Ventricular tachycardia (VT): Mortality implications in patients with cardiomyopathy, impact of VT ablation and development of new invasive treatment strategies

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Doctoral Thesis

Ventricular tachycardia (VT): Mortality implications in patients with cardiomyopathy, impact of VT ablation and development of new invasive treatment strategies.

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Barcelona, 2019

Acknowledgements:

A la Gabriela pel seu suport incondicional i per ser la magnífica persona que em fa ser una millor ànima sempre, i pels temps que vindran.

Al Pare i la Mare i als meus germans Joan i Clara. Companys de viatge durant tants anys i sempre enriquint la meva curiositat. Gràcies per obrir-me les portes de les oportunitats. Jana i Olivia, vosaltres sou les noves generacions i les nostres esperances ara ja estan posades en vosaltres.

Nantha, every clinician-scientist needs a mentor: A person that awes you and helps you. You have been that person for me. I will always be grateful for all your efforts on helping me in my research endeavours and for guiding my career at each step.

To all the co-authors, co-fellows and scientists in the research lab. Thanks for your help in moving all these challenging research projects forward. I will always be grateful for your contribution.

Abstract:

Background

Ventricular tachycardia (VT) is a common complication affecting patients with structural heart disease and poor left ventricular systolic function. Its occurrence is linked to increased mortality despite treatment with an implantable cardioverter defibrillator (ICD) and there are several challenges that are still to be solved. This thesis will focus on 4 unanswered aspects of the management of VT in a translational fashion, encompassing large registry data and cohort studies, development of new mapping tools in humans and validation of novel electrograms in a preclinical swine model. These advancements will add knowledge to the field of this complex and deadly arrhythmia.

Hypotheses and Objectives:

1) To assess the prognostic impact of ICD therapies in secondary prevention patients suffering VT. 2) To quantify the healthcare usage of patients treated with catheter ablation for recurrent VT compared to medical management. 3) To establish a mechanistic VT ablation guided by decrement evoked potential (DEEP) mapping. 4) To prove that omnipolar EGMs used in vivo identify the substrate of VT accurately and without the directional influences that affect bipolar EGMs.

Methodology:

1) Retrospective analysis of the Ontario ICD database and Cox-regression modeling to quantify independent risk factors for mortality in 7020 ICD recipients. 2) Propensity-matched analysis of catheter ablation versus medical management of 100 matched patients. 3) Multicenter prospective study of VT substrate mapping for the detection of DEEP regions in the VT substrate and its correlation to activation mapping and clinical outcomes. 4) Preclinical swine model of ventricular substrate to explore the utility of direction-independent omnipolar EGMs.

Results:

1) Patients treated with secondary prevention ICDs are exposed to an increased mortality after experiencing a life-saving ICD intervention (Antitachycardia pacing, namely ATP or shocks). 2) Patients with symptomatic recurrent VT treated with VT ablation experience a similar healthcare consumption compared to patients treated medically. 3) A mechanistic substrate mapping and ablation strategy targeting DEEP is highly specific for the detection of the critical regions of the VT circuit without the need to induce it. 4) The use of orientation-independent Omnipolar EGMs provide a reliable and physiological way of mapping with higher peak to peak voltages compared to any bipolar EGMs.

Conclusions

The mortality impact of ICD interventions spans from primary to secondary prevention patients. Managing VT ablation invasively yields a decrease in VT burden with respect to the pre-ablation state without incurring in increased healthcare costs when compared to medical treatment. Mechanistic DEEP mapping is a useful tool to assess the VT substrate. Omnipolar EGMs provide a good physiological representation of the VT substrate in a preclinical swine model.

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    c. Part III: **Porta-Sánchez A,** Jackson N, Lukac P, Kristiansen SB, Nielsen JM, Gizurarson S, Massé S, Labos C, Viswanathan K, King B, Ha ACT, Downar E, Nanthakumar K. Multicenter Observational Study of a Mechanistic VT Ablation Strategy with DEEP mapping. JACC: Clinical Electrophysiology. 2018. Feb, 592. doi: 10.1016/j.jacep.2017.12.005……..83
    d. Part IV: **Porta-Sánchez A**, Magtibay K, Nayyar S, Bhaskaran A, Lai PFH, Massé S, Qiang B, Romagnuolo R, Masoudpor H, Biswas L, Ghugre N, Laflamme MA, Deno DC, Nanthakumar K. Omnipolarity Applied to Equi-Spaced Electrode Array for Substrate Mapping. Europace 2019 Feb 4. doi: 10,1093/europace/euy304. [Epub ahead of print]……93
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Acronyms

ATP: Anti tachycardia pacing.

CV: Conduction velocity.

DAD: Delayed after depolarization.

EAD: Early after depolarization.

EGM: Electrogram.

ICD: Implantable cardioverter-defibrillator.

ICM: Ischemic cardiomyopathy.

LAT: Local activation time.

LAT: Local activation time.

LGE-CMR: Late gadolinium-enhanced cardiac magnetic resonance.

NICM: Non-ischemic cardiomyopathy.

OT: Omnipolar technology.

RCT: Randomyzed clinical trial.

VF: Ventricular fibrillation.

VT: Ventricular tachycardia.

Introduction:

a. Ventricular arrhythmia and risk of sudden cardiac death:

The incidence of sudden cardiac arrest is estimated to be of around 350.000 cases per year in the US.(1) The vast majority of these episodes are due to the occurrence of malignant arrhythmias. Ventricular tachycardia (VT) and ventricular fibrillation (VF) being the most common causes.

Heart rhythm disorders are conditions in which timing of contraction does not follow a physiological pattern and that may lead to a decrease in cardiac output. The severity of these conditions may range from mild symptoms of fatigue or lack of energy to the development of a cardiac arrest. Several types of arrhythmias have been described in humans, being the most frequent those that arise and remain mechanistically linked to the atria. Although some of the atrial arrhythmias may lead to blood clots and risk of stroke, mostly they are bening non-life threatening conditions. In contrast, arrhythmias that arise and are confined to the ventricular tissue may cause a very severe and sudden clinical picture that leads to a very small cardiac output. Ventricular tachycardia (VT) and ventricular fibrillation (VF) are arrhythmias that belong to the latter group and they are the most dangerous human ventricular arrhythmias. Ventricular tachycardia and VF are the focus of this work.

a. i. Ventricular arrhythmia definitions and classification:

Ventricular arrhythmias can be defined as those with an exclusive origin below the bifurcation of the His bundle, in the specialized conducting system, the ventricular muscle or a combination of both tissues, without any dependence on the atrial or atrioventricular nodal conduction. The entire circuit or focus is located in the ventricular myocardial muscle. If classified by means of their morphology, ventricular arrhythmias include: ventricular premature beats, idioventricular rhythm, ventricular tachycardia, ventricular flutter, torsade de pointes and ventricular fibrillation:

