Direct comparison of a novel antitachycardia pacing algorithm against present methods using virtual patient modeling

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BACKGROUND Antitachycardia pacing (ATP) success rates as low as 50% for fast ventricular tachycardias (VTs) have been reported providing an opportunity for improved ATP to decrease shocks.

OBJECTIVE The purpose of this study was to determine how a new automated antitachycardia pacing (AATP) therapy would perform compared with traditional burst ATP using computer modeling to conduct a virtual study.

METHODS Virtual patient scenarios were constructed from magnetic resonance imaging and electrophysiological (EP) data. Cardiac EP simulation software (CARPEntry) was used to generate reentrant VT. Simulated VT exit sites were physician adjudicated against corresponding clinical 12-lead electrocardiograms. Burst ATP comprised 3 sequences of 8 pulses at 88% of VT cycle length, with each sequence decremented by 10 ms. AATP was limited to 3 sequences, with each sequence learning from the previous sequences.

RESULTS Two hundred fifty-nine unique ATP scenarios were generated from 7 unique scarred hearts. Burst ATP terminated 145 of 259 VTs (56%) and accelerated 2.0%. AATP terminated 189 of 259 VTs (73%) with the same acceleration rate. The 2 dominant ATP failure mechanisms were identified as (1) insufficient prematurity to close the excitable gap; and (2) failure to reach the critical isthmus of the VT. AATP reduced failures in these categories from 101 to 63 (44% reduction) without increasing acceleration.

CONCLUSION AATP successfully adapted ATP sequences to terminate VT episodes that burst ATP failed to terminate. AATP was successful with complex scar geometries and EP heterogeneity as seen in the real world.

KEYWORDS Antitachycardia pacing; Computational cardiac electrophysiology; Monomorphic ventricular tachycardia; Self-adapting algorithms; Virtual patient

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Introduction

Implantable cardioverter-defibrillators (ICDs) have been repeatedly demonstrated to reduce mortality by providing shock therapy.1 Although defibrillation shock is highly effective, repeated application of painful shocks to patients has been tied to posttraumatic stress symptoms, reduction in quality of life,2–5 and increased mortality.6 Pace termination of ventricular tachycardia (VT) provides a pain-free alternative to defibrillation shock. Modern ICDs reduce the frequency of shock by applying antitachycardia pacing (ATP) to treat ventricular arrhythmias such as monomorphic ventricular tachycardia (MVT). Efforts to reduce inappropriate and unnecessary therapy by delaying arrhythmia detection have been demonstrated to be clinically beneficial6,7 and are now part of programming guidelines.7,8 However, delayed detection has resulted in lowering ATP success in fast VT (ADVANCE [Avoid DeliVering TherApies for Non-sustained Arrhythmias in ICD PatiEnts]
III trial: cycle length 200–320 ms) to approximately 50%,9 necessitating improved ATP therapies to further reduce shock. Unfortunately, advancements in ATP algorithms have largely stagnated for the past 2 decades.10,11

Lack of improvement in ATP therapy can largely be explained by the expense and difficulty in conducting randomized controlled clinical trials to compare ATP algorithms. Moreover, the mechanism by which ATP disrupts MVT is not well understood. Computational electrophysiological (EP) models have demonstrated potential for predicting MVT ablation targets.12,13 Using these same models to augment clinical trials and clarify ATP mechanisms may help improve ATP performance.14 Cardiac EP models of realistic MVT have the unique potential to evaluate different ATP algorithms at high spatial and temporal resolution. This can help identify new approaches that merit further evaluation in the clinical setting.

In 2017, Yee et al15 evaluated a new automated antitachycardia pacing (AATP) algorithm that used the postpacing interval (PPI) to design the next ATP sequence based on analysis of the prior failed ATP sequence. This observational study was not designed to quantify safety or efficacy but did demonstrate the algorithm was feasible in ambulatory patients. Although not statistically powered to evaluate endpoints, the results suggested AATP was as effective as current ATP and possibly safer because of low VT acceleration. When clinical studies are insufficient, computational models may be used to build confidence in new therapies such as AATP.

The purpose of this modeling study was to compare AATP to burst ATP under real-world conditions. The heart models were designed from patient-specific data to provide realistic and accurate test scenarios with substantial variation in scar heterogeneity and EP properties; to allow a direct comparison of the overall efficacy of the 2 ATP algorithms; and, importantly, to allow analysis of mechanisms of success and failure.

