Antitachycardia pacing success in implantable cardioverter-defibrillators by patient, device, and programming characteristics

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BACKGROUND Antitachycardia pacing (ATP) is an established implantable cardioverter-defibrillator (ICD) therapy that terminates ventricular tachycardias (VTs) without painful ICD shocks. However, factors influencing ATP success are not well understood.

OBJECTIVE The purpose of this study was to examine ATP success rates by patient, device, and programming characteristics.

METHODS This retrospective analysis of the PainFree SmartShock Technology study included spontaneous ATP-treated monomorphic VT episodes. ATP success rates were calculated for various factors. Also, the relationship of ATP programming on shock burden and syncope were investigated.

RESULTS Of the 2770 enrolled patients (2200 [79%] male; mean age 65 years), 1699 (61%) received an ICD and 1071 (39%) a cardiac resynchronization therapy – defibrillator. ATP had >80% rate of success for terminating VTs overall, with similar rates observed between ICD and cardiac resynchronization therapy – defibrillator devices (82.2% vs 80.3%, respectively; P = .81) as well as between primary and secondary prevention patients with ICDs (77.2% vs 83.9% respectively; P = .25). Arrhythmias with a median cycle

length of ≥320 ms had a significantly higher ATP success rate (88.0%; 95% confidence interval 84.8%–90.6%). The cumulative percentage of ATP success increased from 71% at 1 ATP sequence delivered to 87% at ≥8 sequences delivered. Programming more ATP sequences was associated with lower shock burden (P = .0005). There was no evidence that more sequences were associated with higher rates of syncope (P = .16).

CONCLUSION Delivering more ATP sequences resulted in a higher overall success of terminating VTs, while programming more ATP was associated with decreased shock burden and no evidence of increased syncope or acceleration. This suggests that more ATP sequences should be programmed when possible, but confirmation in prospective studies will be necessary.

KEYWORDS Antitachycardia pacing; Implantable cardioverter-defibrillator; Cardiac resynchronization therapy; defibrillator; Shock reduction; Device programming

Introduction

Implantable cardioverter-defibrillators (ICDs) improve mortality for primary and secondary sudden cardiac death prevention patients through termination of life-threatening arrhythmias using either shock or antitachycardia pacing (ATP).[1,2] While defibrillation shocks are highly effective at converting arrhythmias into sinus rhythm, previous studies have shown that inappropriate and appropriate shock treatment has been linked to increased mortality[3–5] and lower

quality of life[6–11] in patients with ICDs. For these reasons, preventing shocks by terminating arrhythmias with ATP is desired when possible.

Various strategies have been used to decrease inappropriate or unnecessary shocks including implementing novel rhythm discrimination algorithms, increasing the number of intervals to detect (NID) an arrhythmia (ie, the duration threshold), and ATP programming strategies.[12–16] However, the factors that influence ATP success remain

unclear. A better understanding of the factors affecting ATP success could lead to improved ATP therapy programming, better rates of success, and lower shock burden. Here we use data from the PainFree SmartShock Technology (SST) study to see how ATP success rates vary by programming and patient characteristics in a recent clinical investigation.

Methods
The PainFree SST study design has been previously described in detail.[17] This study was a prospective evaluation of SST in Medtronic (Minnesota) single- and dual-chamber ICDs and cardiac resynchronization therapy – defibrillators (CRT-Ds). SST is a collection of algorithms and nominal settings that includes discrimination algorithms for lead noise screening, T-wave oversensing, identification of supraventricular tachycardia to minimize the risk of inappropriate therapies, and ATP during charging nominally programmed "on" in the ventricular fibrillation (VF) zone. By study protocol, all supraventricular tachycardia discriminators were programmed "on" for cycle lengths down to 260 ms and the VF NID was set at 30/40 (meaning 30 of 40 consecutive beats faster than the VF detection interval) for all primary prevention patients, and randomized 1:1 to either 30/40 or 18/24 in secondary prevention patients. All other VF zone settings as well as ventricular tachycardia (VT) detection and therapies including zone cutoffs, NID, and ATP and shock programming were left to the discretion of the physician. The study complied with the Declaration of Helsinki, and the institutional review board of each participating center approved the study protocol.

