

The Use of Diltiazem for Treating Rapid Atrial Fibrillation in the Out-of-Hospital Setting

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Study objective: We sought to evaluate the use of intravenous diltiazem for treatment of rapid atrial fibrillation or flutter (RAF) in the out-of-hospital setting.

Methods: This study is a retrospective review of data with historical control subjects. Data were drawn from out-of-hospital patients reported to a statewide paramedic system who presented with atrial fibrillation or flutter and a ventricular response rate (VRR) of 150 beats/min or greater. The intervention (diltiazem) group included patients who received diltiazem during a 9-month period in 1999. The control group included patients from 1998 who did not receive diltiazem. Patients who were intubated or underwent cardioversion were omitted. Therapeutic response was defined as the occurrence of change to sinus rhythm, reduction of VRR to 100 beats/min or less, or reduction of baseline VRR by 20% or greater. Data were analyzed by using the χ^2 test, the Student's *t* test, and odds ratios (ORs). A Bonferroni adjusted *P* value of .005 was used to define statistical significance.

Results: Forty-three patients receiving diltiazem and 27 control subjects were included in the study. The mean total diltiazem dose was 19.8 mg (95% confidence interval 17.8 to 21.8). The diltiazem and control groups did not significantly differ with respect to age; sex; history of atrial fibrillation; prior use of digitalis, β -blockers, or calcium channel blockers; concurrent out-of-hospital therapies; or baseline VRR or systolic blood pressure (*P* = .09 to 1.00). The difference in VRR reduction between the diltiazem and control groups was 38 beats/min (95% confidence interval 24 to 52); this difference was statistically significant (*P* < .001). The mean percentage reduction of VRR in the diltiazem group was -33.1%. The difference in systolic blood pressure change between the diltiazem and control groups was not statistically significant (*P* = .17). The diltiazem group had a higher prevalence of achieving VRR reduction to 100 beats/min

or less than did the control group (OR 22.6; $P < .001$), of achieving a VRR reduction of 20% or greater (OR 19.3; $P < .001$), and of achieving overall therapeutic response (OR 19.3; $P < .001$). Few changed to sinus rhythm in either group (estimated OR 6.3; $P = .15$). No patients in the diltiazem group required treatment for hypotension, endotracheal intubation, resuscitation from cardiac arrest, or emergency treatment of unstable dysrhythmias.

Conclusion: The effects of diltiazem on RAF can be appreciated within the constraints of the out-of-hospital environment. Diltiazem should be considered as a viable field therapy for rate control of RAF.

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INTRODUCTION

Atrial fibrillation (AF) is a common dysrhythmia encountered in clinical practice, with a prevalence in the United States ranging from 2.3% in persons older than 40 years to 5.9% in persons older than 65 years.^{1,2} Uncontrolled or rapid AF (RAF; atrial fibrillation with an accelerated ventricular response rate [VRR]) can result in impaired diastolic filling, loss of atrial kick, decreased ventricular output, and decreased coronary perfusion. The priority in managing RAF is control of ventricular rate.^{1,3,4} Pharmacologic agents, such as digitalis, β -blockers, calcium channel blockers, and other antiarrhythmic agents, are commonly used for controlling RAF.³⁻⁸

Diltiazem hydrochloride is a commonly used calcium ion channel inhibitor. Diltiazem slows atrioventricular (AV) nodal conduction, prolongs the AV nodal refractory period, and is useful for ventricular rate control of AF.^{4,9-11} Intravenous diltiazem has been demonstrated as an effective treatment for RAF and is widely used in contemporary emergency medicine practice.¹²⁻¹⁴ The out-of-hospital use of diltiazem has been relatively limited because of difficulties with field storage of the drug; the original solution requires refrigerated storage at 2°C to 8°C (35.6°F to 46.4°F).¹⁵ However, the introduction of lyophilized diltiazem has permitted the storage and use of diltiazem under field conditions. This system uses a dual-chamber syringe containing lyophilized diltiazem powder and a benzyl alcohol-based diluent and may be stored at 15°C to 30°C (59°F to 86°F).⁹ There have been few reports of diltiazem

use in the out-of-hospital setting for RAF.^{15,16} The purpose of this study was to evaluate the utility and safety of intravenous diltiazem for treating RAF within the clinical constraints of out-of-hospital care.

MATERIALS AND METHODS

This study is a retrospective review with historic control subjects. Data were drawn from out-of-hospital charts for 3 county-based paramedic systems. Each system is autonomous but operates by using statewide standing orders for patient care. Each system uses 2-person paramedic units, and a total of 15 units (plus supervisor units) serves the state at any given time. The 3 systems serve a population of approximately 745,000 in urban, suburban, and rural settings. All paramedics are trained in accordance with the US Department of Transportation national paramedic curriculum.¹⁷ The annual number of paramedic patient contacts is approximately 26,000. The mean and median scene-to-emergency department transport times are approximately 12 and 11 minutes, respectively.

