Comparing the Efficacy and Safety of a Novel Monophasic Waveform Delivered by the Passive Implantable Atrial Defibrillator With Biphasic Waveforms in Cardioversion of Atrial Fibrillation

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**Background**—The passive implantable atrial defibrillator (PIAD) (with no battery or discharging capacitor and powered transcutaneously by radio-frequency energy) delivering a novel monophasic low-tilt waveform is more efficacious than the standard monophasic waveform at atrial defibrillation. Standard biphasic (STB) waveforms, however, are more efficacious and safer than monophasic waveforms. This study compared the efficacy and safety of the PIAD waveform with biphasic waveforms.

**Methods and Results**—Sustained atrial fibrillation (AF) was induced by rapid atrial pacing. Cardioversion was attempted via 2 atrial defibrillation leads. The efficacy of the PIAD was compared with 3 biphasic waveforms (standard, single rounded, and double rounded) at varying voltage settings in 10 pigs. After a synchronized shock, hemodynamic changes between the PIAD, standard biphasic, and monophasic waveforms were compared at 1.5 and 3.0 J in 12 pigs. Myocardial injury (biochemical and histological) after ten 5-J PIAD shocks was compared with a no-shock group in 14 pigs. The PIAD 100-V setting was significantly more efficacious than the STB (100/−50 V: 100% [1.88±0.02 J] versus 90% [0.89±0.0 J]; \( P=0.025 \)). No arrhythmic, hemodynamic, or myocardial injury was observed with the PIAD waveform.

**Conclusions**—Defibrillation with the PIAD is more efficacious than with the STB waveform and appears safe. This device could provide a more effective option for cardioversion. *(Circulation. 2004;109:1686-1692.)*

**Key Words:** arrhythmia ■ fibrillation ■ cardioversion

**Using** an external radio-frequency energy transmitter to transfer energy transcutaneously to the passive implantable atrial defibrillator (PIAD), we recently reported transvenous atrial defibrillation success of 100% at 100 V (1.54±0.02 J) and pulse width of 10 ms. The PIAD (without a capacitor or a battery), delivering a novel monophasic waveform (slow rising and falling times, a negligible tilt, and rounded leading and trailing edges; Figure 1a), was more efficacious than the standard or rounded monophasic waveforms.1

Nevertheless, compared with standard monophasic waveforms, biphasic waveforms have improved efficacy in atrial fibrillation (AF) cardioversion, with a reduction in defibrillation threshold.2 The aims of this study of cardioversion of AF were to compare the efficacy of the PIAD waveform against 3 biphasic waveforms at varying voltage settings in pigs (Figure 1a). Hemodynamic changes after shock delivery with the PIAD, standard monophasic waveforms, and biphasic waveforms were then assessed in 12 pigs, and biochemical and histological evidence of myocardial injury with the use of the PIAD was compared with that in a no-shock group in 14 pigs.

**Methods**

All work was performed in accordance with the United Kingdom Animals (Scientific Procedures) Act of 1986.

**Efficacy Study**

**Equipment**

A 10-ms waveform was chosen for the PIAD because it was associated with 100% success in cardioversion of AF.1 The Ventritex HVSO2 defibrillator (160 μF; Ventritex) generated the 3 biphasic waveforms (6 ms in each phase; Figure 1a). A custom-made capacitor-resistance device added to the output circuit enabled waveform rounding. Waveform rounding reduces the delivered leading edge voltage from the preset voltage on the defibrillator. Therefore, the voltages of the single-rounded biphasic (SRB) and double-rounded biphasic (DRB) waveforms were initially set by delivering across a 50-Ω dry dummy load to achieve the required voltages.

Received October 6, 2003; revision received December 17, 2003; accepted December 30, 2003.

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*Circulation is available at http://www.circulationaha.org* DOI: 10.1161/01.CIR.0000124068.69162.4E

![Image](https://example.com/image.png)
The PIAD was assessed at the 50- and 100-V settings. The biphasic waveforms, at varying voltage settings (10 variables in total), were investigated randomly in 10 anesthetized (pentobarbital, Rhône Poulenc [London] Ltd) adult pigs (5 males; mean weight, 56.4 ± 0.9 kg).

