An Overview of Contemporary Approaches to Antiarrhythmic Therapy

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This review discusses the evolution in the approach to the therapy of cardiac arrhythmias that has occurred during the past 2 decades. The major changes have been driven by advances in understanding arrhythmia mechanisms, in bioengineering, and in clinical trials. It seems likely that progress in understanding the cellular and molecular basis of arrhythmias and their response to drug therapy may allow further identification of patient subsets in which specific therapies are indicated or contraindicated. (*Jpn Circ J* 1999; 63: 655–658)

Key Words: Arrhythmia; Clinical trials; Ion channels

Two decades ago, antiarrhythmic therapy consisted of digitalis (and perhaps β -blockers) for paroxysmal atrial tachycardia ('PAT'); digoxin, quinidine, procainamide, or β -blockers for atrial fibrillation and flutter; quinidine, procainamide, phenytoin, and occasionally β -blockers for premature ventricular contractions (PVCs); and the same drugs for patients with recurrent sustained ventricular tachycardia (VT) or those very few patients who had survived an out-of-hospital cardiac arrest due to ventricular fibrillation (VF). Therapeutic approaches to all of these entities have changed dramatically. This overview will outline the advances that have driven changes in practice. A summary of ongoing areas of clinical and basic research that are likely to further impact arrhythmia management will be presented.

Ablation for Arrhythmic Cure

Ablation for arrhythmic cure is predicated on an understanding of underlying mechanisms. The development of an understanding of the precise locations of fixed macro-reentrant circuits, notably in the Wolff-Parkinson-White syndrome, allowed surgeons,¹ and subsequently electrophysiologists^{2–5} to permanently interrupt circuits and to cure patients. Indeed, it can be said that the only cardiovascular physicians who should properly use the term 'cure' are electrophysiologists who perform ablation of this type. Recognition that some macro-reentrant circuits may not be fixed by strict anatomic landmarks but may also depend on functional characteristics (eg, block at rapid rates) extended the highly successful application of ablative therapies to atrial flutter^{6,7} atrioventricular nodal reentrant tachycardia^{8,9} and ischemic VT arising at the border zone of an old myocardial infarction (MI).^{10,11} Further, electrophysiologic techniques are now routinely used to locate, and then ablate, foci of automatic activity in both the atrium and ventricle. Although catheter ablation does carry with it small but real risks, it has nevertheless emerged as the

treatment of choice for many patients with symptomatic or recurrent episodes of these arrhythmias!²

Patient Subsets

Identifying patient subsets can direct therapy. We now recognize different clinical subsets, and different underlying mechanisms, that drive therapeutic considerations. For example, among the ventricular arrhythmias, post-MI PVCs are no longer an appropriate target for treatment!¹³ Ventricular tachycardia arising in the normal heart, often on exercise stress and with distinctive electrocardiographic patterns, lends itself particularly well to ablation in the right ventricular outflow tract or the left posterior fascicle!¹⁴ Rapid polymorphic VT arising without an antecedent pause and at very short coupling intervals, raises the suspicion of ongoing myocardial ischemia as an important contributor!¹⁵ Patients with left ventricular scar due to remote MI frequently have sustained monomorphic VT that lends itself well to ablation. Sustained monomorphic VT arising in a patient with cardiomyopathy raises the possibility of bundle branch re-entry, an entity also treatable by ablation!¹⁶

Similarly, recognition of multiple subsets of the congenital long QT syndromes (LQTS), with different underlying mutations,¹⁷ may drive therapy in that disease. With the identification of specific disease genes has come an increasing understanding of the underlying pathophysiology. This understanding, in turn, has provided a firm rationale for the use of adrenergic therapies in most patients with the disease, but has raised the possibility that other therapies, such as sodium channel block, may also be appropriate for some subsets!¹⁸ Further, genetic studies in LQTS are now identifying patients with minimal or no clinical manifestations at baseline!¹⁹ Some of these patients present with Torsades de Pointes upon exposure to a QT-prolonging drug!^{20–23} Another rare genetic disease that may confer risk upon exposure to exogenous stressors such as drugs or ischemia is the Brugada syndrome. This entity is characterized by a distinctive set of electrocardiographic (ECG) changes (right precordial J point elevation), and sudden death at night due to VF, primarily in young men!^{24–26} In some patients the electrocardiographic pattern is permanent, whereas in others it is evanescent. The ECG pattern can be brought out in some patients by sodium channel blockers such as flecainide, procainamide or ajma-

