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ICD Algorithms in the management of arrhythmias : Pitfalls and advancements

Antonio Frontera

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THÈSE PRÉSENTÉE POUR OBTENIR LE GRADE DE
DOCTEUR DE L'UNIVERSITÉ DE BORDEAUX
SCIENCES DE LA VIE ET DE LA SANTÉ
BIOLOGIE CELLULAIRE ET PHYSIOPATHOLOGIE

Par Antonio Frontera
Né le 30 Juillet 1981 à Catanzaro, Italie

**Pacemaker and defibrillator algorithms in the management
of arrhythmias. Pitfalls and advancements.**

Soutenue le 5 Décembre 2019

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Table of Contents

<i>List of abbreviations</i>	5
<i>List of scientific publications related to the thesis</i>	6
<i>List of oral presentation, posters related to the thesis</i>	8
<i>Acknowledgements</i>	9
<i>Résumé</i>	10
Introduction	12
Objective of the research	15
<i>Pacemaker undersensing leading to malignant arrhythmia</i>	16
<i>Performance of a Specific Algorithm to Minimize Right Ventricular Pacing: A Multicenter Study</i>	19
<i>Pacemaker-mediated tachycardia in a real word setup: A clinical study based to study the accuracy of specific algorithm</i>	44
<i>Complications and consequences of inappropriate therapies shocks in a pediatric population suffering from idiopathic ventricular fibrillation.</i>	54
<i>Performance of algorithm in a real-world setup to prevent inappropriate ICD therapies (due to oversensing)</i>	67

*Performance of morphology discrimination algorithm in current defibrillators.
A clinical study based on 3 different companies 88*

Synthèse / Future perspectives 121

Conclusions 126

List of abbreviations

AUC	Area under the curve
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
CMR	Cardiac magnetic resonance
CRT	Cardiac Resynchronization Therapy
FF	Far field
ICD	Implantable Cardioverter device
ICM	Ischaemic cardiomyopathy
EGM	Electrogram
HCM	Hypertrophic Cardiomyopathy
IVF	Idiopathic Ventricular Fibrillation
PMT	Pacemaker Mediated Tachycardia
NF	Near field
NICM	Non-Ischaemic Cardiomyopathy
RV	Right Ventricle
LV	Left Ventricle
ROC	Receiver Operator Characteristic Curve
SCD	Sudden Cardiac Death
SVT	Supraventricular Tachycardia
VA	Ventricular – Atrial
VT	Ventricular Tachycardia
VF	Ventricular Fibrillation

Manuscripts published

Transient under-sensing of the ventricular lead during abdominal ultrasound as cause of ventricular fibrillation.

Frontera A, Klotz N, Martin R, Haïssaguerre M, Ritter P, Bordachar P.

Pacing Clin Electrophysiology 2018 May 7. doi: 10.1111/pace.13362

Performance of a specific algorithm to minimize right ventricular pacing: A multicenter study.

Strik M, Defaye P, Eschalier R, Mondoly P, Frontera A, Ritter P, Haïssaguerre M, Ploux S, Ellenbogen KA, Bordachar P.

Heart Rhythm. 2016 Jun;13(6):1266-73.

Accuracy of the pacemaker-mediated tachycardia algorithm in Boston Scientific devices.

Strik M, Frontera A, Eschalier R, Defaye P, Mondoly P, Ritter P, Haïssaguerre M, Ploux S, Bordachar P.

J Electrocardiol. 2016 Jul-Aug;49(4):522-9.

Long-Term Follow-Up of Idiopathic Ventricular Fibrillation in a Pediatric Population: Clinical Characteristics, Management, and Complications.

Frontera A, Vlachos K, Kitamura T, Mahida S, Pillois X, Fahy G, Marquie C, Cappato R, Stuart G, Defaye P, Kaski JP, Ector J, Maltret A, Scanu P, Pasquie JL, Deisenhofer I, Blankoff I, Scherr D, Manninger M, Aizawa Y, Koutbi L, Denis A, Pambrun T, Ritter P, Sacher F, Hocini M, Maury P, Jaïs P, Bordachar P, Haïssaguerre M, Derval N.

J Am Heart Assoc. 2019 May 7;8(9):e011172

Multicenter investigation of an implantable cardioverter-defibrillator algorithm to detect oversensing.

Welte N, Strik M, Eschalier R, Mondoly P, Defaye P, Frontera A, Ritter P, Haïssaguerre M, Ploux S, Koneru J, Ellenbogen KA, Bordachar P.
Heart Rhythm. 2017 Jul;14(7):1008-1015.

Real-life assessment of morphology-based algorithms for arrhythmias discrimination by ICDs: a multicenter study.

Frontera A, Strik M, Eschalier R, Biffi M, Pereira B, Welte N, Chauvel R, Mondoly P, Laborderie J, Bernis J, Clementy N, Reuter S; Garrigue S, Deplagne A, Vernooy K, Pillois X, Haïssaguerre M, Dubois R, Ritter P, Bordachar P, Ploux S.

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List of oral presentations, posters related to the thesis

Poster presentations - Heart Rhythm Society San Francisco May 2016:

Accuracy of the pacemaker-mediated tachycardia algorithm in Boston Scientific devices.

Oral presentation at Heart Rhythm Society Boston May 2018:

Real-life assessment of morphology-based algorithms for arrhythmias discrimination by ICDs: a multicenter study.

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Algorithmes de Pacemaker et Défibrillateurs pour traitement d'arythmies. Désavantages et optimisation de programmation.

L'objectif de ma recherche était d'étudier les méthodes de fonctionnement des dispositifs cliniques, tels que les DAI et la PM, pour détecter les arythmies les plus communes rencontrées dans la pratique clinique. Récemment, des algorithmes spécifiques de discrimination sont implémentés dans les dispositifs actuels. Les pièges de la prise en charge des patients souffrant d'arythmie ne sont pas rares. Fréquemment, il s'agit d'erreurs de détection et de discrimination susceptibles de favoriser ou empirer l'arythmie ou de déterminer des thérapies inappropriées tels que des chocs. En fait, la discrimination incorrecte des arythmies malignes pourrait avoir un impact significatif sur la morbidité et la mortalité. La meilleure gestion des arythmies devrait envisager des améliorations des algorithmes actuels des DAI propriétaires implantés dans la pratique clinique.

Keywords: Algorithme; Defibrillateur; Pacemaker, Trouble du rythme, complications; tachycardie ventriculaire; fibrillation ventriculaire.

ICD Algorithms in the management of arrhythmias. Pitfalls and advancements

The objective of my research was to investigate the manner in which clinical devices, such as ICDs and PMs, detect the most common arrhythmias encountered in clinical practice. Nowadays, specific algorithms of discrimination are implemented in current devices. The pitfalls in the management of patients with arrhythmias are not uncommon; most often these include errors in detection and discrimination which may promote and/or perpetuate the arrhythmia or determine inappropriate therapies such as shocks. In fact, the incorrect discrimination of malignant arrhythmias could have a significant impact on morbidity and mortality. The best management of arrhythmias should consider improvements of current algorithms of proprietary based ICDs implanted in the clinical practice.

Keywords: Algorithms; defibrillator; pacemaker, complications; ventricular tachycardia; ventricular fibrillation.

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INTRODUCTION

In the last three decades the electrophysiology world changed with the advent of technologies as pacemakers, implantable defibrillators (ICDs) and catheter ablation. This has lead, over the time, to a significant change into the management and treatment of arrhythmias.

Pacemakers have been conceived to “pace” the heart when needed, for example when an heart block is diagnosed. Pacemakers are considered life-saver and are widely used for the treatment of brady arrhythmias. However, even if rarely, these could be pro-arrhythmic(1)(2)(3). One of the potential pitfalls is represented by transient or permanent under-sensing event, with a paced stimuli that could fall into a vulnerable period of repolarization and so may promote ventricular arrhythmias.

Pacemakers can also be responsible for initiating tachycardia. These are called pacemaker-mediated tachycardia (PMT) which are defined as re-entrant rhythm, with one limb of the re-entrant loop being the patient’s retrograde conduction, and the other the pacemaker(4). This phenomenon has been observed early after the introduction of dual-chamber pacing in patients having an intrinsic ventriculo-atrial (VA) conduction(5). When PMT occurs this could lead to symptoms ranging from palpitations, light-headness to syncope and chest discomfort. Prolonged PMT may be poorly tolerated or even lead to cardiac decompensation in patients suffering from underlying heart disease(4). The incidence of PMT varies as a function of patient characteristics, programming of the device and the specificities of the algorithms provided by the manufacturers. Few data is available on the

incidence of PMT across pacemaker and defibrillator recipients. Depending on the manufacturer, one must understand the specific means of prevention, diagnosis and termination of PMT in order to optimize the management of device recipients. Each device manufacturer has a proprietary algorithm to detect and terminate PMT, with a large proportion of similarities, including the phases of suspicion, confirmation and termination.

ICDs are indeed the cornerstone of current treatment of malignant arrhythmias and in the prevention of sudden death. They became commercially available in the early '90s and their benefit in survival curves was confirmed by prospective trials like the AVID(6), the CASH(7), which compared ICD therapy with antiarrhythmic drug therapy, predominantly with amiodarone, in those patients survivors of life threatening ventricular arrhythmias. Lee et colleagues (8) in their meta-analysis (of these studies) showed a 25% reduction in all cause mortality, entirely attributable to a 50% reduction of sudden cardiac death. Another meta-analysis(9) showed that the effect was primarily limited to those patients with left ventricular ejection fraction (LVEF) <35%. ICDs must comply with correct detection of malignant rhythms such as ventricular tachycardia (VT). In order to fulfill this task, modern ICDs are now equipped with processing speeds capable of running specific algorithms for a faster and more reliable discrimination of arrhythmias. In fact, one of the crucial points of the clinical treatment and subsequent management of arrhythmias is the correct detection of supraventricular and ventricular rhythms.

Rate and rate derived measurements (based on cycle-by-cycle interval measurements) include average/median cycle length, rapid deviation in

cycle length (onset), minimal deviation of cycle length (stability). A third algorithm, morphology discrimination, has been implemented in the detection process in order to withhold VT therapy delivery on sinus tachycardia and supraventricular rhythms. Current guidelines suggest the use of morphology-based algorithms, recommended as first-line and stand-alone discriminator for single chamber ICDs(10).

Current research of manufacturers producing implantable defibrillators is to increase the accuracy of discrimination of arrhythmias: differentiating benign from malignant tachycardias is still crucial and difficult to perform. Inappropriate electrical therapy has been reported during documented periods of sinus rhythm, sinus tachycardia, and supraventricular tachycardias including atrial flutter and atrial fibrillation(11). Inappropriate therapy (shocks) due to misclassification of (SVT) as (VT) is the most reported complication. These inappropriate shocks reduce quality of life, endanger patients and, moreover, influence mortality(12). Therefore ameliorating existing VT discrimination algorithms can lead to improved ICD function and targeted appropriate therapy.

In terms of pitfalls, the automatic detection in the ICDs could fall in the double counting and delivery of inappropriate shocks due to T wave oversensing(13). Even if this occurs in less than 4% of transvenous ICD patients, this is usually related to any of these situations: 1) small R waves (ventricular arrhythmogenic cardiomyopathy, new-onset right bundle branch block, fall of the RV signal amplitude due to changes in the lead-tissue interface, use of anti-arrhythmic drugs) 2) tall or delayed T waves (hypertrophic cardiomyopathy, long QT, post-paced T waves in CRT-D, electrolytes imbalance). It is usually managed by delaying the increase of ventricular

sensitivity towards its maximum value (Abbott and Biotronik devices), or by detecting the T wave with a dedicated algorithm (Medtronic).

In the setting of inappropriate shocks, a population which request a special consideration is the pediatric because represented by a constantly growing patients. Although these patients represent a small minority of ICD recipients, they may experience inappropriate shocks which are not only due to supraventricular arrhythmias but also due to lead fracture or dislodgement(14)(15)(16).

Inappropriate shocks represent a current issue in the treatment and management of arrhythmias. When delivered inappropriately to patients in the awake state, only a few shocks are enough to induce lasting psychological distress(17). Furthermore shocks can be arrhythmogenic(18).

Objective of the research

My research sought to evaluate the performance of proprietary algorithms of pacemakers and defibrillators in a real world setup by remote monitoring follow-up. The aim was to assess the diagnostic and therapeutic efficacy of the algorithms, to highlight pitfalls, and to investigate whether these algorithms could be optimized for improved performance.

Pacemaker under-sensing leading to malignant arrhythmia

Pacemakers are implanted worldwide in patients with complete heart block or extreme bradycardia. Despite life saving benefits, devices can, rarely, cause potentially lethal arrhythmias. In correctly functioning pacing systems, in the absence of reversible phenomena as electrolyte disorders or acute ischemia, the incidence is very low. During these years, we have encountered a case of an 81 year old man who was referred to our department after an episode of sudden cardiac arrest due to ventricular fibrillation (VF). This case encouraged me to start research on device function, and algorithms implemented in both brady and tachycardia rhythms.

Description. We present the case of an 81-year-old man who was referred to our department after an episode of sudden cardiac arrest due to ventricular fibrillation (VF). The ECG on admission demonstrated atrial fibrillation with occasional appropriate VVI pacing. He had presented earlier that day to a nearby hospital with epigastric pain. During abdominal ultrasound on the epigastric area, with deep inspiration, he suffered a sudden cardiac arrest. After immediate cardiopulmonary resuscitation, he was cardioverted from VF with a single DC shock after 7 minutes. He was transferred to our center. The serum troponin was elevated at 33ng/ml. Emergency coronary angiography and transthoracic echocardiography were unremarkable. He had a Boston Scientific Accolade MRI pacemaker with a 58 cm active-fix lead (Medtronic 5054), implanted 11 years previously for atrial fibrillation with a slow ventricular response. On interrogation of the pacemaker, lead parameters were within normal ranges. On examination of the memorized EGMs, we identified three episodes immediately before the onset of VF where a normal QRS had been undersensed and followed by stimulation. In the first episode, the coupling interval of the paced beat was 320ms, without sequelae. In the second episode, the coupling interval was 300ms, followed by non-sustained ventricular tachycardia (VT). In the third episode, the coupling interval was 200ms, initiating VF (Figure 1). A chest X-ray showed the course of the RV lead to follow the inferior floor of the right ventricle. At the time of ventricular lead replacement, in our laboratory, we could have demonstrated deep inspiration as cause of repetitive under-sensing of ventricular events. Furthermore, once extracted nothing was noted on the extravascular portion of the ventricular lead to explain intermittent loss of sensing. We speculated that deep inspiration during abdominal ultrasound may have caused a temporary micro-dislodgment of the ventricular catheter causing the transitory under-sensing. Pacemaker and algorithm-induced ventricular arrhythmias has been described^{1,2}, but our report describe and point out that a transitory under-sensing of the ventricular lead could occur during an abdominal ultrasound causing a pacemaker-induced fatal arrhythmia.

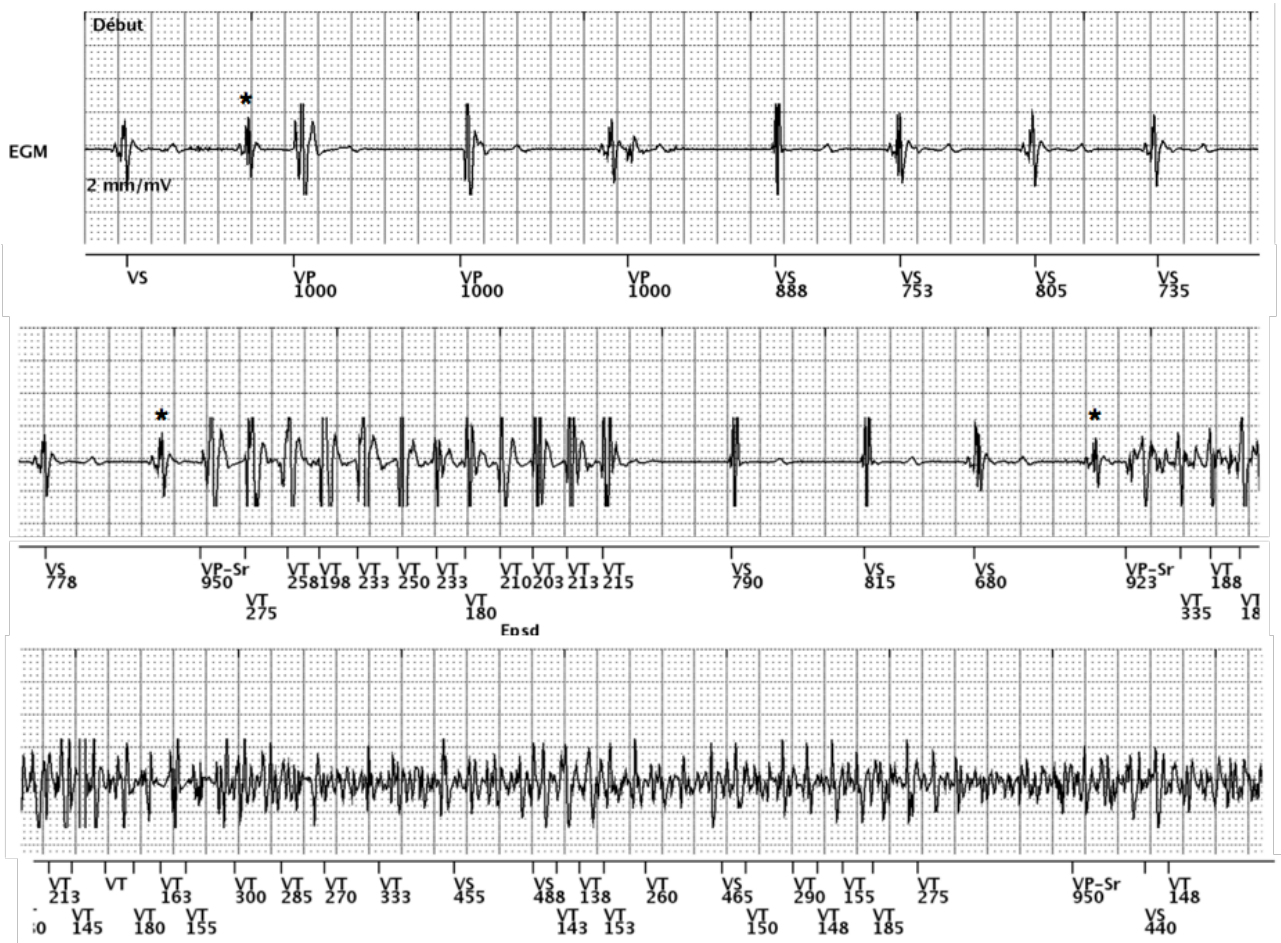


Figure 1. Endocavitary EGMs recording of the transient episode of undersensing which caused initiation of ventricular fibrillation. Under-sensed ventricular EGMs are marked with an asterisk.

References

1. Vogelgesang D1, Vogelgesang S. Pacemaker-induced ventricular Europace. 2008 Jan;10(1):46-7. Epub 2007 Dec 14.
2. Galand V, Behar N, Martins RP. Ventricular fibrillation triggered by mediated tachycardia protection algorithm. Europace 2017 Apr 10.1093/europace/eux028.

Performance of a Specific Algorithm to Minimize Right Ventricular Pacing: A Multicenter Study

1. Study outline

Right ventricular pacing is associated with deterioration of cardiac function and adverse cardiac remodeling (19). Furthermore, clinical trials have shown that long-term right ventricular pacing increases the risk of atrial fibrillation and heart failure(20). In this setting pacemaker manufacturers have developed specific algorithms designed to minimize right ventricular pacing by favoring intrinsic ventricular conduction in non-pacemaker dependent patients. The algorithms differ amongst companies; the one provided by Boston Scientific, RYTHMIQ™ operates in AAI mode with VVI back-up pacing and switches to DDD mode if a loss of atrioventricular conduction is suspected. We evaluated the performance of this algorithm determining 1) the appropriateness of the switch from the AAI(R) with backup VVI pacing to the DDD(R) mode in case of suspected loss of AV conduction and 2) the rate of recorded pacemaker mediated tachycardia (PMT) when AV hysteresis searches for restored AV conduction. In this multicenter study, we included 157 patients with a dual chamber Boston Scientific device (40 pacemakers and 117 ICDs) without permanent AV-conduction disorder and with the RYTHMIQ algorithm activated.

2. Implications

The RYTHMIQ algorithm has some limitations. In the study we documented lot of inappropriate switch and high rate of PMT induction. This may have clinical implications in terms of selection of the patients and suggest improvements in the algorithm architecture.

3. Manuscript

Performance of a Specific Algorithm to Minimize Right Ventricular Pacing: a Multicenter Study.

Short title: Performance of algorithm to minimize pacing

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Abstract

Background

In Boston Scientific dual-chamber devices, the RYTHMIQ™ algorithm aims to minimize right ventricular pacing.

Objective

We evaluated the performance of this algorithm determining 1) the appropriateness of the switch from the AAI(R) with backup VVI pacing to the DDD(R) mode in case of suspected loss of AV conduction and 2) the rate of recorded pacemaker mediated tachycardia (PMT) when AV hysteresis searches for restored AV conduction.

Methods

In this multicenter study, we included 157 patients with a dual chamber Boston Scientific device (40 pacemakers and 117 ICDs) without permanent AV-conduction disorder and with the RYTHMIQ™ algorithm activated. We reviewed the last 10 remote monitoring-transmitted RYTHMIQ™ and PMT episodes.

Results

We analyzed 1266 episodes of switch in 142 patients (90%): 16% were appropriate and corresponded to loss of AV-conduction, 84% were inappropriate of which 66% were related to compensatory pause (PAC 7%, PVC 56% or both 3%) or to a PVC falling in the post-atrial pacing ventricular refractory period interval (21%) and 10% were related to a pacemaker dysfunction. 154 PMT episodes were diagnosed in 27 patients (17%). In 69% of correctly diagnosed episodes, the onset of PMT was directly related to the algorithm related prolongation of the AV-delay promoting AV-dissociation and retrograde conduction.

Conclusion

This study highlights some of the limitations of the RYTHMIQ™ algorithm: high rate of inappropriate switch and high rate of induction of PMT. This may have clinical implications in terms of selection of the patients and may suggest required changes in the algorithm architecture.

KEY WORDS

pacemaker; RYTHMIQ; dual-chamber; right ventricle; ventricular pacing; dyssynchronopathy; AV block; AV conduction; pacemaker algorithm; Boston Scientific

Introduction

Right ventricular pacing is associated with deterioration of cardiac function and adverse cardiac remodeling.^{1,2} Large clinical trials have shown that long-term right ventricular pacing increases the risk of atrial fibrillation and heart failure.³⁻⁵ Subsequently, pacemaker manufacturers have developed specific algorithms designed to minimize right ventricular pacing by favoring intrinsic ventricular conduction in non-pacemaker dependent patients.^{6,7} The decreased pacing burden provided by these algorithms has been shown to reduce the incidence of atrial fibrillation and to increase the anticipated median device longevity.^{8,9} On the other hand, the ANSWER study reports no effects on deaths, syncope or the composite of hospitalization for heart failure, atrial fibrillation, or cardioversion, nor in the individual components.¹⁰ The algorithms provided by each manufacturer vary in design and may be suitable for specific patient subgroups.

The RYTHMIQ™ algorithm, implemented in Boston Scientific dual-chamber pacemakers and implantable cardioverter-defibrillators, operates in AAI mode with VVI back-up pacing and switches to DDD mode if a loss of atrioventricular conduction is suspected. While in DDD mode, the AV Search+™ algorithm is used to search for return of AV conduction with periodic automatic extension of the AV interval. Increasing the AV interval has been associated with the development of pacemaker-mediated tachycardia.¹¹ However, there is currently little published data on the performance of the RYTHMIQ™ algorithm.¹²

In this multicenter study, we evaluated the performance of the RYTHMIQ™ algorithm assessing: 1) the appropriateness of the RYTHMIQ™ events (switch from AAI with backup VVI pacing mode to DDD mode in case of suspected loss of AV conduction) and 2) the rate of recorded pacemaker mediated tachycardia (PMT) when AV Search+™ periodically checks for return of intrinsic conduction.

Methods

Selection of patients

In the present study, only patients with a dual-chamber Boston Scientific pacemaker (ACCOLADE™, VITALIO™ or INGENIO™) or implantable-cardioverter defibrillator (AUTOGEN™ or INCEPTA™) with RYTHMIQ™ algorithm switched ON and followed by remote monitoring were included in this observational French multicenter study. RYTHMIQ algorithm was activated in patients with sinus node dysfunction, brady-tachycardia syndrome, chronotropic incompetence and paroxysmal AV-block. RYTHMIQ was systematically switched OFF in patients with complete AV block and in patients with dual-chamber ICDs with no pacing needs (who were programmed to VVI mode at 40 beats per minute). Patients with permanent atrial fibrillation or complete permanent AV block were

excluded. All patients gave written, informed consent for analysis of the data providing from remote monitoring and patient information was de-identified prior to analysis of the episodes.

Description of the RYTHMIQ™ algorithm

The RYTHMIQ™ algorithm is available for DDD or DDD(R) modes only and requires to be switched on.

Primary Pacing Mode: AAI(R) with VVI Back-up

This algorithm provides AAI(R) pacing with asynchronous VVI back-up pacing. The two modes operate nearly independently from one another but to avoid cross-talk, atrial pacing generates ventricular refractory periods (blanking and noise windows). Ventricular pacing is only delivered when the heart rate falls below 15 (fixed value) beats per minute (bpm) slower than the programmed lower rate limit (LRL) with a minimal value of 30 (for LRL < 45 bpm, the VVI back-up LRL will be 30 bpm) and a maximal value of 60 bpm (for LRL > 75 bpm, the VVI back-up LRL will be 60 bpm).

Switch from AAI(R) to DDD(R) mode

The device switches from AAI(R) to DDD(R) mode when 3 slow ventricular beats are detected in a window of 11 beats. A slow ventricular beat is defined as a ventricular paced (VP) beat (by VVI back-up pacing), a VP due to noise response, a VS–VS interval of at least 150 ms longer than the LRL (interval is slower than the atrial rate but not slow enough to trigger a VP) or a VS–VS interval of at least 150 ms longer than the AAIR sensor indicated rate (interval is slower than the atrial rate but not slow enough to trigger a VP).

AV Search+™

In DDD(R) mode, the algorithm uses the AV Search+™ to periodically check for return of intrinsic conduction. After a certain number of cardiac cycles in DDD mode (default value at

32 cycles), the AV Search Interval is activated and the AV delay is extended to the programmed AV Search+™ value (default value 300 ms). If a V-sense is detected within the 8 cycles period of AV Search+™ (primary phase), hysteresis continues in the secondary phase. The AV Conduction Detector Counter is initialized at “0” and is incremented by each ventricular sensed event (marked as VS-Hy). When the AV Conduction Counter has reached 25, sustained conduction is detected and the device switches back to the primary AAI(R) mode with VVI back-up. The device maintains DDD(R) pacing and does not switch back to the AAI(R) mode when no intrinsic conduction is detected within the first 8 cycles search period (primary phase) or when two out of the last 10 ventricular events are paced (sliding window during secondary phase).

Recording of a RYTHMIQ™ switch episode

The mode switch to DDD(R) is recorded in the Arrhythmia Logbook as a RYTHMIQ™ episode; a 20 second EGM is stored (ten seconds before and ten seconds after the switch to DDD). The number of EGMs available for analysis is limited owing to the low memory allocation priority. The counter for the total number of RYTHMIQ™ switch episodes cannot be reset and indicates the total number of events since device implantation.

Description of the pacemaker-mediated tachycardia termination algorithm

The PMT termination algorithm is applied when 16 consecutive AS-VP cycles occur at the maximum tracking rate and the associated V-A intervals do not vary by more than 32 ms. The post ventricular atrial refractory period (PVARP) is extended to 500 ms for one cycle following the 16th ventricular paced beat aiming to terminate retrograde V-A conduction.

Data analysis

We reviewed up to ten of the most recent remote monitoring-transmitted EGMs of RYTHMIQ™ events and determined the appropriateness of the mode switch. Similarly, we

reviewed up to ten of the last remote monitoring-transmitted EGMs of PMT.

Statistical analysis

Categorical variables are expressed as absolute numbers and percentages and continuous variables were expressed as mean \pm SD. *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

Across four French centers, we screened 923 patients with Boston Scientific devices who were connected to the Boston LatitudeTM system; 644 patients had devices who were equipped with the RYTHMIQTM algorithm. We included 157 patients who had RYTHMIQTM activated. The demographics and device specifications of these patients are shown in Table 1.

Switch to DDD mode

142 patients (90%) demonstrated at least 1 episode of RYTHMIQTM episode. We analyzed 1266 RYTHMIQTM episodes (Table 2) of which 16% were diagnosed as appropriate as they occurred as a result of actual loss of AV conduction (Figure 1). Patients with predominantly appropriate RYTHMIQTM mode switches experienced 28% (0 to 92%) of cumulative RV pacing. The remainder of episodes (84%) were considered as inappropriate. Patients who had predominantly inappropriate episodes experienced 10% (0 to 92%) of cumulative RV pacing (*p* = 0.002 as compared with patients with predominantly appropriate mode switches) with 10 patients who had more than 50% RV stimulation.

1. Two-thirds of inappropriate episodes (66%) were related to compensatory pauses generated by premature atrial contractions (7%), premature ventricular contractions (56%, Figure 2) or both (3%),
2. 21% were related to premature ventricular contractions falling in the post-atrial pacing ventricular refractory period interval (Figure 3) leading to asynchronous ventricular pacing.
3. 10% were related to a paroxysmal lead dysfunction: atrial undersensing (3%), ventricular undersensing (2%), atrial capture failure (2%) and atrial noise oversensing (3%). An example of a mode switch in the context of ventricular undersensing is shown in Figure 4.
4. 4% were related to ventricular events occurring during the post atrial ventricular blanking period after a very long PR interval.

The average time spent in the secondary DDD mode after an inappropriate RYTHMIQ™ event was 4 hours and 48 minutes per episode (median: 1 minute and 3 seconds, minimum 46 seconds and maximum 289 hours).

Pacemaker mediated tachycardia episodes

Twenty seven patients (17%) exhibited at least 1 recorded episode labeled as PMT. We analyzed 154 episodes labeled PMT of which 30 (20%) were misdiagnosed during sinus tachycardia (normal tracking of intrinsic atrial events at the maximal tracking rate). In 85 episodes (69% of true PMT episodes) the onset of PMT (Figure 5) was directly related to the prolongation of the AV delay (AV search+™). Indeed, the last ventricular pacing cycle before the onset of the tachycardia was performed with a prolonged AV delay prompting the occurrence of a retrograde atrial activation. The usual triggers for PMT were observed in the remaining episodes; PVC (20%) and PAC (11%). The analysis of the labelled PMT episodes

incidentally revealed a deleterious effect of the systematic AV search hysteresis (every 32 cycles) during ventricular tracked sinus tachycardia in ventricular pacing dependent patients. In 20 episodes (across 3 patients) we discovered that the AV Search+™ algorithm induced a 2:1 block during 8 cycles (16 atrial cycles) since every other atrial event occurred during the post-ventricular atrial refractory period (Figure 6).