Diltiazem was introduced to the study systems in 1999 for treating stable tachycardias, such as RAF and paroxysmal supraventricular tachycardia (PSVT). Cardizem Lyo-Ject (Hoechst Marion Roussel, Inc, Kansas City, MO), lyophilized diltiazem in a prefilled syringe system, was used for drug administration.⁹ The administration of 0.25 mg/kg (maximum 20 mg) diltiazem was permitted for patients with stable narrow-complex tachycardias (eg, RAF and PSVT) with a VRR of more than 150 beats/min and a systolic blood pressure (SBP) of at least 80 mm Hg. Diltiazem use was authorized by standing orders; preapproval by online medical direction was not required. Repeat doses of diltiazem and diltiazem use for patients that did not meet standing order criteria were authorized by online medical direction only. Diltiazem was permitted for patients who had an underlying AF uncovered by the use of adenosine, as well as for PSVT refractory to adenosine. Diltiazem administered by means of continuous intravenous infusion was not used. Patients were allowed to receive other concurrent therapies as clinically indicated (eg, oxygen, intravenous fluid, aspirin, sublingual nitroglycerin, nitroglycerin paste, nebulized albuterol, and furosemide). Cardioversion was specified for unstable tachycardias, including unstable RAF (RAF with SBP <80 mm Hg).

Before the availability of diltiazem, the study systems treated all RAF by using conventional therapies as clinically indicated (eg, aspirin, sublingual nitroglycerin,

nitroglycerin paste, furosemide, morphine, nebulized albuterol, adenosine, and cardioversion).

The intervention (diltiazem) group for this study consisted of all out-of-hospital patients who received diltiazem for RAF during the period from January 1999 to October 1999. Historical control subjects were drawn from patients during the period from January 1998 to December 1998 who presented with RAF but did not receive diltiazem. However, 1 county EMS system did not begin using diltiazem until March 1999, and therefore patients from this county who presented with RAF during the period from January 1999 to February 1999 were included as control subjects. Patients who had an underlying AF uncovered by adenosine, diltiazem, or other therapy were included in the study. Patients who did not meet standing order criteria for diltiazem but received the drug per online medical direction were included in the study. Patients who were intubated, underwent cardioversion, experienced cardiac arrest, or had an underlying rhythm other than AF or flutter were excluded.

For control subjects, start-of-treatment (baseline) VRR and SBP were based on the first set of vital signs appearing on the paramedic chart. For the intervention group, start-of-treatment VRR and SBP were defined from vital signs immediately before diltiazem administration. End-of-treatment VRR and SBP for both groups were based on the last set of vital signs appearing on the chart. Because it was inconsistently measured and reported, effects on diastolic blood pressure (DBP) were not evaluated.

Therapeutic response was defined as the occurrence of any one of the following events: (1) change to sinus rhythm, (2) reduction of VRR to 100 beats/min or less, or (3) reduction of VRR by 20% or greater from baseline. These definitions were based on criteria used by other studies evaluating diltiazem for treating RAF.^{12-14,18-22} Only patients who maintained changes until hospital arrival were considered to have achieved therapeutic response. Elapsed time from start of treatment to therapeutic response or ED arrival were noted.

Cardiac rhythms were noted on the basis of paramedic interpretations. Diltiazem dosages were noted. Recurrences of RAF after initial response to diltiazem therapy were noted. Clinically significant complications occurring after the initiation of field therapy were noted, specifically hypotension (SBP <90 mm Hg), respiratory failure requiring intubation, cardiac arrest, or the onset of unstable dysrhythmias requiring emergency intervention (eg, cardioversion or defibrillation). Subjective symptoms associated with drug use (eg, chest pain, weakness, dizzi-

ness, dyspnea, nausea, and headache) were not evaluated. Concurrent out-of-hospital therapies (other than diltiazem) were noted for both groups. Patient history of AF, digitalis use, β -blocker use, or calcium channel blocker use were noted.

Data were abstracted from paramedic charts by the principal investigator and reviewed for accuracy by a second investigator. Data were compiled by using Microsoft Excel (Microsoft, Redmond, WA) and SPSS statistical software (SPSS Inc, Chicago, IL) packages. Data were analyzed by using the χ^2 test (with the Fisher exact test where appropriate) and the Student's *t* test. Odds ratios and 95% confidence intervals (CIs) were calculated where appropriate. Because multiple (10) comparisons of outcomes data were performed, a Bonferroni adjustment was used to define a critical *P* value of .05 divided by 10 (.005) for statistical significance.

