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A Brief Review of a Common Clinical Question: Intravenous Diltiazem or Metoprolol for Atrial Fibrillation with Rapid Ventricular Response?

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Abstract

Two classes of rate controlling medications—beta blockers (BBs) and non-dihydropyridine calcium channel blockers (CCBs)—are given to patients who present with atrial fibrillation (AF) with rapid ventricular response (RVR). Both are Class I recommendations from the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) for the management of AF with RVR. Multiple studies support the view that diltiazem is more effective than metoprolol, even though data from the AFFIRM trial suggests BBs are more frequently used. CCBs are generally avoided in AF with RVR patients who have concomitant heart failure with reduced ejection fraction (HFrEF) for concern of triggering decompensation. However, some recent studies indicate this idea may be unfounded. The aim of this article is to compare the efficacy of diltiazem and metoprolol for rate control in AF with RVR and examine the use of diltiazem in patients with both AF with RVR and HFrEF.

Keywords

Atrial Fibrillation, Rapid Ventricular Response, Diltiazem, Metoprolol, Heart Failure with Reduced Ejection Fraction

1. Introduction

AF is a leading cause of emergency room visits and the most common presenting cardiac arrhythmia worldwide [1]. During AF, the sinus node does not function as the pacemaker; instead, ectopic foci of atrial activity fire irregularly, resulting in rapid and ineffective atrial contractions. Commonly these foci are lo-

cated near the pulmonary veins [2]. The irregular atrial activity is conducted through the atrioventricular (AV) node and His-Purkinje System resulting in ventricular depolarization. When the ventricular rate is >120 bpm, it is termed "RVR" [1]. AF with RVR can be triggered by an underlying cardiac condition or be reactive to other noncardiac processes. RVR is more likely to induce symptoms such as palpitations, dyspnea, dizziness, and anxiety. Heart failure (HF) symptoms can be precipitated, or worsened, by the increased myocardial oxygen demand during RVR [3].

BBs and non-dihydropyridine CCBs are considered first line therapies in AF with RVR [4]. Within these classes, diltiazem and metoprolol are the most commonly used agents. Multiple studies suggest diltiazem has a faster onset, leads to greater reduction in ventricular rate, and has less effect on systolic blood pressure than metoprolol [1]. Some studies are challenging the notion that diltiazem leads to worse short-term outcomes in AF with RVR patients who also have HFrEF [10] [11].

Due to the prevalence of AF, clinicians often face a specific question: diltiazem or metoprolol for ventricular rate reduction? Considering the trigger of AF, concurrent illnesses, and underlying comorbidities, one medication may be more appropriate given the clinical context.

Consider the following clinical scenario:

> A 67-year-old Caucasian man with past medical history of hypertension and type 2 diabetes mellitus presents to the emergency department with complaints of palpitations and dyspnea for the past day. He has no history of HF. Vital signs are significant for a blood pressure of 147/88 mmHg and heart rate (HR) of 153 beats-per-minute (bpm). Electrocardiogram reveals AF. He is placed on therapeutic anticoagulation. Should he receive intravenous (IV) diltiazem or metoprolol for AF with RVR?

In this review analysis, we will discuss these two medications, their mechanisms of action, formulations, and which clinical scenarios they may be more efficacious. We will also outline pertinent studies comparing diltiazem and metoprolol, and explore their use in patients with concomitant HFrEF.

2. Comparative Analysis of Diltiazem and Metoprolol

Acute management of AF with RVR includes rate controlling medications and anticoagulation to improve symptoms and reduce the risk of stroke. The decision to employ a rate or rhythm control strategy in patients with AF is nuanced and depends on many factors; however, rate control is generally preferred in the acute setting [4].

Diltiazem is a non-dihydropyridine CCB that preferentially blocks calcium influx in myocardial cells resulting in negative inotropic effects. CCBs also act on the sinus and AV nodes decreasing chronotropy and dromotropy. These effects lead to a reduction in myocardial oxygen demand and HR. CCBs affect vascular

smooth muscle and lead to vasodilation and reduced systemic vascular resistance, although this is more significant in dihydropyridine CCBs [5].

Metoprolol is a BB that selectively inhibits beta-1 receptors in cardiac tissue [6]. This inhibition causes negative inotropic and chronotropic effects, similar to diltiazem. The overall outcome is reduced cardiac output. BBs decrease myocardial oxygen demand which improves anginal symptoms. Metoprolol also has a negative effect on the renin-angiotensin-aldosterone system (RAAS), thus lowering sodium and water retention and reducing blood pressure. Inhibiting RAAS also decreases beta adrenergic activity. For this reason, metoprolol is a better option for RVR in hyperadrenergic states [7].

Both medications are available in IV and oral formulations which is helpful in transitioning patients once acute rate reduction is achieved. The onset of diltiazem is shorter – approximately 3 minutes compared to 20 minutes with metoprolol after IV push. Duration of action also tends to be shorter with diltiazem, although this depends on how long it is infused (**Table 1**). Diltiazem is administered as an initial IV bolus of 0.25 mg/kg, then transitioned to a maintenance dose of 5 - 15 mg/hour for the ventricular rate reduction. Continuous infusion is limited to 24 hours to limit drug accumulation [5]. Unlike diltiazem, metoprolol cannot be infused continuously. It is given at a dose of 2.5 - 5 mg via IV push.

Diltiazem and metoprolol share several contraindications due to their AV nodal blocking and negative chronotropic and inotropic effects. They should not be used in patients with sick-sinus syndrome, high degree AV block, cardiogenic shock, or hypotension [5] [6].