Discussion

In the present study, we evaluated the RYTHMIQ™ algorithm, the specificity of the switches to DDD and its relation with pacemaker-mediated tachycardia by analyzing over one thousand episodes in a large group of patients. The analysis was only possible because mode switch episodes are recorded in Boston Scientific devices. Sorin is the sole other manufacturer which records mode switches (SafeR™) while Medtronic (Managed Ventricular Pacing™), Biotronik (Vp suppression™) and St Jude Medical (Ventricular Intrinsic Preference™) have algorithms designed to reduce ventricular pacing, but do not record the mode switch episodes. Similarly, suspected pacemaker mediated tachycardias are only recorded in Boston Scientific and St Jude Medical devices. The limited recording features of the other device manufacturers renders comparison impossible, therefore the aim of this article is not to suggest the superiority or inferiority of this algorithm compared to the other ones. However, we did observe limitations and repetitive inappropriate switches that may help improve patient selection for this algorithm.

Limitations of the RYTHMIQ™ algorithm

Large number of inappropriate AAI to DDD switches

In the present study, the percentage of appropriate switches and thus the specificity of the RYTHMIQ™ algorithm was low (16%). However, the percentage of appropriate versus inappropriate switches is not only reliant on the performance of the algorithm but also on

the indication for implantation and the degree of ventricular pacing dependency. Indeed, selection of patients with a higher degree of AV conduction disorder, would have probably led to a higher percentage of appropriate switches. This is also evidenced by the higher percentage of cumulative RV pacing in the patients with predominantly appropriate switches as compared with patients with predominantly inappropriate switches (28% versus 10%). The large number of analyzed episodes does permit us to draw important conclusions about the triggers for inappropriate switches and about the characteristics of patients less likely to benefit from this algorithm.

Compensatory pauses following atrial or ventricular extrasystoles

In patients with frequent atrial or ventricular extrasystoles, the VVI back-up mode prevents occurrence of prolonged pauses since the minimal ventricular pacing rate is programmed between 30 bpm (pause 2 seconds) to 60 bpm (pause 1 second). On the other hand, the VVI back-up mode renders this algorithm particularly sensitive to switching pacing mode following compensatory pauses. The number of these inappropriate switches may be sustained by additional extrasystoles that can cause a significant increase in percentage of ventricular pacing. This malfunction is specific for this algorithm and is much less frequently observed with other AAI/DDD algorithms. Patients with frequent atrial or ventricular extrasystoles may therefore not be the most suitable candidates for the RYTHMIQ™ algorithm.

Ventricular extrasystoles within the refractory period

Ventricular extrasystoles which occur relatively late in the cardiac cycle are also an important contributor to inappropriate commutations. When the late extrasystole occurs in the post atrial pacing ventricular refractory period (blanking or noise window), it does not inhibit ventricular stimulation. The algorithm is designed to function in AAI to reduce

ventricular pacing with a parallel independent VVI back-up mode to prevent pauses. In fact, the AAI and VVI modes do not operate completely independently since during atrial pacing, a ventricular post atrial stimulation-blanking period is mandatory to inhibit cross-talk and the associated risk of asystole. This type of inappropriate mode switch is also observed in other AAI/DDD algorithms such as in Sorin, Medtronic and Biotronik devices (even though these episodes are not recorded in the 2 latter manufacturers pulse generators).

High rate of pacemaker mediated tachycardia

In DDD mode, the AV Search+™ algorithm periodically and systematically prolongs the AV interval in order to search for spontaneous AV conduction. This method, also chosen by St Jude Medical and Biotronik devices, has as a main advantage: to avoid non-conducted atrial depolarizations and ventricular pauses. In contrast, a blocked-P wave is possible during the search phase with Medtronic and Sorin devices. On the other hand, AV interval prolongation is accompanied with a risk of pacemaker mediated tachycardia induction. Since EGMs of suspected PMTs were recorded, we were able to investigate the underlying mechanism. Besides Boston Scientific, this is only possible for St. Jude Medical devices. In our study the majority of PMTs (69%) was associated with the AV Search+™ algorithm. An important note is that PMTs at a rate under the programmed maximal tracking rate (for instance because of prolonged PR interval or programming of a high maximal tracking rate) are not diagnosed as a PMT by the device and will not be saved into the memory. For this reason it is conceivable that the RYTHMIQ algorithm induces more PMTs than apparent from the device memory.

Risk of 2-to-1 AV block during exercise

In patients who switched to DDD mode for atrioventricular block, the algorithm searches for spontaneous conduction by prolongation of the AV interval for 8 consecutive cycles. When this search occurs during sinus tachycardia, the increased AV interval favors the risk of

developing 2-to-1 block with a sudden drop in ventricular pacing rate. In this case, every other atrial event occurs during the post-ventricular atrial refractory period (PVARP) and is thus not followed by a ventricular paced beat. This study is not able to determine the exact incidence of this anomaly since it was accidentally recorded during episodes misdiagnosed as PMT, even though the risk seems important in patients with sinus tachycardia who have been switched to DDD mode for atrioventricular block. The symptomatic importance of these episodes is also yet to be determined.

Diagnosis of pacemaker dysfunction

An important advantage of recording mode-switch episodes is the possibility of diagnosing paroxysmal pacemaker dysfunction (undersensing, loss of atrial capture or oversensing) that induce inappropriate switches to the DDD mode. Many of these episodes were not sustained and would not have been detected by the device which indicates that diagnosing pacemaker dysfunction is one of the pleiotropic effects of the RYTHMIQ algorithm. In our study population, 23 patients (15%) exhibited inappropriate mode switches related to pacemaker dysfunction. Undersensing, atrial capture failure or oversensing indicate either inadequate programming of the device (incorrect sensitivity, pacing threshold too low) or lead dysfunction which should alarm the programmer to investigate the issue further.

Suggestions for improving the algorithm

Two-thirds of inappropriate mode switches were related to premature atrial or ventricular contractions. Different options may be proposed to decrease the rate of inappropriate switches. 1) The specific sequence, premature contraction- compensatory pause (short-long cycle), could be recognized by the device, and the compensatory pause would not be considered as a slow ventricular beat and not be integrated in the 3/11 count. When the compensatory pause would not be considered as a slow ventricular beat, we would expect

an important decrease in inappropriate mode switches and thus a significant decrease in cumulative RV pacing. 2) The amount of 'slow ventricular beats' required for a mode switch is not programmable (fixed at ≥ 3 out of 11). Having the possibility to program a higher number of required slow beats may be beneficial in patients with frequent extrasystoles. However, increasing the amount of required slow ventricular beats would result in fewer commutations in patients with second degree AV block. In other words, increasing the specificity could result in a decrease in sensitivity.

The other major contributors of inappropriate mode switches, namely refractory period and pacemaker dysfunction, are more complex to improve. A post-atrial pacing refractory period is imperative to protect the ventricular channel from oversensing. The detection of paroxysmal pacemaker dysfunction we actually consider as a desired side-effect of this algorithm.

This study confirmed that prolongation of the AV interval is associated with PMTs since the majority of PMTs were related to the AV Search+™ algorithm. During DDD mode the AV Search+™ algorithm searches for spontaneous conduction every 32 beats. Progressively increasing this amount would also considerably reduce the amount of PMTs. Finally, we suggest to suspend AV Search+™ during tachycardia, as this can initiate 2-to-1 block as we have discovered by chance in the PMT labelled episodes (which were in fact sinus tachycardia at maximal tracking).

Suggestions on patient selection for RYTHMIQ

The RYTHMIQ algorithm is most suited for patients with sinus node dysfunction, brady-tachycardia syndrome and chronotropic insufficiency. In these patients, RYTHMIQ works well to limit the burden of ventricular pacing, however most of the switches were inappropriate

since the percentage of true AV block is very limited and we demonstrated frequent inappropriate mode switches for other events such as premature contractions. We believe that in these patients, modification of the algorithm may improve the specificity. Patients with intermittent AV block are not the ideal candidates but if the goal is to decrease the burden of ventricular pacing while avoiding long pauses by AV-block, this population would paradoxically show higher accuracy than patients with preserved AV conduction, since more episodes of AV block will increase specificity. Patients with higher degree or permanent AV block should not be programmed to RYTHMIQ. Programming RYTHMIQ in these patients is probably not harmful but it is not logical either.

Limitations

This study has several limitations, namely the retrospective nature of the analysis and the limited proportion of RYTHMIQ™ episodes with stored EGMs (in relation to the total number of RYTHMIQ™ episodes). Nevertheless, based on the large amount of episodes we can conclude that the specificity of the algorithm is low. Calculating the sensitivity was not possible since we were only able to investigate the events which triggered the algorithm to perform a mode switch. Finally, we cannot conclude the prevalence of AV Search+™ induced 2-to-1 block since this phenomenon was seen by chance in misdiagnosed PMT episodes.

Conclusion

This study highlights some of the limitations of the RYTHMIQ™ algorithm: 1) high rate of inappropriate switch related to premature ventricular or atrial contractions and 2) high rate of induction of PMT. This may have clinical implications in terms of selection of the patients and may suggest required changes in the algorithm architecture.

Acknowledgements

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References

1. Prinzen FW, Augustijn CH, Arts T, Allesie MA, Reneman RS. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. *Am J Physiol* Aug 1990;259:H300-308.
2. Prinzen FW, Cheriex EC, Delhaas T, van Oosterhout MF, Arts T, Wellens HJ, Reneman RS. Asymmetric thickness of the left ventricular wall resulting from asynchronous electric activation: a study in dogs with ventricular pacing and in patients with left bundle branch block. *Am Heart J* Nov 1995;130:1045-1053.
3. Sweeney MO, Prinzen FW. Ventricular pump function and pacing: physiological and clinical integration. *Circulation Arrhythmia and electrophysiology* Jun 1 2008;1:127-139.
4. Barsheshet A, Moss AJ, McNitt S, Jons C, Glikson M, Klein HU, Huang DT, Steinberg JS, Brown MW, Zareba W, Goldenberg I. Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator. *Heart Rhythm*;8:212-218.
5. Sweeney MO, Prinzen FW. A new paradigm for physiologic ventricular pacing. *J Am Coll Cardiol* Jan 17 2006;47:282-288.
6. Sweeney MO, Ellenbogen KA, Casavant D, Betzold R, Sheldon T, Tang F, Mueller M, Lingle J, The Marquis MVPDI. Multicenter, Prospective, Randomized Safety and Efficacy Study of a New Atrial-Based Managed Ventricular Pacing Mode (MVP) in Dual Chamber ICDs. *Journal of Cardiovascular Electrophysiology* 2005;16:811-817.
7. Olshansky B, Day JD, Moore S, Gering L, Rosenbaum M, McGuire M, Brown S, Lerew DR. Is dual-chamber programming inferior to single-chamber programming in an implantable cardioverter-defibrillator? Results of the INTRINSIC RV (Inhibition of Unnecessary RV Pacing With AVSH in ICDs) study. *Circulation* Jan 2 2007;115:9-16.
8. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, Lamas GA. Minimizing Ventricular Pacing to Reduce Atrial Fibrillation in Sinus-Node Disease. *New England Journal of Medicine* 2007;357:1000-1008.
9. Stockburger M, Defaye P, Boveda S, Stancak B, Lazarus A, Sipotz J, Nardi S, Rolando M, Moreno J. Safety and efficiency of ventricular pacing prevention with an AAI-DDD changeover mode in patients with sinus node disease or atrioventricular block: impact on battery longevity-a sub-study of the ANSWER trial. *Europace* Nov 26 2015.
10. Stockburger M, Boveda S, Moreno J, Da Costa A, Hatala R, Brachmann J, Butter C, Garcia Seara J, Rolando M, Defaye P. Long-term clinical effects of ventricular pacing reduction with a changeover mode to minimize ventricular pacing in a general pacemaker population. *European heart journal* Jan 14 2015;36:151-157.
11. Monteil B, Ploux S, Eschaliere R, Ritter P, Haissaguerre M, Koneru JN, Ellenbogen KA, Bordachar P. Pacemaker-Mediated Tachycardia: Manufacturer Specifics and Spectrum of Cases. *Pacing Clin Electrophysiol* Sep 25 2015.

12. Akerstrom F, Arias MA, Pachon M, Puchol A, Jimenez-Lopez J, Rodriguez-Padial L. The reverse mode switch algorithm: how well does it work? Heart Rhythm Aug 2013;10:1146-1152.

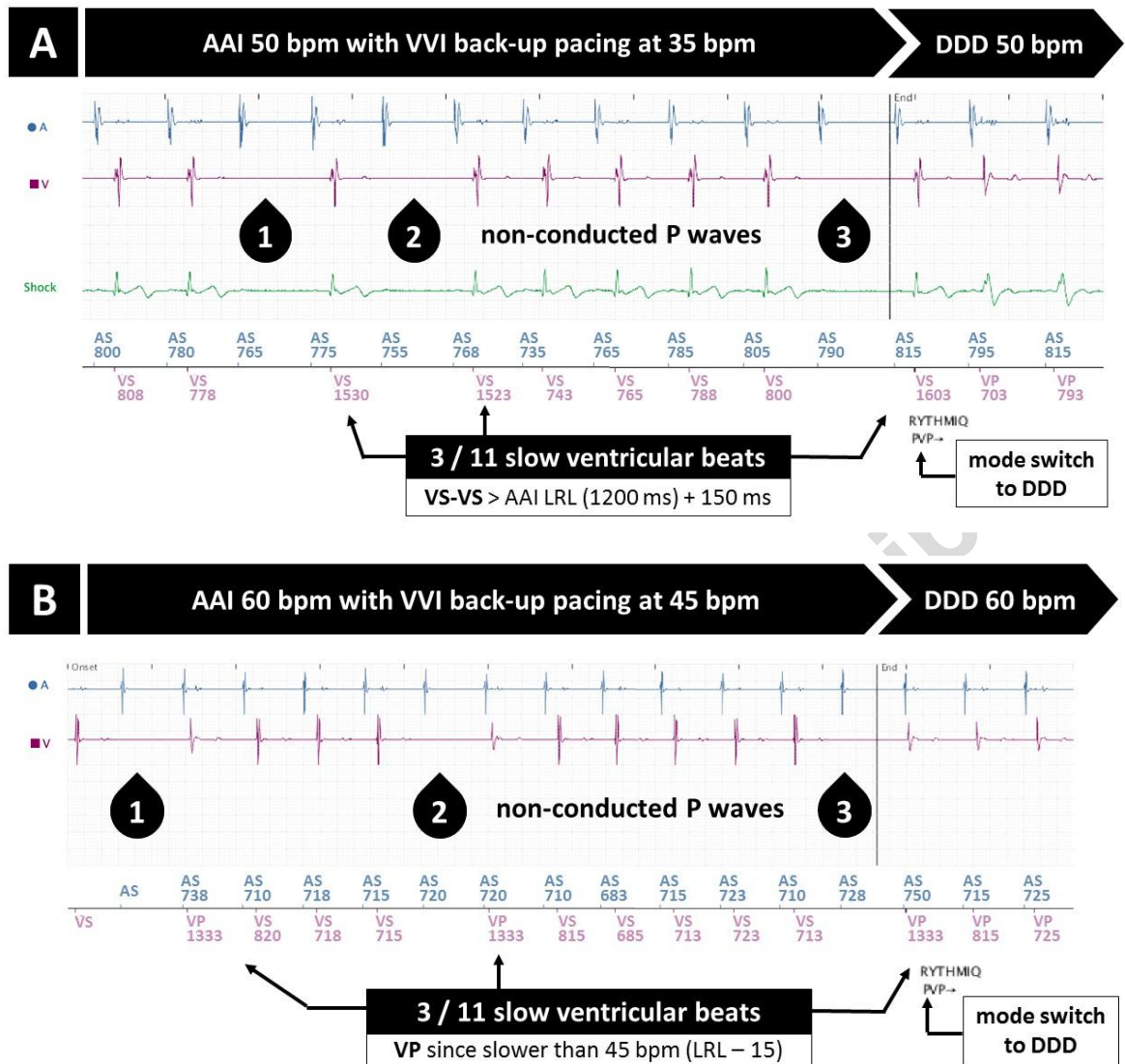


Figure 1. Examples of appropriate RYTHMIQ™ episode showing non-conducted P waves. The loss of spontaneous AV conduction results in dropped ventricular rate. When the algorithm discovers three slow ventricular beats in a window of 11 cycles, it executes a switch to DDD mode. **Panel A** shows 3 non-conducted P waves which result in VS-VS intervals which are slower than 1350 ms (LRL (1200 ms) + 150 ms) but not slow enough to trigger a VP (1714ms). **Panel B** shows 3 non-conducted P waves with VS-VP intervals of 1333ms (60.000/(LRL 60 - 15)) also considered as a slow ventricular beat.

AAI 60 bpm with VVI back-up pacing at 45 bpm

DDD 60 bpm

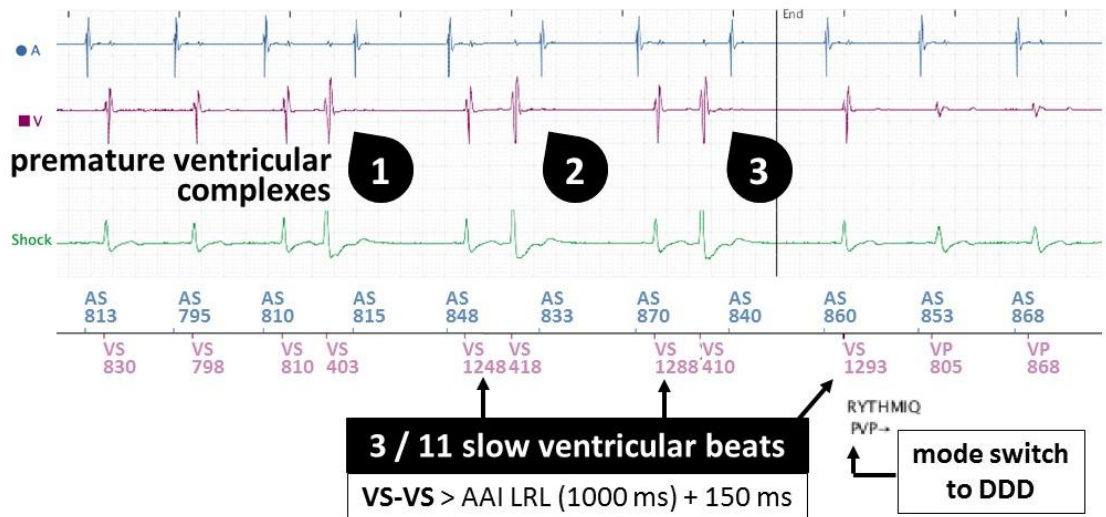


Figure 2: Example of an inappropriate RYTHMIQ™ episode induced by premature ventricular contractions (PVCs). The PVCs (1, 2 and 3) result in a compensatory pause and the following ventricular event is considered a slow ventricular beat. Since in a window of 11 beats, three PVCs resulted in three slow ventricular beats, RYTHMIQ™ induced a mode switch from AAI to DDD.

AAI 65 bpm with VVI back-up pacing at 50 bpm

DDD 65 bpm

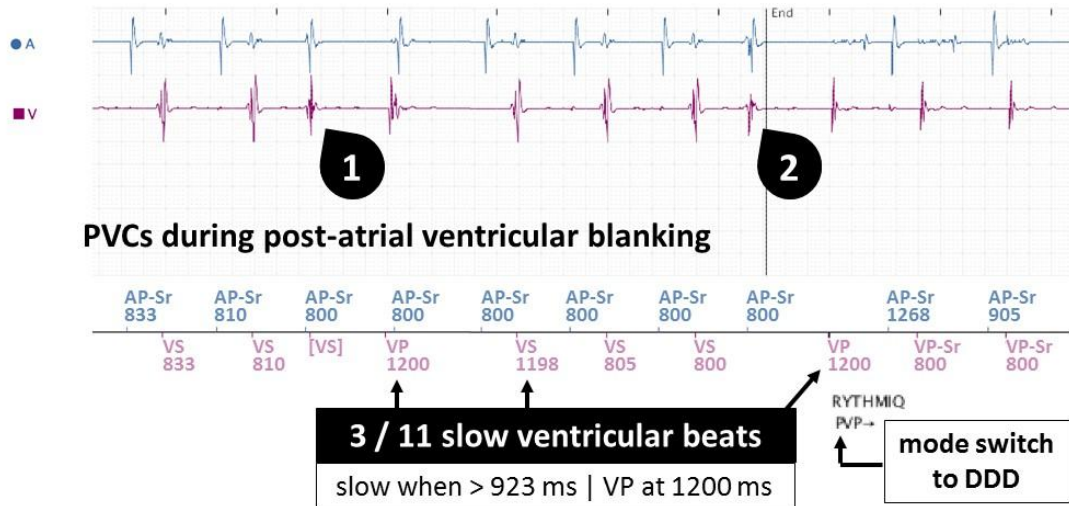


Figure 3: Example of an inappropriate RYTHMIQ™ episode related to post-atrial ventricular refractory periods (blanking and noise window). During atrial stimulation, a post-atrial ventricular blanking period on the ventricular channel is essential to prevent cross-talk. Especially at higher atrial paced rates (sensor), premature ventricular contractions (PVC) can fall within this noise window (1, marked [VS]) and blanking (2, no mark) which triggers backup ventricular pacing. In addition, the stimulated beat acts as a PVC which triggers a compensatory pause which is also classified as slow.

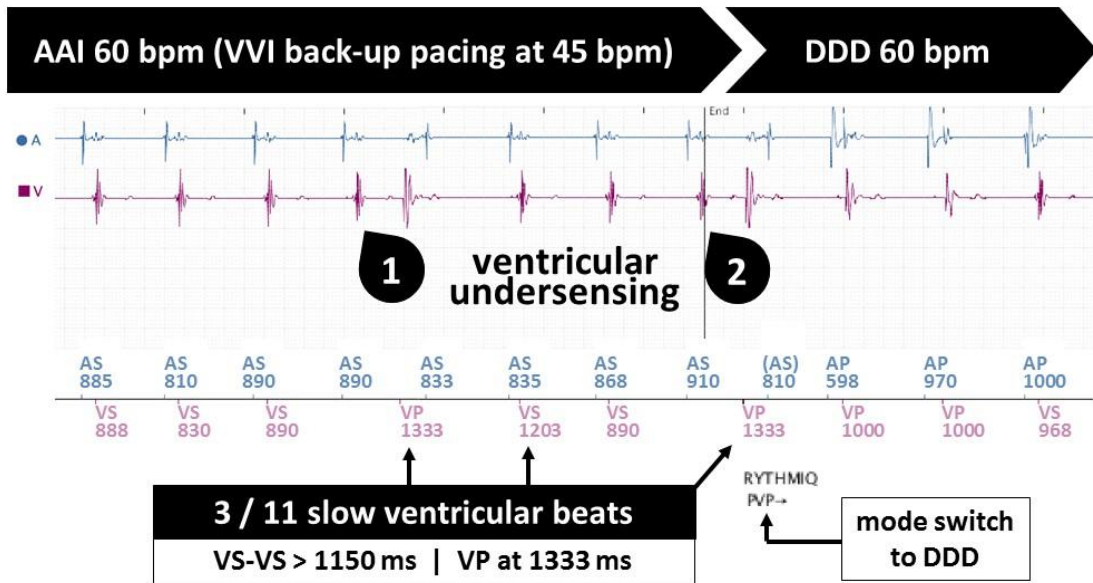


Figure 4. Example of inappropriate RYTHMIQ™ episode unmasking ventricular undersensing.

In this example a ventricular event was not sensed (1) which induced a back-up VP (15 bpm slower than LRL at 60 bpm = 1333 ms). In addition, the VP functions as a premature ventricular contraction which induces a compensatory pause. Both events are counted as slow ventricular beats so a second ventricular undersensed event sufficed for mode switch to DDD.

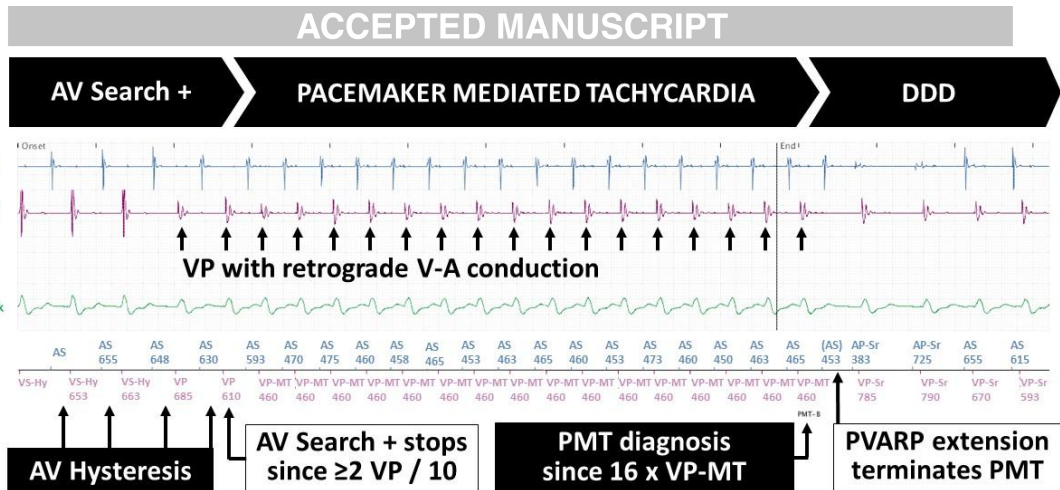


Figure 5: Example of pacemaker mediated tachycardia induced by AV Search+™. During this AV Search+™ protocol, the first ventricular events occur after spontaneous AV conduction (Vs-Hy). The fourth atrial event is not conducted to the ventricle within the extended AV delay (300ms) and triggers a VP. This VP has a long AV interval which enabled retrograde ventriculo-atrial conduction. Since 2 cycles were stimulated, AV Search +™ was terminated ($\geq 2/10$ VP in the secondary phase terminates AV Search+™). However, retrograde V-A conduction is maintained and the ventricle is stimulated at maximal tracking rate (VP-MT). The electronic re-entry is sustained until the pacemaker correctly labels the event as PMT (16 cycles of VP-MT) and increases the post-ventricular atrial refractory period (PVARP) to 500 ms a single time. The following retrograde atrial conduction falls within the PVARP, thus does not trigger a ventricular stimulation and the PMT is terminated.

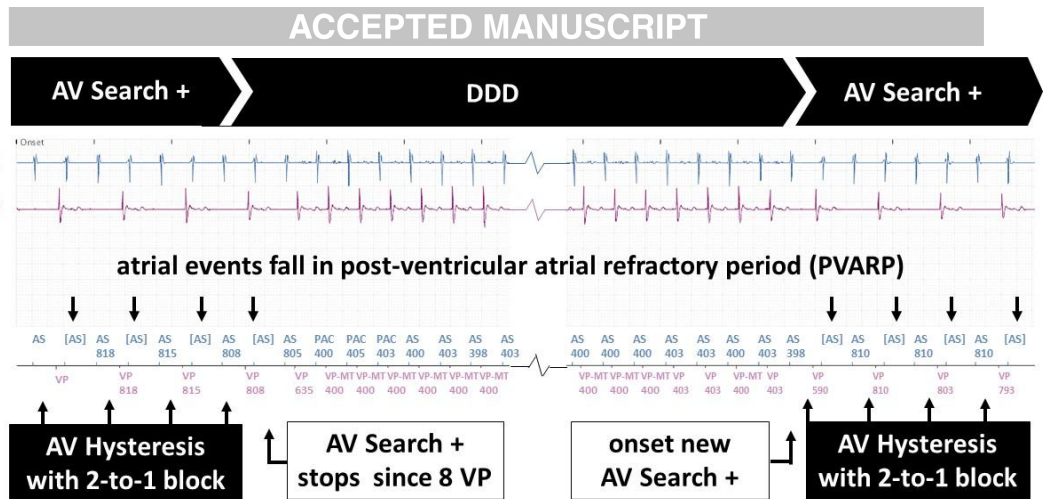


Figure 6. Example of an episode labeled pacemaker-mediated tachycardia unmasking 2-to-1 AV block during AV Search +™. 16 consecutive ventricular stimulations at the maximal tracking rate (16 X VP-MT) triggered the recording which is labeled PMT but is in fact sinus tachycardia. This tracing reveals that AV Search+™ is activated, since the AV interval is significantly delayed during the first and last events, as compared with the center part. The prolonged AV interval and the following post-ventricular atrial refractory period (PVARP) result in every other atrial event to fall in the blanking. A 2-to-1 AV block occurs with a sudden drop in ventricular rate during sinus tachycardia, which restored when AV Search+™ is stopped (stop criterion is 8 X VP in the primary phase). When AV Search+™ is re-initiated 32 ventricular cycles later, the 2-to-1 block re-occurs in identical fashion.

Tables

Table 1. Demographics and device specifications of patients with dual chamber Boston Scientific devices and RYTHMIQ™ algorithm activated.

	RYTHMIQ™ ON
Patient demographics	
Age [years]	67±13
Male sex [n]	101 (64%)
Device type	
Pacemaker [n]	40 (25%)
ICD [n]	117 (75%)
Device programming	
Lower Rate Limit [bpm]	55±7
Upper Tracking Rate [bpm]	132±7
Device output	
Percentage ventricular pacing [%]	16±28 (0-100)
Percentage atrial pacing [%]	33±35 (0-100)
Median Respiratory Rate [per min]	17±3 (11-26)
Activity Level [% of day]	8±7 (0-50)

Pacemaker-mediated tachycardia in a real word setup: A clinical study based to study the accuracy of specific algorithm.

1. Study outline

A pacemaker-mediated tachycardia (PMT) can be defined as any condition in which a pacemaker paces the ventricles at rates that are inappropriately fast. This can be due to a rate response setting that is too sensitive, tracking of atrial noise (such as what may occur with electromagnetic interference), inappropriate pacemaker manipulation with rate response turned on, or tracking of an atrial tachyarrhythmia related to upper rate settings. This phenomenon has been observed and understood early after the introduction of dual-chamber pacing in patients presenting with intrinsic ventriculo-atrial (VA) conduction (21). The majority of patients are asymptomatic but patients may report symptoms ranging from palpitations, rapid heart rates, light-headness, syncope, or chest discomfort. Prolonged PMT may be poorly tolerated or even lead to cardiac decompensation in patients suffering from underlying heart disease (22). The incidence of PMT varies as a function of patient characteristics, programming of the device and the specificities of the algorithms provided by the manufacturers(22). There is few data on the incidence of PMT across pacemaker and defibrillator recipients [5–9]. Studies to compare the respective effectiveness of these various algorithms of detection and termination of PMT are non-existent. In Boston Scientific devices, episodes of PMT are recorded in the memory. In this multicenter study, we included 328 patients implanted with a Boston Scientific device: 157 non-dependent patients with RYTHMIQ™ activated (RYTHMIQ group), 76 patients

with permanent AV-conduction disorder (AV-block group) and 95 Cardiac Resynchronization

Therapy patients (CRT group). For each patient, we reviewed the last 10 remote monitoring transmitted EGMs labelled as PMT.

