Transthoracic Incremental Monophasic Versus Biphasic Defibrillation by Emergency Responders (TIMBER)
A Randomized Comparison of Monophasic With Biphasic Waveform Ascending Energy Defibrillation for the Resuscitation of Out-of-Hospital Cardiac Arrest due to Ventricular Fibrillation

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Background—Although biphasic, as compared with monophasic, waveform defibrillation for cardiac arrest is increasing in use and popularity, whether it is truly a more lifesaving waveform is unproven.

Methods and Results—Consecutive adults with nontraumatic out-of-hospital ventricular fibrillation cardiac arrest were randomly allocated to defibrillation according to the waveform from automated external defibrillators administered by prehospital medical providers. The primary event of interest was admission alive to the hospital. Secondary events included return of rhythm and circulation, survival, and neurological outcome. Providers were blinded to automated defibrillator waveform. Of 168 randomized patients, 80 (48%) and 68 (40%) consistently received only monophasic or biphasic waveform shocks, respectively, throughout resuscitation. The prevalence of ventricular fibrillation, asystole, or organized rhythms at 5, 10, or 20 seconds after each shock did not differ significantly between treatment groups. The proportion of patients admitted alive to the hospital was relatively high: 73% in monophasic and 76% in biphasic treatment groups (P=0.58). Several favorable trends were consistently associated with receipt of biphasic waveform shock, none of which reached statistical significance. Notably, 27 of 80 monophasic shock recipients (34%), compared with 28 of 68 biphasic shock recipients (41%), survived (P=0.35). Neurological outcome was similar in both treatment groups (P=0.4). Earlier administration of shock did not significantly alter the performance of one waveform relative to the other, nor did shock waveform predict any clinical outcome after multivariate adjustment.

Conclusions—No statistically significant differences in outcome could be ascribed to use of one waveform over another when out-of-hospital ventricular fibrillation was treated. (Circulation. 2006;114:2010-2018.)

Key Words: cardiopulmonary resuscitation ■ defibrillation ■ heart arrest

Hundreds of thousands of transthoracic defibrillators worldwide provide life-saving therapy for cardiac arrest from ventricular fibrillation (VF). Monophasic waveform defibrillators account for a substantial proportion of those in current clinical use and are estimated to number well over one half million in the United States alone (oral communication, Medtronic Emergency Response Systems, Inc, April 2006).1 Recently, the safety and efficacy of biphasic waveform shocks have been demonstrated in a variety of settings,2-5 reported to have greater success than monophasic shocks in terminating VF,6-10 and heralded by many as the new standard for defibrillation. On the basis of this perceived superiority, there is likely to be mounting pressure on hospitals and particularly on prehospital providers to replace all monophasic with biphasic defibrillators, despite considerable expense and little evidence that either waveform is more lifesaving.

Clinical Perspective p 2018

This randomized prehospital trial (Transthoracic Incremental Monophasic Versus Biphasic Defibrillation by Emergency Responders [TIMBER]) tested whether transthoracic biphasic or monophasic waveform defibrillation improves clinical outcome after out-of-hospital cardiac arrest.

Methods

Seattle, Wash, is a city of 550 000 residents served by a single fire department–based, 2-tiered Emergency Medical Service (EMS)11 that follows treatment protocols adhering to American Heart Association guidelines.12 From November 1, 2002, to September 30, 2004, all adults in Seattle with nontraumatic out-of-hospital cardiac arrest were included.
arrest occurring before EMS arrival who had an initial recorded rhythm of VF and received all defibrillator shocks by EMS personnel were prospectively studied. Typically, emergency medical technicians (EMTs) initiated chest compressions with ventilation (CPR) and administered shocks from external defibrillators with automated rhythm analysis (automated external defibrillators [AEDs]). All patients received 90 seconds of CPR from EMS responders before the first shock. Up to 3 shocks were administered consecutively after the initial AED analyses, unless there was an interim no-shock advisory. Single shocks were given thereafter with intervening periods of CPR. On their arrival on the scene, paramedics provided advanced life support, including manually administered defibrillator shocks. In ~10% of cases, paramedics arrived on the scene before or simultaneously with EMTs.

