Randomized comparison between Ramp and Burst+ atrial antitachycardia pacing therapies in patients suffering from sinus node disease and atrial fibrillation and implanted with a DDDRDP device

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Introduction
Atrial fibrillation is the most common sustained cardiac arrhythmia in clinical practice and is a major cause of mortality, morbidity, and impairment of quality of life. Antiarrhythmic drugs (AADs) are the mainstay of atrial fibrillation management. In the long-term, however, they are often ineffective or associated with adverse events. Atrial flutter and atrial tachycardia during AAD therapy for atrial fibrillation are frequent complications and are...
usually treated with catheter ablation or AAD change. In patients receiving a pacemaker for bradycardia, device-delivered antitachycardia pacing (ATP) therapies may be considered for the treatment of regular and slow atrial tachyarrhythmias (ATs).

In the 1980s, ATP therapies were proposed to treat supraventricular re-entrant tachycardia. Recently, ATP has shown promising results over a wider spectrum of AT, in both defibrillator7–10 and pacemaker11–14 patients.

A high incidence of AT has been reported15,16 in patients implanted with pacemakers for sinus node disease (SND). Glotzer et al17 and Capucci et al18 have recently shown that AT episodes, as detected by pacemaker diagnostics, are associated with an increased risk of death, stroke, or embolic complications. Recently, Gillis et al19 have reported a significant correlation between the efficacy of AT termination and the reduction in AT burden in patients paced for bradycardia and frequent symptomatic AT. These data underline the prognostic significance of AT episodes and convey the clinical importance of defining optimized ATP modes.

Newer generations of pacemakers enable delivery of different ATP therapies, such as Ramp, which consists of a decremental drive of pulses, and Burst+, which uses a constant drive of pulses followed by up to two extrastimuli.

The PITAGORA (Prevention Investigation and Treatment: A Group for Observation and Research on Atrial arrhythmias) trial was a randomized cross-over study of patients with AT who were undergoing pacemaker implantation for SND. The goal was to compare the efficacy of Ramp and Burst+ pacing for the termination of AT. The study also aimed to evaluate the synergistic effect of AAD and ATP therapies in a hybrid approach to treat AF.

Methods

Patient selection

We studied 176 patients implanted with a DDDR pacemaker (AT500, Medtronic Inc., MN, USA) in 27 Italian cardiology centres (Appendix).

Study enrolment lasted from January 2001 to December 2003. The last follow-up examination was performed in March 2005.

Patients were eligible for the study if they had SND and at least three appropriately documented (12-lead ECG or 24-h Holter monitoring) symptomatic AT episodes in the year before implantation. Exclusion criteria were: permanent AT, AT due to any reversible cause, life expectancy <1 year, an implanted cardiac mechanical valve and abnormal thyroid function. The study was approved by the Institutional Review Board or Ethics Committee. Every patient gave written informed consent to participate in the study.

Study design

The PITAGORA trial was a prospective, randomized, multi-centre study aimed at comparing the efficacy of Ramp and Burst+ in terminating AT, as evaluated through an 8-month randomized cross-over design (4 months vs. 4 months). This objective was pursued via a hybrid therapy approach. After implantation, all patients were discharged on AAD therapy: 101 patients (57.4%) on class III agents and 75 patients (42.6%) on class IC agents. Daily AAD doses were adjusted according to the patients’ characteristics and were 494 ± 191 mg for propafenone, 153 ± 47 mg for flecainide, 211 ± 58 mg for amiodarone and 136 ± 69 mg for sotalol. Physicians were requested to maintain AAD doses as stable as possible during the whole study period.

A study flow-chart is shown in Figure 1. In the initial 5-month observation period, three patients died (one sudden cardiac death, one non-sudden cardiac death, and one non-cardiac death) and three patients refused to return to the hospital for regular follow-up visits. Thereafter, ATP therapies were enabled in the remaining 170 patients, with patients being randomized to Ramp or Burst+ programming. ATP therapies were enabled in all study patients, regardless of the presence of AT episodes during the initial observation period. Four months later, subjects crossed over. One hundred fifty-seven patients reached 13-month follow-up.

