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EFFICACY OF ANTITACHYCARDIA PACING IN PATIENTS WITH ISCHEMIC AND NON - ISCHEMIC CARDIOMYOPATHY

Tesi di Dottorato

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1. Introduction

In patients with heart failure and reduced left ventricular ejection fraction (LVEF < 35%), there is an increased risk of sudden cardiac death (SCD) due to ventricular arrhythmias (VA), with the highest risk in those who survived an episode of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT)[1]. Implantable cardioverter-defibrillator therapy (ICD) is beneficial in both the prevention of primary[2,3,4,5,6] and secondary[7,8,9] SCD. While ICD shocks may be lifesaving, inappropriate shocks for VT, inappropriate shocks for SVT, and premature shocks for NSVT are associated with significant morbidity and mortality[10,11,12,13]. ICD-specific anxiety, depression, and post-traumatic stress disorder are common among patients who have received multiple ICD shocks and are associated with increased mortality independent of cardiac disease severity[14]. Antitachycardia pacing (ATP) was developed to terminate reentrant ventricular arrhythmias without the need for painful ICD shock. ATP therapy has been shown to reduce shocks, morbidity, mortality, and healthcare expenditure[15,16]. For many years, ATP therapy was considered advantageous. However, the value of ICD and ATP, particularly in primary prevention in non-ischemic cardiomyopathy patients (NICMP), is increasingly questionable. In the 2016 ESC Heart Failure Guidelines, the IIA recommendation for ICD implantation was assigned to nonischemic patients, rather than the class 1A recommendation for patients with ischemic heart failure, which has remained a

constant indication[17,18]. In the American Heart Association Guidelines, on the

other hand, ICD implantation for primary prevention of SCD in patients with

symptomatic systolic heart failure is a class 1A recommendation, with no

differentiation between patients with ischemic and non-ischemic

cardiomyopathy[19] . This difference arises from the trials on which the guidelines

are based: the American Heart Association Guidelines refer to the Sudden

Cardiac Death in Heart Failure Trial (SCD-HeFT), the 2016 European

Guidelines consider the Defibrillators in Non-Ischemic Cardiomyopathy

Treatment Evaluation (DEFINITE), while the latest version of the ESC

Guidelines grounds its recommendations on the DANISH study. The SCD-HeFT

trial proved the benefit of ICD implantation in patients with nonischemic heart

failure with respect to all-cause mortality[6]. With opposite results, the more recent

randomized Danish Study to Evaluate the Efficacy of ICDs in Patients with Non-

ischemic Systolic Heart Failure on Mortality (DANISH) trial demonstrated a

significant reduction in SCD in patients with LVEF 35%, but without a

significantly lower long-term rate of death from any cause compared to usual

clinical care[20]. However, the subgroup analyses of the DANISH trial have shown

contrasting results, a reduction in all-cause mortality was demonstrated both in

patients under 70 years of age and in patients with less severe heart failure[21].

Contrary to the results of the DANISH trial, there are meta-analyses showing a

significant survival benefit due to ICD implantation in patients without ischemic

cardiomyopathy[22,23,23]. Given the mechanisms underlying the development of

ischemic cardiomyopathy (ICM), there is a general belief that ICM patients tend

to have greater amounts of myocardial scar when compared with patients with

NICM. This suggests that monomorphic ventricular tachycardia (MVT), often the result of reentry around scar tissue, is more common in patients with ICM, and thus these patients would more likely benefit from ATP. Considering the available data from the literature, it is justifiable to ask whether we need to reconsider the indication of ICD therapy in primary prevention in the entire nonischemic population. In the current study, our aim is to demonstrate if NICM patients have ATP therapy with similar efficacy compared to ICM patients.

2. Mechanism of sustained monomorphic VT in coronary artery disease

The pathophysiological basis for sustained monomorphic VT due to prior myocardial infarction is well understood. The mechanism of arrhythmogenesis in this setting is reentry[24,25]. The anatomical substrate for reentry is the interlacing of viable myocardium and connective tissue (scar) at sites of prior myocardial infarction[26,27]. This specific pathological condition is the basis for low-amplitude fractionated endocardial electrograms at the sites of origin of VT[26]. Poor cell coupling at sites where fractionated electrograms are recorded results in slow propagation of impulses necessary for initiation and maintenance of sustained VT[26,27]. Such abnormalities of conduction, along with altered refractoriness, enhanced automaticity, and areas of no excitability form the electrophysiological substrates for reentry caused by prior myocardial infarction. Evidence for reentry obtained from electrophysiology studies includes reproducible initiation and termination of tachycardia by critically timed extra

stimuli, response of the tachycardia to stimulation or drugs, and activation mapping demonstrating reentrant excitation[28]. Reentry is a self-perpetuating mechanism by which a wave front propagates repetitively throughout a closed rotational circuit long enough to allow cardiac tissue to be excitable by the time the wave front reaches it (Figure 1A). Reentry can occur in presence of two indispensable conditions: *a)* unidirectional block of conduction (i.e., successful conduction in only one direction)*,* and *b)* a circuit cycle longer than any of the refractory periods throughout the circuit. The circuit length necessary for reentry depends directly on the tissue refractory period, but also on the conduction velocity of the wave front. The unidirectional block of conduction can be anatomical, caused by discontinuities in ventricular muscle[29], branching strands of slow conduction[30,31], or tissue discontinuation due to gap junction abnormalities[32] present in the areas of scar. It can also be functional, due to dispersion of refractoriness, a phenomenon that has been described for both the VT associated with healed MI and for the VT complicating acute ischemia[32]. Reentry in the presence of MI mainly originates from surviving bundles of myocardium within the scar, separated by connective tissue, fibrosis and disordered intercellular coupling[33](Figure 1B) . Myocardial infarction is the most common pathology producing the substrate for reentry, but reentry VT is also seen in patients with non-ischemic cardiomyopathy, particularly those with hypertrophic cardiomyopathy, cardiac sarcoidosis, and arrhythmogenic right ventricular cardiomyopathy[34].
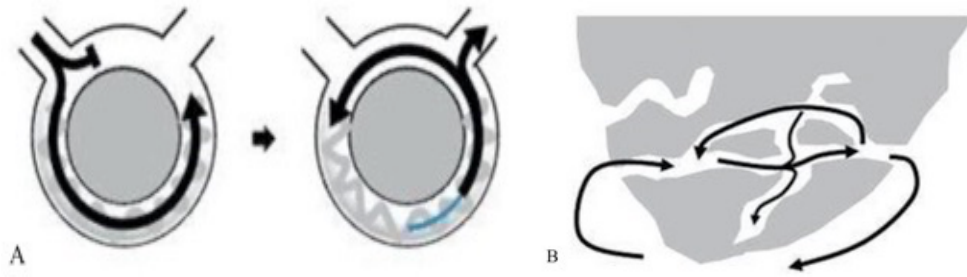
Figure 1. Examples of reentry circuits. **A:** Diagram representing a single circuit of reentry that initiates with a unidirectional block. The circuit length must be longer than the longest refractory period in the circuit. **B**: Anatomical labyrinth circuit, created by strands of viable myocardium within the scar, with potential for multiple reentry circuits.

