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BIPHASIC TRIAL

A Randomized Comparison of Fixed Lower Versus Escalating Higher Energy Levels for Defibrillation in Out-of-Hospital Cardiac Arrest

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Background—There is little clear evidence as to the optimal energy levels for initial and subsequent shocks in biphasic waveform defibrillation. The present study compared fixed lower- and escalating higher-energy regimens for out-of-hospital cardiac arrest.

Methods and Results—The Randomized Controlled Trial to Compare Fixed Versus Escalating Energy Regimens for Biphasic Waveform Defibrillation (BIPHASIC Trial) was a multicenter, randomized controlled trial of 221 out-of-hospital cardiac arrest patients who received ≥ 1 shock given by biphasic automated external defibrillator devices that were randomly programmed to provide, blindly, fixed lower-energy (150-150-150 J) or escalating higher-energy (200-300-360 J) regimens. Patient mean age was 66.0 years; 79.6% were male. The cardiac arrest was witnessed in 63.8%; a bystander performed cardiopulmonary resuscitation in 23.5%; and initial rhythm was ventricular fibrillation/ventricular tachycardia in 92.3%. The fixed lower- and escalating higher-energy regimen cases were similar for the 106 multishock patients and for all 221 patients. In the primary analysis in multishock patients, conversion rates differed significantly (fixed lower, 24.7%, versus escalating higher, 36.6%; $P=0.035$; absolute difference, 11.9%; 95% CI, 1.2 to 24.4). Ventricular fibrillation termination rates also were significantly different between groups (71.2% versus 82.5%; $P=0.027$; absolute difference, 11.3%; 95% CI, 1.6 to 20.9). For the secondary analysis of first shock success, conversion rates were similar between the fixed lower and escalating higher study groups (38.4% versus 36.7%; $P=0.92$), as were ventricular fibrillation termination rates (86.8% versus 88.8%; $P=0.81$). There were no distinguishable differences between regimens for survival outcomes or adverse effects.

Conclusions—This is the first randomized trial to compare fixed lower and escalating higher biphasic energy regimens in out-of-hospital cardiac arrest, and it demonstrated higher rates of ventricular fibrillation conversion and termination with an escalating higher-energy regimen for patients requiring multiple shocks. These results suggest that patients in ventricular fibrillation benefit from higher biphasic energy levels if multiple defibrillation shocks are required. (*Circulation*. 2007;115:1511-1517.)

Key Words: defibrillation ■ fibrillation ■ heart arrest ■ resuscitation ■ cardiopulmonary resuscitation

Out-of-hospital sudden cardiac arrest is an important healthcare problem, with some 300 000 such cases occurring annually in the United States. The vast majority of such patients do not survive, with hospital discharge rates uncommonly exceeding 5%.^{1,2} The American Heart Association's (AHA's) 4-link chain of survival concept has been developed to better explain community response to out-of-hospital cardiac arrest.³ Much interest and focus have been directed toward improving interventions for out-of-hospital cardiac arrest. Recent initiatives have, in particular, addressed

the second (early cardiopulmonary resuscitation [CPR]), third (early defibrillation), and fourth (early advanced life support [ALS]) links.⁴ Although optimal therapy is multifaceted, most survivors of out-of-hospital cardiac arrest are those patients who present in ventricular fibrillation (VF) and are rapidly and effectively defibrillated.⁵

Clinical Perspective p 1517

Recent AHA-sponsored guidelines for emergency cardiovascular care have endorsed newer technology for the defi-

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brillation of cardiac arrest patients in VF: the use of biphasic waveform energy.^{6,7} Compared with older monophasic waveforms,⁸ the new biphasic waveform technology is more effective in terminating VF and may reduce shock-related myocardial damage. What has not been clearly established, however, is the optimal energy level of first and subsequent biphasic defibrillation attempts. Current research confirms that biphasic shock energies from 150 to 360 J are safe and effective.^{9–16} Although both escalating higher and nonescalating lower energy defibrillators are available, data are insufficient to recommend one approach over another.

We believe that large clinical trials are required to further determine the impact of biphasic energy levels and energy regimens on patient survival and morbidity. Such trials would likely require thousands of patients to be definitive for the most clinically important outcome, survival to hospital discharge with good neurological function. Our objective was to perform a preliminary randomized controlled trial to compare fixed lower-energy or escalating higher-energy regimens of biphasic waveform defibrillation during automated external defibrillator (AED) use. We sought to examine a number of important electrical, clinical, and adverse outcomes in the present clinical trial.