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line, or by β -blockade, and can be ameliorated by isoproterenol.^{27,28} Studies demonstrating that the ECG manifestations, and rapid re-entrant excitation, could be elicited by sodium channel block in an in vitro right ventricular preparation^{29,30} provided another crucial clue that led to identification of function-altering mutations in the sodium channel gene in some patients with the Brugada syndrome.³¹ These in vitro studies also suggested that the manifestations of the syndrome would be exacerbated by myocardial ischemia. Thus, one could create a scenario wherein patients with mutations might not have any overt phenotype until exposed to an ischemic stress, when the likelihood of VF would be increased.

Another arrhythmia in which identifying patient subsets has begun to have an impact on therapeutic approaches is atrial fibrillation. One subset of patients that is useful to identify are those with predominant atrial flutter whose symptoms may be improved by ablation. Similarly, patients with very frequent episodes of paroxysmal atrial fibrillation, especially those that appear to have relatively organized (atrial tachycardia-like) activity at the initiation of the arrhythmia, may be candidates for ablation of foci of abnormal activity, often within the pulmonary veins.^{32,33} Placement of linear lesions within the atria to prevent perpetuation of re-entrant excitation that underlies atrial fibrillation can be accomplished surgically as the maze procedure³⁴ and catheter-based approaches are under active investigation. Finally, a familial form of the arrhythmia has been described and the chromosomal locus has been assigned.³⁵ Although the specific gene, and the function-altering mutations in it, have not yet been identified, it seems likely that, as with LQTS and the Brugada syndrome, an understanding of underlying molecular mechanisms may have important implications for therapy not just for the familial entity, but also for the common acquired arrhythmia.

Partnership With Bioengineering

A partnership with the bioengineering community has advanced care for patients with arrhythmias. Two decades ago, 'device' therapy for cardiac arrhythmias was confined to relatively primitive (at least by today's standards) bradypacing devices. The development of implantable cardioverter/defibrillators (ICDs) has revolutionized care for patients with serious ventricular arrhythmias. Among those judged to be at very high risk of recurrent syncope or death due to VF (eg, those who have already been resuscitated from one cardiac arrest), placement of an ICD confers better survival than drug therapy. In the AVID trial, survival at 2 years in patients randomized to ICD therapy was 82%, whereas that in patients randomized to antiarrhythmic drugs (primarily amiodarone) was 75%.³⁶ However, in this and other trials (such as CIDS and CASH, which showed a non-significant trend to ICD benefit), there is an increased use of β -blockers among patients randomized to device therapy (often to reduce shocks due to supraventricular arrhythmias), potentially confounding interpretation of the results.

Advances in device engineering have, almost paradoxically, raised further questions about which subset of patients are most appropriate for this therapy. Because the devices are becoming easier to implant (but perhaps correspondingly more difficult to manage because of their increasingly sophisticated programming capabilities), there may be a tendency for patients in other subsets judged, for one reason or another, to be at high risk for sudden death, to receive the

devices. Whether such widespread use of an expensive therapy is justified in subsets at lower risk than those studied in AVID or similar trials requires further study.