Defibrillation leads, one in the lateral right atrium (Perimeter RA7205, InControl Inc) and the other in the distal coronary sinus (Perimeter CS7109, InControl Inc) were positioned transvenously. The PIAD was implanted subcutaneously and connected to the interface device (Figure 1b). The PIAD or the Ventritex defibrillators were connected to the defibrillation leads depending on the protocol. After induction (burst pacing; 100 Hz, duration 2 ms, 5 V for 5 seconds; Grass S44 stimulator) of sustained AF (sustained AF duration >30 seconds; mean duration: 31.5 ± 0.2 seconds), attempted R-wave synchronized cardioversion was performed with the use of the 4 randomly assigned waveforms. Five attempts at cardioversion were made at each waveform and voltage setting to assess the percent success of the shock. If an attempt was successful, AF was reinduced. A recovery period of approximately 30 seconds was allowed between shocks.

The shock data were recorded and stored with the use of an oscilloscope (Tektronix TDS 420A, Tektronix Inc). From these data, the mean delivered peak voltage, peak current, impedance, and energy were calculated with customized software. A schematic diagram of the equipment layout is shown in Figure 1b. The surface ECG (lead II), synchronization spikes (timed with the R wave), and arterial blood pressure tracings were displayed on a polygraph (Gould 2400S). Body temperature, oxygen saturation, blood electrolytes, and arterial blood gases were monitored and maintained.

**Procedure**

**Equipment**

Biochemistry

Peripheral blood samples for electrolytes, cardiac troponin I, creatine kinase (CK)–MB mass, and myoglobin were collected before shock or dummy and hourly thereafter up to 8 hours. After centrifugation, the serum was stored at −70°C. Cardiac troponin I, CK–MB mass, and myoglobin were analyzed with the Stratus CS STAT fluorometric analyzer (Dade Behring Inc).

For pyruvate and lactate estimations, simultaneous samples were taken from the coronary sinus and the aorta before shock and at 1, 2, 5, and 15 minutes and 1 hour after shock. The coronary sinus samples were obtained, without reflux of the right atrial blood, with the use of a flow-directed balloon-tipped 7F catheter (Arrow balloon wedge catheter). The balloon was inflated before blood sampling. Blood samples were deproteinized by adding 1 mL of blood to a glass tube containing 8% perchloric acid at 0°C to 4°C, mixed thoroughly, and centrifuged. The clear supernatant was analyzed for lactate and pyruvate (by a colorimetric method; Sigma kit; Roche Cobas Fara II).

Lactate and pyruvate percentage extractions were calculated as follows: Percent Extraction =

\[
\left( \frac{\text{Aortic Sample (mmol/L)} - \text{Coronary Sinus Sample (mmol/L)}}{\text{Aortic Sample (mmol/L)}} \right) \times 100.
\]

**Histology**

After an experiment, the heart was fixed in a 10% formalin solution. Full-thickness (epicardium to endocardium) tissue samples were taken from the right atrial appendage, the left atrial appendage, the right and left ventricles, and the coronary sinus (taken at 1 and 2 cm from the os), with a transverse section taken perpendicular to the atrioventricular groove containing the adjacent left atrial and ventricular tissues. All tissue blocks were fixed in 10% formalin solution, processed through an automated vacuum-impregnating...
process (14 hours), fixed in 99% alcohol, and polymerized in wax. After embedment in wax, 5-μm samples were sectioned, dried, and stained with hematoxylin-eosin and Masson trichrome. These were inspected (magnification ×1.5 to ×400) for evidence of injury.

Procedure
Ten-millisecond and approximately 5-J, R-wave synchronized, PIAD shocks were delivered during sinus rhythm. Fourteen anesthetized and ventilated adult pigs were randomized to no-shock (n=6) and shock groups (n=8; 2 of the 8 were assessed for lactate and pyruvate only).