- Ventricular premature beats: Isolated ventricular contractions lasting less than 2 beats.
- Idioventricular rhythm: Three or more ventricular premature beats at a rate of less than 100 bpm.
- Ventricular tachycardia is a heartbeat with ventricular origin that lasts for more than 2 consecutive beats at a rate over 100 beats per minute (bpm).
- Ventricular flutter: An extremely fast repetitive ventricular rhythm (250 to 350bpm) that has a sinusoidal QRS classification preventing the identification of the actual QRS morphology.
- Torsade de pointes: Polymorphic VT associated almost exclusively to a long QT interval (acquired or inherited) that has an electrocardiographic pattern consisting of twisting of the peaks and QRS complexes around the isoelectric line during the arrhythmia.
- Ventricular fibrillation: This is a rapid (usually >350 bpm) irregular ventricular rhythm with marked variability in QRS morphology, amplitude and cycle length beat to beat. Mechanically this is a rhythm that will never generate an effective cardiac contraction.

(Figure 1)

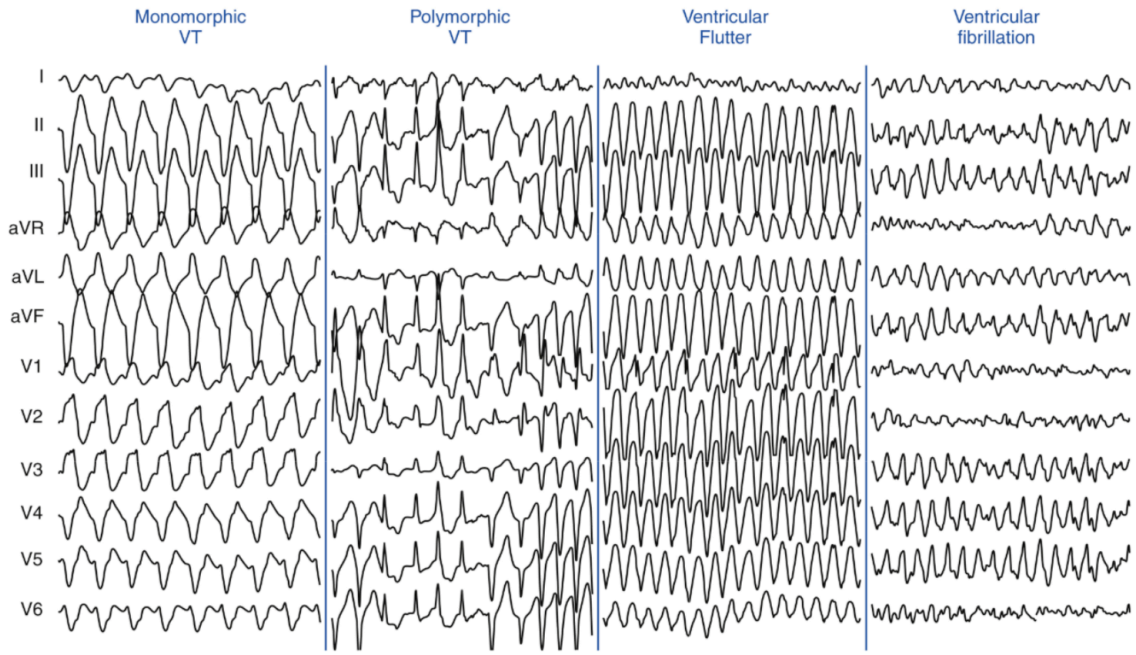

Figure 1. General types of ventricular arrhythmias. Modified from Issa Z, Miller JM, Zipes DP. Clinical Arrhythmology and Electrophysiology. Second edition. 2012.

a.ii. Mechanisms of ventricular arrhythmia:

We define the mechanisms responsible for cardiac arrhythmias generally in 2 groups: disorders of the impulse formation (abnormal automaticity and triggered activity) and disorders of the impulse conduction (reentry) or a mix of the 2 conditions. Diagnosis of the underlying mechanism of a ventricular arrhythmia is of key importance to guide the appropriate treatment strategy. Different mechanisms have been described to be responsible for the appearance of VT or VF:

1. Abnormal automaticity: In a normally functioning heart, automaticity is limited to the sinus node and the other specialized conducting tissues (AV node, His-Purkinje system). In contrast with those areas, normal working ventricular myocardium does not have spontaneous diastolic depolarization and that leads to lack of initiation of spontaneous beats even if they are not excited for long periods of time by neigbouring propagating impulses. In the normal heart, cardiomyocytes with very negative resting membrane potential (-85 to -95mV) do not depolarize spontaneously. In contrast, when the resting membrane potential is

depolarized to -70 to -30mV, spontaneous diastolic depolarizations can occur, leading to abnormal beats. The most common ventricular arrhythmias caused by abnormal automaticity are idopathic VPBs, the idioventricular rhythm and VT that occur during myocardial ischemia.

2. Triggered activity: This is impulse initiation in the myocardium caused by afterdepolarizations. Those are oscillations in the resting membrane potential that follows the upstroke of a preceding action potential. If they occur during the repolarization phase of the action potential they are called early afterdepolarizations (EAD). If they occur after the repolarization phase is completed they are defined as delayed afterdepolarizations (DAD). An important difference with abnormal automaticity is that triggered activity is not a self-generating rhythm but a response to a preceding impulse. The most common cause for the presence of DADs is an intracytoplasmic calcium overload. In contrast, EADs occur at the time of the action potential interrupting the normal repolarization of the cardiomyocyte. They are mainly due to small imbalances in an extremely sensitive phase of the action potential when very little current flow is present (the plateau phase). Small changes in these flows can have large impacts on the action potential morphology by reactivating the Na^+-Ca^+ exchanger. If an EAD or a DAD is large enough and occurs in a sizeable group of cardiomyocytes at the same time this may induce a triggered beat. The ability of these triggered action potentials to propagate into the neighbouring tissue is key to the development of arrhythmia.
3. Reentry: The normal cardiac cycle is characterized by the extinction of the excitation and is followed by a subsequent excitation propagating from the sinus node. Physiological excitation waves are extinguished after the entire heart is activated due to the long duration of refractoriness in the cardiac tissue in comparison to a very short excitation period. Reentry occurs when the impulse fails to extinguish

