Prospective Randomized Multicenter Trial of Empirical Antitachycardia Pacing Versus Shocks for Spontaneous Rapid Ventricular Tachycardia in Patients With Implantable Cardioverter-Defibrillators

Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) Trial Results

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Background—Successful antitachycardia pacing (ATP) terminates ventricular tachycardia (VT) up to 250 bpm without the need for painful shocks in implantable cardioverter-defibrillator (ICD) patients. Fast VT (FVT) >200 bpm is often treated by shock because of safety concerns, however. This prospective, randomized, multicenter trial compares the safety and utility of empirical ATP with shocks for FVT in a broad ICD population.

Methods and Results—We randomized 634 ICD patients to 2 arms—standardized empirical ATP (n=313) or shock (n=321)—for initial therapy of spontaneous FVT. ICDs were programmed to detect FVT when 18 of 24 intervals were 188 to 250 bpm and 0 of the last 8 intervals were >250 bpm. Initial FVT therapy was ATP (8 pulses, 88% of FVT cycle length) or shock at 10 J above the defibrillation threshold. Syncope and arrhythmic symptoms were collected through patient diaries and interviews. In 11±3 months of follow-up, 431 episodes of FVT occurred in 98 patients, representing 32% of ventricular tachyarrhythmias and 76% of those that would be detected as ventricular fibrillation and shocked with traditional ICD programming. ATP was effective in 229 of 284 episodes in the ATP arm (81%, 72% adjusted). Acceleration, episode duration, syncope, and sudden death were similar between arms. Quality of life, measured with the SF-36, improved in patients with FVT in both arms but more so in the ATP arm.

Conclusions—Compared with shocks, empirical ATP for FVT is highly effective, is equally safe, and improves quality of life. ATP may be the preferred FVT therapy in most ICD patients. (Circulation. 2004;110:2591-2596.)

Key Words: defibrillators, implantable pacing tachyarrhythmias

Implantable cardioverter-defibrillators (ICDs) can terminate ventricular tachyarrhythmias with shocks or antitachycardia pacing (ATP). Although ICDs are well tolerated by most patients, reports of clinically significant anxiety and depression are common.1,2 ICD patients receiving shocks exhibit a decline in quality of life (QoL),3,4 although this finding is not universal.5 The principal merit of ATP from the patient’s perspective is the avoidance of painful shocks.

Numerous studies have demonstrated that ATP terminates 78% to 94% of ventricular tachycardias (VTs) <188 to 200 bpm with a 2% to 4% risk of acceleration.6–9 Accordingly, ATP has conventionally been applied to only slower, presumably hemodynamically tolerated VTs. Fast VT (FVT, 188 to 250 bpm) is typically programmed to receive painful shock therapy even though ATP might be successful. More recently, high success and low acceleration rates for FVT were demonstrated in coronary artery disease patients10,11 but in a nonrandomized fashion, so a comparison with shocks for safety and QoL was not performed. This trial examined the efficacy, safety, and QoL associated with treatment of FVT with ATP compared with shocks in a broad ICD population.

Methods

Study Design

The Pacing Fast VT Reduces Shock Therapies (PainFREE Rx II) trial was a prospective, randomized, multicenter study that tested...
whether empirical ATP is effective, is as safe for FVT as shocks, and affords better QoL than shocks in a broad ICD population. We postulated that initial treatment with ATP may yield a small but clinically irrelevant increase in episode duration. Thus, to assess safety, the primary objective tested whether duration for FVT episodes initially treated with ATP was not >6 seconds longer than those treated by shock. Secondary objectives included self-reported QoL, ATP efficacy and acceleration, and syncope.