Defibrillation lead placements and PIAD implantation and setup are described in the previous studies.

After blood sampling at preshocks and postshocks or dummy shocks at the prespecified time intervals, the defibrillation leads were carefully removed. Sedation and ventilation were continued until completion of the protocol (8 hours). The heart was then removed, inspected for any gross evidence of injury, fixed in a 10% formalin solution, and processed for histological analysis.

Protocol
After baseline measurements, animals in the shock group received ten 5-J shocks, delivered 3 minutes apart. After the last shock, blood samples for lactate and pyruvate were taken at 1, 2, 5, and 15 minutes and 1 hour after shock. Markers of myocardial injury were taken at baseline and at 1-hour intervals after the last shock, up to 8 hours.

Similar time delays and sampling intervals were used for the no-shock group. A pause for 30 minutes, simulating time taken for shock delivery, followed baseline measurements before the sampling continued.

Statistical Analysis
The nonparametric Friedman test was used to evaluate differences between the variables within a waveform and energy setting or variable. If a significant result was seen, the nonparametric Wilcoxon signed rank test was used to evaluate comparisons between 2 sets of variables. The differences between delivered peak voltage, current, and energy were compared with the Student t test. All statistical analyses were performed with the use of SPSS statistical software (SPSS version 10, SPSS Inc). Differences were considered significant if P<0.05.

Results

Efficacy Study
A total of 500 shocks were delivered without arrhythmic or hemodynamic complications. The mean measured impedance was 50.0±0.56 Ω.

The PIAD 100-V setting (100%; 1.88±0.02 J) was significantly more efficacious than the STB 100/−50-V (90.0±6.2%; 0.89±0.0 J; P=0.025), SRB 100/−50-V (74.0±11.6%; 1.19±0.0 J; P=0.005), STB 100/−100-V (86.0±6.7%; 1.35±0.0 J; P=0.008), DRB 100/−100-V (88.0±5.4%; 1.95±0.01 J; P=0.014), and any of the 50-V first-phase setting waveforms (P<0.005; Figure 2). Although the PIAD 100-V setting had a better success rate than the DRB 100/−50-V setting (96.0±2.7%; 1.29±0.0 J), this did not reach statistical significance.

There was a strong trend toward improved efficacy with the STB 100/−50-V compared with the PIAD 50-V (76.0±5.0%; 0.48±0.01 J; P=0.052). There were no statistically significant differences present in cardioversion success rates between the PIAD 50-V and the SRB 100/−50-V (P=0.317), STB 100/−100-V (P=0.251), and DRB 100/−100-V (P=0.157) settings (Figure 2). The DRB 100/−50-V setting, however, was more efficacious (P=0.008) than the PIAD 50-V setting. Compared with the 50-V first-phase setting waveforms, there were no significant differences between the PIAD 50-V and the DRB 50/−50-V or the DRB 50/−25-V settings, but the PIAD 50-V setting was more efficacious than the STB 50/−50-V setting (46.0±7.3%; 0.38±0.0 J; P=0.009).

The conventional biphasic waveform (100 V in first phase) shared similar efficacy with the other 100-V biphasic first-phase settings, although the DRB 100/−50-V setting seemed to have an overall better mean success rate (96±2.7%; 1.29±0.0 J). The DRB 100/−50-V setting was also more efficacious than the SRB 100/−50-V setting (P=0.034). Both the DRB 50/−25-V (84.0±7.7%; 0.37±0.0 J) and the 50/−50-V (74.0±11.6%; 0.58±0.0 J) settings were more efficacious than the STB 50/−50-V setting (46±7.3%; 0.38±0.0 J; P<0.0001 and P=0.002, respectively).

