Safety and Efficacy of Prehospital Diltiazem for Atrial Fibrillation with Rapid Ventricular Response

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Abbreviations:
AFIB: atrial fibrillation
ALS: Advanced Life Support
ECG: electrocardiogram
EMS: Emergency Medical Services
ePCR: electronic patient care record
OCEMS: Orange County EMS
RVR: rapid ventricular response
SVT: supraventricular tachycardia
WPW: Wolff-Parkinson-White

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Abstract

Introduction: Atrial fibrillation (AFIB) with rapid ventricular response (RVR) is a common tachydysrhythmia encountered by Emergency Medical Services (EMS). Current guidelines suggest rate control in stable, symptomatic patients.

Problem: Little is known about the safety or efficacy of rate-controlling medications given by prehospital providers. This study assessed a protocol for prehospital administration of diltiazem in the setting of AFIB with RVR for provider protocol compliance, patient clinical improvement, and associated adverse events.

Methods: This was a retrospective, cohort study of patients who were administered diltiazem by providers in the Orange County EMS System (Florida USA) over a two-year period. The protocol directed a 0.25mg/kg dose of diltiazem (maximum of 20mg) for stable, symptomatic patients in AFIB with RVR at a rate of >150 beats per minute (bpm) with a narrow complex. Data collected included patient characteristics, vital signs, electrocardiogram (ECG) rhythm before and after diltiazem, and need for rescue or additional medications. Adverse events were defined as systolic blood pressure <90mmHg or administration of intravenous fluid after diltiazem administration. Clinical improvement was defined as a heart rate decreased by 20% or less than 100bmp. Original prehospital ECG rhythm interpretations were compared to physician interpretations performed retrospectively.

Results: Over the study period, 197 patients received diltiazem, with 131 adhering to the protocol. The initial rhythm was AFIB with RVR in 93% of the patients (five percent atrial flutter, two percent supraventricular tachycardia, and one percent sinus tachycardia). The agreement between prehospital and physician rhythm interpretation was 92%, with a Kappa value of 0.454 (P <.001). Overall, there were 22 (11%) adverse events, and 112 (57%) patients showed clinical improvement. When diltiazem was given outside of the existing protocol, the patients had higher rates of adverse events (18% versus eight percent; P = .033). Patients who received diltiazem in adherence with protocols were more likely to show clinical improvement (63% versus 46%; P = .031).

Conclusion: This study suggests that prehospital diltiazem administration for AFIB with RVR is safe and effective when strict protocols are followed.

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Introduction

Atrial fibrillation (AFIB) is an increasingly common dysrhythmia in the aging population. It affects an estimated 2.7-6.1 million people within the United States, with a prevalence as high as nine percent in people 65 and older.[1] Atrial fibrillation can cause a wide variety of symptoms, including palpitations, shortness of breath, fatigue, syncope, and chest pain. Over 750,000 hospitalizations each year are attributed to this condition.[2] While the irregularity of AFIB can cause symptoms, most patients decompensate when AFIB leads to a rapid ventricular response (RVR). Symptomatic AFIB with RVR can be attributed to decreased cardiac output secondary to loss of ventricular diastolic filling time, as well as loss of the atrial kick, both of which are required for optimal ventricular filling. As with other tachydysrhythmias, patients can also suffer from decreased coronary artery perfusion

leading to cardiac ischemia. Currently, the American Heart Association (Dallas, Texas USA) and the American College of Cardiology (Washington, DC USA) recommend rate control as the initial treatment for patients with acute onset of stable, symptomatic AFIB with RVR. Depending on patient's comorbid health conditions, guidelines recommend use of non-dihydropyridine calcium channel blocker, beta blocker, digoxin, or amiodarone to establish rate control in symptomatic patients.[1] Given that Emergency Medical Services (EMS) providers are often the first to provide care for patients with AFIB when they develop complications from RVR, the ability to safely provide prehospital rate control is appealing.