after a normal period of excitation and persists and consequently reexcites the heart after the refractory period has finished. The fact that the reexcitation perpetuates is due to the wavefront always encountering excitable tissue. Historically reentry has been classified as anatomical reentry and functional reentry. In anatomical reentry the tissue characteristics avoid normal propagation of the electrical impulse thus leading to a prolonged activation that allows for reentry to occur. In functional reentry, the circuit occurs at places without any clearly defined anatomical boundaries. Several conditions need to coexist to allow for reentry to develop: 1) Substrate: The presence of myocardial tissue with pathways that have different electrophysiological properties, conduction and refractoriness is key to the formation of a circuit. The properties may be due to an electrical disease of the heart or the presence of a substitution of cardiac tissue by fibrotic tissue, 2) Area of block: A center of non-excitable tissue is needed to allow for a long precession of the impulse to allow for recovery of the area where reentry will initiate. The lack of a non-excitable core may lead to the wavefront reaching the tissue where it originated too early to re-excite it, 3) Unidirectional conduction block: This results from heterogeneous properties of the myocardium and is essential to allow for the limbs of the excitation wavefront to be activated sequentially and not in parallel. At least transiently one limb of the circuit needs to have unidirectional block to allow for reentry, 4) Area of slow conduction: Conduction of the circulating wavefront must be sufficiently delayed in one limb of the circuit to allow for the recovery of refractoriness and perpetuate the presence of excitable tissue ahead of the activating wavefront, 5) Critical tissue mass: a critical mass of cardiac tissue is needed to achieve sustained reentry, 6) Initiating trigger: The milieu for the initiation of reentry needs to be invoked most of the times by a trigger that may be caused by automaticity or triggered activity. (2)

(Figure 2)

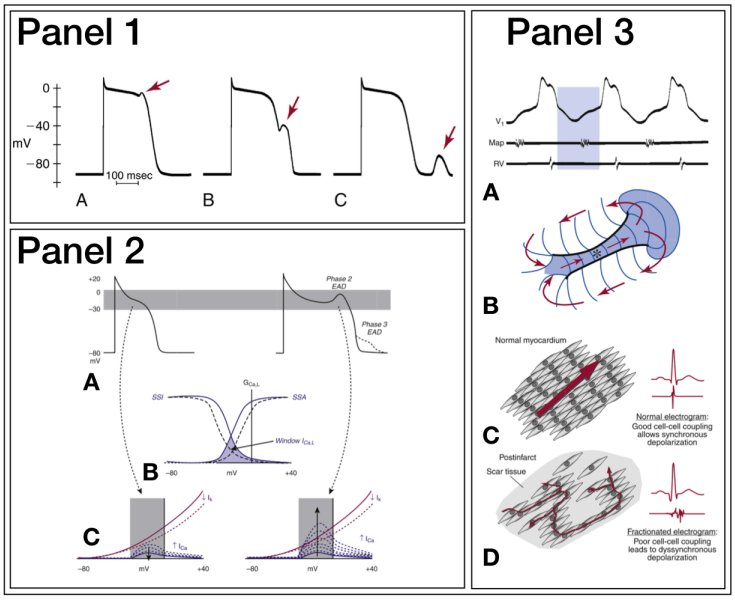

Figure 2. Panel 1 illustrates the action potential of an isolated cardiomyocyte with the occurrence of a Phase 2 early afterdepolarization (EAD) (A), a Phase 3 EAD (B) and a delayed afterdepolarization (DAD) (C). Panel 2 illustrates an action potential with and without an EAD (A) and the concept of the window of L-type inward Ca+ current (B) where minimal shifts (C) in the window can lead to generation of EADs. Panel 3 illustrates an ongoing ventricular tachycardia on the ECG with a diastolic recording of the reentry circuit inside the heart chamber (A) and its schematic representation (B). Normal conduction of the cardiac impulse (C) vs zig-zag conduction in diseased and fibrotic intermingled tissue (D) with their respective electrograms (EGMs). Adapted from Issa Z, Miller JM, Zipes DP. Clinical Arrhythmology and Electrophysiology. Second edition. 2012.

a. iii. Epidemiology of ventricular arrhythmias:

Information on the precise incidence and prevalence of ventricular arrhythmia in the general population is unclear. Ascertaining the actual episodes of ventricular arrhythmia is of great difficulty worldwide as there will always be selection and referral biases and geographical variations and definition methods. The incidence of life threatening ventricular arrhythmias is estimated from retrospective and prospective observational studies and registries of sudden cardiac death (SCD). SCD is defined as hemodynamic collapse and death occurring within 1 hour of

symptoms onset from a stable clinical state due to a cardiac cause. Epidemiological data has shown that the incidence of SCD in the United States is estimated to range between 180.000 and 400.000 cases yearly whereas in the European Union is estimated to range between 50 and 100 per 100.000 inhabitants/year. (3). Episodes of ventricular arrhythmia may be missed due to the lack of recordings of the true moment of the event, thus likely being underestimated. Unfortunately, SCD can be the first manifestation of a cardiac condition and only a small proportion of all SCD overall will happen in patients with well recognized risk factors for SCD as severe left ventricular systolic dysfunction(4). The vast majority of patients with SCD studied by clinical autopsy have coronary artery disease and 15% suffer from non-ischemic cardiomyopathy and 5% have a primary electrical disorder(5, 6).

Data has shown a steady decline in the rates of fatal ventricular arrhythmia in the last decades. Ventricular arrhythmia in the Framingham Study demonstrated a 49% decrease in age-adjusted risk from 1950-1699 to 1990-1999(7). In the Netherlands, rates have dropped by 48% from 1994 to 1999 and the incidence of cardiac arrest due to ventricular arrhythmia currently is below 30%(8). Nowadays the majority of out-of-hospital cardiac arrest has been documented to be due to pulseless electrical activity and asystole(9).

The prognostic impact of those arrhythmias is mainly driven by the presence of an arrhythmic substrate, meaning the areas of the heart where the normally functioning cardiac tissue has been replaced by fibrous tissue that impairs the cell to cell propagation of the electrical impulse. Other causes of ventricular arrhythmia are related exclusively to the heterogeneity in the electrical properties of the ion channels that regulate the electrical impulse propagation (channelopathies). Those are less frequent conditions and will not be the focus of our work.

