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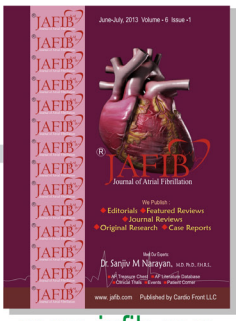

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Rate Control in Atrial Fibrillation: Methods for Assessment, Targets for Ventricular Rate During AF, and Clinical Relevance for Device Therapy

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Abstract

Rate control is a widely used treatment strategy for management of patients with atrial fibrillation (AF). Multiple studies have shown that pharmacologic rate control is as effective as pharmacologic rhythm control for management of AF. A snapshot ECG or intermittent monitoring using Holters is the most widely used technique for assessing ventricular rate during AF. Patients with implantable devices, such as pacemakers, implantable cardioverter defibrillators, cardiac resynchronization therapy devices, and implantable loop recorders provide the ability for continuous long term monitoring of AF and ventricular rate during AF. It has been shown that continuous monitoring of AF and ventricular rate during AF by implantable devices is the most comprehensive method for assessment of AF occurrence and poor rate control, particularly in patients with paroxysmal and asymptomatic AF. Rapid ventricular rate during AF, as assessed by implantable devices, has been shown to cause reduction in cardiac resynchronization therapy, predict inappropriate defibrillation therapy, and identify increased risk for cardiovascular hospitalizations. The ventricular rate targets for achieving good rate control during AF depend on the patient characteristics with stricter targets recommended for patient with compromised functional capacity, such as patients with HF. Thus it can be hypothesized that timely intervention based on continuous assessment of AF and poor rate control, with ventricular rate targets defined based on cardiovascular disease state, may improve clinical outcomes in patients with AF.

Introduction

Controlling ventricular rate during atrial fibrillation (AF) has been shown to be as effective as anti-arrhythmic pharmacologic therapies for AF.[1,2] In the absence of rhythm control strategies with long term efficacy, rate control strategies have been considered as a reasonable option for managing patients with AF.[3,4] Despite wide adoption of rate control therapy for AF, it has been shown that guideline defined adequate rate control targets are not achieved in a significant proportion of patients.[5] The recently completed RACE-II study did not show the benefits of stricter rate control compared to lenient rate control[6] in permanent AF patients with clinically adequate functional capacity and fewer symptoms during rapid rates. However, the RACE-II study included very few patients with poor functional capacities and lower tolerance for rapid ventricular rates during AF, such as patients with heart failure (HF), where stricter rate control may be more beneficial.

AF and HF are the most common cardiovascular diseases and cause significant economic burden, morbidity, and mortality. In the United States, more than 2.2 million people have AF and more than 5.7 million have HF.[7] HF is the primary cause of a significant proportion of hospitalizations with close to 1 million discharges for HF in the United States in 2007.[7] Among patients hospitalized with AF, the most common primary diagnosis is HF.[7] AF is common in heart failure patients[8-11] with an estimated AF prevalence of about 5% in those with New York Heart Association functional Class I to about 50% in those with Class IV symptoms.[8] In the Framingham Heart study, the incidence of HF in AF patients was 33 per 1000 person-years and the incidence of AF in HF patients was 54 per 1000 person-years.[9] In patients with AF or HF, subsequent development of the other condition was associated with increased mortality.[9] The Euro Heart Surveys showed that HF is present in 34% of AF patients[10] and AF is present in 42% of HF patients.[11] The CHARM study reported that 15% of HF patients with left ventricular systolic dysfunction and 19% of HF patients with preserved systolic function

Disclosures:
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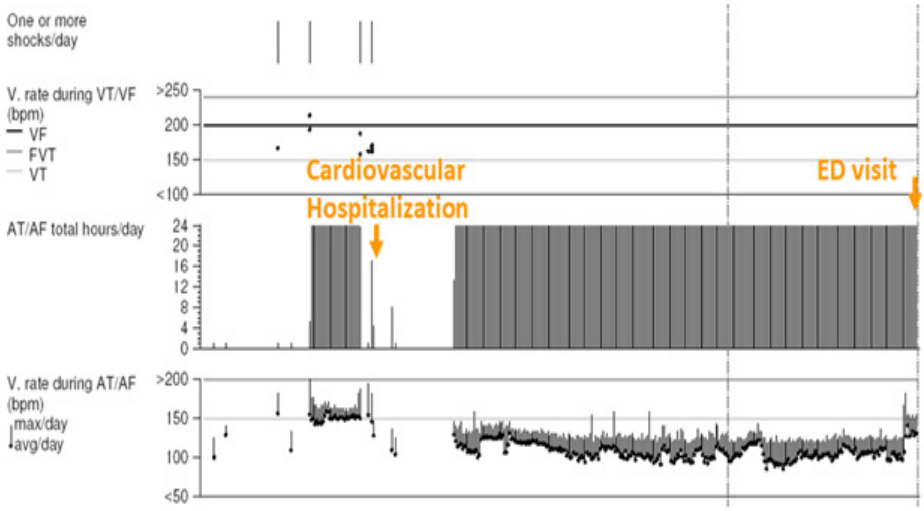