The electrophysiological substrate for reentry due to a prior myocardial infarction is remarkably durable. Long-term follow-up of patients who present with sustained monomorphic VT has demonstrated a 3%-5% per year incidence of recurrent VT up to 15 years after presentation[28]. Sustained monomorphic ventricular tachycardias induced early after myocardial infarction among patients with spontaneous VT can be reproducibly induced up to a year later, regardless of whether the induced VT occurred spontaneously[35]. Sustained monomorphic VT induced among patients with prior myocardial infarction, reduced left ventricular ejection fraction, and no history of spontaneous sustained VT is reproducibly (> 90%) inducible up to 6 years later[36]. These studies establish that the substrate for reentry after myocardial infarction can remain persistent anatomically for many years.

2.1 Relationship Between Monomorphic VT and Ventricular Fibrillation

The underlying mechanism of ventricular fibrillation not associated with acute myocardial infarction is poorly understood. Ambulatory monitoring has clearly demonstrated that sustained monomorphic VT precedes some episodes of VF[37,38]. The destabilization of monomorphic VT may be related to ischemia, left ventricular dysfunction, electrolyte imbalances, sympathetic nervous system activation, or other poorly understood factors. Analysis of stored electrograms recovered from ICD has provided additional information on the initiation of VF in the context of chronic coronary artery disease. The occurrence of spontaneous monomorphic VT was observed to be higher among patients who presented with VT (54%) versus those who presented with VF (18%) in one study[39]. Abrupt-onset VF (not preceded by monomorphic VT) was recorded in 11% of patients who presented VF[40]. These observations suggest that in some patients spontaneous VF is a primary event, rather than a destabilization of monomorphic VT. An example of VF initiated by sustained VT is shown in Figure 2. The clinical importance of this observation is that termination of VT by ATP may prevent VF in some patients.
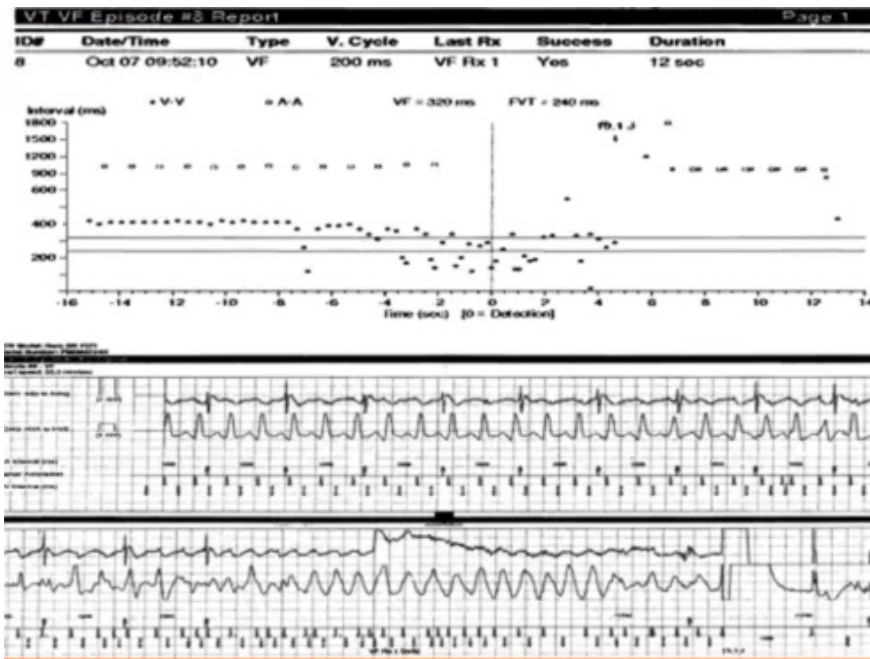
Figure 2. The tracements are from a 79-year-old male with ischemic cardiomyopathy and a history of cardiac arrest. The patient had a Medtronic 7271 ICD system, and the pre-onset electrogram storage feature was enabled. The ICD stores up to 15 seconds of electrogram before the onset of the episode. (Panel A) Interval plot associated with episode of ventricular fibrillation. The interval plot shows each VV interval (X-axis) with its corresponding interval value in milliseconds (Y-axis). Time zero is at episode detection. Note that detection is triggered by short VV intervals with wide cycle-length variability (150-320 ms) in the VF zone (< 320 ms). The VV intervals proceeding detection are stable at 400-410 ms and dissociated from the AA intervals (1,000 ms). This is consistent with stable monomorphic VT. (Panel B) Stored local bipolar atrial and far-field ventricular electrograms confirm sustained monomorphic ventricular tachycardia that degenerates to ventricular fibrillation (arrow). Had pre-onset electrogram storage not been enabled, the onset of VF would have been assumed to be abrupt.

3. Mechanism of Sustained Monomorphic VT in Nonischemic Dilated Cardiomyopathy

Sustained monomorphic VT in nonischemic dilated cardiomyopathy is less common than in ischemic cardiomyopathy. The pathophysiological basis for sustained monomorphic VT associated with NICM is poorly understood compared to chronic coronary artery disease, and probably different. Autopsy

series have demonstrated visually evident left ventricular scars (replacement fibrosis) in patients with NICM[41] . Interlacing of replacement fibrosis and viable myocardium can produce fractionated, broad, low amplitude, endocardial electrograms compatible with slow conduction zones as seen in chronic myocardial infarction[31]. These are capable of maintaining reentry[42]. However, most patients with NICM have relatively normal endocardial activation and electrograms, not significantly different than normal individuals. Only those rare patients with NICM and sustained monomorphic VT have fractionated endocardial electrograms[28,43,44]. The electrophysiological mechanisms of ventricular arrhythmia in nonischemic idiopathic dilated cardiomyopathy were studied by intraoperative mapping just before explanation among patients undergoing cardiac transplantation by Pogwizd etal[45]. zones of functional conduction were demonstrated in the epicardium and, less frequently, in the midmyocardium and endocardium. In these locations, extensive interstitial fibrosis was consistently found in continuous linear bundles extending from the endocardium to the midmyocardium. However, premature ventricular beats and non-sustained VT induced by programmed stimulation were found to arise primarily in the subendocardium by a focal mechanism without evidence of macroreentry. These initiation sites were consistently distant from zones of functional conduction delay and block that did not contribute to the onset of VT. The investigators hypothesized that focal initiation of VT could be due to triggered activity (delayed afterdepolarizations [DADs], or early afterdepolarizations [EADs]) citing the observation that triggered activity can be initiated in the myocardium of NICMP[46]. Monomorphic VT occurs less

commonly due to reentry and occurs with a lower frequency in NICMP. These fundamental differences in substrate are important for interpretation of clinical trials of ATP in ICD patients since no reentrant VT would not be expected to respond to ATP.