It has been clearly documented that patients with structural heart diseases are much more prone to the development of ventricular arrhythmia and SCD. This is due to the remodeling that occurs in the cardiac tissue, involving changes in ionic channels and their currents, calcium handling abnormalities and decreases in the

gap junctional coupling of the cardiac cells(10). Those abnormalities have been linked in explanted human hearts to important transmural gradients that can lead to the presence of conduction blocks and reentrant rhythms.(11)

Several cardiac or non-cardiac conditions can lead to the development of a structural heart disease or cardiomyopathy. Currently, the leading cause worldwide of cardiomyopathy is ischemic heart disease. This condition is characterized by the replacement of cardiomyocytes by fibrous tissue in an area where there has been a prolonged ischemia leading to nechrosis. The electrical properties of the fibrous tissue are far from close to those of the normally working myocardium thus causing a delay in the propagation of the electical stimulus that may lead to the pernicious development of a reentrant ventricular rhythm. Most of the arrhythmias in ischemic heart disease patients occur during the acute phase of a myocardial infarction. A small proportion of patients will develop ventricular arrhythmia after having had a healed myocardial infarction. The most frequent risk factor for SCD due to ventricular arrhythmia is the presence of heart failure and left ventricular systolic dysfunction. SCD can be responsible of up to more than half of the total mortality of a heart failure population with severely depressed LV function(12).

Other conditions can lead to the scarring of the cardiac tissue due to inflammation (myocarditis) or due to an abnormal growth of the cardiac tissue (hypertrophy) that leads to areas of ischemia due to oxygen demand/supply mismatch. In other cases, the cause of the cardiac disease remains elusive. Most of these conditions not only affect the electrical conduction of the cardiac impulse but also are responsible for a pumping failure that causes symptoms of heart failure. Causes of non-ischemic cardiomyopathy (NICM) include: idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, sarcoidosis, amyloidosis, hemochromatosis, Chagas cardiomyopathy and valvular heart disease. In contrast with the decline in ventricular arrhythmia in the ischemic population mainly due to early reperfusion strategies and better primary and secondary prevention, the

incidence of ventricular arrhythmia in NICM seems to be steady(13). Hypertrophic cardiomyopathy has an incidence of ventricular arrhythmia and SCD of 0.5-2%. Arrhythmogenic cardiomyopathy is an uncommon disorder where there is fibrofatty replacement of the myocardial tissue that affects predominantly the right ventricular chamber. Cardiac sarcoidosis is responsible for a small proportion of ventricular arrhythmias and Chagas cardiomyopathy has a very limited geographical distribution currently.

b. Current treatment of patients with structural heart disease and ventricular arrhythmias:

b.i. Medical therapy with antiarrhythmic drugs for ventricular arrhythmias related to structural heart disease:

Therapy with antiarrhythmic drugs is used to either terminate or to prevent episodes of ventricular arrhythmia. The acute medical treatment of a patient presenting with ventricular arrhythmia is not the focus of our work and we will describe the evidence for the chronic preventive treatment in patients with structural heart disease. Antiarrhythmic drug usage in the long-term may be useful to alter the electrophysiological properties of the substrate thus leading to increased difficulty for the circuit to trigger or initiate or sustain a reentrant rhythm that underlies the majority of VT episodes.

Several antiarrhythmic drugs are available for the treatment of ventricular arrhythmia but long term toxicities or arrhythmogenicity limit their usage in the population of structural heart disease patients. One clear example of the toxicity of antiarrhythmic drugs was documented in the CAST I and CAST II trials, where class Ic antiarrhythmic drugs were given in ICM patients and patients having suffered a recent myocardial infarction that had a high burden of non-sustained VT or frequent VPBs (14, 15). In contrast, amiodarone usage was proven to increase survival compared to placebo in patients who survived myocardial infarction and had frequent VPBs in the CAMIAT trial(16).

In the era of ICD therapy reliable data is available to understand the effects of antiarrhythmic drugs in our population of patients. Sotalol was compared to placebo showing efficacy in reducing ICD therapies both appropriate and inappropriate without any difference in total mortality(17). In the OPTIC trial patients were randomized to amiodarone and betablocker, sotalol or betablocker alone and there was evidence of significantly less shocks in the amiodarone + betablocker arm but no statistical difference was seen between sotalol and betablocker alone. No differences in mortality were encountered(18). Pooled data

of 13 trials in a meta-analysis showed a mortality benefit with amiodarone compared to conventional therapy(19).

(Figure 3)

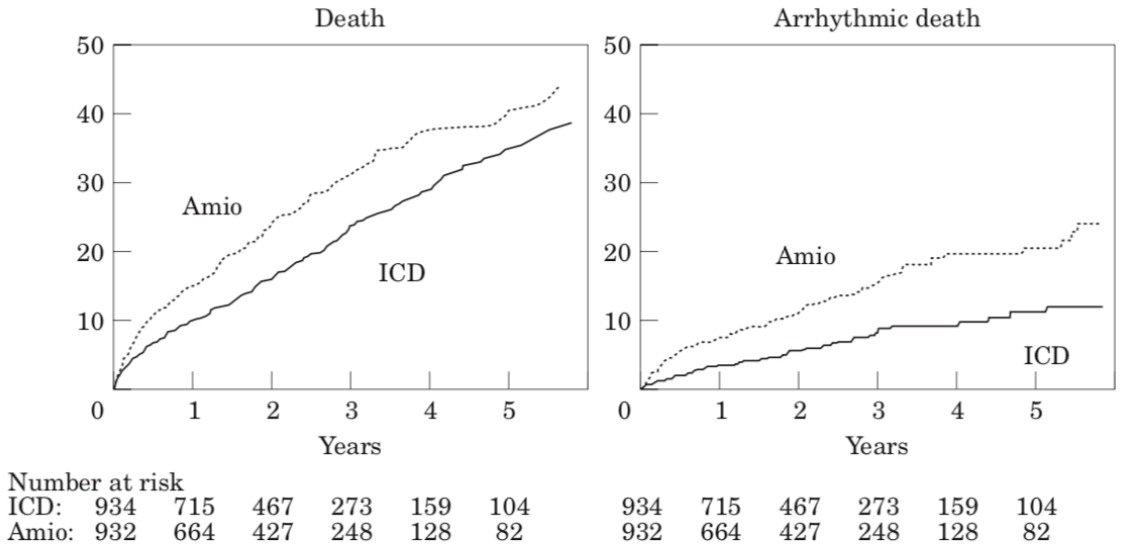

Figure 3. Results of the meta-analysis of CASH, CIED and AVID trials in secondary prevention patients comparing ICD vs antiarrhythmic treatment with amiodarone. Modified from Connolly S, Am J Cardiol 2000.

b.ii. Prevention of sudden cardiac death:

Since the introduction of ICDs in the 1980s, large scale randomized clinical trials have demonstrated that ICDs have improved survival in ischemic cardiomyopathy. In the late 90s a number of trials compared the clinical evolution of patients with structural heart disease at risk of ventricular arrhythmia or with a high burden of non-sustained episodes of ventricular arrhythmia treated medically or with an ICD(20). A number of studies followed and reinforced the evidence that ICDs were associated with a better prognosis in this population of patients with severe structural heart disease characterized mainly by poor left ventricular ejection fraction (LVEF) treated with ICD. The combination of improved medical treatment and the advent of ICD implantation has translated into better outcomes for patients suffering from these types of debilitating conditions. (21) The survival benefit of

such ICD therapy in non-ischemic cardiomyopathy is not as clear as for ICM. In the DEFINITE trial, NICM patients had a trend towards ICD benefit but no survival benefit was demonstrated(22). This was similar when analyzing the NICM patients included in the SCD-HeFT trial. Recent data from the DANISH trial has shown no differences in survival of NICM patients treated with medical treatment vs ICD (23).

b.iii. Catheter ablation for ventricular arrhythmia:

Despite the effectiveness of ICD therapies in terminating acutely the VT episodes, ICD therapy does not completely solve the clinical importance of VT or VF episodes, as it has been seen that in primary prevention patients (those that have not experienced an episode of cardiac arrest) the presence of VT that needs treatment by the ICD is linked to decreased survival (24, 25). Because of the fact that the ICD does not prevent arrhythmias, patients who experience frequent symptoms due to VT are often in need of additional treatment. There are 3 main indications for antiarrhythmic drugs in patients with structural heart disease along with an ICD: to reduce the burden of VT, to make them more amenable to ICD termination or to suppress the triggers of those VTs. An alternative to antiarrhythmic drugs is to perform an invasive catheter ablation technique were electrodes equipped with radiofrequency tips are used to stop the circuits that lead to VT. To date, it is unproven that treatment with catheter ablation versus antiarrhytmic drugs in patients with VT and an ICD leads to better survival (26) but the benefits of suppressing VT and decreasing its burden are well proven in this population(27). One of the main issues is that the rate of recurrence after VT ablation remains high and that the comorbidities of patients and the clinical instability at the time of the procedure comes with important safety concerns (28).

Figure 4)

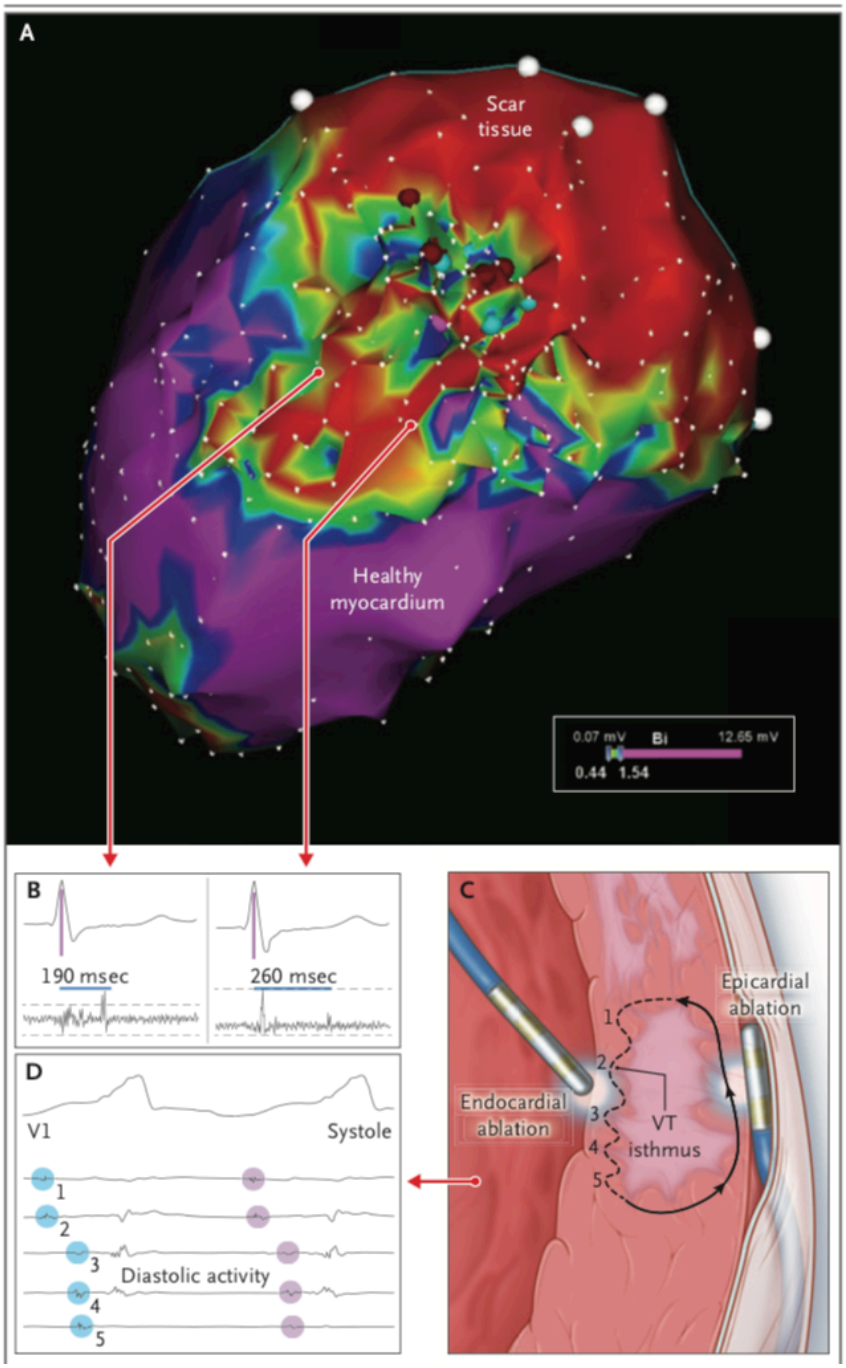

Figure 4. Panel A shows an electroanatomical colour-coded map of the left ventricular chamber highlighting the areas of low voltage in red. Panel B illustrates the timing of late activating regions during substrate mapping (late potentials). Panel C shows a schematic representation of the substrate of VT with ablation catheters in the areas of interest. Panel D illustrates how activation mapping depicts activity of the VT circuit. Modified from Shivkumar K, NEJM 2019.

b.iv. Current knowledge gaps in the ventricular arrhythmia field leading to this study:

Life threatening VT in patients with structural heart disease is the main focus of our study. We will focus on answering questions regarding the important patient issues that are unsolved and to develop new strategies for their treatment. Of all the questions that remain unanswered in the field of VT this thesis will provide a translational point of view that encompasses a swine model of ventricular tachycardia substrate to validate new tools for the treatment of VT, passing by human studies with new substrate mapping to a population based registry to assess the mortality impact of VT and the healthcare impact of catheter ablation of VT.

c. Part I: The impact of ICD therapies in a large population-based registry that includes secondary prevention patients.