Diltiazem is a non-dihydropyridine calcium channel blocker which is commonly used as a first-line agent for rate control in patients with AFIB with RVR. Over the past 30 years, it has become increasingly popular in the treatment of acute, rapid AFIB due to its short time of onset as well as its relatively safe side effect profile. In multiple randomized control trials, diltiazem has been shown to affect rate control on patients with AFIB with RVR in a timely manner when compared to other commonly used agents such as beta blockers (metoprolol or esmolol), digoxin, and amiodarone.[3–8]

Used judiciously, diltiazem has proven to be a safe and effective medication when given to patients with appropriate indications in a hospital setting.[3,6] However, selecting the appropriate patients to administer diltiazem to requires an accurate history, detailed physical examination, analysis of vital signs, and correct interpretation of a patient's electrocardiogram (ECG). This can be challenging in the prehospital setting. Despite the fact that diltiazem administration has been implemented in many EMS protocols throughout the nation, there is a paucity of data to demonstrate the efficacy and safety of this medication in the prehospital setting. The goal of this study was to determine whether the prehospital administration of diltiazem to adult patients with rapid AFIB, in accordance with a carefully developed EMS protocol in a large regional EMS system, was safe and effective. This study evaluated protocol compliance, patient clinical improvement, and adverse events after the administration of diltiazem.

Methods

Design and Setting

This was a retrospective, cohort study of all patients who were administered diltiazem by prehospital providers in the Orange County EMS (OCEMS; Florida USA) system over a two-year period from August 1, 2014 through August 6, 2016. Orange County, Florida is an urban/suburban region with a population of approximately 1.2 million individuals. The OCEMS system is a single tier, multi-agency EMS system comprised of eight Advanced Life Support (ALS) response agencies responding to approximately 200,000 EMS calls annually under unified medical direction. Patient care is documented by electronic patient care record (ePCR), including uploaded 12 lead ECGs and/or rhythm strips obtained with the LifePak15 monitor (Physio-Control Inc.; Redmond, Washington USA). Prehospital patient care records create a unique identifying number for each patient; cardiac monitoring and vital signs are automatically uploaded into the ePCR. For the purposes of this study, the Office of the Medical Director queried the records of all patients that received diltiazem over a two-year period. This study was deemed exempt, not requiring consent because personal confidential information was protected, by the Orlando Health Institutional Review Board (Orlando, Florida USA).

Inclusion criteria included all adult (>18 years old) patients that were administered diltiazem for AFIB with RVR. The OCEMS system paramedics may administer diltiazem by standing order. The protocol for treatment of "Atrial Fibrillation/Flutter" directed paramedics to administer a dose of diltiazem 0.25mg/kg (maximum dose of 20mg) to adult patients with stable, symptomatic AFIB or atrial flutter with RVR at a rate greater than 150 beats per minute (bpm) with a narrow complex rhythm (Figure 1). The standing orders precluded patients from receiving diltiazem who had a systolic blood pressure less than 90mmHg with acutely altered mental status or signs of shock, wide complex tachycardia (QRS interval greater than 120msec), or a history of Wolff-Parkinson-White (WPW) syndrome. The "Atrial Fibrillation/Flutter" protocol is the only protocol that directs paramedics to administer diltiazem; there are no other accepted indications without consultation from online medical control. Exclusion criteria included those with unavailable prehospital records.

The OCEMS protocols for cardiac patients are evidence-based and function within current Advanced Cardiac Life Support guidelines. Paramedics are trained to obtain, read, and interpret 12-lead ECGs. Paramedics have access to physician consultation 24-hours a day, as well as the ability to transmit ECGs to any receiving facility or the OCEMS base station for physician consultation. Only STEMI ECGs are mandated to be transmitted to the receiving facility in real-time per protocol. The ECGs in the current study were read by paramedics – they were not transmitted in real-time for physician review.

Data Collection

Data were abstracted from the prehospital ePCR by emergency physicians trained on the data abstraction using set inclusion and exclusion criteria. These patient encounters were evaluated for protocol compliance, clinical improvement, and presence of adverse events after the administration of diltiazem. Data collected included patient characteristics and demographics, initial and post-administration vital signs, initial and final ECG rhythm, and the need for rescue medications, intravenous fluids, or cardioversion. Patient clinical improvement was defined as a decrease in heart rate by 20% or achieving a goal heart rate less than 100bpm. Adverse events were defined as a systolic blood pressure of less than 90mmHg or the need for administration of intravenous fluids after diltiazem was given. Original prehospital ECG rhythm interpretations by EMS providers were compared to physician ECG interpretations retrospectively. Physicians were blinded to initial ECG interpretation.