Methods

Study Design and Setting

We conducted a triple-blinded (ie, blinded to patients, healthcare providers, and researchers), randomized controlled trial with 2 biphasic waveform defibrillation study groups: a fixed lower-energy (150-150-150 J) regimen and an escalating higher-energy (200-300-360 J) regimen. We conducted the present study in out-of-hospital locations in 3 Canadian cities: Windsor, Ontario (population, 200 000); Vancouver, British Columbia (population, 2 million); and Edmonton, Alberta (population, 1 million). Windsor and Vancouver use a multitiered emergency medical service with first-responding firefighters and both basic life support and ALS paramedics. Edmonton has a 2-tiered emergency medical service response with first-responding firefighters and full ALS paramedics.

Study Population

We included all patients who suffered witnessed out-of-hospital cardiac arrest in the study communities and who required defibrillation according to standard AHA protocols (ie, either initial or subsequent rhythm as VF or pulseless ventricular tachycardia). The inclusion criteria were further restricted to patients whose initial defibrillation was provided by first responders using an AED. We excluded patients who were <8 years of age, who had documented terminal illness, who were without basic CPR for >10 minutes, who were acute trauma victims, who had exsanguinations, who suffered cardiac arrest while in an acute care hospital, and whose initial defibrillation was provided by ALS paramedics. The respective research ethics boards approved the trial without the need for informed consent.

Intervention

The treatment of patients followed standard basic and advanced cardiac life support protocols recommended by the AHA and was provided by well-developed 2-tiered emergency medical services. First-responding firefighters and basic life support paramedics used an AED (Medtronic Emergency Response Systems LIFEPAK 500 AED, Redmond, Wash). ALS paramedic providers used manual defibrillators employing either monophasic or biphasic defibrillation waveforms. These ALS providers were not involved in the present study, and their manual defibrillation energy protocols were not affected by the study. The LIFEPAK 500 AED devices were

randomly programmed to provide, blindly, either a fixed lower-energy regimen of 150 J for all shocks or an escalating higher-energy regimen of 200 J (first shock), 300 J (second shock), and 360 J (all remaining shocks). Escalation of the second and third shock dose occurred regardless of the outcome of the preceding shock. The AED devices were configured to have the energy level display turned off so that the providers were unable to determine which energy regimen was being used. The intervention was randomly allocated for each patient. At the beginning of the present study and after each use, the AED devices were randomly programmed to deliver either the fixed lower- or the escalating higher-energy regimen. Randomization was stratified within each of the study communities. First-responding firefighters and basic life support paramedics were trained in a session that involved explanation of the rationale and procedures of the present study. A supervisor was trained to collect case information and to reprogram the AED devices after each use.

Outcome Measures

Outcome measures can be considered electrical, clinical, or adverse events. The primary outcome of the present study was the electrical outcome measure successful conversion, defined as the termination of VF and the establishment of organized rhythm within 60 seconds. An organized rhythm required at least 2 QRS complexes separated by no more than 5 seconds. This outcome measure was chosen because it not only reflects the ability of a shock to accomplish its primary function—removal of VF—but also is sensitive to any transient deleterious shock effects that could inhibit postshock restoration of organized electrical activity. A secondary electrical outcome was termination of VF for at least 5 seconds after the shock, regardless of the resulting rhythm.⁶

We also evaluated a number of clinical outcomes, including survival to hospital discharge, resuscitation with a continuous pulse and blood pressure for at least 1 hour, any return of spontaneous circulation, and survival to 24 hours. In addition, we evaluated the functional status of patients surviving to hospital discharge according to the 5-point scale of Cerebral Performance Category.¹⁷

Adverse effects were evaluated in terms of myocardial damage by evaluating ECG changes for ischemia or infarction within the first 6 hours after treatment, the levels of the cardiac enzymes creatinine kinase and troponin within the first 6 hours, and left ventricular ejection fraction <35% as measured during hospital admission.