Methods

Basic mechanisms of VT termination by ATP have been explained using simple ring or loop diagrams.16 However, these 2-dimensional constructs do not consider the complexity of realistic scar heterogeneity and the 3-dimensional interactions that result. Nor do these simplified models include the conduction velocity (CV) and action potential duration (APD) restitution that occur as the heart is paced at varied rates. To evaluate the mechanisms of ATP success and failure, a set of virtual patient scenarios was constructed to capture realistic scar and EP (CV and APD) behavior in modern VTs.

Model construction

Patient-specific data

Patient data were collected retrospectively following the Declaration of Helsinki and as approved by a University of Utah institutional review board committee. Coupled image and EP data were collected on 4 subjects to build patient-derived models. Patients presenting to the University of Utah Medical Center for ICD implantation who had already undergone cardiac late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) and an EP study during ICD implantation were retrospectively selected for this analysis. During ICD implantation, programmed stimulation was performed to identify effective refractory periods (ERPs) at 2 different pacing cycle lengths using the implanted ICD lead. Single, double, or triple extrastimuli were used to induce ventricular arrhythmias in the subjects with sequential reduction in the coupling intervals in increments of 10 ms but with a minimum coupling interval of 200 ms between pulses (Supplemental Table S1). Twelve-lead electrocardiograms (ECGs) were collected during the inducibility testing to capture the morphology of any induced arrhythmias. From a set of subjects experiencing sustained MVT, a subset was used for inclusion in this study. Patients were selected for the completeness and quality of the imaging that facilitated the model construction (Supplemental Material, Sections 1 and 2). The patient-specific data were augmented with data from the literature to fully characterize the cardiac substrate.

The imaging and EP data were combined into finite element models that closely resembled the actual patients. To ensure that model EP properties responded to paced stimulation realistically, each model was paced from the same location and with the same pacing protocol as used clinically. Perturbations to the EP parameters were applied to account for the natural variability in cardiac conduction.

Model construction

Computational biventricular models were constructed from the LGE MRI data, which consisted of healthy myocardium, dense scar, and peri-infarct zones (Figure 1). Dense scar and peri-infarct zones were identified using common thresholding techniques,17 where signal intensity (SI) >70% of the myocardium was identified as dense scar, followed by smoothing techniques (Supplemental Material, Section 3, and Supplemental Figures S1 and S2). Scar burden ranged from 6.9% to 21.4% (Supplemental Table S2). The peri-infarct was defined as SI >40% and was restricted to be no more than 5 mm from the dense scar.18 Fiber orientations were added to the model using a rule-based method that approximates the helical angle of the myocyte.19

Multiscale finite element models, with an average mesh resolution of 0.4 mm, were used to represent cardiac conduction, including changes in CV and APD, as a function of diastolic interval. This is achieved by coupling a membrane dynamics model20 to a tissue-level model (monodomain reaction diffusion). This was previously shown to accurately replicate human APD restitution data21 and to study ATP.22,23 At the tissue level, CV is a result of intracellular and extracellular conductivity of the anisotropic myocardial fiber structure. The finite element EP modeling software CARPEntry (Numericer, Graz, Austria) was used for all EP simulation,24 which is well established in the literature.14,18,24

The EP behavior of the healthy myocardium was tuned to best match the 2 patient-specific ERP measurements (Supplemental Material, Sections 4 and 5). The major parameters of
the underlying cell model that govern the repolarization times ($I_{\text{Na}}$, $I_{\text{Ca,L}}$, $I_{\text{Ks}}$, $I_{\text{Kr}}$) along with the tissue conductivity were tuned to best replicate the APD restitution behavior observed in the clinical data. The CV was held at approximately 0.55 m/s when paced at an 800ms interval. The CV was further tuned during the pace induction step. The parameter fit was done by building a responses surface for ERP and CV using a small slab model to iterate through 2000 combinations of input values. The 2000 combinations were used by a boosted tree machine learning approach to build a full response surface that would predict the ERP for any set of ionic properties and tissue conductivities. The workflow along with the resulting parameter fit for model 2 are illustrated in Supplemental Figures S3 and S4. Validation of the computational model’s APD restitution is shown in Supplemental Figures S5 and S6.