The primary outcomes were patient clinical improvement and adverse events in the protocol compliant group versus the protocol non-complaint group. Secondary outcomes included overall clinical improvement and adverse event rate across all patients administered diltiazem, and agreement of physician and paramedic ECG interpretation.

Data Analysis

Data were described using means and proportions with 95% confidence intervals. Comparative statistics were used to compare those who did and those who did not comply with the protocol, and included Pearson Chi-square test and Fisher's Exact test for

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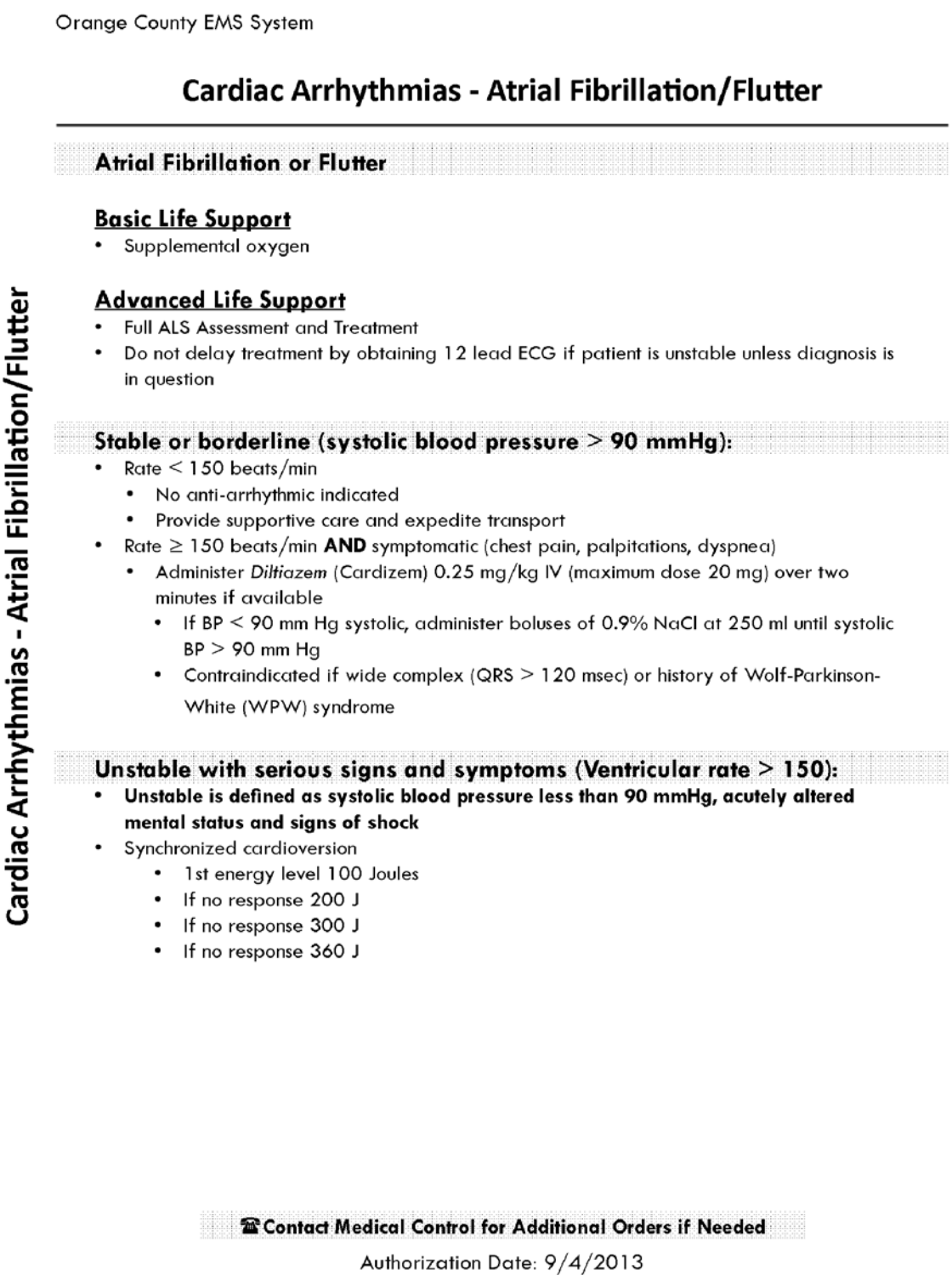

Figure 1. Orange County EMS Protocol for Atrial Fibrillation/Flutter.
Abbreviations: ALS, Advanced Life Support; BP, blood pressure; EMS, Emergency Medical Services.

categorical variables and the independent sample t-test and the Mann Whitney U test for continuous variables. Significance was set at 0.05. Data were entered into a Microsoft Excel (Microsoft Corp.; Redmond, Washington USA) spreadsheet and analyzed using STATA (StataCorp; College Station, Texas USA).

