodeling: biventricular hypertrophy without fibrosis. All these findings have been confirmed at the cellular level (43-45). Moreover, patch clamping has revealed that the ionic remodeling is

premdominantly related to changes in Ik and NCX. In both ventricles IkS is downregulated while nCX is upregulated in both modes (44-45).

Thus, the lengthening in APD in the CAVB dog is the result of changes in ionic currents. Block of asperically the currents responsible for repolarization by class III agents will affect the diminished strength of repolarization (decrease in repolarization reserve) further so that the-pro- arrhythmic potential of these drugs is facilitated. The proposed mechanisms for acquired TdP include (a) a focal initation through early after depolarizations which occur more readily in prolonged APDs and (b) perpetuation by reentrant activity that is precipitated by the very market dispersion.

Balance between anti- arrhythmic efficacy and pro- arrhythmic consequence

Unfortunately, drug effectiveness and pro-arrhythmia seem to be related. In direct comparisons, (quinidine vs sotalol (14) or ibulitide vs sotalol (12), the more effective drug also showed a higher pro- arrhythmic potential. In the case of quidine (14), this was associated with an increased precordial QT dispersion. Similar findings were obtained with the experimental drug almokalant (38). Certain clinical conditions may adversely affect the balance between anti- arrhythmic and pro- arrhythmic drug effects. The most important example is congestive heart failure (CHF), since it frequently complicates atrial fibrillation and vice versa. Patients with CHF have a higher risk to die suddenly. The underlying mechanisms are unkown, although an increase in the QT-time or in the ventricular APD has been described consistently. This predisposition for SCD could be related to drug-induced TdP. This concept is consistent with the observed increased mortality in patients with AF and heart failure treated with anti- arrhythmic drugs in the SPAF trial (37).

In figure 1, we have summarized our concepts concerning the balance between pro-and anti-arrhythmic drug action. The conditions atrial fibrillation and heart failure should be kept in mind when reading thorugh this figure. For the sake of clarity, we have assumed in the preparation of this figure that the contribution of the ionic channels to the atrial and the ventricular action potentials is the same (which is not). Also we did not incorporate transmural or interventricular differences in ionic currents responsible for ventricular heterogeneity in APD.

Depending on the mechanism of AF, 3 atrial action potentials can be composed: (a) normal APD in the case of CHF induced AF (upper left panel), (b) slightly shortened APD with early signs of electrical remodeling, e.g. AF existing less than 48 hours (left middle), and (c) severely shortened atrial APD due to persistent AF with electrical, contractile and structural remodeling (lower left). To the right, 3 ventricular action potentials have been illustrated, again under 3 different conditions: (a) normal ventricular APD (upper right panel), (b) prolonged APD associated with hypertrophy, e.g. hypertension (right middle), and (c) severely prolonged APD as is the case in CHF (lower right). In addition to the electrophysiologic remodeling as outlined here, rate is another important modifier of drug effects. Most class III drugs exhibit reverse use-dependancy, i.e. they act stronger during bradycardia but weaker during tachycardia.

Therefore, administration of a class III drug in the acute treatment of AF can give variable results depending on the atrial and ventricular APD as well as the atrial and ventricular rate (in AF the atrial rate is 3 to 4 times higher than normal). When the atrial repolarization is still sufficiently long. AF will be terminated due to sufficient lengthening of APD and despite reversed use-dependency. When the drug is given to tissue which is severely electrically remodeled, the results will be disappointing: no termination of AF because atrial APD is not increased. At the ventricular level, the APD will also increase after the drug and again depending on the existing situation, the end-result may differ between only mild QT-time prolongation, to the initiation of ectopic beats or in the worst scenario TdP.