This study was approved by expedited review with waiver of informed consent by the institutional review board.

Table 1.
Summary of study groups.

Variable	Diltiazem (n=43)	Control (n=27)	P Value
Demographics			
Male	14	13	.19
Female	29	14	
Mean age (y)	72.3	69.3	.34
95% CI	69.3-75.3	63.9-74.7	
Previous history			
AF or atrial flutter	15	9	.89
β -Blocker use	7	4	1.00
Calcium channel blocker use	9	3	.35
Digitalis use	15	9	.89
Concurrent out-of-hospital therapies			
Aspirin	11	3	.14
Sublingual nitroglycerin	17	6	.13
Nitroglycerin paste	16	6	.19
Morphine	4	2	1.00
Furosemide	5	2	.70
Nebulized albuterol	2	2	.64
Adenosine	6	3	1.00
Rhythm at start of treatment			
Sinus tachycardia	0	0	.42
AF	38	24	
Atrial flutter	4	1	
PSVT	1	2	
Rhythm at end of treatment			
Sinus tachycardia	4	0	.25
AF	37	25	
Atrial flutter	2	2	
PSVT	0	0	

RESULTS

For the intervention period, there were 17,048 patient contacts, with administration of diltiazem identified in 50 cases. Six patients were omitted because the underlying rhythm was PSVT, and 1 was omitted because of inadequate documentation, resulting in a total of 43 subjects in the diltiazem group. No patients receiving diltiazem required exclusion because of intubation, cardioversion, or resuscitation from cardiac arrest. For the control period, there were 25,924 patient contacts, resulting in 38 subjects with RAF and a VRR greater than 150 beats/min. Two patients were excluded for cardioversion, 2 were excluded because of intubation (including 1 cardiac arrest), and 7 were excluded because of inadequate documentation, resulting in a control group of 27 subjects.

Patient demographics are summarized in Table 1. The difference between the diltiazem and control groups with regard to age, sex, history of AF or flutter, and history of β -blocker, calcium channel blocker, and digitalis use was not statistically significant ($P=.19$ to 1.00). The diltiazem and control groups were statistically similar with regard to concurrent therapies ($P=.13$ to 1.00). Six patients receiving diltiazem and 3 control patients received adenosine that uncovered underlying RAF; this difference was not statistically significant ($P=1.00$). One patient receiving diltiazem and 2 control subjects had an initial rhythm described as PSVT but were included in the analysis because an underlying AF was uncovered by using concurrent therapies.

The mean total administered dose of diltiazem in the intervention group was 19.8 mg (95% CI 17.8 to 21.8). Three patients received a second dose of diltiazem (range 10 to 25 mg). No patients received more than 2 doses of diltiazem. Nine patients with VRR of less than 150 beats/min (range 112 to 146 beats/min) received diltiazem per online medical direction.

Changes in VRR and SBP are summarized in Table 2. The difference in baseline VRR between the diltiazem and control groups was not statistically significant. The difference in ending VRR between the diltiazem and control groups was 47 beats/min (95% CI 33 to 61); this difference was statistically significant ($P<.001$). The difference in VRR reduction between the diltiazem and control groups was 38 beats/min (95% CI 24 to 52); this difference was statistically significant ($P<.001$). The mean percentage reduction of VRR in the diltiazem group was -33.1% . SBP data were reported for 41 patients in the diltiazem group and 24 in the control group. The differences in baseline, ending, and change in SBP between the diltiazem and control groups were not statistically significant. The mean percentage change of SBP in the diltiazem group was -7.5% . Nine patients received diltiazem per medical direction, with a starting VRR of less than 150 beats/min. If these patients are omitted, the difference in ending VRR is 42 beats/min (95% CI 27 to 57); this difference is still statistically significant ($P<.001$). Likewise, if the 9 patients receiving diltiazem are omitted, the difference in ending SBP is still not statistically significant ($P=.77$).

Response to diltiazem therapy is summarized in Table 3. The difference between the number of patients receiving diltiazem and control patients in whom conversion to

Table 2.
Effect of diltiazem on VRR and SBP.