Data Collection

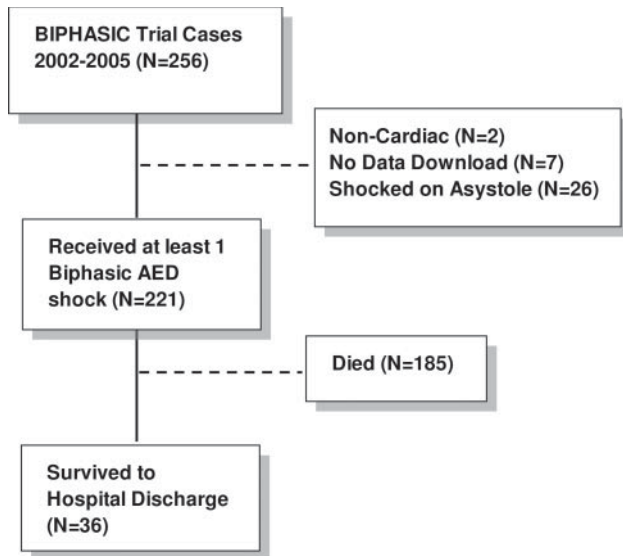
Local study personnel provided the data coordinating center with hard copies of the ambulance call report, first-responder medical report, and dispatch times, along with the electronic device record downloaded from the AED. In addition, research staff reviewed emergency department and in-hospital records for relevant demographic and clinical outcome measures.

Data Analysis

For survival, process, and adverse outcomes, comparisons were made between the total patients in each study group. For electrical outcomes, comparisons were made between all electrical shocks delivered by the study AED devices in the 2 study groups.

The primary study hypothesis, stated in the affirmative, was that the escalating higher-energy regimen, in patients requiring >1 shock, would be associated with increased rates of conversion to an organized rhythm. The multishock data within each patient were considered a cluster, taking into consideration that the results for these shocks may be more related to one another than shocks between patients. We used χ^2 procedures with SEs adjusted for the cluster design effect using a group-specific variance inflation factor to compare the constant with escalating shock protocol in the multishock patient group.^{18–20} As a secondary analysis, we also performed cluster analyses on the subgroup of patients who presented in VF.

We used χ^2 analysis to test differences between the 2 study groups for survival outcomes. All probability values were 2 tailed. The 95% CIs were calculated for the absolute difference in outcome rates



Flow of patients in the Pilot Randomized Controlled Trial to Compare Fixed Versus Escalating Energy Regimens for Biphasic Waveform Defibrillation (BIPHASIC Trial).

between groups. Differences between groups for the Cerebral Performance Category score were assessed with the Wilcoxon rank sum test. Comparisons of patient and treatment characteristics were tested with χ^2 , Fisher exact, or Student *t* test analyses as appropriate for the data. We arbitrarily chose a sample size of 200 patients a priori with the expectation that this size would allow a reasonable estimate of outcome event rates in both study groups, recognizing that it would not give sufficient power for survival outcomes.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

From March 2002 to September 2005, we enrolled 221 patients into the study; none were lost to follow-up. Another 26 patients received defibrillatory shocks from the study defibrillators but were later determined by a blinded review to have been in asystole rather than VF and were excluded. This misclassification could have occurred if chest compression or other motion artifact was present during a rhythm analysis interval and the motion detection feature of the AED was configured off per local protocol. Another 9 patients were excluded: 2 cases were determined to be of traumatic origin, and the download of defibrillator data was incomplete in 7 (the Figure). Patients in the fixed lower regimen ($n=114$) and the escalating higher regimen ($n=107$) groups were similar for most demographic and clinical characteristics (Table 1). There were slight differences between groups in the initial presenting rhythm of asystole, but response with the defibrillator was equally rapid in both study groups. Table 1 also gives a detailed description of the number of shocks received and indicates that 51 patients from the fixed lower study group and 55 from the escalating higher study group received ≥ 2 defibrillatory shocks by the study defibrillators. For these multishock patients, the study groups also were similar for most demographic and clinical characteristics.

Table 2 shows subsequent ALS paramedic intubation and medication interventions for the 221 biphasic study patients

and for the 106 multishock patients. Information on the number and type of ALS defibrillation shocks was not available.

Overall, 498 shocks were delivered to the 221 study patients by the study AED devices: 292 in the fixed lower-energy and 206 in the escalating higher-energy study groups. Forty-eight percent of patients, the multishock patients, required ≥ 2 shocks from the study AEDs because of either failed termination of the first shock or recurrence of VF. In the primary cluster analysis in multishock patients, in which the energy regimens diverged, conversion rates differed significantly (fixed lower, 24.7%; escalating higher, 36.6%; $P=0.035$; absolute difference, 11.9%; 95% CI, 1.2 to 24.4). VF termination rates also were significantly different between groups (71.2% versus 82.5%; $P=0.027$; absolute difference, 11.3%; 95% CI, 1.6 to 20.9) (Table 3).