Figure 1: **Example showing the atrial fibrillation diagnostics measured in ICD devices. This patient had cardiovascular hospitalization and emergency department visits after long duration episodes of poor rate control during AF. The patient also had multiple days with defibrillator therapy on days with rapid ventricular rate during AF.**

had AF at baseline, and AF developed in another 8% and 5% of patients in the respective groups during follow-up.[12] Further, HF patients with AF have a significantly increased risk of cardiovascular death or HF hospitalization compared to HF patients without AF.[12] It has been shown that pharmacologic rate control is as effective and pharmacologic rhythm control in HF patients with AF.2 Implanted devices such as Cardiac Resynchronization Therapy (CRT) devices and Implantable Cardioverter Defibrillators (ICD) are commonly utilized in patients with HF. These devices provide continuous long term monitoring of AF and ventricular rate during AF, thus providing an opportunity to proactively monitor for timely rate or rhythm control interventions to reduce the risk of cardiovascular and HF events.

In this review we will discuss (1) the mechanisms of ventricular response during AF, (2) novel methods for assessment of rapid ventricular rate during AF, (3) the clinical relevance of identifying rapid ventricular rate during AF with respect to cardiovascular and specifically HF hospitalizations, loss of cardiac resynchronization therapy, and inappropriate ICD shocks, (4) the ventricular rate targets to achieve adequate rate control during AF, and (5) the conventional and investigational treatment strategies for achieving rate control.

Ventricular Response During AF

Ventricular response during AF is characterized by a faster ventricular rate compared to normal sinus and an irregularly irregular or "random" sequence of RR intervals.[13] There are multiple theories which try to explain the exact reason for the randomness of RR intervals. One theory suggest that multiple atrial impulses continuously arrive at the AV-node in a random fashion leading to various degrees of concealed conduction through the AV-node depending upon its refractory state.[14] Ventricular rate during AF is widely believed to be dependent on the refractory period of the AV-node and the refractory period of the atrial myocardium. An increased refractory period of the AV-node will delay transmission of atrial impulses to the ventricles, thus reducing the ventricular rate during AF.[15,16] A shortened refractory period of the atrial myocardium leads a larger number of atrial impulses reaching the AV-node which increases the degree of concealed conduction thus reducing the number of atrial impulses reaching the ventricles.[15] The conductivity and refractoriness of the AV-node and the atrial tissue may be altered by changes in autonomic tone and pharmacologic agents.

Ventricular response during atrial tachycardia (AT), including atrial flutter, has not been widely reported in literature. AT can have regular, regularly irregular, and irregularly irregular ventricular response depending on the response of the AV-node to atrial activation. AT with regular ventricular response is a result of regular atrial activations with a consistent atrial to ventricular (A:V) conduction ratio (e.g. 2:1, 3:1, etc.). AT with regularly irregular ventricular response is a result of the mechanism called "group beating".[17] In this case the different degrees of block in the AV-node may lead to different ventricular intervals such as "short-short-long", "short-long-short", "long-short-long, or "long-short-short" RR intervals. AT with irregularly irregular ventricular response results from atrial activations from multiple sources and inconsistent AV node conduction for each cycle, similar to ventricular response during AF.

Methods for Measuring Ventricular Rate During AF

In implantable devices with a lead in the atrium, AF is detected when there is a fast atrial rate (PP intervals nominally <360 ms) with an AV conduction ratio ≥ 2:1. Methods for rejection of far field r-wave sensing in the atrial leads are also frequently incorporated.[18] AF burden is defined as the total cumulative duration of detected AF during a 24 hour period. Implantable devices have been shown to have a very high accuracy (> 99%) for detecting AF burden using