Clinical Trials

Clinical practice is improved when driven by appropriately designed clinical trials. By the beginning of the 1980s, β -blockade was becoming well established as an appropriate therapy for survivors of MI. The development of well-tolerated therapies that were highly effective in suppressing PVCs then allowed a test of the 'PVC hypothesis' in the CAST study.¹³ The demonstration in CAST that flecainide, encainide, and moricizine actually increased mortality despite suppressing PVCs was important not only for further understanding arrhythmia mechanisms, but also for thinking about alternate pharmacologic and nonpharmacologic antiarrhythmic strategies. Trials of ICD therapy in high-risk secondary prevention (ie, in patients who have already presented with a sustained ventricular tachyarrhythmia event) demonstrate a benefit of ICDs, as outlined before.³⁶ A more vexing question is whether subsets of patients can be identified who might benefit from primary prevention (ie, prevention of a first sustained VT/VF event in a patient at risk). In the MADIT study, a benefit of ICD therapy over 'conventional' therapy was demonstrated, although the study was small and included a bias in favor of β -blockers, as described earlier.^{37,38} The recently completed MUSTT studied patients with coronary disease, depressed ejection fraction, and asymptomatic nonsustained VT. Patients then underwent electrophysiologic testing and those with inducible VT were then randomized to standard therapy or active antiarrhythmic therapy. The overall result was that survival was better in patients randomized to active therapy compared with those on conventional therapy, and unlike in other trials, there was actually less β -blocker use in the active therapy arm. Importantly, the difference in survival was driven essentially exclusively by patients in the active treatment arm who received an ICD and, in fact, patients in the active treatment arm who received drugs (and no ICD) fared slightly worse than standard therapy patients (ie, those receiving no antiarrhythmic). Although it should be recognized that this very powerful result does not represent an analysis pre-planned by study design, nor was assignment to ICD or antiarrhythmic drug in any way randomized, it nevertheless provides further evidence that some subsets of patients who might benefit from ICD therapy in primary prevention could be identifiable. Ongoing trials are assessing this idea in cardiomyopathy. An issue in all these trials is power: as event rates become lower in the control arm, it becomes increasingly difficult to demonstrate benefit of any therapy unless very large numbers of patients (thousands, and in some cases tens of thousands) of patients are randomized. This is a daunting task in any trial, let alone one evaluating a complex device.

In atrial fibrillation, a finding of major importance from large clinical trials was the demonstration that anticoagulation with coumadin dramatically reduces the incidence of stroke.³⁹ This result has been reproduced in multiple trials and although there are some outstanding questions, such as the role of aspirin, the optimal target INR, or the treatment of the very elderly, the result nevertheless has widespread and important applicability to cardiovascular care. New drugs are in development for maintenance of sinus rhythm

in atrial fibrillation. Because of the results of CAST, it seems likely that such development programs will need to include survival data in large numbers of patients randomized to drug or placebo. Indeed, the dextro-rotary isomer of sotalol was found to increase mortality in one such trial, the SWORD study.⁴⁰ Interestingly, dofetilide, a drug with very similar electrophysiologic properties to d-sotalol, was found to produce no change in mortality in patients with advanced heart failure or those with recent MI in the DIAMOND trial. The differences in outcome between DIAMOND and SWORD likely reflect differences in trial design, particularly titration to relatively high doses of d-sotalol in SWORD versus a more conservative QT-limited (and in-hospital initiation) strategy in DIAMOND. ALIVE is a large mortality trial comparing placebo with azimilide, another drug under development for atrial fibrillation.

The National Heart, Lung, and Blood Institute is sponsoring AFFIRM, a very large (5,300 patients) trial comparing a rate control strategy with a rhythm control strategy in patients with atrial fibrillation.⁴¹ The primary endpoint of this ongoing trial is death. Another interesting, recently completed study is the Canadian Trial of Atrial Fibrillation (CTAF). CTAF randomized 400 patients, half with paroxysmal atrial fibrillation and half with persistent atrial fibrillation (ie, patients with atrial fibrillation in whom sinus rhythm was restored by DC cardioversion). Patients were randomized to receive low dose amiodarone, or comparator therapy (sotalol or propafenone) one quarter sotalol, and one quarter propafenone. The primary endpoint was time to first recurrence of symptomatic atrial fibrillation (documented by transtelephonic monitoring). At the end of 1 year, approximately 30% of patients randomized to amiodarone had reached the primary endpoint, whereas nearly 70% of those randomized to sotalol or propafenone had done so. The incidence of side effects was similar in the 2 groups, although there was a 2.5% incidence of pulmonary adverse effects in the amiodarone-treated group. Thus, studies such as CTAF, DIAMOND and AFFIRM, along with molecular studies, ablative approaches, and atrial defibrillators in selected patients, are likely to change therapeutic approaches to this most common and vexing arrhythmia.