**MVT induction**

A key indicator that the model portrayed realistic EP behavior was that it exhibited similar pace inducibility as the corresponding clinical case. Each model heart was paced for induction from the right ventricular apex using the same induction protocol that induced MVT in each patient at the time of ICD implant. In order to produce realistic EP behavior in the critical isthmus and peri-infarct zone, the CV and APD of the peri-infarct tissue were adjusted, using the same parameters as before, to produce an extended refractory period relative to the healthy tissue. This heterogeneity allowed for unidirectional block to establish during overdrive pacing. Each model was tuned to match the induction behavior of the clinical date. The CV was also adjusted to fit the ventricular tachycardia cycle length (VTCL).

**Customized scar models**

Three additional heart models were generated in which the heart geometry was taken from imaging data, but the distribution of scar was not derived from LGE-MRI (Supplemental Material, Sections 6 and 7). In this way, scar phenotypes that were underrepresented or difficult to capture in imaging data, such as long narrow channels of surviving tissue, could be represented in the models.

The scars were manually placed in the perfusion bed of the left anterior descending artery and replicated realistic scars in terms of size and shape while preserving multiple narrow channels (Supplemental Figure S7). The healthy myocardium was tuned to the average patient-specific values. MVTs were induced in the custom scar models using pacing protocols similar to the patient-derived scar models.

**Virtual study design**

The virtual patient scenarios were constructed based on the 7 tuned heart models (4 with patient-specific scar distributions and 3 with customized scar distribution). To generate each VT, small variations (< 20%) in CV and APD were introduced by altering the parameters of the underlying cell model and the conductivity of the myocardial tissue. These perturbations produced 35 unique MVTs with VTCLs ranging from 285 to 480 ms (Figure 2). On each of the 7 geometries, 10 locations were defined for ATP pacing (Supplemental Table S3). Combining the 10 pacing locations with the 7 unique scar distributions that had 5 variations of EP parameters produced 350 unique virtual patient scenarios; however, pacing locations that fell within dense scar or EP states that resulted in self-terminating or unstable MVTs were removed from the analysis. This produced 259 unique virtual patient scenarios on which different therapies could be evaluated.

The strength and duration of the modeled pacing pulse were taken from bidomain models of pacing leads (Supplemental Figure S7) and calibrated to device data (Supplemental Material, Section 8, Supplemental Figure S8). The stimulus in the ATP models was applied as a transmembrane current of 50 μA/cm² to a hemisphere of 5 mm in diameter at the pacing tip of the lead.

A paired comparison between traditional burst ATP and the new AATP algorithm was conducted on the 259 virtual patient scenarios. Burst ATP therapy was defined as 3 sequences of 8 pulses at 88% of the VTCL, with the pacing cycle length decremented by 10 ms in every subsequent ATP sequence. AATP did not require setting of programmed parameters and likewise was limited to 3 sequences of ATP.
AATP used a protocol that broke the ATP sequence into 2 functions. The first function used an S1 coupling interval of fixed percentage of VTCL (88%) to advance S1-VT wavefront collisions forward until, just entering the VT circuit. The second function decremented an S2 pulse each sequence until an S2 was found that closed the excitable gap in the VT circuit and terminated the arrhythmia. Thus, the algorithm automatically attempted to optimize (1) the number of pulses needed to reach the circuit with an S1 train at 88% VTCL; and (2) an S2 that achieved conduction block within the VT circuit.

The S1-S2 sequence was optimized using device-recorded heart rate history and PPI of failed ATP sequences. A detailed explanation is provided by Yee et al. The calculations of the AATP algorithm were emulated in models by generating electrograms at electrode locations and for the algorithms to evaluate (Supplemental Material, Section 9).

**Results**

The initial MVTs from all 7 models are shown in Figure 3. The arrows indicate the direction of the reentrant arrhythmia as it exits the critical isthmus formed by the scar. In model 4, the reentrant circuit was very small and completely formed in the midmyocardium. Observation from either the epicardial or endocardial surfaces would look like an ectopic foci, but in the model the midmyocardial reentrant circuit could be identified.