Three randomized clinical trial evaluated the effect of antiarrhythmic drugs vs ICD in survivors of a cardiac arrest: AVID, CASH and CIDS(29, 30) (31). The AVID trial showed a significant risk reduction in total mortality in patients treated with ICD therapy. The CASH and CIDS study showed a trend towards reduced mortality but it did not reach statistical significance. The patient-level data was pooled by means of a metanalysis that showed a 28% relative risk reduction of overall mortality in ICD treated patients versus amiodarone treated patients almost entirely related to a 50% reduction in arrhythmic death(32).

With regards to patients at high risk for SCD but who had not experienced episodes of cardiac arrest, randomized clinical trials demonstrated a mortality reduction compared to medical therapy when implanting a prophylactic ICD (20, 33-35). Those initial trials included patients with ICM displaying other markers of risk for SCD such as inducible VT on the electrophysiological testing, abnormal findings on the signal averaged ECG or spontaneous presence of non-sustained VT on the Holter monitoring. Further studies compared medical therapy to ICD implantation in ICM patients showing no other risk factor but the presence of a severely reduced LVEF of less than 31%. (36) These positive findings in the ICM population led to other studies that included also NICM patients with poor LVEF and symptoms of heart failure or other risk features for ventricular arrhythmia(37). The NICM population did not benefit as clearly as the ICM population from an overall mortality perspective, but sudden arrhythmic death risk reduction was clearly documented. To further add to the mortality conundrum in NICM patients a recent study focusing on primary prevention ICD therapy vs medical therapy failed to show mortality benefits in the NICM population with the ICD therapy(22, 23).

The positive findings mainly in the ICM population led to the widespread use of ICD therapy both in primary prevention (prophylactically) and secondary prevention clinical scenarios.

However, the often life-saving ICD shocks have a number of negative effects, including psychological morbidity and reduced quality of life and also come with an economic burden. Observational studies and RCTs have demonstrated impact in mental wellbeing after a single shock that was even more pronounced when further shocks ocurred(38, 39). Shocks also increase healthcare usage and come with a reduction in device longevity. More importantly, despite the fact that these trials showed a consistent reduction in the risk of sudden arrhythmic death, the presence of ICD shocks due to recurrent VT was seen to be independently associated with an increased risk of mortality during follow up: In the landmark of primary prevention ICD studies the hazard regression analysis demonstrated a threefold increase in mortality after a first therapy for VT and there was a twofold to fivefold increase in mortality associated with having experienced inappropriate ICD shocks (40, 41). This is, patients who experienced live-saving ICD shocks due to arrhythmia were not completely safe only with the ICD and those therapies were indeed markers of a poor prognosis. Data from several randomized clinical trials was analysed post-hoc confirming this hypothesis (42)and registry data confirmed the findings (24, 41, 43) and there was a clear association between shocks and mortality that increases with repeated shocks and is worse for appropriate than inappropriate shocks. An open question was whether the ICD shocks themselves were markers of increased mortality due to the injury created in the heart after defibrillation or those were only markers of increased mortality risk because of the underlying potentially lethal arrhythmic episodes. Data is contradictory in this field: There is evidence in favour of ICD shocks being followed by pulseless electrical activity in a large series of ICD patients (44) that had sudden death thus linking them to myocardial stunning that could be fatal in some patients. However, the fact that defibrillation testing had been performed systematically in large numbers of patients without any impact on mortality argues against the harm of ICD shocks (45) and there was also clear data showing that only spontaneously occurring arrhythmias treated with shocks were linked to increased mortality(46). A number of observational datasets with large number of patients also showed that shocks delivered due to supraventricular

arrhythmias (inappropriate) were not linked to increased mortality but there is conflicting data when analyzing the substudies of the SCDHeF and MADIT II trials where inappropriate shocks had a negative impact on survival (24, 43). Further information on whether arrhythmic substrate causing VT leading to ICD therapies is linked to increased mortality can be analyzed from the impact of arrhythmia terminated with ATP on mortality. In observational studies involving primary prevention patients there was a clear evidence on the increased long-term mortality linked to appropriate ATP therapies (47, 48).

In contrast with the overwhelming amount of data in primary prevention patients, in patients with secondary prevention ICD implantation there was paucity of data regarding the impact of ICD shocks due to ventricular arrhythmia in long-term mortality. When focusing on the secondary prevention trials, data from the AVID trial showed that the impact of receiving appropriate ICD shocks during follow up was neutral (49). When looking at data from large registries including secondary prevention patients treated with ICDs and comparing outcomes as a function of the ICD indication there was the interesting finding that patients with secondary prevention ICDs had the same prognosis as the primary prevention counterparts. But data from those registries did not compare the impact of appropriate ICD shocks on mortality.(50, 51).

In summary, there was a clinical need to answer the question whether contemporary secondary prevention ICD-treated patients experienced the same prognostic implications from having appropriate ICD therapies (ATP and shocks) during follow up. Also, large reliable contemporary data on their clinical profile and ICD shock and ATP rates in a non-randomized clinical trial population was needed.

The Ontario ICD database (Canada) was created in 2008 with the aim of enrolling the whole population of the province of Ontario treated with de novo ICD implants and follow their long term clinical outcome.(52) The events were adjudicated by electrophysiologists and their clinical outcome was assessed by means of using administrative databases in a province where the Ministry of Health is the single

healthcare provider. The combination of those factors makes the registry a very robust dataset that has delivered several publications that shed light on clinical questions not answered by randomized clinical trials (53-56). By means of using this prospective, population-based registry of consecutive patients receiving ICD for both primary and secondary prevention we focused on answering the impact of ICD therapies including ATP and shocks in a secondary prevention population compared to those patients treated with ICD for primary prevention and with those treated but not receiving ICD shocks. This is a critical question when defining the outcomes of patients presenting to our daily practice with ICD shocks with a secondary prevention device. Characterizing that population is the main aim of the population-based part I of this thesis.

d. Part II: Comparison of the clinical outcomes and healthcare costs of catheter ablation vs medical therapy for recurrent VT.

The compelling evidence of increased mortality in patients experiencing recurrent episodes of VT and the partial efficacy of antiarrhythmic drugs with their long-term side effects has led to several attempts to demonstrate a mortality benefit of catheter ablation. Catheter ablation of ventricular tachycardia is one of the most commonly used treatments to improve symptoms in patients with malignant ventricular arrhythmia (57). The basis of catheter ablation in patients with structural heart disease lies in the fact that creating a lesion in the circuit that either initiates, perpetuates or could potentially be implicated in the arrhythmia may render its induction more difficult or impossible. Multiple strategies for this catheter based arrhythmia treatment have been used and they have been demonstrated to lead to a reduction in the recurrence of VT in patients treated(27, 58). Despite this important impact on the reduction of VT the effects on hard clinical outcomes such as heart failure, mortality and health care resource consumption compared with medical therapy remained uncertain(59).