Human Genome

A very important scientific advance of the early 21st century will be completion of the initial sequence of the human genome. This will provide a crucial set of reagents to scientists interested in understanding molecular mechanisms underlying variability in human physiology and its response to drugs. It therefore seems likely that this new tool, combined with evolving understanding of mechanisms, patient subsetting, and bioengineering, will continue to move the electrophysiology community forward to meet the challenge of providing rational and improved therapy for the treatment and prevention of cardiac arrhythmias.

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References

- Wallace AG, Sealy WC, Gallagher JJ, Svenson RH, Strauss HC, Kasell J: Surgical correction of anomalous left ventricular pre-excitation: Wolff-Parkinson-White (type A). *Circulation* 1974; **49**: 206–213
- Gallagher JJ, Svenson RH, Kasell JH, German LD, Bardy GH, Broughton, et al: Catheter technique for closed-chest ablation of the atrioventricular conduction system. *N Engl J Med* 1982; **306**: 194–200
- Weber H, Schmitz L: Catheter technique for closed-chest ablation of an accessory atrioventricular pathway. *N Engl J Med* 1983; **308**: 653–654
- Jackman WM, Friday KJ, Scherlag BJ, Dehning MM, Schechter E, Reynolds, et al: Direct endocardial recording from an accessory atrioventricular pathway: localization of the site of block, effect of antiarrhythmic drugs, and attempt at nonsurgical ablation. *Circulation* 1983; **68**: 906–916
- Morady F, Scheinman MM: Transvenous catheter ablation of a posteroseptal accessory pathway in a patient with the Wolff-Parkinson-White syndrome. *N Engl J Med* 1984; **310**: 705–707
- Touboul P, Saoudi N, Atallah G, Kirkorian G: Electrophysiologic basis of catheter ablation in atrial flutter. *Am J Cardiol* 1989; **64**: 793–823
- Saoudi N, Atallah G, Kirkorian G, Touboul P: Catheter ablation of the atrial myocardium in human type I atrial flutter. *Circulation* 1990; **81**: 762–771
- Epstein LM, Scheinman MM, Langberg JJ, Chilson D, Goldberg HR, Griffin JC: Percutaneous catheter modification of the atrioventricular node: A potential cure for atrioventricular nodal reentrant tachycardia. *Circulation* 1989; **80**: 757–768
- Haissaguerre M, Warin JF, Lemetayer P, Saoudi N, Guillem JP, Blanchot P: Closed-chest ablation of retrograde conduction in patients with atrioventricular nodal reentrant tachycardia. *N Engl J Med* 1989; **320**: 426–433
- Fitzgerald DM, Friday KJ, Wah JA, Lazzara R, Jackman WM: Electrogram patterns predicting successful catheter ablation of ventricular tachycardia. *Circulation* 1988; **77**: 806–814
- Morady F, Frank R, Kou WH, Tonet JL, Nelson SD, Kounde S, et al: Identification and catheter ablation of a zone of slow conduction in the reentrant circuit of ventricular tachycardia in humans. *J Am Coll Cardiol* 1988; **11**: 775–782
- Morady F: Radio-frequency ablation as treatment for cardiac arrhythmias. *N Engl J Med* 1999; **340**: 534–544
- The CAST Investigators: Preliminary Report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; **321**: 406–412
- Morady F, Kadish AH, DiCarlo L, Kou WH, Winston S, deBuitler M, et al: Long-term results of catheter ablation of idiopathic right ventricular tachycardia. *Circulation* 1990; **82**: 2093–2099
- Wolfe CL, Nibley C, Bhandari A, Chatterjee K, Scheinman M: Polymorphous ventricular tachycardia associated with acute myocardial infarction. *Circulation* 1991; **84**: 1543–1551
- Caceres J, Jazayeri M, McKinnie J, Avitall B, Denker ST, Tchou P, et al: Sustained bundle branch reentry as a mechanism of clinical tachycardia. *Circulation* 1989; **79**: 256–270
- Roden DM, Lazzara R, Rosen MR, Schwartz PJ, Towbin JA, Vincent GM, et al: Multiple mechanisms in the long QT syndrome: Current knowledge, gaps, and future directions. *Circulation* 1996; **94**: 1996–2012
- Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cant F, Towbin JA, et al: Long QT syndrome patients with mutations of the *SCN5A* and *HERG* genes have differential responses to Na⁺ channel blockade and to increases in heart rate: Implications for gene-specific therapy. *Circulation* 1995; **92**: 3381–3386
- Priori SG, Napolitano C, Schwartz PJ: Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999; **99**: 529–533
- Napolitano C, Priori SG, Schwartz PJ, Cantu F, Paganini V, Matteo PS, et al: Identification of a long QT syndrome molecular defect in drug-induced Torsades de Pointes. *Circulation* 1997; **96**: I-211
- Schulze-Bahr E, Haverkamp W, Hordt M, Wedekind H, Borggrefe M, Funke H: Do mutations in cardiac ion channel genes predispose to drug-induced (acquired) long QT syndrome? *Circulation* 1997; **96**: I-211
- Donger C, Denjoy I, Berthet M, Neyroud N, Cruaud C, Bennaceur M, et al: KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. *Circulation* 1997; **96**: 2778–2781
- Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, et al: MiRP1 forms K⁺ potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999; **97**: 175–187
- Martini B, Nava A, Thiene G, Buja GF, Canciani B, Scognamiglio R, et al: Ventricular fibrillation without apparent heart disease: description of six cases. *Am Heart J* 1989; **118**: 1203–1209
- Brugada P, Brugada J: Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and