2. Implications

We have observed that the AV Search + (RYHTMIQ) algorithm in Boston Scientific devices was associated with PMT induction in a selected group of patients. In this study, we assessed the diagnostic and therapeutic efficacy of the PMT algorithm in Boston Scientific devices. This was associated with a high rate of incorrect PMT diagnosis during exercise resulting in inappropriate therapy with non conducted P-waves, loss of CRT and limited risk of pro-arrhythmic events.

3. Manuscript



Accuracy of the pacemaker-mediated tachycardia algorithm in Boston Scientific devices

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Abstract

Introduction: The incidence of pacemaker-mediated tachycardia (PMT) varies as a function of patient characteristics, device programming and algorithm specificities. We investigated the efficacy of the Boston Scientific algorithm by reviewing PMT episodes in a large device population.

Methods: In this multicenter study, we included 328 patients implanted with a Boston Scientific device: 157 non-dependent patients with RYTHMIQ™ activated (RYTHMIQ group), 76 patients with permanent AV-conduction disorder (AV-block group) and 95 Cardiac Resynchronization Therapy patients (CRT group). For each patient, we reviewed the last 10 remote monitoring-transmitted EGMs diagnosed as PMT.

Results: We analyzed 784 PMT episodes across 118 patients. In the RYTHMIQ group, the diagnosis of PMT was correct in most episodes (80%) of which 69% was directly related to the prolongation of the AV-delay associated with the RYTHMIQ algorithm. The usual triggers for PMT were also observed (PVC 16%, PAC 9%). The remainder of the episodes (20%) in RYTHMIQ patients and most episodes of AV-block (66%) and CRT patients (74%) were incorrectly diagnosed as PMT during sinus tachycardia at the maximal tracking rate. The inappropriate intervention of the algorithm during exercise causes non-conducted P-waves, loss of CRT (sustained in six patients) and may have been pro-arrhythmogenic in one patient (induction of ventricular tachycardia).

Conclusion: Algorithms to minimize ventricular pacing can occasionally have unintended consequences such as PMT. The PMT algorithm in Boston Scientific devices is associated with a high rate of incorrect PMT diagnosis during exercise resulting in inappropriate therapy with non-conducted P-waves, loss of CRT and limited risk of pro-arrhythmic events.

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Keywords:

Clinical: implantable devices – pacemaker-bradyarrhythmias; Clinical: implantable devices – biventricular pacing/defibrillation; Clinical: implantable devices – ventricular tachycardia/fibrillation; Clinical: implantable devices – physiologic pacing; Clinical: cardiac mapping – electrogram analysis

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Introduction

Pacemaker mediated tachycardia (PMT) describes a repetitive sequence of sensed retrograde atrial events followed by ventricular pacing. This phenomenon has been observed and understood early after the introduction of dual-chamber pacing in patients presenting with intrinsic ventriculo-atrial (VA) conduction [1–3]. The majority of patients are asymptomatic but patients may report symptoms

ranging from palpitations, rapid heart rates, lightheadedness, syncope, or chest discomfort. Prolonged PMT may be poorly tolerated or even lead to cardiac decompensation in patients suffering from underlying heart disease [4].

The incidence of PMT varies as a function of patient characteristics, programming of the device and the specificities of the algorithms provided by the manufacturers [4]. While many isolated clinical cases of PMT have been described, there is few data on the incidence of PMT across pacemaker and defibrillator recipients [5–9]. Depending on the manufacturer, one must understand the specific means of prevention, diagnosis and termination of PMT in order to optimize the management of device recipients. Each device manufacturer has a proprietary algorithm to detect and terminate PMT, with a large proportion of similarities, including the phases of suspicion, confirmation and termination. Studies to compare the respective effectiveness of these various algorithms of detection and termination of PMT are non-existent. In Boston Scientific devices, episodes of PMT are recorded in the memory. The ability to view the electrograms enables identifying and resolving the trigger of the tachycardia but also offers the opportunity to assess the frequency of this problem. Recently, we observed that their AV Search+ algorithm, which increases the atrioventricular delay in search for intrinsic conduction, was associated with PMT induction in a selected group of patients [10]. In the present study, we assessed the diagnostic and therapeutic efficacy of the PMT algorithm by reviewing EGMs of PMT episodes in a large population of implanted patients.

Methods

In this multicenter study, we included 337 patients implanted with a Boston Scientific device across four French centers. We distinguished 3 groups: 157 patients with a dual chamber device, without permanent AV conduction disorder and with the RYTHMIQ™ algorithm activated (RYTHMIQ group), 76 patients with a dual chamber device, permanent AV conduction disorder and RYTHMIQ™ algorithm not-activated (AV-block group) and 95 patients with a triple-chamber Cardiac Resynchronization Therapy device (CRT group). To be enrolled, patients needed to be programmed in AAI with VVI Backup (RYTHMIQ group) or DDD(R) mode (AV-block and CRT groups). When available, we reviewed the last 10 remote monitoring-transmitted EGMs labeled PMT with focus on determining the specificity of the algorithm and the etiology of the events. All patients gave written, informed consent for analysis of the data providing from remote monitoring and patient information was de-identified prior to analysis of the episodes.

Description of the anti-PMT algorithm

Boston Scientific devices label and save an episode as PMT when two criteria are met.

1. Sixteen consecutive ventricular pace (VP) and atrial sense (AS) cycles occur at the programmed maximum

tracking rate. Default value of 130 beats per minute (coupling interval of 430 ms).

2. The variance between ventriculo-atrial intervals does not exceed 32 ms.

There exists no confirmation phase in Boston Scientific devices. Directly after diagnosis of PMT, the algorithm executes an automatic lengthening of the PVARP to 500 ms following the 16th cycle for a single cycle.

RYTHMIQ algorithm with AV search+

The RYTHMIQ™ algorithm, implemented in Boston Scientific dual-chamber pacemakers and implantable cardioverter-defibrillators, is designed to minimize ventricular pacing by favoring intrinsic ventricular conduction in non-pacemaker dependent patients. When RYTHMIQ is activated, the device operates in AAI(R) mode with VVI back-up. RYTHMIQ executes a mode switch to DDD(R) mode when AV-conduction disorder is suspected. In DDD(R) mode, the algorithm uses the AV Search+™ to periodically check for return of intrinsic conduction. After a certain number of cardiac cycles in DDD mode (default value at 32 cycles), the AV Search Interval is activated and the AV delay is extended to the programmed AV Search+™ value (default value: 300 ms). If a V-sense is detected within the 8 cycles period of AV Search+™, hysteresis continues. The AV Conduction Detector Counter is initialized at “0” and is incremented by each ventricular sensed event (marked as VS-Hy). When the AV Conduction Counter has reached 25, sustained conduction is detected and the device switches back to the primary AAI(R) mode with VVI back-up. The device maintains DDD(R) mode and does not switch back to the AAI(R) mode when no intrinsic conduction is detected within the first 8 cycles search period or when two out of the last 10 ventricular events are paced (sliding window).

Statistics

Continuous variables were expressed as median [min–max] and categorical variables were expressed as absolute numbers (percentages). Differences in baseline characteristics between groups were evaluated with the use of the Kruskal–Wallis H test for continuous data and Pearson’s chi-square test for categorical data. Statistical significance was assumed at $p < 0.05$. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

Results

Demographics and device programming

Patient demographics and device specifications are specified per group in Table 1. All CRT patients were equipped with ICDs while 17% of AV-block patients and 25% of RYTHMIQ patients were pacemaker recipients ($P < 0.001$ for comparison between three groups). CRT and AV block patients had a median cumulative ventricular pacing percentage of 99%, while RYTHMIQ patients had only a median of 1% cumulative ventricular pacing ($P < 0.001$ for comparison between three groups). The

Table 1

Demographics and device specifications of patients with dual chamber Boston Scientific devices divided in three groups according to underlying etiology. Categorical variables are expressed as absolute numbers (percentages), continuous variables are expressed as median [min–max].

	RYTHMIQ <i>n</i> = 157	AV-block <i>n</i> = 76	CRT <i>n</i> = 95	<i>P</i> -value
Patient demographics				
Age [years]	68 [23–95]	75 [1–96]	68 [44–89]	<0.001
Male sex [<i>n</i>]	101 (64%)	49 (65%)	70 (74%)	0.319
Device type				
Pacemaker [<i>n</i>]	40 (25%)	63 (17%)	0 (0%)	<0.001
ICD [<i>n</i>]	117 (75%)	13 (83%)	105 (100%)	
Device programming				
Lower rate limit [bpm]	55 [35–80]	60 [40–80]	60 [40–70]	<0.001
Maximal tracking rate [bpm]	130 [100–155]	130 [110–170]	130 [110–160]	0.172
Minimum sensed AV delay [ms]	65 [60–220]	65 [50–220]	100 [55–200]	<0.001
Maximum sensed AV delay [ms]	150 [100–350]	150 [80–340]	120 [70–200]	<0.001
Minimum paced AV delay [ms]	80 [80–220]	80 [50–220]	140 [80–200]	<0.001
Maximum paced AV delay [ms]	180 [150–350]	180 [80–340]	160 [100–300]	<0.001
Device output				
Percentage ventricular pacing [%]	1 [0–100]	99 [0–100]	99 [0–100]	<0.001
Percentage atrial pacing [%]	18 [0–100]	25 [0–100]	8 [0–100]	0.023
Median respiratory rate [per min]	16 [11–26]	16 [11–23]	17 [11–26]	0.090
Activity level [% of day]	7 [0–50]	7 [0–28]	9 [0–35]	0.056

programmed maximal tracking rate was similar between the three groups (*P* = NS).

Anti-PMT algorithm performance

118 patients had at least one PMT episode with a median of 40 episodes per patient. Out of all 46.375 PMT episodes, we analyzed 784 EGMs. An overview of the anti-PMT algorithm performance is shown in Table 2. In the RYTHMIQ group, the diagnosis of PMT was correct in the majority of episodes (124/154) which resulted in a specificity of 80%. The usually reported triggers for PMT such as premature atrial contractions (PACs) and premature ventricular contractions (PVCs) were together responsible for less than one-third of PMT episodes (PAC 11% and PVC 20%). An example of PMT triggered by PAC is shown in Fig. 1 (EGM and schematic) while Fig. 2 shows PMT induced by two consecutive PVCs. In the majority (69%) of correctly diagnosed PMT episodes, the onset of PMT was directly related to the prolongation of the AV delay associated with the AV Search+ protocol (as part of the RYTHMIQ™ algorithm). Fig. 3 shows an example of PMT in the context of AV hysteresis during AV Search+. This

algorithm may be on its own responsible for the PMT induction but the risk is increased when premature atrial or ventricular contractions occur during AV hysteresis.

The algorithm incorrectly labeled PMT in 20% of cases in response to normal tracking of intrinsic atrial events at the maximal tracking rate during sinus tachycardia. This occurs in patients where RYTHMIQ previously executed a mode switch from AAI to DDD mode so that atrial sensed events trigger ventricular pacing, a required component for PMT. Fig. 4 shows an example of a patient in sinus tachycardia at maximal tracking rate where PMT was incorrectly diagnosed by the device and which results in a non-conducted P-wave due to the extension of the PVARP after the 16th cycle. In the other patient groups (AV block group and CRT group), the incorrect diagnosis of PMT during sinus tachycardia at maximal tracking rate was responsible for the majority of episodes (66% and 74%, respectively). The correctly diagnosed PMT episodes (specificity of 44% in AV-block patients and 26% in CRT patients) occurred in the context of premature atrial or ventricular contractions. In dependent patients (AV block group) incorrect PMT labeling resulted into an inappropriate PVARP extension and therefore in non-conducted P-waves while in non-dependent CRT

Table 2

Diagnostic overview of the PMT algorithm for the three patient groups. When available, up to 10 PMT episodes were analyzed per patient. Categorical variables are expressed as absolute numbers (percentages). PVC: premature ventricular contraction. PAC premature atrial contraction.

	RYTHMIQ <i>n</i> = 156	AV-block <i>n</i> = 76	CRT <i>n</i> = 95	<i>P</i> -value
Patients with PMT episodes	27 (17%)	30 (39%)	61 (64%)	<0.001
Total amount of PMT episodes	13.379	18.699	14.297	
PMT episodes analyzed	154	214	416	
Incorrect PMT diagnosis	30 (20%)	142 (66%)	306 (74%)	<0.001
Correct PMT diagnosis	124 (80%)	72 (44%)	110 (26%)	
PAC [<i>n</i> , % of correct]	14 (11%)	54 (82%)	32 (29%)	<0.001
PVC [<i>n</i> , % of correct]	25 (20%)	12 (18%)	64 (58%)	<0.001
RYTHMIQ [<i>n</i> , % of correct]	85 (69%)	–	–	

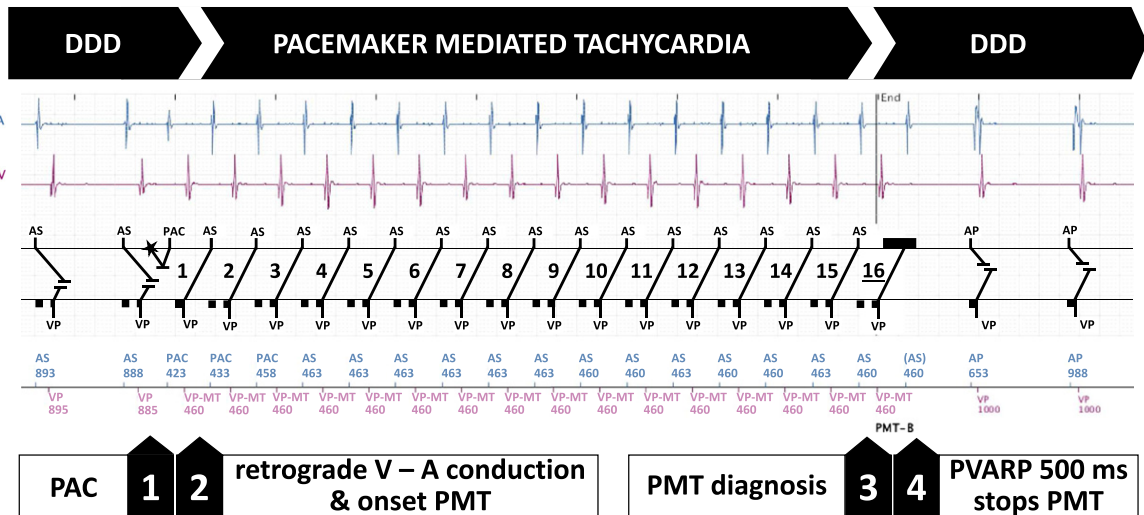


Fig. 1. Example of pacemaker-mediated tachycardia in the context of premature atrial contraction. [1] A premature atrial contraction (PAC) triggers a ventricular pace at the maximal tracking rate (VP-MT). [2] The triggered VP results in retrograde V-A conduction which is sensed as a PAC and on its turn, again triggers a VP (PMT). [3] PMT is diagnosed after 16 stable VP-AS at maximal tracking rate. [4] After the 16th VP-MT, the PVARP is extended to 500 ms which terminates the PMT.

patients the inappropriate therapy resulted in intrinsic ventricular conduction and therefore loss of resynchronization therapy. We have also observed a certain number of phenomena which were less frequent. In the CRT group, inappropriate intervention of the algorithm during exercise was associated with sustained interruption of biventricular pacing in 6 patients. In these patients having sinus tachycardia and with prolonged PR intervals, the intervention (extension of PVARP) resulted in an intrinsic ventricular beat where due to the left bundle branch block the RV sense was also delayed so the succeeding sinoatrial event occurred during the following PVARP. Fig. 5 shows an example where this sequence of sinoatrial events occurring in the PVARP of the preceding intrinsic ventricular events caused

extended loss of CRT. In one patient, the inappropriate intervention of the algorithm may have been pro-arrhythmogenic. Fig. 6 shows that directly after the PVARP extension a ventricular tachycardia (VT) is initiated. This patient was equipped with an ICD and the VT was treated with anti-tachycardia pacing. While three burst treatments were ineffective, a ramp treatment succeeded into VT termination.

Discussion

PMT remains a common phenomenon among patients with cardiac stimulation devices. This study permits us to draw important conclusions about PMT in general and about the specificities of the Boston Scientific algorithm.

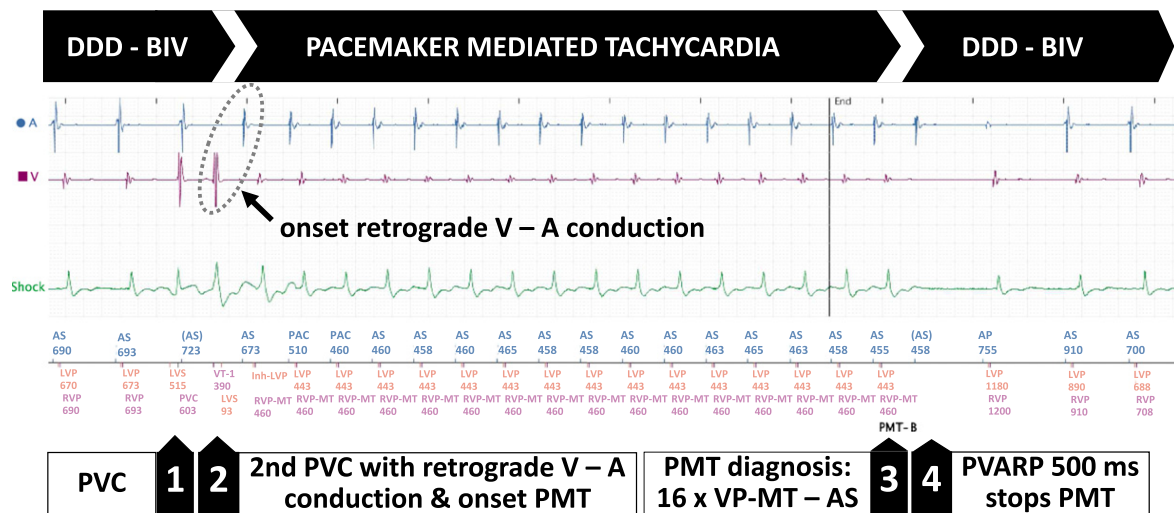


Fig. 2. Example of pacemaker-mediated tachycardia in the context of premature ventricular contraction (PVC). [1] The first PVC occurs simultaneously with a sinoatrial event, the refractory AV node inhibits retrograde (V-A) conduction. [2] However, the second PVC initiates retrograde conduction which results in AS and an AV delay for BIV stimulation. The RV is stimulated at the maximal tracking rate while LV stimulation is inhibited (Inh-LVP) since it is too soon after the preceding LVS. [3] After PMT diagnosis, [4] a single prolongation of the PVARP to 500 ms terminates the PMT.

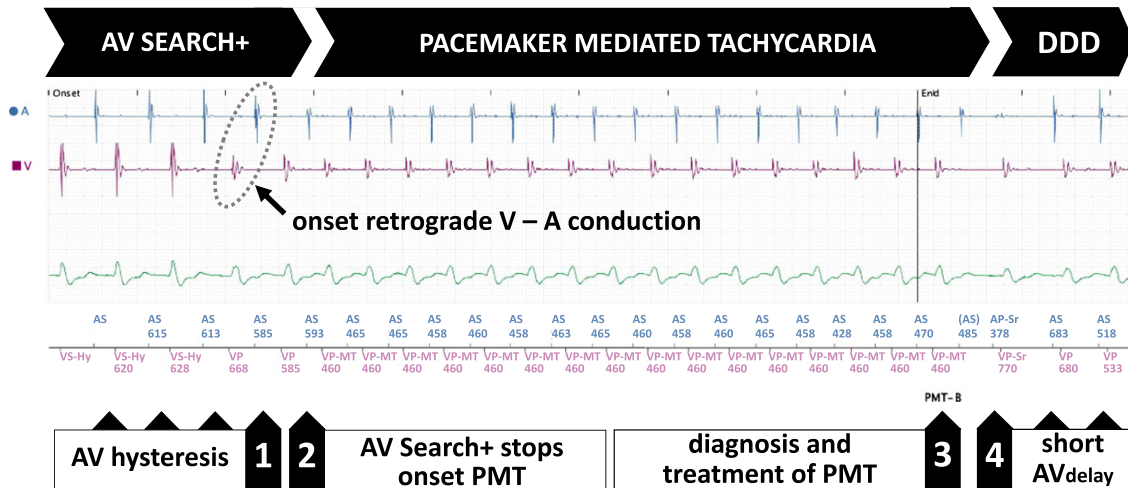


Fig. 3. Example of pacemaker-mediated tachycardia in the context of AV Search+™ (RYTHMIQ™). [1] During AV Search+, the AV delay is extended to search for intrinsic ventricular conduction (marked as VS-Hy). [2] After the third VS-Hy, intrinsic conduction is too slow which triggers a VP. After 2 VPs in a sliding window of 10 the AV Search+ protocol is terminated and the device returns to DDD mode. However, because there is AV block and a prolonged AV delay, the AV-node has recovered by the time the ventricular stimulus occurs enabling retrograde V-A conduction and the ventricle is stimulated at maximal tracking rate (VP-MT). [3] The electronic re-entry is sustained until the pacemaker correctly labels the event as PMT (16 cycles of VP-MT) and increases the post-ventricular atrial refractory period (PVARP) to 500 ms for one cycle which terminates the PMT. [4] Since the AV Search+ phase was terminated, ventricular pacing continues at short AV delay.

Overall performance of the anti-PMT algorithm

The heterogeneous performance of the Boston Scientific anti-PMT algorithm between patient groups indicates that its accuracy is highly dependent on underlying patient etiology. The overall specificity of the anti-PMT algorithm is low (39%) which is caused by incorrect diagnosis of PMT during sinus tachycardia at the maximal tracking rate, especially in patients with a disabled RYTHMIQ algorithm (AV-block group and CRT group). Even though sinus tachycardia at exactly the maximal tracking rate (with variance of at most a few milliseconds) seems to be an unlikely event and the overall incidence of sinus tachycardia is unknown, the sheer

number of episodes we found with this issue (478) actually reveals it is quite a common trigger. The other 306 episodes were ‘true’ PMTs (correctly diagnosed) which were associated with premature atrial contractions (especially in the AV block group), premature ventricular complexes (especially in the CRT group) and surprisingly by the RYTHMIQ algorithm (exclusively in the RYTHMIQ group).

AV Search +

The AV Search+ protocol is part of the RYTHMIQ algorithm which aims to lower the ventricular pacing burden by favoring intrinsic conduction. During AV hysteresis (or

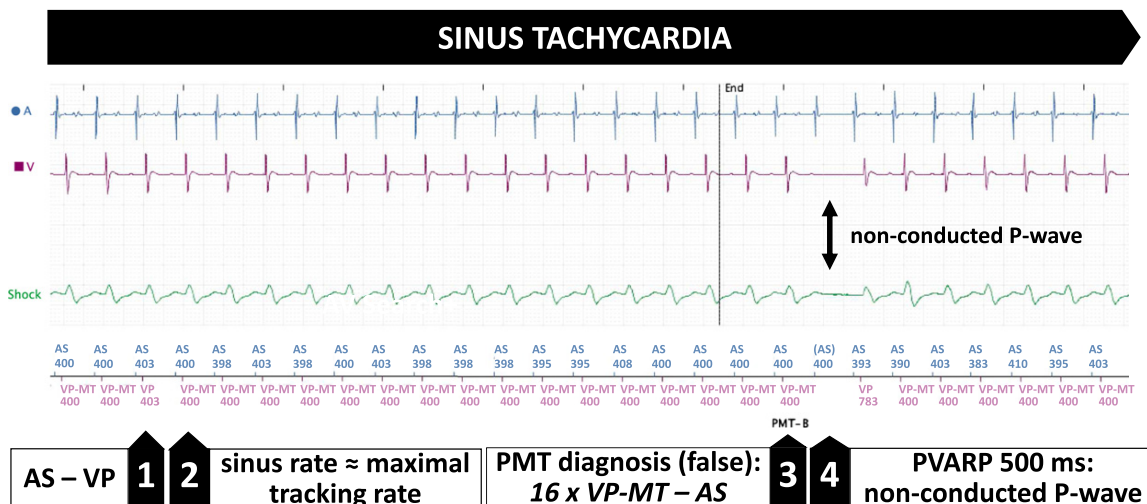


Fig. 4. Incorrectly labeled ‘PMT’ episode in the context of sinus tachycardia at maximal tracking rate. [1] Atrial sensing during sinus tachycardia close to the maximal tracking rate (≈ 150 bpm). [1] When the atrial coupling interval is just above maximal tracking (403 ms > 400 ms), a regular VP resets the PMT counter (0/16). [3] Sixteen atrial events at (or slightly faster than) maximal tracking trigger sixteen VP-MT-AS which establishes the diagnosis of ‘PMT’. [4] Like all PMTs, the 16th VP-MT is followed by a PVARP extension to 500 ms during which a true atrial sense occurs which is not followed by a ventricular stimulation (non-conducted P-wave).

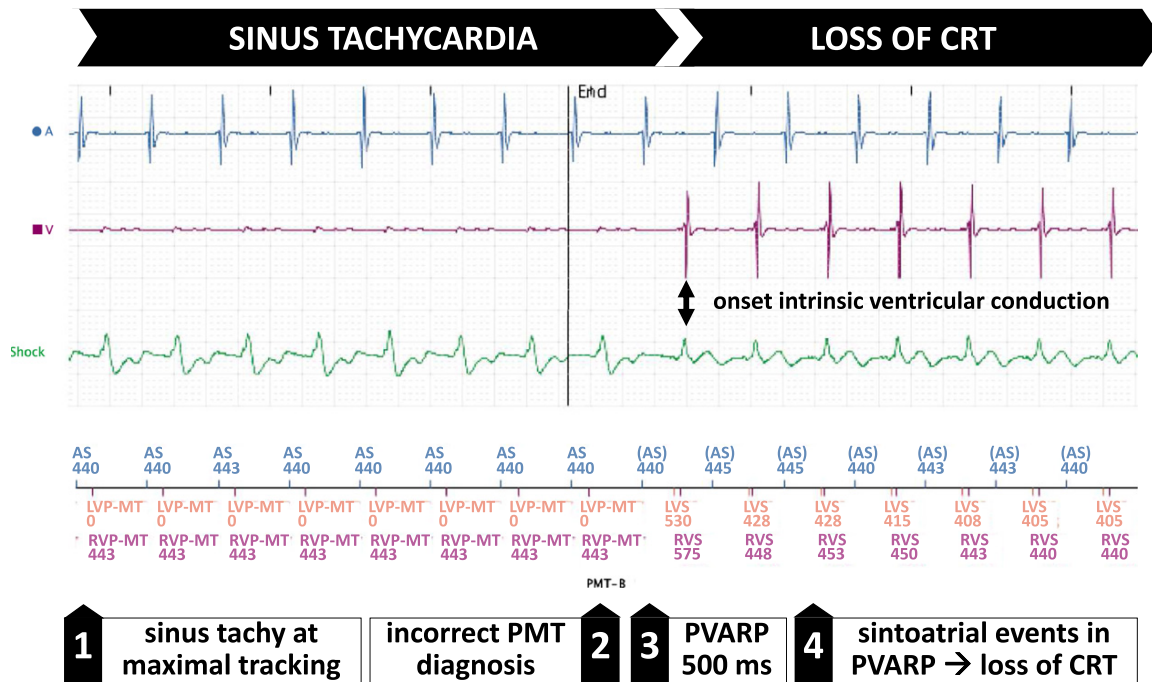


Fig. 5. Example of loss of biventricular stimulation in the context of inappropriate PMT therapy. [1] Patient is in sinus tachycardia which approximates maximal tracking rate. [2] After sixteen sequences of VP-MT-AS the device inappropriately declares PMT. [3] The PMT algorithm results in extension of the PVARP to 500 ms during a single cycle which induces intrinsic ventricular conduction with a relatively long PR interval. [4] Since atrial coupling cycle is short and PR interval is long, every atrial event occurs during the PVARP which induced extended period of loss of biventricular stimulation.

one-step extension of the AV delay) the device determines if intrinsic ventricular events follow atrial events. In some patients, intermittent AV block and a prolonged AV delay permit recovery of the AV refractory period which enables retrograde VA conduction. The possibility of retrograde VA conduction due to a long AV delay may be present at only certain moments of time. Previously, a case report has described the occurrence of PMT associated with this type of algorithm (St. Jude Medical) [11].

We report here the initiation of pacemaker-mediated tachycardia (PMT) by the normal function of a RYTHMIQ AV Search+ algorithm in a large number of patients. This study demonstrates that the link between a prolonged AV delay and initiation of PMT is not rare and was previously underreported. The extension of the AV delay on its own may initiate a PMT (such as shown in Fig. 3) but a combination with a PAC or PVC, which derails atrial and ventricular activation, is also a possible trigger of PMT. The high rate of patients with enabled RYTHMIQ™ and PMT exposes the weakness of using this type of algorithm. Other algorithms do not search for spontaneous conduction by extending the AV delay but rather perform a direct mode switch to AAI (Sorin and Medtronic). This decreases the risk of PMTs while the risk of non-conducted P waves is increased which can be symptomatic in some patients. During DDD mode the AV Search+™ algorithm searches for spontaneous conduction every 32 beats. Progressively increasing this amount may considerably reduce the amount of PMTs. Of important note, after disabling the RYTHMIQ algorithm, the AV Search+™ algorithm remains active and needs to be manually disabled. When not switched off, AV

Search+™ will continue to search every 32 beats, even when in permanent DDD mode.