**Patient Selection**

Enrollment followed institutional review board acceptance of the protocol and informed consent in patients with standard ICD indications from January 2001 through March 2002 at 42 US centers. Inclusion criteria were broad, excluding only ICD patients believed unlikely to have substrate for stable monomorphic VT susceptible to ATP (hypertrophic cardiomyopathy, long-QT syndrome, or Brugada syndrome). Transvenous defibrillation leads were positioned at the right ventricular apex. Defibrillation thresholds (DFTs) were determined by use of a binary search protocol with a minimum 10-J DFT safety margin required for enrollment. Patients who met enrollment and implantation criteria were randomized to either ATP or shock as the first therapy for FVT. All patients were seen every 3 months for 1 year. Patient diaries and interviews were used to capture symptoms possibly related to spontaneous ventricular arrhythmias (eg, palpitations, lightheadedness, dizziness, near syncope, or syncope). Syncope required complete loss of consciousness with loss of postural tone, and near syncope was defined as severe dizziness or lightheadedness without complete loss of consciousness. Symptoms were correlated with ICD-recorded episode data of spontaneous ventricular arrhythmias. Data were transferred to a central database for analysis.

**Device Description and Programming**

Device programming was standardized except for the initial randomized therapy for FVT. Detection in the ventricular fibrillation (VF) zone required that 18 of the last 24 R-R intervals had a cycle length (CL) <320 ms (>188 bpm). Only ICDs capable of programming a FVT detection zone defined within the VF zone (FVT via VF) for a CL of 240 to 320 ms (250 to 188 bpm) were used (Medtronic models 7227, 7229, 7231, 7271, 7273, and 7275). When any one of the final 8 R-R intervals preceding the moment of detection was <240 ms (>250 bpm), the episode was classified as VF and received a DFT+10 J shock followed by maximal shocks if necessary. When all of the last 8 R-R intervals were ≥240 ms (≥250 bpm), the episode was detected as FVT. In the ATP arm, the first therapy in the FVT zone was a single ATP sequence (8-pulse burst pacing train at 88% of the VT CL). Failed ATP was followed by shock at DFT+10 J and then maximal shocks as necessary. In the shock arm, first therapy was DFT+10 J followed by maximal shocks. A VT zone with a CL of 320 to ≥360 ms (≥167 to 188 bpm) was programmed in all patients. ATP in the VT zone was programmed to 3 sequences of 8 pulses at 88% of the VT CL with 20-ms decrement between sequences. Supraventricular tachycardia (SVT) discrimination was programmed “on” in the VT zone of all dual-chamber ICDs with the SVT limit of 320 ms. All devices were programmed to store the far-field electrogram (EGM) before the onset of detected episodes to aid in rhythm classification.

**Rhythm Classification and Definitions**

The principal investigator at each site reviewed and classified the detected rhythm of all spontaneous episodes of VT with stored EGM. Each episode was also reviewed by one of 5 electrophysiologists on an episode review committee. When both reviewers agreed on both the detected rhythm and final rhythm after therapy, the episode received no further review. On any disagreement, the episode was reviewed by a different committee member. Classification was taken on agreement by any 2 physicians. All other episodes were classified by a joint committee review with majority rule applied.

Arrhythmia CL was reported as the median of the final 12 intervals preceding detection. Episode duration was measured from the first tachycardia beat in the detection window to the first nontachycardic return beat. Acceleration was defined as ≥10% CL reduction after therapy.

**QoL Assessment**

Self-reported health-related QoL was measured at baseline and at 12 months with the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) that included 8 subscales and 2 summary measurements.12 Scores ranged from 0 to 100, with higher scores representing better QoL. The change in score from baseline to 12 months was compared between the ATP and shock arms for each scale.

**Statistical Analysis**

Data were analyzed on an intention-to-treat basis. To adjust for multiple episodes per patient, the generalized estimating equations method was used in calculations of therapy delivery, syncope, acceleration, and episode duration estimates and comparisons unless otherwise noted.13 Baseline QoL and change in QoL over time were compared between randomization groups by use of a Wilcoxon test. Paired nonparametric exact methods were used to compare each patient’s change in QoL over time. Mortality rate was determined by Kaplan-Meier estimation. Summary statistics for episode measures such as CL were adjusted for multiple episodes per patient by calculating the median for each patient and then calculating summary statistics on the basis of each patient’s median. Statistical analyses were performed with SAS (version 8).

**Results**

**Patient Characteristics**

We randomized 634 patients to ATP (n=313) or shock (n=321). Mean follow-up was 11±3 months. Baseline demographic variables were not different between treatment groups (Table 1). Six patients crossed over to the other treatment arm during the trial. Four patients switched from shock to ATP by physician preference, and 2 switched from ATP to shock: 1 after FVT associated with syncope and 1 because of a programming error.

