Atrial Fibrillation Detection and R-Wave Synchronization by Metrix Implantable Atrial Defibrillator
Implications for Long-Term Efficacy and Safety

Hung-Fat Tse, MB, BS; Chu-Pak Lau, MD; Jasbir S. Sra, MD; Harry J.G.M. Crijns, MD; Nils Edvardsson, MD; Salem Kacet, MD; D. George Wyse, MD, PhD; for the Metrix Investigators

Background—The long-term efficacy of atrial fibrillation (AF) detection and R-wave synchronization are critical safety requirements for the development of an implantable atrial defibrillator (IAD) for treatment of AF.

Methods and Results—The long-term efficacy of the Metrix IAD for AF detection and R-wave synchronization was tested in 51 patients. The mean duration of follow-up was 259±138 days (72 to 613 days). AF detection tests were performed 2240 times during observed operation with 100% specificity and 92.3% sensitivity for differentiation between sinus rhythm and AF; 2219 episodes and their electrograms stored in the device during AF detection were analyzed. The positive predictive value of the AF detection algorithm was 97.4% (lower 95% confidence limit [CL], 94.5%) in the out-of-hospital setting. A total of 242 435 R waves were analyzed for R-wave synchronization. Of these, 49% were marked for synchronized shock delivery, 82% of sinus rhythm and 36% of AF R waves, respectively. All shock markers were properly synchronized and within the R wave (overall synchronization accuracy, 100%; lower 95% CL, 99.999%). Overall, 3719 shocks have been delivered via the IAD with no instance of unsynchronized shock delivery or any episode of proarrhythmia. The observed proarrhythmic risk was 0%, with an estimated maximum proarrhythmic risk of 0.084% per shock (95% upper CL).

Conclusions—The Metrix IAD can appropriately detect AF with a high specificity and sensitivity and reliably synchronize within a suitable R wave for shock delivery to minimize the risk of ventricular proarrhythmia. (Circulation. 1999;99:1446-1451.)

Key Words: fibrillation • atrium • heart-assist device • defibrillation

Recent studies suggest that atrial fibrillation (AF) is not a benign arrhythmia. The development of AF carries an ominous prognosis with increased morbidity and mortality. Transthoracic electrical cardioversion is an effective method to restore sinus rhythm (SR), but the procedure requires general anesthesia and has limited applicability in patients with frequent AF episodes. The successful application of low-energy biphasic atrial shocks delivered between electrodes in the right atrium (RA) and the coronary sinus (CS) for cardioversion of AF in humans has prompted the development of an implantable atrial defibrillator (IAD). However, the potential ventricular proarrhythmic risk of atrial defibrillation shocks remains a major concern. Atrial shocks when delivered asynchronously or after a short preceding ventricular cycle length can induce potentially lethal ventricular arrhythmias. Therefore, the efficacy of an IAD for AF detection and R-wave synchronization for shock delivery is critically important with regard to ventricular proarrhythmia and safety of the device.

Wellens et al recently reported the overall clinical results of the multicenter study of the Metrix IAD and demonstrated the safety and efficacy of this device in patients with AF. The aim of this study was to report in detail the efficacy and safety for AF detection and R-wave synchronization algorithms of the Metrix IAD in the same cohort of patients in this multicenter study.

Methods

Patients
The study population included 51 patients (40 men, 11 women; mean±SD age, 58±9 years) with drug-refractory symptomatic AF who received an IAD. Their clinical characteristics have been described elsewhere. The protocol was approved by the ethics committee or institutional review board of each participating center. Informed consent was obtained from all patients.

IAD and Lead System
InControl Metrix IADs (model 3000 or 3020) were used; they have been described elsewhere. The device uses 2 defibrillation leads: 1
RA active fixation lead (Perimeter RA model 7205) and 1 CS passive fixation lead (Perimeter CS model 7109). The RA-CS lead configuration is used for both atrial sensing and defibrillation. A bipolar endocardial ventricular pacing lead is used for R-wave synchronization and ventricular pacing. The device can monitor intracardiac atrial and ventricular electrograms (EGMs) and use them in specific algorithms for AF detection and R-wave synchronization (see below). The device stores the intracardiac EGM data from the last 6 successfully treated AF episodes (or those marked for treatment when the device is in monitor mode) and provides data on 170 AF episodes in an episode log. The IAD can deliver R-wave synchronized biphasic shocks of 3 ms/3 ms (model 3000) or 6 ms/6 ms (model 3020) at a selected voltage, with a maximal intensity of 300 V and a maximal energy of 3 or 6 J, respectively, for AF induction or defibrillation.

