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ESMOLOL COMPARED WITH AMIODARONE IN THE TREATMENT OF RECENT-ONSET ATRIAL FIBRILLATION (RAF): AN EMERGENCY MEDICINE EXTERNAL VALIDITY STUDY

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☐ **Abstract—Background: Recent-onset atrial fibrillation (RAF) is the most frequent supraventricular dysrhythmia in emergency medicine. Severely compromised patients require acute treatment with injectable drugs Objective: The main purpose of this external validity study was to compare the short-term efficacy of esmolol with that of amiodarone to treat severe RAF in an emergency setting. Methods: This retrospective survey was conducted in mobile intensive care units by analyzing patient records between 2002 and 2013. We included RAF with (one or more) severity factors including: clinical shock, angina pectoris, ST shift, and very rapid ventricular rate. A blind matching procedure was used to constitute esmolol group (n = 100) and amiodarone group (n = 200), with similar profiles for age, gender, initial blood pressure, heart rate, severity factors, and treatment delay. The main outcome measure was the percentage of patients with a ventricular rate control defined as heart frequency ≤ 100 beats/min. More stringent (rhythm control) and more humble indicators (20% heart rate reduction) were analyzed at from 10 to 120 min after treatment initiation. Results: Patient characteristics were comparable for both groups: age 66 ± 16 years, male 71%, treatment delay < 1 h 36%, 1–2 h 29%, > 2 h 35%, chest pain 61%, ST shift 62%, ventricular rate 154 ± 26 beats/min, and blood pressure 126/73 mm Hg. The superiority of esmolol was significant at 40 min (64% rate control with esmolol vs. 25% with amiodarone) and for all indicators from 10 to 120 min after treatment onset. Conclusion: In "real life emergency medicine," esmolol is better than amiodarone in the treatment of RAF.** **© 2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—atrial fibrillation; esmolol; emergency medicine**

INTRODUCTION

Atrial fibrillation (AF) is the most frequent dysrhythmia managed in emergency medicine. It represents 0.5–1.0% of emergency department (ED) activity throughout the world and 1.5% of mobile intensive care unit (MICU) activity in the French Service d'Aide Médicale Urgente (SAMU [emergency medical services]) network (1–4). AF diagnosis relies on an electrocardiogram showing irregular RR intervals and no discernible P waves. Recent-onset AF (RAF) is typically defined as AF that has been present for < 48 h (2,5,6). Acute management of RAF implies relief of symptoms and the assessment of associated risks (2,7–9). Most cases of RAF encountered in emergency medicine present with a rapid ventricular rate, sometimes associated with myocardial dysfunction, hypotension, or signs of heart failure. The severity of symptoms guides the clinician in making his decision on acute treatment (3,5,6,8,10,11). ED practices show a great variation in RAF management (1,2,5,10,12–15).

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Although electrical cardioversion is safe and effective in the ED, pharmacological treatment is the preferred approach at the early stage for the majority of emergency physicians (EPs) (1,10,15–19). Adherence to guidelines (Table 1) is rather low (7,8,13,14,20,21,23,24). In Europe, the proportion of the distribution of antidysrhythmic agents used to treat RAF is: amiodarone 52%, flecainide or propafenone 27%, dronedarone 8%, sotalol 11%, and other 2% (10). Most patients eligible for AV-node blocking agents do not receive beta-blockers or calcium antagonists as recommended in the literature and recent guidelines (5,7,8,20–23,25–35). There are many pharmacological options for the treatment of RAF (10,19,36). For most of these medications, clinical trials and external validity studies are still lacking in the domain of emergency medicine (10,12,13,36,37).

In an acute setting, control of ventricular rate (heartbeat $\leq$ 100 beats/min) is a priority target (12,38,39). This aim can be achieved using beta-blockers or calcium antagonists as first-line drugs (25,29,30,32,40–46). Beta-blockers can alter hemodynamic condition, and ought to be used with caution in case of hypotension, heart failure, or depressed left ventricular function. In these cases, some authors advocate administration of amiodarone (Table 1) (7,8,20-22).

Esmolol belongs to the beta-blocker group but, unlike many others, it has a specific on–off effect. Fast-acting and short-lasting drugs allow repeated shots at increasing dosages and, if necessary, subsequent administration of second-line antidysrhythmic agents with limited risk of cumulative adverse effects (Tables 2 and 3) (19,45,47).