A simple, computer-generated 1:1 randomization table was used to allocate patients to ATP modes. Patients were blind to the type of ATP therapy.

The study protocol suggested that ATP should be enabled during a period of sinus rhythm, but the choice of atrial cardioversion was left to the discretion of each investigator, according to his or her usual clinical practice.

Device characteristics and programming

The Medtronic AT500 is a dual-chamber rate-responsive pacemaker, which has been previously described. Rhythm classification has been reported to have a sensitivity of 100%20,21 and a specificity of 97%. On implantation, pacemaker features not related to AT were programmed according to each physician’s discretion. Mean lower rate was 64 ± 6 bpm and mean upper tracking rate was 121 ± 7 bpm. Paced and sensed AV delays were programmed in order to promote the patient’s intrinsic conduction: median sensed AV delay was 120 ms [25th–75th interquartile (IQ) range between 120 and 200 ms] and median paced AV delay was 150 ms (IQ range between 150 and 220 ms). Atrial sensitivity was programmed at 0.3, 0.45, and 0.6 mV in 96, 39, and 41 patients, respectively.

Detection features were programmed in order to classify any AT episode with AT cycle length (ATCL) <170 ms as atrial fibrillation and any episode with ATCL in the range 170–360 ms as atrial tachycardia. Any AT episode, regardless of its classification at the onset, was continuously monitored and may have been reclassified according to its ATCL.

ATP programming

The device automatically delivers ATP therapies when an episode is classified as atrial tachycardia and lasts longer than a programmable ‘time to first therapy’ (in our study, 1 min).
Ramp therapy consists of a decremental drive of a programmable number of pulses, starting at a rate proportional to the current ATCL. Ramp was programmed in order to deliver 3 series of 10 sequences each, so that each patient could receive up to 30 termination attempts. Each series began with a train of 10 pulses. The first pulse of each of the three series was delivered at 91, 84, and 81% of the underlying ATCL, respectively. In each series, subsequent pulses were delivered with a decrement in pacing coupling interval of 10 ms each.

If a previous train failed to terminate AT, an additional stimulus was added to the next train.

Burst+ therapy uses a drive of a programmable number of atrial pulses, the rate of which is proportional to the current ATCL, followed by up to two extrastimuli. Burst+ was programmed in order to deliver 3 series of 10 sequences each; each sequence was made up of 15 pulses followed by two extrastimuli. As in the Ramp programming, each patient could receive up to 30 termination attempts. The first scan of each series was released at 84% of the underlying ATCL. The first extrastimulus was delivered at 81% of the underlying ATCL; the second extrastimulus was delivered with an interval reduced by 20 ms. In the event of failure, the ATP train coupling interval was decreased by 10 ms for each subsequent scan.

For both therapies, the minimal pacing interval (MPI) was 150 ms, so that pulses programmed at a shorter pacing interval than the MPI were delivered at the MPI value.

**Prevention algorithms**

After the 5-month observation period, atrial pacing preference and/or atrial rate stabilization were enabled, whereas post-mode switch overdrive pacing was left disabled.

**Data analysis**

At follow-up examinations, performed 1, 5, 9, and 13 months after implantation, device diagnostics supplied detailed data on up to 35 newly detected AT episodes: the date, time of day, 48 atrial and ventricular cycles with marker annotations, and cycle lengths were stored at the onset and on detection and termination of the AT. Additionally, the ATCL and four seconds of atrial electrograms (EGMs) were collected at the onset and before the first ATP.

All treated AT episodes, and those contiguous with them, were independently reviewed by three electrophysiologists, who studied the appropriateness of detection and termination by analysing atrial EGMs and marker channel annotations stored by the devices at the onset and on detection of the episode, on the first ATP therapy, and on termination.