Variable	Diltiazem (95% CI)	Control (95% CI)	Difference (95% CI)	P Value
Mean VRR at start of treatment (beats/min)	166 (159 to 173)	176 (169 to 183)	9 (-2 to 20)	.09
Mean VRR at end of treatment (beats/min)	111 (102 to 120)	158 (147 to 169)	47 (33 to 61)	<.001
Change in VRR from baseline (beats/min; % change)	-55; -33.1% (-63 to -47)	-17; -9.4% (-29 to -5)	38 (24 to 52)	<.001
Mean SBP at start of treatment (mm Hg)	145 (135 to 156)	135 (120 to 150)	-10 (-28 to 8)	.29
Mean SBP at end of treatment (mm Hg)	132 (123 to 141)	134 (121 to 147)	2 (-14 to 19)	.77
Change in SBP from baseline (mm Hg; % change)	-13; -7.5% (-20 to -6)	-6; -2.2% (-14 to 2)	8 (-3 to 19)	.17

Table 3.
Response to diltiazem therapy.

Variable	Diltiazem (n=43) No. (%)	Control (n=27) No. (%)	Odds Ratio (95% CI)	P Value
Conversion to sinus rhythm	4 (9.3)	0 (0)	NA*	.15
VRR reduction to ≤ 100 beats/min	20 (46.5)	1 (3.3)	22.6 (2.8 to 181.9)	<.001
VRR reduction by $\geq 20\%$ from baseline	35 (81.4)	5 (16.7)	19.3 (5.6 to 66.4)	<.001
Overall therapeutic response (any of above 3 criteria)	35 (81.4)	5 (16.7)	19.3 (5.6 to 66.4)	<.001

*Estimated odds ratio (by method of Haldane³⁹) of 6.3 (95% CI 0.3 to 121.2).

sinus rhythm occurred was not significant. The difference between the number of patients receiving diltiazem and control subjects who experienced VRR reduction to 100 beats/min or less was statistically significant. The difference between the number of patients receiving diltiazem and control subjects who experienced reduction of baseline VRR by 20% or greater were statistically significant. The difference in the number of patients achieving overall therapeutic response between the diltiazem and control groups was statistically significant. All subjects in the diltiazem group who achieved change to sinus rhythm or reduction of VRR 100 beats/min or less also achieved 20% or greater VRR reduction.

For the diltiazem group, the mean and median times to therapeutic response were 11.0 (95% CI 8.3 to 13.6) and 6 minutes, respectively. For the control group, the mean and median total treatment times (drug-to-ED arrival) were 11.3 (95% CI 8.9 to 13.7) and 9 minutes, respectively. There were 8 diltiazem treatment failures. There was one instance of transient therapeutic response that reverted to RAF; this patient received two 20-mg doses of diltiazem. The remaining 7 diltiazem treatment failures were in patients who received a single dose of diltiazem (range 10 to 35 mg) over total treatment times ranging from 2 to 23 minutes.

No patients receiving diltiazem required endotracheal intubation, resuscitation from cardiac arrest, or emergency treatment of unstable dysrhythmias. One patient in the diltiazem group and 1 patient in the control group had a baseline SBP of less than 80 mm Hg; SBP did not decrease in either case. One patient with an SBP of 72 mm Hg received diltiazem; SBP did not change in this case. Except for the one patient with a low baseline SBP who received diltiazem, there were no instances of SBP reduction below 90 mm Hg after diltiazem therapy.

DISCUSSION

The morbidity associated with AF is attributed to excessive ventricular rate, syncope after cessation of AF, systemic embolization, loss of atrial contribution to cardiac output, and anxiety from palpitations.²³ The clinical approach to AF in the ED depends on the condition of the patient. In the setting of a clinically compromised patient, urgent cardioversion is usually indicated.^{3,6,23,24} Patients who have AF with a rapid VRR but who are clinically stable may benefit from a short trial of pharmacologic therapy.

The primary benefit of pharmacotherapy over urgent cardioversion is that sedation is not necessary; sedation

for cardioversion carries inherent risks, such as respiratory failure, hypotension, aspiration, and cardiovascular deterioration. Pharmacotherapy can provide an effective temporizing measure, controlling VRR so that cardioversion, if necessary, can be performed electively at a later time. Diltiazem has gained general acceptance for the pharmacologic treatment of RAF because it is rapid acting (compared with agents such as digitalis) and causes less hypotension than other calcium channel blockers (eg, verapamil).^{10,12-14,18,19,25,26} However, although cardioversion in the field can expose providers to physical risk,²⁷ diltiazem is not a substitute for emergency cardioversion in clinically unstable patients.

The only reports of diltiazem use in the field for RAF include one case report and one reference to a small case series.^{15,16} In the case series of Elam and Bolar-Softich,¹⁶ 26 out-of-hospital patients were treated with diltiazem for RAF over a 20-month period, and 88% were "effectively treated"; successful therapeutic outcome, however, was not defined. There have been no formal comparisons of diltiazem versus conventional field therapies for RAF in the field.

