



Rate Control in Atrial Fibrillation: Avoiding Morbidity

Thomas D. Callahan, IV, MD, FACC, FHRS.

Introduction

Despite great strides in our understanding and treatment of atrial fibrillation over the past decade or so, much remains to be learned. Debate continues over the relative merits of rate versus rhythm control strategies. More recently, even the optimal targets for rate control have come into question. Specifically, the results of the RACE II trial support a more lenient rate control target compared to more traditional targets. This paper will review the role elevated heart rates play in the morbidity associated with atrial fibrillation, tools available for rate control and their relative merits as well as the targets for rate control.

There is no doubt that atrial fibrillation is associated with profound morbidity. Atrial fibrillation can be associated with astounding morbidity. The cost associated with atrial fibrillation and its sequelae is estimated at over 6.5 billion dollars.¹ A European study of hospitalized patients with atrial fibrillation by ECG or holter found close to 70% of patients experienced symptoms.² Despite treatment, RACE and RACE II reported exacerbation of heart failure in approximately 4% of patients,³ and myocardial infarction occurred in 6% of all patients in AFFIRM.⁴ While the exact incidence is difficult to determine, atrial fibrillation is the most common cause of tachycardia-mediated cardiomyopathy.⁵⁻⁷ Finally, in patients with atrial fibrillation and left ventricular dysfunction, some element of tachycardia mediated cardiomyopathy is seen in 25-50%.⁸⁻¹⁰

What is more difficult to discern is the contribution of elevated heart rates in atrial fibrillation to the morbidity relative to the atrial fibrillation itself. Multiple trials including RACE, AFFIRM, PIAF and STAF have compared a rate control strategy to maintenance of sinus rhythm with anti-arrhythmics and found that patients managed with rate control have similar symptom reduction, mortality rates and rates of stroke and heart failure progression as those managed with anti-arrhythmics.¹¹ However, this does not mean that the risk associated with atrial fibrillation is solely the result of elevated heart rates. Other data implicates atrial fibrillation itself in generation of morbidity and not simply elevated heart rates. Analyses of AFFIRM and DIAMOND support a mortality benefit from the maintenance of sinus rhythm and it has been postulated that this benefit is completely offset by the risks of currently available antiarrhythmics.^{12,13} Pulmonary vein isolation offers a potential cure for atrial fibrillation, however, it too carries potential morbidity and less-than-perfect success rates. Studies to tell us how it stacks up to anti-arrhythmics and rate control are still underway, but should provide additional insight into the contributions of arrhythmia and elevated heart rate in the development morbidity in atrial fibrillation.

With limited data regarding the contributions of rate and rhythm to the morbidity of atrial fibrillation, the decision to choose a rate control or a rhythm control strategy may be challenging. Currently, symptoms are the most helpful fac-

Corresponding Address : Thomas D. Callahan, IV, MD, FACC, FHRS, Associate Program Director, Cardiology Fellowship, Robert and Suzanne Tomsich, Dept of Cardiovascular Medicine, Sydell and Arnold Miller Family Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue / J2-2, Cleveland, Ohio 44195.

tor in choosing a strategy. When symptoms persist despite adequate heart rate control, a rhythm control strategy is clearly indicated. Conversely, in patients who are completely asymptomatic in atrial fibrillation, rate control may be sufficient. Challenges arise when patients report mild symptoms or nebulous symptoms such as fatigue or shortness of breath which could be the result of other processes such as pulmonary disease, obesity or deconditioning. In these cases we often pursue a rhythm control strategy and fall back to rate control if symptoms do not improve when sinus rhythm is restored. Other challenges include patients with prior CVA and young patients with atrial fibrillation. In these cases, data supporting the mortality benefit of maintenance of sinus rhythm, while limited, may seem to have more sway. Finally, patients refractory to heart rate control, with very elevated ventricular rates despite medical therapy, would likely benefit from maintenance of sinus rhythm.