Table 1. Guidelines for Rate Control During Acute Setting of AF Treatment (7,8,20-22)

Class IA Recommendation	In the absence of preexcitation, intravenous administration of beta-blockers or nondihydropyridine calcium channel antagonists is recommended to slow the ventricular response to AF, exercising caution in patients with hypotension or heart failure.
Class IB Recommendation	To control the heart rate in patients with AF and concomitant hypotension or heart failure, intravenous administration of digitalis or amiodarone is recommended; intravenous administration of beta-blockers or nondihydropyridine calcium channel antagonists is also possible with cautious hemodynamic monitoring.
Class IC Recommendation	In preexcitation, preferred drugs are class I antidysrhythmic agents or amiodarone.

AF = atrial fibrillation.

Table 2. Pharmacokinetics of Intravenous Beta-Blockers and Calcium Antagonists Considered as Class Ia Recommendations to Treat Recent-Onset Acute Atrial Fibrillation

	Reacting Time	Clinical Half-Life
Beta-blocker agents		
Esmolol	2 min	5–10 min
Landiolol	2 min	5–10 min
Acebutolol	5 min	10 min–3 h
Timolol	5 min	2–4 h
Labetolol	5 min	5–6 h
Atenolol	5 min	6 h
Sotalol	5 min	10–20 h
Propranolol	5–10 min	2–6 h
Metoprolol	10–20 min	3–4 h
Pindolol	60 min	2–4 h
Calcium antagonists		
Verapamil	2–5 min	30 min–5 h
Diltiazem	5–10 min	3 h

In France, most EPs systematically choose amiodarone, only a few prefer esmolol as a first-line drug to treat symptomatic RAF. Many studies compare the effects of intravenous esmolol to that of verapamil or to that of diltiazem, but none compare the effectiveness of esmolol to that of amiodarone.

OBJECTIVES

The main purpose of this study was to compare the short-term effectiveness of intravenous esmolol to that of intravenous amiodarone to treat severe RAF in an emergency setting. The secondary goal was to point out other determinants of successful treatment.

METHODS

Study Design and Setting

This retrospective survey was conducted in three different MICUs by analyzing patient records between 2002 and 2013. In France, emergencies are managed by the SAMU network, with a single nationwide phone number: 15. Medical dispatchers evaluate incoming calls and decide on the type of help needed. In the more severe cases, a MICU is sent to the scene. A MICU team is comprised of a trained ambulance driver, an EP, a nurse, and sometimes a medical student (48).

Two cohorts were constituted, with patients responding to the inclusion criteria (Table 4). The esmolol group (n = 100) was comprised of 100 consecutive patients treated with esmolol. To constitute the amiodarone group (n = 200), a blind matching procedure two for one was employed: we selected 200 patients among 1200 who met the inclusion criteria and had been treated with amiodarone. All identifying information and outcome data

Table 3. Pharmacokinetics of Intravenous Drugs Considered as Second-Level Option to Treat Recent-Onset Acute Atrial Fibrillation (Beyond Class Ia Recommendations)

	Reacting Time	Clinical Half-Life
Quinidine class		
Hydroquinidine	2–5 min	4–8 h
Quinidine	2–5 min	4–8 h
Disopyramide	2–5 min	4–8 h
Amiodarone class		
Amiodarone	15 30 min	4–>24 h
Dronedarone	> 60 min	>24 h
Other		
Vernakalant	2–5 min	3 h
Propafenone	2–5 min	2–10 h
Ibutilide	2–5 min	6 h
Cibenzoline	2–5 min	7 h
Flecaïnid	12 min	14 h
Digoxin	10–30 min	36 h

were masked during the matching procedure (see criteria Table 5). A three-level categorization for elapsed time between symptom onset and drug administration was utilized in the matching process to test the impact factor of treatment delay on clinical outcome. This enabled us to obtain cohort comparability regarding initial patient profile, clinical presentation, acuteness, and treatment delay (36). The main outcome measure was the percentage of patients with a ventricular rate $\leq$ 100 beats/min within 40 min after i.v. treatment initiation. The complete list of efficacy criteria is shown in Table 6. The MICU standard procedure for intravenous amiodarone or esmolol is explained in Table 7.

Table 4. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Acute atrial fibrillation (suspected onset delay < 12 h) 2. Male or female aged ≥ 18 y 3. Prehospital management by investigating MICU 4. Clinical presentation including one or more of the following: a. Chest pain (angina pectoris) b. ST shift c. Shock (BP < 90/50, cerebral flow impairment) d. Very high HR (>MHR + 30) 5. Amiodarone or esmolol infusion by MICU	• Symptom onset > 12 h • Electric counter-shock by MICU • Acute pulmonary edema • Suspected STEMI • Hemorrhagic shock • Severe COPD • Asthma

MICU = mobile intensive care unit; STEMI = ST-elevation myocardial infarction; BP = blood pressure; COPD = chronic obstructive pulmonary disease; HR = heart rate; MHR = maximum heart rate.