Cardioversion Parameters
The delivered mean peak voltage and current are shown (Table). No significant differences were seen between the waveforms for the set and delivered voltage for the waveforms.
Delivered Peak Voltage and Current for Efficacy Study

<table>
<thead>
<tr>
<th>Voltage, V</th>
<th>PIAD (50 V)</th>
<th>PIAD (100 V)</th>
<th>STB (100 V)</th>
<th>STB (50 V)</th>
<th>STB (100 V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 V</td>
<td>53.2±0.5</td>
<td>101.22±0.6</td>
<td>102.7±0.2/56.3±0.2</td>
<td>54.8±0.1/55.2±0.4</td>
<td>102.9±0.2/103.8±0.2</td>
</tr>
<tr>
<td>Current, A</td>
<td>1.32±0.1</td>
<td>2.61±0.02</td>
<td>2.45±0.02/1.21±0.1</td>
<td>1.34±0.01/1.16±0.01</td>
<td>2.44±0.01/2.29±0.01</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM.

Hemodynamic Study

A total of 72 synchronized shocks were delivered during sinus rhythm. The mean measured lead impedance before (52.3±1.01 Ω) and after (53.3±1.07 Ω) the experiment did not change significantly. The mean heart weight (wet) was 248.8±6.7 g.

Cardiac Output Measurements

The baseline and 15-minute cardiac outputs were similar for all the variables (Figure 3). There was a rise in cardiac output immediately after shock delivery for all settings, but this returned to baseline by the 15-minute measurement. Importantly, cardiac output for the PIAD system did not deteriorate after shock delivery.

Left Ventricular Peak Systolic and End-Diastolic Pressures

There was an initial drop in peak systolic pressure immediately after the shock for all energy and waveform settings (Figure 4). Apart from the PIAD 1.5-J setting, this reduction was statistically significant for all the other waveforms compared with baseline. All returned to baseline by 1 minute.

Immediately after the shock, left ventricular end-diastolic pressure increased significantly for all the settings (Figure 4) but returned to baseline by 3 minutes, without significant differences between waveforms.

Overall, these changes in left ventricular pressure were small, and left ventricular end-diastolic pressure did not reach left ventricular failure levels (∼20 mm Hg).

Right Atrial Pressure

There was no significant change in right atrial pressure between the PIAD, STB, and standard monophasic waveforms or between the waveforms for each time interval after shock delivery.

Heart Rate

The baseline heart rate was similar for all the settings. A postshock rise was observed for all shock types but was significant only for the biphasic waveform settings (1.5 J: 79.5±1.7 to 81±1.7 bpm [P=0.036]; 3.0 J: 79.7±1.8 to 82.4±1.5 bpm [P=0.002]). All normalized by 15 minutes.

Safety Study

There was no difference between the no-shock and shock groups at baseline (mean weight: no shock=52.7±0.7 kg, shock=53.5±0.7 kg; internal lead impedance: no shock=53.0±0.68 Ω, shock=53.03±1.08 Ω). Eighty synchronized shocks were delivered during sinus rhythm. No atrioventricular block or ventricular proarrhythmia was observed after shock delivery. The mean energy delivered for each shock was 5.2±0.17 J. The mean peak voltage and current were 156±1.26 V and 4.04±0.08 A, respectively. Oxygen saturation, end-tidal CO₂, body temperature, full blood count, and electrolytes did not change significantly throughout the experiment.

Cardiac Troponin I

Although cardiac troponin I increased from baseline and peaked at 4 hours after shock therapy (0.51±0.11 to
1.07±0.21 ng/mL; P=0.028), a similar rise was observed for the no-shock group (0.71±0.1 to 1.05±0.24 ng/mL; P=0.028), with no difference observed between the 2 groups at any time interval (Figure 5).

Lactate and Pyruvate
Although there was a trend toward an increased myocardial percent lactate extraction after shock delivery, this did not reach statistical significance compared with the no-shock group (Figure 6) for any of the time intervals. Hence, a reduced myocardial extraction of lactate, characteristic of cell injury, was not seen in this study.

Similarly, the percent extraction of pyruvate remained unchanged over time for both the shock and no-shock groups, suggesting preservation of myocardial cellular function.