The goals of therapy with rate control in atrial fibrillation are quite simple: To minimize or eliminate symptoms and to prevent morbidity associated with elevated heart rates. That said, the target heart rate that best achieves those goals are less certain. Until recently, an average heart rate of less than 80 beats per minute was recommended.¹⁴ Since many patients with satisfactory resting heart rates in atrial fibrillation will develop marked tachycardia with exertion, heart rates of 90 to 115 with submaximal exercise or a maximum heart rate of less than 110 beats per minute during a 6 minute walk have also been recommended as goals for therapy. A sub-analysis of the Affirm data grouped patients according to achieved heart rate and found no difference in survival free from cardiovascular hospitalization or death from any cause.¹⁵ In RACE II, patients with atrial fibrillation were randomized to strict heart rate control (<80 bpm at rest and <110 bpm with moderate exercise) or lenient heart rate control (<110 bpm at rest). No difference was seen between the groups with regard to the composite endpoint which included death from cardiovascular causes, hospitalization for CHF, CVA, systemic embolization, major bleed or life-threatening arrhythmias.³ However, it should be noted that mean resting heart rates did not differ greatly with a mean resting heart rate of 85 in the lenient group and 76 in the strict control group. These findings are also tempered

by follow-up of only a few years, and it is possible that certain subgroups may benefit from tighter control. New or increasing symptoms should prompt an investigation with either ambulatory cardiac monitoring and/or exercise testing to ensure satisfactory rate control.

While goals of therapy may be changing, our tools for heart rate control have changed little recently. Pharmacologic strategies are typically used. AV node ablation, while effective, necessitates implantation of a pacing device with the attendant risks. The mainstays of pharmacologic rate control are beta-blockers, calcium channel blockers and digoxin. Less frequently used medications include amiodarone, dronedarone and sotalol.

Beta-blockers are generally effective for rate control in patients with atrial fibrillation, but not all beta-blockers are equivalent in this regard. Blockade of the beta-1 receptor is primarily responsible for the heart rate effects of beta blockers. The beta-2 receptor blockade effects predominantly the blood vessels and bronchi with little effect on heart rate. As a result, beta-1 selective agents such as atenolol, esmolol, metoprolol and bisoprolol, are generally more effective for heart rate control in patients with atrial fibrillation. Patients with a history of congestive heart failure may be prescribed non-selective beta-blocker such as carvedilol preferentially. This can be titrated to suppress the ventricular rate, but in patients on non-selective beta-blockers in whom rate control is not achieved, we will typically change to a Beta-1 selective drug. Concomitant use of multiple beta-blockers should be avoided. The side-effects of fatigue, hypotension, worsening reactive airway disease, depression, and increased risk of hypoglycemia in insulin-dependent patients may be seen patients on beta-blockers and may limit the maximum tolerated dose.

Calcium channel blockers are also effective in heart rate control in atrial fibrillation. As with beta-blockers, the calcium channel blockers are not all equally effective. Calcium channel blockers block the L-type calcium channels found in vascular smooth muscle, cardiac myocytes and cardiac nodal tissue. The dihydropyridine calcium channel blockers exert their effect primarily on the L-type calcium channels of the vascular smooth muscle. Non-dihydropyridine calcium channel

blockers, verapamil and diltiazem, are relatively selective toward cardiac L-type calcium channels. As a result, the non-dihydropyridine calcium channel blockers may provide control of the heart rate in atrial fibrillation by slowing conduction down the AV node while the dihydropyridines are largely ineffective in that regard. Compared to beta-blockers, non-dihydropyridine calcium channel blockers alone do not appear quite as efficacious as beta-blockers alone for heart rate control.¹⁶ Diltiazem and verapamil may have a negative inotropic effect as well and are relatively contraindicated in patients with systolic heart failure. Verapamil may also decrease the excretion of digoxin by 30%.

Digoxin has long been used for heart rate control in patients with atrial fibrillation. It acts by enhancing vagal tone resulting in slowing of the sinus rate and prolonging AV node refractoriness.^{17,18} However, with even minimal activity, sympathetic activation typically overwhelms any parasympathetic activation of the AV node. Thus, digoxin may be effective in bed-bound patients or hospitalized patients but may be much less effective when the patient leaves the hospital and is active.¹⁹ When used in combination with beta-blockers or calcium channel blockers, however, digoxin improves heart rate control even in active patients.^{20,21} The combination of beta-blockers with digoxin may be somewhat more efficacious than calcium channel blockers with digoxin.¹⁶

While classified as anti-arrhythmics, sotalol, amiodarone and dronedarone have been shown to decrease the average heart rate for patients in atrial fibrillation.²²⁻²⁶ Guidelines support the use of amiodarone for rate control in patients with CHF.²⁷ In our practice amiodarone and dronedarone are used for rate control only in special circumstances given the less-favorable side-effect profile of these medications compared to other available rate control agents. Additionally, the risk of chemical cardioversion with the use of amiodarone and dronedarone may limit their use as rate control agents. Invasive strategies for rate control are usually reserved for those who cannot tolerate a pharmacologic strategy or those in whom medications have failed. AV node ablation is highly effective at reducing ventricular rates in atrial fibrillation. Recurrence of conduction is seen about 5% of patients undergoing complete AV node ablation.²⁸ However, this commits the patient to an implant-