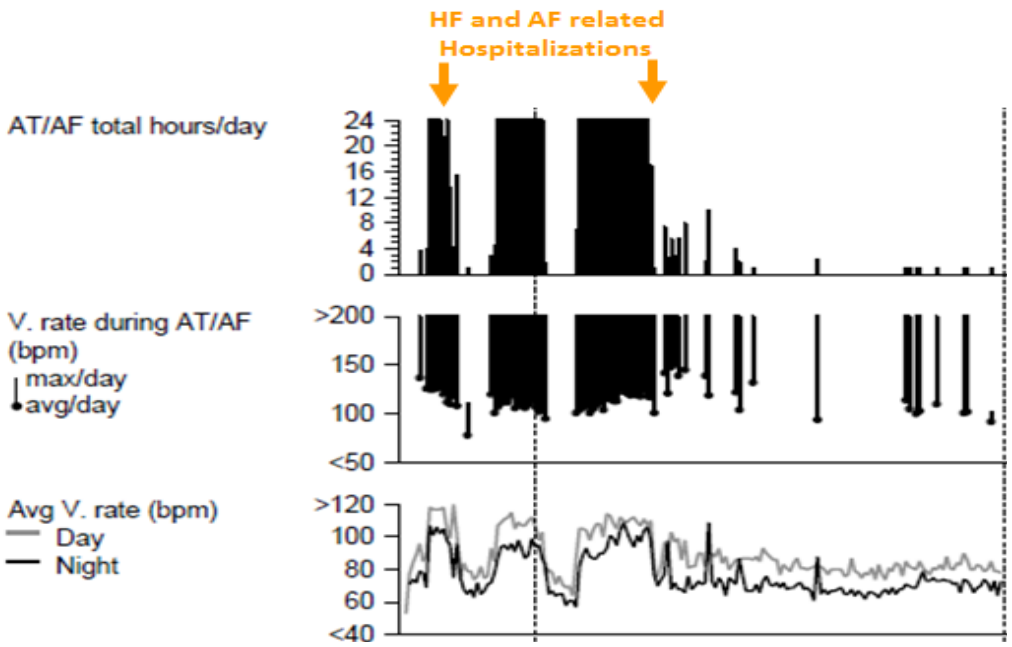

Figure 2: **Atrial Fibrillation and poor rate control as detected by an implantable loop recorder. This patient was admitted multiple times with HF symptoms of shortness of breath and edema and was found to have AF with rapid ventricular rate on presentation. The patient had to be treated with IV diuretics during both admissions.**

sensing leads in the atrium[18-21] and are considered as the gold standard for continuous long term AF detection. In implantable loop recorder devices, PP intervals cannot be sensed reliably and hence AF detection is performed using information regarding RR intervals. During AF, the AV-node rather than the SA-node controls ventricular response leading to characteristic signatures of incoherence in RR intervals. AF is detected by looking for incoherence of RR interval time-series over a period of time.[22] Implantable loop recorders have been shown to have high accuracy (>98%) in detecting AF burden, though not as accurate as implantable devices with leads in the atrium.[23] Since fewer than 10% of AF episodes are reported as being symptomatic[24, 25] and only 1 out of every 5 patient symptoms correlate with the presence of AF, [24, 26] intermittent monitoring techniques are commonly used to search for AF and corroborate symptoms. However, studies have shown that implantable continuous monitoring can detect when patients are having AF more reliably than intermittent monitoring using ECGs and Holter recordings.[27,28] In a study of patients with paroxysmal AF, simulations of quarterly Holter monitoring were found to miss 46% of patients who actually had AF, while also incorrectly predicting that patients do not have AF in 71% of cases.[27] Continuous monitoring becomes more relevant for patients with paroxysmal AF and asymptomatic AF.

Ventricular rate during AF, a measure of rate control, is computed as the average ventricular rate during periods of detected AF and is commonly reported for each 24 hour period. In addition to implantable devices which can continuously monitor AF parameters for 3-10 years, external monitoring devices[29,30] also have the ability to monitor AF and ventricular rate during AF continuously for periods of 1-4 weeks. However in most clinical situations, ventricular rate during AF is assessed using a snapshot measurement of AF with electrocardiograms (ECG). In many studies[1,2,6] the adequacy of rate control is assessed using the ECG or using intermittent 24 hour Holters. It has been shown recently that monitoring using intermittent techniques such as Holter recorders underestimates the incidence of poor rate control in patients with permanent AF.[31] For example, the sensitivity of a single 24-hour Holter recording to identify the presence of poor rate control in ICD or CRT-D patients was found to be less than 10%. Increasing the monitoring duration to 7 consecutive days still failed to raise the sensitivity above 20%. Thus, continuous long term monitoring of AF and ventricular rate during AF using implantable devices with remote access and wireless alerting capabilities is the most comprehensive technique to provide dynamic assessment of AF type and rhythm[32] and rate control status, thus providing the opportunity to optimize pharmacologic treatment strategies in a timely manner.

Clinical Relevance of Rapid Ventricular Rate During AF

Cardiovascular Hospitalizations

The primary treatment goal for patients with AF is to reduce the risk for stroke by use of anti-thrombotic therapies. Secondary to reducing the risk of stroke, patients with AF are managed to reduce clinical morbidity, such as cardiovascular hospitalizations and symptoms. Implantable device detected AF and poor rate control has been shown to be associated with increased risk for mortality in a very large cohort of patients with cardiac resynchronization therapy defibrillator (CRT-D) devices.[33] A review of hospital discharges in the United States from 1996-2001 showed that more than 2 million discharges with primary diagnosis of AF occurred during the 5 year period.[34] Further, over that time period admission with a primary diagnosis of AF increased 34%. The number of hospitalizations due to AF is projected to increase with an aging population and presents a huge economic burden to the health care