Spontaneous episodes that were detected by devices in the trial were adjudicated by a physician panel and those characterized as monomorphic ventricular tachycardia (MVT) were included in the analysis. Episodes successfully terminated by ATP without shock were deemed as having ATP success. If a patient had >3 ventricular arrhythmias in 1 day, then only the first 3 are analyzed. Using the logistic regression generalized estimating equation (GEE) method, ATP success rate and its 95% confidence interval (CI) were calculated for specific device types, indications, median ventricular cycle length levels, NID programming, the number of ATP sequences delivered, and additional patient characteristics. For this analysis, *short NID programming* is defined as VF NID $\leq$ 18/24 and VT NID $\leq$ 16. *Extended NID programming* is defined as VF NID > 18/24 (most commonly 30/40) and VT NID > 16 (most commonly 24). Both multivariate and univariate GEE logistic models were analyzed for these parameters. The characteristics to analyze were chosen before analysis execution. An exchangeable within-subject correlation structure was assumed, meaning each subject's episodes were assumed to be equally correlated.

Also, we characterized and modeled the relationship between ATP programming and shock delivery. Using a GEE logistic model and end point of whether a shock was delivered for an episode, we investigated the relationship with ATP programming after accounting for the median ventricular tachycardia cycle length (VTCL) for an episode. An exchangeable within-subject correlation structure was again assumed.

Furthermore, we characterized and modeled the relationship between ATP programming and patient-reported syncope. An *episode* was defined as having related syncope if it was the nearest episode to a syncope within a 24-hour window. This is similar to the definition used in Sterns et al.[18] The mean number of ATP sequences programmed was calculated by median VTCL for episodes with and without related syncope. Using a generalized linear logistic model, we tested the hypothesis that more ATP programming was associated with higher rates of syncopal events after accounting for the median VTCL.

Last, we characterized and modeled the relationship between ATP programming and *device-recorded VT acceleration*, which is defined as an episode detected in the VT zone that is redetected in the VF zone. Using a GEE logistic model, we investigated the relationship between the end point of whether the episode accelerated to VF and the number of ATP sequences programmed, again assuming an exchangeable within-subject correlation structure.

Results
Patient characteristics
Of the 2770 enrolled patients (2200 [79%] male; mean age 65 years), 1699 (61%) had an ICD implanted and 1071 (39%) received a CRT-D system; 1917 (69%) were reported as primary prevention patients, and 847 (31%) were secondary prevention patients. Patient baseline characteristics are summarized in Table 1. Over a mean follow-up of 22 ± 9 months, 375 patients (17%) had 2278 ATP-treated episodes that were adjudicated as MVT; 208 patients (9%) had an episode with a median VTCL of $\geq$320 ms, and 256 patients (11%) had an episode with a median VTCL between 240 and 320 ms.

ATP success by patient indication, device type, and VT cycle length
The unadjusted ATP success rate was 86.8% (1978 of 2278), with the GEE estimated success of 81.4%. ATP had similar rates of success observed between ICD and CRT-D devices (Figure 1; GEE estimated 82.2% vs 80.3%, respectively; P = .81). Secondary prevention patients had a trend toward higher ATP success compared with primary prevention patients, but the difference was not statistically significant (Figure 1; GEE estimated 83.9% vs 77.2%, respectively; P = .25).

Arrhythmias with a median VTCL of $\geq$320 ms were significantly associated with a higher ATP success rate (Figure 1; 88.0%; 95% CI 84.8%–90.6%) vs VTs with a median VTCL of $\geq$240 and <320 ms (Figure 1; 75.0%; 95% CI 70.7%–78.8%; P $\leq$ .0001). In both patients with ICD and CRT-D, most of the arrhythmias treated with ATP fell into the lower median VTCL range (Figures 2A and 2B; 1417 episodes $\geq$320 ms). These trends were observed regardless of implant indication, although there was more variability in