4. Mechanism of ATP

Once initiated, reentry VT may perpetuate unless perturbed at the critical time point. If the propagating VT wave front encounters depolarized tissue, then antegrade propagation is arrested. Direct-current cardioversion depolarizes all excitable tissue, including those that are in front of the propagating VT wave front and terminates the tachycardia. A critically timed single pacing stimulus may also terminate reentry, but the pacing stimulus must not only depolarize tissue in front of the VT wavefront but also collide with its refractory tail otherwise a new wavefront will initiate. Thus, if both antegrade and retrograde collisions do not occur, the tachycardia will perpetuate. The ease at which a critically timed stimulus may terminate the tachycardia by this mechanism is dependent on (1) the excitable gap, (2) distance of the VT circuit from the site of stimulation, and (3) refractoriness of intervening tissue.

4.1 The Excitable Gap

To achieve both antegrade and retrograde collision, the pacing stimulus must reach the excitable gap, a region of excitable tissue between the depolarizing wave front and the end of its refractory tail. The excitable gap is smaller in fast VT (FVT) compared to slow VT (SLVT) because faster conduction creates a

longer period of refractoriness (Figure 3A). This is one reason why ATP is less effective at terminating FVT compared to slow VT (SLVT)[47,48]. Additionally, the location of the excitable gap relative to the pacing stimulus is always changing. For example, at a given time point, the pacing stimulus may be in line with the excitable gap, but at a later point the excitable gap may be remote from the pacing stimulus (Figure 3B). With faster VT, the probability that the pacing stimulus is in line with the excitable gap is reduced. Often multiple pacing stimuli are delivered at a frequency, slightly faster than rate of the VT to assure that a given pacing impulse approaches the VT circuit at differing times in its rotation and to increase the probability the pacing stimulus enters the excitable gap (Figure 3). Just because the pacing stimulus enters the excitable gap, the tachycardia may not terminate; the timing of when the pacing stimulus enters the excitable gap is also critically important for termination. If the pacing impulse enters late in the excitable gap, the impulse may collide with the propagating tachycardia wave front and cause retrograde block, but antegrade block does not occur because the tissue in front of the pacing stimulus remains excitable. A new propagating wave front develops and the reentrant tachycardia continues. This so-called entrainment of the tachycardia advances the timing of the VT for one beat (Figure 3C top). If the pacing impulse enters early in the excitable gap, blockage occurs in both the retrograde and antegrade directions. Pacing stimulus propagation in the antegrade direction encroaches on the refractory tail and is blocked; thereby preventing a new wavefront from developing. At the same time, the pacing stimulus propagates retrogradely and collides with the wavefront of

the tachycardia, terminating the tachycardia (Figure 3C bottom) and restoring sinus rhythm.

4.2 Refractoriness and Distance to the Excitable Gap

The refractoriness and distance of tissue between pacing stimulus and the VT circuit govern whether a paced impulse may reach the excitable gap at the critical time for VT termination[49,50] (Figure 3D). As the VT circuit spins, it depolarizes regions of the myocardium that are more remote from the circuit, including those between the pacing stimulus and the VT circuit. A single pacing stimulus may therefore encounter refractory tissue which was previously activated by the propagating VT wavefront. One method of reducing tissue refractoriness is to increase the current strength of the pacing stimulus[51]. Another method for reducing refractories is to increase the number of pacing stimuli to "peel back refractories" of the region. Multiple pacing impulses and pacing impulses with shorter and shorter coupling intervals push back the region of collision with the depolarizing wavefront of the VT, increasing the probability that a pacing stimulus may enter the excitable gap and terminate the tachycardia. However, such efforts to overcome refractoriness and distance may also increase the risk of inducing different, faster, and more unstable VT or VF as pacing may interacts with other myopathic regions comprising the arrhythmic substrate.
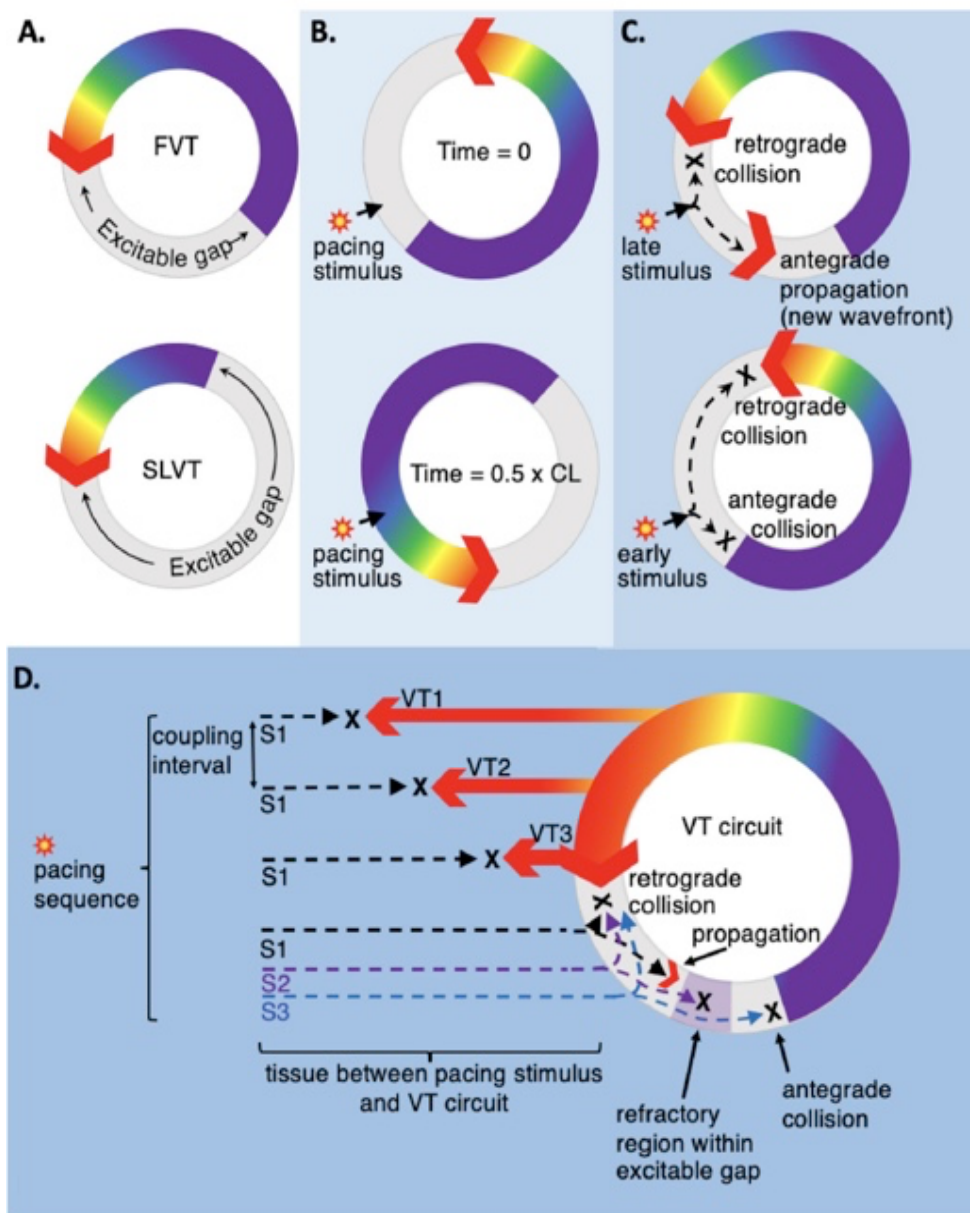
Figure 3. A Shown is a reentrant tachycardia with propagating wave front (red) and tail of refractory, non-excitable tissue (purple). The gray portion of the circuit represents a region of excitable tissue, so-called excitable gap. If the propagating wavefront encounters excitable tissue, the tachycardia persists. With FVT, the fast conduction results in a longer tail of refractoriness, and the excitable gap is small. With slow VT, slow conduction shortens the tail of refractoriness, and the excitable gap is larger. **B** The location of the excitable gap relative to a fixed pacing stimulus changes with time as the propagating wavefront spins around the circuit. At time 0 ms, the pacing stimulus is in line with the excitable gap. At a time that is half of the VT cycle length (CL), the VT wavefront has moved halfway around the circuit, and the excitable gap