Santangeli et al pooled together in a meta-analysis the data available from RCTs comparing catheter ablation for VT vs medical therapy. The results showed that antiarrhythmic drugs and catheter ablation had a clear effect on reduction in VT burden compared to medical therapy and that amiodarone treatment was the only antiarrhythmic drug that effectively reduced the recurrence of ICD therapies at the cost of increased long-term all cause mortality likely due to toxicities. More importantly, neither VT ablation or antiarrhythmic drugs showed a positive impact in survival(60).

More importantly, recent data in ICM patients comparing VT ablation vs escalated medical therapy (VANISH trial) showed there was no mortality reduction with the invasive strategy but VT ablation was linked to a clear reduction in VT burden compared to antiarrhythmic drugs (26). Subsequent analysis from the VANISH trial

showed that the subgroup that experienced breakthrough VT despite being treated with amiodarone experienced a mortality benefit from VT ablation(61).

(Figure 5)

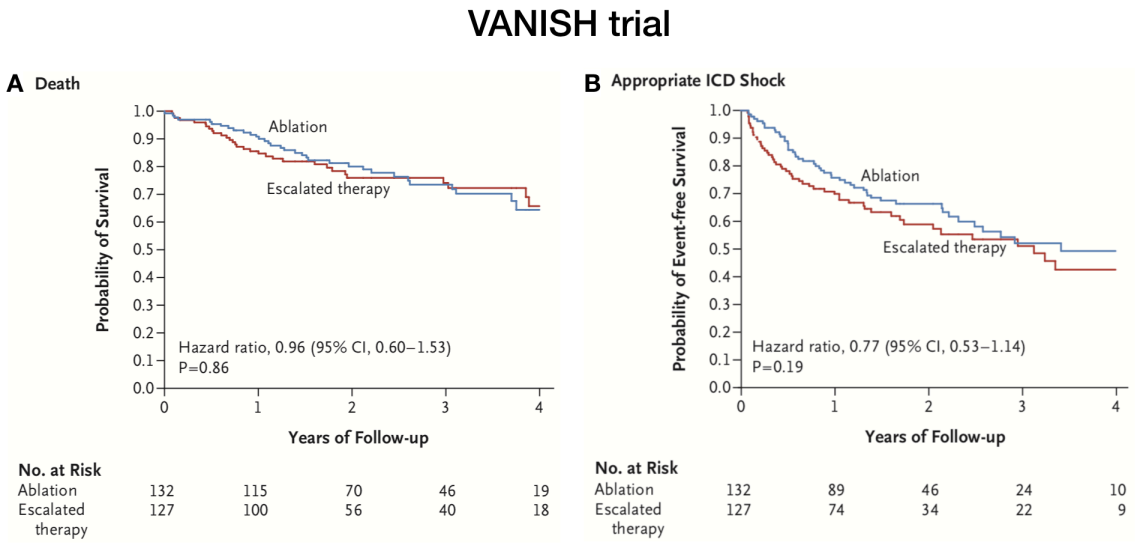

Figure 5. Kaplan Meier survival curves of the VANISH randomized clinical trial. Panel A illustrates the overall mortality between the 2 treatment strategies. Panel B illustrates the appropriate ICD shocks in each arm. Both strategies resulted in non-statistically significant differences for both outcomes. Modified from Sapp J et al. NEJM 2015

This is of critical importance as it is a treatment that comes with a risk of mortality (28) in frail patients some of them with advanced heart failure states (62). Other previous randomized studies did not consider heart failure outcomes and admissions in their population and the comparison group in some was only treated with ICD and no antiarrhythmic drugs (63-65)

It may seem counterintuitive the fact that a treatment with proven ability to reduce VT episodes is not able to reduce mortality when compared to antiarrhythmic drugs. One could hypothesise that the reduction in VT episodes that patients experience is counterbalanced by an increase in other outcomes such as heart failure admissions or admissions for non-cardiac reasons as a result of the

treatment. Also, some of the VT ablation strategies are very aggressive by targeting the entire substrate both in the endocardium and the epicardium that shows some abnormal electrical pattern (66) or by isolating large areas of myocardium where myocardial bundles are located but diseased (67). This destruction of large areas of myocardium may lead to a decreased pumping function thus solving the issue of VT but secondarily provoking increased heart failure events, that more importantly could be triggers of further arrhythmic events.

This clinical equipoise leads to part II of our study where the benefits of VT ablation in a population of ICM and NICM patients with ICD and poor LVEF not represented in RCTs are studied.

A critical aspect of the invasive management of patients with recurrent VT is their healthcare usage. In the current era, when economical constrains are present and health care costs are increasing with the population having a longer life expectancy it is of relevance to evaluate all the direct and indirect quantifiable consequences of such a treatment. In 2000, a model-based analysis describing the cost-effectiveness of catheter ablation for VT was published showing that -compared to amiodarone- VT ablation led to greater quality-adjusted-life-years (QALY)(68).

Recent data from registries of patients treated for recurrent VT pointed towards a reduction in the admission rates and expenditure in healthcare in the population treated with catheter ablation but unfortunately there was no control group in the study and the procedural characteristics were lacking. (69) Additionally, data derived from the VANISH trial demonstrated greater QALY with catheter ablation than antiarrhythmic drugs but at higher costs mainly due to the upfront cost of the VT ablation procedure. Factors such as the type of previous antiarrhythmic drug used may play a critical role in the effects of catheter ablation in this setting(70). However, the VANISH trial did only include patients with ischemic cardiomyopathy and that excludes a large proportion of the patients currently treated with VT ablation.

Thus there is a need for additional information not answered to date in the current literature with regards to 1) healthcare outcomes, 2) admissions and 3) healthcare costs and this will be the main focus of Part II of this thesis.

e. Part III: Introduction and validation of DEEP mapping as a novel strategy for a mechanistic VT ablation strategy.