The main objective of the study was to compare the efficacy of Ramp and Burst+ in terminating AT. ATP was deemed successful if, in any given episode, five consecutive beats of sinus rhythm were recorded within 30 s of the last ATP delivery and no evidence of atrial undersensing was seen in the EGM recordings, either at the onset of the episode or on detection of the following episode.

The correlation between ATP efficacy and clinical variables, such as the number of ATP attempts and ATCL, was evaluated. Each follow-up visit also included a clinical history assessment. Data on presence and number of AT-related symptoms, such as palpitations, dizziness, dyspnoea, and fatigue, were collected. Quality of life was evaluated, with the use of the EuroQol questionnaire, on a scale between 0 and 100, with 100 indicating the worst possible condition and 0 the best possible condition.

**Statistical analysis**

Descriptive statistics were computed as mean and standard deviation for continuous variables, or median and quartiles if skewed, and as absolute and relative frequencies for categorical variables. ATP efficacy was provided as a raw estimate (episodes successfully terminated by ATP divided by all treated episodes). However, because the calculation of ATP efficacy may be biased if individual patients have multiple treated episodes, we estimated an adjusted efficacy using the generalized estimating equation (GEE) method. This method provides an average patient response to the therapy by correcting for individuals contributing to a greater extent than others.

ATP efficacy proportions were compared by $\chi^2$ test.

ATP efficacy as a function of ATCL was fitted by linear functions, using the method of least squares. The accuracy of the fit was assessed by means of the coefficient of determination $R^2$, which, when multiplied by 100, gives the proportion of variation in the studied quantity that is explained by the proposed model.

Quality-of-life scores and numbers of symptoms were compared by paired t-test and paired Wilcoxon test, respectively, whereas changes in quality of life and symptoms were compared by unpaired tests.

Computation was performed by means of SPSS (SPSS Inc., Chicago, USA) software, version 11.5. Two-sided P-values less than 0.05 were regarded as statistically significant.

**Results**

Patient baseline characteristics are shown in Table 1. Permanent pacing indication was SND in all patients, 32/176 (18%) patients also suffered from AV disturbances.

Atrial leads were placed at the right atrial appendage in 151 (85.8%) patients, at the free lateral wall in 16 (9.1%) patients and at the coronary sinus ostium in 9 (5.1%) patients.

Over the study duration, 6127 AT episodes were detected in 114 patients: 2460 AT episodes occurred during the initial 5 months, when ATP therapies were disabled, whereas 3667 episodes occurred in 78 patients in the following 8 months, when ATP therapies were enabled (1838 in the first crossover period and 1829 in the second period). Out of these 3667 AT episodes, 1943 (53.0%) AT episodes in 75 patients were treated, whereas 1218 (33.2%) AT episodes spontaneously terminated within 1 min before any ATP was delivered and 506 (13.8%) had an atrial cycle length shorter than...
170 ms for their whole duration. Out of the 1943 treated AT episodes, 39 (2%) were excluded because AT detection was induced by intermittent runs of premature atrial contractions. No far-field R-wave oversensing was observed.

During sinus rhythm, median percentage of atrial pacing was 92% (IQ between 80 and 97%), mean atrial rate was 74 ± 11 bpm, median percentage of ventricular pacing was 82% (IQ between 36 and 99%), and mean ventricular rate was 72 ± 7 bpm.

**ATP efficacy**

Out of the 1904 appropriately detected and treated AT episodes, 934 (49.1%) were successfully terminated, yielding a GEE-adjusted ATP efficacy of 43% (95% CI 37–49). Median time between the last ATP therapy and episode termination was 15 s (25th–75th quartile range equal to 9–24 s).

Burst+ successfully terminated 387 out of 873 AT episodes (44.3%) in 58 patients, yielding a 38% GEE-adjusted efficacy (95% CI 32–44). Ramp successfully terminated 547 out of 1031 AT episodes (53.1%) in 56 patients, yielding a 43% GEE-adjusted ATP efficacy (95% CI 37–45). The efficacy of Ramp was significantly higher than that of Burst+ (P < 0.001).