Loss of resynchronization by the ant-PMT algorithm

For a good response to CRT, sustained and adequate biventricular stimulation is imperative [12,13]. The function of a CRT device during a heart rate above the maximal tracking rate depends on the quality of the AV-conduction of the patient. In a resynchronized patient with complete AV-block and preserved chronotropic capacity, a Wenckebach phenomenon occurs when the sinoatrial rate accelerates above the maximal tracking rate. When the sinoatrial rate accelerates above the maximal tracking rate in a resynchronized patient with preserved AV conduction and good chronotropic capacity, the intrinsic activation wave front will dominate ventricular activation and ventricular stimulation is interrupted. In both cases, biventricular stimulation will be re-initiated when the heart rate falls below the maximal tracking rate. However, our study does reveal certain cases of prolonged loss of biventricular stimulation in patients with prolonged intrinsic PR-intervals. The intervention during sinus tachycardia by the PMT algorithm causes a non-conducted P-wave (since the atrial sense occurs within the PVARP) followed by an intrinsic ventricular beat. During exercise, the RP interval is short which increases the risk of the following atrial event to again occur during the PVARP, even though the PVARP is shortened automatically. This phenomenon can result in sustained loss of biventricular stimulation even when the sinoatrial rate falls below the maximal tracking rate. As long

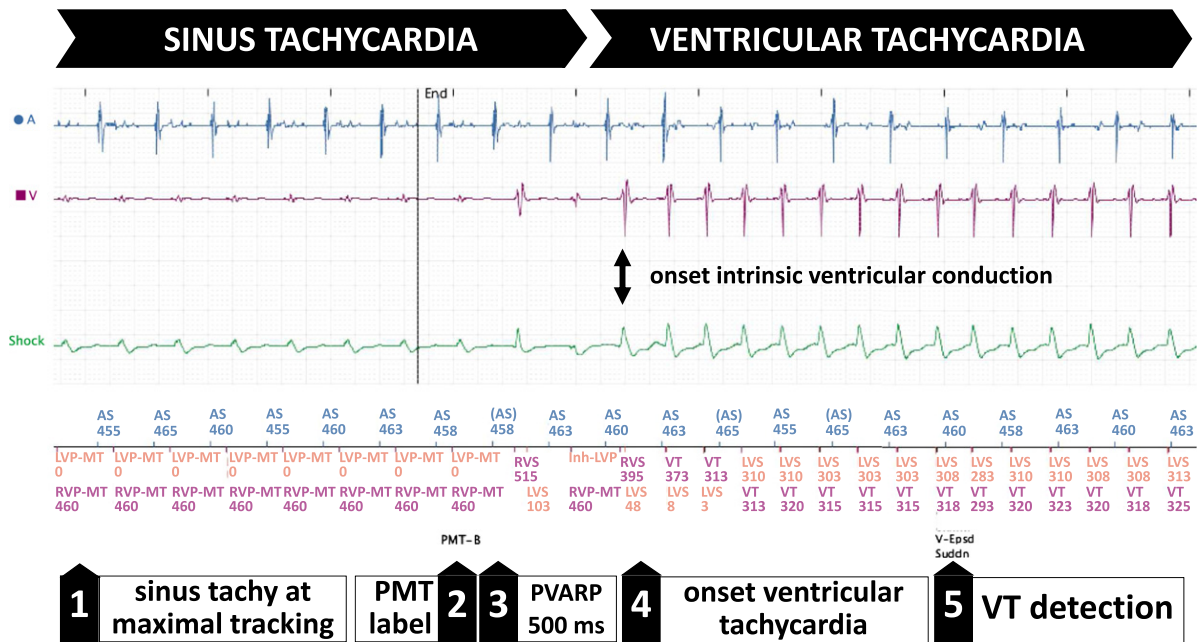


Fig. 6. Example of ventricular tachycardia in the context of inappropriate PMT treatment. [1] Sinus tachycardia at maximal tracking rate, [2] after 16 beats of RVP-MT-AS the device classifies PMT and [3] for a single cycle, the PVARP is extended to 500 ms. [4] After an intrinsic ventricular event (ventricular stimulation is inhibited since the atrial sense occurs during the PVARP) and a stimulated right ventricular event (inhibition of left ventricular pacing), a monomorphic ventricular tachycardia arises. [5] After 8 intervals in the VT zone, the ICD detects the tachycardia and labels “V-Epsd” with criteria of sudden onset (“Suddn”).

as the V-A interval occurs during the PVARP, biventricular stimulation will be withheld. Resynchronized patients with long PR-interval need careful programming of the maximal tracking rate and consideration of disabling the anti-PMT algorithm.

Possible arrhythmogenesis

The “short-long-short” ventricular sequence is a well-known phenomenon responsible for the initiation of polymorphic ventricular arrhythmias in long QT syndromes and monomorphic VTs in ICD patients. A case report in the context of a similar device model has previously shown the development of a VT after an inappropriate intervention by the anti-PMT algorithm during sinus tachycardia [14]. The combination of exercise, release of catecholamines and the short-long-short sequence is the probable responsible factors for the induction of the arrhythmias described in the report and in our study. This is the first study that provides data to assess the frequency of the problem. Since inappropriate intervention during sinus tachycardia is common, and we only observed one patient with an associated VT, one may consider it a rare problem. VT induction in pacemaker patient may be more dangerous than in a defibrillator patient, even though their arrhythmogenic risk would probably be lower. To avoid recurrence, it is essential to raise the maximal tracking rate which decreases the risk of inappropriate intervention by the algorithm during sinus tachycardia.

Non-detection of PMT under the maximal tracking rate

The heart rate during PMT depends on a combination of the retrograde conduction time, the programmed maximum

rate and the AV delay. An important note is that PMTs below the maximum tracking rate will not meet Boston Scientific’s algorithm criteria for PMT, will therefore not be saved to the memory as an episode and will not be treated. This causes difficulties in programming the maximal tracking rate since patients with relatively prolonged retrograde V-A conduction risk developing relatively slow PMTs which will not be diagnosed by the device when the maximal tracking rate is programmed too high. The optimal setting of this parameter must, therefore, strike a balance between the needs of the patient with respect to 1:1 tracking to prevent a Wenckebach periodicity during effort (need to program a high maximal tracking rate) on the one hand, and the risk of non-detection and termination of a PMT (need to program a low maximal tracking rate) on the other hand.

Specificities of the Boston Scientific algorithm

This study is only made possible because a sequence of events classified as PMT is saved into the memory of the device. This is also the case for St. Jude Medical devices but not for Medtronic, Biotronik and Sorin devices. A definite comparison of the PMT algorithms between pacemaker manufacturers is not possible and the results cannot be extended to other algorithms but there are some observations to be made. For the suspicion phase, 8 consecutive AS-VP cycles are required for the devices of all the manufacturers, except for Boston Scientific, which requires 16 cycles, causing a slight delay in the diagnosis and a prolongation of the episodes. During suspicion only the criteria of stability between V-A intervals needs to be met, there is no confirmation phase such as modification of the AV delay

to differentiate between sinus tachycardia, atrial tachycardia and PMT. This explains the low specificity in stimulated patients (dependent or resynchronized patients) with the risk of at least one non-conducted P wave in dependent patients or loss of resynchronization in CRT patients. The algorithms of Biotronik, Saint Jude Medical and Sorin devices are included with a confirmation phase with modulation of the AV delay and analysis of the following VP-AS interval, which limits the risk of intervention for sinus tachycardia during exercise. Saint-Jude Medical also relies on AV hysteresis to search for intrinsic conduction which is a potential trigger for PMT.

Limitations

This study has several limitations, namely the retrospective nature of the analysis and the limited proportion of PMT episodes with stored EGMs (in relation to the total number of PMT episodes). Nevertheless, based on the large amount of episodes we can conclude that the specificity of the algorithm is low. Calculating the sensitivity was not possible since we were not able to investigate PMTs which did not trigger the algorithm to diagnose PMT and save the episode to the device.

Conclusion

Algorithms to minimize ventricular pacing can occasionally have unintended consequences such as PMT. In Boston Scientific devices, the absence of confirmation phase leads to a high rate of incorrect diagnosis of PMT during exercise resulting in non-conducted P waves and loss of biventricular stimulation. The pro-arrhythmogenic risk (long–short cycle) seems limited.

Author contributions

- Strik M: data analysis/interpretation, drafting article, critical revision of article
- Frontera A: critical revision of article
- Eschalier R: data collection
- Defaye P: data collection
- Mondoly P: data collection
- Ritter P: data collection
- Haissaguerre M: data collection

- Ploux S: critical revision of article, statistics
- Bordachar P: concept/design, drafting article, critical revision of article

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References

- [1] Furman S, Fisher JD. Endless loop tachycardia in an AV universal (DDD) pacemaker. *Pacing Clin Electrophysiol* 1982;5:486–9.
- [2] Ripart A, Pioger G. Detection and characteristics of retrograde P waves. *Pacing Clin Electrophysiol* 1983;6:372–5.
- [3] Elmqvist H. Prevention of pacemaker mediated arrhythmias. *Pacing Clin Electrophysiol* 1983;6:382–6.
- [4] Monteil B, Ploux S, Eschalier R, Ritter P, Haissaguerre M, Koneru JN, et al. Pacemaker-mediated tachycardia: Manufacturer specifics and spectrum of cases. *Pacing Clin Electrophysiol* 2015;38(12):1489–98, <http://dx.doi.org/10.1111/pace.12750> [Epub 2015 Nov].
- [5] van Gelder LM, el Gamal MI, Baker R, Sanders RS. Tachycardia-termination algorithm: A valuable feature for interruption of pacemaker-mediated tachycardia. *Pacing Clin Electrophysiol* 1984;7:283–7.
- [6] Lamas GA, Antman EM. Pacemaker-mediated tachycardia initiated by coincident P-wave undersensing and ventricular blanking period. *Pacing Clin Electrophysiol* 1985;8:436–9.
- [7] Oseran D, Ausubel K, Klementowicz PT, Furman S. Spontaneous endless loop tachycardia. *Pacing Clin Electrophysiol* 1986;9:379–86.
- [8] Morin DP. An uncommon cause of pacemaker-mediated ventricular tachycardia. *J Cardiovasc Electrophysiol* 2014;25:107–9.
- [9] Barold SS, Stroobandt RX. Atrial lead malfunction presenting as new onset pacemaker-mediated tachycardia. *Europace* 2012;14:1060–1.
- [10] Strik M, Defaye P, Eschalier R, Mondoly P, Frontera A, Ritter P, et al. Performance of a specific algorithm to minimize right ventricular pacing: A multicenter study. *Heart Rhythm* 2016, <http://dx.doi.org/10.1016/j.hrthm.2016.02.008> [pii: S1547-5271(16)00171-5, Epub ahead of print].
- [11] Barold SS, Stroobandt RX. Pacemaker-mediated tachycardia initiated by an atrioventricular search algorithm to minimize right ventricular pacing. *J Electrocardiol* 2012;45:336–9.
- [12] Strik M, Ploux S, Vermooy K, Prinzen FW. Cardiac resynchronization therapy: Refocus on the electrical substrate. *Circ J* 2011;75:1297–304.
- [13] Strik M, van Middendorp LB, Houthuizen P, Ploux S, van Hunnik A, Kuiper M, et al. Interplay of electrical wavefronts as determinant of the response to cardiac resynchronization therapy in dyssynchronous canine hearts. *Circ Arrhythm Electrophysiol* 2013;6:924–31.
- [14] Van Gelder BM, Meijer A, Dekker LR, Bracke FA. Initiation of ventricular tachycardia by interruption of pacemaker-mediated tachycardia in a patient with a dual-chamber implantable cardioverter defibrillator. *Pacing Clin Electrophysiol* 2009;32:1227–30.

Complications and consequences of inappropriate therapies shocks in a pediatric population suffering from idiopathic ventricular fibrillation.

1. Study Outline

The majority of cases of arrhythmic sudden cardiac death (SCD) in young patients are attributable to either inherited structural cardiac diseases or primary arrhythmic syndromes(23). In a subset of patients, the cause of ventricular fibrillation remains undefined despite comprehensive diagnostic evaluation, referred to as idiopathic VF (IVF). According to contemporary guidelines, IVF is defined as resuscitated cardiac arrest that occurs in the absence of cardiac, metabolic, toxicological, and respiratory causes (24). Overall, idiopathic VF accounts for up to 8% of arrhythmic sudden cardiac death cases(25). ICD implantation is indicated in this population despite their young age.

This is the first study to systematically evaluate long-term outcomes among pediatric patients with an initial diagnosis of idiopathic ventricular fibrillation. Patients were included from an International Registry of IVF (consisting of 496 patients). Inclusion criteria were: 1) VF with no identifiable cause following comprehensive analysis for ischemic, electrical or structural heart disease and 2) age ≤ 16 years. The aim of the present study was to define the long-term outcome in pediatric VF patients, defining complications and incidence of appropriate and inappropriate ICD therapies.

2. Implications

The management of this population is unique, and there is paucity of data regarding recurrence of fatal arrhythmias as well as the long-term outcomes in patients of pediatric age in whom ICD is implanted. We demonstrate that among pediatric idiopathic ventricular fibrillation patients, arrhythmias commonly occur in the context of high adrenergic tone, and there is a high incidence of recurrent arrhythmic events. Due to their young age, the incidence of ICD-related complications in this pediatric population is relatively high. Inappropriate shocks, and device-related complications were the most frequent complications encountered. Lead fracture, lead insulation defect, and late lead dislodgement were the main complications occurred. Mean time from implant to complication was 41 months with a mean number of inappropriate shocks of 1.9. All patients were not followed up remotely: most of these inappropriate shocks could have been avoided.

3. Manuscript

Long-Term Follow-Up of Idiopathic Ventricular Fibrillation in a Pediatric Population: Clinical Characteristics, Management, and Complications

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Background—The natural history and long-term outcome in pediatric patients with idiopathic ventricular fibrillation (IVF) are poorly characterized. We sought to define the clinical characteristics and long-term outcomes of a pediatric cohort with an initial diagnosis of IVF.

Methods and Results—Patients were included from an International Registry of IVF (consisting of 496 patients). Inclusion criteria were: (1) VF with no identifiable cause following comprehensive analysis for ischemic, electrical or structural heart disease and (2) age ≤ 16 years. These included 54 pediatric IVF cases (age 12.7 ± 3.7 years, 59% male) among whom 28 (52%) had a previous history of syncope (median 2 syncopal episodes [interquartile range 1]). Thirty-six (67%) had VF in situations associated with high adrenergic tone. During a median 109 ± 12 months of follow-up, 31 patients (57%) had recurrence of ventricular arrhythmias, mainly VF. Two patients developed phenotypic expression of an inherited arrhythmia syndrome during follow-up (hypertrophic cardiomyopathy and long QT syndrome, respectively). A total of 15 patients had positive genetic testing for inherited arrhythmia syndromes. Ten patients (18%) experienced device-related complications. Three patients (6%) died, 2 due to VF storm.

Conclusions—In pediatric patients with IVF, a minority develop a definite clinical phenotype during long-term follow-up. Recurrent VF is common in this patient group. (*J Am Heart Assoc.* 2019;8:e011172. DOI: 10.1161/JAHA.118.011172.)

Key Words: idiopathic • defibrillator • ventricular fibrillation • complications • ventricular tachycardia • syncope

The majority of cases of arrhythmic sudden cardiac death (SCD) in young patients are attributable to either inherited structural cardiac diseases or primary arrhythmic syndromes.¹ In a subset of patients the cause of ventricular

fibrillation remains undefined despite comprehensive diagnostic evaluation and is referred to as idiopathic ventricular fibrillation (VF). According to contemporary guidelines idiopathic VF is defined as resuscitated cardiac arrest that occurs

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Accompanying Tables S1 and S2 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011172>

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Clinical Perspective

What Is New?

- This is the first study to systematically evaluate long-term outcomes among pediatric patients with an initial diagnosis of idiopathic ventricular fibrillation.
- We demonstrate that among pediatric idiopathic ventricular fibrillation patients, arrhythmias commonly occur in the context of high adrenergic tone, and there is a high incidence of recurrent arrhythmic events.
- Only a small minority of patients develop evidence of an underlying cardiac phenotype during long-term follow-up.

What Are the Clinical Implications?

- Over the years, the risk of recurrent arrhythmic events continues to be elevated, and therefore, in addition to implantation of cardiac defibrillators, these patients should be followed up closely.
- The incidence of complications related to implanted cardioverter/defibrillators in this pediatric population is relatively high, which may have important implications in terms of choice of device.

in the absence of cardiac, metabolic, toxicological, and respiratory causes.² Overall, idiopathic VF accounts for up to 8% of arrhythmic sudden cardiac death cases.³

There is a relative paucity of data on the natural history and long-term outcome in patients of pediatric age who present with idiopathic VF (IVF). Available studies have largely focused on adult cohorts with IVF.⁴ The aim of the present study is to define the long-term outcome in pediatric VF patients.

Methods

Data Collection

Patients were included from an International Registry of Idiopathic Ventricular Fibrillation (IVF) that consists of 496 IVF patients⁵ from 45 tertiary cardiac centers worldwide (collected between March 2004 and December 2015). The data are available on request from the authors. Criteria for inclusion in the registry were (1) sudden cardiac arrest with documented VF as the cause of arrest, (2) an absence of an underlying cause following comprehensive analysis for ischemic, electrical, infectious, or structural heart disease, and (3) age ≤ 16 years. The diagnostic criteria for IVF were based on the latest consensus guidelines.¹

Patients were systematically assessed at the referring centers after the index VF episode (before being assigned a diagnosis of IVF). Data on past clinical symptoms, including previous syncope episodes, were collected. Family history of

SCD was defined as a sudden death that occurred before 55 years of age in the absence of any known underlying pathological conditions.

The clinical workup consisted of a baseline ECG, blood tests (including cardiac enzymes and electrolytes), toxicology screening, and cardiac imaging (echocardiography and/or cardiac magnetic resonance imaging). Ajmaline testing was performed in order to exclude a diagnosis of concealed Brugada syndrome. Isoproterenol or epinephrine testing and exercise stress testing (using a modified Bruce protocol adapted for pediatric patients) were performed to exclude long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia (VT). The aforementioned tests were performed at the investigating physician's discretion at the referring center. Signal-averaged ECG and endomyocardial biopsies were also performed at the investigating physician's discretion. Time of implanted cardioverter/defibrillator (ICD) implantation and device programming were left to the decision of the referring physician (according to latest guidelines in order to reduce the possibility of inappropriate ICD shocks). The study was approved by the Institutional Review Board at CHU Bordeaux (inclusion in the IVF registry was approved by the institutional review boards at the respective institutions).

IVF Characteristics

The circumstances during the index VF event were categorized as (1) at rest, (2) daily activity, (3) sleep, (4) emotional stress, or (5) sport/strenuous activity. "At rest" was defined as SCD that occurred during no physical activity. "Daily activity" was defined as SCD that occurred during routine activities with very light physical activity. "Sleep" was defined as SCD occurring during bedtime or while asleep. Emotional stress was defined as intense emotion. Strenuous activity was defined as moderate to severe exercise (including in the setting of sport).

ECG Analysis

All ECGs (during the index hospitalization and at follow-up) were reviewed by 2 independent electrophysiologists (K.T., V.K.). In case of disagreement, the ECG was reviewed by a third electrophysiologist (N.D.). ECGs were analyzed at a paper speed of 25 mm/s and an amplitude of 10 mm/mV. Digital calipers were used to perform measurements (EP Calipers version 1.8 [<http://www.epstudiossoftware.com/>], EP Studios, 2017). P-wave duration and dispersion were calculated from the standard ECG during sinus rhythm where dispersion was defined as the difference between the minimum and maximum P-wave duration. Early repolarization was defined according to the latest consensus guidelines.⁶

Abnormal QRS fragmentation was defined as either ≥ 4 spikes in 1 lead or >1 notches in the nadir of the R or S wave in 2 consecutive leads. Davignon criteria⁷ were used to exclude right and left ventricular hypertrophy. S waves were characterized in terms of amplitude and duration in lead I. T peak–T end interval was measured from the peak to the end of the T wave in the precordial leads.

Invasive Electrophysiology Study

Programmed ventricular stimulation was performed at the investigating physicians' discretion. A consistent stimulation protocol from the right ventricular apex and outflow tract was used (2 drive cycle lengths [600 and 400 ms] and 3 extrastimuli with a minimal coupling up to 180 ms [unless ventricular arrhythmia was induced or the ventricular effective refractory period was reached]). A sustained VT/VF episode, defined as an episode lasting >30 s or VT/VF requiring direct current cardioversion, was considered a positive electrophysiological study. Nonsustained episodes (<30 s) were classified as negative electrophysiological study.

Genetic Testing

When available, genetic testing for variants implicated in heritable cardiomyopathies and/or channelopathies (long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia) was performed per consensus guidelines. When a putative mutation was identified, cascade screening was performed in family members.² The choice of genes targeted during genetic analysis was at the treating physician's discretion. Assignment of pathogenicity of identified variants was based on conventional guidelines.³ Repeat genetic testing with more extensive genetic panels was performed at the treating physician's discretion.

Follow-Up

Patients were followed up with sequential ICD interrogations (at least every 4 months), ECG, and cardiac imaging (echocardiography). Appropriate and inappropriate therapies with an implantable defibrillator were documented. Genotype and phenotype reevaluations during follow-up were performed at the investigating physician's discretion. Phenotypic reevaluation included repeat cardiac imaging, exercise stress testing, and pharmacological stress testing.

Statistical Analyses

Continuous variables were expressed as mean \pm standard deviation. Categorical variables were expressed as percentages. Qualitative variables were compared using the Fisher

exact test, whereas the Mann-Whitney test was used for continuous variables. Kaplan-Meier analysis was also performed for arrhythmia-free survival. A $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

Fifty-four of the 496 patients in the IVF registry fulfilled inclusion criteria. Patient characteristics are summarized in

Table 1. Population Study

Age, y	12.7 \pm 3.7
Male, n (%)	32 (59%)
Ethnicity, n (%)	
White	45 (84%)
Afro-Caribbean	5 (9%)
Asian	4 (7%)
Circumstances of SCD, n (%)	
Sport/strenuous activity	15 (28%)
Daily activity	11 (20%)
Emotional stress	11 (20%)
Rest	12 (22%)
Sleep	5 (10%)
Confirmation of IVF, n (%)	
Coronary angiogram	24 (44%)
Imaging	
Echo	54 (100%)
CMR	38 (70%)
Treadmill test	45 (83%)
Pharmacological tests, n (%)	
Isoproterenol	38 (70%)
Ajmaline	24 (44%)
Flecainide	13 (24%)
Endomyocardial biopsy	7 (13%)
Before the SCD event, n (%)	
Syncope	28 (52%)
Epilepsy	5 (9%)
Palpitations	2 (4%)
Family history of SCD, n (%)	
First degree	10 (67%)
Second degree	3 (20%)
Third degree	2 (13%)

CMR indicates cardiac magnetic resonance; Echo, echocardiogram; IVF, idiopathic ventricular fibrillation; SCD, sudden cardiac death.

Table 1. At the time of the index VF episode, the mean age was 12.7±3.7 years. Thirty-two patients (59%) were male. Patients were predominantly of white descent (45 white [84%]; 5 Afro-Caribbean [9%]; 4 Asian [7%]). Twenty-eight patients (52%) had a prior history of syncope (median 2 syncopal episodes, interquartile range 1). Twenty-four (85%) had effort-induced syncope. The syncopal events occurred 54±10 days before the sudden cardiac arrest. Five patients (9%) had previously been diagnosed with epilepsy. None of the patients had a history of recreational drug use. Specific details of the circumstances of the index episode are included in Table 1. All 54 patients underwent ICD implantation.

Fifteen patients (28%) had a family history of SCD (10 [67%] a first-degree relative; 3 [20%] a second-degree relative; 2 [13%] a third-degree relative). The mean age of sudden cardiac death in the relatives was 35.9 years (SD 19.7). In 1 case, sudden death occurred in 2 siblings.

Investigations

Imaging and Biopsy

Transthoracic echocardiography demonstrated a structurally normal heart in all patients (ejection fraction 61.5±6.2%). Cardiac magnetic resonance imaging was performed in 38 patients (70%) and confirmed the absence of structural heart disease. Coronary angiography was performed in 24 patients (44%) with no cases of anomalous coronary anatomy or significant stenosis identified. Seven patients (13%) underwent endomyocardial biopsy with negative results in all cases.

Table 2. Electrocardiographic Characteristics

Characteristics	Mean Value (SD)
Heart rate, bpm	76.3 (21.2)
P wave duration, ms	96.9 (17.2)
P wave dispersion, ms	36.8 (17.6)
P wave amplitude, mV	0.63 (3.66)
PR duration, ms	159.4 (30.98)
QRS duration, ms	82.9 (14.7)
IVS (Cornell), mm	1.26 (0.79)
QTc (Bazett), ms	416 (48.8)
S wave duration (I), ms	30.3 (12.2)
S wave amplitude (I), mV	0.23 (0.18)
T peak–T end, ms	88.4 (22.2)
QRS fragmentation, N (%)	25 (46.3%)
U wave, N (%)	27 (50%)

IVS indicates interventricular septum thickness (in mm); U wave, evidence of U wave on the 12-lead ECG.

Exercise and Pharmacological Testing

Forty-five patients (83%) underwent exercise stress testing, and 38 patients (70%) had an isoproterenol challenge. There were no QT interval abnormalities or sustained arrhythmias during these tests. In 1 patient the isoproterenol test induced multifocal ventricular ectopic beats. Ajmaline/flecainide challenge was performed in 37 patients (69%) and excluded Brugada syndrome.

ECG

None of the patients presented with left or right ventricular hypertrophy (based on the Davignon criteria). The early repolarization pattern was present in 31 patients (57.4%). Electrocardiographic characteristics are summarized in Table 2. The characteristics of the subset of patients with an early repolarization pattern are included in Table 3.

Invasive Electrophysiology Studies

An electrophysiological study was performed in 34 patients (63%). VF was induced in 3 patients (9%). There were no cases of inducible VT. Three patients (9%) had inducible atrial tachycardia.

Genetic Analysis

Forty-five patients (83%) underwent genetic testing. A putative pathogenic mutation was identified in 15 of the 45 (33%) patients (RYR2 [n=7]; TRDN [n=2]; CALM1 [n=1]; CASQ2

Table 3. ECG Characteristics of Subset of Patients With Early Repolarization

	No ER (n=23)	ER (n=31)	P Value
Female sex, N (%)	9 (40.9%)	11 (35.5%)	0.63
Age, y	12.2	13.1	0.77
HR (bpm) mean	79	74.4	0.45
P wave duration, ms	97.8	96.6	0.78
P wave amplitude, mV	0.16	0.99	0.11
P wave dispersion, ms	38.4	36.06	0.58
PR, ms	152.5	164.6	0.18
QRS duration, ms	83.6	81.7	0.60
QRS fragmentation, n (%)	10 (45.5)	14 (45.2)	0.92
IVS, mm	10.9	13.7	0.22
QTc, ms	426.5	408.8	0.19
S wave duration, ms	26	17	0.82
S wave amplitude, mV	0.156	0.162	0.21
U wave, N (%)	12 (54.5)	15 (50)	0.66
T Peak–T end, ms	94.1	84.5	0.12

ER indicates early repolarization; IVS, interventricular septum thickness (in mm).

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Table 4. Pathogenic Mutation Identified in 15 of 45 Patients

Patient	Gene	Identified Variant	Homozygote/ Heterozygote	MAF in gnomAD
1	<i>RYR2</i>	R4608Q	Heterozygote	0
5	<i>SLC22A5</i>	R471H	Heterozygote	0
6	<i>CASQ2</i>	Deletion of Exon1	Heterozygote	0
17	<i>KCNH2</i>	A429P	Heterozygote	0
18	<i>RYR2</i>	D4112N	Heterozygote	0
19	<i>RYR2</i>	D4112N	Heterozygote	0
22	<i>RYR2</i>	R4497C	Heterozygote	0
29	<i>SCN5A</i>	R1644H	Heterozygote	0
37	<i>MYH7</i>	F48L	Heterozygote	0
46	<i>CALM</i>	N98S	Heterozygote	0
47	<i>TRDN</i>	c./53_56delACAG p.(Asp18AlafsTer14)	Compound heterozygote	0
48	<i>TRDN</i>	c.502G>T p.(Glu168Ter)	Compound heterozygote	0
49	<i>RYR2</i>	c.7273T>C	Heterozygote	0
50	<i>RYR2</i>	G3930R	Heterozygote	0
51	<i>RYR2</i>	c.11648A>G	Heterozygote	0

MAF indicates minor allele frequency.

[n=1]; *SCN5A* [n=1]; *KCNH2* [n=1]; *MYH7* [n=1]; *SLC22A5* [n=1]). Two patients did not provide consent for disclosure of their genetic results. Based on the rapidly emerging data on genetic variation in normal populations, we reevaluated the prevalence of the reported genetic variants in the gnomAD database, which spans ≈123 000 exomes (<http://gnomad.broadinstitute.org/>). All variants were confirmed to be unique (Table 4).

Pharmacotherapy

Twenty patients (37%) were discharged following the index VF with no drug therapy. Eighteen (33%) were commenced on a selective β-blocker. One patient was discharged with quinine.

Outcomes

Arrhythmia Recurrences

Patients were followed up for a median time of 109±12 months after the index VF episode. Thirty-one patients (57%), experienced a recurrence of ventricular arrhythmias (23 [74%] had only VF; 8 [26%] had only sustained VT). Four patients (13%) experienced both VT and VF episodes. The patients with recurrences experienced a median of 2 appropriate shocks (interquartile range 5.5). The first recurrence of ventricular arrhythmia occurred after a

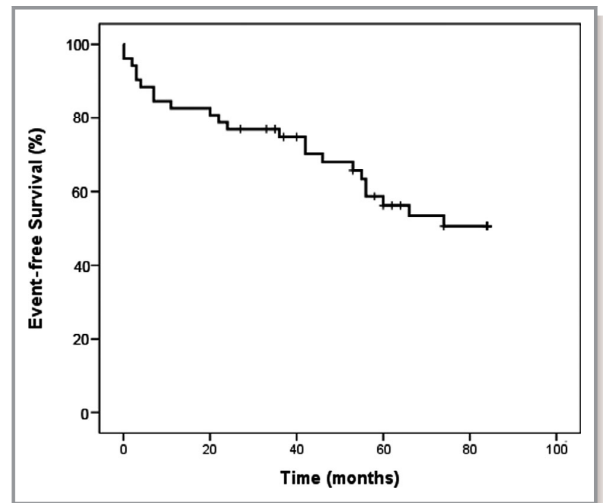


Figure 1. Kaplan–Meier curve demonstrating freedom from ventricular arrhythmias.

mean of 6.4 years after the index VF episode (Kaplan–Meier curve, Figure 1).

In 12 of 31 patients (39%), recurrences of ventricular arrhythmia occurred in the context of high adrenergic tone (exercise or intense stress/emotion), and the remaining recurrences occurred at rest. The arrhythmia recurrences according to clinical characteristics and specific genotypes are represented in Tables S1 and S2. One patient developed paroxysmal atrial fibrillation. The characteristics of individuals with VT/VF-related ICD shocks are included in Table 5. Nine (33%) patients with VF recurrences were drug-naive. Among the 36 patients in whom the index VF episode occurred in the context of high adrenergic tone, 15 (42%) had recurrent ventricular arrhythmias. In the remaining 18 patients (nonadrenergic group), 12 (67%) experienced a recurrence of VF. Recurrence of arrhythmia occurred in 4 patients treated with selective β-blockers and in 1 patient treated with mexiletine. Three patients (6%) died during follow-up. Two died due to an arrhythmic storm. One patient remained in a neurovegetative state following the arrest until death.