**Defibrillators**

LIFEPAK 500 (Medtronic Emergency Response Systems Inc, Redmond, Wash) AEDs were used by all EMTs. Paramedics used the LIFEPAK 12 from the same manufacturer, which permitted rhythm interpretation and manual defibrillation. The respective monophasic and biphasic waveform defibrillators used for this study were identical in appearance and were differentiated by an anonymous numerical code. According to the manufacturer, monophasic defibrillators delivered a damped sinusoidal waveform of 3100 to 4450 V at 200- and 360-J settings, respectively. Biphasic defibrillators provided a truncated exponential waveform of 1400 to 2000 V at similar settings. All AEDs used an identical rhythm detection algorithm, voice prompts, and automatically escalating energy settings (200—200—360 J). Energy settings on manual defibrillators were selectable but were almost exclusively administered at 360 J after they replaced AEDs. Although indistinguishable in their physical appearance, the waveform of manual defibrillators was identifiable by information displayed on their screens during use.

**Randomization**

Patients were assigned to defibrillation according to the waveform of the device (typically AED) deployed for the first shock. Randomization occurred at the level of each EMS unit, to which a monophasic or biphasic defibrillator was randomly allocated and changed for its counterpart quarterly. Insofar as possible, AEDs and manual defibrillators were matched to achieve use of the same waveform throughout a resuscitation. Assignment of defibrillators with matching waveform was derived from review of prior years' reports of cardiac arrest, identifying EMS and paramedic units most likely to be paired. All responders were blinded to the waveform of the AED and whether the corresponding manual defibrillator administered a matching waveform.

**Data**

Prehospital data included a narrative report and detailed sequence of resuscitation events. AEDs with real-time clocks provided audio records of the resuscitation and continuous tracings of cardiac rhythm, recorded from cutaneous defibrillator patches that approximated a lead II configuration. Waveform type was unavoidably reported by analytical software on retrieved rhythm tracings. These were interpreted by a research nurse and characterized at 5, 10, and 20 seconds after each shock, as suggested by others, with the use of the objective criteria defined below. Rhythms whose diagnosis was uncertain underwent separate blinded review by 2 cardiologists. Functional status before cardiac arrest and neurological condition and disposition at hospital discharge were evaluated from the medical record. Before cardiac arrest, patients were characterized as independent if able to perform activities of daily living and manage their personal affairs without assistance. Neurological condition at discharge was assessed with the use of the Cerebral Performance Category (CPC) and by an index of functional status (whether discharged home rather than to a skilled-care facility). Except as noted above for rhythm analysis, all data were collected and analyzed without knowledge of treatment assignment.

**Definitions**

VF was defined as irregular, disorganized ventricular activity of variable amplitude (>0.1 mV) without distinct QRS complexes. Ventricular tachycardia (a wide QRS [>120 ms] rhythm without associated P waves, at rate >120 bpm) was uncommon in both treatment groups (ranging from 3 to 6 patients [1.8% to 5.6%] after initial shocks) and was grouped together with VF. Termination of VF was defined as its displacement to a nonshockable rhythm (organized or asystole). Asystole was defined as 0 to 1 QRS complex occurring over any 5-second time interval (<12 bpm), and an organized rhythm was defined as ≥2 QRS complexes with rate ≤120 bpm. Return of spontaneous circulation (ROSC) meant confirmed palpation of an arterial pulse or recordable blood pressure for any duration associated with an organized rhythm; sustained ROSC meant that these persisted until hospital arrival. Dispatch time was defined as the time when EMS providers were sent to the scene, and arrival time was defined as the time when responders reached the appropriate street address.

**Events**

The primary event of interest was admission of patients to the hospital (formal assignment to a bed) with a spontaneously perfusing rhythm. Secondary events included termination of VF, return of an organized rhythm, and ROSC, regardless of their duration; the number of shocks required for and time to sustained ROSC; survival to hospital discharge; and neurological status at discharge.