In 28 patients, who had more than six episodes treated by both therapies, individual Ramp and Burst+ efficacies were measured and compared: mean ATP efficacy per patient was 47.5% (41% GEE-adjusted efficacy) for Burst+ and 57.4% (47% GEE-adjusted efficacy) for Ramp (P = NS).

**ATP efficacy as a function of ATCL**

ATP efficacy was evaluated as a function of the ATCL of the episode. Figure 2 shows that the efficacy of Ramp displayed a significantly (P < 0.01) increasing trend as a function of ATCL, whereas the efficacy of Burst+ showed a flat distribution as a function of ATCL. Ramp efficacy was higher than Burst+ efficacy in AT episodes with ATCL ≥ 240 ms (1210/1904 or 64% of treated episodes).

**ATP efficacy as a function of ATP attempts**

Figure 3 shows the cumulative efficacy of ATP therapy as a function of ATP attempts for Ramp and Burst+. The continuous line in the figure represents the difference between the two cumulative efficacy values. The higher efficacy of Ramp therapy was evident within the first six sequences. Subsequent ATP attempts yielded similar results for both ATP modes. For both modes, the median number of ATP attempts needed to terminate AT was three (25th–75th quartile range was equal to 1–7).

**ATP efficacy and AAD therapy**

In order to exclude the possibility of a bias induced by AAD therapy, we verified that AT episodes treated by Ramp or Burst+ were uniformly distributed among the AADs used: the percentage of AT episodes treated, respectively, by Ramp and Burst+ was 52 and 50% (P = NS) in patients on III class AAD and 48 and 50% (P = NS) in patients on IC class AAD.

**Quality of life and symptoms**

In the overall population, quality of life scores, as measured by the EuroQoL questionnaire, significantly improved from 55 ± 14 at the baseline to 68 ± 16 at the last follow-up visit (P < 0.01). The number of AT-related symptoms also...
improved significantly, falling from 2.3 ± 1.0 at the baseline to 0.7 ± 0.9 at the last follow-up visit (P < 0.001).

Quality of life and number of AT-related symptoms were compared between two subgroups of patients selected as a function of ATP efficacy in 70 patients who experienced at least five treated AT episodes. In these patients the median ATP efficacy was 60%. In patients with ATP efficacy ≥60%, the quality-of-life score was 53 ± 18 at the baseline and 72 ± 14 at the last follow-up visit (P < 0.001); in patients with ATP efficacy <60%, the quality-of-life score was 56 ± 11 at the baseline and 65 ± 18 at the last follow-up visit (P < 0.05). The difference in quality-of-life scores between the last follow-up visit and the baseline was 21 ± 26 in patients with high ATP efficacy and 10 ± 19 in patients with low ATP efficacy (P < 0.05).

The number of AT-related symptoms was 2.5 ± 1.1 at the baseline and 0.6 ± 0.7 at the last follow-up visit (P < 0.0001) in patients with ATP efficacy ≥60%, whereas it was 2.2 ± 1.0 at the baseline and 0.8 ± 1.0 at the last follow-up visit (P < 0.001) in patients with ATP efficacy <60%. The difference in the number of symptoms between the last follow-up visit and the baseline was 1.9 ± 1.1 in patients with high ATP efficacy and 1.3 ± 1.1 in patients with low ATP efficacy (P < 0.04).

Adverse events
During the study, three patients died. Only one death was cardiac, and this was not related to ventricular tachyarrhythmias. One non-fatal sustained ventricular tachycardia, unrelated to ATP therapies, was documented by the device memory function in a patient taking sotalol. During follow-up, we observed no clinical complications related to automatic ATP therapy delivery. No ATP-induced ventricular arrhythmias were observed, nor were any episodes of syncope reported by the patients.