Device-Related Complications

Ten patients (18%) experienced device-related complications (ventricular lead fracture [n=5]; lead insulation defect [n=1]; further device procedures due to lead recall [n=2]; late lead dislodgement [n=1]; device infection [n=1]). Eleven patients (20%) experienced inappropriate shocks (sinus tachycardia [n=1]; atrial arrhythmias [n=3]; noise on the ventricular channel [n=3], lead fracture [n=3]; sensing lead insulation defect [n=1]). The mean time from implant to complication was 41±14 months; the mean number of inappropriate shocks was 1.9±1 (Table 6).

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Table 5. Recurrences of Ventricular Arrhythmias

	Sex	Past Syncope	Family History	EP Study	Genetic	Death
VF group (n=23)	16 male	12/23 (52%)	8/23 (35%)	Performed in 3/12 Inducible (13%)	18/23 (78%) 1 CALM+ 2 Triadin + 4 RyR2+	2 (9%)
VT group (n=8)	6 male	5/8 (62.5%)	5/8 (62%)	Performed in 6/8 (75%) No inducible ventricular tachycardia	Performed in 7/8 (88%) RyR2+ (2) and Triadin+ (2)	1 (14%)

EP indicates electrophysiological; VF, ventricular fibrillation; VT, ventricular tachycardia.

Repeat Testing

Patients underwent systematic phenotype reevaluation 78±11 months after the index VF episode: all patients underwent repeat ECGs and transthoracic echocardiography. Forty-five percent had a repeat cardiac magnetic resonance; 90% had a repeat stress test (with adult exercise testing protocols); 62% had a repeat isoproterenol challenge. Repeat genetic sequencing with an extended genetic panel was performed in 54% of the population at the discretion of the treating physician. One patient (2%) developed phenotypic evidence of hypertrophic cardiomyopathy during follow-up. Of note, that patient had previously been identified as a *MYH7* variant carrier (patient 37, Table 4). None of the patients who

underwent repeat exercise stress testing or isoproterenol challenge had exercise-induced arrhythmias. Repeat genetic testing did not reveal additional variants. None of the long QT gene carriers had a prolonged QT interval at the time of the index event; 1 of the patients (patient 29 in Table 4) had evidence of QT prolongation during follow-up (*SCN5A* mutation carrier; QT interval 495 ms). The results of phenotypic reevaluation are included in Figure 2.

Discussion

The main findings of the present study are as follows: (1) the majority of SCD events in pediatric IVF patients occur in the context of high adrenergic tone; (2) close to a fifth of pediatric IVF patients have variants in genes implicated in catecholaminergic polymorphic ventricular tachycardia; (3) pediatric IVF patients have a high risk of recurrent arrhythmic events during long-term follow-up; (4) only a small minority of patients develop evidence of an underlying cardiac phenotype during long-term follow-up. (5) The incidence of ICD-related complications in this pediatric population is relatively high.

The majority of reports on IVF to date have focused on adult populations. There is a relative paucity of data on IVF in pediatric populations. In a large cohort of adult IVF patients, Visser and colleagues reported that, during long-term follow-up, a specific diagnosis was identified in up to a fifth of patients⁴ of whom almost 50% were found to have an underlying cardiomyopathy. In contrast to these findings, during a similar follow-up period specific diagnoses were identified in only 4% of our pediatric cohort. It is important to emphasize, however, that because our cohort was of pediatric age at the index VF event, the initial evaluation was less comprehensive than that routinely performed in adult cohorts. Further, although reevaluation of our cohort during follow-up did not reveal a specific underlying diagnosis, the strategies for reevaluation were variable. Our findings may, however, suggest that the underlying arrhythmogenic substrate in pediatric patients is distinct from that of adult IVF patients and may have a low diagnostic yield.

A potential pathogenic genetic variant was identified in a third of the patients in our cohort. In turn, variants in *RYR2*

Table 6. ICD Characteristics and Complications Encountered During the Follow-Up

ICD characteristics	
Endocardial implant, n (%)	47 (87%)
Single-chamber ICD	45 (96%)
Dual-chamber ICD	2 (4%)
Epicardial implant	4 (7%)
Subcutaneous ICD	3 (6%)
ICD complications	
Inappropriate shocks, n (%)	11 (20%)
Sinus tachycardia	1 (9%)
Atrial arrhythmias	3 (27%)
Lead fracture	3 (27%)
Noise on the V channel	3 (27%)
Lead insulation defect	1 (9%)
Device-related complications, n (%)	10 (18%)
Lead fracture	5 (50%)
Lead recall	2 (20%)
Pocket infection	1 (10%)
Sensing lead insulation defect	1 (10%)
Lead dislodgement	1 (10%)

ICD indicates implanted cardioverter/defibrillator.

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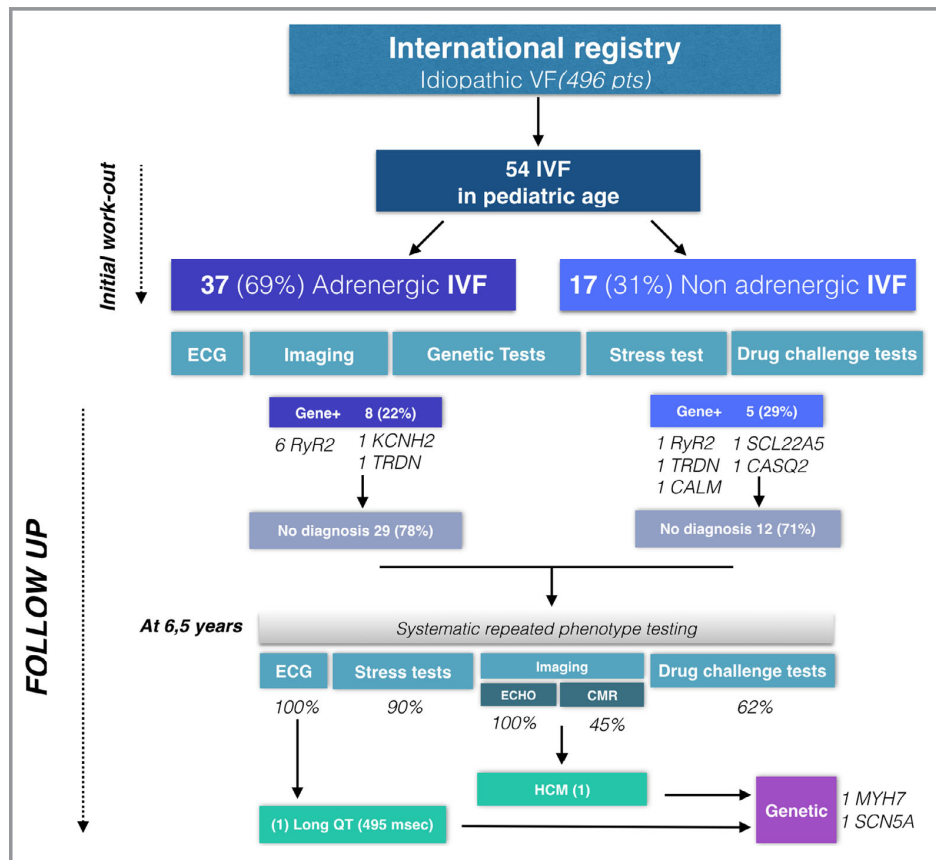


Figure 2. Summary of phenotypic evaluation following index episode and at follow-up (78±11 months). CMR indicates cardiac magnetic resonance; ECHO, echocardiogram; HCM, hypertrophic cardiomyopathy; IVF, idiopathic ventricular fibrillation; VF, ventricular fibrillation.

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were identified in close to half of the genotype-positive patients. Consistent with our finding, Lahrouchi et al⁸ reported that in patients with sudden arrhythmic death syndrome, *RYR2* variants were the most commonly identified pathogenic/likely pathogenic variants following postmortem genetic testing (43% of genotype-positive cases). In the study by Visser and colleagues,⁴ on the other hand, the overall yield for genetic testing was lower at 15%, with only a quarter of genotype-positive patients harboring catecholaminergic polymorphic ventricular tachycardia gene variants. Of note, patients included in our study (as in that of Lahrouchi et al) were significantly younger than the patients included by Visser et al. It is important to note, however, that a significant proportion of apparently pathogenic *RYR2* variants may not be disease causing.⁹ Furthermore, although the yield of genetic test may increase with broad multiphenotype genetic testing, this approach may be associated with a higher incidence of variants of uncertain significance.¹⁰

Further, in the study of Visser and colleagues,⁴ a third of adult IVF patients experienced recurrent arrhythmic events.

We observed a higher frequency of recurrent arrhythmic events in our pediatric IVF cohort, with close to half of cases experiencing recurrences. Importantly, despite an overall higher arrhythmic burden, the recurrent arrhythmic events in our cohort occurred at a later stage as compared with those reported in the adult population. These findings suggest that, in pediatric IVF patients, the disease process is associated with a more malignant course, with ongoing arrhythmic risk extending over a more prolonged period of time.

The choice of ICD device is an important consideration in pediatric populations. In recent years increasing evidence has emerged supporting the use of subcutaneous ICD as an alternative to transvenous systems.¹¹ Close to a fifth of patients in our cohort experienced device-related complications, which predominantly consisted of lead-related issues. These findings may support the use of subcutaneous ICD in pediatric populations.

In addition to a family history of SCD, ECG features such as Tpeak-Tend >100 ms with U waves and right bundle branch block were associated with more arrhythmia recurrences in

our cohort. Our findings are in line with similar results in the adult population,¹² and these ECG markers could potentially modulate arrhythmic risk stratification. However, based on the limited size of our cohort, these results should be interpreted with caution.

Limitations

Patients were recruited from a large number of centers over a prolonged period of time (more than a decade) in multiple countries. Therefore, the workup of patients following the VF episode and ICD programming was not standardized. It must be emphasized that guidelines for evaluation of these patients evolved over the time period of the study; therefore, there was some variation in the investigation of patients following episodes of aborted sudden death. During follow-up, close to half of the population did not undergo comprehensive genetic testing. Medications were prescribed at the physician's discretion, and we acknowledge that is also a potential confounding factor. Among patients who did not have a cardiac magnetic image performed (30%), we acknowledge that a diagnosis of myocarditis could have been missed. Genetic testing was performed in the absence of a clear phenotype and on a discretionary basis. Where performed, genetic testing involved a candidate-gene approach that targeted the common genes implicated in cardiac channelopathies and cardiomyopathies.

Conclusion

Our findings suggest that both the clinical course and underlying arrhythmogenic substrate in pediatric patients with IVF are distinct from those previously reported for adult IVF cohorts.

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Disclosures

Drs Haïssaguerre, Hocini, Jaïs, and Sacher have received lecture fees from Biosense Webster and Abbott. Drs Denis, Derval, Jaïs, and Sacher received speaking honoraria and consulting fees from Boston Scientific. The remaining authors have no disclosures to report.

References

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N; ESC Scientific Document Group. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793–2867.
2. Priori SG, Wilde AA, Horie M, Cho Y. HRS/EHRA/APHS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHS in May 2013 and by ACCF, AHA, PACES, and AEPCC in June 2013. *Heart Rhythm*. 2013;10:1932–1963.
3. Myerburg RJ, Kessler KM, Zaman L, Conde CA. Survivors of prehospital cardiac arrest. *JAMA*. 1982;247:1485–1490.
4. Visser M, van der Heijden JF, van der Smagt JJ, Doevendans PA. Long-term outcome of patients initially diagnosed with idiopathic ventricular fibrillation: a descriptive study. *Circ Arrhythm Electrophysiol*. 2016;9:e004258.
5. Haïssaguerre M, Derval N, Sacher F, Jesel L. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;358:2016–2023.
6. Macfarlane PW, Antzelevitch C, Haïssaguerre M, Huikuri HV. The early repolarization pattern: a consensus paper. *J Am Coll Cardiol*. 2015;66:470–477.
7. Davignon A, Rautaharju P, Boisselle E, Sourmis F. Normal ECG standards for infants and children. *Pediatr Cardiol*. 1980;1:123–131.
8. Lahrouchi N, Raju H, Lodder EM, Papatheodorou E. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. *J Am Coll Cardiol*. 2017;69:2134–2145.
9. Kapplinger JD, Pundi KN, Larson NB, Callis TE, Tester DJ, Bikker H, Wilde AAM, Ackerman MJ. Yield of the RYR2 genetic test in suspected catecholaminergic polymorphic ventricular tachycardia and implications for test interpretation. *Circ Genom Precis Med*. 2018;11:e001424.
10. Mellor G, Laksman ZWM, Tadros R, Roberts JD. Genetic testing in the evaluation of unexplained cardiac arrest: from the CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry). *Circ Cardiovasc Genet*. 2017;11:e001686.
11. Burke MC, Gold MR, Knight BP, Barr CS. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE study and EFFORTLESS registry. *J Am Coll Cardiol*. 2015;65:1605–1615.
12. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C. Prolonged Tpeak-to-Tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2011;4:441–447.

SUPPLEMENTAL MATERIAL

Supplemental References:

1. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793-867.
2. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies: This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011;13:1077-109.
3. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-24.

Table S2. Clinical characteristics of genotype-positive patients.

	CALM1	TRDN	MYH7	SCN5A	KCNH2	SCL22A	CASQ2	RyR2
N (%)	1	2	1	1	1	1	1	7
Circumstances of SCD	Rest	Moderate effort (1) Rest (1)	Emotion	Rest (1)	Sport	Asleep (1)	Asleep (1)	Moderate effort (3) Sport (2) School (1) Rest (1)
Phenotype	Negative	Negative	Developed HCM	1 (Long QT)	Negative	Negative	Negative	Negative
Recurrence of shocks	-	100%	-	-	-	-	100%	57%

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Table S1. Characteristics of Patients with RyR2 and Triadic mutations.

	Gene	Mutation	Age at VF	Family history SCD	Adrenergic related index VF episode?	Previous Syncope?	ETT Findings	Isoprenaline challenge positive?	U waves
1	<i>RYR2</i>	R4608Q	7	n	y	n	Normal	n	n
18	<i>RYR2</i>	D4112N	12	y	n	y	Normal	n	y
19	<i>RYR2</i>	D4112N	7	n	y	y	Normal	n	n
49	<i>RYR2</i>	c.7273T>C	14	n	y	n	Normal	n	n
50	<i>RYR2</i>	G3930R	14	n	y	y	Normal	n	y
51	<i>RYR2</i>	c.11648A>G	13	n	y	n	Normal	n	y
22	<i>RYR2</i>	R4497C	11	Y	y	y	Normal	n	y
47	<i>TRDN</i>	c/53_56delACAG p.(Asp18AlafsTer14)	2	n	n	n	Normal	n	n
48	<i>TRDN</i>	c.502G>T p.(Glu168Ter)	1,5	n	y	n	Normal	n	n

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Performance of an algorithm in the real-world to prevent inappropriate ICD therapies

1. Study outline

The implantable cardioverter-defibrillator (ICD) is effective in reducing mortality in patients at risk of fatal ventricular arrhythmias (VAs)(26)(27). The delivery of inappropriate shocks (through wrongful detection of VA) occurs in 21% of patients with implants and remains a limitation of ICDs(28)(29). Inappropriate shocks have important consequences on the quality of life and increase mortality (30) and in most cases, inappropriate shocks are caused by erroneous discrimination of supraventricular tachycardia. In 10% of cases, inappropriate shocks are associated with various types of oversensing; oversensing of cardiac signals (P, R, or T wave), oversensing of pectoral or diaphragmatic muscle, oversensing of electromagnetic interference, or oversensing of signals originating from a defective lead(31). Specific dedicated algorithms have been developed by the company to detect oversensing. Secure sense right ventricular is the algorithm proprietary of Abbott medical devices initially designed to detect lead fracture and to prevent inappropriate therapies.

The hypothesis was to verify the optimal accuracy of the algorithm which is important to reduce the occurrence of inappropriate therapy and to not misdiagnose VA as oversensing and wrongly withhold treatment, which would result in sudden cardiac death. There we investigated the performance of Secure

Sense in a real-world setup using a large population of patients implanted with an ICD, followed by remote monitoring across multiple centers.

2. Implications

The algorithm SecureSense™ is capable to detect oversensing of physiological signals, which made up more than half of the episodes in our study. Apparently, lead dysfunction most often starts with non-physiological signals on the near field channel while the far field channel remains free from additional signals. SecureSense™ correctly withheld inappropriate therapy in three patients with accurate diagnosis of oversensing (caused by lead dysfunction or oversensing of physiological signals).

3. Manuscript

Multicenter Investigation of an Implantable Cardioverter Defibrillator Algorithm to Detect Oversensing

Running title: ICD algorithm against oversensing

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Background.

The SecureSense™ RV Lead Noise Discrimination algorithm is designed to detect lead fracture and other types of oversensing in order to decrease inappropriate therapy.

Objective.

We studied the real-life accuracy of the SecureSense™ algorithm in ICD patients followed by remote-monitoring across multiple centers.

Methods.

Across three French centers, we studied 486 patients with a St. Jude Medical device who were followed by remote-monitoring and who had the SecureSense™ algorithm activated. We reviewed up to ten of the most recent remote monitoring-transmitted EGMs of nonsustained oversensing, RV lead noise and VT/VF which received therapy.

Results

SecureSense™ inhibited 22 inappropriate therapies (lead dysfunction in 10 cases, P-wave oversensing in 12 cases). 57 patients (12%) sent ≥ 1 nonsustained oversensing episode (total of 393 episodes) with multiple etiologies: noise on the near-field channel (38%), oversensing of T-waves during ventricular pacing (33%), oversensing of the sinus P-wave (12%) and oversensing of the paced P-wave (6%). Two episodes (0.5%) of non-sustained VT were undersensed by the far-field channel. Of 336 analyzed episodes of ventricular tachyarrhythmia, 15 episodes (4%) in four patients were related to oversensing of intrinsic P-waves in 11 episodes or oversensing of external noise due to electrical cautery for the remaining 4 episodes.

Conclusion

12% of ICD patients equipped with SecureSense™ developed episodes of oversensing. The SecureSense™ algorithm prevented inappropriate ICD therapies with accurate diagnosis of oversensing (caused by lead dysfunction or oversensing of physiological signals). P-wave oversensing in integrated bipolar leads, electrical cautery and electromagnetic interference are prone to be missed by SecureSense™.

Keywords: ventricular tachycardia; securesense; sjm; ICD; ventricular fibrillation; noise; algorithm; EGM; electrogramme; devices

Introduction

The implantable cardioverter-defibrillator (ICD) is effective in reducing mortality in patients at risk of fatal ventricular arrhythmias (VA).^{1, 2} The delivery of inappropriate shocks (through wrongful detection of VA) occurs in up to 21% of implanted patients and remain a limitation of ICDs.^{3, 4} Inappropriate shocks have important consequences on the quality of life and increases mortality.⁵ In most cases inappropriate shocks are caused by erroneous discrimination of supraventricular tachycardia. In approximately 10% of cases, inappropriate shocks are associated with various types of oversensing; oversensing of cardiac signals (P-, R- or T-wave), oversensing of pectoral or diaphragmatic muscle, oversensing of electromagnetic interference or oversensing of signals originating from a defective lead.⁶ Specific dedicated algorithms have been developed with the aim to detect oversensing. The SecureSense™ RV Lead Noise Discrimination (St Jude Medical, St Paul, MN) algorithm was initially designed to detect lead fracture and to prevent inappropriate therapies. The algorithm is based on a continuous comparison between the conventional near-field channel and an additional far-field channel and acts when there is a discrepancy in detection between both channels. An optimal accuracy of the algorithm is important to reduce the occurrence of inappropriate therapy, and to not misdiagnose VA as oversensing and wrongly withhold treatment resulting in sudden cardiac death. Unfortunately, data concerning the evaluation of the SecureSense™ algorithm is insufficient: it consists of selected cases⁷ and of an analysis of episodes of noise induced by the cardiologist through lead manipulation during implantation⁸. The objective of the present study was to investigate the performance of SecureSense™ in a real-world setup using a large population implanted with an ICD, followed by remote-monitoring across multiple centers.

Methods

Patient population.

Patients implanted in university hospitals of three centers in France (Bordeaux, Grenoble and Toulouse) since 2013 with a St. Jude Medical ICD (models ELIPSE™, UNIFY™, QUADRA™ or ASSURA™ models) with SecureSense™ algorithm switched ON were enrolled in the study and included in this observational study. All patients gave written, informed consent for analysis of the data providing from remote monitoring and patient information was de-identified prior to analysis of the episodes.

The SecureSense™ algorithm

The algorithm is based on a near field (NF) electrogram derived from the right ventricular (RV) tip-to-ring (bipolar) or tip-to-coil (integrated bipolar) which is constantly compared with a far field (FF) electrogram derived from the RV coil-to-can or tip-to-can. A 1-to-1 association between a near-field and a far-field signal from the ICD lead is considered as physiologic cardiac activation. Oversensing is diagnosed when the algorithm senses NF events that do not correspond to FF events. A schematic representation of the SecureSense algorithm is shown in Figure 1. During a true ventricular arrhythmia, the counter should be constantly reset by the occurrence of fast intervals on the FF channel. When the ICD diagnoses a ventricular arrhythmia while the counter is at least 10, therapy is withheld. After a charge and just before shock delivery, the counter is reconfirmed. When the counter is greater than 10, the algorithm declares the episode as RV lead noise and an alert is transmitted through Merlin™ remote monitoring. After high voltage therapy, SecureSense™ is disabled until the episode terminates. SecureSense™ may also be activated for nonsustained tachycardia events that fall in a tachycardia zone without fulfilling the duration criteria. In non-sustained events and when the counter reaches 10, the EGM is saved into the device memory as “non-sustained oversensing” and an alert is sent.

To decrease the risk of incorrect therapy inhibition during true VT/VF with undersensing on the FF channel, the algorithm checks 3 conditions on the FF EGM to determine whether undersensing may be occurring: the amplitude, the number and rate of sensed events. If any of the following 3 conditions are met, the algorithm declares undersensing on the FF channel and refrains from therapy inhibition:

1. more than 2 sensed events have amplitude less than 0.6 mV
2. less than 2 sensed events
3. intervals between events are longer than 2200 milliseconds

The device issues an undersensing alert and switches SecureSense™ to passive mode. Basic sensing parameters are not programmable for the FF channel. Sensing on the discrimination channel is nominally set to the RV coil-to-can configuration; an alternative RV tip-to-can configuration may be programmed. The filters for the discrimination channel are similar to the filters of the primary pace-sense channel except that the low-frequency attenuation filter is disabled. Unfiltered signals of the discrimination channel can be viewed on any VT/VF or nonsustained oversensing stored EGM, but this signal is different from internally filtered signals that are used for discrimination by the device. The signals used for sensing and discrimination are internally filtered. The ICD stores both the unfiltered and the filtered sensing (ventricular sense amplitude) signal, but only the unfiltered discrimination signal. Furthermore, filtering usually differs for the 2 analyzed channels. By default, the programmable low-frequency attenuation filter is on for the sensing channel, but it does not apply to the discrimination channel. Important to note is that this low-frequency attenuation filter has been recently identified as a reversible cause of diaphragmatic myopotential oversensing.⁹

Data analysis and statistics.

For every patient, we reviewed up to ten of the most recent remote monitoring-transmitted EGMs of “non-sustained oversensing” (episodes where the noise counter reached 10 while the tachycardia counter was not completed) and “RV lead noise” (episodes where tachycardia counter was completed while the noise counter was ≥ 10). Similarly, we reviewed up to ten of the last remote monitoring-transmitted EGMs of VT or VF which received at least one therapy. All EGMs were dated between April 2013 to June 2016 and were independently interpreted by two cardiologists, experienced in EGM interpretation.^{10, 11} Categorical variables are expressed as absolute numbers and percentages. Bivariate comparisons were performed using the t-test for normally distributed continuous variable or the Mann-Whitney U test for variables not normally distributed. Bivariate comparisons of categorical variables were performed with the χ^2 test. A value of $P < 0,05$ was considered statistically significant.

Results

Across the three French centers there were 742 patients with remote monitoring and a St Jude Medical ICD of which 486 (65%) had the SecureSense™ algorithm activated. Baseline patient and device characteristics are summarized in table 1.

Sustained oversensing.

Of 486 included patients, 3 (0.6%) sent at least one RV lead noise episode through remote-monitoring with inhibition of therapy. In total, 22 shock deliveries were inhibited by the algorithm (Table 2). Of these 22 episodes, 10 were caused by lead dysfunction in a single patient (Figure 2) and 12 corresponded to P-wave oversensing in two patients (Figure 3). In one patient it was because of an early lead dislodgment. In the other patient it was caused by the coil of an integrated bipolar lead straddling the tricuspid valve.

Non-sustained oversensing

Of the 486 included patients, 57 (12%) sent at least one nonsustained oversensing episode through remote-monitoring. We analyzed 393 episodes of non-sustained oversensing (Table 2) of which 150 episodes (38%) across 23 patients were indeed associated with lead dysfunction. In these patients, the algorithm exposed intermittent non-physiological signals on the NF channel characteristic of lead dysfunction but never reached the VT/VF counter so that therapy inhibition never occurred. 36 episodes (in 4 patients) were attributed to diaphragmatic myopotential oversensing provoked by the Low Frequency Attenuation filter. In 19 patients (114 episodes) lead noise was an early sign of lead failure and a lead replacement has been necessary. Other causes of oversensing comprised: oversensing of the T-wave during ventricular pacing (128 episodes, 33% of cases), oversensing of the intrinsic P-wave (48 episodes, 12%), oversensing of the paced P-wave (24 episodes, 6%).

The incidence of P wave oversensing appears high, but in fact concerned only 7 out of 486 patients (1,4%): 4 patients had non sustained oversensing of intrinsic P wave, 2 patients had non-sustained oversensing of paced P wave and one patient had both. The 4 patients with oversensing of intrinsic P waves had integrated bipolar leads straddling the tricuspid valve. The 2 patients with oversensing of the paced P wave had a bipolar lead in the RV. This oversensing phenomenon disappeared when we switched off the low frequency attenuation filter. The patient with both oversensing of intrinsic and paced P wave also experienced impedance disturbances on the RV lead, revealing an insulation defect located in the right atrium..

Less frequent triggers for a nonsustained oversensing episodes were:

- Loss of ventricular capture (21 episodes, 5%).
- Fast ventricular events on the NF channel during atrial fibrillation with concomitant undersensing on the FF channel (10 episodes, 3%).
- Temporal offset between detection on the NF and detection on the FF channel (5 episodes, 1%). Because the two channels use different sensing circuits, a small timing variation can occur. Thus, an interval can be classified as fast on the NF channel but slow on the FF channel and the noise counter can be incremented.
- Oversensing of intrinsic T-wave (2 episodes, 0,5%).
- R-wave double counting (3 episodes, 0,8%).
- Two episodes (0.5%) exposed non-sustained VT which were undersensed by the FF channel (example is shown in Figure 4).

Ventricular tachyarrhythmia.

Of the 486 included patients, 83 (17%) sent at least one VT or VF episode through remote-monitoring which required therapy. We analyzed 336 episodes of which 295 (88%) were true VT or VF with appropriate therapy, 26 episodes (8%) were in fact supraventricular tachycardia where discrimination failed in the VT zone (18 episodes) or who were in the VF zone where there is no discrimination (8 episodes). 15 episodes (4%) in four patients were related to oversensing which was not diagnosed by the SecureSense™ algorithm. The inappropriate therapies occurred because of either oversensing of intrinsic P-waves in 11 episodes (Figure 5A for an example) or oversensing of external noise due to electrical cautery in the remaining 4 episodes (Figure 5B). The therapies were not withheld by the algorithm since in both cases the oversensing occurred on both channels (NF and FF). It is important to note that for the case of an integrated bipolar RV lead, the RV coil is common to both the NF channel and the FF channel, thus oversensing on both channels is more likely to occur which was the case for P-wave oversensing.

Discussion

In the present study, we evaluated the ability of the algorithm to detect and correctly diagnose ICD-lead oversensing. 12% of ICD-patients transmitted SecureSense™ alerts

revealing oversensing of physiologic (P-wave, R-wave, T-wave) and non-physiologic (lead dysfunction) signals. SecureSense™ correctly withheld inappropriate therapy in three patients. We identified no wrongful inhibition of appropriate therapies.

Performance and specificities of the SecureSense™ algorithm.

In 413 out of 415 episodes labeled as sustained or nonsustained oversensing, the algorithm indeed revealed oversensing. The two remaining episodes revealed non-sustained VT incorrectly diagnosed as oversensing. Would these VTs have been sustained, these wrongful classifications may have led to inhibition of appropriate therapies. 321 out of 336 treated episodes labeled as “VT/VF” (95.5%) were true ventricular arrhythmias. In the remaining 15 episodes there was in fact oversensing, not detected by the algorithm, due to P-wave oversensing (integrated bipolar leads) and electrocautery. These are expected complications since they pose simultaneous fast events on both channels. Oversensing of the P-wave on the NF is likely to also occur on the FF. Electric cauterization or electromagnetic interference are vulnerable by design and the SecureSense™ algorithm does not protect against these problems.

Predictors of oversensing

The occurrence of hypertrophic cardiomyopathy was significantly higher in the group with non-sustained or sustained oversensing episodes than in the group without oversensing episodes. This is more likely a consequence of younger age in this population than a direct consequence of the cardiomyopathy itself. Indeed, an age below 70 years has been shown to be associated with a higher risk of lead failure in several studies.^{12, 13} The higher proportion of biventricular devices in the oversensing group is explained by the fact that the post paced T-wave oversensing was almost always associated with LV pacing, and post paced T-wave oversensing was the second leading cause of non-sustained oversensing. In many cases, the SecureSense algorithm permitted to diagnose the cause of the diminution of biventricular pacing.

Clinical and future perspectives

Apparently, lead dysfunction most often starts with non-physiological signals on the near field channel while the far field channel remains free from additional signals. Even though SecureSense™ is designed to diagnose lead dysfunction, the algorithm is also capable to detect oversensing of physiological signals, which made up more than half of the episodes in our study.