**Study Protocol**

During this study, all devices were programmed into the physician-activated monitor mode. During the monitor mode, the device is automatically activated at a regular interval (programmable from 1 to 120 minutes) to detect AF, and the EGMs are stored in the device memory. However, all the atrial defibrillation therapies are delivered under close observation by the physician. Device testing was performed during implantation, at discharge, at 1 and 3 months of follow-up, and during spontaneous AF episodes. During testing, AF detection and R-wave synchronization were performed with patients in both SR and AF. After the R-wave synchronization process had been tested, R-wave synchronized shocks were delivered during SR to induce AF or during AF for defibrillation.

**AF Detection Algorithm**

The AF detection algorithm consists of 2 phases: collection and qualification of EGMs and rhythm analysis. After collecting an 8-second sample of EGM data from the existing rhythm in the RA-CS vector and in the RV bipolar vector, the device analyzes the signals and checks quality for noise contamination. Then, the sensitivity setting for each channel is optimized independently by use of automatic gain control (AGC) (default) or by manual programming of sensitivity. AGC provides automatic increases or decreases in sensitivity on the basis of the amplitude of detected signals and permits sensing over a large dynamic range of input signals while minimizing the incidence of oversensing and/or undersensing. After the detected R waves have been blanked out to avoid contamination by the ventricular signal, a 300-ms detection window is used for atrial sensing in the RA-CS vector. For sensing of the RA-CS EGM, the RA-CS sense margin ratio parameter (programmable from 2.0 to 3.4) allows the physician to specify the relationship between the RA-CS channel sensitivity threshold and the average peak amplitude of sensed atrial signals. The greater the sense margin ratio, the wider the range of RA-CS signal amplitudes the device can sense. The sensitivity threshold is determined by dividing the average peak signal amplitude by the sense margin ratio. The device proceeds to rhythm analysis only when signal amplitude of the 8-second signal strip is considered adequate and the AGC successfully sets the gain.

Rhythm analysis starts with the “quiet-interval” analysis that segregates SR from an atrial tachyarrhythmia. There is only a short period of time in which atrial electrical activity can be detected during SR. However, during most atrial tachyarrhythmias, especially AF, the percentage of time with quiescent atrial electrical activity is much lower. The quiet-interval algorithm observes the 8-second EGM sample to look for periods in which the device has not detected events in the RA-CS vector for at least 170 ms (programmable from 130 to 220 ms). The cumulative percent time of these quiet intervals (quiet time) is calculated by dividing the total time by 8 seconds and multiplying by 100%. If the quiet time is >25% (programmable from 10% to 30%) of the total sample, the rhythm is considered non-AF rhythm; if <25%, the rhythm is considered to be possible AF (Figure 1).

The device proceeds to implement the “baseline-crossing” analysis only after the quiet-interval analysis results in detection of a possible AF. This algorithm detects the presence of atrial electrical activity at the ST-T region of the cardiac cycle, which is usually quiescent during SR and most non-AF atrial tachyarrhythmias. During AF, however, the atrial electrical activity is random and present throughout the entire cardiac cycle. The algorithm constructs a detection window in the RA-CS EGM with a programmable width (nominal width, 200 ms) beginning 80 ms after the end of each detected R wave. A sensitivity threshold level is set by the AGC as described above to allow optimal signal detection. The device then determines the number of times that the atrial signal crosses both the positive and negative sensitivity threshold levels within each detection window. The average baseline crossing is the average number of baseline crossings per window (per R wave) in the 8-second strip. If the average baseline crossing is >2.0 (programmable from 1.6 to 3.0), then the rhythm is considered to be AF (Figure 2). This analysis is designed to be highly specific for detection of AF. Furthermore, AF detection will not proceed when the minimum R-R interval is <400 ms during the 8-second segment. This restriction prevents false-positive AF detection due to other rapid supraventricular tachycardias.