Table 5. Matching Criteria

Matching Criteria		
Patient profile: • Age • Gender • Initial blood pressure • Initial heart rate	Delay from symptom-onset to treatment (3-level categorization): • Delay < 1 h • Delay = 1–2 h • Delay = 2–6 h	Severity factors: • Chest pain • ST shift • HR>250−−age • Shock

HR = heart rate.

Statistical Analysis

Chi-squared tests were employed for qualitative classifications (percentage of patients responding to rate control or responding to rhythm control). Student's *t*-tests were employed for quantitative variables (mean ventricular frequency, mean blood pressure).

Ethical Considerations

The study protocol was reviewed and approved by an ethics committee.

RESULTS

Patient Population

It took 11 years (2002–2013) to complete the esmolol group with 100 consecutive patients. During this period, 1200 patients responding to the inclusion criteria had been treated with amiodarone. This retrospective report analysis revealed that among MICU EPs of the institutions studied, very few utilized esmolol to treat RAF.

History of previous RAF was estimated at 10% in the esmolol group and 8% in the amiodarone group ($p > 0.05$). Previous severe RAF (with chest pain, ST shift, shock, or very high heart rate) was not registered.

Table 6. Outcome Criteria to Compare Esmolol and Amiodarone Short-Term Efficiency

List of Outcome Measures
Outcome criteria: ventricular rate ≤ 100 beats/min within 40 min after i.v. treatment initiation
Secondary outcome criteria:
1. Rhythm control (conversion to sinus rhythm) from 10 to 120 min after treatment initiation
2. Ventricular rate ≤ 90 beats/min from 10 to 120 min after treatment initiation
3. Rate control = ventricular rate ≤ 100 beats/min from 10 to 120 min after treatment initiation
4. Ventricular rate ≤ 120 beats/min from 10 to 120 min after treatment initiation

Table 7. MICU Institutional Procedure for Intravenous Amiodarone or Esmolol

Intravenous Amiodarone Protocol	Intravenous Esmolol Protocol
1. Standardized infusion for all patients: 300 mg given intravenously for 30 min with electric syringe through regular flow (10 mg/min) 2. If weight < 40 kg, consider 150 mg during 30 min i.v. regular flow (5 mg/min) 3. If weight > 90 kg, consider 450 mg during 30 min i.v. regular flow (15 mg/min)	Goal-guided therapy: every 3 to 5 min inject 0.5 mg/kg i.v. bolus combined with four-step increasing electric syringe flow: 0.05, 0.10, 0.15, and 0.20 mg/kg/min. When desired result is observed (conversion to sinus rhythm or ventricular rate stabilized), stop bolus sequence and maintain electric syringe flow at its level. If undesirable side effects appear, cease esmolol administration. Maximum dose is 4 times the 0.5 mg/kg i.v. bolus and 0.20 mg/kg/min electric syringe flow.

MICU = mobile intensive care unit.

Thirty percent of the patients were receiving oral antidysrhythmic treatment prior to study enrollment. There was no statistical difference between the esmolol and amiodarone groups for ongoing treatment prevalence: beta-blocker agents 17% in the esmolol group and 16% in the amiodarone group, amiodarone 4% and 3%, calcium antagonists 1% and 1%, other 8% and 6%, respectively ($p > 0.05$). Response to an i.v. drug was not affected by ongoing oral treatment: 40 min after drug initiation, rate control was 39% for patients with ongoing oral treatment and 38% for patients without ongoing oral treatment (60% and 66%, respectively in the esmolol group, 28% and 24% in the amiodarone group, $p > 0.05$).

Gender did not affect treatment effectiveness. But successful treatment was highly related to the elapsed time between symptom onset and drug administration ($p < 0.001$). The relationship between treatment delay (amiodarone or esmolol) and short-term electrocardiogram evolution is shown in Figure 1.

The blind matching procedure enabled us to ensure the compatibility of the esmolol and amiodarone groups for all harmonizing criteria and for other derivative parameters (Table 8).