Results

Over the study period, a total of 197 adult patients received diltiazem by prehospital providers. One hundred and thirty-one patients were in the "protocol compliant" group (66%), and 66 were in the "protocol non-compliant" group (34%). The average age was 65

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years old (SD = 14), and males represented 55% of the study population (Table 1). There were no significant differences in patient demographics (age, race, gender, and ethnicity) between patients in the protocol compliant and protocol non-compliant groups (Table 1).

The most common presenting rhythm as assessed by prehospital providers was AFIB, accounting for 93% of patients (Table 1). An additional five percent of patients were found to be in atrial flutter, and the remaining patients' initial rhythms were identified as either sinus tachycardia or supraventricular tachycardia (SVT; Table 1). One hundred and thirteen patients (58%) who received diltiazem showed clinical improvement defined as final pulse <100bmp or a decrease in pulse by 20% (Table 2). Overall, adverse events were seen in 11% of patients (Table 2). The most commonly seen adverse event was hypotension. There were no cases of patients converting from a narrow complex tachycardia to a wide complex tachycardia, such as ventricular tachycardia or ventricular fibrillation, nor were there cases of cardiac arrest or airway compromise. Blinded physicians retrospectively interpreted ECGs for all patients; their interpretations were compared to the interpretations by prehospital providers. The agreement between prehospital providers' rhythm interpretation and physician interpretation was 92% (κ=0.454; P <.001; Table 3).

Patients who received diltiazem in adherence to the protocol had a significantly higher mean initial pulse rate when compared to the protocol non-compliant group (174 versus 144; P <.001; Table 4). There were no significant differences in any other initial vital signs (temperature, systolic blood pressure, diastolic blood pressure, oxygen saturation, or end tidal CO2) between the two groups (Table 4). Patients in the protocol compliant group were more likely to show clinical improvement with 63% improved when compared to 46% improved in the non-compliant group (P = .031; Table 2). Patients responding to diltiazem administration with a decrease in pulse of at least 20% the initial pulse rate were more commonly found in the protocol compliant group (47% versus 19%; P = .002; Table 2). Additionally, adverse events were more commonly seen in the protocol non-compliant group (18%) when compared to the protocol adherent (eight percent; P = .033; Table 2).

Discussion

This study suggests that prehospital diltiazem administration is relatively safe and effective for the treatment of AFIB with RVR, and that strict compliance with standing orders improves the efficacy and safety of drug administration. In the protocol compliant group, 63% of patients showed clinical improvement with only eight percent having adverse events. Among adverse events, the most common was hypotension requiring fluids. However, there were no documented malignant arrhythmias, cardiac arrests, or sustained episodes of hypotension.

Two prior studies have evaluated prehospital use of diltiazem. A small, retrospective review comparing patients with rapid AFIB who received diltiazem to historical control subjects suggested that diltiazem was safe and effective in treating AFIB in the prehospital setting without increased incidence of hypotension.[9] A larger study also demonstrated the effectiveness of prehospital diltiazem use for AFIB with RVR with rarely recorded hypotensive episodes.[10] While these studies showed few adverse events, administration of diltiazem is not without risk. Several studies have raised concern for increased incidence of hypotension, which is thought to be mediated through the negative inotropic effects of the medication.[1,7,11] Additionally, there is also a theoretical risk of causing decompensation of a stable, narrow complex tachycardia into a wide complex tachycardia after administration of diltiazem due to is atrioventricular nodal blocking properties. Therefore, diltiazem administration is contraindicated in patients with evidence of pre-excitation on ECG or history of WPW syndrome.[1,12] The current study adds to this existing literature suggesting diltiazem may be a safe and effective prehospital treatment, and compared compliance with standing orders to identify which patients may be at higher risk for adverse events.