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is remote from the pacing stimulus. **C** When a pacing stimulus enters the excitable gap late (close to the propagating tachycardia wavefront) retrograde collision occurs, but the pacing stimulus propagates antegrade in the excitable gap, creating a new propagating wavefront (top) and persistence of VT. If the pacing stimulus enters early in the excitable gap, block occurs in both the retrograde and antegrade directions and terminates VT (bottom). **D** Regions outside of VT circuit including that between the circuit and the pacing stimulus are depolarized by the passing VT wavefront. The pacing stimulus must overcome the refractoriness of the tissue to interact with the VT circuit. The first pacing stimulus collides with depolarizing VT wavefront (VT1). A second S1 stimulus encroaches closer to the VT circuit before colliding with the second revolution of the VT circuit (VT2). The third S1 stimulus peals back additional refractoriness, allowing the fourth S1 to reach the VT circuit and enter the excitable gap. Entrainment without termination of the VT may occur if the S1 pacing stimulus enters too late in the excitable gap. A closer coupled stimulus (S2) at the end of the S1 pacing train advances the stimulus within the excitable gap encroaching on the tail of refractoriness and increase likelihood of antegrade collision. An even closer coupled stimulus (S3) may be necessary to overcome regional refractoriness within the excitable gap and allow for antegrade collision.

5. Modes of ATP

There are two principal modes of ATP, burst pacing and ramp pacing, that are designed to overcome the refractoriness of tissue between the fixed pacing site and the VT circuit. With burst pacing, a set number of pulses are delivered at a constant cycle length, which is a set percentage (usually 75–90%) shorter than the tachycardia cycle length (TCL) or faster rate. Subsequent ATP sequences may be repeated with a preset, fixed decrease in the pacing cycle length (slightly faster rate). Additionally, ATP sequence increases likelihood of successful termination of VT[52] . With ramp pacing, the initial pacing coupling interval of the first pacing stimuli is a percentage of the TCL but subsequent pacing stimuli within the ATP sequence are decreased by a fixed interval (usually 8–10 ms or 3–5% of cycle length reduction). Subsequent pacing sequences contain

additional pacing stimuli that reach a shorter coupling interval by the end of the sequence. A minimum coupling interval is set to minimize risk of inducing faster and more unstable VT (Figure 4). In single and dual chamber ICDs, ATP is delivered via the right ventricular (RV) defibrillation lead, while, in biventricular ICDs, ATP may be delivered simultaneously via the RV lead and the left ventricular lead. In general, biventricular delivery of ATP has been shown to have similar efficacy as RV-delivered ATP; although it may be more effective for FVT in ischemic cardiomyopathy[53] .
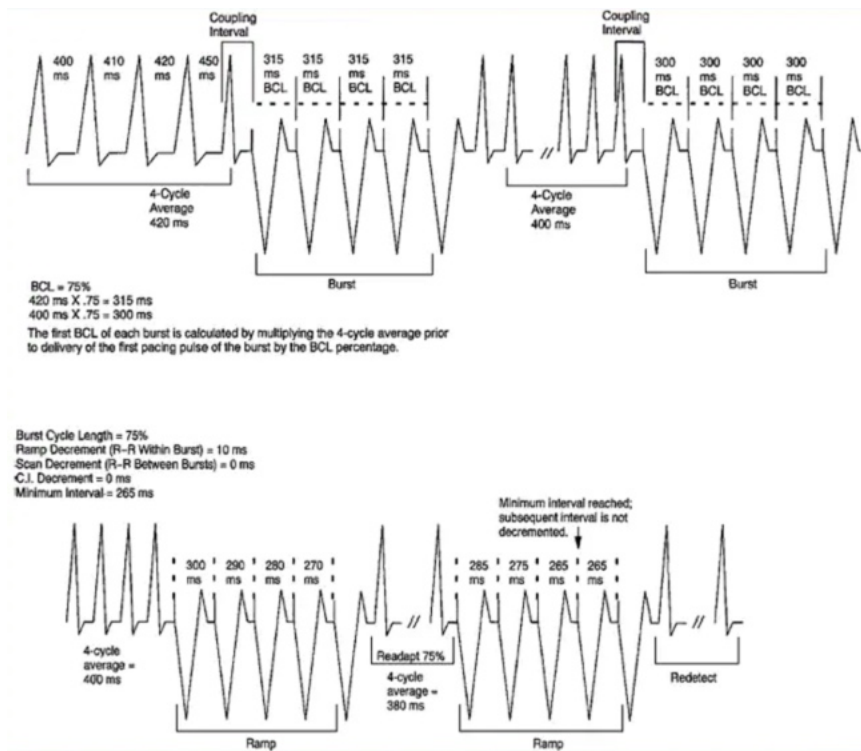

Figure 4. (Top) Simple burst-pacing scheme. (Bottom) Simple ramp-pacing scheme.

6. Efficacy of ATP Schemes

Early studies comparing the effectiveness of burst and ramp pacing with VT induced in the EP laboratory were contradictory[54,55]. ATP has greater efficacy in terminating spontaneous VT compared to induced VT[56,57], but induced VT tends to be faster and has a poor morphologic correlation with spontaneous VT. One of the first, though small, studies comparing the two ATP modes did not show any difference in efficacy for spontaneous VT[56]. The larger PITAGORA ICD study found that burst pacing was significantly more effective than ramp for spontaneous FVT[58]. However, there were several limitations to this study, including an imbalance of FVT events in the two arms and the inability to compare the efficacy of the scheme in individual patients. A very recent meta-analysis of 13 studies comprising 30,117 VT episodes in 1672 patients showed no difference in VT termination or acceleration with burst or ramp ATP sequences[59]. ATP efficacy was approximately 90% with a 2-3% risk of acceleration.

