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Heart rate outcomes with concomitant parenteral calcium channel blockers and beta blockers in rapid atrial fibrillation or flutter

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ABSTRACT

Background: Patients who present with atrial fibrillation (AF) or flutter with rapid ventricular response (RVR) and hemodynamic stability may be managed with either an intravenous (IV) nondihydropyridine calcium channel blocker (CCB) or a beta-blocker (BB). Patients without improved heart rates may need to switch to, or add, a second AV nodal blocker.
Objective: To evaluate the incidence of rate control achievement and bradycardia in patients in AF or atrial flutter with RVR who receive both an intravenous CCB and a BB.
Methods: A retrospective chart review of patients who received concomitant intravenous CCB or BB for the treatment of rapid AF or atrial flutter from April 2016 through July 2018 in the emergency department. Patients were excluded if the second agent was ordered but not administered, or if they received IV amiodarone or digoxin.
Results: A total of 136 patients were included in the analysis, and of those, 46% ($n = 62$) of patients achieved a heart rate <110 bpm without bradycardia, and 3.7% ($n = 5$) developed bradycardia. Age, initial heart rate, time between CCB and BB administration, addition of an oral CCB or BB administration, or administration of IV magnesium did not impact target heart rate achievement.
Conclusion: Adding a second nodal blocker in patients who did not achieve rate control with the first agent resulted in heart rate control 46% of the time. The development of symptomatic bradycardia was uncommon.

1. Introduction

Atrial fibrillation (AF) is the primary diagnosis for approximately 3.9 million emergency department (ED) visits annually [1]. The American College of Cardiology/American Heart Association guideline recommends monotherapy administration of either an intravenous (IV) nondihydropyridine calcium channel blocker (CCB) or IV beta-blocker (BB) to obtain rate control in the management of AF with rapid ventricular rate (RVR) in patients without significant heart failure or hemodynamic instability [2]. Studies comparing the two medication classes, both in ED and non-ED patients, demonstrate both CCBs and BBs, used monotherapy, are safe and effective at attaining acute rate control [3-9]. However, patients' individual responses to these atrioventricular (AV) nodal blocking agents vary, which may result in the need to switch to, or add, a second AV nodal blocker. There is a theoretical concern that combining two IV AV nodal blockers increases the risk for symptomatic bradycardia or heart block, potentially leading to hemodynamic instability. However, a paucity of data exists around this concern. Therefore, the question remains whether dual IV AV nodal blockade is effective in obtaining rate control and whether concomitant use increases the risk of adverse effects. The purpose of this study was to evaluate the frequency of rate control achievement and bradycardia in patients with AF or atrial flutter with RVR who received both an IV CCB and IV BB within 4 h of each other in the ED.

2. Methods

This was a retrospective, single center, study of patients who received an IV CCB and IV BB for the treatment of AF or atrial flutter with RVR from April 2016 through July 2018. Adult patients (age ≥ 18 years) who presented to the ED with AF or atrial flutter with RVR with initial heart rate >120 beats per minute (bpm) and received an IV CCB and BB within 4 h of each other were included. We selected this time frame to account for one half-life of overlap between the most commonly used CCBs (diltiazem, verapamil) and BB (metoprolol). Patients

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were excluded if the second rate-control agent was ordered but not administered, if the first dose of the second agent was administered outside of the ED, if post-administration heart rates were not documented, or if IV amiodarone or digoxin were administered. Lack of post-administration blood pressure documentation was not an exclusion criterion. IV magnesium could be given at the discretion of the treating clinician given its potential to increase the AV node refractory period [10,11].

Baseline data extracted from the medical record included age, sex, initial rhythm, home rate control agent(s), IV rate control agents administered in the ED, doses of rate control agents, time elapsed between the two agents, and administration of oral CCB or BB or IV magnesium during the ED stay. The heart rate prior to administration of the first rate control agent and average hourly heart rates prior to second agent administration were also collected, as were blood pressures, when available. Given the high variability of the number of recorded heart rates around the times of IV CCB and IV BB administration, we collected the average heart rate at 15, 30, 60, and 120 min following the last administered dose of the second agent. We defined the target heart rate as <110 bpm and rebound as the recurrence of a heart rate >110 bpm within 2 h after receiving the last dose of the second agent. Hypotension was defined as a systolic blood pressure < 90 mmHg.