Effect of Drug Treatment on Heart Rhythm

In the esmolol group, heart rate decreased from 154 ± 26 beats/min (initial) to 95 ± 27 beats/min (final), whereas in the amiodarone group, heart rate decreased from 154 ± 25 beats/min to 115 ± 32 beats/min. Average heart rate after drug administration was significantly

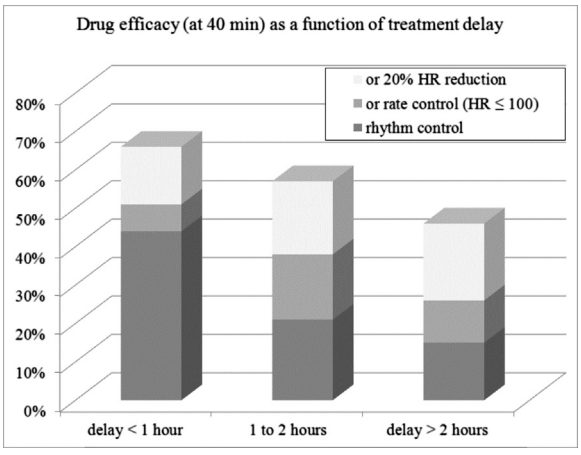

Figure 1. Drug efficacity in percentage. Percentages of rhythm control, HR < 100 and 20% HR reduction. Treatment delay: delay <1 h, 1 to 2 h, delay >2 h. HR = heart rate.

lower in the esmolol group compared with the amiodarone group ($p < 0.001$).

As shown in Table 9 and Figure 2, 20 min, 40 min, and 60 min after drug initiation, adequate response is obtained much more frequently with esmolol than with amiodarone. Short-term superiority of esmolol is observed for rhythm control and for rate control.

If we consider the main outcome measure (ventricular rate ≤ 100 beats/min, 40 min after drug initiation), esmolol's efficiency is 64%, whereas amiodarone's efficiency is 25%. Results of subgroup analysis (Table 10) seem to indicate that esmolol's superiority over amiodarone is validated for all clinical presentations.

All the different curves representing the cumulated drug efficacy as a function of treatment duration (Figure 2) have a similar silhouette, with a breakpoint 40 min after the start of antidysrhythmic therapy. This reveals that the percentage of patients responding to treatment increases sharply during the first phase and much less after. With esmolol, the second phase is almost horizontal, reflecting that the drug benefit is essentially concentrated in the early stage. With amiodarone, the primary hard slope rise is delayed, indicating almost no clinical effect during the first 20 min, but beyond the 40-min breakpoint, the ascension trend continues. At 15 min, the percentage of response to esmolol is 30% vs. 5% with amiodarone, whereas tough indicators at 60 min show an efficacy quotient of 46–56% with esmolol vs. 22–23% with amiodarone.

Cardioversion

Three patients involved in this study were treated with electrical cardioversion (1 out of 100 in the esmolol group and 2 out of 200 in the amiodarone group) due to persisting very rapid atrial fibrillation with chest pain or clinical shock. All 3 patients converted to sinus rhythm and were

Table 8. Group Comparability Prior to Antidysrhythmic Administration

	Esmolol, n = 100	Amiodarone, n = 200	*p*-Value
Age (average ± σ)	65.9 ± 16	65.9 ± 16	>0.05
Male %	71%	71%	>0.05
Female %	39%	39%	>0.05
T delay < 1 h	36%	36%	>0.05
T delay = 1–2 h	29%	29%	>0.05
T delay > 2 h	35%	35%	>0.05
Initial heart rate (average ± σ)	154 ± 26	154 ± 25	>0.05
Initial blood pressure (average systolic/ diastolic BP)	126/73	125/74	>0.05
Clinical shock	16%	16%	>0.05
Among which clinical shock with BP < 90/ 50 mm Hg	10%	13%	>0.05
Among which clinical shock with BP ≥ 90/ 50 mm Hg	6%	3%	>0.05
Chest pain	62%	62%	>0.05
ST shift	61%	61%	>0.05
Very high HR (>MHR + 30 - age)	23%	23%	>0.05
Association chest pain + ST shift	24%	27%	>0.05
Association very high HR + ST shift	21%	17%	>0.05
Association shock + ST shift	11%	10%	>0.05
Association shock + chest pain	9%	9%	>0.05
Association very high HR + chest pain	8%	10%	>0.05
Association shock + Very high HR	6%	6%	>0.05
Association very high HR + ST shift + chest pain	6%	7%	>0.05
Association very high HR + ST shift + shock	6%	5%	>0.05
Association shock + ST shift + chest pain	5%	6%	>0.05
Association very high HR + chest pain + shock	2%	3%	>0.05
Very high HR + shock + chest pain + ST shift	2%	2%	>0.05

BP = blood pressure; HR = heart rate; MHR = maximum heart rate.

symptom free after electrical procedure (one patient in the amiodarone group required two attempts).