**Consent**

This study was approved by the University of Washington institutional review board. Because it evaluated Food and Drug Administration–approved defibrillators during standard resuscitation procedures, the study was viewed as having minimal risk and was conducted with exception from informed consent, in compliance with interpretation of the federal policy for the protection of human subjects. Survivors or their families were later notified of their participation, and consent was obtained for review of hospital records. Records of patients who did not survive or could not be contacted after discharge were accessed through a confidentiality agreement.

**Statistical Analysis**

On the basis of reported admission rates after biphasic defibrillation in another prehospital trial and those observed historically with monophasic defibrillation in Seattle (65%), we estimated that it would require 150 patients to detect a 30% relative improvement in the proportion of those admitted alive to the hospital after biphasic defibrillation, with 80% power and a 2-sided α of 0.05. Differences in continuous and dichotomous variables were analyzed with the Student t test or the χ² test. Logistic regression analyses that included demographic and resuscitation care variables were also performed, proper selection of which was confirmed by the goodness-of-fit χ² (Hosmer-Lemeshow) test. Statistical significance was indicated by 2-tailed P<0.05.

**Blinding**

Even when statistically significant differences are not evident, subtle biases may affect the manner in which data are presented and interpreted, once treatment assignment is disclosed. So as not to sway objectivity, in addition to our attempts to collect and analyze data anonymously, the primary writers were unaware of treatment assignment until after the article was formally accepted and revised for publication.

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

**Results**

**Patients**

Of 862 consecutive patients treated for cardiac arrest from all causes during the trial period, 168 met eligibility criteria and...
were allocated to either monophasic or biphasic defibrillation (Figure 1). Of these, 80 patients (48%) and 68 patients (40%) consistently received the same shock waveform (monophasic or biphasic, respectively) throughout their resuscitation. Twenty patients received shocks of both waveform types because of a “mismatch” in defibrillators deployed by EMTs and paramedics, including 3 for whom the identity of the first administered waveform was not known. The characteristics of these patients are shown in the Table. No statistically significant differences in these parameters were observed.
between monophasic and biphasic treatment groups; bystander CPR was more common and paramedics arrived later in patients who received shocks of both waveform types than in those treated exclusively with monophasic or biphasic shocks.

Because patients in the mixed-shock group each received shocks of both types during resuscitation, events that followed the administration of >1 shock could not necessarily be ascribed to consistent use of one or the other waveform. Hence we determined, a priori, to evaluate events after the first shock strictly in patients who were treated consistently with the same waveform throughout resuscitation. Conversely, responses to the first shock were determined in all patients in whom the waveform type was known by combining patients from the mixed-shock group with those having the corresponding waveform in the monophasic or biphasic shock groups, denoted as monophasic1 and biphasic1 shock groups, respectively, for these comparisons. Inclusion of patients with mixed-waveform shocks in all analyses would not have altered study findings or conclusions.

Response to the First Shock

Whether evaluated at 5, 10, or 20 seconds after the first shock, the prevalence of VF, asystole, or organized or unidentifiable rhythms was similar in both treatment groups (Figure 2). VF was terminated by the first shock in 75 patients in the monophasic1 treatment group (82%) and 65 in the biphasic1 group (88%) (P=0.33), resulting in an organized rhythm in 24 (26%) and 24 patients (34%), respectively (P=0.30) (Figure 5) and sustained ROSC in 18 patients in each group (20% and 24%, respectively) (P=0.51). VF recurred in 18 of 75 patients in the monophasic group (24%) and in 16 of 65 in the biphasic1 treatment group (25%) (P=0.9).