**R-Wave Synchronization**

In each patient, the synchronization algorithm was performed during both AF and SR. Both RV and RV-CS vectors are used for the synchronization process, which ensures that all shocks are delivered synchronous to an R wave. The R-wave synchronization algorithm
AF Detection and Shock Synchronization by IAD

Figure 2. Baseline-crossing algorithm for detection of AF by use of a detection window in RA-CS EGM.

Shock Delivery

After proper synchronization was confirmed by use of the shock marker, R-wave–synchronized, biphasic shocks were delivered by the device for AF induction or defibrillation. Atrial defibrillation shocks for follow-up testing or treating spontaneous AF episodes (amplitudes varying from 120 to 300 V) were delivered either manually via the device’s induction feature or by use of the device’s automatic mode. The automatic mode combines the individual

Statistical Analysis

Numerical values are expressed as mean±SD. Data for calculation of the sensitivity and specificity of the AF detection algorithm were collected at implantation, before discharge, at 1 and 3 months, and during spontaneous episodes. The sensitivity of the AF detection algorithm was calculated by use of the β binomial model, and the specificity of the AF detection algorithm was calculated by use of the truncated exponential model.

To determine the positive predictive value of the AF detection algorithm, at each follow-up visit, the episodes, if any, in the 6 registers of the episode data log were printed. The data for this analysis from each encounter consisted of (1) the number of EGMs recorded (maximum of 6), including the number of times the device detected AF, and (2) the number of these EGMs that truly documented the presence of AF. The positive predictive value of the AF detection algorithm was then calculated with the β binomial model. At each follow-up visit, five 1-minute segments of EGMs during AF and during SR were stored and analyzed for the total number of R waves and the number of incorrect shock indicators. Synchronization accuracy was then estimated with the exponential Poisson model.

The total number of atrial defibrillation shocks delivered and the total number of instances of ventricular proarrhythmia observed were determined for each subject. The mean risk of ventricular proarrhythmia was estimated with the truncated exponential model.

Results

Forty-seven patients (92%) completed the study protocol after a mean follow-up of 259±138 days (range, 72 to 613 days). As reported elsewhere, 3 patients had their devices explanted for complications and 1 patient underwent atrioventricular junction ablation and permanent pacing due to frequent AF episodes.

AF Detection Algorithm Performance During Observed Operation

The AF detection test was performed 2240 times in 51 patients (Table 1). During SR, the AF detection test was performed 1062 times, and identification of SR was successful for all of these, corresponding to a 0% false-positive rate. During AF, the AF detection test was performed 1178 times. There were 109 episodes (9%) of false-negative detection (determination of SR when the actual rhythm was AF). The majority of false-negative detections were due to atrial flutter or related to low signal amplitude with a noisy background signal (Figure 5). However, all of these false-negative episodes were transient, and the device was able to correctly detect AF in the next cycle of rhythm analysis during the same episode of arrhythmia or after reprogramming of the device parameters. The remaining 1069 detection tests identified as AF were all confirmed as being AF by the attending physician, corresponding to a 100% true-positive rate. Overall, the AF detection algorithm had 100% (lower 95% confidence limit [CL], 99.7%) specificity for normal SR and 92.3% (lower 95% CL, 89.3%) sensitivity for AF detection.

AF Detection Algorithm Performance During Monitor Mode Operation

A total of 2219 eight-second EGM data segments stored in devices in which AF was detected by the algorithm during the monitor mode were available for analysis. In 2211 of these episodes, the EGMs were confirmed to be AF. However,
there were 8 episodes of false-positive AF detection in 3 patients, in which the device identified SR as AF. Thus, the positive predictive value of the AF detection algorithm was 97.4% (lower 95% CL, 94.5%). Seven of the 8 episodes of false-positive AF detection were from 2 patients and occurred within the first 3 months after implantation. A third patient had a single episode of false-positive AF detection 4 months after implantation. All of these episodes of false-positive AF detection occurred during sinus tachycardia and had an R-R interval of 500 ms (Figure 5). However, in all 3 patients, the devices could be successfully reprogrammed to avoid AF detection, and none of them had further false-positive AF detection thereafter.