Table 1   Patient baseline characteristics

Characteristic	Value
Male sex	2200 (79.4)
Age (y)	64.8 ± 12.3
LVEF (%)	32.2 ± 13.2
QRS duration (ms)	125.9 ± 33.0
Device type	
ICD	1699 (61.3)
CRT-D	1071 (38.7)
Indication	
Primary prevention	1917 (69.2)
Secondary prevention	847 (30.6)
NYHA class	
I	419 (15.1)
II	1104 (39.9)
III	853 (30.8)
IV	38 (1.4)
No heart failure	354 (12.8)
General cardiovascular history	
Congenital heart disease	74 (2.7)
Coronary artery disease	1256 (45.3)
Familial or inherited conditions with high risk of VT	127 (4.6)
idiopathic structural heart disease	20 (0.7)
Hypertension	1444 (52.1)
Syncope, any	432 (15.6)
Valve dysfunction, any	697 (25.2)
Atrial arrhythmias	
Atrial fibrillation	818 (29.5)
Supraventricular tachycardia	69 (2.5)
Ventricular arrhythmias	
Ventricular fibrillation	288 (10.4)
Ventricular tachycardia, nonsustained	588 (21.2)
Ventricular tachycardia, sustained	492 (17.8)
AV junctional arrhythmias and blocks	
AV block, any	404 (14.6)
Left bundle branch block	699 (25.2)
Right bundle branch block	215 (7.8)
Medication—main drug classes	
Cardiovascular medication, any	2724 (98.3)
β-Blocker	2370 (85.6)
ACE inhibitor or ARB	2133 (77.0)
Antiarrhythmic	519 (18.7)

Values are presented as mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AV = atrioventricular; CRT-D = cardiac resynchronization therapy – defibrillator; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VT = ventricular tachycardia.

success for secondary prevention CRT-D patients (Figure 2B).

There were no significant relationships between ATP success and the following factors: left ventricular ejection fraction at baseline, history of coronary artery disease, use of antiarrhythmic prescription at baseline, and use of β-blocker prescription at baseline (Figure 1).

ATP success vs device programming

Overall, there was no significant difference between episodes detected for different detection durations ($P = .30$). In the multivariate model, the GEE estimated success for episodes with an extended NID was 79.9% vs 83.3% with a short NID (Figure 1). However, among episodes with a median VTCL of 240–320 ms, the unadjusted GEE estimated success for episodes detected with an extended NID was 69.5% vs 78.4% with a short NID ($P = .011$). Among episodes with a median VTCL of ≥320 ms, the unadjusted GEE estimated success for episodes detected with an extended NID was 90.4% vs 88.0% with a short NID ($P = .48$).

The percentage of arrhythmias terminated by a given ATP sequence decreases with each additional ATP sequence delivered. However, as the number of ATP sequences increases, the cumulative percentage of ATP success increases for episodes with a median VTCL of <320 ms from 68.6% at 1 sequence delivered to 82.5% at 7 sequences delivered and for episodes with a median VTCL of ≥320 ms from 71.6% at 1 sequence delivered to 91.2% at ≥8 sequences delivered (Figure 3). Figure 3 shows that adding sequences of ATP can terminate arrhythmias that earlier sequences of ATP do not. However, the marginal benefit of additional ATP sequences appears to decrease. Note that episodes treated with ATP During Charging are nominally 240–320 ms and are limited to at most 2 sequences of ATP.