Discussion
Main study findings
Ramp terminated a significantly higher percentage (53.1%) of AT episodes than Burst+ (44.3%). The advantage of Ramp can be justified according to the theory of pacing for the termination of ATs with a presumed re-entry mechanism. Waldo et al.24,25 showed entrainment and interruption of atrial flutter and ventricular tachycardias, suggesting that a Ramp pacing protocol progressively penetrates toward the re-entry circuit, thereby incrementally peeling back refractoriness of myocardial tissues until the nth earlier pulse results in invasion and interruption of the re-entry circuit. The decrease in local refractoriness that occurs after premature stimuli may allow earlier activation of local tissues by subsequent stimuli, thereby explaining the superiority of Ramp, which has 10 different coupling intervals, over Burst+, which only has three different coupling intervals.

ATP efficacy as a function of ATCL
Several previous studies10–12,26,27 have directly correlated ATP efficacy with ATCL: this observation may be related either to a higher degree of AT organization or to a longer excitable gap19–30 associated with slower arrhythmias. We observed a statistically significant increase in ATP efficacy as a function of ATCL for Ramp therapies (Figure 2) but, rather unexpectedly, a flat relation for Burst+ therapies. The correlation observed in previous studies10–12,26,27 may
have been strongly influenced by the fact that all these studies chose Ramp as the therapy to be delivered in the first 5–10 termination attempts, and that we observed that ATP efficacy was greatest during the initial six attempts.

To explain the difference between Ramp and Burst+ observed in our study, a difference which increased at longer ATCL, we can hypothesize that because Ramp delivers a greater number of differently coupled pulses within each therapy sequence, it has a greater chance of capturing the atrium, thereby terminating the ongoing arrhythmia, or perhaps degenerating it to a faster and/or more disorganized one that is prone to spontaneous termination.11,12

We did not observe significant differences between the efficacy of the two ATP modalities when applied to ATCL < 240 ms. This fact may have a reasonable explanation: when the device delivers a Ramp during a relatively fast episode, it reduces the coupling interval to the programmed minimum pacing interval (150 ms) and then proceeds to deliver every subsequent pulse with this timing. Thus, AT with ATCL between 190 and 240 ms would receive (as a function of ATCL), respectively, one to nine Ramp-like decremental pulses, followed by the remaining ones at the constant coupling interval of 150 ms, as in Burst+ therapy.

ATP efficacy as a function of ATP attempts

The pacemaker used can deliver a maximum number of 30 ATP sequences during each AT episode. On examining the ATP efficacy of each attempt, we found that the superiority of Ramp over Burst+ was evident within the first six sequences, whereas subsequent ATP attempts showed comparable performances for both therapies (Figure 3). A possible explanation could be that AT episodes not terminated by the first six attempts or longer lasting AT represent a viable explanation could be that AT episodes not terminated by the first six attempts or longer lasting AT represent a
terminations unrelated to ATP.

Comparison with findings from previous studies

To the best of our knowledge, all comparative studies of the efficacy of Ramp and Burst+ have involved different patient populations and tachyarrhythmias from ours. Moreover, the results have been contradictory.33,34