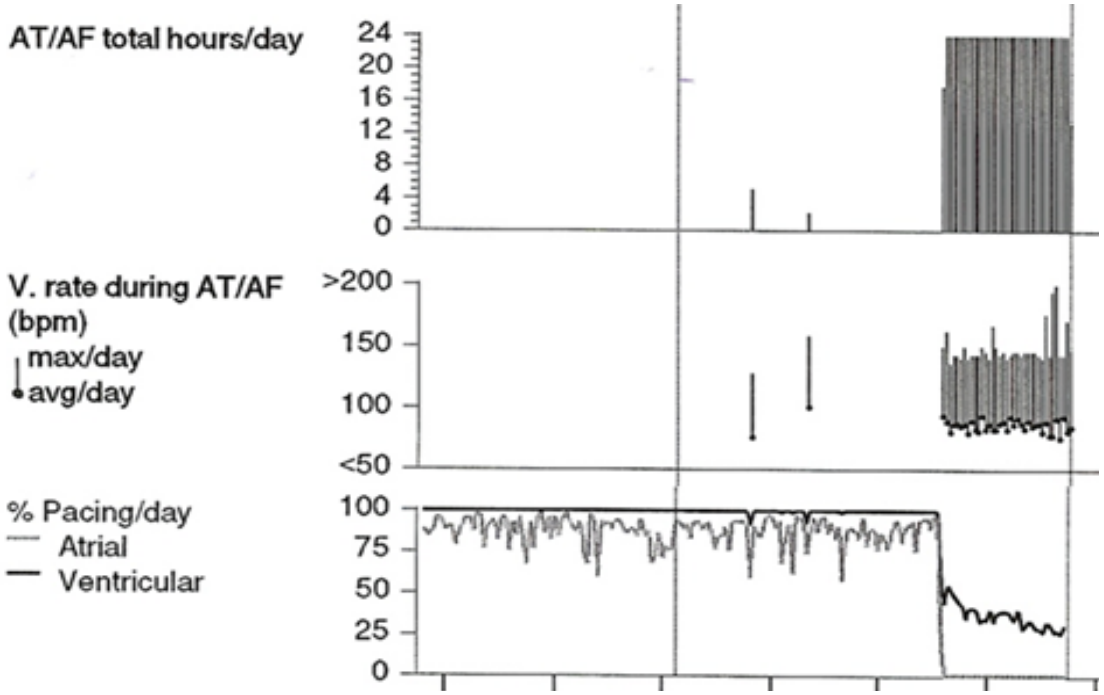

Figure 3: **Prolonged period of loss of cardiac resynchronization therapy pacing due to poor rate control during atrial fibrillation as documented by diagnostics provided in CRT-D devices.**

system.[35] It is widely believed that higher ventricular rate and RR interval variability during AF leads to symptoms during AF such as palpitations, shortness of breath, dizziness, and fatigue. However it has been shown that symptoms correlate very poorly with presence of AF and that there are no significant differences between ventricular rates for symptomatic and asymptomatic episodes of AF[24]

One approach for prevention of clinical morbidity would be to continuously monitor patients for AF and high ventricular rates during AF, irrespective of the presence of symptoms, and treat patients in a timely manner to prevent hospitalizations and symptoms. Figure 1 and Figure 2 show examples of patients with long periods of AF with rapid ventricular rates, as detected by different kinds of implantable devices, prior to hospital admissions. Controlling the ventricular rate during AF in a timely manner may prevent tachycardia induced cardiomyopathy and improve the hemodynamics by allowing for a larger ventricular filling time during the cardiac cycle. The CONNECT study investigated the utility of remote care alerts for high AF burden and poor rate control in patients with implantable cardioverter defibrillator (ICD) or CRT-D devices in a randomized multi-center study.[36] The study showed that continuous monitoring, with wireless remote alert capabilities, allows providers to make clinical decisions more than 2 weeks earlier compared to performing in-office follow-ups. Though the number of cardiovascular related hospitalizations was not different between the two arms in the study, the length of stay was reduced significantly in the remote monitoring arm compared to in-office follow-up arm thereby providing a potential cost savings to the health care system. In the ATHENA study,[37] it has also been argued that the rate control effect of dronedarone was responsible for the reduction in cardiovascular hospitalizations and all-cause mortality shown. Thus, identifying when patients have poor rate control and taking therapeutic actions if necessary may lead to a reduction in length of stay and the number of cardiovascular hospitalization.

Heart failure Hospitalizations

HF hospitalizations comprise a large proportion of cardiovascular hospitalizations and consequently impose a large economic burden on the health care system. Recently it has been shown that in HF patients with implanted CRT-D devices capable of continuously monitoring for AF, device detected AF is associated with an increased risk for death or HF hospitalization.[38] In a similar patient cohort of HF patients with CRT-D devices, 34% of patients with device detected AF had average ventricular rate > 80 bpm and maximum ventricular rate during AF > 110 bpm on AF days.[39] Further, it was shown that rapid ventricular rate during AF, as defined above, was associated with an increased risk of death or HF hospitalization. In a recent report it has been shown that device detected AF > 6 hours on a single day in the last 30 days with good rate control increased risk for HF hospitalization in the next 30 days.40 The risk increased to more than 3 times when there were a greater number of days with AF burden > 6 hours in the last 30 days. Further, patients with more than 6 hours of AF and with an average ventricular rate during AF of > 90 bpm on a single day in the last 30 days are close to 6 times more likely to be hospitalized for HF in the next 30 days compared to patients with no AF. Interestingly, patients with persistent AF in the last 30 days exhibited an increased risk for HF hospitalization in the

next 30 days only in the setting of poor rate control. Figure 2 shows an example of a patient being monitored by an implantable loop recorder with AF detection capabilities. There were long periods of AF with rapid ventricular rates prior to HF related hospitalizations which needed IV diuresis treatment during the admission.