CK-MB mass
There was no significant difference in CK-MB mass between the no-shock (before shock: 4.81±1.12 ng/mL; 8 hours: 4.85±1.72 ng/mL) and shock (before shock: 3.19±0.44 ng/mL; 8 hours: 3.15±0.52 ng/mL) groups, nor did the values change significantly at any time interval between the groups.

Myoglobin
There were no significant differences in myoglobin between the no-shock (before shock: 65.0±15.1 ng/mL; 8 hours: 78.7±16.4 ng/mL) and shock (before shock: 45.9±6.1 ng/mL; 8 hours: 87.2±26.6 ng/mL) groups.

Histopathology
Gross Histopathology
A total of 14 hearts were examined. The mean wet heart weight was statistically similar between the groups (no shock: 250.3±24.8 g; shock: 242.3±13.2 g). There was no evidence of blood-stained fluid in the pericardial sac before the heart was removed, nor was there any evidence of injury to the myocardium. The coronary sinus and great cardiac veins were intact. Changes in tissue contour or turidity were not evident.

Microscopic Histopathology
Twelve (n=6 for shock group) of the 14 pig hearts were examined histologically. Inspection with hematoxylin-eosin and Masson trichrome stains (magnification ×1.5 to ×400) showed no evidence of cellular injury; the architecture was maintained without fiber disruption, muscle fiber swelling, eosinophilia of the sarcoplasm, inflammatory infiltrate, contraction bands, interstitial tissue swelling, or epicardial and endocardial hemorrhages (Figure 7).

Discussion
Shock Waveform and Efficacy
In this study the novel monophasic waveform delivered by the PIAD 100-V setting was significantly more efficacious than the STB 100/−50-V waveform (100% [1.88±0.02 J] versus 90.0±6.2% [0.89±0.0 J]; P=0.025) in cardioversion of AF. Furthermore, a favorable efficacy was observed with the PIAD 50-V setting (76.0±5.0%; 0.48±0.01 J), with a comparable efficacy observed with the STB 100-V waveform (P=0.052), despite delivering significantly lower mean energy (P<0.0001).

However, various experimental and clinical studies have suggested that standard biphasic waveforms are superior to standard monophasic waveforms for both atrial and ventricular defibrillation. During transvenous atrial defibrillation in humans, Cooper and coworkers2 showed that biphasic waveforms with total pulse durations of 4 to 20 ms were more efficacious than monophasic waveforms of the same duration. The differences in outcome between our study and previous investigators using the standard monophasic waveform could be attributed to the significant differences that exist with the novel PIAD waveform (slow rising and falling times, a negligible tilt, and rounded leading and trailing edges; Figure 1a).

Waveform Optimization
Modifying the STB waveform has further improved transvenous atrial defibrillation outcome. Reduction in waveform tilt has improved efficacy.3 Harbinson and coworkers4 showed that rounding of the first phase of a STB waveform reduced the peak delivered voltage, current, and energy while maintaining efficacy. A similar result was observed with rounding of both phases.5 Waveform rounding effectively reduces the tilt of the delivered shock waveform (Figure 1a). Although the present study was not designed for assessment of tilts, we observed an improvement in efficacy when the tilt...
of the biphasic waveform was reduced from 50% (standard) to 30% (first-phase rounded; Figure 1a). The PIAD 100-V waveform, however, had a better success rate than the other waveforms, with favorable outcome even for the 50-V setting.

To optimize a capacitor discharge biphasic waveform for an implantable defibrillator will at present result in a larger device because of capacitor, battery, and circuitry changes. The PIAD is unique in that an optimum waveform is delivered without the need for an implanted battery or discharging capacitor. Furthermore, an optimized monophasic waveform, as shown in these studies, may be adequate for transvenous atrial defibrillation, negating the need for large capacitors and complex circuitry systems to deliver biphasic waveforms.