We evaluated the subgroup of 206 patients who initially presented in VF and found results similar to those for the overall group. Comparing the fixed and escalating groups with cluster analysis showed that conversion rates were 41.6% and 37.5% ($P=0.66$) for first shocks and 25.7% and 36.0% ($P=0.075$) in multishock patients. The respective termination rates were 88.3% and 88.3% ($P=1.0$) for first shocks and 71.8% and 81.8% ($P=0.050$) in multishock patients.

Survival outcomes with regard to return of spontaneous circulation, survival for 1 hour, survival for 24 hours, and survival to hospital discharge were not different between the fixed lower and escalating higher groups. Similarly, the median Cerebral Performance Category scores were the same (Table 4). With regard to adverse outcomes, elevations of troponin levels, creatinine kinase levels, and ECG ST segments were similar in both study groups. There was, however, a nonsignificant trend toward more patients with left ventricular ejection fraction $<35\%$ in the group treated with fixed lower-energy shocks (24.3% versus 10.5%; $P=0.12$).

Discussion

The present study is the first randomized controlled trial to compare fixed lower- with escalating higher-energy regimens for biphasic defibrillation in out-of-hospital cardiac arrest. Rates of conversion to an organized rhythm and VF termination were statistically indistinguishable for first shocks of 150 and 200 J. For approximately half of the patients in each group, this first shock was the only defibrillation required during the period of AED use. In the other half, in whom persistent or recurrent VF necessitated delivery of additional AED shocks, we found a significant benefit from the escalating higher-energy regimen for both conversion to an organized rhythm and termination of VF. The present study did not find a difference in survival rates between regimens but was not powered to do so. In addition, we found a trend toward fewer patients with decreased left ventricular ejection fraction in the escalating higher-energy group, possibly because this group required substantially fewer shocks during the basic life support/AED phase of resuscitation care.

Although biphasic waveforms were first introduced into external defibrillators more than a decade ago, the optimal energy levels and dosing strategies for the various clinical

TABLE 1. Prehospital Clinical and Demographic Characteristics of BIPHASIC Study Patients

	BIPHASIC Study Patients (n=221)		Multishock Patients (n=106)	
	Fixed Lower (n=114)	Escalating Higher (n=107)	Fixed Lower (n=51)	Escalating Higher (n=55)
Age, y, mean (SD)	66.0 (14.2)	66.1 (14.5)	66.7 (13.4)	66.2 (13.8)
Range	20–90	24–94	31–89	36–94
Male gender	88 (77.2)	89 (83.2)	40 (78.4)	47 (85.5)
Arrest witnessed by				
Bystander	74 (64.9)	68 (63.6)	34 (66.7)	36 (65.5)
EMS	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.8)
Unwitnessed	40 (35.1)	38 (35.5)	17 (33.3)	18 (32.7)
CPR started by				
Bystander	28 (24.6)	24 (22.4)	12 (23.5)	9 (16.4)
First responder (fire/police/ambulance)	85 (74.6)	82 (76.6)	39 (76.5)	45 (81.8)
Other	1 (0.9)	1 (0.9)	0 (0.0)	1 (1.8)
Initial rhythm				
VT/VF	103 (90.4)	103 (96.3)	47 (92.2)	53 (96.4)
Asystole	6 (5.7)	0 (0.0)	2 (3.9)	0 (0.0)
Pulseless electrical activity	5 (4.4)	4 (3.7)	2 (3.9)	2 (3.6)
Response with defibrillator ≤8 min (n=114:104)	107 (93.9)	96 (92.3)	47 (92.2)	49 (92.5)
Initial defibrillation				
Fire defibrillation	94 (82.5)	91 (85.1)	38 (74.5)	43 (78.2)
EMS defibrillation	20 (17.5)	16 (15.0)	13 (25.5)	12 (21.8)
Median response intervals, min (IQR)				
From call receipt to crew notification (n=114:106)	0.7 (0.4–1.5)	0.8 (0.4–1.2)	0.8 (0.4–1.6)	0.7 (0.4–1.1)
From crew notification to vehicle mobile (n=114:106)	0.9 (0.0–1.3)	0.8 (0.3–1.3)	0.9 (0.0–1.4)	0.8 (0.0–1.2)
From fire vehicle mobile to fire arrival at scene (n=89:88)	2.9 (2.0–4.0)	2.6 (2.0–4.0)	3.0 (2.0–4.0)	2.6 (1.9–4.0)
From vehicle mobile to ambulance (BLS) at scene (n=78:66)	5.8 (4.0–7.6)	5.1 (3.8–8.3)	7.1 (3.0–7.0)	5.8 (3.4–9.0)
From vehicle mobile to ambulance (ALS) at scene (n=100:99)	6.3 (4.3–9.1)	6.7 (4.6–8.4)	4.8 (4.7–9.9)	7.0 (4.9–9.0)
From vehicle at scene to patient's side (n=114:104)	1.4 (0.6–2.0)	1.2 (0.7–1.7)	1.5 (0.7–2.0)	1.3 (0.9–1.8)
From patient's side to departure from scene (n=95:83)	25.2 (18.7–37.0)	24.2 (18.7–37.0)	24.2 (15.7–38.6)	29.0 (20.9–37.6)
From departure from scene to arrival at hospital (n=95:82)	7.4 (4.0–10.4)	7.0 (4.2–10.0)	5.8 (3.4–10.4)	7.1 (3.7–10.0)
AED power-on to power-off interval, min (IQR)	4.2 (2.3–6.8)	3.6 (1.9–5.3)	5.2 (3.8–8.2)	4.7 (3.1–6.9)
Minimum shocks received				
1 only	63 (55.3)	52 (48.6)	0 (0.0)	0 (0.0)
≥2	51 (44.7)	55 (51.4)	51 (100.0)	55 (100.0)
≥3	32 (28.1)	26 (24.3)	32 (62.7)	26 (47.3)
>3	23 (20.2)	11 (10.3)	23 (45.1)	11 (20.0)