In this study, we sought to demonstrate the effects of diltiazem on RAF within the constraints of the out-of-hospital environment. Compared with the control group, patients receiving diltiazem experienced a statistically significant reduction of mean VRR from baseline ($P < .001$). Significantly more patients receiving diltiazem achieved VRR reduction to 100 beats/min or less ($P < .001$) and of VRR reduction by 20% or more from baseline ($P < .001$). Overall, 81.4% of patients receiving diltiazem achieved therapeutic response. In-hospital studies of diltiazem have cited successful response rates to bolus therapy ranging from 75% to 97%^{13,14,18-20}; the higher success rates seen in some of these studies may be due to the expanded treatment time frames available when studying diltiazem in a controlled hospital setting. Although we did not show a significant difference in the rate of conversion to sinus rhythm (9.3% versus 0.0%, $P = .15$), this observation is similar to those in other studies of diltiazem for treatment of AF.^{12,13} In RAF diltiazem is useful primarily for control of VRR.

Eight patients in our series did not respond to diltiazem treatment. In 7 of these patients, only 1 bolus dose of medication was given; 1 patient received 10 mg, 2 received 15 mg, 3 received 20 mg, and 1 received 35 mg. The 1 remaining nonresponder received 2 diltiazem boluses of 20 mg (total 40 mg). Of patients that did achieve therapeutic response, 2 subjects received 2 boluses of diltiazem; in one case the patient received 2

diltiazem boluses of 10 mg (total 20 mg), and in the other case, the patient received diltiazem boluses of 20 and 25 mg (total 45 mg). Other studies have demonstrated a similar need for repeat boluses of diltiazem to achieve therapeutic response.^{12,13,18} The manufacturer recommends that diltiazem be administered with an initial bolus of 0.25 mg/kg (typical adult dose 20 mg) followed by a second bolus of 0.35 mg/kg (typical adult dose 25 mg) if therapeutic response is not observed⁹; the nonresponders in this series may have achieved therapeutic response if additional diltiazem was administered in this manner.

Although calcium channel blockers are known to cause hypotension, we did not observe a significant difference in SBP reduction in the diltiazem group compared with control subjects ($P = .17$). However, our series did not have adequate power (39.7%) to detect the observed change in SBP; an estimated 140 subjects would have been required to achieve 80% power. Selected studies have demonstrated a significant decrease in SBP with diltiazem.^{13,14} Of note, in our series diltiazem was administered to 3 patients with SBP below 100 mm Hg; however, none of these patients experienced a reduction in SBP. We did not report DBP changes because repeat DBP measurements were not consistently measured or reported in the study system; in general, repeat blood pressure measurements in the field are often facilitated by radial palpation and not auscultation. Similarly, it was not possible to compare mean arterial pressure measurements; mean arterial pressure may arguably be a better assessment of drug effects on blood pressure. Future studies with automated blood pressure measurement and data recording may facilitate more precise field assessments of diltiazem's effects. It should be noted that in this series, intravenous calcium was not used for pretreatment before administering diltiazem.

Although the paramedic standing order for diltiazem precludes its use in the setting of congestive heart failure (CHF), we observed that many of the patients receiving diltiazem had clinical signs of CHF, such as audible rales and jugular venous distention. It should not be surprising that diltiazem was efficacious in these instances because diltiazem has been demonstrated to be safe in the setting of CHF.²⁸ Diltiazem is believed to increase cardiac output by relieving CHF resulting from RAF. Thus, RAF-associated CHF may not necessarily be an absolute contraindication to diltiazem. However, we recommend that diltiazem use in any patients with signs of CHF be performed judiciously.

We did not observe any adverse effects from diltiazem use, specifically clinical deterioration requiring endotra-

cheal intubation, resuscitation from cardiac arrest, or emergency treatment of dysrhythmias. We did not observe significant hypotension requiring treatment or deleterious effects on patients with CHF. However, this study has a relatively limited sample size for effectively evaluating drug safety, and thus we hesitate to conclude that administration of diltiazem in the field is free from risks. Other authors have evaluated the safety of diltiazem in in-hospital trials. Salerno et al¹³ investigated the use of bolus diltiazem on 105 patients with RAF. Only 7 cases of hypotension (SBP <90 mm Hg) were noted, and none were symptomatic. Other minor side effects included flushing (n=3), itching at the intravenous site (n=3), and nausea (n=1). Ellenbogen et al¹⁴ evaluated the safety of diltiazem in 84 patients receiving bolus followed by continuous infusion of diltiazem. Of the 11 (13%) patients experiencing hypotension, only 3 (3.6%) had symptoms sufficient to require treatment; these patients all responded to normal saline solution boluses. The only factors associated with hypotension were the concurrent use of digoxin or a baseline DBP of less than 75 mm Hg. Other minor side effects included headache (n=2), pruritis (n=2), nausea (n=1), dizziness or confusion (n=1), and bradycardia (n=1). It should be noted that in our series we did not evaluate side effects of a more subjective nature, such as chest pain, dyspnea, nausea/vomiting, weakness, or lightheadedness; these side effects can be significant in certain clinical scenarios.