Several authors3–14,26,27 recently studied ATP therapies in patients suffering from atrial fibrillation with pacemaker or ICD indications. In most of these studies, which differed in patient selection, programming of ATP therapies, method of documentation (all detected episodes or only appropriately detected ones), and definition of ATP success, ATP efficacy ranged between 40 and 60%. Our study may be better compared with two previous ones11,12 that used the same pacemaker, in a similar patient population, with the same or similar criteria for defining ATP success, and in which only appropriately detected AT episodes with stored EGMs were considered. In the study by Disertori et al.,11 2065 out of 5593 (36.9%) AT episodes were terminated by ATP therapies. In the study of Israel et al.,12 ATP therapies were successful in 43% of AT episodes (36% adjusted success rate). In these studies,11,12 ATP therapies were delivered during AT episodes with ATCL ≥ 270 ms or episodes with ATCL between 220 and 260 ms, classified as regular by a regularity algorithm. A lower overall ATP efficacy could be expected in our study, in which all AT episodes with an ATCL ≥ 170 ms were treated. On the contrary, our results show a slightly higher overall efficacy of ATP therapy. Three possible explanations may be proposed: first of all, in our study, all patients were either on class III or class IC AADs, whereas in previous studies, only 4011 and 26%12 were; it is known35–37 that class III and class IC AADs may be associated with higher ATP efficacy in terminating atrial flutter. A second possible explanation may be that the earlier-mentioned regularity algorithm may cause a therapy delay, which has been associated with lower ATP efficacy.11,12

Finally, both studies programmed as first ATP therapies the same eight Ramp sequences, each composed of four pulses, whereas we adopted a more aggressive approach: 10 Ramp sequences, each consisting of 10 pulses or 10 Burst+ sequences each consisting of at least 15 pulses.

Three other studies13,26,27 evaluated the efficacy of Ramp and Burst+ programmed to be delivered sequentially, but reported only overall ATP efficacy ‘as defined by the device’ on all treated episodes. In patients with bradycardia and AT13 implanted with the same pacemaker as in our study, ATP efficacy was 54%. In patients suffering from ventricular tachyarrhythmias and atrial tachyarrhythmias and implanted with a dual chamber defibrillator able to deliver Ramp and Burst+ sequences to treat regular AT, Gillis et al.26 reported a 25% adjusted ATP efficacy. Adler et al.27 performed a non-randomized comparison of Burst+ vs. Ramp. They found no statistically significant differences between Burst+ efficacy (raw estimation equal to 48.4%) and GEE-adjusted estimation equal to 35.2%) and Ramp efficacy (raw estimation equal to 41.3% and GEE-adjusted estimation equal to 35.5%).

ATP efficacy mechanisms

Most (93%) of our patients had a history of atrial fibrillation. Some authors33,38,39 have shown an excitable gap even during clinical atrial fibrillation and observed that rapid atrial pacing may locally capture small areas of atrial myocardium, although not be effective in terminating atrial fibrillation. Nevertheless, electrophysiological studies30 and endocardial mapping41 have revealed organized atrial rhythm or discrete atrial complexes separated by isoelectric tracts concealed within multiple wavelets in patients whose surface ECG shows only atrial fibrillatory waves. Furthermore, Israel et al.42 described monomorphic discrete signals, with a minimal cycle length ≥ 200 ms, separated by an isoelectric line in 43% of visually analysed, device-stored atrial EGM of AT episodes. These observations support the concept that a transitional-organized atrial activity observed at the onset or intermittently during atrial fibrillation episodes, regardless of their regularity, may be interrupted or modified by ATP.
Quality of life and symptoms
In the overall population, quality of life and the number of symptoms significantly improved from the baseline to the last follow-up visit. The study was not designed to assess differences in quality of life or symptoms as a function of the ATP mode programmed. The observed quality-of-life improvement could have been simply the result of pacing in an SND patient population; nevertheless, our results did reveal that patients with high ATP efficacy enjoyed significantly greater improvements in both areas of quality of life and AT-related symptoms. This result suggests that attempts to optimize ATP therapy may have a significant impact on clinical outcomes.

Clinical implications of our results
The heterogeneity of individual responses to ATP therapy means that the clinical benefits of ATP therapies are not available to a wide range of patients. Indeed, Gillis et al.\textsuperscript{19} have recently shown that \textasciitilde{} 30\% of patients with frequent episodes of AT following pacemaker implantation for the management of bradycardia experience a significant reduction in AT burden following the activation of atrial ATP therapy. The clinical effect would probably be enhanced by optimizing ATP therapy. On the basis of our results, we could therefore advise choosing Ramp rather than Burst\(\textsuperscript{+}\) as the first ATP attempted, at least for patients whose episodes have an AT-CL longer than 240 ms. The observation that Ramp needed a median of three scans to be effective (Figure 3) offers guidance to choose 13 pulses as first Ramp configuration.