3. Analysis

A total of 14 studies were reviewed in a systematic review and meta-analysis by Sharda, *et al.* Diltiazem was associated with increased success of rate control in patients hospitalized with AF with RVR as compared to metoprolol [8]. There was no significantly increased risk of hypotension or bradycardia in patients who received IV diltiazem. These results were supported by another meta-analysis which demonstrated that IV diltiazem led to greater ventricular rate reduction and faster onset of action with no significant difference in adverse events compared to metoprolol [1]. In a third meta-analysis, Jafri, *et al.* concluded that patients treated

Table 1. Formulations and pharmacokinetics of diltiazem and metoprolol.

	Diltiazem	Metoprolol
Formulations	IV (bolus, continuous infusion), oral (IR, ER)	IV (push), oral (IR, ER)
Onset of action (IV)	3 minutes (bolus)	20 minutes
Duration of action (IV)	1 - 3 hours (bolus), 0.5 - 10 hours (infusion)	5 - 8 hours
Half-life (IV)	3 - 4 hours (bolus), 4 - 5 hours (infusion)	2 - 6 hours

with IV diltiazem had a greater decrease in HR compared to those given IV metoprolol at 5, 10, and 15 minutes, although these findings were not statistically significant (Table 2) [9].

Some studies have challenged the concept that diltiazem may precipitate, or worsen, HF symptoms in patients with HFrEF. Long-term CCB use has been shown to worsen ejection fraction in HFrEF patients, but this has not been clearly replicated in the acute setting [10]. Diltiazem and metoprolol have been analyzed retrospectively in patients who had AF with RVR and concomitant HFrEF. There was no significant difference in safety outcomes, including hypotension, intensive care unit (ICU) admission, or in-hospital mortality [10] [11]. Metoprolol was associated with a higher rate of cardioversion in AF patients

Table 2. Major findings from studies comparing IV diltiazem and metoprolol in the treatment of atrial fibrillation with rapid ventricular response.

Study	Study design and sample size	Patient population*	Endpoints analyzed	Outcome
Sharda, *et al.*	Meta-analysis and systematic review Total studies: 14 - 3 RCTs and 11 retrospective studies N = 1732 patients (pooled analysis was done with 1477 and 1203 patients studies when analyzing the risk of hypotension and bradycardia, respectively)	Patients ≥ 18 years old with AF with RVR**	• Achievement of rate control target • Risk of hypotension with diltiazem compared to metoprolol • Risk of bradycardia with diltiazem compared to metoprolol	Diltiazem was associated with increased achievement of reaching the rate control target without a significantly increased risk of hypotension and bradycardia.
Lan, *et al.*	Meta-analysis Total studies: 17 - 9 RCTs and 8 cohort studies N = 1214 patients	Patients ≥ 18 years old with AF with RVR and a ventricular rate ≥ 120 bpm	• Ventricular rate reduction • Average onset of action time • Rate of adverse events with diltiazem compared to metoprolol	Diltiazem was associated with a greater decrease in ventricular rate and shorter onset of action time. There was no association with increased risk of adverse events compared to metoprolol.
Jafri, *et al.*	Meta-analysis and systematic review Total studies: 3 - 3 RCTs N = 140 patients	Patients ≥ 18 years old with AF with RVR**. Patients with hypotension were excluded.	• MD in ventricular rate reduction at 5 minutes • MD in ventricular rate reduction at 10 minutes • MD in ventricular rate reduction at 15 minutes	Treatment with diltiazem resulted in greater MD if ventricular rate at 5, 10 and 15 minutes, although not statistically significant.

RCT: randomized control trial. MD: mean difference. *"Patient population" does not represent the complete inclusion and exclusion criteria of each study. **RVR was defined as ≥120 bpm in most studies; however, some termed "RVR" as a ventricular rate of ≥100 bpm or ≥110 bpm.

with HFrEF [11]. HF symptoms are often driven by tachycardia and increased myocardial oxygen demand in patients with AF and RVR. Therefore, whichever agent provides swift rate reduction is efficacious. Current AHA/ACC/HRS guidelines, however, recommend not using CCBs in patients with AF with RVR and HFrEF due their negative inotropic effects and concern of triggering decompensation. Instead, BBs or a rhythm control strategy is advised in this setting [4].

The decision to use IV diltiazem or metoprolol in AF with RVR is complex and patient specific. The acute treatment goal for AF with RVR is improvement of symptoms while mitigating stroke risk through rate reduction and anticoagulation. IV diltiazem has a faster onset of action and is not associated with an increased risk of hypotension or bradycardia when compared to IV metoprolol. Diltiazem is also available as a bolus and continuous infusion, while IV metoprolol is given as a push dose. AF with RVR patients in hyperadrenergic states are better suited for IV metoprolol due to its antiadrenergic effects.

IV diltiazem was not associated with an increased risk of ICU admission, in-hospital mortality, or worsening HF in two small retrospective studies in patients with both AF with RVR and HFrEF. Acute treatment with IV diltiazem may be beneficial by reducing the ventricular rate when AF is the trigger of HF symptoms. Further larger prospective studies are needed to fully evaluate the short-term effect of CCBs in AF with RVR patients with concomitant HFrEF.

4. Conclusion

In summary, diltiazem has been shown to improve ventricular rate in AF with RVR without a significantly increased risk of adverse events when compared to metoprolol in several meta-analyses and systematic reviews [1] [8] [9]. Patients who develop post-operative, trauma related, or other hyperadrenergic etiologies of AF are more likely to improve with BBs [7]. The safety and efficacy of IV diltiazem in AF with RVR and HFrEF has also been investigated, although further prospective studies with larger sample sizes should be performed to determine if diltiazem has a greater role in this clinical scenario [10] [11]. While diltiazem and metoprolol are both effective at reducing ventricular rate in AF with RVR, the choice of agent should depend upon the clinical context, underlying comorbidities, and potential contraindications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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