Values are expressed as n (%) unless otherwise indicated. CPR indicates cardiopulmonary resuscitation; VT, ventricular tachycardia; IQR, interquartile range; and BLS, basic life support.

settings in which biphasic external defibrillators are now used remain unknown. Initial clinical investigations of external biphasic defibrillation were conducted in the electrophysiology laboratory setting where shocks were administered to treat induced arrhythmias of brief duration. These studies, performed primarily to support US Food and Drug Administration clearance of new biphasic waveforms, documented

that a variety of biphasic shock doses can terminate VF at least as effectively as conventional monophasic shocks of 200 J.^{21–24}

More recent studies have described the performance of specific biphasic energy doses during attempted resuscitation from in-hospital and out-of-hospital cardiac arrest. High VF termination rates have generally been reported for initial 150-

TABLE 2. EMS ALS Interventions for BIPHASIC Study Patients

	BIPHASIC Study Patients (n=221)		Multishock Patients (n=106)	
	Fixed Lower (n=114)	Escalating Higher (n=107)	Fixed Lower (n=51)	Escalating Higher (n=55)
ALS interventions				
Attempted	97 (85.1)	93 (86.9)	38 (74.5)	49 (89.1)
Successful	95 (83.3)	92 (86.0)	38 (74.5)	49 (89.1)
Intravenous medications				
Epinephrine	81 (71.1)	84 (78.5)	34 (66.7)	48 (87.3)
Atropine	65 (57.0)	68 (63.6)	29 (56.9)	38 (69.1)
Lidocaine	38 (33.3)	41 (38.3)	20 (39.2)	27 (49.1)
Fluid bolus	26 (22.8)	24 (22.4)	10 (19.6)	14 (25.5)

Values are expressed as n (%).

to 200-J biphasic shocks delivered from first-responder AEDs.^{9,11-13,25,26} Several other studies have reported markedly lower VF termination rates for 100- to 150-J biphasic shocks delivered during ALS-level resuscitation care.^{10,16} These published reports have focused predominantly on the first shock performance of a single biphasic waveform and energy level. A recent report demonstrated that the efficacy of shocks is lower for subsequent episodes than for initial episodes of VF, even when energy levels up to 360 J are used.²⁷ Thus, current evidence indicates that various biphasic waveforms and energies still leave room for improvement in defibrillation performance in some clinical settings and patient cohorts. However, previous clinical comparison of different biphasic energy levels and dosing regimens is limited to a single, nonrandomized study.¹⁰

The present study extends this body of evidence on biphasic defibrillation during cardiac arrest resuscitation in several important ways. We compared 2 different commonly used biphasic AED first-shock energy doses and documented