Effect of Drug Treatment on Blood Pressure

In the esmolol group, blood pressure (systolic/mean/diastolic) decreased from 126 ± 26/91 ± 17/73 ± 16 mm Hg (initial) to 117 ± 13/81 ± 9/63 ± 8 mm Hg (final), and in the amiodarone group, blood pressure decreased from 125 ± 30/91 ± 19/74 ± 21 mm Hg (initial) to 111 ± 19/78 ± 12/61 ± 10 mm Hg (final). Prevalence of transient hypotension (mean arterial pressure < 70 mm Hg for < 30 min) was 14% in the esmolol group and 12% in the amiodarone group, whereas prevalence of durable hypotension (mean arterial pressure < 70 mm Hg lasting over 30 min) was 4% in the esmolol group and 9% in the amiodarone group. Among patients with initial mean arterial pressure (MAP) ≤ 70 mm Hg, blood pressure improved with amiodarone in 15 out of 24 (63%) cases and with esmolol in 9 out of 11 (82%) cases. Although the comparison for blood pressure evolution seems to show slight differences in favor of esmolol, statistical tests were all nonsignificant ($p > 0.05$). Our study therefore indicates both drugs have fairly similar hemodynamic effects on this patient population.

Table 9. Prevalence of Rhythm Control, Rate Control, and Heart Frequency Decrease By at Least 20% for Esmolol and Amiodarone, 20, 40, 60, and 90 Min After Treatment Initiation

	Esmolol	Amiodarone	*p*-Value
Rhythm control (Conversion to sinus rhythm)			
t 20 min	24%	2%	<0.01
t 40 min	44%	18%	<0.01
t 60 min	46%	22%	<0.01
t 90 min	46%	24%	<0.01
Rate control Main criteria (HR ≤ 100 beats/min)			
t 20 min	35%	4%	<0.01
t 40 min	64%	25%	<0.01
t 60 min	69%	32%	<0.01
t 90 min	71%	36%	<0.01
Heart frequency decreased by at least 20%			
t 20 min	40%	8%	<0.01
t 40 min	80%	37%	<0.01
t 60 min	85%	49%	<0.01
t 90 min	88%	57%	<0.01

HR = heart rate.

DISCUSSION

Predominant Use of Amiodarone

Although the advantage of rapid and short-lasting agents like esmolol is advocated worldwide by many authors and recommendations, in France many EPs seem more comfortable with amiodarone (ratio amiodarone/esmolol = 1200/100). The justifications used to explain this preference are diverse. In France, esmolol is available in < 25% of emergency pharmacies, whereas intravenous amiodarone is considered a mandatory and vital medication in all EDs and all MICUs. Even when esmolol is present, its utilization is low compared with that of amiodarone, probably because EPs mainly manage severe and acute RAF, with poorly documented medical histories, and they often think beta-blocker agents might