7. Novel Automatic ATP Schemes

Newer automatic or smart ATP algorithms have been recently designed and proposed[60]. In the case where ATP fails to terminate the tachycardia, these automatic algorithms use real-time data to determine why ATP failed and to alter the subsequent ATP sequence. The return cycle length, the time between last ATP pacing stimulus, and the subsequent VT-sensed event provide information on three possible outcomes related to ATP failure. First, there may be a failure to reset or entrain the tachycardia because the pace does not reach the VT circuit

due to the refractories of the intervening tissue. By adding an additional pacing stimulus with the same coupling cycle length (S1) to the ATP sequence, the refractoriness of the intervening tissue can be overcome (Figure 3D) and tachycardia entrainment can be achieved. Second, the pacing stimulus reaches the excitable gap too late to cause an antegrade collision. In this case, entrainment is confirmed but the VT persists. When delivering a pacing stimulus (S2) with a coupling interval shorter than that of the S1 pulse sequences, the pacing stimulus S2 enters earlier within the excitable gap and encroaches on the refractory tail of the VT. This increases the likelihood of achieving antegrade block. Third, the refractoriness within the excitable gap prevents the S2 stimulus from reaching and colliding with the propagating wave front (antegrade collision). An additional pacing stimulus (S3) with a shorter coupling interval than that of S2 is added to peel back the refractoriness in the excitable gap and increase the likelihood that S3 propagates far enough within the excitable gap to cause antegrade collision and terminate VT. Such automatic algorithms have not yet been tested in randomized controlled studies, but may have value to improve ATP efficacy in particular in patients with VT and those with ICD for secondary prevention.

8. Efficacy of ATP for slow and fast VT

Early data on ATP showed that it worked remarkably well for terminating slow VT (SLVT, < 200 beat/min) irrespective of pacing regimen but that it was less effective for faster VT (FVT, > 181–200 beat/min) and had a higher rate of VT acceleration[47, 48,54]. Therefore, due to safety concerns regarding delaying shock

therapy with ATP, which can be less effective and accelerate VT, it was felt that FVT was best treated with an immediate shock. In the early 2000s, there was growing evidence supporting the use of ATP for FVT (Figure 5). PainFree Rx I trial[61] was designed to test the efficacy and safety of ATP for FVT and to reduce shocks from ICD in patients with coronary disease and ICD for secondary prevention. FVT was defined as VT with CL of 240–320 ms (188–250 beats/min). It showed that ATP with 8 S1 pulses at 88% of VTCL was safe and very effective for FVT. The success rate was 89% for termination, with only 1.1% of the patients having syncope and 1.8% having acceleration of VT. While the PainFREE Rx I trial enrolled patients with coronary disease, PainFREE Rx II[62] was designed to test the efficacy of ATP in a wider population of patients with ICD, including those with a non-ischemic substrate for stable, monomorphic VT. It was a prospective, multicenter study that randomized 634 patients to initial treatment of FVT (< 250 bpm) with ATP or shocks. ATP was programmed to a non-aggressive regimen of 88% of the TCL. ATP was found to have an efficacy of 73% in terminating FVT with very low risk of acceleration of VT (2%) or syncope (0.7%) compared to the shock arm. There was no difference in mortality between the two groups. Many other studies including EnTrust[63] , PREPARE[64], and ADVANCE-D[62], enrolled patients with primary and secondary prevention ICD indications and demonstrated efficacy and safety of ATP for FVT (CL < 320 ms). With increasing evidence supporting the efficacy of ATP for FVT, ICDs were increasingly viewed as primarily ATP devices with an occasional need for backup defibrillation.
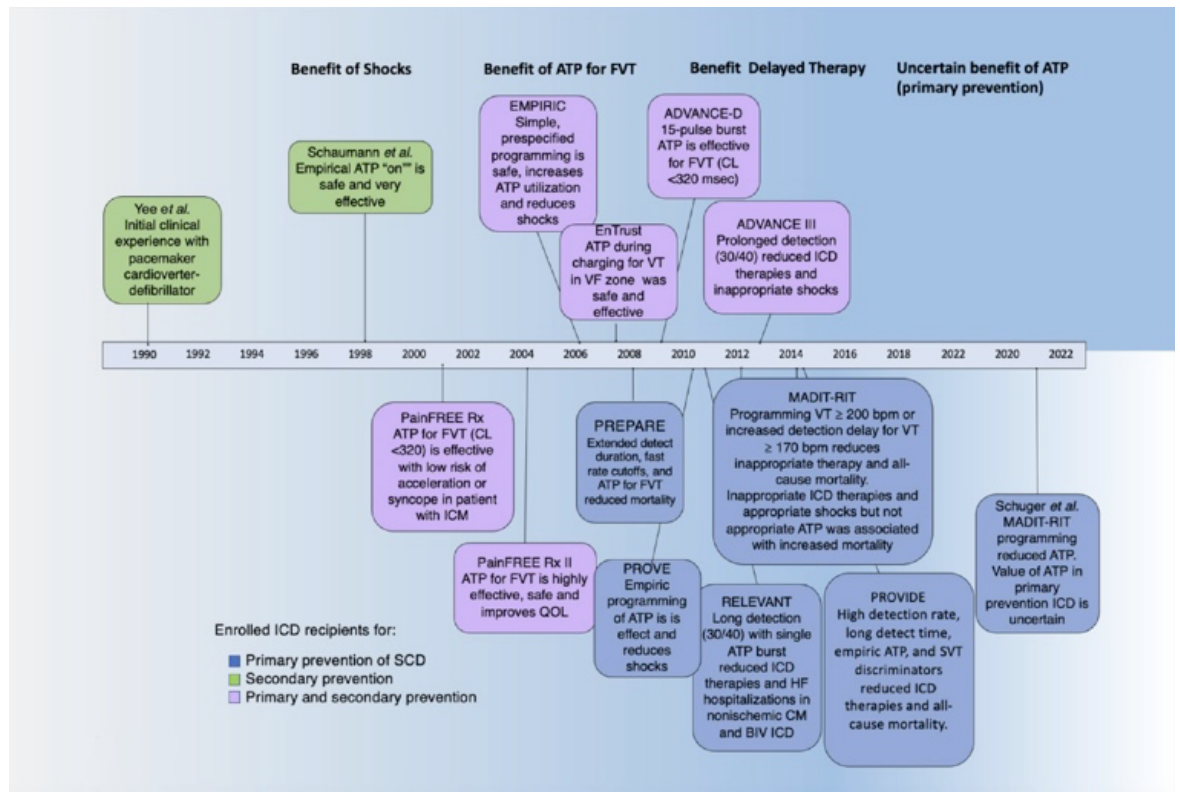
Figure 5. Timeline of major relevant ICD clinical trials. Trials enrolling patients for primary and secondary prevention are shown in blue and green, respectively. Trials that enrolled both types of patients are shown in purple.