In general, as the number of ATP sequences programmed increases, the number of shocks delivered shows a decreasing trend from an average of 24% (105 episodes shocked/446 episodes programmed with 1 ATP) of arrhythmias receiving shock with only 1 ATP programmed to 12% (30/260) with 4 ATP sequences programmed to 6% (3/77) with ≥8 ATP sequences programmed (Figure 4). Even after accounting for episode VTCL, the number of ATP programmed sequences is still significantly associated with a lower chance of an arrhythmia receiving shock ($P = .0005$).
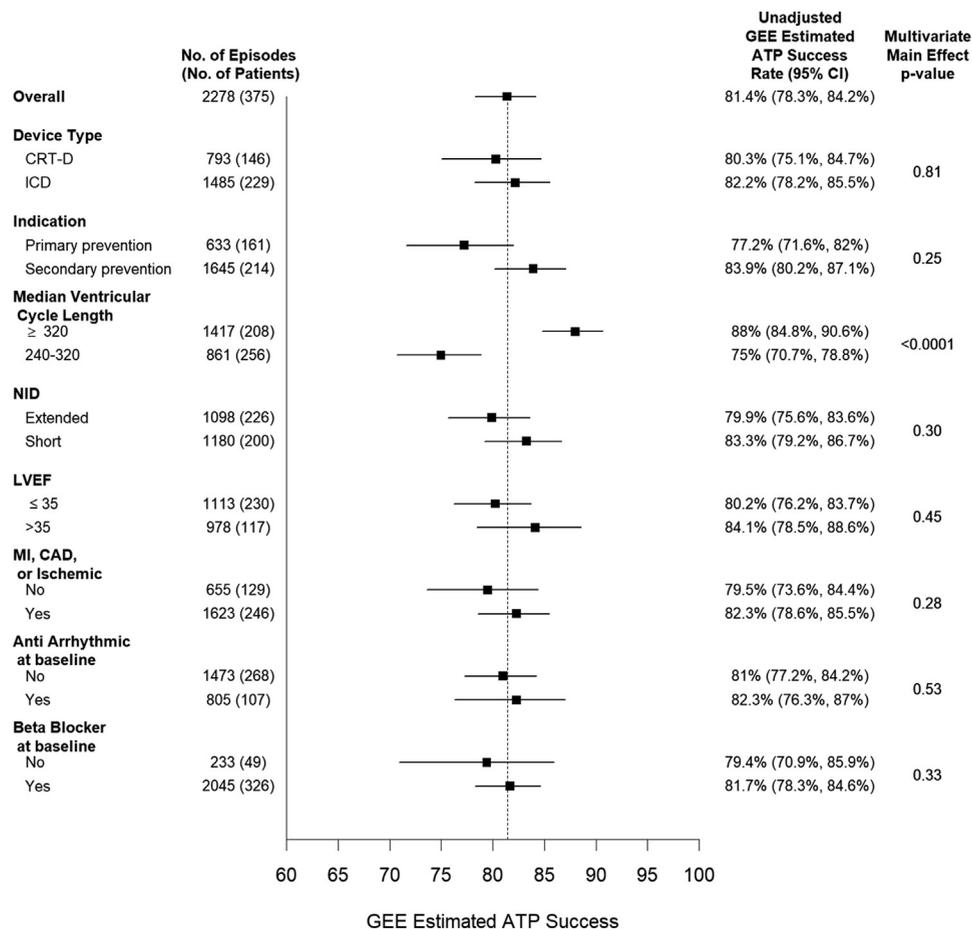
Syncope vs ATP programming

There were 29 episodes (1.3%) with related syncope. Table 2 presents the mean number of ATP sequences programmed for episodes with and without related syncope. After accounting for the median VTCL, there is no evidence of an association between the number of ATP sequences programmed and related syncope ($P = .16$).

Device-detected VT acceleration vs ATP programming

There were 79 VT episodes (4.9%) that were redetected as VF episodes. Figure 5 suggests that there is no evidence of a relationship between the number of ATP sequences programmed and device-detected VT acceleration, which is supported by the GEE model ($P = .12$).

Discussion

This retrospective analysis of the PainFree SST trial found an overall success rate of >80% for ATP terminating MVTs. However, ATP had a higher success rate for VTs with a median VTCL of >320 ms (88% success rate) than did those with a median VTCL of <320 ms (Figure 1; 75% success rate). Interestingly, as more ATP sequences are delivered,

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|	No. of Episodes (No. of Patients)		Unadjusted GEE Estimated ATP Success Rate (95% CI)	Multivariate Main Effect p-value
Overall	2278 (375)		81.4% (78.3%, 84.2%)	
Device Type				
CRT-D	793 (146)		80.3% (75.1%, 84.7%)	0.81
ICD	1485 (229)		82.2% (78.2%, 85.5%)	
Indication				
Primary prevention	633 (161)		77.2% (71.6%, 82%)	0.25
Secondary prevention	1645 (214)		83.9% (80.2%, 87.1%)	
Median Ventricular Cycle Length				
≥ 320	1417 (208)		88% (84.8%, 90.6%)	<0.0001
240-320	861 (256)		75% (70.7%, 78.8%)	
NID				
Extended	1098 (226)		79.9% (75.6%, 83.6%)	0.30
Short	1180 (200)		83.3% (79.2%, 86.7%)	
LVEF				
≤ 35	1113 (230)		80.2% (76.2%, 83.7%)	0.45
>35	978 (117)		84.1% (78.5%, 88.6%)	
MI, CAD, or Ischemic				
No	655 (129)		79.5% (73.6%, 84.4%)	0.28
Yes	1623 (246)		82.3% (78.6%, 85.5%)	
Anti Arrhythmic at baseline				
No	1473 (268)		81% (77.2%, 84.2%)	0.53
Yes	805 (107)		82.3% (76.3%, 87%)	
Beta Blocker at baseline				
No	233 (49)		79.4% (70.9%, 85.9%)	0.33
Yes	2045 (326)		81.7% (78.3%, 84.6%)	