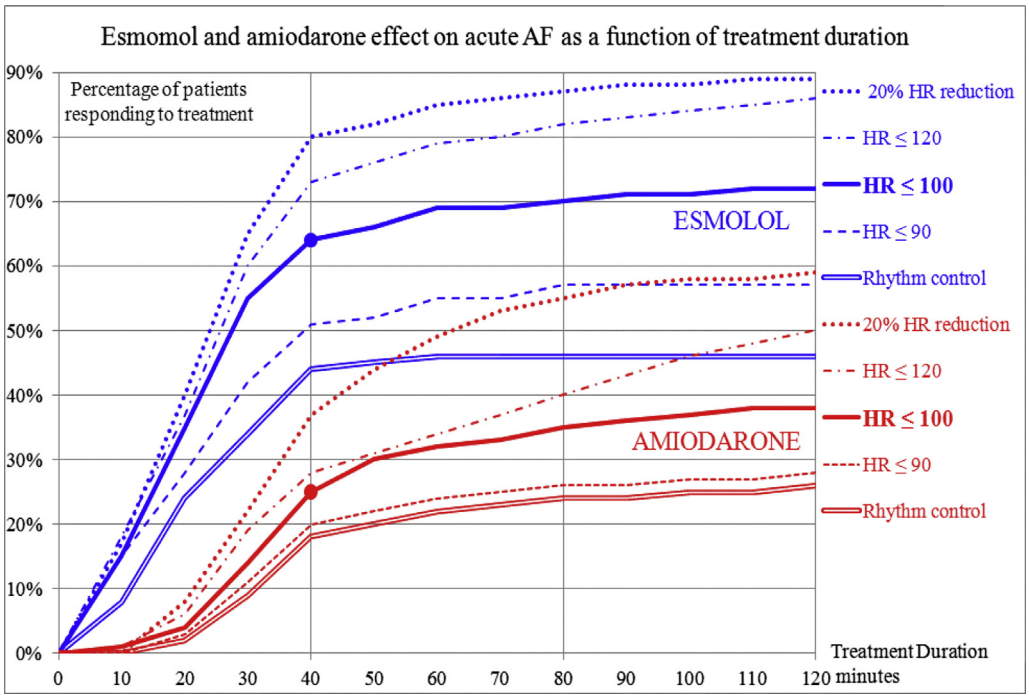

Figure 2. Percentage of patients responding to treatment. Percentages of rhythm control, HR ≤ 90, HR ≤ 100, HR ≤ 120, 20% HR reduction as a function of esmolol or amiodarone administration. Treatment duration (minutes). HR = heart rate; AF = atrial fibrillation.

aggravate rather than improve left ventricular function, particularly when patients present with hypotension. Another possible explanation is that amiodarone injection is a simple procedure (electric syringe with unchanged speed during 30 min), whereas esmolol administration is more laborious (repeated intravenous direct injections and increasing electric syringe flow that have to be adjusted to the patient's response). Due to these drawbacks, few EPs have developed lengthy experience with esmolol, but those who have believe this drug deserves a better place in clinical practice. The dominance of amiodarone and lack of knowledge regarding alternative medications were the principal motivations of this study. Diltiazem was not included in this retrospective review because in France (and all over Europe), cardiologists and EPs almost never utilize calcium channel antagonists as a first-line drug to treat recent-onset RAF.

Table 10. Subgroup Analysis for Main Outcome Measure (Percentage of Patients with HR ≤ 100 Beats/Min, 40 Min After Treatment Administration)

	Amiodarone	Esmolol	*p*-Value
Chest pain (angina pectoris)	32%	69%	<0.05
ST shift	30%	67%	<0.05
Shock	28%	56%	<0.05
Very high HR (>MHR + 30)	17%	60%	<0.05
Female gender	30%	64%	<0.05
All	25%	64%	<0.05

HR = heart rate; MHR = maximum heart rate.

Impact of Elapsed Time from Symptom Onset to Treatment Initiation

The impact of treatment delay on drug efficacy shown in our study (Figure 1) has previously been reported (14,23,39,49). The fact that the success of rapid response to pharmacological therapy decreases with ongoing time should be an encouragement to start intravenous infusion as soon as possible whenever RAF is associated with severe symptoms (8). The delay–efficacy relation is probably a major confusion factor in RAF study interpretation. Clinical trials including RAF occurring during anesthesia or intensive care with ultra-short treatment delays, present higher efficacy percentages than those including AF lasting for several days … external validity evaluations exploring the topic in the emergency context are therefore necessary (12,17,32,46,50,51). In our study, the time needed for esmolol to control heart rate was much shorter than that of amiodarone, which means real-life observation corroborates pharmacokinetic data (respectively, 4 min reacting time and 9 min half-life vs. 20 min reacting time and 80 days half-life) (52). Amiodarone depresses the atrioventricular node, acts as a calcium antagonist, and has sympatholytic properties. Due to its substantial ability to obtain conversion to sinus rhythm and its complementary capacity to facilitate ventricular rate control, this drug is suitable for AF management. But it is now considered a second-line therapy in emergency settings due to its low response rates and its important adverse effects (7,14,50,53). Its potential

short-term toxicity leads to limited dosage and lengthy intravenous protocols (5 mg/Kg in no less than 30 min) (25,54,55). It has a slow onset and long-lasting action. Esmolol is quicker and more efficient. We admit that its administration might be considered complicated, because response to beta-blockade action varies greatly from one patient to another. But severe RAF demands close monitoring and urgent treatment. The proven delay–efficacy relation means "the sooner the better!" and should encourage utilization of rapid-acting agents.

Patients with Hemodynamic Instability

Guidelines stipulate amiodarone is considered effective and safe in critically ill patients, and in particular, for those with severely impaired left ventricular systolic function.