While the algorithm may withhold inappropriate therapy, it does not resolve the underlying problem. The treating physician or technician is required to act on the SecureSense™ alert by reprogramming the device or by changing the lead. Using the FF channel to detect noise can be considered as a revolution in the field of ICDs. The benefits of the SecureSense™ algorithm but also the potential disastrous consequences of undersensing on the FF channel raise the need for evaluation of FF detection in the future. Quality of the FF signal and ability to correctly detect events would need to be determined during implantation and during follow-up by periodic measurement of the R-wave amplitude with eventual options for programming detection parameters such as sensibility, threshold start and delay. We advise to avoid the combination of integrated bipolar RV leads and the SecureSense™ algorithm. The RV coil is used for both the NF channel and the FF channel which increases the risk of oversensing on both channels. An additional protection against therapy inhibition during true arrhythmia is the implementation of a timeout which switches off the SecureSense™ algorithm during prolonged episodes since the more sustained fast cycles on the FF channel, the more likely it is an arrhythmia, and not noise. This timeout is disabled by default but may be activated. It also exists for the latest generations Medtronic ICDs (RV Lead Noise: On+Timeout as part of the SmartShock™ algorithm) and is 45 seconds by default. St. Jude Medical and Medtronic are the only companies that offer algorithms which use the FF channel to detect noise and withhold therapies. Even though differences exist between these algorithms, they share a common philosophy. We could easily imagine that Boston Scientific or Biotronik, who currently use the FF channel for discrimination, will implement similar algorithms in the future.

Study limitations

We could not calculate the exact sensitivity and specificity of this algorithm for two reasons: this would require permanent monitoring of the patients to discover any noise events not detected by the algorithm; and in the most extreme case, a fatal VT/VF episode due to inhibition of SecureSense™ could not be sent to the remote-monitoring network. We did not assess other methods for inappropriate therapy avoidance to which we compared the benefit of the SecureSense™ algorithm. Finally, the programmable feature that multiple oversensing episodes are required for a specific alert transmission indicates that we did not receive all oversensing episodes.

Conclusion

12% of ICD patients equipped with SecureSense™ transmitted episodes of oversensing. The SecureSense™ algorithm prevented inappropriate ICD therapies with accurate diagnosis of oversensing (caused by lead dysfunction or oversensing of physiological signals). P-wave oversensing in integrated bipolar leads, electrical cauterization and electromagnetic interference are prone to be missed by SecureSense™. We encourage the development of a feature which enables an evaluation and detection on the far-field channel during implantation and during follow-up.

References

1. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.
2. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-237.
3. Daubert JP, Zareba W, Cannom DS, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008;51:1357-1365.
4. Ellenbogen KA, Levine JH, Berger RD, Daubert JP, Winters SL, Greenstein E, Shalaby A, Schaechter A, Subacius H, Kadish A. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;113:776-782.
5. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;367:2275-2283.
6. Powell BD, Asirvatham SJ, Perschbacher DL, Jones PW, Cha YM, Cesario DA, Cao M, Gilliam FR, 3rd, Saxon LA. Noise, artifact, and oversensing related inappropriate ICD shock evaluation: ALTITUDE noise study. *Pacing Clin Electrophysiol* 2012;35:863-869.
7. Koneru JN, Kaszala K, Bordachar P, Shehata M, Swerdlow C, Ellenbogen KA. Spectrum of issues detected by an ICD diagnostic alert that utilizes far-field electrograms: Clinical implications. *Heart Rhythm* 2015;12:957-967.
8. Beau S, Greer S, Ellis CR, Keeney J, Asopa S, Arnold E, Fischer A. Performance of an ICD algorithm to detect lead noise and reduce inappropriate shocks. *J Interv Card Electrophysiol* 2016;45:225-232.
9. Ploux S, Swerdlow CD, Eschalier R, Monteil B, Ouali S, Haïssaguerre M, Bordachar P. Diaphragmatic Myopotential Oversensing Caused by Change in Implantable Cardioverter Defibrillator Sensing Bandpass Filter. *Pacing Clin Electrophysiol* 2016;39:774-778.
10. Strik M, Defaye P, Eschalier R, Mondoly P, Frontera A, Ritter P, Haissaguerre M, Ploux S, Ellenbogen KA, Bordachar P. Performance of a specific algorithm to minimize right ventricular pacing: A multicenter study. *Heart Rhythm* 2016.
11. Strik M, Frontera A, Eschalier R, Defaye P, Mondoly P, Ritter P, Haissaguerre M, Ploux S, Bordachar P. Accuracy of the pacemaker-mediated tachycardia algorithm in Boston Scientific devices. *J Electrocardiol* 2016;49:522-529.
12. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation* 2007;115:2474-2480.
13. Ricci RP, Pignalberi C, Magris B, Aquilani S, Altamura V, Morichelli L, Porfili A, Quarta L, Saputo F, Santini M. Can we predict and prevent adverse events related to high-voltage implantable cardioverter defibrillator lead failure? *J Interv Card Electrophysiol* 2012;33:113-121.

Figure legends

Figure 1: Schematic representation of the SecureSense™ algorithm. When 2 ventricular events in a roving window of 3 are detected as fast on the NF channel (interval shorter than the longest programmed tachycardia detection interval), the algorithm initiates sensing on the FF channel. A fast interval on the FF channel is defined as an interval shorter than the longest programmed tachycardia detection interval plus 50 ms (30 ms in previous versions of the software) or 400 ms if only a single tachycardia detection zone is programmed. Subsequently, a counter is started which increments by 1 for every fast interval (interval in a tachycardia zone) on the NF channel and it is reset to 0 when two fast intervals occur on the FF channel. During a true ventricular arrhythmia, the counter should be constantly reset by the occurrence of fast intervals on the FF channel. When the ICD diagnoses a ventricular arrhythmia while the counter is at least 10, therapy is withheld.

Figure 2: Example of correct detection of oversensing by the SecureSense™ algorithm with inhibition of inappropriate therapy. Fast intervals on the NF channel (created by non-physiologic events) do not match with slow intervals on the FF channel which increments the noise counter by 1. Meanwhile the fast intervals increment the VF counter which is completed at 16. Since at that time the noise counter is ≥ 10 , inappropriate therapy is withheld and the device stores the episode as RV lead noise.

Figure 3: Example of correct detection of oversensing by the SecureSense™ algorithm with inhibition of inappropriate therapy. Here, only one VF zone was programmed at 222 bpm (270 ms) with a counter of 12. Thus, a fast interval on the FF channel is an interval shorter than 400ms. The noise counter is incremented by 1 for every fast interval on the NF channel (i.e. shortest than 270ms). On the NF channel, most R-wave are preceded by P-wave oversensing while on the FF channel only R-waves are detected. Meanwhile the fast intervals increment the VF counter which is reached at 12. The noise counter is never reset to zero because there is no fast interval (i.e. shorter than 400 ms) on the FF channel. Since at that time the noise counter is ≥ 10 , inappropriate therapy is withheld and the device stores the episode as RV lead noise.

Figure 4: Example of incorrect function of the SecureSense™ algorithm with undersensing of VT. A monitor VT zone at 130 beats/min (462 ms) and a VF zone at 200 beats/min (300ms) are programmed. A fast interval on the FF channel is an interval shorter than $462+50=512$ ms. The Noise counter is incremented by 1 for for each interval on the NF channel shorter than 462 ms. On the NF channel, fast events are correctly sensed. After two fast events (first two “-”) + 350 ms (which includes third “-”) the noise counter commences. On the FF channel, there is undersensing and only few of these R-waves are detected, there are no short intervals (i.e. < 512 ms) and the noise counter is not reset to zero. Non-sustained oversensing (NSO) is declared. This is a non-sustained VT but if the VT would have continued, the noise counter remained ≥ 10 , the algorithm remained active and appropriate therapy could have been incorrectly withheld.

Figure 5: Examples of simultaneous oversensing on NF and FF channels caused by P-wave oversensing (A) or electrical cauterization (B). While the VF counter increases, the noise counter is continuously reset because of (oversensed) fast intervals on the FF channel. Because at completion of the VF counter, the noise counter is <10, therapy will be delivered inappropriately.

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Tables

Table 1. Baseline characteristics

	Entire population (n=486)	Patients with NSO or SO episodes (n=60)	Patients without oversensing episodes (n=426)	p
Age (years)	65,4±12,9	65,7±16,6	65,3±12,2	NS
Male	79,0%(384)	88,3%(53)	77,7%(331)	0,06
LVEF				
Preserved ^a	17,7%(86)	20,0%(12)	17,4%(74)	NS
Moderately impaired ^b	8,8%(43)	6,7%(4)	9,2%(39)	NS
Severely impaired ^c	73,5%(357)	73,3%(44)	73,5%(313)	NS
Indication				
Primary prevention	68,1%(331)	66,7%(40)	68,3%(291)	NS
Secondary prevention	31,9%(155)	33,3%(20)	31,7%(135)	NS
Underlying heart disease				
Coronary heart disease	57,8%(281)	43,3%(26)	59,9%(255)	0,02
Primary dilated cardiomyopathy	24,9%(121)	30,0%(18)	24,2%(103)	NS
Hypertrophic cardiomyopathy	5,3%(26)	13,3%(8)	4,2%(18)	0,003
Channelopathy	2,5%(12)	3,3%(2)	2,3%(10)	NS
Other cardiac disease	9,5%(46)	10,0%(6)	9,4%(40)	NS
Implanted device				
Single Chamber	37,2%(181)	15,0%(9)	40,4%(172)	<0,001
Dual chamber	14,8%(72)	21,7%(13)	13,8%(59)	NS
Biventricular	47,9%(233)	63,3%(38)	45,8%(195)	0,01
RV Lead				
Integrated bipolar	10,5%(51)	10,0%(6)	10,6%(45)	NS
True bipolar	89,5%(435)	90,0%(54)	89,4%(381)	NS

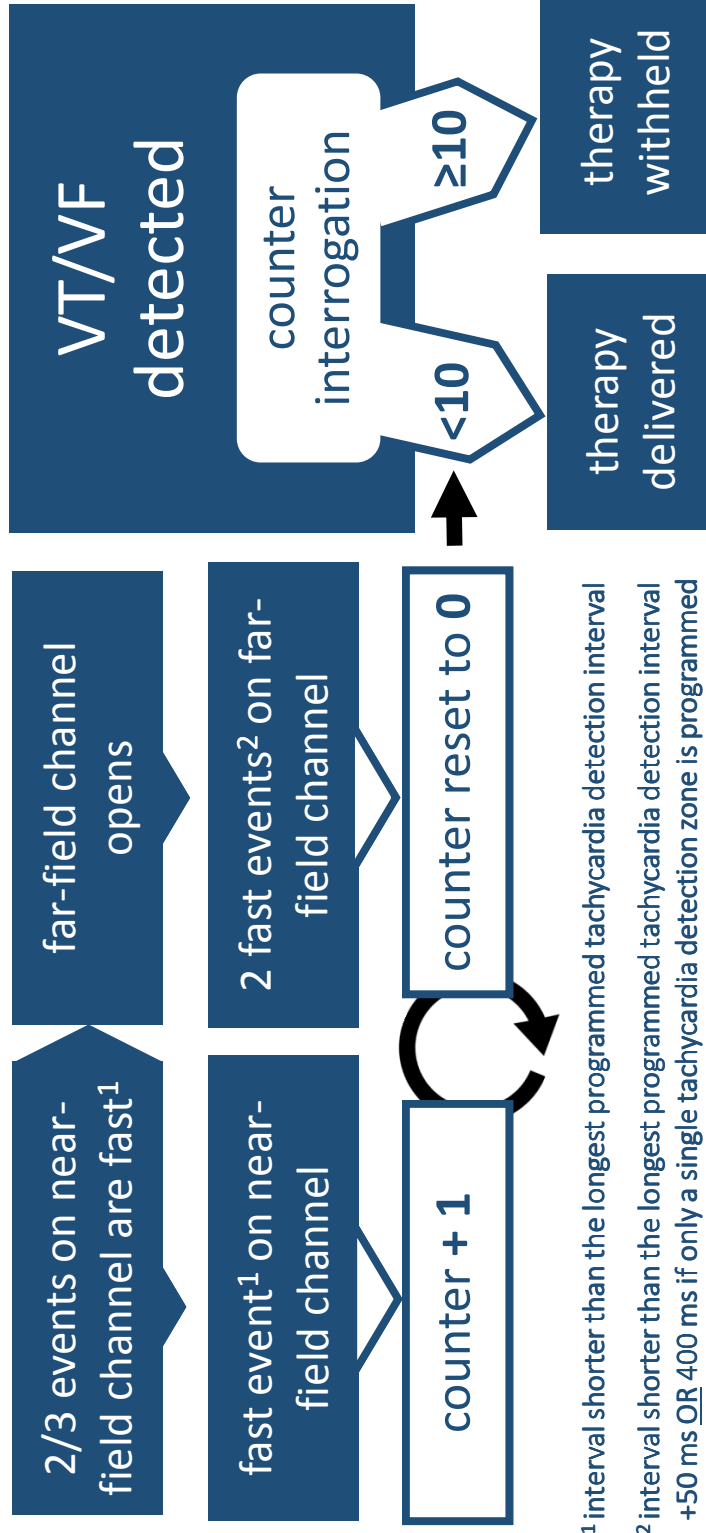
Data are presented as mean ± standard deviation of mean or percentage (number). NSO : non-sustained oversensing, SO : sustained oversensing, LVEF : left ventricular ejection fraction, RV : right ventricle
^a>50%, ^b35-50%, ^c<35%.

Table 2 Oversensing Episodes

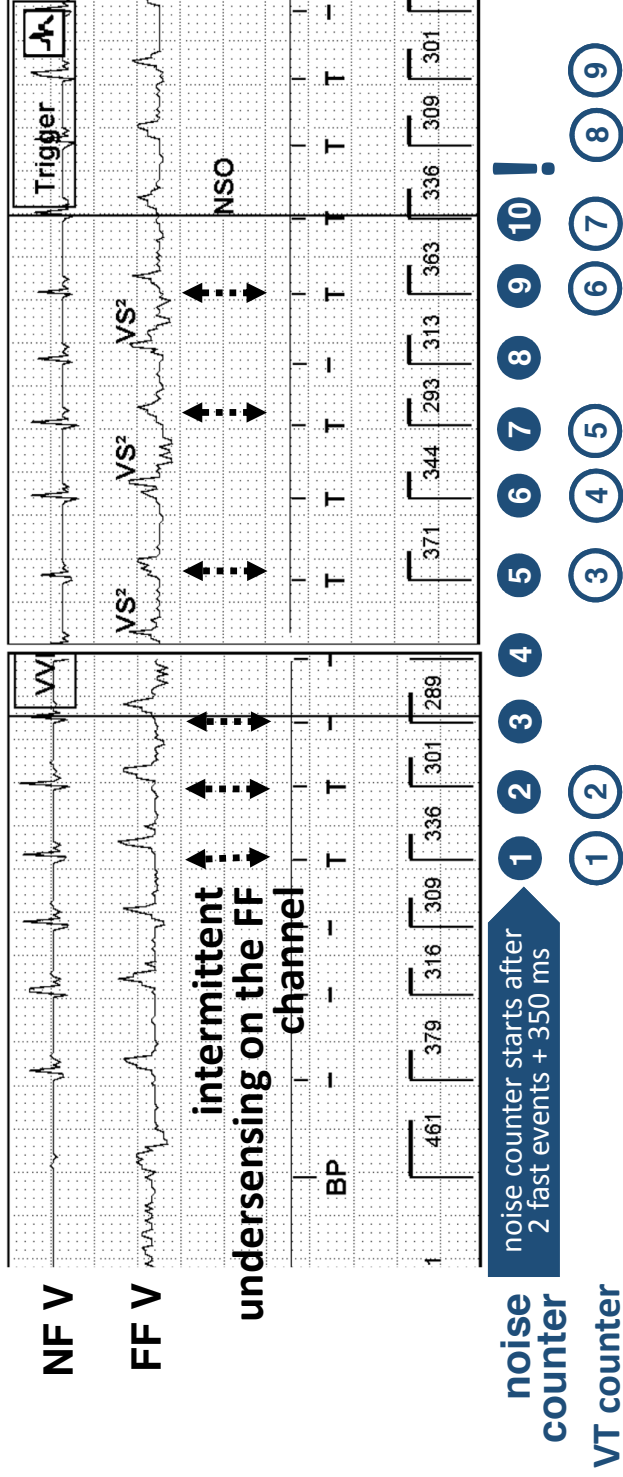
Diagnosis	Patients	Episodes n (%)
Sustained oversensing	3	22
Intrinsic P-wave oversensing	2	12 (55)
Lead dysfunction	1	10 (45)
Nonsustained oversensing	57	393
Lead noise	23	150 (38)
diaphragmatic myopotential oversensing due to LFA filter	4	36 (9)
T-wave oversensing during ventricular pacing	19	128 (33)
Intrinsic P-wave oversensing	5	48 (12)
Paced P-wave oversensing	3	24 (6)
Loss of capture	3	21 (5)
Undersensing on the FF channel	1	10 (2,5)
Temporal offset between NF and FF channel	3	5 (1,3)
R-wave double counting	2	3 (0,8)
Intrinsic T-wave oversensing	1	2 (0,5)
Undersensed VT on the FF channel	2	2 (0,5)

Values are presented as n (%)
 FF = Far Field ; LFA = Low Frequency Attenuation ; NF = Near Field ; VT = Ventricular Tachycardia

SecureSense™ algorithm

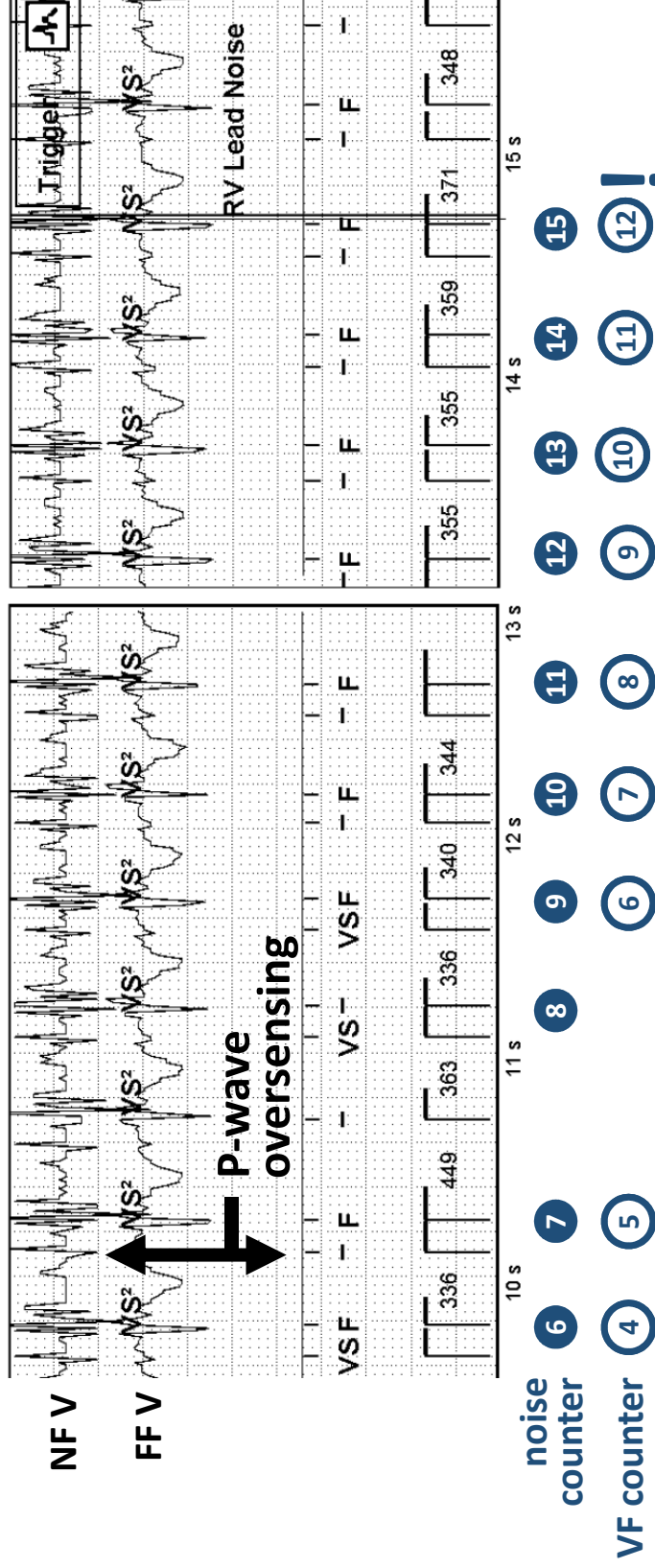


undersensed VT on the FF channel



Episode is saved as non-sustained oversensing when the noise counter reaches 10. VT counter is not reached

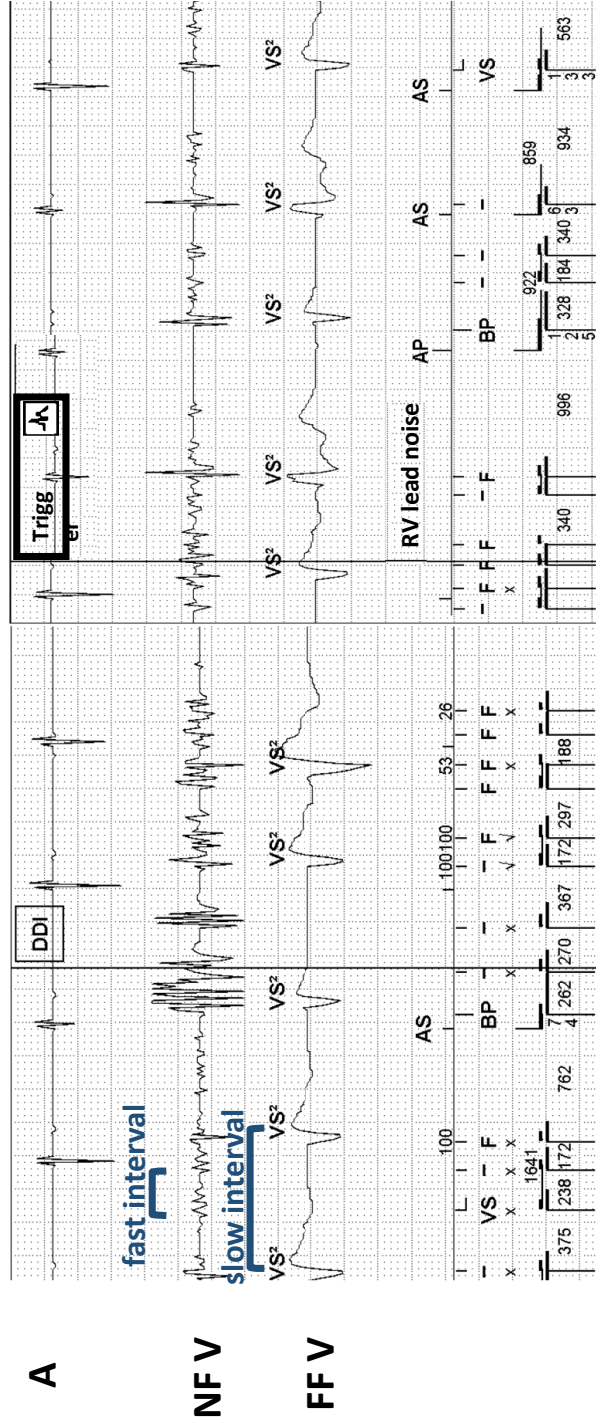
correct detection of oversensing (P-wave)



the noise counter is never reset to zero
(no ≥ 2 fast intervals on the FF channel)

VF counter reached while noise
counter $\geq 10 \rightarrow$ RV Lead Noise

correct detection of oversensing (noise)



noise
counter

10

11

13

14

15

11

11

19

21

VF counter

9

10

11

11

14

16

fast interval on NF but
not on FF = counter +1

VF counter reached while noise counter
≥10 SecureSense™ declares RV Lead Noise

Sensibility and sensitivity to detect arrhythmias of current defibrillators. A clinical study based on 3 different companies analyzing the discrimination algorithm based on morphology

1. Study Outline

Inappropriate shocks represent the most common adverse event in implantable cardioverter defibrillator (ICD) recipients and remain a major concern in view of their incidence and consequences(4). They reduce quality of life and are even associated with increased mortality. The 2015 HRS/EHRA/APHRS/SOLAECE consensus statement on optimal ICD programming provides recommendations stressing the importance of using long detection intervals, high-rate therapy and arrhythmia discrimination(5). These strategies aim to reduce inappropriate device interventions for supraventricular tachycardia (SVT) while maintaining a high level of ventricular tachycardia (VT) detection. Suggested programming settings for each manufacturer are proposed in an addendum of the consensus statement. This innovative and practical document offers rate detection thresholds and duration suggestions for each ICD model.

2. Implications

Arrhythmia discrimination is encouraged and is essentially based on comparison of morphology, as standalone discriminator in single chamber devices and as part of the dual chamber discrimination algorithm. Such generic recommendations are based on the premise that proprietary morphology algorithms performed equally well at their nominal settings. In this multicenter study, we hypothesized that technical specificities and changes in the programming would impact the discrimination accuracy. We assessed and compared the morphology discriminators of three manufacturers and proposed optimized settings whenever possible.

3. Manuscript

METHODS

Principles of discrimination based on morphology

Morphology discrimination is designed to withhold inappropriate detection during episodes of conducted supraventricular tachycardia. The algorithm compares the patient's current ventricular electrogram (EGM) with a stored template acquired during intrinsic ventricular conduction. Ventricular

tachycardia detection is withheld if the current morphology sufficiently matches the template. A match is assumed when predefined level of similarity is reached between the morphology during tachycardia and the stored template. The percentage threshold can be programmed, the higher the value the higher chance for a rhythm to be classified as VT. If a minimum of X (number of matches) over Y (detection window) complexes sufficiently match the stored template, the device withholds detection. Technical details are summarized in table 1. In the present study, we assessed and compared the Abbott *Far Field MD*TM, the Boston Scientific *RhythmID*TM and the Medtronic *Wavelet*TM morphology discriminators.

Table 1: Technical data and settings of the 3 morphology discriminators

Data collection

We have retrospectively collected arrhythmia episodes through remote monitoring in seven French, one Dutch and one Italian center. All patients gave written, informed consent for analysis of the data provided from remote monitoring and patient information was de-identified prior to analysis of the episodes.

Inclusion criteria were tachycardia episodes from nondependent patients implanted with a dual chamber (less than 20% ventricular pacing) or cardiac resynchronization therapy (CRT) defibrillator (ventricular dependency

excluded from medical records) with a functional atrial lead. Single chamber defibrillators were excluded since we used the atrial EGM for identification of the rhythm. The morphology algorithm could be programmed either “On” or “Monitor”. The EGM morphology source was to be programmed Coil to Can. All devices had template auto update function except Medtronic CRT defibrillators for which the template was acquired manually. For Abbott and Boston Scientific CRT defibrillators, the “hysteresis” and “active method” were to be programmed in order to favor intrinsic activity.

All stored episodes of tachycardia <250bpm were analyzed regardless of the final device diagnosis (VT or SVT). An episode was included when a manual diagnosis of either monomorphic VT or SVT could be made with near certainty as follows:

- *VT definition*: ventricular intervals shorter than atrial intervals. For each patient, up to 10 VT episodes were included which had to differ either in rate (>10 bpm) or in time of occurrence (>24 hours).
- *1:1 SVT definition*: similar atrial and ventricular rates with P-R association. The ventricular rhythm being driven by the atrial activity evidenced by either 1) beginning with an atrial premature event, or 2) anticipated atrial events induce anticipated ventricular events, or 3) premature ventricular complexes do not

influence the atrial rhythm. Up to 5 episodes were included which had to differ either in rate (>10 bpm) or in time of occurrence (>24 hours).

- *Atrial fibrillation definition:* atrial activity compatible with atrial fibrillation and obvious irregular ventricular rhythm. Up to 5 episodes were included which had to differ either in rate (>10 bpm) or in time of occurrence (>24 hours).

Each episode was reviewed by three trained electrophysiologists which all had to agree on the diagnosis for the episode to be included. Every questionable episode was discarded. SVT tracings from Medtronic displaying EGM truncation were rejected.(6) The same number of episodes was required for each manufacturer, with a sample size estimated from Bujang and Adnan tables, assuming that the VT prevalence was 60% and the expected sensitivity was 80% with a power of at least 80% and a p-value of at least 0.05.(7–9) For each episode, the percentages match prior to the final ICD diagnosis of the arrhythmia were collected (last 8 for Medtronic, last 10 for Boston Scientific and up to 20 for Abbott devices).

Statistical analysis

Continuous variables were expressed as mean \pm Standard Deviation and compared using either the one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Categorical variables were expressed as absolute numbers (%) and compared using the Pearson's chi-square test or Fisher's Exact Test. Sensitivity was defined as the number of VT episodes correctly classified by the morphology discriminator divided by the total number of VT episodes labelled by the physicians. Specificity was defined as the number of SVTs classified by the morphology discriminator divided by the total number of SVTs labelled by the physicians. Because the patients contributed for an unequal number of episodes, a generalized linear mixed model (GLMM) was constructed and fitted to the repeated measurements as described by Liu H and Wu T.(10) From this model were computed area under a receiving operating characteristics curve (ROC) for repeated measures. Sensitivity and related specificity of each manufacturer discriminator were determined at various values of percentage match thresholds (i.e. programmable threshold above which an EGM will satisfy SVT morphology) from ROC analysis. A summary of the ROC construction is presented in supplemental figure S1. A sensitivity analysis was conducted by introducing the ratio of dual chamber/CRT defibrillator as a covariate into the GLMM. ROC curves of figure 1 were constructed using a fixed nominal matches/detection window ratio. Statistical significance was

assumed at $p < 0.05$. Statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois) and the Stata software (version 15, StataCorp, College Station).

Algorithms performances

Sensitivity and specificity were extracted from the ROC curves at nominal percentage match thresholds for the different algorithms. These values were compared to 3 alternative match thresholds defined as: 1) the threshold associated with 90% sensitivity, 2) the threshold associated with 90% specificity, 3) the optimal threshold corresponding to the highest number of correctly classified cases ($((\text{true positive} + \text{true negative})/168)$). A lower bound of 75% sensitivity (allowing 25% VTs being missed) and 75% specificity (25% of inappropriate therapies, i.e. applied VT therapies on SVT episodes) were considered as minimal acceptable cutoffs and were required for each configuration. A specific analysis was conducted for Abbott, looking at the effect of changing the number of required matches over a variable detection window. The effect of the template amplitude was investigated in the Medtronic group.