Subsequent Shocks

A comparable proportion of patients in both treatment groups had either unremitting or recurrent VF that required a second shock after their first (70 of 91 patients in the monophasic1 group [77%] and 54 of 74 in the biphasic1 group [73%] [P=0.5]) or a third shock after their second (54 of 80 patients treated with monophasic shocks [68%] and 43 of 68 treated with biphasic shocks [63%] [P=0.7]). The prevalence of rhythms assessed at 5, 10, or 20 seconds after the second and third shocks paralleled our observations after the first shock and, when we considered the multiple comparisons of data, did not significantly differ between treatment groups (Figures 2 and 3).
3 and 4). There were also no statistically significant differences between groups in the proportion of patients in whom 1 to 3 shocks terminated VF or returned an organized rhythm (Figure 5) or in whom circulation was restored during resuscitation (Figure 6). The mean ± SD time from first shock to sustained ROSC was 14.4 ± 12.8 minutes in recipients of monophasic shocks and 11.6 ± 6.7 minutes in those receiving biphasic shocks (P = 0.3). Patients treated with a monophasic waveform tended to require more shocks before sustained ROSC than recipients of the biphasic waveform (4.9 ± 4.2 [mean ± SD] [median 4] compared with 3.8 ± 3.7 [median 2.5] shocks, respectively [P = 0.18]).

Outcome
Among patients treated with monophasic waveform shocks, 58 (73%) were resuscitated and admitted alive to the hospital, as compared with 52 recipients of biphasic shocks (76%) (P = 0.58). Twenty-seven patients (34%) who received monophasic shocks and 28 recipients of biphasic shocks (41%) were discharged alive (P = 0.35); 18 (23%) and 16 patients (24%), respectively, went home rather than to a skilled-care facility (P = 0.48) (Figure 6). Before their cardiac arrest, a comparable proportion of surviving patients in both treatment groups (24 of 27 survivors treated with monophasic shocks [89%] and 22 of 28 treated with biphasic shocks [79%] [P = 0.5]) were functionally independent; baseline functional status was not known in 3 (11%) and 4 survivors (14%), respectively. Neurological condition at hospital discharge (CPC) could be determined in all but 2 surviving patients (1 from each treatment group); 2 additional patients from the biphasic treatment group had neurological recovery that could not be distinguished from the medical record as being either full or partial. No statistically significant differences were observed between treatment groups in their neurological outcome at hospital discharge (P = 0.4) (Figure 7).

Early Shock
To determine whether treatment with one waveform or the other was more effective when administered earlier in the course of cardiac arrest, a prespecified subgroup of 91 patients was identified with witnessed cardiac arrest and no reported delay in summoning EMS and who were shocked...
within 10 minutes of EMS dispatch. After this first shock, an organized rhythm returned in an identical proportion of patients in the monophasic, (16 of 48 [33%]) and biphasic, treatment groups (14 of 43 [33%]). Of 81 patients who were treated thereafter with the same waveform, circulation returned in 38 of 42 recipients of monophasic shocks (90%) and 36 of 39 recipients of biphasic waveform shocks (92%) (P=0.7). Among patients treated with monophasic shocks, 34 patients (81%) were admitted alive to the hospital compared with 30 recipients of biphasic shocks (77%) (P=0.6); 18 (43%) and 20 patients (51%), respectively, were discharged alive (P=0.5).

By comparison, among patients who received their first shock >10 minutes after EMS dispatch, clinical outcomes were poorer than in the former group but were not statistically different between recipients of the 2 waveforms. Seven of 12 such patients treated with monophasic shocks (64%) compared with 5 of 7 recipients of biphasic shocks (71%) were admitted alive to the hospital (P=0.7); 2 (18%) and 1 patient (14%), respectively, were discharged alive (P=0.9).

Predictors of Mortality

Death was independently predicted only by older age (odds ratio, 1.67 per 10-year increment; 95% confidence interval, 1.24 to 2.23). Multivariate adjustment did not alter the absence of an association between defibrillation waveform and mortality (odds ratio for biphasic versus monophasic waveform shock, 0.57; 95% confidence interval, 0.26 to 1.23). No variable was found that independently predicted the likelihood of admission alive to the hospital.