- electrocardiographic syndrome: A multicenter report. *J Am Coll Cardiol* 1992; **20**: 1391–1396
26. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, et al: Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997; **96**: 2595–2600
 27. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S: Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996; **27**: 1061–1070
 28. Roden DM, Wilde AA: Drug-induced J point elevation: a marker for genetic risk of sudden death or ECG curiosity? *J Cardiovasc Electrophysiol* 1999; **10**: 219–223
 29. Krishnan SC, Antzelevitch C: Flecainide-induced arrhythmia in canine ventricular epicardium: Phase 2 reentry? *Circulation* 1993; **87**: 562–572
 30. Lukas A, Antzelevitch C: Differences in the electrophysiological response of canine ventricular epicardium and endocardium to ischemia: Role of the transient outward current. *Circulation* 1993; **88**: 2903–2915
 31. Chen QY, Kirsch GE, Zhang DM, Brugada R, Brugada J, Brugada P, et al: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998; **392**: 293–296
 32. Jais P, Haissaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, et al: A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation* 1997; **95**: 572–576
 33. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; **339**: 659–666
 34. Cox JL, Boineau JP, Schuessler RB, Jaquiss RDB, Lappas DG: Modification of the maze procedure for atrial flutter and atrial fibrillation. 1. Rationale and surgical results. *J Thorac Cardiovasc Surg* 1995; **110**: 473–484
 35. Brugada R, Tapscott T, Czerskiewicz GZ, Marian AJ, Iglesias A, Mont, et al: Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997; **336**: 905–911
 36. Mcanulty J, Halperin B, Kron J, Larsen G, Raitt M, Swenson R, et al: A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; **337**: 1576–1583
 37. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996; **335**: 1933–1940
 38. Friedman PL, Stevenson WG: Unsustained ventricular tachycardia: To treat or not to treat. *N Engl J Med* 1996; **335**: 1984–1985
 39. Singer DE: Anticoagulation for atrial fibrillation: epidemiology informing a difficult clinical decision. *Proc Assoc Am Physicians* 1996; **108**: 29–36
 40. Waldo AL, Camm AJ, DeRuyter H, Friedman PL, MacNeil DJ, Pitt B, et al: Survival with oral d-Sotalol in patients with left ventricular dysfunction after myocardial infarction: Rationale, design, and methods (the SWORD trial). *Am J Cardiol* 1995; **75**: 1023–1027
 41. Wyse DG, Anderson JL, Antman EM, Cooper ES, Dalquist JE, Davis KB, et al: Atrial fibrillation follow-up investigation of rhythm management: The AFFIRM study design. *Am J Cardiol* 1997; **79**: 1198–1202