The above principles also apply during chronic drug treatment. However, during chronic drug treatment one additional factor comes into play: time-dependent changes of the electrophysiologic substrate: for instance, in the course of time patients may develop heart failure due to underlying (non)cardiac disease or due to tachycardia (tachycardiomyopathy). Another important example is reversed electrical remodeling after successful electrical cardioversion of persistent atrial fibrillation (see also above, the different types of recurrences). Presumably, reversed remodeling is associated with a progressive increase in the atrial APD. As a consequence, early after the conversion the atrial anti- arrhythmic efficacy in terms of prophylaxis – even considering marked drug action due to reversed use-dependency at the relative slow atrial rate – is rather limited. However, at the same time, the ventricular pro- arrhythmic potential may be high due to electrophysiologic adaptations associated with left ventricular dysfunction and neurohumoral activation. By contrast, late after cardioversion class III drugs may appear more effective against recurrent AF drugs may appear more effective against recurrent AF and safer in terms of producing TdP.

To maintain a favorable balance between anti- and pro- arrhythmic drug effects is a well known challenge for clinicians for which the above principles may be helpful. These notions may help to avoid futile drug interventions and to target drug treatment to clinical situations where they are most effective.

Future developments

The tachycardia-induced changes in densities and function of channels governing repolarization affect the action of anti- arrhythmic drugs. A potassium channel blocker may be ineffective in the rapid pacing model due to a relative absence of its target channels. By contrast, it may be extremely effective in atrial hypertrophy related AF of short duration. Also, reversal of electrical remodeling after restoration of sinus rhythm may render AF suppressing drugs effetive initially but useless later on and vice versa. One consequence might be that after cardioversion of long-lasting AF a time dependent differential anti- arrhythmic approach applies, focused at the stage of (reversed) electrical remodeling. A targeted use of drugs may reduce the time spent on the drug which limits the exposure to pro- arrhythmia and other side effects. A promising example in this respect is the use of ami odarone during 1 month before and after cardioversion (in combination with repeat shocks if necessary) rather than prolonged use for years. To establish optimal use of anti- arrhythmic drugs, i.e. highest efficacy at the cost of only few side effects, the above considerations surely apply. It helps to avoid futile drug applications. In addition, exploration of the various atrial and ventricular electrophysiologic conditions patients experience during the course of AF may help to find specific drug targets and avoid pro- arrhythmic conditions. Indeed, future clinical strategies should take not only static factors into account such as QT time, QT dispersion, renal function and drug dosage, but also dynamic factors such as remodeling, reversed remodeling, use – and reversed use – dependency, time dependent change in renal function, and so on. Concerning new drug development, one way to prevent pro- arrhythmic activity and maintain a strong anti- arrhythmic effect against AF is to develop drugs that are atrium-specific. Alternatively, one may search for drugs safe and effective regardless heart rate and remodeling.

References

1. Vaughan Williams Em. Classification of anti- arrhythmic drugs, in Sandoe E, Flensted-Jensen E, Olesen K (eds): Cardiac arrhythmias. Sodertalije, Sweden, AB Astra, 1971: 44%,72.
2. Wellens HJJ, Smeets JL, Vos MA, Gorgels APM. Anti arrhythmic drug treatment: need for continous vigilance. Heart 1992; 67: 25-33.
3. Smeets JLRM, Allessie MA, Lammers WJEP, Bonke FIM, Hollen SJ. The wave length of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. Cric Res 1986; 58: 96-108.
4. Hondeghem LM, Synders DJ. Class III anti- arrhythmic agents have a lot of potential but a long way to go: reduced effectiveness and dangers of reverse-use dependencey. Circulation 1990; 81: 687-90.
5. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake, chronically instrumented goats. Circulation 1995; 92: 1954-68.
6. Morillo Ca, Klein GJ, Jones DL, Guiraudon Cm. Chronic rapid atrial pacing: structural, functional and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995; 91: 1588-95.
7. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs. Atrial remodeling of a different sort. Circulation 1999; 100: 87-95.
8. Nattel S, Liu L, St-Georges D. Effects of the novel anti arrhythmic agent azimilide on experimental atrial fibrillation and atrial electrophysiological properties. Cardiovasc Res 1998; 37: 627-35.
9. Wijffels MCEF, Dorland R, Alessie MA. Pharmacologic cardioversion of chronic atrial fibrillation in the got by class Ia, Ic, and III drugs: a comparison between hydroquinidine, cibenzoline, flecainide, and d-sotalol. J Cardiovasc Electorphysiol 1999; 10: 178-93.
10. Li D, Benardeau A, Nattel S. Contrasting efficacy of dofetilide in differing experimental models of atrial fibrillation. Circulation 2000; 102: 104-12.
11. Fresco C, Proclemer A. Clinical Challenge II. Management of recent onset atrial fibrillation, PaFIT-2 investigators. Eur H J 1996; 17: (Suppl. C: 41-7).
12. Vos MA, Golitsyn SR, Stangl K, et al. For the Ibutilide/Sotalol Comperator Study Group. Superiority of ibutilide (a new class III agent) over dl-sotalol in the converting atrial flutter and fibrillation. A multicenter trial with 300 patients. Heart 1998; 79: 568-75.
13. Nattel S, Hadjis T, Talajic M. The treatment of atrial fibrillation. An evaluation of drug therapy, electrical modalities and therapeutic considerations. Drugs 1994; 48: 345-71.