**Spontaneous Episodes Detected**

Among 4230 spontaneous episodes retrieved from ICD counters that the device detected as ventricular tachyarrhythmia, 1837 had complete electrogram data and were included in the analysis. Missing data were due to ICD memory limitations, incomplete interrogation, or cleared memory. The proportion of patients with missing EGMs for spontaneous episodes was similar between treatment arms. All reported episodes of syncope and death are included in the analysis.

Of the 1837 spontaneous episodes with stored EGMs, 491 (27%) were determined to be inappropriately detected SVT, and 4 (0.2%) were nonphysiological artifact. Thus, 1342 of 1837 detected episodes (73%) were true ventricular arrhythmia and were subjected to analysis. Of these, 775 (58%) were detected as VT, 431 (32%) as FVT, and 134 (10%) as VF. Figure 1 shows the CL distribution of rhythms according to detection zone.

The ATP arm had 284 FVT episodes in 47 patients compared with 147 episodes in 51 patients in the shock arm. Two ATP patients had 56 and 75 episodes, accounting for the large difference in episode numbers between arms. There was no difference in median FVT CL between treatment groups (290 ms for ATP versus 300 ms for shock; P=0.10). A total of 13 polymorphic VT episodes were detected as FVT (ATP,
n=11; shock, n=2). Four episodes in the shock arm were terminated by ATP in crossover patients.

Therapy Efficacy

The shock arm had 147 detected FVT episodes, yet only 99 episodes (64%) were treated by 110 shocks (Figure 2). The reduction in shocked episodes was due to spontaneous termination during the 3.3 seconds (median) of capacitor charging (44 episodes, 34%) and 4 episodes in crossover patients that were terminated by ATP.

In the ATP arm, the first ATP attempt terminated 229 of 284 FVT episodes (81% unadjusted, 72% adjusted; 95% CI, 60 to 81), including 8 in which VT reinitiated so quickly that the device assumed that the ATP had failed and advanced therapy to a shock. ATP was not attempted in 1 episode because of crossover. Of the 54 episodes in which ATP failed, 49 episodes were shocked, whereas 5 were terminated by additional ATP. In all, 57 episodes (31%) received 62 shocks. Within individuals, ATP success was 100% in 26 patients and 0% in 7 patients and ranged from 25% to 89% (unadjusted) in the remaining 14 patients. Thus, 40 of 47 patients (85%) presumably had at least 1 FVT shock prevented by ATP. In patients who had ATP failure of the first FVT episode, the efficacy of ATP overall was 45% (95% CI, 22 to 70).

Figure 3 shows ATP efficacy for FVT by detected CL. The ATP success rate was similar for FVT with CL between 280 to 320 ms and 240 to 280 ms (76% versus 62%; P=0.38).

Clinical Safety of ATP for FVT

Relative safety of ATP versus shocks was assessed by comparing the FVT episode duration, incidence of acceleration, syncope, first shock efficacy, and sudden death between treatment arms (Table 2).

The median FVT episode duration was 10.0 seconds in the ATP arm (mean±SE, 12.7±0.8 seconds) and 9.7 seconds in the shock arm (mean±SE, 10.7±0.7 seconds). This included failed therapies and spontaneously terminating shock episodes. Thus, the primary objective of the trial was satisfied (P<0.001).
Acceleration of FVT was similarly low between treatment groups. Acceleration occurred in 4 of 273 monomorphic VT episodes (2%) in the ATP arm versus 2 of 145 (1%) in the shock arm. No FVT acceleration required >1 shock to terminate.

Syncope during FVT was also similarly low between treatment groups. There were 3 episodes of syncope during treatment for FVT (ATP, n=2; shock, n=1). The FVT episodes associated with syncope were short (15, 10, and 9 seconds) and rare, so the effect of episode duration on risk of syncope could not be measured. Presyncope or milder symptoms with FVT were reported for 23 of 284 (13%) in the ATP arm and 15 of 147 (10%) in the shock arm. The proportion of FVT episodes with symptoms was 38% in the ATM arm and 66% in the shock arm (P<0.01). Other syncope included 4 VF, 1 SVT, and 26 nonarrhythmic syncopal episodes, none associated with missing ICD data.