GEE Estimated ATP Success

Figure 1 ATP success by device type and patient characteristics. GEE estimated ATP success is shown by device type, patient indication, median ventricular cycle length, and other patient baseline characteristics. ATP = antitachycardia pacing; CAD = coronary artery disease; CI = confidence interval; CRT-D = cardiac resynchronization therapy – defibrillator; GEE = general estimated equation; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NID = number of intervals to detect.

the cumulative ATP success increases (Figure 3) despite the success rate of each added sequence trending down. Both observations were true for episodes with the median VTCL

above and below 320 ms. This increasing ATP success rate appears to level off as more ATP sequences are delivered, suggesting that while delivering multiple ATP sequences
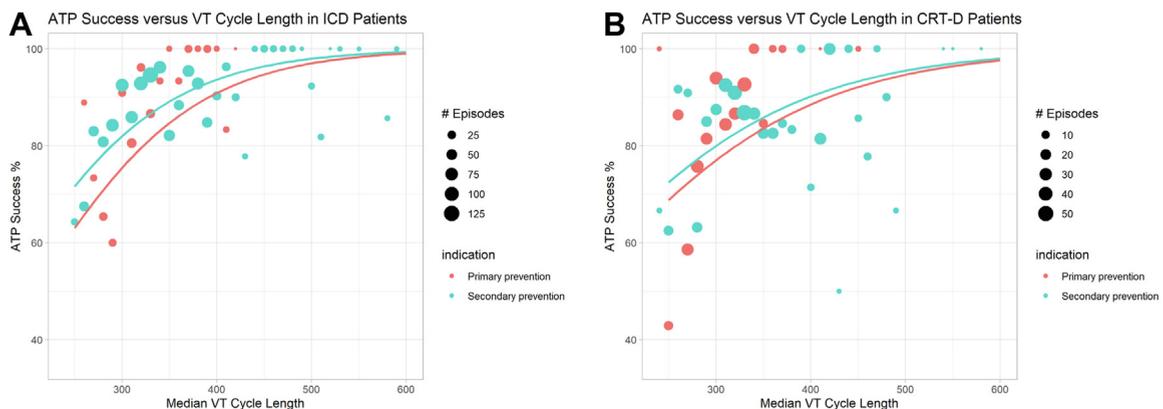