14. Hohnloser SH, van de Loo A, Baedeker F. Efficacy and pro-arrhythmic hazards of pharmacologic cardiversion of atrial fibrillation: prospective comparison of satolol versus quindine. J. Am Coll Cardiol 1995; 26: 852-8.
15. Norgaard BL, Wachtell K, Christensen PD, et al. Efficacy and safety of dofetilide iv. In acute termination of atrial fibrillation and flutter: a multi-center, randomized, double-blind, placebo controlled trial. Am Heart J 1999; 137: 1062-9.
16. Parkinson J, Campbell M. The quinidine treatment of auricular fibrillation. Q J Med 1929; 22: 281-303.
17. Tieleman RG, Bosker H, Van Gelder IC, Kingma T, Allessie MA, Crijns HJGM for the MEDCAr investigators. The MEDCAr Study: clinical evidence for recovery from atrial electrical remodeling after cardioversion of atrial fibrillation (abstract). Europace, in press.
18. Olsson SB, Cotoi S, Varnauskas E. Monophasic action potential and sinus rhythm stability after conversion of atrial fibrillation. Acta Med Scand 1971; 190: 381-7.
19. Attuel P, Childers R, Cauchemez B, Poveda J, Mugica J, Coumel P. Failure in the rate-adaptation of the atrial refractory periods: its relationship to vulnerability. Int J cardiol 1982; 2: 179-7.
20. Boutjdir M, Le Heuzey JY, Lavergne T, et al. Inhomogeneity of cellular refractoriness in human atrium: factor of arrhythmia? Pacing Clin Eelctrophysiol 1986; 9: 1095-100.
21. Franz M, Karasik PL, Li C, Moubarak J, Chavez M. Electrical remodeling of the human atrium: similar effects in patients with chronic atrial fibrillation and atrial flutter. J Am Coll Cardiol 1997; 30: 1785-92.
22. Olsson Sb, Broman H, Hellstrom C, Talwar KK, Volkmann R. Adaptation of human atrial muscle repolarisation after high rate stimulation. Cardiovasc Res 1984; 19: 7-14.
23. Pandozi C, Bianconi L, Villani M, et al. Electrophysiological characteristics of the human atria after cardioversion of persistent atrial fibrilation. Circulation 1998; 98: 2860-5.
24. Yu WC, Lee SH, Tai CT, et al. Reversal of atrial electrical remodeling following cardioversion of long-standing atrial fibrillation in man. Cardiovasc Res 1999; 42: 470-6.
25. Tieleman RG, Gelder IC van, Crijns HJGM, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the tria? J Am Coll Cardiol 1998; 31: 167-73.
26. Van Gelder IC, Tuinenburg AE, Schoonderwoerd BS, Tieleman RG, Crijns HJGM. Pharmacological versus directcurrent electrical cardioversion of atrial flutter and fibrillation. Am J Cardiol 1999; 84: 147R-51R.
27. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res 1997; 81: 512-25.
28. Gaspo R, Bosch RF, BouAbboud E, Nattel S. Tachycardia induced changes in Na-current in a chronic dog model of atrial fibrillation. Circ Res 1997; 81: 1045-52.
29. Van der Velden HM, Ausma J, Rook M, et al. Gap junctional remodeling in relation to stabilization of atrial fibrillation in the goat. Cardiovasc Res 2000; 46: 476-86.
30. Van Wagoenr DR, Pond Al, McCarthy PM, Timmer JS, Nerbonne JM. Outward K-current densities and Kv 1.5 expression are reduced in chronic human atrial fibrillation. Circ Res 1997; 80: 772-81.
31. Bosch RF, Zeng X, Grammer JB, Popovic K, Mewis C, Kuhlkamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. Cardiovasc Res 1999; 44: 121-31.
32. Brundel BJJWM, Van Gelder IC, Henning RH, et al. Alterations in potassium channel gene expression in atria of patients with persistent and paroxysmal atrial fibrillation. Differential regulation of protein and mRNA levels for K+ channels. J Am Coll Cardiol, in press.
33. Ausma J, Wijffels M, Thone F, Wouters L, Alessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997; 96: 3157-63.
34. Selzer A, and Wray HW. Quinidine syncope – paroxysmal ventricular fibrillation occuring during treatment of chronic atrial arrhythmias. Circulation 1964; 30: 17-26.
35. Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. Arch Mal Coeur 1966; 59: 263-72.
36. Coplen SE, Antman Em, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials [erratum Circulation 1991; 83: 714]. Circulation 1990; 82: 1106-16.
37. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Anti- arrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke prevention in atrial Fibrillation Investigators. J Am Coll Cardiol 1992; 20: 527-32.
38. Houltz B, Darpo B, Edwarsson N, et al. Electrocardiographic and clinical predictors of torsade de pointes induced by almokalant infusion in patients with chronic atrial fibrillation or flutter: a prospective study. PACE 1998; 21: 1044-57.
39. Vos MA, Verduyn SC, Gorgels APM, Lipcsei GC, Wellens HJJ. Reproducible induction of early afterdepolarizations and Torsade de Pointes arrhythmias by d-sotalol and pacing in dogs with chronic AV-block. Circulation 1995; 91: 864-72.
40. Verduyn SC, Vos MA, Van der Zande J, Van der Hulst FF, Wellens HJJ. Role of interventricular dispersion of repolarization in acquired Torsade de Pointes arrhythmias reversal by Magnesium. Cardiovasc Res 1997; 34: 453-63.