TABLE 3. Electrical Outcomes for All 498 Shocks Delivered by Study AED Devices in the BIPHASIC Study and Analyzed as Clusters*

Electrical Outcomes	Fixed Lower (n=292), %	Escalating Higher (n=206), %	P
Successful conversion†			
Shocks in multishock patients (n=229:154)	24.7	36.6	0.035‡
First shocks only (n=112:98)	38.4	36.7	0.92
Termination of VF within 5 s			
Shocks in multishock patients (n=229:154)	71.2	82.5	0.027§
First shocks only (n=114:107)	86.8	88.8	0.81

*The multishock data within each patient were considered as a cluster and were analyzed with χ^2 procedures, with SEs adjusted for the cluster design effect.

†Successful conversion is defined as termination of VF within 60 seconds and establishment of an organized rhythm within 60 seconds.

‡Absolute difference, 11.9%; 95% CI, 1.2 to 24.4.

§Absolute difference, 11.3%; 95% CI, 1.6 to 20.9.

TABLE 4. Clinical and Adverse Outcomes for All 221 BIPHASIC Study Patients

	Fixed Lower (n=114)	Escalating Higher (n=107)	P
Clinical outcomes			
Return of spontaneous circulation, n (%)	58 (50.9)	52 (48.6)	0.73
Resuscitation, survival for 1 h, n (%)	54 (47.4)	44 (41.1)	0.35
Survival to ≥ 24 h after arrest, n (%)	37 (32.5)	38 (35.5)	0.63
Survival to hospital discharge, n (%)	19 (16.7)	17 (15.9)	0.88
Cerebral Performance Category scores			
Median (IQR)	2 (1.0-3.0)	2 (1.0-2.0)	0.72
Category 1 and 2, n (%)	12 (63.2)	14 (82.4)	0.21
Adverse outcomes, mean, n (%)*			
Cardiac enzymes elevation (CK or TNT) (n=54:44)	43 (79.6)	35 (79.6)	0.99
Troponin level >0.10 $\mu\text{g/L}$	41 (75.9)	33 (75.0)	0.92
Creatinine kinase level >215 U/L	23 (42.6)	24 (54.6)	0.24
ECG ST-segment elevation (n=54:44)	15 (27.8)	13 (29.6)	0.85
LV ejection fraction <0.35 (n=37:38)	9 (24.3)	4 (10.5)	0.12

IQR indicates interquartile range; CK, creatine kinase; TNT, troponin T; and LV, left ventricular.

*For patients who survived >1 hour.

that they both provide high rates of VF termination and comparable rates of conversion to an organized rhythm. We also evaluated the performance of 2 different, commonly used AED energy dosing regimens for shocks after the first shock. These additional shocks are required not only in the small percentage of patients for whom the first shock fails to terminate VF but also in the large percentage of patients in whom VF reappears ≥ 1 time in the seconds to minutes after successful VF termination.^{9,14,27,28} Our finding that rates of both conversion to an organized rhythm and VF termination are significantly affected by the energy level of subsequent shocks has not previously been reported. This finding explicitly confirms an implication of the data reported by Walsh et al¹⁰ and does so in a setting in which many subsequent shocks were delivered for recurrent VF, not solely for persistent VF.

The present study had the strengths of being a randomized controlled trial performed in a true clinical setting, ie, that of out-of-hospital cardiac arrest. We used multiple sites to increase the generalizability of the findings. Study group allocation was masked to the healthcare provider, and the intervention was triple blinded. The primary limitation of the study is the relatively small sample size of 221 patients, of whom only 106 received ≥ 2 shocks from the AED. Because the fixed lower-energy or escalating higher-energy nature of the dosing regimen comes into effect only for second and subsequent shocks, this smaller sample size of multishock patients did not afford adequate power to evaluate most clinical outcomes in a meaningful way. For example, reliably detecting a difference in the rate of survival to discharge, if in fact that rate doubled for multishock patients when escalating higher energy was used, would require enrollment of ≈ 3 times as many patients. If the underlying difference between the 2 groups were less dramatic, sample size would need to be

even larger; a 50% increase in survival would require a study with a multishock group >10 times as large to reliably detect. A second important limitation is that the study did not control defibrillation waveforms or energy regimens during the ALS tier of care in the multitiered emergency medical service. The median AED use interval of roughly 4 minutes made up only a small portion of the total duration of the prehospital resuscitation effort, and additional shocks of varied waveforms and energy levels were delivered during the ALS phase of care. If clinical outcomes are affected by shock energy regimens, they are likely affected by defibrillation practices throughout the entire resuscitation effort. Thus, the clinical outcomes we report likely do not provide a strict reflection of the subset of defibrillation care that was randomized within the study. The present study did, however, provide a reasonable estimate of event rates and was able to evaluate electrical outcomes.

