

Atrioventricular Conduction in Atrial Fibrillation: Pathophysiology and Clinical Implications

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1. Introduction

The atrioventricular (AV) node is the only conduction pathway between the atria and ventricles, it is located at the base of the right atrium. The conduction through the atrioventricular node is slow to allow the atria to pump blood into the ventricles before they contract. It also acts as a backup pacemaker, in case the sinoatrial node fails and limits the number of action potentials conducted to the ventricles during atrial fibrillation (AF). Despite this filtering function, adequate ventricular rate control in atrial fibrillation often requires utilization of pharmacological and/or non-pharmacological treatment modalities.

2. Functional anatomy of the atrioventricular junction

The AV node is part of the cardiac pacemaker and conduction system. It develops from the embryonic myocardium that maintains essential features of its primitive phenotype, while the adjacent myocardium differentiates into working myocardium (Bakker et al., 2010). The AV node is a heterogenous structure, histologically consists of 3 layers: superficial/subendocardial, intermediate/midpart and deep innermost. A central fibrous body surrounds the distal structures (compact node and penetrating bundle), while the proximal part merges with the atrial myocardium via the inferior nodal extension and the transitional zone (Figure 1).

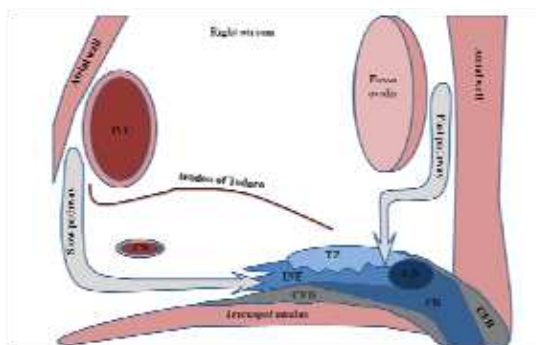


Fig. 1. Schematic anatomy of the AV node. View from the right atrium. IVC: inferior vena cava. CS: ostium of the coronary sinus. CFB: central fibrous body. INE: inferior nodal extension. TZ: transitional zone. PB: penetrating bundle. CN: compact node.

Based on the morphology of the recorded action potentials, there are 3 distinct regions: atrionodal, compact nodal and nodo-His. At least 6 different cell types have been described so far based on action potential morphology, excitability and refractory period. The correlation between histologic, microstructural and electrophysiological properties is still not fully elucidated despite recent advances in this field using voltage-sensitive fluorescent dyes. The slow and fast pathways of AV nodal activation involve extranodal areas in the right atrium, in posteroinferior (crista terminalis) and anterosuperior (interatrial septum) locations, respectively. The AV node receives both sympathetic and parasympathetic innervation (Meijler & Janse, 1988; Kurian et al., 2010).

3. Ion channels, currents and their modulation in the atrioventricular node

The electrical activity is determined by the expression of ion channels in the myocytes making up the conduction system. The ion channel expression in the AV node is specialized, similar to the sinoatrial node. There is very little expression of K_{ir2} channels, responsible for the I_{K1} K^+ current, the main current to keep working cardiomyocytes at a negative resting potential. Other K_{ir} channel subunits ($K_{ir3.1}$, $K_{ir3.4}$, $K_{ir6.2}$ and SUR2) are also poorly expressed in the nodal tissues. The hyperpolarization-activated cyclic nucleotide-gated Na^+ channels, responsible for the pacemaker current I_f , are highly expressed in the sinoatrial and atrioventricular node. Conduction through the AV node is slow in order to introduce a delay between atrial and ventricular systole, which is due to the lack of connexin Cx43 expression and Na^+ channel Nav1.5. The upstroke of the nodal action potential is Ca^{2+} - dependent, but instead of the myocardial L-type Ca^{2+} channel, Cav1.2, the alternative Cav1.3 is expressed, which has a more negative activation threshold, thus more appropriate for a Ca^{2+} -dependent action potential. Data regarding the presence and distribution of T-type Ca^{2+} channel is less consistent. Ion channel expression is plastic and may change with aging, heart failure, diabetes or athletic training (Boyett et al., 2009; Greener et al., 2011). Neurohormonal stimuli have a significant role in the behavior of the AV node during atrial fibrillation. Sympathetic activity (increased sympathetic nerve activation or release of circulating catecholamines) acts via β_1 -receptors/increased cAMP/protein kinase A activation, enhances the T-type Ca^{2+} and I_f currents, increases the slope of diastolic depolarization (which plays no significant role during atrial fibrillation in the AV node), increases the rate and completeness of I_K deactivation (which decreases the effective refractory periods, thus decreasing the efficacy of the filtering function of the AV node in AF). Parasympathetic stimuli act via M_2 muscarinic receptors/ G_i protein activation, which activate the I_{KAch} K^+ current, leading to membrane hyperpolarization, and inhibition of I_{Ca} Ca^{2+} - and I_f Na^+ currents via reducing cAMP and protein kinase A activity (Boyett et al., 2009).