When heart rate rises, diastole time is much more affected than systole time (Figure 3) (56,57). Diastole shortening impairs myocardial perfusion and ventricular filling (28,57–60). Persistence of high-frequency dysrhythmia can lead to systole or diastole ventricular dysfunction (61,62). Among drugs affecting cardiac frequency, beta-blocker agents have demonstrated long ago their ability to specifically increase diastole duration when heart rate is increased and thus, enhance myocardial perfusion and ventricular filling (28,57,58,63,64). Beta-blockers can be considered the most effective drug class for ventricular rate control, particularly esmolol and landiolol due to their very short half-life and high efficacy (26,30–32,40,47,52,62,65–75). When administered to patients with clinical shock or reduced ejection fraction due to very high heart frequency, treatment initiation with beta-blockers requires cautious hemodynamic monitoring, although these medications have shown their ability to raise or maintain systolic blood pressure or cardiac output in high-frequency AF (particularly short-acting compounds) (75-77). On the other hand, amiodarone can also cause hypotension due to its direct inhibition of heart contractility and vascular resistance, and because it increases norepinephrine metabolism. In our study, for all patients as well as for hemodynamically unstable patients, the slight trend in favor of esmolol was not significant; we can at least admit both agents have similar effects on blood pressure, and conclude there is no strong argument in favor of amiodarone superiority.

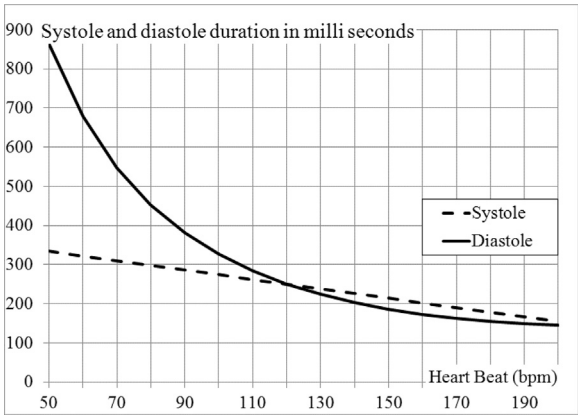

Figure 3. Systole duration in milliseconds as a function of heart beat. Diastole duration in milliseconds as a function of heart beat.

Outcome Criteria, Tough or Humble Indicator for Drug Efficacy?

Our main outcome measure was ventricular rate ≤ 100 beats/min within 40 min after i.v. treatment initiation. As secondary outcome criteria, we also registered rhythm control and rate control from 10 to 120 min after treatment initiation (Table 6). We admit the 2-h outer limit is short, but patients involved in this study presented with severe symptoms (chest pain, ST shift, very rapid ventricular rate, or clinical shock). For these patients, short-delay drug effect was the key question: rate control should be obtained within the first 2 h. Our study focused on "very short term efficacy" of drugs administered to treat "very severe RAF."

Rate control is now considered the priority goal treatment for RAF (38–40,66,78–81). The optimal ventricular frequency is unknown and might depend on a patient's specific traits (30,59–61). Our main outcome indicator was "ventricular frequency ≤ 100 beats/min" because this characteristic is often presented to describe rate control as a consensual marker of treatment success (25,29,75). The instant situated 40 min after treatment initiation seemed to be in conformity with both pharmacodynamics and with the designated target. Compliant indicators are interesting because at the very early stage, humble clinical goals such as heart rate ≤ 120 beats/min or 20% heart rate reduction from baseline can sometimes be significant to improve ventricular filling and myocardial perfusion (29,61,62,77,81). More stringent objectives such as rhythm control or heart rate ≤ 90 beats/min are less sensitive, but more specific in ensuring successful treatment (19,32,39,49,51,67,82,83,81). Finally, the combination of these indicators enhances their descriptive power. In our series, all indicators combine to demonstrate esmolol's superiority over amiodarone.

Recently, new medications (vernakalant, dofetilide, dronedarone, ranolazine) with high pharmacological cardioversion potential (40–60%) have been presented to treat AF (22,39,49,84–89). This ability to restore sinus pattern (rhythm control) might be similar or perhaps slightly better than that of esmolol, but their ability to slow ventricular frequency on the remaining AF seems insufficient for rate control in emergency situations (49,52,87–89).

Slow-Onset Wait-and-Watch Strategy vs. Acute Clinical Goal-Guided Therapy

Many authors consider that the most suitable drug for RAF management in emergency medicine should combine quick-onset action, high response rate, and short duration (19,28,41,45,62,90). Long-lasting medications generate a higher risk of interaction complications when sequential administration of several antidysrhythmic agents is necessary, and they potentially reduce the success rate of electrical cardioversion (19,70,91).