### R-Wave Synchronization

In total, 242,435 R waves were analyzed, 119,241 (49%) of them marked as “shockable” by the device (Table 2). The percentages of R waves marked for shock during SR and AF were 82% and 36%, respectively. The main reason for rejecting R waves for shock was violation of the minimum R-R interval of >500 ms. However, during all the episodes of AF, successful R-wave synchronization was achieved by repeating the synchronization test. All shock markers were within the R wave, and none of them were outside the R wave (overall synchronization accuracy, 100%; lower 95% CL, 99.9987%).

### Shock Delivery Results

The overall clinical result for shock delivery in this study was recently reported. No instance of inaccurately synchronized shock delivery and no ventricular proarrhythmia was noted during the study. The observed ventricular proarrhythmic risk of the atrial defibrillation shock was 0%, with a maximum ventricular proarrhythmic risk of 0.084% per shock (upper 95% CL).

### Discussion

Recent advances in technology have made the IAD a prospective new therapeutic approach for patients with drug-refractory AF. However, the nonlethal nature of AF requires a high level of safety and efficacy before such a device gains general acceptance. The reliability and accuracy of AF detection and R-wave synchronization for shock delivery are the most important considerations in assessment of the safety and feasibility of the IAD.

#### Detection of AF

The ability to detect AF automatically and reliably via intracardiac EGMs is a challenging task. Atrial EGMs are smaller and more variable in amplitude than ventricular EGMs. There is greater variability and a substantial loss in signal amplitude between AF and SR. Thus, AF detection requires special methodology for reliable and accurate detection. The high-gain settings required may render AF detection more prone to electrical interference and far-field QRS oversensing. Although a previous short-term study showed that the AF detection algorithm of Metrix IAD can accurately detect AF, there are no long-term data on the efficacy of AF detection algorithms during implantation and in an ambulatory setting with permanent leads.

The results of this study confirm that AF detection algorithms of the IAD can detect AF appropriately in ambulatory patients during long-term follow-up. The combination of quiet-interval and baseline-crossing analysis can discriminate between AF and SR with a high degree of sensitivity (92%) and specificity (100%). AF detection during daily activities while the IAD is in the monitor mode shows that the positive predictive value of this AF detection algorithm is 97%.
False-positive AF detection is potentially more important than false-negative AF detection. Unlike defibrillation for ventricular tachyarrhythmia, a delay of defibrillation therapy because of false-negative detection during AF would not be likely to be harmful. On the other hand, false-positive detection of AF during SR may result in an inappropriate defibrillation shock.

In ≈9% of the AF episodes in the present study, the IAD determined that the rhythm was SR when in fact it was AF. There are several possible explanations for these episodes of false-negative AF detection. First, the most common cause of false-negative AF detection is atrial flutter or a more organized AF in which the atrial rate is regular and slow, resulting in a low baseline-crossing count (Figure 5). Second, the device will reject those AF signals with poor signal quality due to a noisy background signal (Figure 5) or those during a rapid ventricular rate (R-R interval, 400 ms). Finally, if the AF signal levels are too small, the algorithms sense a low number of events and calculate a high percent quiet interval.

Of more concern are those episodes of false-positive AF detection observed during sinus tachycardia (Figure 5). Overall, 8 episodes (0.3%) of false-positive AF detection occurred in 3 patients. Because both the quiet-interval and baseline-crossing algorithms are closely related to the atrial rate, any rapid atrial rhythm may potentially be mistaken for AF. In the majority of supraventricular tachyarrhythmias, a short R-R interval (<400 ms) during tachycardia would prevent AF detection. However, during sinus tachycardia, when the atrial cycle length is shortened but the R-R interval is 400 ms, these algorithms may have difficulty discriminating AF from sinus tachycardia. In the present study, all the false-positive AF detection episodes occurred during sinus tachycardia. Importantly, in all of these false-positive episodes during sinus tachycardia, the R-R intervals were >500 ms, and inappropriate shock therapy might have resulted if the device were programmed to the fully automatic mode. Nevertheless, successful reprogramming of the IAD prevented further false-positive AF detection in all 3 of these patients. Thus, before the device is programmed to the fully automatic mode, an initial period of observation in the monitor mode or testing during sinus tachycardia is advisable to achieve optimal device programming.