In the 4 patient-derived models (Figure 3), the simulated VTs were adjudicated by expert review, including 1 electrophysiologist to verify that the simulated VT exit sites correlated with the clinically observed VTs (Figure 4). Based on 12-lead ECG, the exit site of the MVT was localized and marked on the endocardial schematic. Construction of the virtual VTs was blinded to the clinically induced VT exit site location and 12-lead ECG. Without previous knowledge of the VT, 3 of the 4 models had a strong correlation (<2-cm difference) to the clinical VTs, and 1 model had a moderate correlation (2- to 3-cm difference). Of the 4 models, 1 needed to be revised after the evaluation. The revision consisted of identifying additional dense scar that was not captured by the thresholding methodology. All the models could be tuned so that they matched both ERP values ±20 ms and could be induced using the induction protocol.

**Figure 3** Left: Patient-derived monomorphic ventricular tachycardia models used to build the virtual study. Right: Custom scar models that were created to augment the virtual cohort. Color scale indicates activation time from the moment the wavefront leaves the critical isthmus. Arrows indicate the direction of reentry except for heart 4, in which reentry was completely in the midmyocardium.
In 259 unique patient scenarios, AATP was 73% effective compared to burst ATP at 56% (P < .001) (Table 1). Burst ATP seemed to be more sensitive to the location of the pacing electrode, showing an absolute difference of 20% between right- and left-sided efficacy. AATP was also more effective on the left side, but not to the same extent as burst ATP (Table 1). The VT acceleration rate for both therapies was low at 1.9% (Figure 5 and Supplemental Material, Section 10).

The success rate of burst and AATP improved with the number of sequences (Figure 6). Whereas the first sequence success of AATP had only a modest improvement over burst ATP, the third sequence success was higher by an absolute increment of 17%. Burst ATP showed very little improvement from the second sequence to the third, suggesting that adding more sequences might have little additional effect for burst ATP, whereas AATP was still trending upward after 3 sequences.

In this study, the most substantial failure mechanism for both types of ATP was insufficient prematurity to terminate VT, that is, the ATP pulse train was able to reset the VT circuit timing but was unable to close the excitable gap. The burst ATP therapy used in this study, although commonly used, was not sufficiently aggressive in many cases. The AATP algorithm adapted to have a more aggressive S2 and S3, which decreased insufficient prematurity failures by 28%; however, 27 of the 54 failures persisted because the S2 wavefront only partially blocked conduction in the critical isthmus. There were 5 observed cases in which AATP failed to fully block the critical isthmus, although a less premature burst ATP therapy was successful.

The second most frequent mode of failure occurred when the ATP pulse train failed to reach the VT circuit. This mode of failure is easily correctable in a laboratory setting but is impossible to predict a priori. The AATP algorithm was able to correct for 65% of this mode of failure. Even with this improvement, this still represented the second largest mode of failure for AATP. In some cases, the PPI was artificially lengthened when AATP altered the path of the return cycle. The AATP algorithm makes the simplifying assumption of uniform return cycle path, so in cases of nonuniform path, the algorithm may not be able to appropriately lengthen the S1 train.

An automated classification of ATP failure modes from ICD data (CareLink) was recently reported. The study used the failed ATP in VF, FVT, and VT zones to classify the failure modes. The automated classification was applied to 19,658 ATP sequences, in 8538 shocked episodes, in 3615 patients by evaluating the pre-/post-ATP VTCL and PPI for each sequence. Figure 7 compares the rate-based acceleration, insufficient prematurity (reset), and failure to reach the circuit (reset failure) to the same failure modes of the modeling study. Using the \( \chi^2 \) test, a statistically significant association was found between the ICD and the custom

### Table 1

<table>
<thead>
<tr>
<th>Location</th>
<th>Failed ATP (n)</th>
<th>Total ATP (n)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All locations</td>
<td>114</td>
<td>259</td>
<td>56</td>
</tr>
<tr>
<td>Right-sided</td>
<td>81</td>
<td>155</td>
<td>48</td>
</tr>
<tr>
<td>Left-sided</td>
<td>33</td>
<td>104</td>
<td>68</td>
</tr>
<tr>
<td>Burst ATP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided</td>
<td>47</td>
<td>155</td>
<td>70</td>
</tr>
<tr>
<td>Left-sided</td>
<td>23</td>
<td>104</td>
<td>78</td>
</tr>
<tr>
<td>AATP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided</td>
<td>70</td>
<td>259</td>
<td>73</td>
</tr>
<tr>
<td>Left-sided</td>
<td>47</td>
<td>155</td>
<td>70</td>
</tr>
<tr>
<td>All locations</td>
<td>70</td>
<td>259</td>
<td>73</td>
</tr>
</tbody>
</table>

AATP = automated antitachycardia pacing; ATP = antitachycardia pacing.
*Compared by a virtual modeling study with 259 virtual patient scenarios broken down by right-sided and left-sided pacing locations.
scar and imaged scar model’s modes of failure ($P < .0001$) in both cases.