Discussion

We found no statistically significant differences between waveforms in the likelihood of terminating VF, restoring an organized rhythm or circulation, improving hospital admission, or survival after cardiac arrest. This contrasts with the reported greater efficacy of biphasic shock for electively terminating atrial arrhythmias or VF of brief duration under controlled circumstances.18–20 Such discordance could result from the reduced performance of any shock waveform under the conditions typically encountered in cardiac arrest. For example, when VF is protracted or associated with acute myocardial ischemia, the energy required for its termination increases substantially regardless of waveform.21–26 These and other differences between the experimental and cardiac arrest environment23,27 underscore the importance of evaluating the efficacy and effectiveness of shock waveforms under the same clinical conditions in which defibrillation is most likely to be emergently needed and used.

Clinical Studies

Nearly all previous clinical evaluations of shock waveform in cardiac arrest were potentially confounded by the use of AEDs from different manufacturers. Different AEDs vary widely in waveform design,28,29 in the magnitude of voltage and current delivered even at identical energy settings,4,28 and in the “hands off” time each requires to analyze rhythms, charge, and shock.30 Apart from delaying shock, interruption of CPR for these analyses has recognized adverse consequences.31 The potential for unconscious bias in the manner in which resuscitation might be conducted is also higher when devices are easily distinguishable to care providers.

Notably, the greater apparent defibrillation efficacy of biphasic shock reported in most studies has not been regularly accompanied by improved clinical outcomes; in fact, these have sometimes even trended in the opposite direction. For example, although biphasic shocks were found, retrospectively, to be better than escalating energy monophasic shocks for terminating VF, no statistically significant differences in ROSC (67% with biphasic versus 69% with monophasic shocks; P=0.82) or survival (31% versus 41%, respectively; P=0.32) were observed between treatment groups.3 A similar study found that an organized rhythm was restored more frequently after biphasic than monophasic shocks, but this was not accompanied by significant differences in ROSC (55% with biphasic versus 65% with monophasic shocks; P=0.1) or in survival (20% versus 30%, respectively) between treatment groups.32
Randomized Trials
In a multicenter prehospital trial, biphasic shocks proved better than escalating energy monophasic shocks for terminating VF, resulting in improved hospital admission rates (69% versus 46%, respectively; \( P=0.02 \)) but not survival rates (33% versus 27%; \( P=0.45 \)) or the proportion of survivors found suitable for discharge home (63% versus 50%; \( P=0.3 \)).

When patients in VF were defibrillated by AEDs that differed only in waveform, the return of an organized rhythm was independently predicted by receipt of a biphasic rather than monophasic shock. Notably, ROSC did not significantly differ between treatment groups (61% versus 65% of patients, respectively; \( P=0.62 \)), nor did hospital admission rates (40% versus 48%; \( P=0.35 \)) or survival (14% versus 19% in biphasic versus monophasic groups, respectively; \( P=0.46 \)).

Another prehospital trial observed a higher conversion rate to an organized rhythm in recipients of biphasic compared with monophasic waveform defibrillation. However, ROSC, survival, and neurological recovery were virtually identical between treatment groups.

Favorable Trends
Our randomized trial consistently administered the same waveform type at the same ascending energy settings throughout resuscitation, used defibrillators that were identical apart from waveform type, and emphasized the uniform provision of CPR before the first shock. That we did not find statistically significant differences in clinical outcome, under conditions that we believe tested the unique contribution of waveform type more rigorously than in previous studies, should not necessarily be taken to mean that the differences seen were unimportant. For example, several beneficial trends were observed in this trial that consistently favored treatment with biphasic waveform shock. These included a higher reversion of VF and return of an organized rhythm after the first shock; a requirement for fewer shocks and a shorter mean time from first shock to sustained ROSC; and a higher proportion of patients in whom circulation was restored and who survived. Most intriguing of these, a 21% relative (7% absolute) improvement in survival was observed with biphasic compared with monophasic waveform defibrillation, more than has ever been ascribed to any single intervention during cardiac arrest, except perhaps for defibrillation itself. That none of these differences was statistically significant could be attributed to true absence of benefit or to lack of statistical power, proof of which would require performance of considerably larger trials. For example, to establish statistical significance for the differences we observed in hospital admission and survival rates, with 80% power and a 2-sided \( \alpha \) of 0.05, would demand enrollment of at least 3700 and 1300 patients, respectively, and would take decades to complete.