4. Activation of the atrioventricular node in atrial fibrillation

In sinus rhythm, the action potential enters the AV node via the penetrating bundle (and then passes to the ventricles) via a fast pathway (formed partly by the transitional zone) and a slow pathway (formed partly by the inferior nodal extension). During AF, the node is continuously bombarded from different directions with varying degrees of penetration. Propagation is dependent on the relative timing of the septal inputs to the AV node at the crista terminalis and interatrial septum, and also depends on atrial input frequency (Garrigue et al., 1999). The constant bombardment of atrial impulses creates varying degree

of concealed conduction, when most stimuli enter the AV node but do not conduct to the ventricle, creating a wave of refractoriness encountered by subsequent impulses (Fujiki et al., 1990). This generally slows down the resulting ventricular rate, which becomes irregularly irregular. The atrial cycle length also changes continuously and may not be the same between different atrial regions (Duytschaever et al., 2001). As electrophysiological remodeling of the atrial myocardium occurs early during AF, with changes in effective refractory period and excitability, the input signals arriving to the AV node may vary significantly. Results from experimental studies are heterogeneous as various methods for AF induction have been used, that affect the resulting atrial electrical activity and atrioventricular conduction (Roka et al., 2008) (Figure 2). The randomness of the ventricular rhythm is still debated (van den Berg et al., 1995; Stein et al., 1999; Roka & Merkely, 2008).

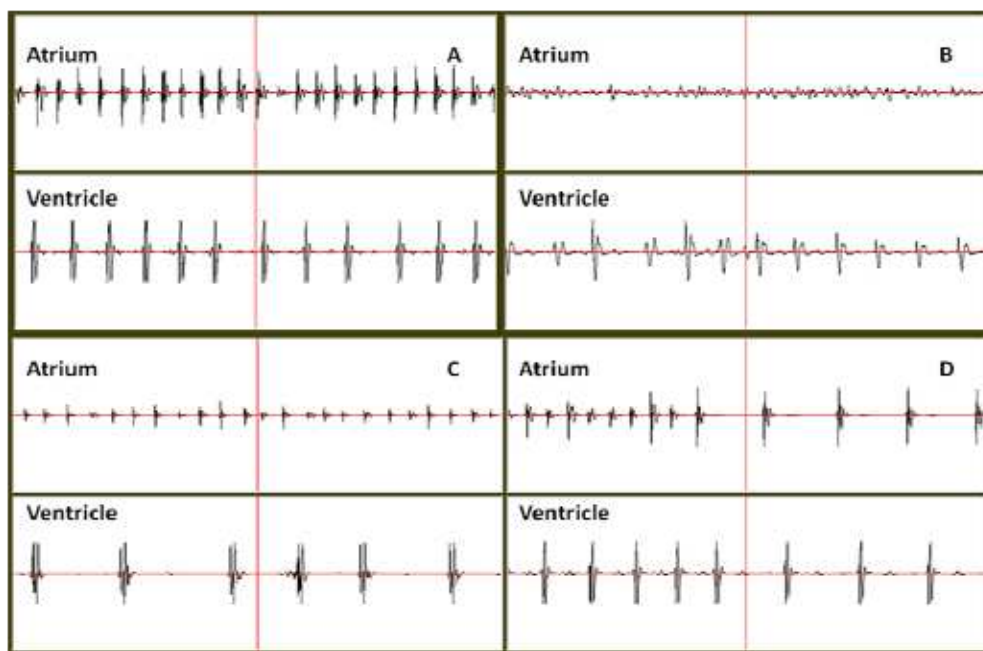


Fig. 2. Intracardiac recordings from healthy dogs with atrial fibrillation, induced by 50 Hz alternating current stimulation of the atria. Signals are recorded near the bundle of His (Ventricle) and near the AV node (Atrium). Atrial signal morphology is highly variable even in similar subjects with similar induction methods. A: discrete high frequency atrial signals with rapid, irregular ventricular rate. B: high frequency atrial signals without identifiable isoelectric baseline. C: discrete atrial signals with slower ventricular rate. D: spontaneous cardioversion of atrial fibrillation.

Main factors affecting the ventricular rate in AF are the electrophysiological properties of the AV node, rate and organization of atrial inputs, autonomic tone and effect of medications on the AV node. Increased parasympathetic and reduced sympathetic tone exert negative dromotropic effects on AV nodal conduction, while the opposite is true in states of decreased parasympathetic and increased sympathetic tone. Vagal tone also enhances the negative chronotropic effects of concealed conduction in the AV node (van den

Berg et al., 1997). Fluctuations in autonomic tone can produce wide variations in ventricular rate - slow ventricular rate during sleep but accelerated ventricular response during exercise. Several other factors also play a significant role, such as exercise (Bootsma et al., 1970), retrograde conduction after premature or ventricular paced beats (Greenhut et al., 1996), drugs, age and gender (Hnatkova et al., 1998).

5. Clinical relevance of AV node function in atrial fibrillation

If untreated, the ventricular rate is generally 90-170/minute in AF. Rates below 60/minute are seen with intrinsic AV node disease, high vagal tone or due to medications. Rates higher than 200/minute may be due to hyperthyroidism, presence of an accessory pathway or high catecholaminergic state. Regular ventricular rate during AF may indicate AV block with junctional or ventricular escape, or accelerated junctional activity. Occasionally, regularly irregular or group beating may be observed if the lower nodal pacemaker activity has a Wenckebach type exit block (Figure 3).