### Postshock Hemodynamics

Postshock hemodynamic impairment has been attributed more to monophasic than to biphasic shock waveforms, although these studies involved ventricular fibrillation. It is unclear whether a similar effect would be seen with AF defibrillation because the potential ischemic insult that the ventricle undergoes is significantly less during AF than that seen in ventricular fibrillation.

When high-energy transthoracic defibrillation under physiological conditions was studied, some investigators have shown no hemodynamic effect. Studies using repetitive transthoracic shocks with delivered energy up to 460 J again did not show any contractile abnormality in dogs, suggesting that multiple high-energy shocks under physiological conditions may not cause myocardial impairment.

A similar nontoxic effect with transvenous shocks was observed in our study. The hemodynamic changes seen for shock delivery with the novel PIAD waveform were comparable to those seen with the STB waveform. Perhaps the issue of waveform safety may not be important when low voltage, current, and energy are used, as in transvenous atrial defibrillation.

### Postshock Myocardial Injury

Feng and coworkers showed that cardiac troponin I, myoglobin, and CK-MB increased significantly from baseline (normal range: cardiac troponin I = 0.001 to 0.235 μg/L; CK-MB = 0.64 to 2.64 μg/L; myoglobin = 0.90 to 3.62 μg/L) after coronary artery stenosis was induced in the pig. The sensitivity and specificity for cardiac troponin I were higher than for CK-MB or myoglobin, with raised cardiac troponin I observed as early as 3 hours and myoglobin peaking by 6 hours. We used similar assays, with the animals ventilated and maintained within physiological parameters for 8 hours after the last shock. Any difference in the cardiac markers between shock and no-shock groups, therefore, should become evident. No difference in cardiac markers was found between the 2 groups.

The plasma levels of lactate and pyruvate reflect the equilibrium between cytoplasmic production from glycolysis and consumption by various tissues. The heart utilizes lactate for aerobic metabolism. Production of lactate suggests a substantial impairment of aerobic metabolism in the myocardium. Mitochondrial dysfunction and free radical generation caused by electric shock therapy have been proposed as a cause for this impairment. No significant change in lactate or pyruvate extraction compared with control was observed with multiple PIAD shocks. This could be due to the lower energy and the mode of shock delivery used (transvenous system), demonstrating the safety of the PIAD waveform.

The accepted dual-lead configuration for transvenous atrial defibrillation is the right atrial and coronary sinus. The safety of coronary sinus lead positioning has been questioned, primarily because of the thin vessel wall. Reports of microscopic injury have been shown with shocks of 200 J. Delivery of shocks to approximately 30 J has been shown to be safe. We did not observe any histological evidence of coronary sinus or myocardial injury, despite delivering repeated shocks. This is possibly due to the low energy (5 J).
and the defibrillation leads used (large surface area). Thus, in these studies repeated defibrillation shocks at >200% (5 J) of the energy delivered for optimum cardioversion (100% success; mean energy, 1.88 J), with an approximate cumulative energy of 50 J (×10 shocks), delivered by the PIAD system did not cause any histological changes in the myocardium.

Conclusions

The PIAD at a very low voltage, current, and energy, delivering a novel monophasic low-tilt waveform, was more efficacious than the STB waveform. Biphasic waveform rounding (DRB 100/−50 V) improved cardioversion efficacy compared with STB waveform, with levels comparable with the PIAD waveform. The PIAD should enable better tolerability of shocks, with less risk of the postshock bradyarrhythmias and hemodynamic deterioration that are sometimes observed with high-voltage, -current, and -energy shocks. Furthermore, no detrimental effect on cardiac function or metabolism was observed with high-energy PIAD waveform shocks. This novel waveform delivered by the PIAD system would therefore provide an additional option in managing patients with paroxysmal AF.

Acknowledgments

Dr Manoharan received Royal Victoria Hospital and Heart Trust Fund fellowships.

References


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_Circulation._ 2004;109:1686-1692; originally published online March 29, 2004; doi: 10.1161/01.CIR.0000124068.69162.4E

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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