The primary outcome was achievement of the target heart rate within 2 h of the second agent. The secondary safety outcome was the development of bradycardia, defined as a heart rate <60 bpm, within 2 h after the last dose of the second agent.

Descriptive statistics (percentages, means, medians) were calculated using Microsoft Excel. SPSS was used for logistic regression statistical analysis.

3. Results

Over the 26-month study period, we identified 229 charts for review. Of these, 93 met exclusion criteria leaving 136 for analysis (Fig. 1). The most common reason for exclusion was that the second agent was administered more than 4 h after the last dose of the first agent. The mean age was 69.4 years (SD 11.9), and 57.4% of patients were male. The mean heart rate at presentation was 146.4 bpm (SD 18.6) and 85.3% of patients had AF as the initial rhythm. Regarding home medications, 65 (47.8%) patients were on an oral BB, 5 (3.7%) patients were on an oral CCB, 16 (11.8%) patients were on both an oral CCB and BB, and 45 (33.1%) patients were not on any rate control agents. The remaining 5 patients were on amiodarone or digoxin home medications.

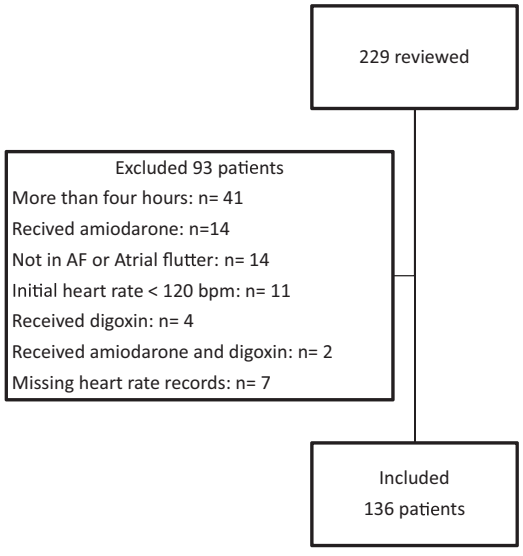

Fig. 1. Flow chart of inclusion and exclusion.

Baseline characteristics are listed in Table 1 and treatment allocations, including medication doses, in Table 2. Ninety-two (67.7%) were treated with metoprolol as the first-line agent. The mean time between the last dose of first nodal blocker and first dose of second nodal blocker was 88.4 min (SD 61.2). There were 56 patients who received the second agent within 60 min of the last dose of the first agent.

Sixty-two patients (46%) achieved a heart rate <110 bpm without bradycardia or rebound in heart rate within the two-hour monitoring period following the last dose of the second rate control agent (Fig. 2). Logistic regression analysis found no association between patient age, initial heart rate, time between IV CCB and BB, oral CCB or BB administration, or administration of IV magnesium administration on target heart rate achievement (Table 3). Fifty two patients received IV magnesium, and 23 (44.2%) of those achieved target heart rate.

Five patients (3.7%) developed bradycardia (Table 4). Four patients did not develop any symptoms or need intervention, including one patient who experienced a 15 s sinus pause and was given atropine despite remaining asymptomatic during the episode. The fifth patient developed symptomatic bradycardia that required the administration of vasopressors and intensive care unit admission. Hypotension developed after the predefined two-hour evaluation period.

Blood pressure (BP) was recorded in 120 patients (88.2%) within 1 h after receiving the first agent (BP range 90–225/50–118). No patients developed hypotension after the first agent. BP was recorded in 89 patients (65.4%) within 2 h after receiving the second agent. Eight patients (9%) developed hypotension, most within 1 h (7 patients). The lowest systolic BPs for these patients ranged 72–88 mmHg. Of these 8 patients, five (62.5%) also received intravenous magnesium. None of the patients who developed hypotension were concomitantly bradycardic during the evaluation period.