Fig. 3. Atrial fibrillation - variations of rate response. A: "typical" irregularly irregular rhythm. B: quasi-regular rhythm with occasional longer RR cycles. C: slow ventricular response, with junctional rhythm for most of the tracing. D: slow, irregular ventricular response. E: atrial fibrillation with preexcitation, "FBI tachycardia" - fast, broad, irregular.

A conventional 12-lead electrocardiogram is usually enough to establish the diagnosis. In paroxysmal forms Holter monitoring, event- or loop recording may be necessary (Fuster et al., 2011). In most cases, atrial fibrillation is easily diagnosed by the absence of P waves, presence of f waves and irregularly irregular RR intervals. QRS complexes are narrow unless there is fixed or rate-dependent bundle-branch block or preexcitation. Aberrant conduction is common and facilitated by the irregularity of the ventricular response. When a long interval is followed by a relatively short interval, the QRS complex following the short interval is often aberrantly conducted (Ashman phenomenon). In case of severely decreased AV conduction, junctional escape may lead to a regular rhythm (Figure 4). This may be often observed with digoxin toxicity, due to impaired AV conduction and enhanced junctional automaticity.

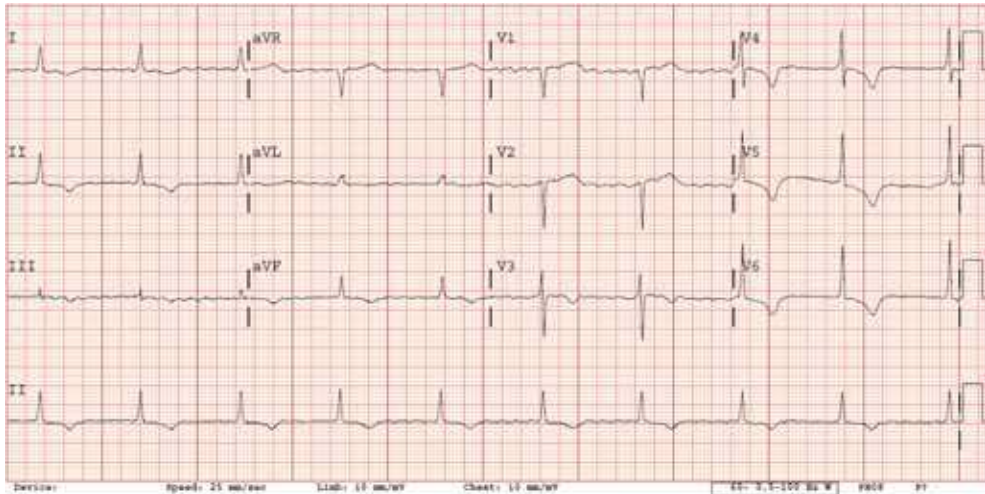


Fig. 4. Atrial fibrillation with junctional escape rhythm – the RR intervals are regular.

Atrial fibrillation may lead to irregular wide QRS tachycardia when it is associated with intraventricular conduction abnormalities, such as bundle branch block (Figure 5). Despite the irregular RR intervals, the QRS morphology shows little variation in these cases and is generally consistent with typical bundle branch block, occasionally showing rate-dependency. The differential diagnosis should include atrial fibrillation with preexcitation (QRS morphology is variable, delta waves are present) and polymorphic ventricular tachycardia (highly variable QRS morphology usually not typical for bundle branch block, atrioventricular dissociation, fusion or capture beats may be visible).



Fig. 5. Atrial fibrillation with rapid ventricular rate and left bundle branch block.

Multiple supraventricular arrhythmias may mimic the irregularly irregular ventricular activation seen in AF, either due to irregular atrial rate or variable atrioventricular conduction. Multifocal atrial tachycardia may be difficult to distinguish from atrial fibrillation if the P wave amplitude is low. In this case, each QRS should be preceded by a P wave, the atrioventricular delay may be slightly variable (Figure 6). In case of very high atrial rate or use of AV-nodal blocking agents non-conducted P waves may be also observed.

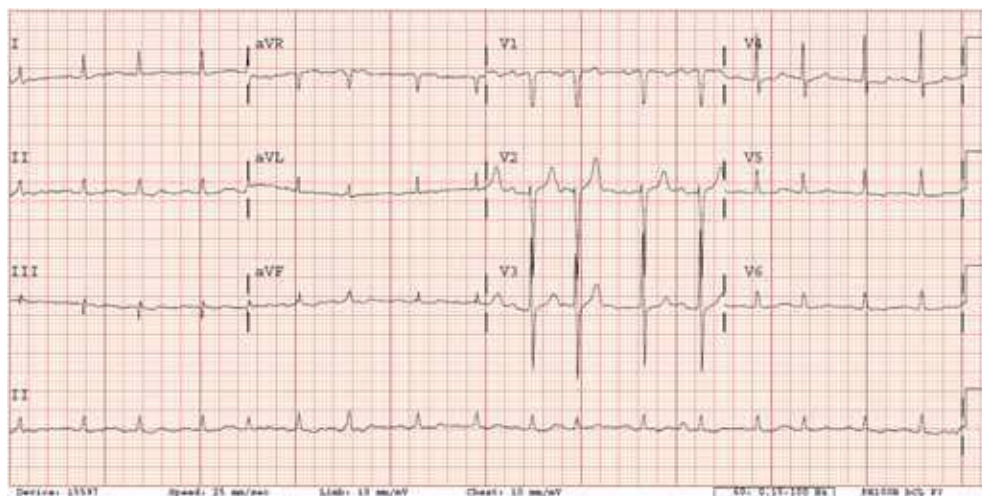


Fig. 6. Multifocal atrial tachycardia with irregularly irregular RR intervals similar to atrial fibrillation, however, each QRS is preceded by a P wave.