The overall rate of compliance with the OCEMS system protocol in this patient population was only 66%. The most common reason for protocol non-adherence was administration of diltiazem to patients with heart rate less than 150bpm. Clinically, diltiazem is often administered for heart rates <150bpm in emergency department settings, and it is likely a safe and effective treatment strategy. However, the standing order was written with a specifically critical subset of patients in mind, so this was considered protocol non-compliance. Despite being non-compliant, it is likely that this group of patients did receive benefit from the drug, which may explain why there was no difference between groups in regards to "final pulse <100bpm" (35% versus 31%; P = .628). Other reasons for non-adherence included administering diltiazem to patients with other cardiac arrhythmias (sinus tachycardia or SVT), patients with initial systolic blood pressure less than 90mmHg, or patients with signs of acute decompensated heart failure such as pulmonary edema. This study showed that patients who received diltiazem outside of the standing protocol had significantly higher incidence of adverse events (18% versus eight percent; P = .033) and significantly lower incidence of clinical improvement (46% versus 63%; P = .031). These findings support that, when given within the parameters of a strict protocol, administration of diltiazem in a prehospital setting is both safe and effective. Further education and training will be necessary to improve protocol compliance and target the correct patient population for treatment.

In this study, each initial ECG and post-diltiazem ECG were evaluated by the treating paramedic and then reviewed retrospectively by an emergency physician. Emergency physicians were blinded to paramedic interpretation and patient outcomes. Overall, the agreement between prehospital and physician rhythm interpretation was 92%, with a Kappa value of 0.454 (P <.001). There were four instances of prehospital providers classifying the initial rhythm as SVT while physicians classified the rhythm as AFIB with RVR; this was the most commonly appearing disagreement. There was one instance the prehospital providers classified a rhythm as AFIB and administered diltiazem; however, the physician classified the rhythm as a junctional rhythm. This patient incurred worsening bradycardia during transport. Lastly, there were two patients that the treating paramedic classified as AFIB with RVR in which the emergency physician interpreted the ECG as a wide complex tachycardia. One patient had no adverse outcome and had a decrease in heart rate from 131bpm to 66bpm after diltiazem administration. Upon further review, this patient was felt to have a left bundle branch block with AFIB and RVR. The second patient with a wide complex tachycardia did have an adverse outcome of hypotension requiring intravenous fluids. This patient's heart rate increased from 135bpm to 166bpm during transport. A high agreement level between paramedics and physicians suggests prehospital providers can properly identify AFIB with RVR without expert consultation, allowing for standing orders for treatment.

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	Did Not Follow Protocol N = 66	Followed Protocol N = 131	Total N = 197	P Value
Age (years)	68 (SD = 15)	64 (SD = 13)	65 (SD = 14)	.039
Gender (% Female)	29 (44%)	60 (46%)	89 (45%)	.880
Race				.936
Asian	1 (2%)	1 (1%)	2 (1%)	
Black	11 (17%)	24 (18%)	35 (18%)	
Hispanic	13 (20%)	25 (19%)	38 (19%)	
White	39 (59%)	79 (60%)	118 (60%)	
Other	2 (3%)	2 (2%)	4 (2%)	
GCS Score				<.001
15	56 (85%)	128 (99%)	184 (94%)	
3-14	7 (21%)	5 (3%)	12 (6%)	
Initial Rhythm (per EMS)				.017
Sinus Tachycardia	1 (2%)	0 (0)	1 (1%)	
SVT	4 (6%)	0 (0)	4 (2%)	
Atrial Flutter	3 (5%)	6 (5%)	9 (5%)	
Atrial Fibrillation	58 (88%)	125 (95%)	183 (93%)	
Wide Complex Tachy	0 (0)	0 (0)	0 (0)	
Junctional Rhythm	0 (0)	0 (0)	0 (0)	
Initial Rhythm (per MD)				.072
Sinus Tachycardia	1 (2%)	0 (0)	1 (1%)	
SVT	1 (2%)	0 (0)	1 (1%)	
Atrial Flutter	3 (5%)	7 (5%)	10 (5%)	
Atrial Fibrillation	58 (88%)	123 (95%)	181 (92%)	
Wide Complex Tachy	2 (3%)	0 (0)	2 (1%)	
Junctional Rhythm	1 (2%)	0 (0)	1 (1%)	
Mean Diltiazem Dose	19.0 [18.2-19.7]	19.1 [18.7-19.7]	19.1 [18.7-19.5]	.610
Diltiazem Dose				.690
5–10mg	3 (5%)	9 (7%)	12 (6%)	
11–15mg	4 (6%)	3 (2%)	7 (4%)	
16–20mg	59 (89%)	118 (90%)	177 (90%)	
21–25mg	0 (0)	0 (0)	0 (0)	
26–30mg	0 (0)	0 (0)	0 (0)	
31–35mg	0 (0)	1 (1%)	1 (1%)	
Electrical Cardioversion	0 (0)	1 (1%)	1 (1%)	.999
Adenosine Given	6 (9%)	7 (5%)	13 (7%)	.366
Any Cardiac Medications[a]	14 (21%)	23 (18%)	37 (19%)	.565
Any Medications[b]	20 (30%)	30 (23%)	50 (25%)	.299
Mean IV Fluid Volume (ml)	160 [116-204]	148 [112-184]	152 [124-180]	.684
IV Fluid Volume				.157
<100	28 (42%)	74 (57%)	102 (52%)	
100–249	16 (24%)	19 (15%)	35 (18%)	
250–499	17 (26%)	24 (19%)	41 (21%)	
500–999	5 (8%)	11 (9%)	16 (8%)	
>1000	0 (0)	2 (2%)	2 (1%)	