In our study, we routinely programmed 30 ATP attempts, as we wanted to evaluate and exploit ATP capabilities as fully as possible. On the basis of our results (Figure 3), recommendations for the future programming of such therapies should discourage enabling more than 15 ATP attempts, because of the limited added value of subsequent scans.

As we observed that Ramp was significantly more effective than Burst\(\textsuperscript{+}\) for AT-CL \(\geq\) 240 ms, the development of new devices able to deliver different therapies in different windows may result in further ATP efficacy optimization.

Even on AAD therapy, ATP therapies were successful in a limited number (49\%) of episodes. Therefore, overdrive pacing should not be considered as a stand-alone therapy but as a part of hybrid therapy.

The MOST atrial diagnostics ancillary study\textsuperscript{17} has shown that atrial high rate episodes detected by an implanted pacemaker in SND patients are associated with a two-fold increase in the risk of death or stroke. More recently, Capucci et al.\textsuperscript{18} showed that AT episodes, longer than 1 day, are associated with a three-fold increase in the risk of stroke or embolic complications. Optimization of ATP therapy may reduce the duration of AT episodes and therefore it may have a role in the prevention of cardioembolic strokes. Nevertheless, long-term anticoagulation should be guaranteed in patients with thromboembolic risk factors, perhaps with the exception of a few patients who never suffer AT recurrences or in whom short AT episodes are systematically ATP terminated, as documented by the device arrhythmia logbook.

Adverse events
No ventricular pro-arrhythmia associated with atrial ATP therapies or class IC AADs was documented.

Study limitations
The results of this study may only be applicable to the type of population studied. Indeed, all patients were receiving either class IC or class III AADs; this may result in enhanced atrial ATP efficacy or differ from daily clinical practice.

Only 5\% of patients received an atrial lead in a septal position. Specific pacing sites could be associated with high ATP efficacies, in any case alternative site pacing was not encouraged in the present study in order to test ATP efficacy in current clinical practice.

The present study evaluated specific Ramp and Burst\(\textsuperscript{+}\) therapies with given pulse numbers and adaptive pacing intervals. It is possible that different programming would yield different results.

The low incidence of AT recurrences limited the paired comparison between Ramp and Burst\(\textsuperscript{+}\) ATP efficacy to a very small sample of 28 patients.

In patients with paroxysmal AT, many episodes may terminate within a few minutes.\textsuperscript{43} In these cases, AT-episode termination may have occurred spontaneously during or immediately after ATP delivery. Although spontaneous episode termination may bias the exact estimation of ATP efficacy values, the probability of this event is likely to be the same after either Ramp or Burst\(\textsuperscript{+}\) delivery: it does not therefore influence the comparison between the two therapies.

It was not our intention to assess the impact of atrial ATP on clinical outcomes, such as death, embolic complications, or hospitalization. Such an objective would have required recruiting a control group without atrial ATP and enrolling hundreds of patients.\textsuperscript{44} Therefore, the lack of a control group should not be seen as a study limitation.

It was not our intention to perform a complete multivariate analysis to correlate ATP efficacy with all patient characteristics. We showed a correlation between ATP efficacy and AT-CL. We are inclined to discount this association being mediated by other confounding factors, on the basis of results recently published by Boriani et al.\textsuperscript{45} who showed AT-CL to be an independent predictor of ATP efficacy.

Conclusions
This randomized cross-over study shows that overall termination efficacy is higher for Ramp than Burst\(\textsuperscript{+}\) therapy and that this superiority is particularly associated with AT episodes with AT-CL \(\geq\) 240 ms. Further studies are required to show the impact of optimized atrial ATP therapies on clinical outcomes.

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Appendix
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References