Atrial flutter may lead to irregular ventricular rate if the atrioventricular conduction does not follow a fixed ratio. Atypical flutters may lack the typical negative F waves in the inferior leads (Figure 7). In certain cases, serial electrograms may show evidence of both atrial fibrillation and flutter in the same patient.

Occasionally, even sinus or atrial tachycardia may be difficult to distinguish from AF, if the P waves are hidden in the QRS-T complex due to high heart rate or prolonged atrioventricular delay and frequent premature beats lead to irregular rate.

Persistently elevated ventricular rate during AF may lead to tachycardia-induced cardiomyopathy. It is important to recognize this condition, in which heart failure is a consequence rather than the cause of AF as control of the ventricular rate may lead to reversal of the myopathic process (Grogan et al., 1992). The time and heart rate required to develop tachycardia-induced cardiomyopathy is less clear, however, heart rate above 130/minute seems to be necessary in most cases (Shinbane et al., 1997).

Irregular ventricular rate itself decreases the cardiac output (Clark et al., 1997) and coronary blood flow (Wichmann et al., 1983). Myocardial contractility is not constant during AF because of force-interval relationships associated with variations in cycle length, this contributes to the largely variable pulse pressures and stroke volumes (Brookes et al., 1998).

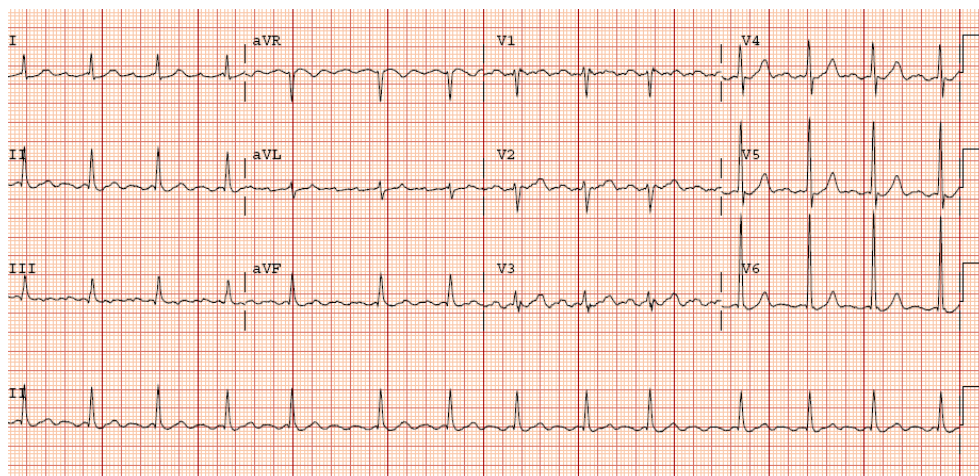


Fig. 7. Atypical atrial flutter with irregular RR intervals due to variable atrioventricular conduction.

Rapid ventricular rate during AF may adversely impact mitral valve function, increasing mitral regurgitation, due to the relationship between left atrial and left ventricular pressures. In addition, rate-related intraventricular conduction delay (such as left bundle-branch block) may further compromise the synchrony of LV wall motion and reduce cardiac output. Such conduction disturbances may further exacerbate mitral regurgitation and limit ventricular filling. Controlling the ventricular rate and regularity may reverse these adverse hemodynamic effects, however, the changes can persist for a prolonged time even after cardioversion (Upshaw, 1997). Tachycardia-induced cardiomyopathy tends to resolve within 6 months of rate or rhythm control; when tachycardia recurs, LV ejection fraction declines and HF develops over a shorter period, this is associated with a relatively poor prognosis (Nerheim et al., 2004). Although it would be clinically important to identify patients where high ventricular rate plays the major role in the development of heart failure, thus may benefit from aggressive rate and/or rhythm control, prospective identification of these cases is difficult, so far heart failure associated with relatively small left ventricular size seems to be predictive (Fujino et al., 2007).

6. Pharmacological rate control

Several complications of atrial fibrillation are due to high, irregular ventricular rate: palpitations, heart failure, and tachycardia-induced cardiomyopathy. The ventricular rate may increase excessively during exercise even when it is well controlled at rest. Medications used to control ventricular rate generally work by increasing the refractory period of the $I_{Ca,L}$ Ca^{+} current, thus increasing the filtering function of the AV node. Non-dihydropyridine (non-DHP) calcium channel inhibitors, such as verapamil and diltiazem, directly inhibit the $I_{Ca,L}$ while adrenergic β -blockers work indirectly through the adrenergic receptors. Digoxin increases parasympathetic vagal activity and is ineffective in situations when vagal tone diminishes, such as exercise. Antiarrhythmic medications, such as amiodarone or dronedarone may also be used for rate control due to their pluripotent effects. When Na^{+} channel blockers are used for cardioversion or maintenance of sinus rhythm, increase in

ventricular rate may occasionally be observed due to vagolytic effects (quinidine, disopyramide) or regularization of atrial activity (such as atrial flutter), which in turn decreases the filtering effect of concealed conduction. Adenosine binds to A1 receptors and activates $I_{K/Ado}$, a subtype of I_k similar to $I_{K/Ach}$, increasing outward K^+ current, similar to parasympathetic stimuli; it also inhibits I_f .