Table 1. Patient Baseline Characteristics Comparing Protocol Compliant and Protocol Non-Compliant Groups
Abbreviations: EMS, Emergency Medical Services; GCS, Glasgow Coma Scale; IV, intravenous; MD, medical doctor; SVT, supraventricular tachycardia.

[a] Nitroglycerine, Dopamine, Aspirin.

[b] Naloxone, Albuterol, Atrovent, Ondansetron, Thiamine.

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	Protocol Non-Compliant N = 66	Protocol Compliant N = 131	Total N = 197	P Value
Adverse Events (n = 196)	12 (18%)	10 (8%)	22 (11%)	.033
Final Pulse <100/min (n = 196)	23 (35%)	40 (31%)	63 (32%)	.628
Pulse Decreased 20% (n = 132)	8 (19%)	42 (47%)	50 (38%)	.002
Clinical Improvement (n = 196)	30 (46%)	83 (63%)	113 (58%)	.031

Table 2. Outcomes Comparing Protocol Compliant and Protocol Non-Compliant Groups

	% Agreement	Kappa	P Value
Initial Rhythm (N = 196)	182/196 (92%)	0.454	<.001
Final Rhythm (N = 176)	161/176 (82%)	0.496	<.001

Table 3. Agreement of Initial and Final ECG Rhythms between Paramedic and Emergency Physician
Abbreviation: ECG, electrocardiogram.

	Protocol Non-Compliant N = 66	Protocol Compliant N = 131	Total N = 197	P Value
Temperature (n = 51)	98.9 [98.2-99.6]	98.1 [97.9-98.3]	98.4 [98.1-98.7]	.011
Systolic Blood Pressure	142 [133-150]	141 [136-146]	141 [137-145]	.927
Diastolic Blood Pressure	88 [81-94]	89 [85-93]	89 [85-92]	.637
O2 Saturation % (n = 192)	95 [94-96]	96 [95-97]	96 [95-96]	.143
ETCO2 (n = 171)	29 [26-32]	29 [28-31]	29 [28-31]	.752
Pulse	144 [136-152]	174 [171-177]	164 [160-168]	<.001

Table 4. Pre-Intervention Vital Signs
Abbreviations: ETCO2, end-tidal carbon dioxide; O2, oxygen.

Limitations

This study has several limitations. It is a retrospective, observational study of a small cohort of patients in a single EMS system; therefore, it may not be generalizable to other patient populations or prehospital agencies. Additionally, the study design did not allow for reporting of patient-centered outcomes following arrival at the emergency department, such as need for further treatments (intravenous fluids, additional cardiac medications, or cardioversion) or in-hospital mortality. Similarly, this study does not provide evidence that treating AFIB with RVR prior to hospital arrival is advantageous to patient outcomes in an EMS system with relatively short transport times.

Conclusion

When given within the standing protocol, diltiazem is both safe and effective in treating AFIB with RVR. The incidence of adverse outcomes increases when diltiazem is given inappropriately, outside of the strict standing protocol. Larger prospective studies should be performed to further evaluate prehospital diltiazem use and its downstream effects on patient outcomes.

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