Clinicians should also be aware of the theoretic risks with the use of calcium channel blockers in any patient with RAF. In patients with RAF secondary to accessory conduction pathways (eg, Wolff-Parkinson-White syndrome), the use of a calcium channel blocker can potentially accelerate conduction through the accessory path, causing fatal dysrhythmias; this effect, however, has been demonstrated primarily with verapamil.^{4,29-35} There is one case report of a fatality that resulted when administered diltiazem precipitated digitalis toxicity.³⁶ There has been extensive debate over the merits of diltiazem versus other calcium channel blockers, such as verapamil.^{25,26,37}

In this study, we did not formally evaluate the speed of response to diltiazem because of limitations inherent to the out-of-hospital environment. First, out-of-hospital providers did not obtain repeated vital signs at precise time intervals. Second, certain subjects, particularly in the control group, arrived at the receiving ED before accomplishing therapeutic response. Furthermore, out-of-hospital treatment time frames varied substantially between subjects (range 1 to 57 minutes). Although it is possible to use survival analysis (Kaplan-Meier log rank

estimator) to compare the speed of therapy between intervention and control groups, the out-of-hospital treatment period is relatively short compared with the potential total treatment period (field+ED+floor/ICU). Thus, the use of survival analysis strictly on the out-of-hospital time course would bias toward a positive effect in the intervention group. A proper application of survival analysis and evaluation of speed of response would incorporate data from the ED and in-hospital course for each patient.

If survival analysis is performed strictly on the out-of-hospital course, the diltiazem group does in fact demonstrate a significantly higher rate of achieving therapeutic response compared with control subjects ($P<.001$) within the observed treatment time frames. We observed a median time to therapeutic response of 6 minutes in the diltiazem group. This trend should not be surprising because other studies have demonstrated similarly rapid responses to bolus diltiazem therapy.^{12-14,19} For example, Schreck et al¹² carried out an analysis of ED diltiazem over a study period of 3 hours; statistically appreciable differences in VRR were observed at 5 minutes after drug administration. Goldenberg et al¹⁸ demonstrated appreciable effects from bolus diltiazem after only 2 minutes; these effects were sustained to 17 minutes. Thus, it is reasonable to consider that the effects of diltiazem can be appreciated within the relatively limited treatment time frames of out-of-hospital care. Speed of response is a pivotal concern in evaluating the utility of any out-of-hospital therapy. In the study system we observed drug-to-ED arrival times ranging from 1 to 35 minutes (median 9 minutes). Medical directors must evaluate on an individual basis whether intervention with diltiazem is merited given the range of transport times observed in a given system.

Our study does have certain limitations. This study is retrospective with historic control subjects. Given the relatively focused goal of therapy and the limited scope of intervention, it is conceivable that this study could be performed as a prospective randomized controlled trial. As discussed previously, the use of automated cardiac and blood pressure monitoring would facilitate more precise measurements of clinical data. Our patient selection criteria were also somewhat strict; standing orders permitted only patients with VRR greater than 150 beats/min to receive diltiazem. Other studies used diltiazem in patients with VRRs as low as 100 beats/min.^{13,14,18,19,22} Hence, our cohort of patients receiving diltiazem could have been expanded with more liberal inclusion criteria.

We did not evaluate long-term outcome. We observed only one case where a patient achieved transient thera-

peutic response but whose rhythm reverted to baseline RAF. It is conceivable that certain cases of therapeutic response may have reverted to RAF after arrival at the ED. In the report by Elam and Bolar-Softich,¹⁶ 23 of 28 patients who received diltiazem in the field responded to therapy; however, one third of patients were described as reverting to RAF and requiring supplemental therapy in the ED. Because of limitations in access to medical records, we did not review ED charts to assess whether patients maintained therapeutic response during their ED course. It is conceivable that a continuous diltiazem infusion could be started as a field intervention to maintain therapeutic response. However, Ellenbogen et al²⁰ demonstrated that even with a continuous diltiazem infusion, only 74% of patients maintain therapeutic response at 24 hours. Thus, diltiazem's role in out-of-hospital care might ultimately be strictly as a bridging therapy until arrival at the hospital. More recently, Wylie³⁸ described the use of intravenous bolus followed by oral diltiazem therapy; compared with patients receiving a continuous diltiazem infusion, patients receiving oral diltiazem maintained therapeutic response at the same rate at 4 hours ($P=.93$). Oral dosing of diltiazem can be readily accomplished in the field and may be a viable and convenient option for maintaining the effects achieved by bolus diltiazem therapy.