The definition of adequate rate control has been based primarily on short-term hemodynamic studies and mostly refers to ventricular rate below a certain limit, but has not been well studied with respect to regularity of the ventricular response. Initial rate control criteria varied with patient age, usually involved achieving ventricular rates between 60-80/minute at rest and between 90-115/minute during moderate exercise. For the AFFIRM trial, adequate control was defined as an average heart rate up to 80/minute at rest and either an average rate up to 100/minute over at least 18 hour ambulatory Holter monitoring with no rate above 100% of the maximum age-adjusted predicted exercise heart rate or a maximum heart rate of 110/minute during a 6-minute walk test (Olshansky et al., 2004). The RACE trial used heart rate less than 100/minute at rest. In the rate control arm, no differences were observed in terms of cardiovascular morbidity, mortality, and quality of life between the patients who achieved resting heart rate <80/minute, compared to those with higher resting heart rate (Groenvelde et al., 2009). A comparison of the rate control arms of the AFFIRM and RACE studies (mean heart rate 76.1 vs. 83.4/minute) showed no significant difference in the primary composite endpoint of mortality, cardiovascular hospitalization and myocardial infarction. However, patients with mean heart rates during AF within the AFFIRM (≤ 80 /minute) or RACE (< 100 /minute) criteria had a better outcome than patients with heart rates ≥ 100 /minute (hazard ratios 0.69 and 0.58, respectively, for ≤ 80 /minute and < 100 /minute compared with ≥ 100 /minute, van Gelder et al., 2006).

The large randomized, prospective RACE II trial compared lenient rate-control (resting heart rate < 110 /minute) vs. strict rate-control strategy (resting heart rate < 80 /minute and heart rate during moderate exercise < 110 /minute), in 614 patients with permanent atrial fibrillation. The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years. The estimated cumulative incidence of the primary outcome at 3 years was 12.9% in the lenient-control group and 14.9% in the strict-control group ($p < 0.001$ for the prespecified non-inferiority margin). The frequencies of the components of the primary outcome were similar in the two groups. More patients in the lenient-control group met the target heart rate: 97.7% vs. 67.0% ($p < 0.001$), with fewer total visits (median 0 vs. 2 per patient, $p < 0.001$). The frequencies of symptoms and adverse events were similar in the two groups (van Gelder et al., 2010). The study population was 66% male with an average age of 68 ± 8 years, body mass index of 29 ± 5 , left ventricular ejection fraction of $52 \pm 12\%$, 65% in NYHA functional class I. Lenient rate control with a resting heart rate < 110 /minute may be adequate for these patients. Patients with moderate to severe heart failure were underrepresented in this study (NYHA III in 4.7%, left ventricular ejection fraction $< 40\%$ in 15% of patients), the optimal heart rate for these patients is less clear.

The clinical outcomes (mortality, morbidity), that can be achieved with focusing on rate control and anticoagulation were similar to those with aggressive rhythm control using antiarrhythmic drugs and cardioversion in the large randomized AFFIRM and RACE trials (Olshansky et al., 2004; Hagens et al., 2005). However, this may be due to the relative inefficacy and poor side effect profile of current antiarrhythmic medications and may

change in the near future as new medications are developed and indications of atrial fibrillation ablation evolve. Patients who actually stayed in sinus rhythm in the AFFIRM trial, independent of treatment strategy, had better outcomes (Corley et al., 2004).

The practice guidelines on the management of atrial fibrillation, including rate control, have recently been updated by the American College of Cardiology Foundation, American Heart Association, and, and the European Society of Cardiology (Fuster et al., 2011, Table 1 and 2).

| Recommendations | Class of recommendation | Level of evidence |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|
| General | | |
| Measurement of the heart rate at rest | I | B |
| In patients with AF-related symptoms during activity, heart rate control should be assessed during exercise | I | B |
| Use of pharmacological rate control for persistent or permanent AF | I | B |
| Acute setting | | |
| Iv. beta-blocker or non-DHP calcium channel antagonist to slow down ventricular rate (caution in hypotensive patients) | I | B |
| Iv. digoxin or amiodarone for patients with AF and heart failure, without preexcitation | I | B |
| Iv. amiodarone when other measures are unsuccessful or contraindicated | IIa | C |
| Iv. procainamide or ibutilide in AF with preexcitation, if electrical cardioversion is not indicated | IIa | C |
| Iv. procainamide, disopyramide, ibutilide, or amiodarone for hemodynamically stable AF with accessory pathway | IIb | B |
| Chronic pharmacological rate control | | |
| Oral digoxin for rate control at rest in patients with HF, LV dysfunction, or sedentary lifestyle | I | C |
| Oral digoxin + beta blocker or non-DHP calcium channel antagonist for rate control at rest and during exercise. Medication choice and doses should be individualized to avoid bradycardia. | IIa | B |
| Oral amiodarone alone or in combination if adequate rate cannot at rest and during exercise cannot be achieved with beta-blocker, non-DHP calcium channel antagonist, or digoxin | IIb | C |
| Non-pharmacological rate control | | |
| Ablation of the AV node or accessory pathway when pharmacological therapy is insufficient or associated with side effects | IIa | B |
| Catheter ablation of the AV node if rate control cannot be achieved by pharmacological agents or tachycardia-mediated cardiomyopathy is suspected | IIb | C |