The present study has several implications. First, from a research perspective, future investigations should evaluate fixed lower- and escalating higher-energy regimens in studies with larger sample sizes to evaluate the impact on clinical outcomes. From a clinical perspective, the present study clearly demonstrates the electrical advantage of using an escalating higher biphasic energy regimen that can reach 360 J. This finding has several implications with respect to the new recommendation in the 2005 AHA guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, which is to resume CPR immediately after every shock.⁶ The significant difference between groups in VF termination rates for subsequent shocks means that among those patients with persistent or recurrent VF— $\approx 50\%$ of the patients in this study—2 things will differ, depending on the selected energy regimen. First, a significantly higher proportion of patients—nearly twice as many in this study—will be left in VF after each subsequent shock and for the entire duration of the ensuing CPR interval when a fixed lower-energy regimen is selected. The specific physiological impact of such a difference in underlying rhythm during postshock CPR is currently unknown. Second, because every failed shock will need to be followed by at least 1 additional shock to reattempt defibrillation, the lower VF termination rate provided by a fixed lower-energy regimen will necessitate additional and more frequent interruptions in CPR for additional defibrillation shocks.

The new AHA/ILCOR guidelines make clear that minimizing interruptions in CPR, whatever their cause, is an important objective. Given the importance of minimizing interruptions in CPR, a related hypothesis to be tested in future studies is whether to start with the highest available energy level, eg, 360 J, for the first delivered shock. Unlike the randomized trial from >2 decades ago that compared 2 energy levels of monophasic waveforms with much higher current levels,⁸ the present study found no indication of any deleterious effects of higher-energy biphasic shocks. An evaluation of higher energy for the first delivered shock might be of particular value in clinical settings such as ALS in-hospital and out-of-hospital defibrillation, in which lower biphasic energies have been reported to provide clearly suboptimal VF termination rates, even for first shocks.^{10,16}

Conclusions

This is the first randomized, controlled clinical trial to compare fixed lower- with escalating higher-energy regimens for biphasic defibrillation. The present study found no difference in clinical outcomes between these regimens but was underpowered to evaluate such outcomes. In contrast, the present study clearly demonstrated higher rates of VF termination and conversion to an organized rhythm with the escalating higher-energy regimen when persistent or recurrent VF necessitated delivery of multiple shocks. No adverse effects from the higher-energy regimen were found. These study findings suggest that patients in VF benefit from higher biphasic energy levels if multiple defibrillation shocks are required.

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CLINICAL PERSPECTIVE

The Pilot Randomized Controlled Trial to Compare Fixed Versus Escalating Energy Regimens for Biphasic Waveform Defibrillation (Biphasic Trial) was the first randomized controlled trial to compare fixed lower- with escalating higher-energy regimens for biphasic defibrillation in out-of-hospital cardiac arrest. This multicenter trial, which enrolled 221 patients, found no difference in clinical outcomes between these regimens but was underpowered to evaluate such outcomes. In contrast, the present study clearly demonstrated higher rates of ventricular fibrillation termination and conversion to an organized rhythm with the escalating higher-energy regimen when persistent or recurrent ventricular fibrillation necessitated delivery of multiple shocks. No adverse effects from the higher-energy regimen were found. The present study clearly demonstrates the electrical advantage of using an escalating higher biphasic energy regimen that can reach 360 J. This has several implications with respect to the new recommendation in the 2005 American Heart Association guidelines to resume cardiopulmonary resuscitation immediately after every shock. First, a significantly higher proportion of patients will be left in ventricular fibrillation after each subsequent shock and for the entire duration of ensuing cardiopulmonary resuscitation when a fixed lower-energy regimen is selected. Second, because every failed shock will need to be followed by at least 1 additional shock to reattempt defibrillation, the lower ventricular fibrillation termination rate provided by a fixed lower-energy regimen will necessitate additional and more frequent interruptions in cardiopulmonary resuscitation for additional defibrillation shocks. The present study findings suggest that patients in ventricular fibrillation benefit from higher biphasic energy levels if multiple defibrillation shocks are required.