41. Verduyn SC, Vos MA, Van der Zande J, Kulscar A, Wellens HJJ. Further observations to confirm the importance of dispersion of repolarization anrd early afterdepolarizations in the genesis of acquired Torsade de Pointes arrhythmias: a comparison between almokalant and d-sotalol using the dog as its own control. J Am Coll Cardiol 1997; 30: 1575-84.
42. Vos MA, De Groot SHM, Verduyn SC, et al. Enhanced susceptibility for acquired Torsade de Pointes arrhythmias in the dog with chronic, complete AV-block is related to cardiac hypertrophy and electrical remodeling. Circulation 1998; 98: 1125-35.
43. Volders PGA, Sipido KR, Vos MA, Kulscar A, Verduyn SC, Wellens HJJ. Cellular basis of biventricular hypertrophy and pro- arrhythmia in dogs with chronic, complete AV-block and acquired Torsade de Pointes arrhythmias. Circulation 1998; 98: 1136-47.
44. Volders PGA, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K+ current in dogs with chronic complete atrioventricular block and acquired Torsade de Pointes. Circulation 1999; 100: 2455-61.
45. Sipido KR, Volders PGA, de Groot SHM, Vos MA. Enhanced cardiac contractile performance and SR Ca-release in dogs with chronic, complete AV-block. Circulation 2000; 102: 2137-44.