RESULTS

Arrhythmia dataset & characteristics

A total of 185 ICDs (123 dual chamber ICDs and 62 CRT defibrillators) provided 534 episodes divided in 330 VT and 204 SVT equally distributed among the 3 manufacturers (110 VT/68 SVT). The VT and SVT cycle lengths were similar between the 3 groups. Among the SVT, the Abbott and Boston Scientific groups showed a near equal distribution between 1:1 tachycardia and AF, whereas AF was less common in the Medtronic group (30%, $p < 0.001$). While for Abbott most ICDs were CRT devices (66%), for Boston Scientific and Medtronic, most ICDs were dual chamber (87% and 75%, respectively, see table 2). This imbalance translate into different QRS durations and left ventricular ejection fractions between the three groups. The QRS duration was significantly shorter for the Boston Scientific group (109 ± 29 ms) than for the Abbott (129 ± 33 ms) and Medtronic (130 ± 34 ms) groups. The mean ejection fraction was significantly lower for the Abbott ($34 \pm 12\%$) group than for the Boston Scientific ($42 \pm 15\%$) and Medtronic ($42 \pm 16\%$) groups. The three groups did not differ in terms of mean age (61 ± 14 y), sex (78% of male) and proportion of ischemic cardiomyopathy (46%).

Table 2: Arrhythmia dataset

Ability to discriminate VT and SVT

In ROC analyses, Abbott Far Field MD (AUC: 0.91; 95%CI [0.81-1]; $p < 0.001$), Boston Scientific Rhythm ID (AUC: 0.94; 95%CI [0.88-1]; $p < 0.001$), and Medtronic Wavelet (AUC: 0.78; 95%CI [0.67-0.9]; $p < 0.001$) show a significant AUC when tested for their ability to discriminate VT from SVT. The results were similar when the ratio dual chamber/CRT ICD was inserted into the model, the AUC for Abbott Far Field MD (AUC: 0.91; 95%CI [0.87-0.96]; $p < 0.001$) and Boston Scientific Rhythm ID (AUC: 0.95; 95%CI [0.92-0.98]; $p < 0.001$) were statistically higher than for Medtronic Wavelet (AUC: 0.81; 95%CI [0.72-0.87]; $p < 0.001$).

Sensitivity and Specificity

The graphs shown in figure 1 indicate that the sensitivity/specificity pattern vary distinctly between manufacturers. On average, percent match scores were higher for Abbott Far Field MD than Boston Scientific RhythmID or Medtronic Wavelet. Therefore, the specificity of the Abbott's algorithm exceeds the sensitivity until a very high value of the percentage match (87%). In comparison, the sensitivity/specificity patterns of Boston Scientific and Medtronic are inverted: they favor sensitivity until a low value of the percentage match (66% and 55% respectively).

Nominal settings versus alternative thresholds

At nominal threshold, Abbott Far Field MD provides both high sensitivity (91%, for VT detection) and specificity (85% for SVT detection). Interestingly, this nominal threshold corresponds to both the 90% sensitivity threshold and is very close to the optimal thresholds. A specificity of 90% is only reachable at the expense of a low sensitivity (71%). In figure 2, VT and SVT tracings from the same patient are presented, exhibiting both high % match scores.

The 94% nominal threshold of the Boston Scientific RhythmID is associated with a suboptimal sensitivity/specificity ratio resulting in an unacceptable 41% specificity. Lowering this threshold to 83% results in an improved specificity of 79% for a similar 100% estimated sensitivity. Figure 3 shows a misclassified atrial fibrillation episode, requiring lowering of the % match threshold.

The nominal Medtronic Wavelet threshold is equal to both the 90% sensitivity and the optimal threshold. All these configurations are associated with a very low specificity (below the predefined 75% boundary). There is no possibility to reach a specificity above 79% which would be associated with an unacceptable 48% of sensitivity (at 40% threshold). Table 3 summarizes the comparisons. Figure 4 shows an example of SVT with inconsistent match of the ventricular complexes with the template.

Table 3: Nominal and optimized match thresholds performances

Number of matches/detection window

Abbott Far Field MD is the sole manufacturer which allows you to alter the number of required matches (ranging from 3 to 20) and the detection window (6 to 20 cycles). The nominal ratio is 3 matches per detection window of 10 cycles. Figure S2 shows the AUCs for ROC curves at different ratio of matches per detection window. This table indicates that the accuracy of the discrimination improves with a lower number of matches and a longer detection window. It also shows that the importance of the window length diminished gradually as the number of matches required decrease. According to this data a single match would give optimal results, but it is not programmable. Within the programmable options no combination significantly outperforms the nominal 3 matches in a window of 10.

Effect of Template amplitude

The Medtronic arrhythmia report allows measurement of the template amplitude in mV. Figure S3 shows the SVT recognition capacity (mean %Match) of the Wavelet algorithm as a function of the template amplitude. This graph shows than a template amplitude $\leq 3\text{mV}$ precludes a proper SVT recognition. When 13(18%) patients with a template amplitude of less than 3mV where exclude from the analysis, the AUC for the ROC analysis rises to 0.94 [95%CI [0.90-0.98]; $p < 0.001$].

Discussion

We report the first study investigating the accuracy of morphology discrimination using a real-life multicenter multivendor approach. Although the systematic use of the morphology discriminator is recommended with shipment settings, we report major differences between manufacturers and suboptimal nominal thresholds.

Limitation of the Morphology as standalone discriminator

This study demonstrates that morphology algorithms have limitations and their use as a standalone discriminator at nominal settings is accompanied by significant missed VT and inappropriate VT classifications. Low specificity at nominal settings (Boston Sc. RhythmID and Medtronic Wavelet) is particularly problematic since morphology only applies at initial detection (one failure of the algorithm, if used as single discriminator, may result in the full treatment delivery). Our results differ from previously published studies which report higher accuracy of the tested algorithms. These discrepancies could be explained by differences in study design. We analyzed episodes extracted from dual-chamber and CRT devices which allow firm diagnosis instead of single-chamber devices in which the arrhythmia diagnosis mostly rely on visual morphology assessment.(7,8,11) In their morphology discrimination evaluation Theuns *et al.* found improved results

for the single-lead ICDs as compared with the dual-lead ICDs.(8) We collected real life cases in contrast to studies where the template and the arrhythmias were externally introduced into the ICD.(12) Finally, we recorded the morphology match percentages associated with the final decision time of the device which does not take into account the selective role of the VT counter (see limitations).

Differences in discrimination accuracy

Although the three algorithms share a common principle and all rely on far field (FF) vector channels for the morphology analysis, we observed significant differences in the algorithms performances. In particular the Medtronic Wavelet algorithm suffers from a lack of specificity. Several technical specificities may account for these results. To begin with, there are differences in the FF signal measurement accuracy which depends on the amplifier range and power. Medtronic uses an 8 bits amplifier which confers at the nominal +/- 12mV range a signal resolution of 0.09mV. Abbott uses an auto-scaling during the in-clinic template acquisition (\sim +/-7 mV to +/- 14 mV), which offers a slightly higher resolution of \sim 0.05 to 0.1 mV. Boston uses a fixed and broader range of +/-32mV in association with a 12 bits amplifier which confers the highest resolution of \sim 0.016mV. Subsequently there are major differences in the signal processing. Two main approaches

can be distinguished with: 1) a time domain analysis (temporal analysis of EGM morphology by Abbott Far Field MD and Boston Scientific RhythmID) and 2) a Haar wavelet domain analysis (implemented by Medtronic). Figure 5 summarizes the principal features of each algorithm. Abbott and Boston Scientific systems construct a quantitative representation of each ventricular EGM based on the coordinates of 8 points including a fiducial point aligned with the peak amplitude time of the near field (NF) EGM. Importantly these two algorithms differ in the way the points are distributed along the QRS complex: 8 points evenly spaced around (and including) the fiducial point for Abbott whereas Boston Sc. uses a more specific distribution including the fiducial point, turning points, intermediate and baseline values (exact formula is protected).(12) These differences could explain that Abbot Far Field MD maintains a high specificity until high values of the %match threshold (easier match) and Boston Scientific maintains consistently an higher level of sensitivity (more demanding) along the programmable range of % match threshold, and this at similar AUC for arrhythmia discrimination. Medtronic uses a completely different approach in the signal processing, applying a wavelet transform (derived from Haar Wavelet) to the FF EGM. The wavelet transform yields a set of 48 wavelet transform coefficients of which a representative subset (8 to 20) is used to represent the ventricular EGM. This type of signal analysis intends to

accurately represent the original signal while providing a high degree of information compression. Surprisingly this algorithm shows difficulties to recognize similar ventricular complexes. Accordingly, the match threshold is nominally set lower than the two competitors (70%) and the automatic template quality check, which is used to determine if the template has become obsolete, tolerates up to 29 non-match complexes out of 100 complexes. A hypothetical explanation would be that the wavelet transform based analysis provides a paradoxically too detailed picture of the ventricular EGM which renders the algorithm intolerant to physiological beat-to-beat signal variations. Another potential limitation may be found in the signals alignment which is based on the greatest absolute value of each FF EGM. This alignment may be less accurate than alignment based on the NF signal: during a ventricular arrhythmia, the location of the alignment point may shift in the NF channel with respect to the shock channel due to differing conduction vectors. This timing difference can accentuate differences already present in the shock channel EGM and facilitate diagnosis of ventricular arrhythmias.

Consequences for programming

Our results indicate that none of the tested morphology algorithm could be considered as a panacea for arrhythmia discrimination. This is expected

considering the inherent limitations of such algorithms, among which: myopotential interference (arm exercises), low amplitude EGM, EGM truncation, alignment error (double peaks), conduction aberrancy and possible others. Considering the limitations of the discrimination process overall it is recommended to limit the therapy zone above 185-200 bpm in primary prevention. The question is: could we optimize the programming to improve the algorithm accuracy?

Our results indicate that the Wavelet algorithm performs badly then the FFEGM amplitude is below 3mV. This is not surprising considering that at this level of amplitude the signal/noise ratio is lower. In such an instance, Medtronic advise to select another EGM source. This option has to be balanced with the potential need to deactivate the RV lead noise discrimination algorithm which uses the same EGM source and requires at least one Coil electrode. This means than with a single coil ICD lead any change in the Wavelet EGM vector will exclude the use of the RV lead noise discrimination algorithm. Alternatively, one may consider to reduce the range of the Wavelet EGM source in order to improve the signal resolution. Above all, this raises the question of the need to test systematically the FF detection at implant, as suggested by others to improve the accuracy of noise detection algorithms that rely on this EGM source.(13)

Regarding the question of optimizing the % match threshold our results indicate that the Abbott and Medtronic nominal thresholds are similar or close to the optimal calculated thresholds. In contrast, the Boston Scientific nominal threshold appeared to be too conservative compared to the optimal threshold which allows a 38% gain in specificity. In fact, the ratio sensitivity/specificity (i.e. the %match threshold) may be determined according to the expected ratio of SVT/VT. For instance, at a lower detection rate, SVTs are more likely to occur, and VTs are more likely to be hemodynamically tolerated. In the “1+1” trial, the percentage of SVTs decreased with the tachycardia rate: 68% of SVTs above 140bpm, 49% of SVTs above 162bpm and 9% of SVTs above 176bpm.(14) Practically the match threshold could be lowered in accordance to the lowest VT zone limit. Whether the morphology algorithm is used as a standalone discriminator or in combination with other criteria represents a second technical challenge. It seems logical to use different thresholds in single chamber (when morphology is a standalone discriminator) versus dual chamber or CRT device (when morphology is part of the discrimination tree). The latter devices benefit from the atrial/ventricular rate comparison. In the branches of $A=V$ and $A>V$, more than 80% of the tachycardia are SVT which argues in favor of aiming for high specificity by lowering match threshold.(15) Of

note, our results do not support modifying the nominal number of 3 matches in a detection window of 10 in Abbott devices.

Limitations

Our results acquired with dual and CRT ICDs may slightly differ in a single chamber device population where the cardiomyopathy and the indications may be different. These results do not reflect the proper discrimination accuracy of each device since detection capabilities and counters rules have not been taken into account. For example, Medtronic uses a particular counter which provides a certain degree of protection against fast conducted atrial fibrillation (each sinus interval resets the VT counter). This counter which acts as a stability discriminator, is presumably responsible for the low number of inappropriate therapy observed with Medtronic ICDs in the prospective randomized RIGHT trial and in the START study.(16,17) The VT counter length and eventually the presence of additional discriminators have influenced the timing of the morphology algorithm intervention, which is therefore different from on patient to the other.

CONCLUSION

Proprietary morphology discriminator specificities and nominal settings translate into major differences in arrhythmia discrimination accuracy. A combination of discriminators and the modification of the nominal percentage match threshold may be considered under certain circumstances.

REFERENCES

1. Daubert JP, Zareba W, Cannom DS, et al.: Inappropriate Implantable Cardioverter-Defibrillator Shocks in MADIT II. *J Am Coll Cardiol* 2008; 51:1357–1365.
2. Wilkoff BL, Fauchier L, Stiles MK, et al.: 2015 HRS/EHRA/APHS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Heart Rhythm* 2016; 13:e50-86.
3. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH, Gillberg JM: Discrimination of ventricular tachycardia from supraventricular tachycardia by a downloaded wavelet-transform morphology algorithm: a paradigm for development of implantable cardioverter defibrillator detection algorithms. *J Cardiovasc Electrophysiol* 2002; 13:432–441.
4. Klein GJ, Gillberg JM, Tang A, et al.: Improving SVT discrimination in single-chamber ICDs: a new electrogram morphology-based algorithm. *J Cardiovasc Electrophysiol* 2006; 17:1310–1319.
5. Theuns DAMJ, Rivero-Ayerza M, Goedhart DM, van der Perk R, Jordaens

- LJ: Evaluation of morphology discrimination for ventricular tachycardia diagnosis in implantable cardioverter-defibrillators. *Heart Rhythm* 2006; 3:1332–1338.
6. Bujang MA, Adnan TH: Requirements for Minimum Sample Size for Sensitivity and Specificity Analysis. *J Clin Diagn Res JCDR* 2016; 10:YE01-YE06.
 7. Liu H, Wu T: Estimating the Area under a Receiver Operating Characteristic Curve For Repeated Measures Design. *J Stat Softw* 2003; 8:1–18.
 8. Toquero J, Alzueta J, Mont L, Lozano IF, Barrera A, Berruezo A, Castro V, Peña JL, Fidalgo ML, Brugada J: Morphology discrimination criterion wavelet improves rhythm discrimination in single-chamber implantable cardioverter-defibrillators: Spanish Register of morphology discrimination criterion wavelet (REMEDIO). *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2009; 11:727–733.
 9. Gold MR, Shorofsky SR, Thompson JA, Kim J, Schwartz M, Bocek J, Lovett EG, Hsu W, Morris MM, Lang DJ: Advanced rhythm discrimination for implantable cardioverter defibrillators using electrogram vector timing and correlation. *J Cardiovasc Electrophysiol* 2002; 13:1092–1097.
 10. Corbisiero R, Lee MA, Nabert DR, Coman JA, Breiter DJ, Schwartz M, McKittrick E, Zhang Y: Performance of a new single-chamber ICD algorithm: discrimination of supraventricular and ventricular tachycardia based on vector timing and correlation. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work*

Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol 2006; 8:1057–1061.

11. Koneru JN, Swerdlow CD, Ploux S, Sharma PS, Kaszala K, Tan AY, Huizar JF, Vijayaraman P, Kenigsberg D, Ellenbogen KA: Mechanisms of Undersensing by a Noise Detection Algorithm That Utilizes Far-Field Electrograms With Near-Field Bandpass Filtering. *J Cardiovasc Electrophysiol* 2017; 28:224–232.

12. Bänsch D, Steffgen F, Grönefeld G, Wolpert C, Böcker D, Mletzko R-U, Schöls W, Seidl K, Piel M, Ouyang F, Hohnloser SH, Kuck K-H: The 1+1 trial: a prospective trial of a dual- versus a single-chamber implantable defibrillator in patients with slow ventricular tachycardias. *Circulation* 2004; 110:1022–1029.

13. Glikson M, Swerdlow CD, Gurevitz OT, Daoud E, Shivkumar K, Wilkoff B, Shipman T, Friedman PA: Optimal combination of discriminators for differentiating ventricular from supraventricular tachycardia by dual-chamber defibrillators. *J Cardiovasc Electrophysiol* 2005; 16:732–739.

14. Gold MR, Ahmad S, Browne K, Berg KC, Thackeray L, Berger RD: Prospective comparison of discrimination algorithms to prevent inappropriate ICD therapy: primary results of the Rhythm ID Going Head to Head Trial. *Heart Rhythm* 2012; 9:370–377.

15. Gold MR, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, Wood MA, Burke MC: Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia

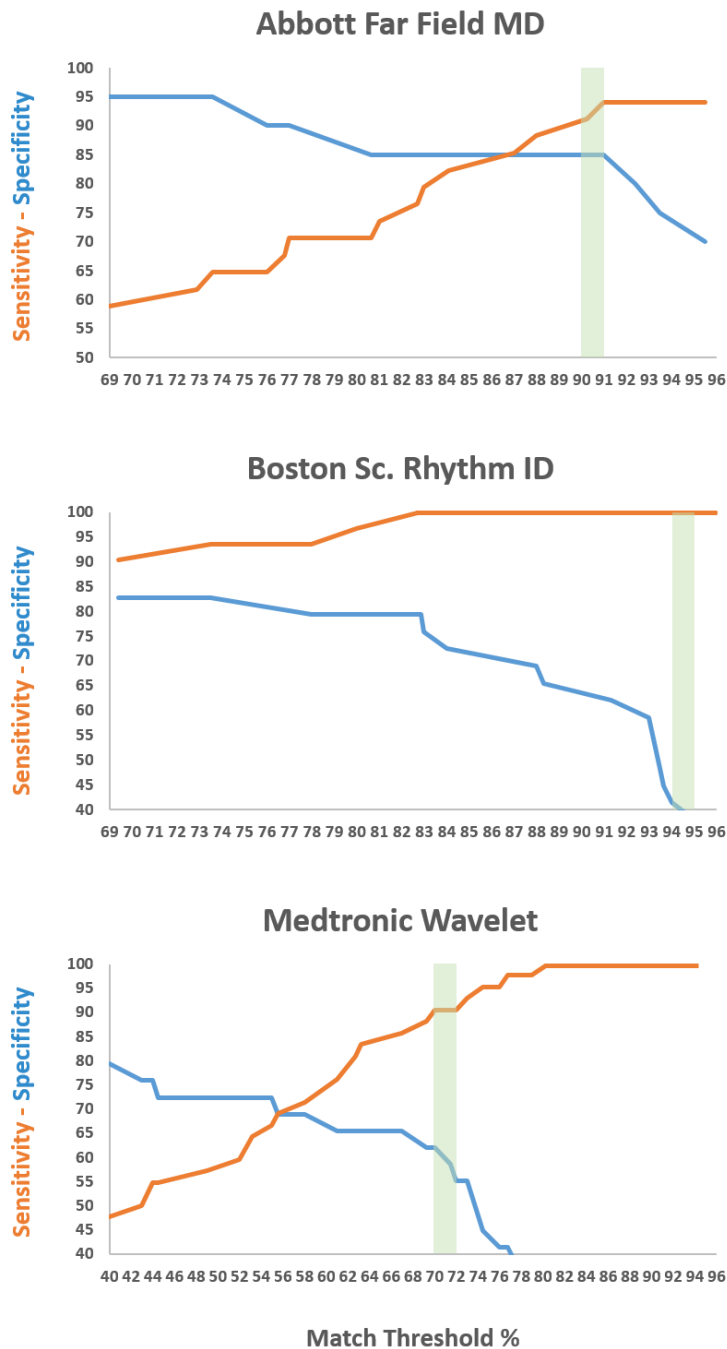
detection algorithms: the START study. *J Cardiovasc Electrophysiol* 2012; 23:359–366.

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FIGURES

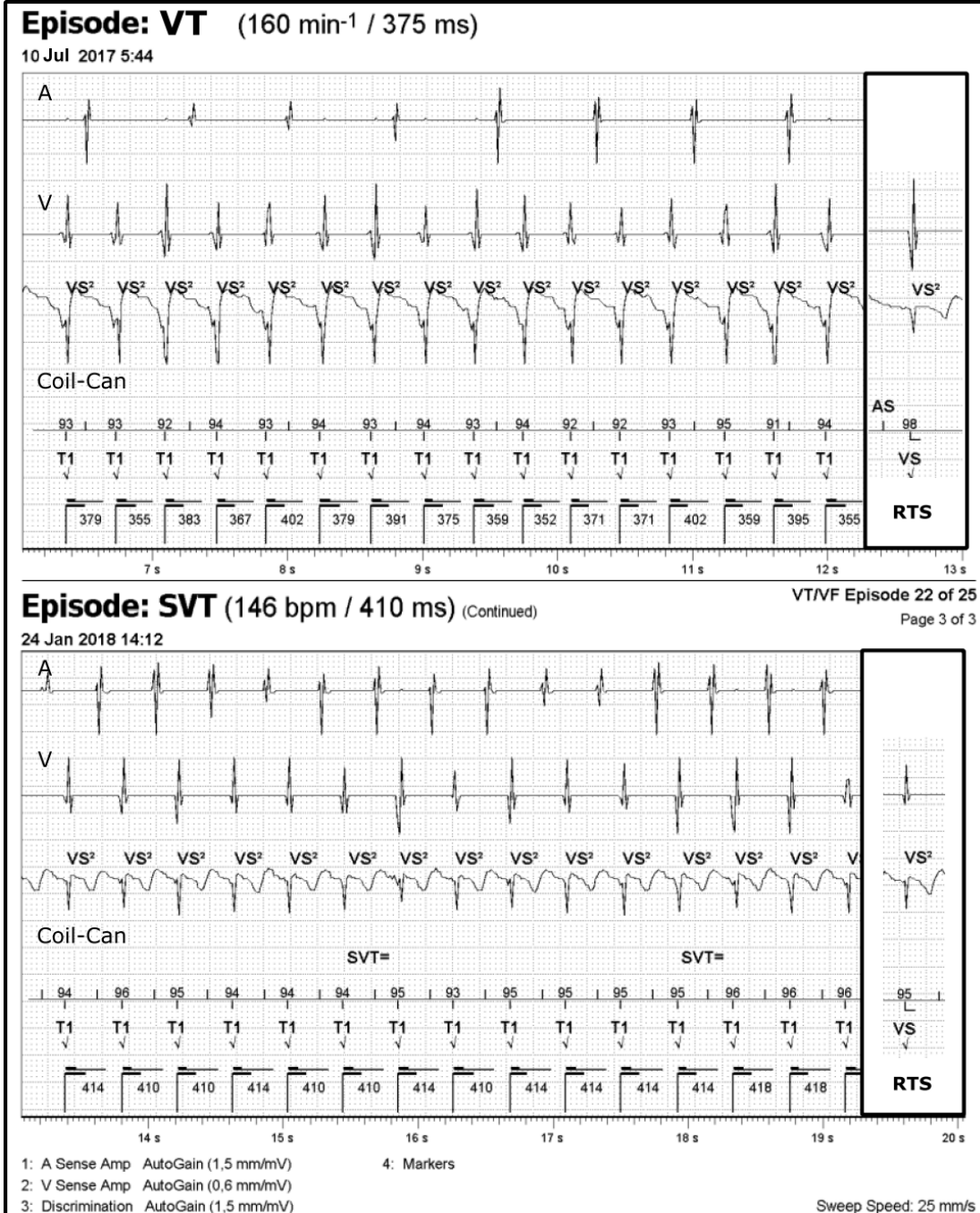
Figure 1



Discriminators performance as a function of the match threshold.

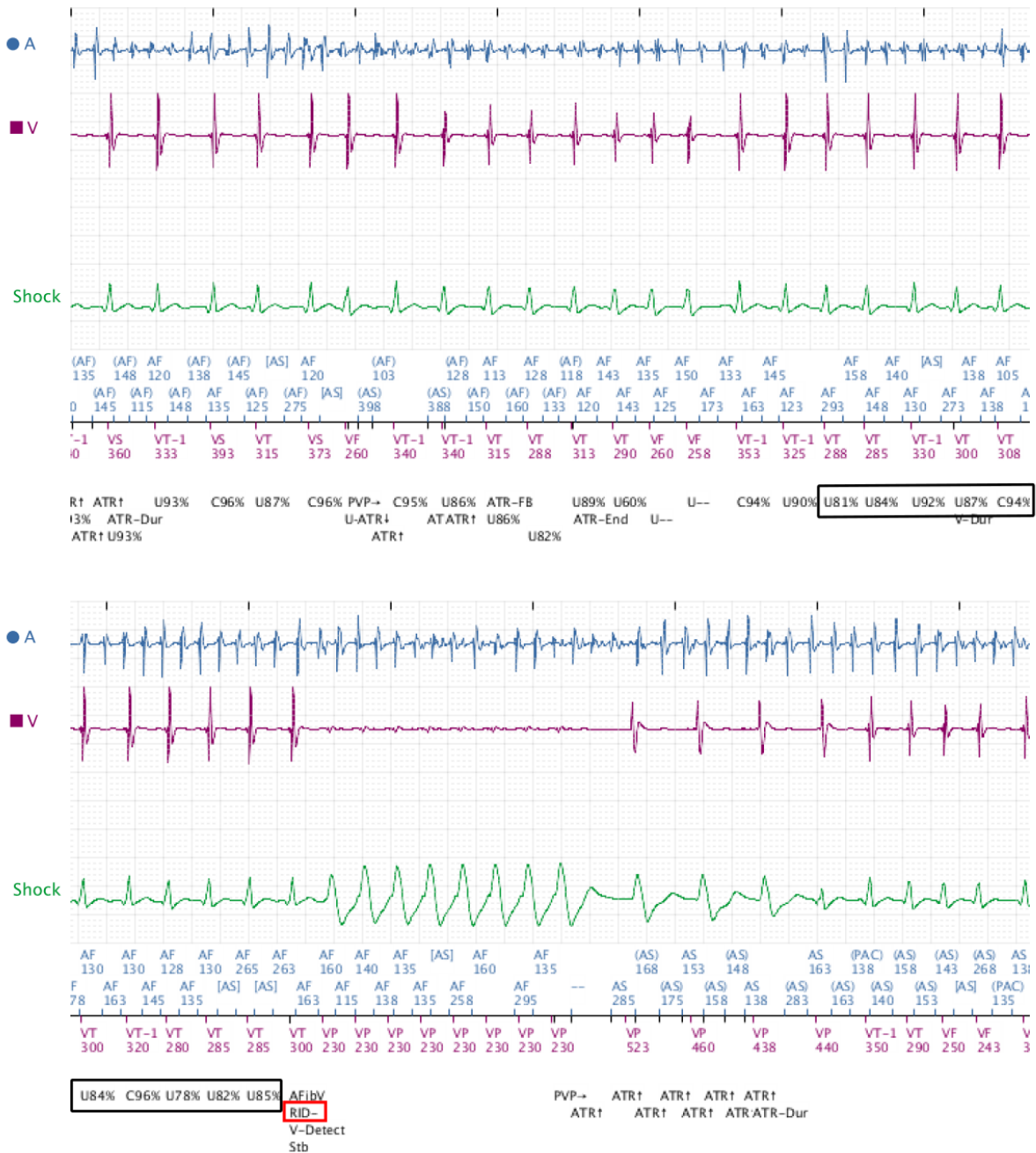
The match threshold percent is shown on the X-axis and on the Y-axis are in blue the sensitivity (percent of true VT episodes identified as VT) and in orange the specificity (true SVT episodes rejected as SVT). Green bars indicate nominal match thresholds. All analysis were performed using the nominal matches/detection window ratio (3/10 for Abbott and Boston Scientific and 3/8 for Medtronic).

Figure 2



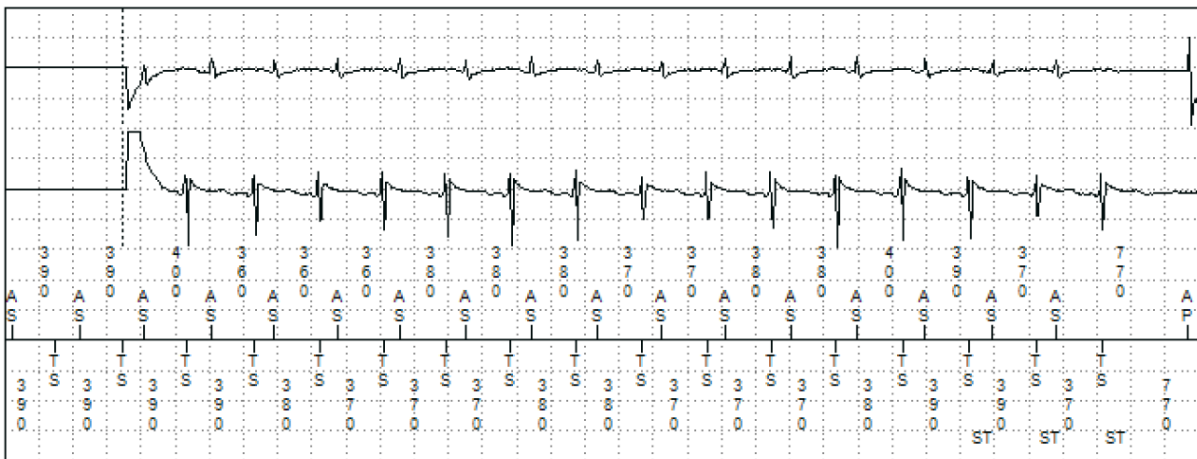
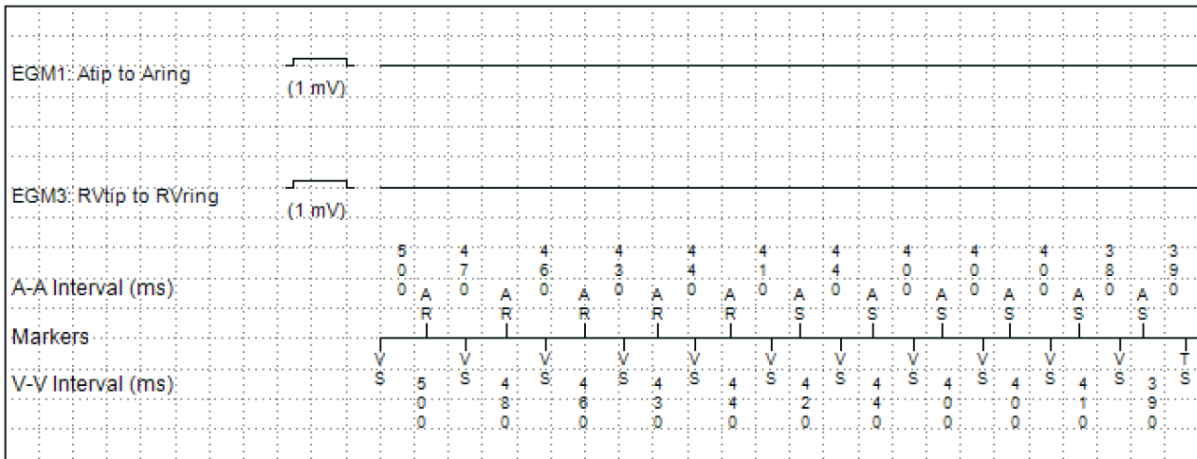
Abbott VT and SVT tracings from the same patient showing high % match scores. Rectangles on the far right show the ventricular EGM after return to sinus (RTS) for each of the episodes. Top panel: Example of a VT episode with high % match despite marked visual disparities between the tachycardia EGM and the sinus rhythm EGM. Bottom panel: atrial tachycardia episode with high % match scores. Using the 90% nominal match threshold and morphology as a standalone discriminator, both of these episodes would have been labelled SVT. Raising the % match threshold to its maximum (95%) and/or changing the detection vector may improve future discrimination.