Shock Energy
Experimental evidence suggests that biphasic defibrillation provokes less ventricular dysfunction, with better hemodynamic recovery from shock.\(^{33} \) We observed that biphasic compared with monophasic waveform defibrillation shortened the time from first shock to sustained ROSC by nearly 3 minutes. That this difference was not statistically significant could be because the study was underpowered or because a waveform effect, if present, was attenuated by the severity of cardiac dysfunction that accompanies protracted VF. It may be argued that the use of ascending energy shocks in both treatment groups may also have been a factor in our failure to see a benefit specific to waveform type. However, the energy settings we used all fell well below thresholds associated with myocardial injury in animals,\(^{34} \) and lower energy shocks might not have been as effective in terminating VF. Notably, others have not confirmed a waveform-dependent reduction in cardiac function after shock\(^{35} \) and suggest that most of the dysfunction in the aftermath of VF is caused by the ischemic period associated with the arrhythmia.\(^{36} \)

Limitations
Although attempted, blinding was imperfect. Although waveform type from manual defibrillators was apparent to paramedics during the later phases of resuscitation, this seems unlikely to have influenced outcome, particularly because initial (blinded) shocks had already been administered from AEDs. Waveform type was unavoidably annotated on rhythm tracings when later retrieved, but these were classified according to strict objective criteria and without knowledge of final outcome. Hospital admission rates were higher than anticipated in both treatment groups, and differences between them were smaller than expected. This may have stemmed from the mandatory provision of CPR before the first shock, which might have “levelled the playing field” and served to make either waveform perform better. As a result, this trial may have been underpowered to assign statistical significance to otherwise potentially important trends in outcome. That a survival benefit associated with biphasic waveform defibrillation, in particular, cannot be summarily dismissed by our findings invites further study. Alternatively, on the basis of the absence of statistical significance and the relatively large numbers of patients that would be required for its achievement, it could be argued that attention to, and expenditures for, aspects of resuscitation other than shock waveform may be more productive ways of improving outcome after cardiac arrest.

This study focused on the treatment of VF arrest in the prehospital setting. Although our results may also pertain to in-hospital cardiac arrest, they should not be taken to apply to elective procedures, such as cardiovascular of atrial fibrillation, for which there is more established advantage in using a specific waveform.\(^{18} \)

Conclusions
Potentially important trends, but no statistically significant differences in outcome, could be ascribed to use of one waveform over another in the treatment of out-of-hospital VF.

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Disclosures

Drs Kudenchuk and Cobb have received speaker honoraria from Medtronic; Michele Olufuka has performed contract work for Medtronic ERS. The remaining authors report no conflicts.

References

CLINICAL PERSPECTIVE

Although biphasic shock is heralded by many as the new standard for defibrillation, proof of whether it is a more life-saving waveform remains elusive. In previous clinical trials, evaluation of shock waveform was confounded by a failure to control for a number of important variables. When controlled for these variables in this trial and uniformly preceded by 90 seconds of CPR, both waveforms performed comparably, although several nonsignificant trends consistently favored treatment with biphasic shock. How are these results reconciled with the recognized superior performance of biphasic shock during elective cardioversion procedures, and how might they guide decisions about whether to retain or replace existing defibrillators? It may be argued that if greater benefit is associated with use of a biphasic waveform, it may be attenuated by the compromising conditions typically encountered in clinical cardiac arrest. From our findings, relatively large numbers of patients would be required to establish such differences. Given that monophasic defibrillators are no longer being manufactured, it is unlikely that such studies will ever be conducted. Alternatively, one possible conclusion from the results of this trial is that biphasic defibrillation was statistically no less effective than monophasic defibrillation. Perhaps, given a larger study, it might have even proved better. Thus, cost issues aside, adoption of biphasic waveform defibrillation seems reasonable. Conversely, faced with the costs of such change, other spending priorities, and the limitations of this trial, we do not have compelling evidence that replacement of monophasic by biphasic defibrillators is mandatory or could not be justifiably deferred until needed for other reasons.
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