Table 1. Recommended procedures and interventions for ventricular rate control in atrial fibrillation. Levels of recommendation: class I – generally recommended. Class IIa – should be considered. Class IIb – may be considered. Levels of evidence: B – single randomized trial or nonrandomized studies. C – consensus opinion of experts, case studies or standard of care. AF: atrial fibrillation. DHP: dihydropyridine. Iv.: intravenous. HF: heart failure. LV: left ventricular. AV: atrioventricular.

| Contraindicated procedures and interventions | Class of recommendation | Level of evidence |
|----------------------------------------------------------------------------------------|-------------------------|-------------------|
| Digoxin alone in paroxysmal atrial fibrillation | III | B |
| Catheter ablation of the AV node without prior attempt of pharmacological rate control | III | C |
| Iv. non-DHP calcium channel antagonist in decompensated HF | III | C |
| Iv. digoxin or non-DHP calcium channel antagonist in AF with preexcitation | III | C |

Table 2. Contraindicated procedures and interventions for ventricular rate control in atrial fibrillation. Levels of recommendation: class III – generally contraindicated as there is no benefit or may be harmful. Levels of evidence: B – single randomized trial or nonrandomized studies. C – consensus opinion of experts, case studies or standard of care. *AF: atrial fibrillation. DHP: dihydropyridine. Iv.: intravenous. HF: heart failure. LV: left ventricular. AV: atrioventricular.*

6.1 Acute rate control

Patients who are symptomatic with rapid ventricular rates during AF require prompt medical management, and cardioversion should be considered if symptomatic hypotension, angina, or heart failure is present. The pharmacological agent of choice depends on the presence of comorbidities, such as heart failure/hemodynamic instability and preexcitation (Fuster et al., 2011; Table 3).

| Medication | Dose in acute setting | Class of recommendation | Level of evidence |
|----------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------|-------------------|
| No heart failure or accessory pathway | | | |
| Esmolol | 500 µg/kg slow iv. bolus, 60-200 µg/kg/min infusion | I | C |
| Metoprolol | 2.5-5 mg slow iv. bolus | I | C |
| Diltiazem | 0.25 mg/kg slow iv. bolus, 5-15 mg/h infusion | I | B |
| Verapamil | 75-150 µg/kg slow iv. bolus | I | B |
| Heart failure | | | |
| Digoxin | 0.25 mg iv. every 2 hours, up to 1.5 mg; followed by 0.125-0.375 mg/day iv. or po., slow onset of action | I | B |
| Amiodarone | 150 mg iv. over 10 minutes, 0.5-1 mg/min infusion | IIa | C |
| Accessory pathway | | | |
| Amiodarone | 150 mg iv. over 10 minutes, 0.5-1 mg/min infusion | IIa | C |
| Accessory pathway and heart failure | | | |
| - | Urgent electrical cardioversion | I | B |

Table 3. Recommendations for acute rate control in atrial fibrillation. Instead of esmolol and metoprolol, similar beta-blocking agents may be used with same class of recommendation. Levels of recommendation: class I – generally recommended. Class IIa – should be considered. Levels of evidence: B – single randomized trial or nonrandomized studies. C – consensus opinion of experts, case studies or standard of care. *Iv.: intravenous.*

Intravenous non-DHP calcium channel antagonists are effective for ventricular rate control (Boudonas et al., 1995), although these agents should be avoided in patients with

heart failure due to systolic dysfunction because of their negative inotropic effects. A randomized trial comparing intravenously administered diltiazem, digoxin and amiodarone found that patients presenting to the emergency department with AF and heart rate >120/min achieved shorter time to rate control (rate <90/minute), largest reduction in AF symptom frequency and severity scores and significantly shorter hospital stay if they were assigned to the diltiazem group, versus digoxin or amiodarone (Siu et al., 2009). Beta blockers may be particularly useful in states of high adrenergic tone, such as postoperative AF, but more data is available for rhythm control in this situation: intravenous esmolol produced more rapid conversion to sinus rhythm than diltiazem after noncardiac surgery, ventricular rates after 2 and 12 hours were similar with both treatments (Balsler et al., 1998).

Combinations may be necessary to achieve rate control, which requires careful dose titration. Although intravenous digoxin may slow down the ventricular response in AF at rest, the onset is delayed for at least 60 minutes in most patients and the peak effect does not develop for up to 6 hours. There is lack of evidence whether a second agent should be added early (to avoid possible dose-related side effects of medications) or only after administration the maximum recommended dose of the first agent. Wide variations in clinical practice exist, however, the outcomes were similar in observational studies (Buccelletti et al., 2011; Stiell et al., 2011).

6.2 Chronic rate control

There is no evidence that long-term pharmacological rate control would adversely influence left ventricular function, although bradycardia and heart block may occur as an unwanted effect of beta blockers, amiodarone, digoxin, or non-DHP calcium channel antagonists. Elderly patients and those with paroxysmal AF are more likely to experience side effects. Some patients develop symptomatic bradycardia that requires permanent pacing, while still having episodes of rapid ventricular rate. Non-pharmacological therapy should be considered when pharmacological measures fail.