4. Discussion

This study evaluated target heart rate achievement when multiple IV nodal blockers were administered. Compared with previous literature that investigated CCB versus BB monotherapy, we found less successful target heart rate achievement [3,4]. However, this patient population is different from those previously studied in that the majority of our patient population were not treatment naïve.

Fifty one percent of patients did not attain rate control based on heart rate goal <110 bpm when switched to a second nodal agent. Additionally, about 4% of patients who received concomitant CCB and BB developed bradycardia, which is infrequent, but not negligible. It is unclear how the total doses of the two nodal blockers used could have affected bradycardia development, as some patients received weight-based doses and others fixed doses of diltiazem [12]. Therefore, combining AV nodal blockers may be an option for patients that fail to achieve rate control with a solitary agent, but close monitoring is advised.

We designed our study to capture dual nodal blocker effect based on the pharmacokinetic profiles of the most commonly used CCBs and BBs for AF and flutter. While our study did not find any patients who were

Table 1
Baseline characteristics.

Baseline characteristics	$N = 136$
Age, years, mean (SD)	69.4 (11.9)
Male, n (%)	78 (57.4)
Initial rhythm, n (%)	
Atrial fibrillation	116 (85.3)
Atrial flutter	20 (14.7)
Initial heart rate, bpm, mean (SD)	146.4 (18.6)
Home medication(s), n (%)	
BB monotherapy	65 (47.8%)
CCB monotherapy	5 (3.7%)
CCB and BB	16 (11.8%)
Other rate control agent	5 (3.7%)
No home rate control agent	45 (33.0%)

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Table 2
Treatment allocations.

First rate agent, n (%)	
Metoprolol	92 (67.7)
Diltiazem	43 (31.6)
Verapamil	1 (0.7)
Second rate agent, n (%)	
Metoprolol	44 (32.3)
Diltiazem	87 (64.0)
Verapamil	5 (3.7)
Median dose of the first agent, mg (95% CI)	
Metoprolol	15 (12.9–15.6)
Diltiazem	20 (23.7–35.2)
Verapamil	30
Median dose of the second agent, mg (95% CI)	
Metoprolol	10 (8.2–12.4)
Diltiazem	10 (14.0–18.5)
Verapamil	5 (1.2–8.8)
Time between IV CCB and BB, minutes, mean (SD)	87.7 (59.7)
Received oral CCB or BB following IV dose, n (%)	107 (79.3)
Received IV magnesium, n (%)	52 (38.2)

Table 3
Logistic regression analysis of the association of reaching a heart rate of <110 bpm.

Variables	Adjusted odds ratio	95% confidence interval	*p* value
Age	0.99	0.96–1.02	0.35
Initial heart rate	0.99	0.98–1.01	0.51
Received oral CCB or BB	0.63	0.27–1.51	0.30
Received IV magnesium	1.53	0.75–3.12	0.25
Time between IV CCB and BB	1.002	0.996–1.008	0.51

simultaneously bradycardic and hypotensive, one patient was noted to develop both after the evaluation time frame of 2 h past the last dose of the second nodal blocking agent. The fifth patient who developed bradycardia was not hypotensive within the evaluation time frame, but did become hypotensive shortly after the 2 h. This patient was symptomatic with nausea, vomiting, and shakiness and required vasopressors and intensive care admission. It is unclear to what extent dual nodal blockers affected her hemodynamic instability.

This study has additional limitations due to the retrospective nature. Confounders, such use of oral rate control agent, the time between IV doses, and use of IV magnesium, could not be controlled for throughout the monitoring period. As the focus of this study was on the efficacy of heart rate control, patients meeting the heart rate inclusion criteria but without concomitantly documented blood pressures were included, meaning that only 88% of patients had blood pressures documented in the 2 h after receiving the second agent. As such, patients may have experienced hemodynamic perturbations that were not recorded. Due to the exclusion of patients who received amiodarone and digoxin, this study cannot evaluate the additionally confounding effects those agents on both the efficacy and safety outcomes. Due to the strict inclusion criteria, the number of subjects included was small, limiting generalizability. In addition, this study lacked a comparator group, with study results only able to be compared to previously published literature of patients receiving monotherapy with either agent. Further controlled studies are warranted to elucidate the effects of dual nodal blockade on target heart rate achievement and adverse effects.