Amiodarone's slow-onset and long-lasting action result in an inflexible protocol (19,37,49). An electric syringe course is programmed for the next 30 to 60 min and remains unchanged, whatever happens. Patient monitoring is mandatory for security reasons, but it almost never leads to flow adaptation because the loading dosage (5 mg/Kg) represents only 25% of the amount required during the first 24 h (20 mg/Kg). Early stage treatment is rigid but easy: it demands no interpretation of the patient's response. Amiodarone is a passive and delayed-effect "wait-and-watch" option.

Due to its remarkable "on-off" action and notable dose–response variability, esmolol provides the dimension of "titratability." Efficacy and security depend on careful dosage titration and cardiovascular monitoring (47,70,72–74). Esmolol injection has to be patient-interactive, because optimal flow to obtain the desired result is not predictable (52). Ventricular rate control can be achieved after one single 0.5-mg/Kg bolus and stabilized at the first-step electric syringe dosage (0.05 mg/Kg/min). But most often, serial loading shots combined with escalating maintenance flow are necessary to obtain the desired steady-state level of beta blockade (Table 4). Electric syringe flow can be slowed or stopped at any time if side effects occur. Esmolol protocol is somewhat complicated because it is very flexible, but it responds to an acute clinical goal-guided therapy and is advocated by many authors as the number 1 first-line antidysrhythmic agent to treat fast RAF (26,28,30,50,52,65,67,71–74).

Limitations

This study is not a randomized trial but only a retrospective analysis. The two groups were established on the basis of treatment option, which itself depended on the experience and knowledge of the MICU deciding member. Therefore, there might be many uncontrolled differences (other than antidysrhythmic option) between the two compared cohorts of this observational study.

It took 11 years to constitute the esmolol cohort with 100 consecutive patients, because < 10% of our EPs are comfortable with the esmolol protocol. To reduce the effect of confounders and biases, we used a two-for-one propensity-matching process by selecting 200 amiodarone patients among 1200 (Table 6) (36). This process is not as satisfying as an authentic randomization procedure, but it permitted us to approach cohort comparability regarding patient profile, clinical presentation, severity and treatment delay. Our work mainly explores external validity and the methodology can be considered accurate for this goal.

Diltiazem and esmolol are known to be equally effective and safe in controlling rapid ventricular-rate atrial fibrillation, but in Europe the prevalence of the diltiazem option to treat RAF is < 1% (10,50). That is why this review was limited to the amiodarone vs. esmolol comparison.

Our study was not designed to explore thromboembolism occurrence, long-term rhythm control, or survival. It is admitted that AF management involves three different objectives: rate control, prevention of thromboembolism, and correction of rhythm disturbance. This work focuses on pharmacological ventricular rate control for patients presenting with severe RAF. Although many Class II antidysrhythmic agents and calcium antagonists are efficient and in accordance with recent guidelines, we deliberately focused our attention on a twofold evaluation: the primary goal investigated was the capacity of esmolol and amiodarone to control ventricular rate within a short period of time after treatment onset (23-25,29,30,44).

CONCLUSION

The first point markedly shown in our study is the delay–efficacy relation observed with both drugs. This should be an encouragement to start i.v. infusion as soon as possible, whenever RAF is associated with severe symptoms. The second point is that esmolol is superior to amiodarone for short-term effectiveness in the context of emergency medicine. Our results are in complete agreement with the investigated drug's pharmacokinetics, with clinical trials, and with recent guidelines. In real life, esmolol is quick, efficient, and safe, and therefore should be considered a primary intention antidysrhythmic agent for RAF acute management. This external validity study enhances esmolol's position among first-line antidysrhythmic agents to treat RAF in emergency settings.

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ARTICLE SUMMARY

1. Why is this topic important?

In emergency medicine, RAF is the most frequent dysrhythmia with high morbidity. ED practices show a great variation in RAF management and adherence to guidelines is rather low. Many pharmacological options for the treatment of RAF exist but for most of these medications, clinical trials and external validity studies are still lacking.

2. What does this study attempt to show?

Esmolol is quick, efficient, safe in patients with RAF and concomitant hemodynamic instability.

Esmolol is superior to Amiodarone to treat RAF in acute setting.

3. What are the key findings?

Short-term superiority of Esmolol for rhythm control and for rate control.

Esmolol is safe in patients with AF and concomitant hypotension or heart failure because of "on-off" action.

This external validity study enhances Esmolol's position among first line antidysrhythmic agents to treat RAF in emergency settings.

4. How is patient care impacted?

The use of Esmolol to treat RAF in acute settings could reduce short-term cardiovascular and neurological complications and could improve the prognosis of patients.