Knowing that the patient has AF or poor rate control identifies which patients are at increased static risk for death or HF hospitalization.[38,39] Additionally, information on when the patient is having AF, amount of AF, type of AF, and changes in rate control status during AF provide an assessment of how the risk status changes in a dynamic fashion on a monthly basis[40] providing an opportunity to provide more clinical attention and resources to selective patients in a timely manner to reduce clinical morbidity.

Reduction in Cardiac Resynchronization Therapy

Rapid ventricular rate during AF has been shown to be one of the primary causes for loss of CRT therapy.[39,41,42] Atrial tachyarrhythmias were identified as the primary cause for loss of CRT pacing in 50% of the patients with loss of CRT pacing.[41] These results were corroborated in a larger cohort of patients, in which atrial tachyarrhythmias accounted for more than 50% of cases with more than 10% loss in CRT pacing.[42] The percent of loss of CRT pacing was linearly related to average ventricular rate during AF in patients with AF.[39] Loss of CRT pacing in HF patients has been shown to be associated with increased risk of mortality and HF hospitalizations.[43-45] Patients with 93-100% CRT pacing had a 44% reduction in hazard for HF hospitalization or all all-cause mortality compared to patients with 0-92% CRT pacing.[43] Similar results were reported in a larger cohort of patients, which showed that reduced CRT pacing is associated with decreased survival.[44] Further, it was shown that a single day with more than 10% loss of CRT pacing in the last 30 days increased the risk for a HF hospitalization in the next 30 days by 2.6 times.[45] The risk increased to 5.5 times if the cause for the loss of CRT pacing was rapid ventricular rate during AF. Patients with loss of CRT pacing in last 30 days caused by rapid ventricular rate during AF were 2.7 times more likely to be hospitalized for HF in the next 30 days compared to patients where the loss of CRT was due to other reasons.

Rapid ventricular rate during AF almost always leads to some degree of loss of CRT pacing, with the amount of loss of CRT pacing depending on the duration of rapid ventricular rate during AF. Figure 3 shows an example of rapid ventricular rates leading to loss of CRT pacing in a patient with CRT-D device. The longer the duration of ventricular rate during AF being greater than the upper tracking rate of the pacemaker, the more significant the amount of loss in CRT pacing and increased likelihood of adverse clinical outcomes in patients. Knowing when rapid ventricular rates are occurring during AF and taking clinical steps to improve rate control in these patients is the simplest solution to improving CRT response in patients.[41]

Inappropriate Defibrillator Shock Therapy

Rapid ventricular rate during AF has long been identified as one of the primary causes of inappropriate detection and shock therapy in ICDs.[46,47] Dual chamber defibrillators are used primarily for the ability of the atrial lead to detect atrial tachyarrhythmias and reduce inappropriate detection and therapy for AF and AT with rapid ventricular response.[46-48] Though significant progress has been made in reducing inappropriate detections in ICDs, rapid ventricular rate during AT and AF, specifically in the ventricular fibrillation rate zone, still remains a primary cause for inappropriate ventricular arrhythmia detection and shock therapy. Recently, it has been shown in a large cohort of ICD patients that AF > 1 hour in a day coupled with an average ventricular rate during AF > 110 bpm identified patients at highest risk of future shock therapy.[49] Figure 1 shows an example where defibrillation therapy was delivered on days with rapid ventricular rate during AF in a patient with ICD device. Thus monitoring for poor rate control during AF provides the opportunity to reprogram ICD devices and provide therapy for aggressive rate control during AF in a timely manner to reduce inappropriate shocks in ICD patients.

Targets for Rapid Ventricular Rate or Poor rate Control During AF

There are various definitions of poor rate in different guidelines. In the United States, the recently updated ACC/AHA/HRS guideline for management of patients with AF[3] states that there are no standard methods for rate assessment during AF to guide management of patients. The guideline suggests that the general consensus for good rate control consists of maintaining ventricular rate during AF in the range of 60-80 beats per minute (bpm) during rest and between 90-115 bpm during moderate exercise, which are primarily derived based on short term benefits in hemodynamics and was used in the AFFIRM study.[1] It is also suggested that the maximum rate limit during exercise be adjusted for age. The ESC guidelines for management of patients with AF[4] also state that the adequate targets for rate control with respect to clinical outcomes is unknown. The guidelines suggest, based on the results of the RACE II study,[6] that patients should initially be managed to maintain a lenient rate control

Table 1: Rate control limits described in various studies for patients monitored using implantable devices.