able pacemaker or defibrillator for life with all the attendant risks including infection and RV pacing-mediated cardiomyopathy. Furthermore, PABA-CHF randomized patients with persistent AF and a depressed EF to either PVI or AV node ablation and biventricular pacemaker implantation and found patient randomized to PVI performed better on a 6 minute walk, and reported a higher quality of life.²⁹ When the strategy of AV node ablation is employed for rate control in AF, implantation of a permanent pacemaker or defibrillator is often performed several days to weeks in advance as lead dislodgement is more common early after implant. Sudden cardiac death may be seen after AV node ablation for atrial fibrillation and is thought to be secondary to changes in cardiac repolarization from long-standing, elevated ventricular rates. Programming the lower rate limit to 80 beats per minute for the first 6 weeks after AV node ablation greatly reduces the risk of sudden cardiac death after this procedure.³⁰⁻³² When patients fail a rate control strategy our practice has been to pursue rhythm control with either medications or ablation. AV node ablation and pacemaker or defibrillator implantation is typically reserved for patients who have failed pharmacologic rate and rhythm control and are deemed too frail to tolerate invasive attempts at rhythm control.

AV node modification may be performed by targeting the slow pathway region and progressively ablating more superiorly on the septum until resting rates of 60 to 80 beats per minute at rest and rates of less than 120 beats per minute with isoproterenol or atropine are achieved. This technique is successful in controlling the heart rate in 25 to 85% of patients.³³⁻⁴⁰ AV node modification is used rarely compared to AV node ablation as it still often results in complete AV block and is limited by relatively frequent recurrence of rapid ventricular response.

The ventricular rate is often elevated in patients with atrial fibrillation and these elevated rates do contribute to morbidity. The mainstays of rate control, beta-blockers, calcium channel blockers and digoxin, either alone or in combination, are effective in controlling the heart rates in many patients. When these fail, ablation of the AV node and implantation of a pacemaker allows absolute control of the heart rate. However, much remains to be learned about how best to use these tools. Aggres-

sive use of rate control agents to achieve “normal” resting heart rates may, in some cases, be counterproductive. AV node ablation leaves the patients forever dependent on a pacemaker, and in some cases, patients remain symptomatic from the atrial arrhythmia. More data is required to determine if certain cohorts benefit from tighter heart rate control. Finally, heart rate control may be inferior to maintenance of sinus rhythm in many patients if not for the toxicities and potential complications of our tools for rhythm control. While we await the results of trials to help answer these questions, patient symptoms continue to serve as one of the most important guides in treatment of challenging and prevalent disorder.

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References

- Martin-Doyle W, Reynolds MR. Is AF Ablation Cost Effective? *Journal of atrial fibrillation* 2010;2:727-39.
- Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *European heart journal* 2005;26:2422-34.
- Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *The New England journal of medicine* 2010;362:1363-73.
- Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *The New England journal of medicine* 2002;347:1825-33.
- Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation* 2009;119:2516-25.
- Nerheim P, Birger-Botkin S, Piracha L, Olshansky B. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. *Circulation* 2004;110:247-52.
- Van Gelder IC, Crijns HJ, Blanksma PK, et al. Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *The American journal of cardiology* 1993;72:5606.
- Edner M, Caidahl K, Bergfeldt L, Darpö B, Edvardsson N, Rosenqvist M. Prospective study of left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial fibrillation. *British heart journal* 1995;74:261-7.
- Luchsinger JA, Steinberg JS. Resolution of cardiomyopathy after ablation of atrial flutter. *Journal of the American College of Cardiology* 1998;32:205-10.
- Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. *Mayo Clinic proceedings Mayo Clinic* 2000;75:790-5.
- Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *The New England journal of medicine* 2002;347:1834-40.
- Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* 2004;109:1509-13.
- Pedersen OD, Bagger H, Keller N, Marchant B, Køber L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigation of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation* 2001;104:292-6.
- European Heart Rhythm A, Heart Rhythm S, Fuster V, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:854-906.
- Cooper HA, Bloomfield DA, Bush DE, et al. Relation between achieved heart rate and outcomes in patients with atrial fibrillation (from the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] Study). *Am J Cardiol* 2004;93:1247-53.
- Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol* 1999;33:304-10.
- Goodman DJ, Rossen RM, Cannom DS, Rider AK, Harrison DC. Effect of digoxin on atrioventricular conduction. Studies in patients with and without cardiac autonomic innervation. *Circulation* 1975;51:251-6.
- JP D. In: Zipes DP, Jalife J, ed. *Cardiac Electrophysiology: From Cell to Bedside*. 3rd ed. Philadelphia: WB Saunders; 2000.
- Rubin DA, Nieminski KE, Reed GE, Herman MV. Predictors, prevention, and long-term prognosis of atrial fibrillation after coronary artery bypass graft operations. *The Journal of thoracic and cardiovascular surgery* 1987;94:331-5.
- Stafford RS, Robson DC, Misra B, Ruskin J, Singer DE. Rate control and sinus rhythm maintenance in atrial fibrillation: national trends in medication use, 1980-1996. *Archives of internal medicine* 1998;158:2144-8.
- Wattanasuwat N, Khan IA, Mehta NJ, et al. Acute ventricular rate control in atrial fibrillation: IV combination of diltiazem and digoxin vs. IV diltiazem alone. *Chest* 2001;119:502-6.
- Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *The New England journal of medicine* 2009;360:668-78.