Figure 3

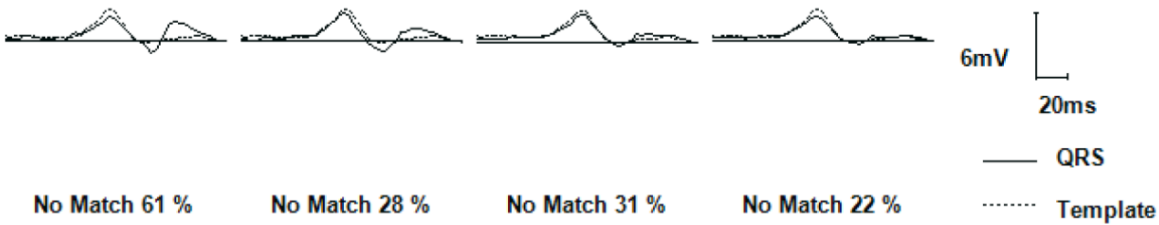


Atrial fibrillation misinterpreted as VT by the RhythmID algorithm. Among the 10 match scores prior to detection (85%, 82%, 78%, 96%, 84%, 94%, 87%, 92%, 84%, 81% -black squares) only two are $\geq 94\%$ (nominal threshold). RhythmID misdiagnoses the episode as VT (RID-, red square). This patient would benefit from a lower % match threshold (e.g. using a 84% threshold would have resulted in a diagnosis of SVT with 7/10 matches).

Figure 4



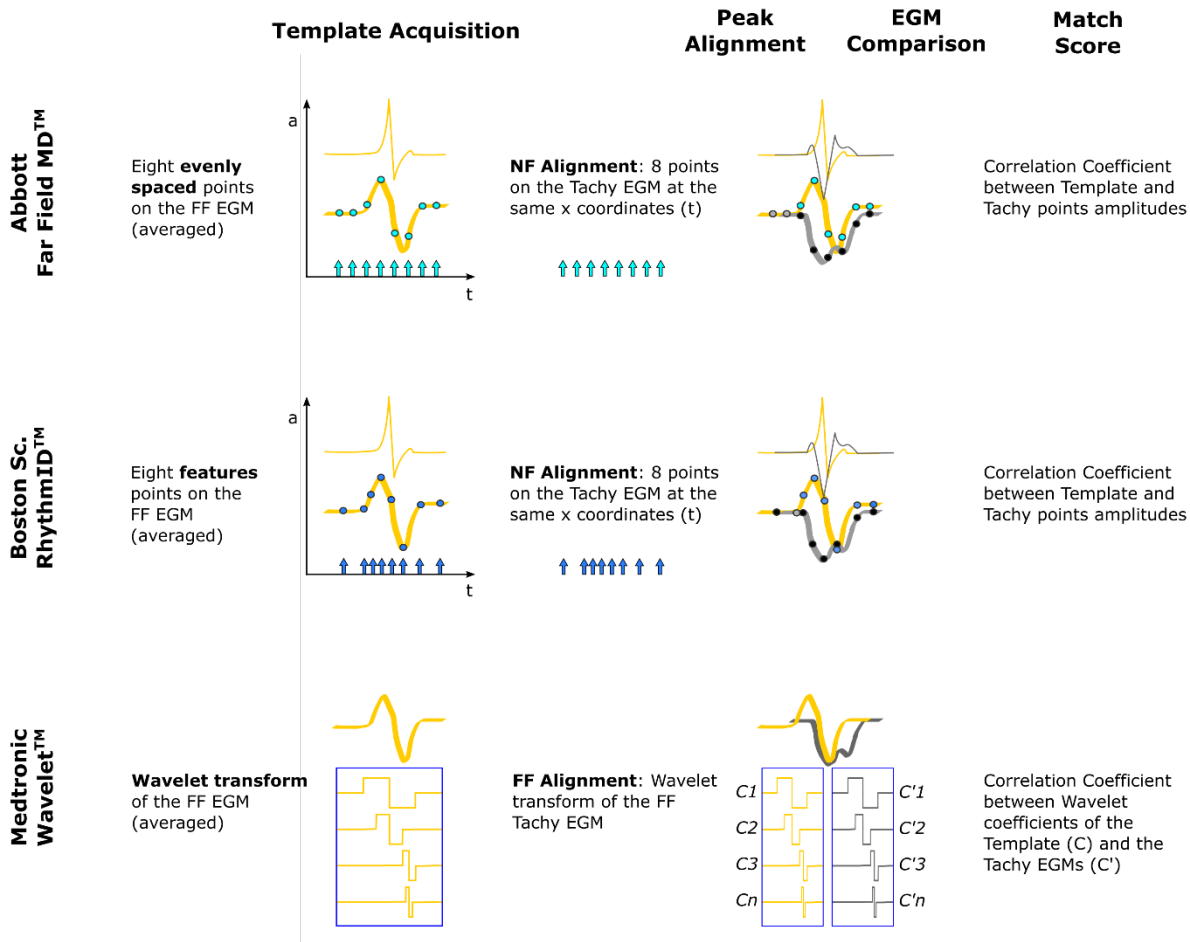
No Match 19 % No Match 43 % Match 76 % Match 76 %



Wavelet measurements

SVT with variable Wavelet match scores. Episode of atrial tachycardia recorded by a Medtronic Evera XT DR with detection withheld by PR Logic after 16 consecutive TS markers. The Wavelet discriminator is not applied but the match scores are shown for the 8 last beats prior to PR Logic decision. If Wavelet had been used as sole discriminator, it would have concluded to VT (only 2 match scores >70%). The Wavelet measurements (bottom) show that subtle changes between the tachycardia EGM (solid lines) and the template EGM (dotted lines) lead to important differences in match score. EGM1: atrial bipolar channel. EGM3: ventricular bipolar channel. The shock channel is not shown on the tracing.

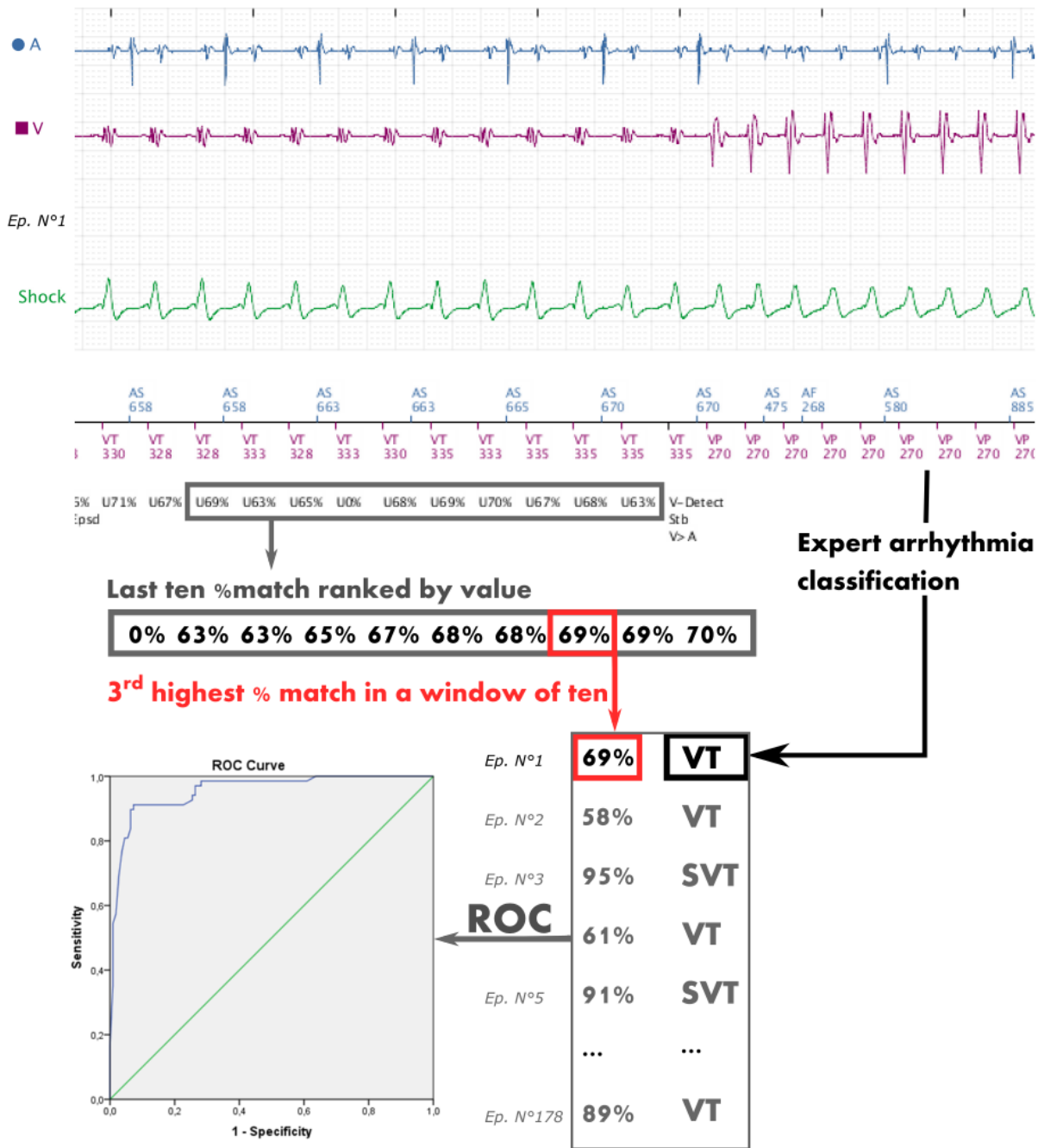
Figure 5



Discriminators specificities in signal processing. For Abbott Far Field MD and Boston Scientific RhythmID, comparison between the arrhythmia and template EGMs is made by computing the product-moment correlation coefficient between two sets of eight points. The way these eight points are chosen over the ventricular EGM differs between the manufacturers: evenly spaced with Abbott Far Field MD (light blue dots) and feature points (dark blue dots which include turning points, intermediates, and baseline values) for Boston Scientific RhythmID. Medtronic applies a wavelet transformation to both the template and the tachycardia EGMs and compares the respective wavelet coefficients (C and C'). t:time; a: amplitude.

SUPPLEMENTAL FIGURES

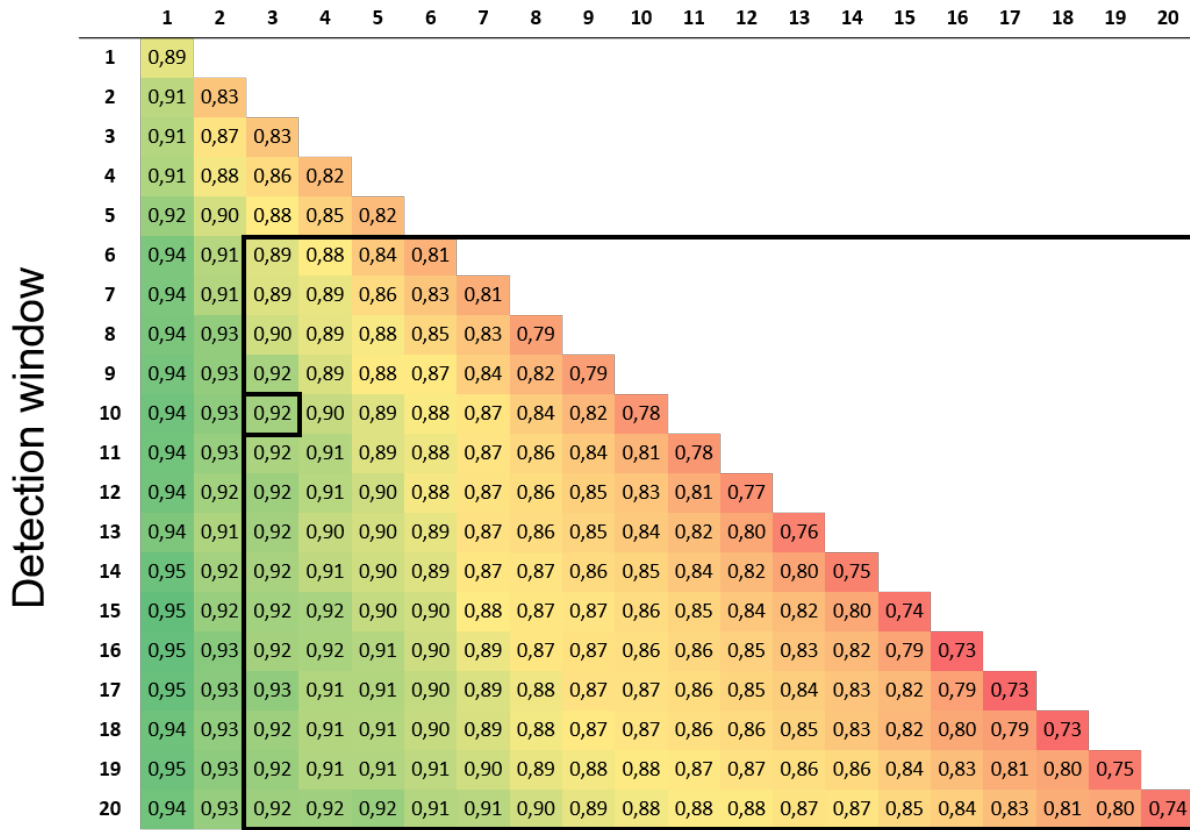
Figure S1



Schematic representation of how the ROC curve was acquired for the Boston Scientific RhythmID algorithm. Shown episode (*Ep N°1*) is classified as VT by the expert committee since there are more ventricular than atrial events. For each of the 178 episodes, the third highest in the last 10 % match score is kept for the analysis in accordance with the 3/10 nominal ratio (number of matches/morphology window size). The third highest match score gives the lowest threshold under which the episode would have been classified SVT, or above which it would have been classified VT. The ROC curve is constructed with 178 match scores coded as either VT or SVT, from the whole Boston Scientific population.

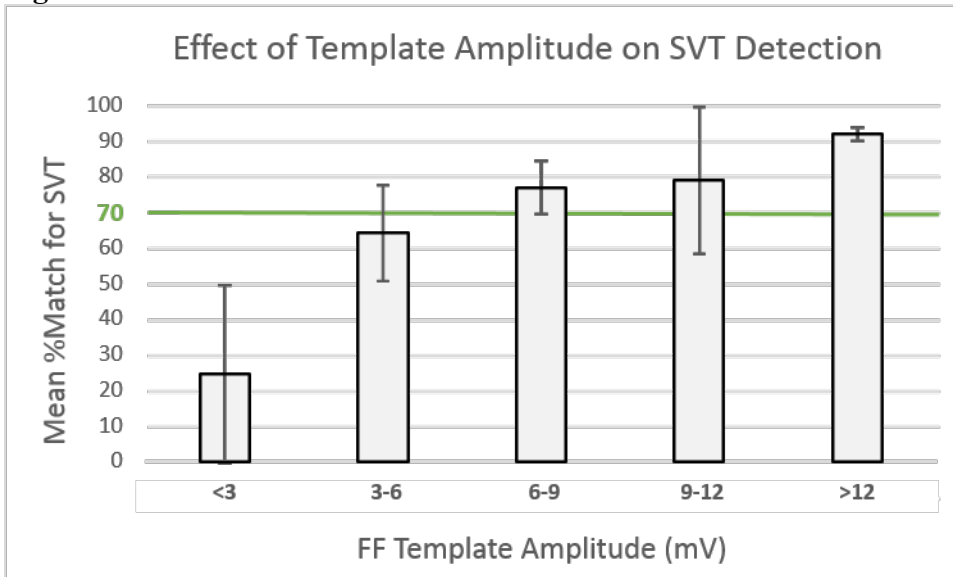
Figure S2

Number of matches required



AUC for ROC curves constructed at different number of matches/detection window ratios for the Abbott MD Far Field. Large black rectangle: AUC for the available combinations at programing. Small rectangle: AUC at nominal ratio 3/10.

Figure S3:



Mean percentage match scores for SVT according to the amplitude of the template. The nominal threshold appears in green.

Table 1: Technical data and settings of the 3 morphology discriminators

	Vector	% Threshold	Nb Matches	Windows size	Auto Update	Hysteresis	Manual
Abbott Far Field MD	RV Coil/Can RV Tip/Can	90 [30-95]	3 [3-20]	10 [6-20]	3h-30d.	Yes	Yes
Boston Sc. RhythmID	RV Coil/Can	94 [70-96]	3	10	2h.	Yes	Yes
Medtronic Wavelet	Can/RV coil Can /RV ring RVtip/ RV coil RVtip/RVring Can/ SVC RV coil/SVC	70 [40-97]	3	8	If Quality Check fails	No	Yes

The last 3 columns refer to the morphology reference template. Abbott Far Field MD and Boston Sc RhythmID periodically update the reference template. Medtronic Wavelet acquires a new template when less than 70 of the last 100 tested ventricular EGMs match the reference. This quality check analyses one EGM every 17 minutes. Hysteresis referred to the ability to temporarily adjust the atrio-ventricular delay or the basic rate to favors intrinsic ventricular EGMs. In grey: nominal settings.

Table 2: Arrhythmia dataset

	N	DR*	VT	VT(bpm)	SVT	SVT(bpm)	AF*
Abbott <i>Far Field MD</i>	54	18 (33)	110	176±21	68	163±18	35 (51)
Boston Sc <i>RhythmID</i>	60	52 (87)	110	180±25	68	169±21	32 (47)
Medtronic <i>Wavelet</i>	71	53 (75)	110	183±26	68	164±36	22 (30)

*:p<0.001 N: number of ICD. DR: number of dual chamber ICD, (%). AF: atrial fibrillation episodes, (%).

Table 3: Nominal and optimized match thresholds performances

	Nominal Settings			90% Sensitivity Th			90% Specificity Th			Optimal Th		
	% Th	SS	SP	% Th	SS	SP	% Th	SS	SP	% Th	SS	SP
Abbott <i>Far Field MD</i>	90	91	85	90	91*	85	77	71	90	91	94	85
Boston Sc <i>RhythmID</i>	94	100	41	69	90	83	63	77	90	83	100	79
Medtronic <i>Wavelet</i>	70	90	62	70	90	62	NR	NR	NR	70	90	62

Th: threshold. %Th: percentage match threshold, in grey. SS: sensitivity. SP: specificity. NR: not reachable (SP max <90%). In red, numbers <75%. * Closest value to 90%. NB: SS and SP are estimated from the model, actual value may differ.

Synthèse and Future Perspectives

Significant technological advancements in the field of cardiac pacing have allowed for the development and miniaturization of devices. Over the years, these devices have evolved from monitoring brady arrhythmias and pacing when needed, to now making clinical decisions based on electric signals from intracardiac electrograms.

Algorithms have been developed to optimize pacemaker responses during arrhythmias, minimize pacing, and for ICDs, to discriminate supraventricular from ventricular rhythms.

The studies described in this thesis showed that algorithms has contributed significantly to pacemaker and ICD function. Despite the sophistication evident in the algorithms' function, there nonetheless remain opportunities for optimization.

In pacemakers, minimizing ventricular pacing has demonstrated clinical benefits(32). This has led to developments of specific algorithms targeting this goal. However, investigating these algorithms more closely reveals several drawbacks.

In our research, the RYTHMIQ™ algorithm was responsible for inappropriate mode switch and a higher rate of PMT. Inappropriate switch occurred mostly in patients with frequent premature (atrial) or (ventricular) beats, mainly related to compensatory pauses, or less frequently, to undersensing or atrial noise oversensing. Pacemaker mediated tachycardia was directly related to prolongation of the AV delay; PVC and PAC were the usual triggers. Therefore, one assumption could be that activation of this algorithm should be performed cautiously in patients with frequent PAC / PVC. Second, the RYTHMIQ™ algorithm should be reserved for patients with sinus node dysfunction or brady-tachy syndrome, as it performs very well limiting the amount of ventricular pacing.

In a subsequent study, we investigated the performance of the anti-PMT algorithm in Boston Scientific devices showing that it is associated with a high rate of incorrect diagnosis of PMT. This performance was highly heterogeneous between patients, mainly depending on the underlying patient etiology. The absence of confirmation phase in the algorithm lead to the high rate of incorrect diagnosis of PMT during exercise resulting in consequences such as non-conducted P waves and loss of resynchronization therapy, and rarely, also arrhythmogenicity.

In the setting of cardiac defibrillators, our research proved the effective performance of Secure sense™ algorithm, preventing inappropriate ICD therapies. Although the algorithm was designed to diagnose lead dysfunction, it also demonstrated the capability to detect oversensing of physiological signals. Lead dysfunction most often starts with non-physiologic signals on the near field channel while the far field channel remains free from additional signals. By alerting the treating cardiologist via online platform, necessary therapy can be undertaken rather than waiting until an adverse clinical event occurs to bring the lead dysfunction to light.

Finally, amongst the algorithms designed to discriminate between supraventricular vs ventricular rhythms, we tested the morphology discrimination algorithm in a real-life multicenter setting. Main result of our study was that nominal values of morphology algorithms may be improved. This is of particular importance in single chamber ICDs, where their use as a standalone discriminator at nominal settings is accompanied by a significant number of missed VTs and inappropriate VT classifications. Amongst the algorithms analyzed in our study, the Wavelet algorithm (Medtronic) performs poorly. This may be in part related to its wavelet transformation which results in an overly detailed ventricular EGMs rendering it intolerable

to beat-to-beat signal variations. This higher sensitivity of 90% comes at the cost of a lower specificity.

Our results indicate that the Abbott and Medtronic nominal thresholds are very close to the optimal thresholds calculated. Boston Scientific devices, however, have nominal thresholds which appear too conservative: the optimal threshold calculated allows for a 38% gain in specificity. Clinicians may lower this match threshold in accordance to the lowest VT zone limit for improved VT discrimination.

The morphology algorithm could be used as standalone discriminator or in combination with other criteria. When morphology is a standalone discriminator, as is the case in single chamber devices, one may err on the side of sensitivity. However, when morphology is part of a discrimination tree, as is the case in dual chamber or CRT devices, the addition of atrial/ventricular rate comparison may allow the clinician to lower the match threshold and thus increase specificity of VT detection.

Notably, these studies were made possible as a result of developments in remote follow up. This feature has been endorsed with an international consensus statement recommending that all patients with implantable

cardioverter-defibrillator (ICD) should be offered remote monitoring (RM) as part of the standard follow-up management(33).

This demonstrates that we are heading to a future with inter-connected devices, allowing the remote transmission of multiparameter data.

Future cardiologists will be required to become acquainted with online platforms for the follow-up of patients with ICDs; these are going to be implemented by all manufacturers. The future is fast moving towards the implementation of artificial intelligence. Recently, Shakibfar and colleagues (34) elegantly demonstrated that the daily remote transmission of ICD can be used to build up machine learning models to predict electrical storms. In their models, artificial algorithms based on data, such as percentage of ventricular pacing and daytime activity, were capable of predicting electrical storms.

Emerging technologies aim to provide continuous hemodynamic information to aid in the management of chronic heart failure(35). Technologies that are being developed include impedance-based monitoring of fluid status, hemodynamic assessment based on pulmonary artery pressure and its derivatives, or direct left atrial pressure monitoring(36)(37). A promising possibility is that the information obtained from monitors may be

used to predict and avoid adverse clinical outcomes earlier than changes in clinical parameters would otherwise indicate, which would allow physicians an opportunity for earlier intervention.

In summary, technological advances have opened new avenues for device therapy and diagnosis in a multitude of cardiovascular conditions. Future efforts must focus on finding the appropriate clinical roles for these new technologies and ensuring that the incremental costs are justified by improvements in outcome for the delivery of more cost-effective care.

Conclusions

Algorithms contribute significantly to the correct function of PM/ICDs. In this research, algorithms tested in a real world setup demonstrated the potential for optimization. Remote follow up allows for early detection of arrhythmias and for improved care of patients, particularly in the pediatric population.

References

1. Di Cori A, Zucchelli G, Romano S, Bongiorni MG. Proarrhythmic effect of pacing mode reprogramation in a patient with a congenital long-QT syndrome. *J Cardiovasc Electrophysiol*. 2013 Nov;24(11):1304–5.
2. Shukla G, Chaudhry GM, Orlov M, Hoffmeister P, Haffajee C. Potential proarrhythmic effect of biventricular pacing: fact or myth? *Heart Rhythm*. 2005 Sep;2(9):951–6.
3. Shimizu W. Proarrhythmic effect of altered ventricular activation sequence in patients with permanent pacemaker. *Heart Rhythm*. 2007 Dec;4(12):1487–8.
4. Alasti M, Machado C, Rangasamy K, Bittinger L, Healy S, Kotschet E, et al. Pacemaker-mediated arrhythmias. *J Arrhythm*. 2018 Oct;34(5):485–92.
5. Barold SS. Repetitive reentrant and non-reentrant ventriculoatrial synchrony in dual chamber pacing. *Clin Cardiol*. 1991 Sep;14(9):754–63.
6. Causes of death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. *J Am Coll Cardiol*. 1999 Nov 1;34(5):1552–9.
7. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation*. 2000 Aug 15;102(7):748–54.
8. Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. *J Am Coll Cardiol*. 2003 May 7;41(9):1573–82.
9. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. *Eur Heart J*. 2000 Dec;21(24):2071–8.
10. Wilkoff BL, et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus

statement on optimal implantable cardioverter-defibrillator programming and testing. *Europace*. 2017 01;19(4):580.

11. Pérez-Rodon J, Doiny D, Miranda B, Rivas-Gandara N, Roca-Luque I, Francisco-Pascual J, et al. Life-threatening and life-saving inappropriate implantable cardioverter defibrillator shocks. *Clin Case Rep*. 2017 Mar 8;5(4):521–5.

12. van Rees JB, Borleffs CJW, de Bie MK, Stijnen T, van Erven L, Bax JJ, et al. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. *J Am Coll Cardiol*. 2011 Feb 1;57(5):556–62.

13. Rasania SP, Mountantonakis S, Patel VV. Inappropriate ICD Shocks caused by T-wave Oversensing due to Acute Alcohol Intoxication. *Pacing Clin Electrophysiol*. 2012 Sep;35(9):e267–71.

14. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. *J Cardiovasc Electrophysiol*. 2004 Jan;15(1):72–6.

15. Gradaus R, Wollmann C, Köbe J, Hammel D, Kotthoff S, Block M, et al. Potential benefit from implantable cardioverter-defibrillator therapy in children and young adolescents. *Heart*. 2004 Mar;90(3):328–9.

16. Silka MJ, Kron J, Dunnigan A, Dick M. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients. The Pediatric Electrophysiology Society. *Circulation*. 1993 Mar;87(3):800–7.

17. Noyes K, Corona E, Veazie P, Dick AW, Zhao H, Moss AJ. Examination of the effect of implantable cardioverter-defibrillators on health-related quality of life: based on results from the Multicenter Automatic Defibrillator Trial-II. *Am J Cardiovasc Drugs*. 2009;9(6):393–400.

18. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol*. 2006 Apr 15;97(8):1255–61.

19. Prinzen FW, Cheriex EC, Delhaas T, van Oosterhout MF, Arts T, Wellens HJ, et al. Asymmetric thickness of the left ventricular wall resulting from asynchronous

electric activation: a study in dogs with ventricular pacing and in patients with left bundle branch block. *Am Heart J.* 1995 Nov;130(5):1045–53.

20. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med.* 2007 Sep 6;357(10):1000–8.

21. Johnson CD. AV universal (DDD) pacemaker-mediated reentrant endless loop tachycardia initiated by a reciprocal beat of atrial origin. *Pacing Clin Electrophysiol.* 1984 Jan;7(1):29–33.

22. Monteil B, Ploux S, Eschalier R, Ritter P, Haissaguerre M, Koneru JN, et al. Pacemaker-Mediated Tachycardia: Manufacturer Specifics and Spectrum of Cases. *Pacing Clin Electrophysiol.* 2015 Dec;38(12):1489–98.

23. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation.* 2009 Mar 3;119(8):1085–92.

24. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm.* 2013 Dec;10(12):1932–63.

25. Myerburg RJ, Kessler KM, Zaman L, Conde CA, Castellanos A. Survivors of prehospital cardiac arrest. *JAMA.* 1982 Mar 12;247(10):1485–90.

26. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002 Mar 21;346(12):877–83.

27. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005 Jan 20;352(3):225–37.

28. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency,

mechanisms, predictors, and survival impact. *J Am Coll Cardiol.* 2008 Apr 8;51(14):1357–65.

29. Ellenbogen KA, Levine JH, Berger RD, Daubert JP, Winters SL, Greenstein E, et al. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation.* 2006 Feb 14;113(6):776–82.

30. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med.* 2012 Dec 13;367(24):2275–83.

31. Powell BD, Asirvatham SJ, Perschbacher DL, Jones PW, Cha Y-M, Cesario DA, et al. Noise, artifact, and oversensing related inappropriate ICD shock evaluation: ALTITUDE noise study. *Pacing Clin Electrophysiol.* 2012 Jul;35(7):863–9.

32. Curtis AB, Worley SJ, Chung ES, Li P, Christman SA, St John Sutton M. Improvement in Clinical Outcomes With Biventricular Versus Right Ventricular Pacing: The BLOCK HF Study. *J Am Coll Cardiol.* 2016 May 10;67(18):2148–57.

33. Slotwiner D, Varma N, Akar JG, Annas G, Beardsall M, Fogel RI, et al. HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. *Heart Rhythm.* 2015 Jul;12(7):e69-100.

34. Shakibfar S, Krause O, Lund-Andersen C, Aranda A, Moll J, Andersen TO, et al. Predicting electrical storms by remote monitoring of implantable cardioverter-defibrillator patients using machine learning. *Europace.* 2019 Feb 1;21(2):268–74.

35. Raj LM, Saxon LA. Haemodynamic Monitoring Devices in Heart Failure: Maximising Benefit with Digitally Enabled Patient Centric Care. *Arrhythm Electrophysiol Rev.* 2018 Dec;7(4):294–8.

36. Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, et al. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet.* 2016 Mar 26;387(10025):1298–304.

37. Feldman T, Mauri L, Kahwash R, Litwin S, Ricciardi MJ, van der Harst P, et al. Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]): A Phase 2, Randomized, Sham-Controlled Trial. *Circulation*. 2018 23;137(4):364–75.