Because we believed that intubation or cardioversion implied higher patient severity (hence, "unstable" condition), we omitted these patients from this study. Two omitted control subjects received cardioversion because of an SBP of 80 mm Hg or less; neither of these cases would have been appropriate for diltiazem use. Two omitted control subjects were intubated; 1 of these patients had RAF after a successful resuscitation from cardiac arrest. We believed that the omission of these patients was appropriate because these subjects would normally not be candidates for the use of diltiazem. Diltiazem should be reserved for use in patients that are hemodynamically stable.

In choosing definitions for therapeutic response, we used criteria used by other studies of diltiazem for treating RAF.^{12-14,18-22} The chief goal of pharmacotherapy for RAF is clinical improvement. However, this term is subjective and rather difficult to quantify. Although there were isolated cases where the paramedic documented that a patient "felt better" after diltiazem treatment, these reports were documented inconsistently. Furthermore, it is difficult to quantify how much better a patient feels after diltiazem treatment. Because the goal of calcium channel blocker therapy is to reduce VRR and improve

hemodynamics, in the setting of RAF, VRR and SBP remain the best objective measures of patient response to therapy.

In this study, we demonstrate that the effects of diltiazem can be appreciated within the constraints of the out-of-hospital environment. Diltiazem should be considered as a standard field therapy for RAF. However, medical directors should decide whether its use is justified given the range of transport times observed in individual systems. Clinicians should also be aware of potential side effects when using diltiazem in the field. Regardless of whether diltiazem is used, out-of-hospital personnel should be prepared to recognize and appropriately treat patients with clinically unstable RAF. Diltiazem should be seen as a field option for stable RAF and not as a substitute for emergency cardioversion of unstable RAF.