Figure 2 ATP success in ICD and CRT-D devices by cycle length. **A:** Percentage of ATP success is shown vs median VT cycle length for patients with ICD. The best fit lines from GEE logistic regression are shown for both primary (*orange*) and secondary (*teal*) prevention patients. The size of each data point is proportional to the number of episodes at the specified median VT cycle length with the vertical axis corresponding to the unadjusted ATP success rate. **B:** Percentage of ATP success is shown vs median VT cycle length for patients with CRT-D. The best fit lines are shown for both primary (*orange*) and secondary (*teal*) prevention patients. The size of each data point is proportional to the number of episodes. VT = ventricular tachycardia; other abbreviations as in Figure 1.
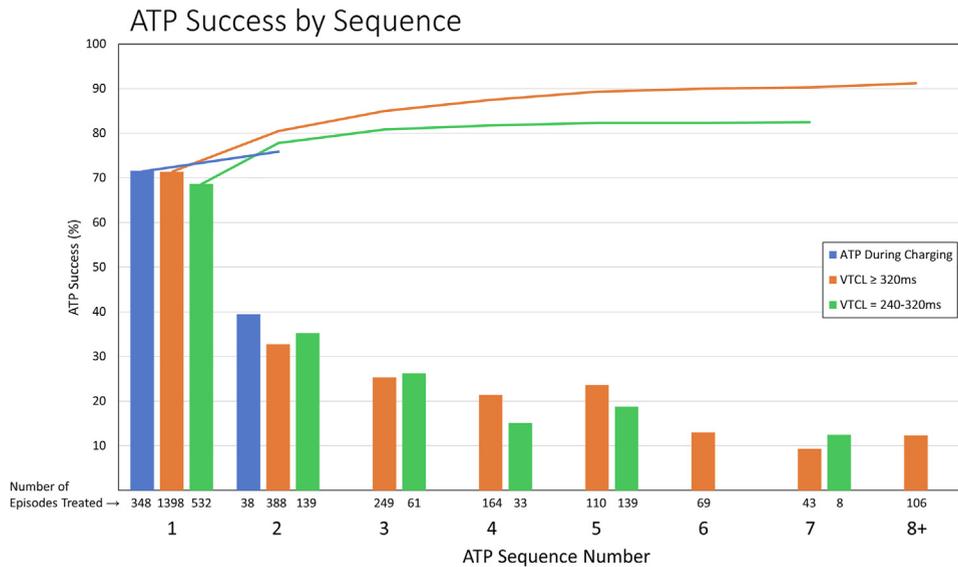
Figure 3   ATP success by sequence number and median VTCL. ATP percent success is shown for each sequence number (*bars*) and cumulative success after each sequence (*lines*). Success is shown for the median VTCL above and below 320 ms. Shown separately are episodes detected within the ventricular fibrillation zone and treated with ATP During Charging (nominal VTCL 240–320 ms) where at most 2 sequences are attempted before shock is delivered. The number of episodes treated at each sequence is listed at the bottom. VTCL = ventricular tachycardia cycle length; other abbreviations as in Figure 1.

may be able to increase VT termination success, there does appear to be a point of diminishing return. The additional success of more ATP sequences beyond 3 sequences for VT <320 ms (80.8% for 3 sequences vs 82.5% for 7 sequences) or 5 sequences for VT >320 ms (89.3% for 5 sequences vs 91.2% for ≥8 sequences) likely adds minimal clinical benefit.

As more ATP sequences were programmed, the number of shocks delivered showed a decreasing trend (Figure 4). While the reasons for physician preference for programming differences between patients were not collected, it was observed that ATP was more likely to be programmed "on" in secondary prevention patients than in primary prevention patients. In the VT zone, 72.3% of secondary prevention
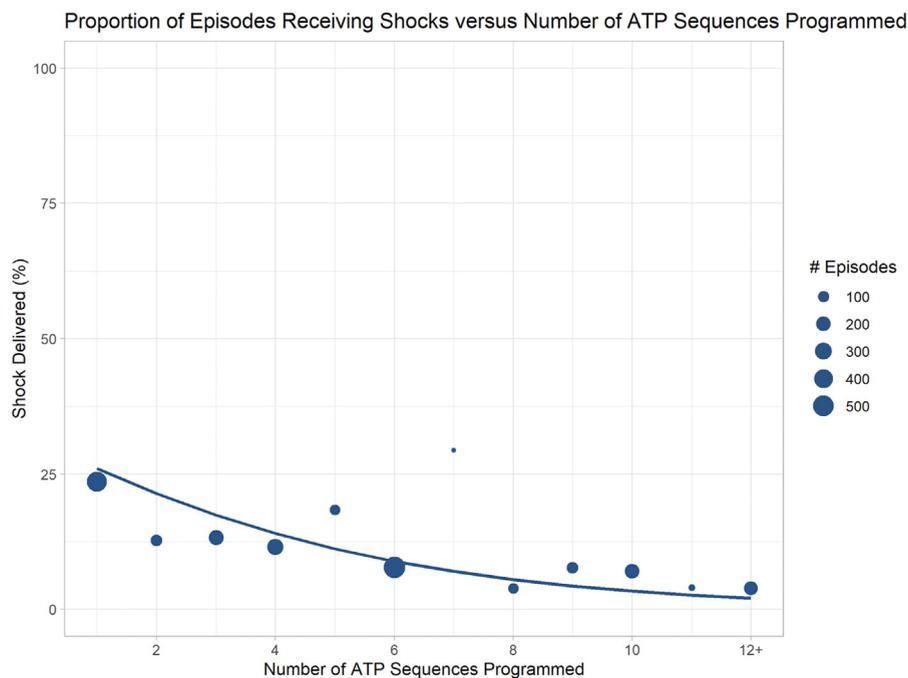
Figure 4   Shock reduction by the number of ATP sequences programmed. The percentage of episodes treated with shock is shown vs the number of ATP sequences programmed with a general estimated equation logistic regression best fit line shown in *blue*. The size of each data point is proportional to the number of episodes. Abbreviations as in Figure 1.