9. Empiric Programming of ATP

Patient-specific outcomes that included mortality had long been held to be best when physicians customized ICD and ATP therapy programming, but with increasing data supporting ATP effectiveness for FVT, several studies tested the value of empiric ATP programming. Early studies in patients with ICD for secondary prevention demonstrated the value of non-invasive electrophysiology testing (EPS) to predict the success of ATP for spontaneous VT; yet, these studies also showed that empiric programming of ATP 'on' was safe and very

effective in patients without EPS and those without inducible VT during EPS[47]. Later, in a cohort of patients with primary and secondary indications for ICD, the EMPIRIC study[16] showed that a strategy of simplified, pre-specified ICD programming increased the proportion of VT episodes treated with ATP and reduced ICD shocks without compromise in safety as compared with physician-tailored programming even though VT detection and therapies were enable for slower VT (> 150 bpm) in the empiric group as compared with 171 bpm in the tailored arm. While EMPIRIC enrolled patients with primary and secondary ICD indications, the PROVE trial[65] demonstrated the value of empirically programing of ATP "on" in patients with primary prevention ICD. Finally, as the ICD technology advanced, features that allowed for ATP during charging were developed. The EnTrust study demonstrated its value in reducing shocks for FVT without delaying shock therapy if ATP failed to terminate or accelerate VT[63]. Without obvious disadvantages, empiric programming of ATP during ICD charge quickly became the clinical standard in patients with primary and secondary indications of ICD.

10. Role of Delayed ICD Therapies

Early studies showed that the energy and efficacy of defibrillation depended on the duration of VF[61], and this influenced early implementation of ICD therapy. The maxim was rapid detection and early shock treatment. However, as ICD technology advanced to incorporate stored electrograms and ICD use was expanded to a larger primary prevention population, the frequency of inappropriate ICD shocks and their impact on mortality was increasingly

recognized[10,12,13,66,] . At the same time, there was increasing data supporting the benefit of ATP for FVT and this increased physician confidence that delaying therapies was not harmful. In the PainFREE II study 34% of FVT spontaneous terminated during ICD charging (~ 3.3 s) and prior to shock therapy without higher incidence of syncope supporting the notion that many ICD therapies are unnecessary if initiated prematurely[67]. It is now known that delaying ICD therapy, particularly in patients with primary prevention ICD indications, reduces inappropriate ICD therapies without effecting mortality[65,68,69,70,71.] MADIT-RIT[69] compared 3 different treatment strategies: 'conventional therapy' (2.5-s delay for VT between 170 and 199 bpm and a 1-s delay for VT / VF <200 bpm) versus 'high rate' therapy (2.5-s delay for VT / VF <200 bpm) versus 'delayed' therapy (a 60-s delay for VT between 170 and 199 bpm, a 12-s delay for VT between 200 and 249 bpm and a 2.5-s delay for VF <250 bpm). In all schemes, ATP was programmed to precede shock therapy. Both high-rate programming and delayed programming significantly reduced inappropriate therapy compared to conventional programming. Although appropriate ICD shock therapy was not different between groups, there was a significant reduction in all-cause mortality with high-rate programming without a difference in syncope. Finally, appropriate, and inappropriate ATP was significantly reduced with high-rate and delayed programming and this reduction was greater than the reduction in inappropriate ICD shocks suggesting that even inappropriate ATP has a mortality effect. Like MADIT-RIT, the PROVIDE[65] and RELEVANT[71] studies showed a similar benefit of delayed therapy in patients with primary prevention ICD, while ADVANCE III[70] showed a benefit

in patients with both primary and secondary indications of ICD. These studies highlight the fact that many VTs self-terminate and that many shocks and ATP therapies, whether appropriate or inappropriate, may be avoidable.

Randomized controlled trials have consistently shown a 2–threefold higher risk of appropriate ICD shock than sudden cardiac death in control groups[72,73] suggesting that more than half of VT/VF episodes would spontaneously terminate if untreated and that ICD therapy is not a surrogate for sudden cardiac death. One of the best predictors of successful ATP is a history of NSVT61, suggesting that nonsustained FVT episodes were certain to terminate regardless of treatment. In studies that used a longer detection time (18 of 24 intervals compared to 12 of 16 intervals), NSVT was no longer predictive of ATP success[67], as presumably delayed detection allowed VT episodes destined to spontaneously terminate to stop prior to the ATP attempt. Furthermore, the relative value of ATP may depend on the substrate for VT. Studies have shown a substantial difference in the frequency, rate, and mechanism of VT in ICD recipients implanted for primary versus secondary prevention indications[74]. The cumulative incidence of VT/VF in secondary prevention patients is twice that in primary prevention patient, and importantly, VT/VF episodes are significantly more likely to spontaneously terminate within 8–12 s in primary prevention patients. A recent secondary analysis of the MADIT-RIT study questioned the value of appropriate ATP for FVT in a primary prevention cohort. MADIT-RIT demonstrated the value of a high detection rate cutoff and delayed programming to reduce inappropriate ICD therapy (ATP and shocks)[69] . The reduction in ICD therapy was largely driven by the reduction in ATP therapy (78%). A secondary

analysis showed that utilization and efficacy of ATP significantly decreased with increasing delay of therapy[75] . ATP utilization decreased from 18 to 5% and 2% when therapy was delayed 2.5 and 12 s as compared with conventional programming. Furthermore, the efficacy of ATP decreased from 76 to 67% and 58% for extended delays of 2.5 s and 12 s, respectively. Thus, in patients with ICD for primary prevention, the benefit of ATP for treating FVT may be falsely elevated if ATP is prematurely initiated for FVT that is predestined to terminate. In a comprehensive review paper of primary prevention programming, therapeutic equivalents of PREPARE-style programming have been applied across other manufacturers to allow consistent application of evidence-based strategies across the different vendors for primary prevention ICD recipients (Table 1)[76].

While inappropriate ATP therapy has been associated with increased all-cause mortality[77] , it is unclear what impact 'appropriate' but unnecessary ATP may have. The APPRAISE-ATP study[78] seeks to better understand the value of ATP in a primary prevention cohort. It is an ongoing multicenter trial that randomizes 2600 subjects with ICD for primary prevention to shock-only versus ATP and shock (standard therapy) using modern delayed therapy programming. This study may provide information on the impact of unnecessary ATP and whether ATP may be more beneficial in a particular subgroup of patients.

	Biotronik	Boston Scientific	Medtronic	St. Jude Medical
VF zone	≥ 250 bpm, 24/30 intervals	≥ 250 bpm, 8/10 intervals + 5-second delay	≥ 250 bpm, 30/40 intervals	≥ 250 bpm, 30 intervals
Therapy	ATP burst (8, 90%) then max shocks	Max shocks	ATP burst during charge then max shocks	Max shocks
VT 2 (fast VT)	≥ 222 bpm, 24/30 intervals	≥ 220 bpm, 8/10 intervals + 7-second delay	≥ 182 bpm, 30/40 intervals	≥ 214 bpm, 30 intervals
Therapy	ATP 1 and 2: Burst (8, 90%)	ATP 1 and 2: Burst (8, 88%)	ATP 1 and 2: Burst (8, 88%)	ATP 1 and 2: Burst (8, 88%)
	ATP 3: Scan (−10 ms)	ATP 3: Scan (−10 ms)	ATP 3: Scan (−10 ms)	ATP 3: Scan (−10 ms)
	Max shocks	Max shocks	Max shocks	Max shocks
VT 1	≥ 182 bpm, 26/30 intervals	≥ 185 bpm, 8/10 intervals + 7 seconds	≥ 167 bpm, 32 intervals	≥ 181 bpm, 30 intervals
Therapy	ATP 1 and 2: Burst (8,90%)	ATP 1 and 2: Burst (8,90%)	Monitor only	ATP 1 and 2: Burst (8,90%)
	ATP 3: Scan (−10 ms)	ATP 3: Scan (−10 ms)		ATP 3: Scan (−10 ms)

Table1. Simplified adaptation of shock avoidance programming for primary prevention patients across device manufacturers. ATP: antitachycardia pacing; VF: ventricular fibrillation; VT: ventricular tachycardia.