Implantable device	Patient Population	Purpose of Monitoring	Rate Control Limits	References
CRT-D	Patients with history of HF and co-morbidities	Prevent loss of CRT therapy; Prevent CV/HF admissions	Avg. V-rate during AF < 90 bpm on days with ≥6 hour AF	38-45
ICD	No history of HF	Prevent inappropriate ICD therapy	Maximum V-rate during AF < 110 bpm on days with ≥1 hour AF	46-49
ICD/ Pacemakers/ Implantable Loop Recorders	Patients with history of HF but maintaining active lifestyle	Prevent CV/HF admissions	Avg. V-rate during AF < 110 bpm on days with ≥6 hour AF	None
ICD/ Pacemakers/ Implantable Loop Recorders	Patients with history of HF and comorbidities with compromised functional capacity	Prevent CV/HF admissions	Avg. V-rate during AF < 90 bpm on days with ≥6 hour AF	None

with resting heart rate < 110 bpm. If the patient feels symptoms related to high rates or irregularity of rates, then a stricter rate control target of < 80 bpm at rest and < 110 bpm during moderate exercise should be followed. Patients who are being treated to achieve stricter rate control targets should be monitored for asystole and bradycardia.

Based on definitions of poor rate control in patients with implantable devices, rate cut-offs for poor rate control in ICD patients have been chosen in some studies at 110 bpm[49] whereas that for CRT-D patients has been chosen at 90 bpm.[40] In CRT-D patients, lower rates were chosen as cutoff due to the potential of reduced CRT pacing at these rates as well as increased risk for tachycardia induced cardiomyopathy. Also studies have shown that patients with CRT-D devices are at increased risk for adverse events when rates are above 90 bpm during AF.[40,45] Thus, the rate control targets should be dependent on the characteristics of the patient. If a patient with an implantable device capable of providing backup pacing or remote notifications for aystole or bradycardia has a hospitalization due to poor rate control during AF or due to HF in the last 6 months, they may be better suited for a strict rate control approach. Similarly, high risk AF patients with age >70 years and a history of hypertention, HF, or diabetes who are less likely to tolerate symptoms of rapid rates during AF may also be suitable for consideration of stricter rate control targets. Conversely, AF patients with an active lifestyle and adequate functional capacity may be able to tolerate occasional surges above stricter rate control targets and could have their rate controlled below the lenient rate control targets to prevent the development of HF. The rate control target for patients with implantable devices described above is summarized in Table 1.

Besides providing information on whether patients are having poor rate control, implantable devices with continuous monitoring capabilities also open the possibility of novel metrics for defining poor rate control. Due to the continuous nature of monitoring, one can quantify the burden or amount of poor rate control over a period of time; for example, the number of days that the average ventricular rate during AF was above 90 bpm during the last 30 days. Also, one can quantify the number of continuous days or the duration of time that a patient had an average ventricular rate during AF above 90 bpm. Besides knowing about the presence of poor rate control, the burden and duration of poor rate control may provide information on when, what, and whether therapeutic action might benefit the patient. In the absence of reported studies in this area, it can be hypothesized that larger amounts of burden or duration of poor rate control may signify a larger risk for adverse events and thus implies a greater necessity for targeting stricter rate control.

Management of Rapid Ventricular Rate During AF

The primary mechanisms of control of ventricular response during AF are the conduction and refractory properties of the AV-node and autonomic tone. Pharmacological agents primarily target these mechanisms to slow down the ventricular rate during AF. β-blockers, non-dihydropyridine calcium channel antagonists, Digoxin and antiarrhythmic agents are often used for rate control in patients.[3,4] In the AFFIRM study[1], β-blockers were found to be the most effective. Calcium channel blockers are very effective for acute control of rate but are normally avoided in patients with HF and left ventricular dysfunction because of negative inotropic effects. Digoxin is no longer the initial drug of choice for rate control except in patients with HF or patients with sedentary lifestyle. Besides pharmacologic agents, AV-node ablation and permanent pacing, more specifically bi-ventricular pacing, is a very effective way of controlling rate during AF.[3,4,51] Several other novel techniques for rate control are under investigation, including selective vagal stimulation[52] and renal nerve denervation.[53]

Most implantable devices are implanted for clinical indications such as cardiac resynchronization therapy for improving clinical outcomes for HF patients, defibrillation therapy for preventing sudden cardiac death, pacing treatment for symptomatic bradycardia, and aiding the diagnosis of unexplained syncope and suspicion of cardiac arrhythmias. Most of these implantable devices also provide continuous long term AF and rate control monitoring capabilities with wireless transmission capabilities and remote alerts that can be very useful in identifying when patients are having poor rate control[36] such that pharmacologic therapy optimization can be performed in a timely manner with the intention of reducing symptoms and cardiovascular hospitalization. In patients with AF and HF, continuous monitoring of AF diagnostics also identifies when patients are at increased risk for HF,[40] thus providing the opportunity to optimize HF therapies, such as diuretics, if necessary in the short term and rate control therapy for AF in the longer term to prevent occurrence of future events. Also, the capability to continuously monitor patients with remote transmission of their data enables timely monitoring of therapy effectiveness.