Table 2   Number of ATP sequences programmed for episodes with and without related syncope

Median VTCL (ms)	Mean number of ATP sequences programmed for episodes with related syncope (n)	Mean number of ATP sequences programmed for episodes without related syncope (n)
240–320	1.94 (17)	2.90 (844)
≥320	6.58 (12)	7.27 (1405)

ATP = antitachycardia pacing; VTCL = ventricular tachycardia cycle length.

patients had ATP programmed "on" and 58.0% of primary prevention patients had ATP programmed "on," although among patients with ATP programmed "on," there was no statistical difference in the number of sequences programmed for each group (5.12 ± 2.13 for primary vs 5.91 ± 3.31 for secondary). There was no evidence of increased VT acceleration, with additional programmed ATP sequences based on the number of episodes originally detected in the VT or fast VT zones being accelerated into the VF zone (Figure 5). Last, there is no evidence that additional ATP increased the chance of syncope. This further supports that programming multiple ATP sequences may be beneficial for reducing shock burden.

These findings are consistent with literature reports. Successful termination of VT by ATP was 89% in the Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx) study,[19] 81% in the PainFREE Rx II study,[20] 91% in the EMPIRIC study,[21] 88% in the Automated Antitachycardia Pacing study,[22] and 74% in the Nippon Storm Study.[23] The present results are also in agreement with multiple previous reports that have shown that ATP success rates are higher for VTs with shorter median VTCLs (>320 ms) vs those with larger cycle lengths.[19,22,24,25] It is also worth noting when interpreting our overall ATP success that the majority of episodes had shorter cycle lengths occurring in fewer patients (1417 episodes in 208 patients) vs larger cycle lengths in more patients (861 episodes in 256 patients).

Furthermore, the trend of more sequences resulting in higher ATP success has been previously reported. In a retrospective analysis of anonymized ICD data, Shakibfar et al[26] reported that 4 sequences had a higher success rate, 97.5% of slow VT terminated, compared with 2 or 3 sequences. Others have also reported the incremental increase in success terminating VT by applying more ATP sequences.[22,25,27–29] Increasing the number of ATP sequences programmed in the device not only increased the ATP success rates but also decreased the number of shocks delivered for episodes of MVT. This has also been seen in other large patient series[12] and suggests that programming more ATP sequences may minimize these uncomfortable and potentially unnecessary shocks.