11.1 Aim of the study

We aim to demonstrate whether in primary prevention, ATP therapy has similar efficacy in patients with ischemic and non-ischemic cardiomyopathy. We identified a subgroup of patients with 'high response' in whom ATP was effective in treating at least three arrhythmic episodes six months apart. We then compared this group with patients in whom ATP was not always effective. ATP was rated effective if it resolved the arrhythmia and ineffective when a shock was needed.

11. 2 Methods

Study Patients

The current analysis saw the selection of consecutive patients who had undergone ICD implantation from January 2000 to May 2021 in our cardiology department's Electrophysiology and Cardiac Pacing Unit, who had an ATP-treated arrhythmic episode during follow-up. Patients of either sex who were

more than 18 years of age (there was no upper age limit) with clinical heart failure and a left ventricular ejection fraction equal to or below 35% despite optimal medical therapy were included. The New York Heart Association (NYHA) functional classes II or III represented inclusion criteria for ICD recipients. Patients with conventional pacemakers and CRT-P were excluded. Exclusion criteria were defined as follows: patients on the urgent waiting list for a heart transplant, uncorrected congenital heart disease, obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, patients positive for human immunodeficiency virus (HIV) with an expected survival of less than 3 years due to HIV, recent history of alcohol or illicit drug abuse disorder (within 3 months), lack of informed consent, age less than 18 years, and severe depression or other major psychiatric illness. Patients were divided into 2 groups: patients with ischemic cardiomyopathy and patients with nonischemic cardiomyopathy. For the ICMP group, patients with a history of previous myocardial infarction documented by the finding of an abnormal Q wave on electrocardiography, elevated cardiac enzyme levels on laboratory tests during hospitalization for acute coronary syndrome, localized akinesia on echocardiography, with evidence of obstructive coronary disease on angiography, and an ejection fraction of 35% or less within three months before entry, as evaluated by echocardiography, were included. In patients with nonischemic systolic heart failure with LVEF 35%, the exclusion of myocardial ischemia was performed by coronary angiography (the majority of patients) and computed tomography. All patients were primarily in functional class II, III, or ambulatory class IV NYHA. Patients with ICD therapy indication, NYHA class

II or III, and a native QRS complex greater than or equal to 130 milliseconds were implanted with a CRT-D. All arrhythmic events that resulted in therapy were included in this analysis. The diagnosis of TV and FV was evaluated by interventional cardiologists with great experience in electrophysiology and cardiac pacing, guidance was provided on utilizing wave morphology and stability of the tachycardia cycle length as ways to distinguish between the two.

ICD Therapy

ICD therapy was selected to consist of ATP therapies and shocks. Single and dual chamber ICDs and biventricular devices were implanted. The goal was to treat only rapid and sustained ventricular tachycardia or ventricular fibrillation, and to minimize excessive interventions, so the devices were uniformly programmed according to the MADIT-RIT delayed therapy arm (170–199 bmp with 60 s delay; 200–249 bmp with 12 s delay; >=250 bpm with 2.5 s delay) and the ADVANCE III trial, with longer delay, 30 of 40 instead of the conventional 18 of 24. A 'monitor only' ventricular tachycardia detection interval was established at 150 bpm for all patients[69,70]. Due to the potential of pacing to worsen congestive heart failure, the minimal pacing rate was set at 40 beats per minute. Rate-responsive pacing was allowed only in patients with chronotropic incompetence[79,80,81].

In general, two or three therapy zones (mainly one VT zone, one VF zone, and possibly an additional fast VT (FVT) zone) were programmed. VT was treated primarily with ATP and possibly consecutive ICD shocks. VF was primarily treated with ICD shock with ATP during charging. Over time, changes in

programming routines have occurred, consisting of further prolongation of the tachycardia duration criteria or an increase of cutoff rates in detection zones, to avoid repetitive inappropriate shocks. Appropriate therapy was defined as shock or ATP for real VT or VF following analysis of the intracardiac electrograms.

Drug Therapy and Follow-up

Follow-up was performed 1 month after discharge and then every six months. The visits consisted of clinical and paraclinical examinations, including interrogation of the devices. Clinical surveillance involved monitoring of patients and anticipated visits in case of worsening of clinical status and occurrence of symptoms, including internal electrical shocks. The medication and, where necessary, the reprogramming of the device were adapted. The patients received optimal chronic medical therapy, including new drug therapy for heart failure (Angiotensin receptor-Neprilysin inhibitor, sodium-glucose cotransporter-2 inhibitors).

11.3 Statistical analysis

Categorical variables are expressed as numbers and percentages, while continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Student's t-test was used for comparison of continuous data and analysis of variance, and chi-squared test was used for comparison of categorical data. A P-value <0.05 was considered statistically significant. Cox regression analysis was used to identify predictors

of ATP efficacy. All statistics were performed with SPSS 20 (IBM, Armonk, NY).

11.4 Results

Baseline characteristics, with ischemic and non-ischemic cardiomyopathy are presented in Table 2. A total of 712 patients, with a median follow-up time of 62 months, were divided into two groups: 328 patients in the NICMP group and 384 patients in the ICMP group. The majority of patients are male (89,8% in ICMP and 76,5 % in NICMP, p: 0,112). The median age of the study population was 60 years $\pm$ 11. The 39% of the patients in NICMP group (128 patients) and 18,2 % (70 patients) in the ICMP group received CRT-D (p < 0,002). There are no other significant differences in baseline characteristics between the two groups.

Characteristics	ICMP Group	NICMP Group	p-value
Median Age – Years	63 ± 10	58 ± 12	0,006
Male Sex, N (%)	345 (89, 8%)	251 (76,5 %)	0,112
Single-Chamber ICD	156 (40,6%)	102 (31,1 %)	0,008
Single – Chamber Vdx- ICD	19 (4,9 %)	10 (3%)	0,201
Dual-Chamber ICD	139 (36,2 %)	88 (26,8 %)	0,007
Biventricular - ICD	70 (18,2 %)	128 (39 %)	0,002
Biotronik device	87 (22, 7%)	59 (18%)	0,124
Boston device	100 (26 %)	118 (36 %)	0,004
Medtronic device	124 (32, 3%)	91 (27,7 %)	0,188
Sorin device	32 (8,1 %)	18 (5,5%)	0,174
St – Jude device	42 (10,9%)	42 (12,8%)	0,441

Table 2. Baseline characteristic of patients. ICD: implantable cardioverter-defibrillator. ICMP: ischemic cardiomyopathy; NICMP: non-ischemic cardiomyopathy.