Beta-blockers are safe and effective for rate control and superior to placebo. They should be initiated cautiously in patients with heart failure who have reduced ejection fraction. Most data are available for nadolol and atenolol. Patients may experience slow rates at rest, or exercise tolerance may be compromised when the rate response is blunted excessively (Segal et al., 2000). Sotalol, in addition to its antiarrhythmic effects, also provides excellent rate control (Anderson & Prystowsky, 1999). Atenolol, metoprolol, and sotalol provide better control of exercise-induced tachycardia than digoxin (Lewis et al., 1989). Carvedilol is similarly effective. Beta blockers were the most effective drug class for rate control in the AFFIRM trial (with or without digoxin), achieving rate control endpoints in 70% of patients, compared to 54% with use of calcium channel blockers (Olshansky et al., 2004).

Non-DHP calcium channel antagonist agents (verapamil and diltiazem) are the only agents that were shown to improve quality of life and exercise tolerance. Direct comparisons of verapamil and diltiazem have demonstrated similar effectiveness (Lundström & Rydén, 1990). These agents may be preferred for long-term use over beta blockers in patients with bronchospasm or chronic obstructive pulmonary disease.

The efficacy of digoxin is reduced in states of high sympathetic tone or in paroxysmal AF. The combination of digoxin and atenolol is effective for rate control (Farshi et al., 1999). In contrast to its limited effect in patients with paroxysmal AF, digoxin is moderately effective

in those with persistent AF, particularly when HF is present. Digoxin administered alone slows the resting heart rate, but it does not slow heart rate during exercise (Segal et al., 2000). Given the multiple interactions and side effects, digoxin should not be considered as first line therapy for rate control. The combination of digoxin and a beta blocker appears more effective than the combination of digoxin with a calcium channel antagonist (Farshi et al., 1999).

Amiodarone has both sympatholytic and calcium antagonist properties, which depresses AV conduction. Intravenous amiodarone is generally well tolerated in critically ill patients who develop rapid atrial tachyarrhythmias refractory to conventional treatment, but efficacy has not been sufficiently evaluated in this indication. It may be considered when first line agents are ineffective or contraindicated (Clemon et al., 1998). The potential toxicity must be carefully weighed (Fuster et al., 2011, Table 4).

| Medication | Maintenance dose | Class of recommendation | Level of evidence |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|
| No heart failure or accessory pathway | | | |
| Metoprolol | 25-100 mg twice a day | I | C |
| Diltiazem | 120-360 mg daily, divided doses or slow release | I | B |
| Verapamil | 120-360 mg daily, divided doses or slow release | I | B |
| Heart failure, no accessory pathway | | | |
| Digoxin | 0.5 mg po. loading, 0.125-0.375 mg/day po. maintenance; slow onset of action (2 days) | I | C |
| Amiodarone | 800 mg daily for 1 week, 600 mg daily for 1 week, 400 mg daily for 4-6 week, maintenance 200 mg po. daily; slow onset of action (1-3 weeks) | IIb | C |
| Accessory pathway | | | |
| - | Ablation should be considered | - | - |

Table 4. Recommendations for chronic rate control in atrial fibrillation. Instead of metoprolol, similar beta-blocking agents may be used with same class of recommendation. Levels of recommendation: class I - generally recommended. Class IIb - may be considered. Levels of evidence: B - single randomized trial or nonrandomized studies. C - consensus opinion of experts, case studies or standard of care. *po.*: oral.

Oral amiodarone decreases the ventricular rate without affecting exercise capacity, quality of life or AF symptoms, even if it is unable to cardiovert the patient (Tse et al., 2001). Dronedronarone has also good rate control characteristics in addition to its antiarrhythmic effects, with a side effect profile more favorable than amiodarone (Page et al., 2011). However, excess mortality and morbidity in elderly patients with permanent AF lead to early discontinuation of the PALLAS trial, so dronedronarone is contraindicated in permanent AF.

In patients with paroxysmal atrial flutter and fibrillation, propafenone or flecainide used for rhythm control may promote 1:1 AV conduction during the flutter, leading to excessive ventricular rate. These agents must be coadministered with AV nodal blocking agents, unless ablation has been performed without recurrence of the flutter.

7. Non-pharmacological rate control

The efficacy of pharmacological interventions designed to achieve rate control in patients with AF has been about 80% in clinical trials (Weerasooriya et al., 2003). Non-pharmacological measures should be considered in patients who are still symptomatic or in whom adequate rate control cannot be achieved.

Ventricular pacing at approximately the mean ventricular rate during AF may regularize the ventricular rhythm during AF by eliminating longer ventricular cycles and reducing the number of short ventricular cycles due to retrograde block (Wittkamp et al., 1988). This may be useful for patients with marked variability in ventricular rates or resting bradycardia during pharmacological treatment. However, frequent right ventricular pacing may lead to left ventricular dysfunction. Patients with paroxysmal AF indicated a preference for the paced regularization strategy in a study, while patients with permanent AF showed no preference despite a 29% improvement of irregularity (Simpson et al., 2001). However, another study showed no benefit in any group (Tse et al., 2004).