R-Wave Synchronization and Risk of Ventricular Proarrhythmia

The proarrhythmic potential of an atrial shock therapy for atrial defibrillation has been well documented previously. In most instances, the ventricular proarrhythmic episodes resulted from shocks that were not properly synchronized within the R wave. Poor synchronization is a major concern with respect to the safety of the IAD, particularly in relation to automatic shock therapy in a device without the capacity for backup ventricular defibrillation. These consid-

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TABLE 2. Real-Time R-Wave Synchronization and Shock Marker

<table>
<thead>
<tr>
<th>Real-Time Synchronization</th>
<th>No. of R Waves</th>
<th>No. of Markers</th>
<th>Percentage Marked, %</th>
<th>Within R Wave, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>242 435</td>
<td>119 241</td>
<td>49.18</td>
<td>100</td>
</tr>
<tr>
<td>SR</td>
<td>71 665</td>
<td>58 420</td>
<td>81.52</td>
<td>100</td>
</tr>
<tr>
<td>AF</td>
<td>170 770</td>
<td>60 821</td>
<td>35.62</td>
<td>100</td>
</tr>
</tbody>
</table>
erations emphasize the importance of achieving reliable R-wave synchronization for shock delivery. However, R-wave synchronization alone may not be sufficient to prevent the ventricular proarrhythmia. Previous studies have demonstrated that as long as the atrial shock was not delivered during the ventricular vulnerable period, ie, the T wave, of the preceding beat, the risk of induced ventricular tachyarrhythmia is nil. However, the ventricular vulnerable period can be affected by the preceding cycle length and rhythm. Even with proper R-wave synchronization, the proarrhythmic risk was higher with shock delivery after a short preceding R-R interval (<300 ms), because the terminal portion of the preceding T wave may encroach on the R wave. Furthermore, the occurrence of a preceding long-short cycle sequence is associated with a higher risk of ventricular proarrhythmia because of an increase in the dispersion of ventricular refractoriness. Thus, delivery of an atrial shock to an R wave with a preceding long-short R-R sequence should also be avoided.

The IAD uses special algorithms to reject R waves for shock delivery if the preceding R-R intervals are below a minimum interval of 500 ms (which is well above the safety limit observed in animal studies) or if the preceding R-R intervals have a long-short cycle-length sequence. The present results demonstrate the efficacy of the R-wave synchronization and shock delivery algorithm of this device. Although only 36% of R waves analyzed during AF were determined by the device to be suitable for shock delivery, all shock synchronization markers and shock delivery were accurately placed within the R wave after an appropriate preceding R-R sequence. Because defibrillation of AF is rarely an emergency, there is no penalty in allowing the device to wait for an appropriate R wave. A total of 3719 shocks were delivered via the IADs in this study with no device to wait for an appropriate R wave. A total of 3719

Conclusions

The results of the present study demonstrate the long-term efficacy and safety of the AF detection algorithms and the R-wave synchronization algorithms of an IAD in a large cohort of patients implanted with this device. The AF detection algorithms of the IAD incorporate the quiet interval, and the baseline-crossing analysis allows sensitive and specific differentiation between SR and AF. The R-wave synchronization algorithms of the IAD reliably and properly synchronize to an R wave appropriate for shock delivery. The proarrhythmic risk of the atrial shocks by the IAD is minimized by avoiding shock delivery within an R wave with a preceding R-R interval <500 ms or with a preceding long-short R-R cycle-length sequence. These findings have positive implications concerning the safety and efficacy of IADs for clinical use.

Appendix

List of Participating Centers and Investigators

References

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