It has been postulated that ATP success would decrease with extended detection, as self-terminating episodes no longer are detected and treated, thus appearing to be pace terminated.[30] In this analysis, after accounting for patient and episode characteristics, ATP success was not
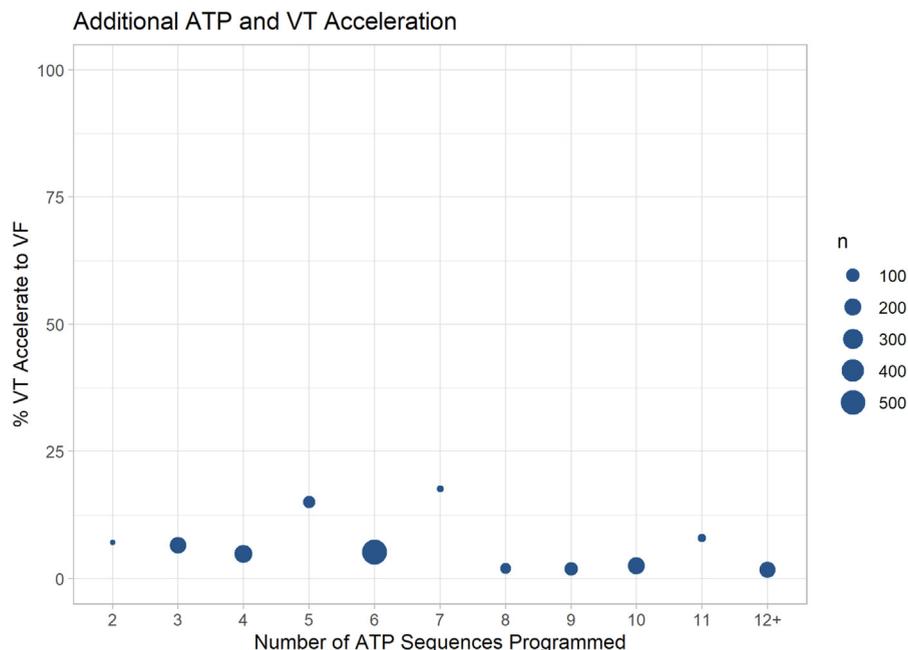
Figure 5   Percentage of VT acceleration by number of ATP sequences programmed. The percentage of VT episodes accelerating into the VF zone as defined by device is shown vs the number of ATP sequences programmed. The size of each data point is proportional to the number of episodes. VF = ventricular fibrillation; other abbreviations as in Figures 1 and 2.

significantly affected by NID programming, although the GEE estimated success was slightly higher in a short NID (83.3% vs 79.9% for an extended NID; $P = .30$). However, in a subgroup analysis of episodes with a VTCL of 240–320 ms, there is a significant, although moderate, impact of NID on ATP success: the GEE estimated success of 69.5% for episodes with an extended NID vs 78.4% with short NID ($P = .011$). Notably, the success rate for VTCL 240–320 ms for extended detection was higher than that reported in extended detection programming used in Primary Prevention Parameters Evaluation Study (PREPARE) (49%),[31] Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) (52%),[32] and Multicenter Automatic Defibrillator Implantation Trial - Reduce Inappropriate Therapies (MADIT-RIT)[30] trials, although ATP therapy in those studies was limited to only 1 sequence.

A few characteristics had no statistically significant effect on ATP success rate, including device type (CRT-D: 80.3%; ICD: 82.2%); implant indication (primary prevention: 77.2%; secondary prevention: 83.9%); history of myocardial infarction, coronary artery disease, or ischemia ("Yes": 82.3%; "No": 79.5%); and β-blocker use ("Yes": 79.4%; "No": 81.7%), meaning ATP can be used successfully in patients with various characteristics. These important data suggest that programming multiple ATP sequences may be beneficial in reducing shocks in patient situations where ATP is not often considered, such as primary prevention implants and nonischemic cardiomyopathies.

Limitations

Some limitations should be considered when interpreting the results of this study. The present report is a retrospective analysis of the PainFree SST study and thus is subject to the same limitations previously described for the study.[16] Specifically, all patients received devices from a single manufacturer and no control group was present. Also, syncopal events were not adjudicated to be arrhythmia related. Accordingly, episodes with related syncope were defined similarly to the definition in a previous PainFree SST analysis.[18] In addition, since there were only 29 episodes with related syncope, we may not have been able to identify a relationship between ATP programming and syncope if one existed. Furthermore, it is possible that VT could terminate spontaneously if given additional time. A potential mechanism for shock reduction associated with an increased number of ATP sequences programmed may be spontaneous VT termination from the additional time it takes for ATP delivery. Finally, it is important to note that programming of the VT therapy zone including VT detection rates and VT NID was left to the physician's discretion. In all primary prevention patients, VF NID was programmed at 30/40, which would include detection of VT in the fast VT zone. In secondary prevention patients, VF NID was randomized 1:1 between 30/40 and 18/24.

Conclusion

We found that ATP success was high in patients in the Pain-Free SST study regardless of indication, device type, and history of ischemia. As the number of ATP sequences delivered increased, the overall rate of success increased and shock burden decreased with no evidence of increased chance of syncope or VT acceleration. This suggests that a potential method for reducing shock burden may be programming more ATP sequences. However, confirmation in prospective studies will be necessary.

Acknowledgments

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