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REFERENCES

- Ellenbogen KA. Role of calcium antagonists for heart rate control in atrial fibrillation. *Am J Cardiol.* 1992;69:36B-40B.
- Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* 1995;155:469-473.
- Stapczynski JS. Disturbances of cardiac rhythm and conduction. In: Tintinalli JE, ed. *Emergency Medicine: A Comprehensive Study Guide.* 4th ed. New York: McGraw-Hill; 1996:141-163.
- Shettigar UR. Management of rapid ventricular rate in acute atrial fibrillation. *Int J Clin Pharmacol Ther.* 1994;32:240-245.
- Blackshear JL, Kopecky SL, Litiin SC, et al. Management of atrial fibrillation in adults: prevention of thromboembolism and symptomatic treatment. *Mayo Clin Proc.* 1996;71:150-160.
- Pritchett EL. Management of atrial fibrillation. *N Engl J Med.* 1992;326:1264-1271.
- Repique LJ, Shah SN, Marais GE. Atrial fibrillation 1992. Management strategies in flux. *Chest.* 1992;101:1095-1103.
- Bolognesi R. The pharmacologic treatment of atrial fibrillation. *Cardiovasc Drugs Ther.* 1991;5:617-628.
- Hoechst-Marion Roussel Inc. Cardizem Lyo-Ject Syringe. In: *Physicians' Desk Reference.* Montvale, NJ: Medical Economics; 1997:1253-1255.
- Buckley MM, Grant SM, Goa KL, et al. Diltiazem. A reappraisal of its pharmacological properties and therapeutic use. *Drugs.* 1990;39:757-806.
- Singh BN, Nademane K, Baky SH. Calcium antagonists. Clinical use in the treatment of arrhythmias. *Drugs.* 1983;25:125-153.
- Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med.* 1997;29:135-140.
- Salerno DM, Dias VC, Kleiger RE, et al. Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. The Diltiazem-Atrial Fibrillation/Flutter Study Group. *Am J Cardiol.* 1989;63:1046-1051.
- Ellenbogen KA, Dias VC, Cardello FP, et al. Safety and efficacy of intravenous diltiazem in atrial fibrillation or atrial flutter. *Am J Cardiol.* 1995;75:45-49.
- Abarbanell NR, Marcotte MA. Out-of-hospital use of intravenous diltiazem (cardizem Lyo-Ject) in the treatment of rapid atrial fibrillation [letter]. *Am J Emerg Med.* 1997;15:618-619.
- Elam K, Bolar-Softich KL. Dilemmas in the acute pharmacologic treatment of uncontrolled atrial fibrillation. *Am J Emerg Med.* 1997;15:418-419.
- United States Department of Transportation. 1998 Emergency Medical Technician Paramedic: National Standard Curriculum. Available at: <http://www.nhtsa.dot.gov/people/injury/ems/EMT-P/index.html>. Accessed October 26, 2000.
- Goldenberg IF, Lewis WR, Dias VC, et al. Intravenous diltiazem for the treatment of patients with atrial fibrillation or flutter and moderate to severe congestive heart failure. *Am J Cardiol.* 1994;74:884-889.
- Tisdale JE, Padhi ID, Goldberg AD, et al. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. *Am Heart J.* 1998;135:739-747.
- Ellenbogen KA, Dias VC, Plumb VJ, et al. A placebo-controlled trial of continuous intravenous diltiazem infusion for 24-hour heart rate control during atrial fibrillation and atrial flutter: a multicenter study. *J Am Coll Cardiol.* 1991;18:891-897.
- Dias VC, Weir SJ, Ellenbogen KA. Pharmacokinetics and pharmacodynamics of intravenous diltiazem in patients with atrial fibrillation or atrial flutter. *Circulation.* 1992;86:1421-1428.
- Gonzalez ER, Omato JP, Lawson CL. Clinical decision analysis modeling: short-term control of ventricular response rate in atrial fibrillation or atrial flutter-digoxin versus diltiazem. *Pharmacotherapy.* 1994;14:446-451.
- Josephson ME, Buxton AE, Marchlinski FE. The Tachyarrhythmias. In: Isselbacher KJ, Braunwald E, Wilson JD, et al eds. *Harrison's Principles of Internal Medicine.* Vol 1. 13th ed. New York: McGraw-Hill; 1994:1019-1036.
- Ellenbogen KA, Chung MK, Asher CR, et al. Postoperative atrial fibrillation. *Adv Card Surg.* 1997;9:109-130.
- Ben Zemenick R. Verapamil or diltiazem for acute rate control [letter]. *Ann Emerg Med.* 1997;30:354-355.
- Phillips BG, Gandhi AJ, Sanoski CA, et al. Comparison of intravenous diltiazem and verapamil for the acute treatment of atrial fibrillation and atrial flutter. *Pharmacotherapy.* 1997;17:1238-1245.
- Gibbs W, Eisenberg M, Damon SK. Dangers of defibrillation: injuries to emergency personnel during patient resuscitation. *Am J Emerg Med.* 1990;8:101-104.
- Heywood JT, Graham B, Marais GE, et al. Effects of intravenous diltiazem on rapid atrial fibrillation accompanied by congestive heart failure. *Am J Cardiol.* 1991;67:1150-1152.
- Gulamhusein S, Ko P, Carruthers SG, et al. Acceleration of the ventricular response during atrial fibrillation in the Wolff-Parkinson-White syndrome after verapamil. *Circulation.* 1982;65:348-354.
- Gulamhusein S, Ko P, Klein GJ. Ventricular fibrillation following verapamil in the Wolff-Parkinson-White syndrome. *Am Heart J.* 1983;106:145-147.
- Harper RW, Whitford E, Middlebrook K, et al. Effects of verapamil on the electrophysiologic properties of the accessory pathway in patients with the Wolff-Parkinson-White syndrome. *Am J Cardiol.* 1982;50:1323-1330.
- Jacob AS, Nielsen DH, Gianelly RE. Fatal ventricular fibrillation following verapamil in Wolff-Parkinson-White syndrome with atrial fibrillation. *Ann Emerg Med.* 1985;14:159-160.
- Klein G J, Bashore TM, Sellers TD, et al. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med.* 1979;301:1080-1085.
- McGovern B, Garan H, Ruskin TN. Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. *Ann Intern Med.* 1986;104:791-794.
- Spurrell RA, Krikler DM, Sowton E. Effects of verapamil on electrophysiological properties of anomalous atrioventricular connexion in Wolff-Parkinson-White syndrome. *Br Heart J.* 1974;36:256-264.
- Moser LR, Panacek EA, Munger MA. Fatality due to intravenous diltiazem for acute ventricular rate control. *Pharmacotherapy.* 1996;16:306-310.
- Ben Zemenick R. Verapamil or diltiazem for acute rate control: which is best [letter]. *Am J Cardiol.* 1995;76:638-639.
- Wylie T. Efficacy of oral diltiazem after IV bolus for controlling rapid atrial fibrillation and flutter [abstract]. *Acad Emerg Med.* 2000;7:466.
- Haldane JBS. The estimation and significance of the logarithm of a ratio of frequencies. *Ann Hum Genet.* 1955;20:309-311.