**Discussion**

AATP outperformed burst ATP because it adapted to the common failure modes without a corresponding increase in accelerations. In this virtual EP study, AATP and burst pacing protocols were delivered head to head to establish their respective ability to successfully terminate MVT when exposed to realistic clinical conditions including complex scar geometries and EP heterogeneity. In this virtual study, the efficacy was 27% greater than burst ATP and showed no increase in accelerations. The success of AATP is primarily derived from the third sequence after the algorithm had a chance to learn from previous failed ATP sequences. This suggests AATP may be even more successful if allowed to deliver >3 sequence as tested in this study.

The primary failure mode of burst ATP was insufficient prematurity. Prematurity may be advanced with increasingly aggressive burst pacing but comes with the tradeoff of increased acceleration. The modest overall success (56%) in terminating VT with burst pacing at 88% of VTCL and a low acceleration rate of 1.9% observed in this study corresponds well with the current state of ATP therapy in current clinical practice. In AATP therapy, the S1 train does not rely on aggressive pacing to reach the VT circuit; however, the aggressive S2 and S3 allow AATP to improve efficacy without increasing the acceleration rate.

An important observation from the virtual modeling study was that, in some instances, particularly when the critical isthmus was wide as in heart 2, paced termination required the development of a functional block over multiple pacing pulses. A single ATP paced wavefront would only partially block the critical isthmus of the channel, and the propagating wave would go around the refractory tissue. Each subsequent ATP pace would extend the functional block until, after several ATP paces, the full critical isthmus was successfully blocked. This effect was evident in the 5 cases in which burst ATP was successful in terminating MVT and AATP was not (Supplemental Video 1).

In a similar manner, acceleration of the VT usually required multiple aggressive paces. In the computational models, localized functional block occurred at any region of tissue heterogeneity. Small regions with slightly different...
EP properties caused conduction disturbances when the dia-
stolic interval between excitation was significantly short-
ened. The regions of functional block would grow with
each subsequent aggressive pace until either functional
reentry occurred or a unidirectional block of a new VT

circuit was formed. This modeling observation supports the idea
that aggressive burst ATP has an increased likelihood of accelera-
tion. AATP avoided multiple aggressive ATP paces by
splitting the therapy into a less aggressive S1 train at 88% and
1 or 2 more aggressive S2 and S3 paces. In this way, the
tradeoff between efficacy and acceleration for AATP is
far better than that of burst ATP, with an absolute improve-
ment of 17% efficacy for AATP.

Study limitations
The construction of physician-validated virtual models was
largely successful; however, one area of subjectivity that
should be addressed in future modeling studies is the identi-
fication of peri-infarct and scar regions. Current approaches
need to be improved with regard to robustness and reproduc-
ibility. However, because the purpose of this study was not to
build patient-specific models but rather plausible human scar
substrate, it does not seem to be a major limitation of this
study.

Another limitation of this study relates to the uncertainty
as to how well the models span the patient population. Effort
was made to augment the variability by adding custom scar
models as well as perturbing the EP states of the models.
Comparisons to ICD data indicated a correlation between
the modes of failure in the models and in the ICD popula-
tion.25 This suggests that the models provided enough
variability to produce realistic distributions of failure even
though the number of cardiac anatomies was limited. Addi-
tionally, these models do not include all the heterogeneity in
EP behavior over the entire heart; however, the heteroge-

neity at the critical isthmus was the main focus of this study
and was included in the models.

Conclusion
AATP successfully adapted ATP sequences to terminate VT
episodes that burst ATP failed to terminate. AATP was
successful, with complex scar geometries and EP heterogene-
ity as seen in the real world.

Appendix
Supplementary data
Supplementary data associated with this article can be found in
the online version at https://doi.org/10.1016/j.hrrthm.2020.
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