First shock success was identical (92%) whether it was administered after a failed ATP attempt (ATP arm) or de novo (shock arm).

Fifty-six patients (9%) died during the study. There were 32 deaths (10%) in the ATP arm and 24 (7%) in the shock arm (P=0.22). The cumulative 12-month survival probability for all-cause mortality was 91% (95% CI, 89 to 93). An independent committee classified the cause of death, with nonsudden cardiac death occurring in 17 patients (5%) in the ATP arm and 15 (5%) in the shock arm. Sudden cardiac death occurred in 1 patient (0.3%) in the ATP arm and 2 patients (0.6%) in the shock arm and was too infrequent for statistical analysis. The 2 shock arm patients died of congestive heart failure and electromechanical dissociation unrelated to shocks. The cause of the ATP arm sudden cardiac death was unknown. This patient’s death in an intensive care unit was immediately preceded by sinus rhythm. However, 16 to 30 minutes before death, the patient had a successful shock for FVT accelerated by ATP with 2 additional VT episodes terminated by ATP.

**Quality of Life**

Of 131 patients with episodes detected in the FVT zone (including inappropriate detections), 98 completed SF-36 measurements at baseline and 12 months (ATP, 43 of 63; shock, 55 of 68). Baseline values were similar (P=0.05) between arms for each subscale and summary score. The shock arm had significantly improved bodily pain scores at 12 months without improvement in the other 9 measures. The ATP arm had significant improvement in 5 subscales—physical functioning, role physical, bodily pain, social functioning, and role emotional—and the 2 summaries, mental and physical. None of the subscale measurements were significantly reduced at 12 months in either arm. Figure 4 compares the change in scores at 12 months. The ATP group had statistically greater improvement in physical functioning (P=0.02), role physical (P=0.04), and mental summary (P=0.03), whereas social functioning was of borderline significance (P=0.053).

**Factors Predictive of ATP Efficacy**

Univariate analyses were performed on selected patient variables to determine their correlation with ATP success. Only left ventricular ejection fraction provided marginally significant prediction; with every 5% increase in left ventricular ejection fraction, the odds of successful ATP for FVT are 18% higher (P=0.06). Other variables that were not predictive of ATP success include prior history of non-sustained VT (NSVT), presence of coronary artery disease, and indication for implant. ATP success was 67% (185 of 232 episodes) in patients with coronary artery disease and 83% (44/52 episodes) in patients without coronary artery disease (P=0.16). Patients with primary and secondary implant indications had comparable ATP success, 74% (107 of 130 episodes) and 71% (122 of 154 episodes), respectively (P=0.77).

**Discussion**

This is the first prospective randomized trial to demonstrate that empirical ATP is safe and effective compared with...
shocks for FVT. In addition to showing no difference in duration of episodes treated by ATP or shocks, the study also demonstrated that ATP terminated 73% of FVT episodes with a very low risk of acceleration and syncope and no difference in mortality. Importantly, FVT episodes made up 76% of all ventricular arrhythmias conventionally programmed to shock (<320 ms). These observations, combined with the established efficacy of ATP for slower VT, reposition the ICD as primarily an ATP device with only occasional backup defibrillation.

Early studies testing ATP for FVT induced in the electrophysiology laboratory had low success, perhaps in part because they were treating induced rather than spontaneous VT. Not only was the success rate low (41% to 68%), but acceleration rates were high (5% to 55%). Other investigations tested ATP for spontaneous FVT in ICDs and found 47% to 79% success with acceleration of 3% to 10%. However, none of these trials compared ATP with shock therapy. Thus, the safety of ATP programming was not established until this trial. Concern over safety has rightfully been the limiting factor for using ATP for FVT. However, we found no safety differences between shock and ATP as initial therapy for FVT.

Our study used an ATP regimen of 88% of VT CL, fairly nonaggressive ATP supported by Peinado et al. that perhaps led to our high efficacy and low acceleration. Given that ATP was programmed empirically, the results also support prior observations that “tailoring” based on electrophysiology study of induced VTs is not necessary in most situations.