Table 3 shows the incidence of arrhythmic events, ATP, and shock intervention. The frequency of VT (93,7 % in the ICMP group and 94,3 % in the NICMP group) and VF (6,3 % in the ICMP group and 5,7 % in the in the NICMP group) is similar between the two groups. ATP was involved in treatment most frequently in the ICMP group (61,3 % in ICMP group vs 56,8 % in NICMP group).

ATP effectively treated 1418 (54,4 %) arrythmias in the ICMP group and 1004 (49,9 %) in the NICMP group (p 0,002).

There were no significant differences in the number of shocks delivered between the two groups (17, 9 % in the ICMP group versus 15,8 % in the NICMP group).

	ICMP Group	NICMP Group	p-value
VT	2443 (93,7%)	1898 (94,3%)	0,376
VF	164 (6,3 %)	114 (5,7 %)	0,411
ATP intervention	1598 (61,3 %)	1143 (56, 8 %)	0,002
ATP efficacy	1418 (54, 4%)	1004 (49,9%)	0,002
Shock intervention	466 (17,9 %)	318 (15,8 %)	0,063

Table 3. Difference in arrhythmic events and treatment between ICMP (ischemic cardiomyopathy) AND NICMP (non-ischemic cardiomyopathy). VT: ventricular tachycardia; VF: ventricular fibrillation; ATP: Anti-tachycardia pacing.

Therefore, we compared the characteristics of high response patients with that group of patients in whom ATP had not always been effective at follow-up. There were no between-groups differences with regards to several baseline patient's' characteristic, including cardiomyopathy etiology (Table 4).

	High-response patients	Not High-response patients	p-value
MEDIAN AGE – YEARS	59 ± 12	62 ± 12	0,252
MALE SEX, N (%)	37 (84,1 %)	109 (86,5%)	0,692
SINGLE-CHAMBER Icd	20 (45,5 %)	56 (44,4 %)	0,908
SINGLE – CHAMBER VDX-ICD	1 (2,3 %)	7 (5,6 %)	0,376
DUAL- CHAMBER ICD	17 (38, 6 %)	31 (24,6 %)	0,075
BIVENTRICULAR - ICD	6 (13,6%)	32 (25,4 %)	0,107
ICMP GROUP	22 (50 %)	72 (57,1 %)	0,412
NICMP GROUP	22 (50 %)	54 (42,9 %)	0,519

Table 4. Difference between ATP (Anti-tachycardia pacing) group always efficacy and ATP group non always efficacy. ICD: implantable cardioverter-defibrillator; ICMP: ischemic cardiomyopathy; NICMP: nonischemic cardiomyopathy.

11.5 Discussion

The role of ICD is well established as a lifesaving intervention in patients with ICM and NICM cardiomyopathy, primarily by aborting ventricular arrhythmias

including monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, and ventricular fibrillation. Since the use of ATP was first described in 1987 to successfully terminate MVT in 22 patients predominantly with ischemic heart disease by Lindsay and colleagues[82], the use of ATP has become a mainstay of transvenous ICD therapy without requiring shocks. Subsequent larger studies have demonstrated the efficacy of ATP to terminate MVT, such as the PainFree RX study, which found that ATP was successful even in fast MVT episodes up to 250 bpm in patients with coronary artery disease[61]. The early ATP studies assessed the efficacy of ATP primarily in patients with ischemic coronary disease. There was a perception that scar-based reentrant VT is more susceptible to ATP and more common in ICM. In contrast, the substrate in NICM was previously not as well defined, and it was unknown whether scar-based MVT may be less common in NICM and whether VT in NICM may be as easily terminated with ATP. In our study we found that patients with NICM experienced VT/VF at similar rates and proportions compared to ICMP. ATP was slightly more effective in terminating VT in patients with ICM vs. NICM (54,4% vs 49,9%). Additionally, in patients with high response, ATP maintains its efficacy at follow-up regardless of the etiology of cardiomyopathy.

These results support the hypothesis that ATP is also effective in patients with NICM compared to ICM, and that the prevalence of VT is similar in the two populations. Although the study does not specifically investigate the mechanisms underlying VT in patients with NICM, these results do suggest that there may be some similarities in the behavior of VT in NICM compared to ICM.

In fact, an attempt to explain these results may shed some light on the substrate and potential mechanisms underlying VA in patients with NICM.

Although the mechanisms of ventricular tachycardia include autonomic, triggered, and reentry, scar-based reentrant VT is the most common and is due to underlying structural abnormalities that create a slowly conducting critical isthmus. One possible explanation why ATP works in patients with NICM is that these patients also frequently have scar substrate. As advanced cardiac imaging and invasive electroanatomic mapping technologies have enabled visualization of the underlying VT substrate at higher resolution, we have learned that myocardial fibrosis is present in many types of dilated, familial, and idiopathic nonischemic cardiomyopathies. In contrast to ischemic cardiomyopathy where fibrosis is located endocardial, fibrosis is often located in the mid-myocardial or epicardial layers in NICM[83]. Furthermore, in many non-ischemic cardiomyopathies, fibrosis can be seen located in characteristic regions, such as the perimitral or aortic annuli[84]. In a meta-analysis of 2850 patients with NICM, late gadolinium enhancement (LGE) on magnetic resonance imaging was a predictor of VA[85], and the size of the LGE region was also correlated with the inducibility of VT in a recently published study by Ghannam et al.[86].

Our study does not address whether the efficacy of ATP translates into difficult outcomes such as mortality benefit, prevention of inappropriate shocks, and risks of proarrhythmia. The Boston Scientific S-ICD PRAETORIAN and UNTOUCHED[87] studies showed that implantation of the S-ICD resulted in no difference in mortality or inappropriate shocks compared to transvenous ICDs,

suggesting that the ability to provide ATP may not be critical. On the other hand, ATP provides potential for shock reduction, improved quality of life, and indirect mortality benefit[13]. The results of this study support the fact that, to reduce ICD shocks, ATP may be useful in some patients with NICM.

11.6 Limitations

Limitations exist in this analysis. First, this was a retrospective analysis. Second, while baseline medications are available, we do not have information on how the use of medications, including antiarrhythmics, changed over time. Third, our analysis focused on primary prevention ICD recipients with cardiomyopathy. The MVT characteristics and response to ATP observed here may differ in secondary prevention patients or those with high risk inherited or acquired conditions such as hypertrophic cardiomyopathy, cardiac sarcoid, or ion channelopathies.

11.7 Conclusion

The present study shows that in primary prevention the efficacy rate of ATP in the treatment of arrhythmias is slightly higher in patients with ischemic cardiomyopathy, but in high-response patients the efficacy of ATP is maintained over time regardless of cardiomyopathy. Ultimately the choice between ATP-capable ICDs compared to SICD should not become a polarized debate between device manufacturers but be a decision based on patient characteristics. The decision to implant an ATP-capable ICD for a patient with cardiomyopathy should not solely be based on whether the patient has NICM versus ICM. Rather,

the decision to select an ICD with ATP capability should take into consideration the potential mechanisms of VA in each patient and other patient factors such as susceptibility to bloodstream infections. Finally, characterization of the extent of scar may also be useful in determining a patient's risk of scar-based VT to help tailor ATP programming.

12. Reference

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