Conclusions:

Ventricular response during AF is primarily controlled by the conduction properties of the AV-node and the autonomic tone. Most treatment strategies for controlling rate during AF target these mechanisms. Continuous monitoring of ventricular rate during AF, as provided by implantable medical devices, provides the most comprehensive method for assessing the presence and burden of poor rate control. The diagnostics provided by implantable devices along with their remote monitoring and alerting capabilities provides an opportunity for timely intervention, particularly in asymptomatic patients. Rapid ventricular rate during AF identifies when patients are at increased risk for loss of cardiac resynchronization therapy, inappropriate defibrillator shocks, and cardiovascular hospitalizations. Thus it can be hypothesized that timely intervention based on continuous assessment of poor rate control may prevent tachycardia induced cardiomyopathy, improve hemodynamics during AF, improve cardiac resynchronization therapy response, reduce inappropriate defibrillator shocks, and reduce cardiovascular hospitalizations.

References:

1. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–1833.
2. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–2677.
3. Fuster V, Ryd´en LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;123:e269–e367.
4. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the

European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369–2429.
5. Hilliard AA, Miller TD, Hodge DO, Gibbons RJ. Heart rate control in patients with atrial fibrillation referred for exercise testing. Am J Cardiol. 2008;102:704–708.
6. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362:1363–1373.
7. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics--2011 Update: A Report From the American Heart Association. Circulation. 2011;123(4):e18-e209.
8. Maisel W, Stevenson L. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91:2D–8D.
9. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107(23):2920-2925.
10. 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. Eur Heart J. 2005;26(22):2422-2434.
11. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442-463.
12. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol. 2006;47(10):1997-2004.
13. Bootsma BK, Hoelsen AJ, Strackee J, Meijler FL. Analysis of R-R intervals in patients with atrial fibrillation at rest and during exercise. Circulation. 1970;41:783-94.
14. Meijler FL, Jalife J, Beaumont J, Vaidya D. AV nodal function during atrial fibrillation: the role of electrotonic modulation of propagation. J Cardiovasc Electrophysiol. 1996;7:843-861.
15. Meijler FL. An "account" of digitalis and atrial fibrillation. J Am Coll Cardiol. 1985;5(5 Suppl A):60A-68A.
16. Toivonen L, Kadish A, Kou W, Morady F. Determinants of the ventricular rate during atrial fibrillation. J Am Coll Cardiol. 1990;16:1194-1200.
17. Duytschaever M, Dierickx C, Tavernier R. Variable atrioventricular block during atrial flutter: what is the mechanism? J Cardiovasc Electrophysiol. 2002;13:950-951.
18. Purerfellner H, Gillis AM, Holbrook R, Hettrick DA. Accuracy of atrial tachyarrhythmia detection in implantable devices with arrhythmia therapies. Pacing Clin Electrophysiol. 2004;27(7):983-992.
19. Swerdlow CD, Schsls W, Dijkman B, et al. Detection of atrial fibrillation and flutter by a dual-chamber implantable cardioverter-defibrillator. Circulation. 2000;101(8):878-885.
20. Passman RS, Weinberg KM, Freher M, et al. Accuracy of mode switch algorithms for detection of atrial tachyarrhythmias. J Cardiovasc Electrophysiol. 2004 Jul; 15(7):773-777.
21. de Voogt WG, van Hemel NM, van de Bos AA, Koïstinen J, Fast JH. Verification of pacemaker automatic mode switching for the detection of atrial fibrillation and atrial tachycardia with Holter recording. Europace. 2006;8(11):950-61.
22. Sarkar S, Ritscher D, Mehra R. A detector for a chronic implantable atrial tachyarrhythmia monitor. IEEE Trans Biomed Eng. 2008; 55(3):1219-1224.
23. Hindricks G, Pokushalov E, Urban L, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT trial. Circ Arrhythm Electrophysiol. 2010;3(2):141-147.
24. Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. Relationship between atrial tachycardias and symptoms. Heart Rhythm. 2005;2:125–131.
25. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation. 1994;89(1):224-227.
26. Quirino G, Giammaria M, Corbucci G, et al. Diagnosis of paroxysmal atrial fibrillation in patients with implanted pacemakers: relationship to symptoms and other variables. Pacing Clin Electrophysiol. 2009;32(1):91-98.
27. 27. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. Heart Rhythm. 2006;3:1445-1452.
28. Botto GL, Padeletti L, Santini M, et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol. 2009;20(3):241-248.
29. Mittal S, Movsowitz C, Steinberg JS. Ambulatory external electrocardiographic monitoring: focus on atrial fibrillation. J Am Coll Cardiol. 2011;58:1741-1749.
30. Vasamreddy CR, Dalal D, Dong J, et al. Symptomatic and asymptomatic atrial fibrillation in patients undergoing radiofrequency catheter ablation. J Cardiovasc Electrophysiol. 2006;17:134-139.
31. Ziegler PD, Koehler JL, Verma A. Continuous versus Intermittent Monitoring of Ventricular Rate in Patients with Permanent Atrial Fibrillation. Pacing Clin Electrophysiol. 2012 May;35(5):598-604.
32. Martinek M, Aichinger J, Nesser HJ, Ziegler PD, Purerfellner H. New insights into long-term follow-up of atrial fibrillation ablation: full disclosure by an implantable pacemaker device. J Cardiovasc Electrophysiol. 2007;18:818-823.
33. Borek P, Koehler J, Ziegler P, Heywood T, Ousdigian K, Wilkoff B. Impact of AF on Mortality in 44,104 Patients with CRT-D. Heart Rhythm. 2010; 7(5 Suppl): S26.
34. Khairallah F, Ezzedine R, Ganz LI, London B, Saba S. Epidemiology and determinants of outcome of admissions for atrial fibrillation in the United States from 1996 to 2001. Am J Cardiol. 2004;94(4):500-504.
35. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation. 2003;108(6):711-716.
36. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) Trial The Value of Wireless Remote Monitoring With Automatic Clinician Alerts. J Am Coll Cardiol. 2011;57(10):1181-1189.
37. Page RL, Connolly SJ, Crijns HJ, et al. Rhythm- and rate-controlling effects of dronedarone in patients with atrial fibrillation (from the ATHENA trial). Am J Cardiol. 2011;107(7):1019-1022.
38. Santini M, Gasparini M, Landolina M, et al. Device-detected atrial tachyarrhythmias predict adverse outcome in real-world patients with implantable biventricular defibrillators. J Am Coll Cardiol. 2011;57(2):167-172.
39. Boriani G, Gasparini M, Landolina M, et al. Incidence and clinical relevance of uncontrolled ventricular rate during atrial fibrillation in heart failure patients treated with cardiac resynchronization therapy. Eur J Heart Fail. 2011;13:868–876.
40. Sarkar S, Koehler J, Crossley GH, et al. Burden of atrial fibrillation and poor rate control detected by continuous monitoring and the risk for heart failure hospitalization. Am Heart J. 2012;164(4):616-624.
41. Knight BP, Desai A, Coman J, FaddisM, Yong P. Long-term retention of cardiac resynchronization therapy. J Am Coll Cardiol. 2004;44:72–77.
42. Cheng A, Landman SR, Stadler RW. Reasons for loss of cardiac resynchronization therapy pacing: insights from 32 844 patients. Circ Arrhythm Electrophysiol. 2012;5(5):884-888.
43. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? J Am Coll Cardiol. 2009;53:355–360.