5. Conclusions

In ED patients presenting with AF or atrial flutter who do not achieve heart rate control with a single agent, the addition of a second rate control agent resulted in heart rate control 46% of the time. While bradycardia was uncommon, occurring in 3.7% of cases, one patient required ICU admission for symptomatic bradycardia. Hypotension was recorded in 9% of patients receiving two IV nodal blocking agents. If dual nodal blockade is utilized, close monitoring is warranted.

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CRediT authorship contribution statement

Shuroug A. Alowais: Methodology, Investigation, Writing - original draft, Visualization. **Bryan D. Hayes:** Methodology, Writing - original draft, Writing - review & editing. **Susan R. Wilcox:** Methodology, Writing - original draft, Writing - review & editing. **Jennifer Le:** Investigation, Validation. **Jennifer L. Koehl:** Methodology, Writing - original draft, Writing - review & editing. **Lanting Fuh:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision.

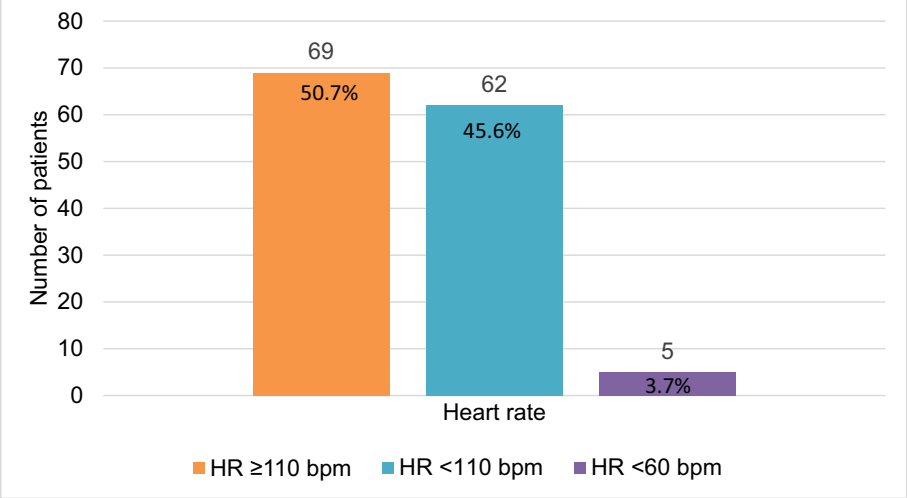

Fig. 2. Heart rate outcomes.

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Table 4
Bradycardia cases.

Age/ gender	Rhythm/ rate	First agent/ total IV dose	Time between two rate agents	Second agent/ total IV dose	IV magnesium	Time to bradycardia development	Lowest heart rate	Time to resolution	Symptoms
67/F	AF/177	Metoprolol/20 mg	66 min	Diltiazem/10 mg	Y	30 min	56	~2 h Patient was discharged	Asymptomatic, no hypotension
68/F	AF/152	Diltiazem/20 mg	127 min	Metoprolol/20 mg	N	89 min	53	4 h and 24 min	Asymptomatic, no hypotension
53/M	AF/127	Diltiazem/60 mg	34 min	Metoprolol/5 mg	Y	53 min	57	10 min	Asymptomatic, no hypotension
73/M	AF/144	Metoprolol/30 mg	17 min	Diltiazem/10 mg	Y	28 min	36	13 h then went above 60 and continued to be fluctuating for 2 days	Asymptomatic, awake and talking during a 15-second sinus pause. No hypotension. Given atropine.
70/F	AF/145	Metoprolol/35 mg	77	Diltiazem/20 mg	Y	115 min	32	15 min	Symptomatic, with nausea/vomiting and shakiness, though mental status maintained. No hypotension during evaluation period, but required vasopressors and intensive care unit admission.

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