AV node ablation in conjunction with permanent pacemaker implantation provides effective control of the heart rate and improves symptoms in selected patients with AF. Patients most likely to benefit from this strategy are those with symptoms or tachycardia mediated cardiomyopathy related to rapid ventricular rate during AF, that cannot be controlled adequately with antiarrhythmic or negative chronotropic medications (Wood et al., 2000). In the Ablate and Pace Trial, 25% of patients with AF who had an ejection fraction below 45% displayed a greater than 15% increase in ejection fraction after ablation (Kay et al., 1998).

The slow pathway of the AV node has a short effective refractory period that may be responsible for maintaining rapid ventricular rate during AF. Catheter ablation of this area (inferior atrial inputs to the AV node) slows the ventricular rate during AF and improves symptoms without pacemaker implantation (Williamson et al., 1995). However, the ventricular rate rises over the 6 months following ablation.

Complete AV nodal ablation and permanent pacemaker implantation demonstrated better symptom relief than AV node modification alone. The 1-year mortality rate after AV nodal ablation and permanent pacemaker implantation is approximately 6.3%, with 2.0% risk of sudden death. Although a causal relationship between the procedure and sudden death still remains controversial, the pacemaker is routinely set to a high basic rate, such as 90/minute for the first month after ablation, to avoid bradycardia-induced tachyarrhythmias after a prolonged period of rapid ventricular rate (Evans et al., 1991). Although the symptomatic benefits of AV nodal ablation are clear, limitations include the persistent need for anticoagulation, loss of AV synchrony, and lifelong pacemaker dependency.

As the adverse hemodynamic effects of right ventricular apical pacing are well known, biventricular devices should be considered in these patients, especially in those with left ventricular dysfunction or heart failure. The PAVE trial showed better exercise tolerance with biventricular pacing, but no mortality benefit was realized over the relatively short follow up period of 6 months (Doshi et al., 2005). A subgroup analysis suggested that functional improvements were confined to patients with left ventricular ejection fraction below 35% before ablation. Upgrade to a biventricular device should be considered after AV node ablation in patients with heart failure and a right ventricular pacing system (Leon et al., 2002).

In patients with heart failure and AF, undergoing cardiac resynchronization therapy, ablation of the AV node should be considered as rapid ventricular rate may lead to suboptimal biventricular stimulation. Biventricular stimulation should be at least 98% to achieve optimal benefits from resynchronization, which may be difficult to achieve in AF without AV node ablation (Hayes et al., 2011; Figure 8). In addition, the irregular rhythm alone adversely affects the hemodynamic function.



Fig. 8. Importance of rate control in patients with cardiac resynchronization devices. These devices improve hemodynamics in patients with severe left ventricular dysfunction and intraventricular conduction delay by simultaneously pacing the right and left ventricle. In case the ventricles get activated before the delivery of the pacing stimuli, such as in atrial fibrillation with suboptimal rate control, the only option left for the device is to pace simultaneously with the sensed beat (sense response pacing). However, this fusion beat may be hemodynamically inferior to the biventricular paced beat. In addition, irregularity of the rhythm adds to the hemodynamic derangement.

Parasympathetic nerve stimulation is an experimental method to achieve rate control via selective stimulation of the parasympathetic nerves supplying the AV node. This may be accomplished with a coronary sinus electrode or an active fixation electrode positioned near the AV node (Vago et al., 2004). This method may be an option in the future for patients with highly symptomatic paroxysmal atrial fibrillation, when medications or ablation are not desired, tolerated or effective. However, in some cases, atrial fibrillation may be vagally mediated and this method of stimulation may potentially increase the incidence of arrhythmias or increase the duration of the episodes.

8. Preexcitation in atrial fibrillation

A bypass tract with non-decremental conduction and short effective refractory period may allow the almost unfiltered propagation of AF to the ventricles, resulting in an extremely high ventricular rate, even >300/minute. Variable QRS morphology and irregular rate may

be useful clues for identification and differentiation from ventricular tachycardia. Prompt recognition and treatment is important as this entity may rapidly degenerate to ventricular fibrillation (Fuster V., 2011). In hemodynamically stable patients with preexcitation, type I antiarrhythmic agents or amiodarone may be administered intravenously. AV nodal blocking drugs are contraindicated as the heart rate increases when the ventricles are activated solely through the bypass tract. The potential for beta blockers to facilitate conduction across the accessory pathway is controversial. In unstable cases, prompt electrical cardioversion is the treatment of choice. Beta blockers and calcium channel blockers may be considered for chronic oral use (Petri et al., 1983).

9. Conclusion

Ventricular rate in atrial fibrillation is determined by a complex interaction between the atrial electrical activity and properties of the AV node. Although the hemodynamic consequences of the rapid and irregular ventricular rate are well known, details of electrophysiology still need to be elucidated.

Rate control is one of the most important aspects in the treatment of patients with atrial fibrillation, with substantial evidence supporting the use of pharmacological agents in both acute and chronic settings. Effective non-pharmacological treatment options may be used in refractory cases.

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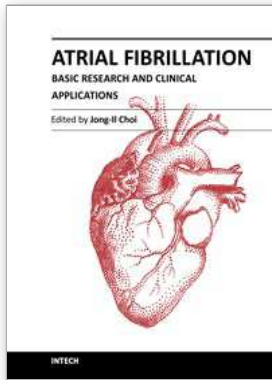
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