44. Ousdigian K, Heywood T, Koehler J, Ziegler P, Borek P, Wilkoff B. Reduced Bi-Ventricular Pacing is Associated with Decreased Survival in 9,360 CRT-D Patients with AF. Heart Rhythm. 2010; 7(5, Suppl): S449.
45. Sarkar S, Koehler J, Crossley GH, Tang WHW, Abraham WT, Whellan DJ. Rapid Ventricular Rate during Atrial Fibrillation, Loss of Cardiac Resynchronization Therapy, and Heart Failure Hospitalizations. Heart Rhythm. 2012;9(5 Suppl.): S235.
46. Kühlkamp V, Dörnberger V, Mewis C, Suchalla R, Bosch RF, Seipel L. Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. J Cardiovasc Electrophysiol. 1999;10(7):905-915.
47. Wilkoff BL, Kühlkamp V, Volosin K, Ellenbogen K, Waldecker B, Kacet S, Gillberg JM, DeSouza CM. Critical analysis of dual-chamber implantable cardioverter-defibrillator arrhythmia detection : results and technical considerations. Circulation. 2001;103(3):381-386.
48. Friedman PA, McClelland RL, Bamlet WR, et al. Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the detect supraventricular tachycardia study. Circulation. 2006;113(25):2871-2879.
49. Fischer A, Ousdigian KT, Johnson JW, Gillberg JM, Wilkoff BL. The impact of atrial fibrillation with rapid ventricular rates and device programming on shocks in 106,513 ICD and CRT-D patients. Heart Rhythm. 2012;9(1):24-31.
50. Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. J Am Coll Cardiol. 2004;43:1201– 8.
51. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review. J Am Coll Cardiol. 2012;59(8):719-726.
52. Zhang Y, Mazgalev TN. Achieving regular slow rhythm during atrial fibrillation without atrioventricular nodal ablation: selective vagal stimulation plus ventricular pacing. Heart Rhythm. 2004;1(4):469-475.
53. Linz D, Mahfoud F, Schotten U, et al. Renal sympathetic denervation provides ventricular rate control but does not prevent atrial electrical remodeling during atrial fibrillation. Hypertension. 2013 Jan;61(1):225-31.