Clinical predictors of ATP success could be found. Diminished left ventricular ejection fraction slightly reduced efficacy but reached only marginal statistical significance. Although VTs with CL of 240 to 280 ms trended toward lower ATP success, they still had nearly two thirds of their FVT safely terminated by ATP. ATP was equally effective in patients without coronary artery disease, a group excluded from the pilot study, PainFREE Rx.

The greatest predictor of ATP success in PainFREE Rx was NSVT. One may infer that the device was claiming ATP success for treating nonsustained FVT episodes that were destined to terminate regardless of therapy, a reasonable conclusion given that VF plus FVT detection used 12 of 16 intervals. Consequently, this trial used 18 of 24 intervals for VF plus FVT detection and found that NSVT was not a predictor of ATP success. The fact that 34% of detected FVT episodes in the shock arm terminated before shock suggests that a longer delay will further reduce unnecessary device detections. It is intuitive that increased duration of tachycardia might increase syncope. However, delaying detection to 18 or 24 beats proved safe because arrhythmic syncope (8 of 1837, 0.5%) did not increase compared with PainFREE Rx (13 of 1248, 2.0%). Multiple factors determine the hemodynamic response to VT, likely explaining the heterogeneous response observed among patients in clinical studies.

In this study, the 3 syncopal FVT episodes lasted 15, 10, and 9 seconds, whereas episodes in other patients were tolerated up to ≥30 seconds without syncope. Most importantly, the additional time required for capacitor charging and delivery of definitive shock therapy did not appear to increase the probability of syncope after failed ATP for FVT. Furthermore, the fast charge time of the newly implanted ICDs in this study may have created a bias favoring shocks that would not be present in other ICDs later in their lifecycles, implying that ATP may have an advantage not shown by these results. This may be especially true for today’s ICDs with short capacitor charge times and the ability to deliver ATP while charging.

ICDs have become a mainstay of therapy because they deliver immediate and nearly absolute therapy of the leading cause of death in cardiovascular patients. Shocks are associated with significant morbidity contributing to anxiety syndrome in 15% to 38% of ICD patients. Despite differences in the literature between study designs and clinical outcomes, the negative impact of ICD shocks on QoL was consistent between studies and was related to the increased number of shocks received. However, whether reduction of shocks by applying ATP therapy improves QoL has not been tested previously. This is the first trial to demonstrate that ATP does improve QoL compared with shock delivery in patients who experience FVT. In the ATP arm, 5 of 8 subscales showed improvement, whereas only 1 subscale improved in shock arm patients. In agreement with previous reports, the summary scales reflect that by virtue of reducing shocks, the main contribution of ATP to improved QoL was mental.

Study Limitations
As with other trials, bias may have been introduced because the analysis could not be performed on episodes of tachycardia without EGM. Analysis was based on 43% of detected arrhythmias, although importantly every episode of syncope and death was included. Reporting only on properly adjudicated episodes increases confidence in data accuracy. Because most ATP episodes are asymptomatic, ATP episodes are potentially under-reported in this trial. Speculatively, underreporting of successful ATP episodes may bias the results toward reduced ATP success.

Like other trials assessing syncope, this trial relied on patient diaries to document syncopal episodes. Although a concerted effort was made to collect unbiased syncope data, the occurrence of syncopal episodes may still be underestimated. However, missing syncope data should be independent of FVT therapy, so safety comparisons should be unaffected.

Conclusions
Empirical ATP is highly effective in treating FVT. It prevents painful shocks without any clinical difference in episode duration, arrhythmic syncope, acceleration, or sudden death while yielding improvement in QoL. The investigators of the PainFREE Rx II trial recommend ATP as the preferred therapy for FVT in most ICD patients.

Appendix
The following investigators and institutions participated in the PainFREE Rx II Trial (listed in descending order of the number of randomly assigned patients): K. Khalighi, Easton Hospital, Easton, Pa; R. Canby, Texas Cardiac Arrhythmia Foundation, Austin, Tex; K. Volosin, Our Lady of Lourdes Hospital, Camden, NJ; L. Siddoway, York Hospital, York, Pa; M. Wathen, Vanderbilt University Medical Center, Nashville, Tenn; C. Machado, Providence Hospital,
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References

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for the PainFREE Rx II Investigators

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