23. Kochiadakis GE, Kanoupakis EM, Igoumenidis NE, Mavrakis HE, Kafarakis PK, Vardas PE. Efficacy and safety of oral amiodarone in controlling heart rate in patients with persistent atrial fibrillation who have undergone digitalisation. *Hellenic journal of cardiology : HJC = Hellēnikē kardiologikē epitheōrēsē*;46:336-40.
24. Lombardi F, Borggrefe M, Ruzyllo W, Lüderitz B. Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial. *European heart journal* 2006;27:2224-31.
25. Perelman MS, McKenna WJ, Rowland E, Krikler DM. A comparison of bepridil with amiodarone in the treatment of established atrial fibrillation. *British heart journal* 1987;58:339-44.
26. Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *The New England journal of medicine* 2007;357:987-99.
27. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. *Journal of the American College of Cardiology* 2006;48:e149-e246.
28. Brignole M, Gianfranchi L, Menozzi C, et al. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. *Circulation* 1997;96:2617-24.
29. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *The New England journal of medicine* 2008;359:1778-85.
30. Sadoul N, Blankoff I, de Chillou C, et al. Effects of radiofrequency catheter ablation on patients with permanent pacemakers. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing* 1997;1:227-33.
31. Darpö B, Walfridsson H, Aunes M, et al. Incidence of sudden death after radiofrequency ablation of the atrioventricular junction for atrial fibrillation. *The American journal of cardiology* 1997;80:1174-7.
32. Ozcan C, Jahangir A, Friedman PA, et al. Sudden death after radiofrequency ablation of the atrioventricular node in patients with atrial fibrillation. *Journal of the American College of Cardiology* 2002;40:105-10.
33. Tebbenjohanns J, Schumacher B, Korte T, Niehaus M, Pfeiffer D. Bimodal RR interval distribution in chronic atrial fibrillation: impact of dual atrioventricular nodal physiology on long-term rate control after catheter ablation of the posterior atrionodal input. *Journal of cardiovascular electrophysiology* 2000;11:497-503.
34. Blanck Z, Dhala AA, Sra J, et al. Characterization of atrioventricular nodal behavior and ventricular response during atrial fibrillation before and after a selective slow-pathway ablation. *Circulation* 1995;91:1086-94.
35. Morady F, Hasse C, Strickberger SA, et al. Long-term follow-up after radiofrequency modification of the atrioventricular node in patients with atrial fibrillation. *Journal of the American College of Cardiology* 1997;29:113-21.
36. Proclemer A, Della Bella P, Tondo C, et al. Radiofrequency ablation of atrioventricular junction and pacemaker implantation versus modulation of atrioventricular conduction in drug refractory atrial fibrillation. *The American journal of cardiology* 1999;83:1437-42.
37. Menozzi C, Brignole M, Gianfranchi L, et al. Radiofrequency catheter ablation and modulation of atrioventricular conduction in patients with atrial fibrillation. *Pacing and clinical electrophysiology : PACE* 1994;17:2143-9.
38. Feld GK. Radiofrequency catheter ablation versus modification of the AV node for control of rapid ventricular response in atrial fibrillation. *Journal of cardiovascular electrophysiology* 1995;6:217-28.
39. Canby RC, Román CA, Kessler DJ, Horton RP, Page RL. Selective radiofrequency ablation of the "slow" atrioventricular nodal pathway for control of the ventricular response to atrial fibrillation. *The American journal of cardiology* 1996;77:1358-61.
40. Ling-Ping Lai J-LL, Shoen J, Stephen Huang. In: Wood SKSH-am, ed. *Catheter Ablation of Cardiac Arrhythmias*. Philadelphia: Saunders; 2006.