Important changes in multiple aspects of the invasive treatment of VT have occurred in the last decades. Only 50 years ago it was a matter of imagination to envision that a deadly rhythm so called ventricular tachycardia could be mapped and then targeted to avoid its recurrence. The improvement of the mapping techniques has been constant and we need to consider that the first and most important revelations on the circuits of VT were obtained in patients undergoing open heart surgery under cardiopulmonary bypass(71, 72). Many years have passed since then and several other works identified the mechanisms leading to the discovery that VT was a reentrant rhythm developing after an area experienced unidirectional conduction block (73). The advent of electroanatomical mapping tools that allowed for closed chest mapping of the electrical circuits of the heart gave rise to the widespread use of steerable catheters to identify and locate the areas thought to be responsible for the arrhythmia episodes. There was clear evidence that the VT circuits were harboured in areas where the ventricular signals were of smaller amplitude, had differential electrical components and had prolonged activation times. Those intraoperative findings allowed to further define the substrate of VT based on the differences of the electrograms of normal ventricles compared to those electrograms recorded with percutaneous catheters in patients with a previous healed myocardial infarction(74, 75). The initial therapies for VT involved the peeling of the subendocardial layer that allocated most of the abnormal signals (the Pennsylvania peel)(72).

(Figure 6)

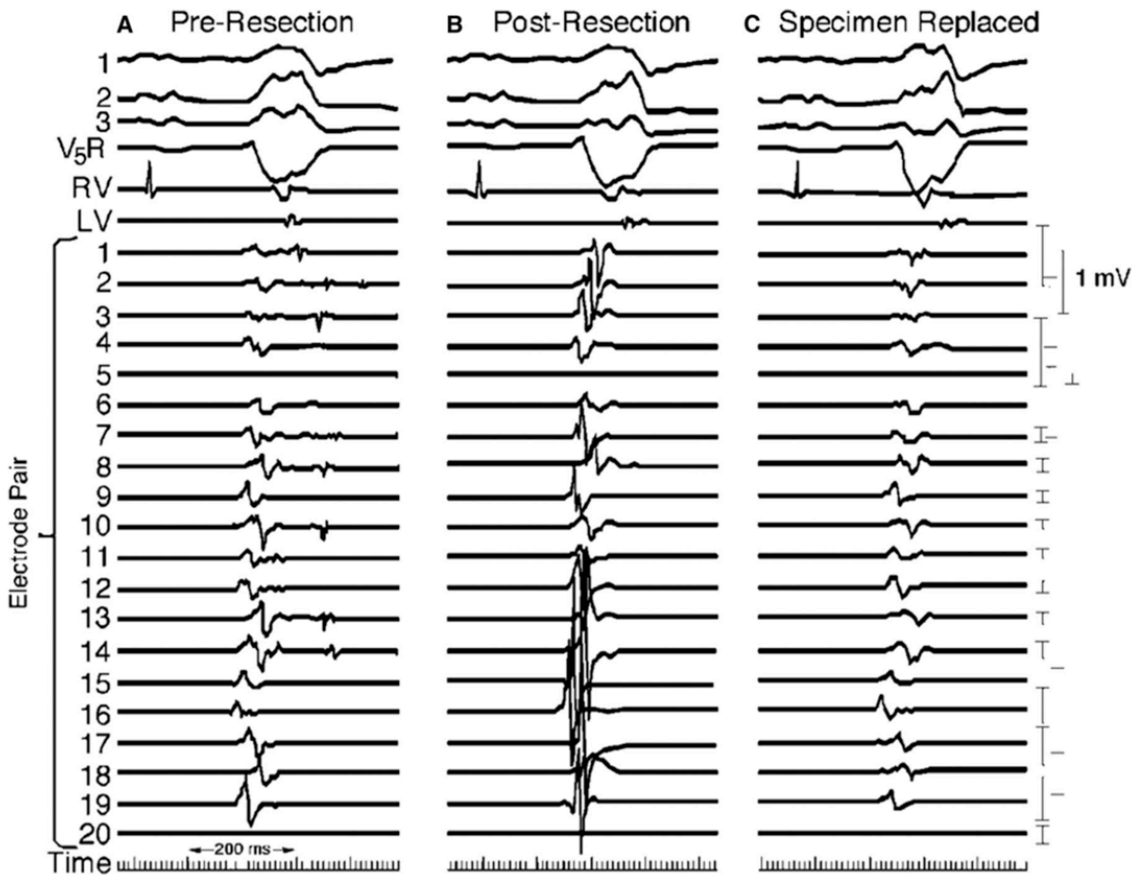

Figure 6. Efffects on the EGM recordings of the resection of the subendocardial layer of myocardium for surgical treatment of ventricular tachycardia. Panel A shows the widespread presence of late potentials. Panel B shows how the voltage of the subendocardial layer is increased when removing the fibrotic tissue highlighting the 3D component of the circuit. Panel C illustrates how the surgical specimen has been electrically isolated and the late potentials have disappeared. Adapted from Miller JM et al Circulation 2005.

Later on, only the areas that demonstrated active participation in the VT by means of defining an isthmus with activation mapping were treated intraoperatively with the aid of an ablation catheter (cryoablation catheter)(76). The initial success rates were very satisfactory with recurrences on the range of less than 10% after more than 4 years of follow-up.

With the need of performing VT ablations in a safer way without requiring to undergo a cardiopulmonary bypass circulation catheter technology evolved enormously and the first series of ablation procedures entirely done in a minimally invasive fashion were published (77, 78). Currently, there are mainly 3 ways of

identifying the VT locations in an invasive way: Activation mapping, pacemapping and substrate based approaches.

e.i. Activation mapping-based strategies for VT ablation:

In those series, hemodynamically stable mappable VT was targeted with radiofrequency without paying much attention to the other areas of abnormal electrograms in the tissue. Mapping during VT means that by using a roving catheter inside the cardiac chamber of interest one collects and analyzes the data regarding the time of activation of each region of the heart. By means of analyzing the pattern of activation of the cardiac chamber one is able to recognize the area or areas responsible for the perpetuation of the VT (isthmus) that then is targeted for ablation after confirming its active participation in the maintenance of the tachycardia. Activation mapping allows for the delineation of the area of the entrance to the diastolic path of the tachycardia, the isthmus and the exit site of it. By targeting with ablative energy the areas critically involved in the VT one is able to terminate the VT and render it non-inducible. Limitations of this technique include the fact that patients need to have their clinical VT inducible at the time of the study, also they have to be in sustained monomorphic VT for prolonged periods of time to allow for activation mapping. Very often, hemodynamic tolerance to the VT is not good and it may lead to organ failure or collapse. Additionally, multiple runs of VT may need to be terminated with defibrillation, that may carry additional risks. Moreover, it was soon recognized that if other VTs were present at electrophysiological testing there was a very high rate of recurrences during follow up. Because of the limitations of activation mapping there was then a transition towards also evaluating the substrate of VT and a number of strategies were developed to target unmappable VTs (79, 80), the so called substrate based approaches and the pacemapping approaches.

(Figure 7)

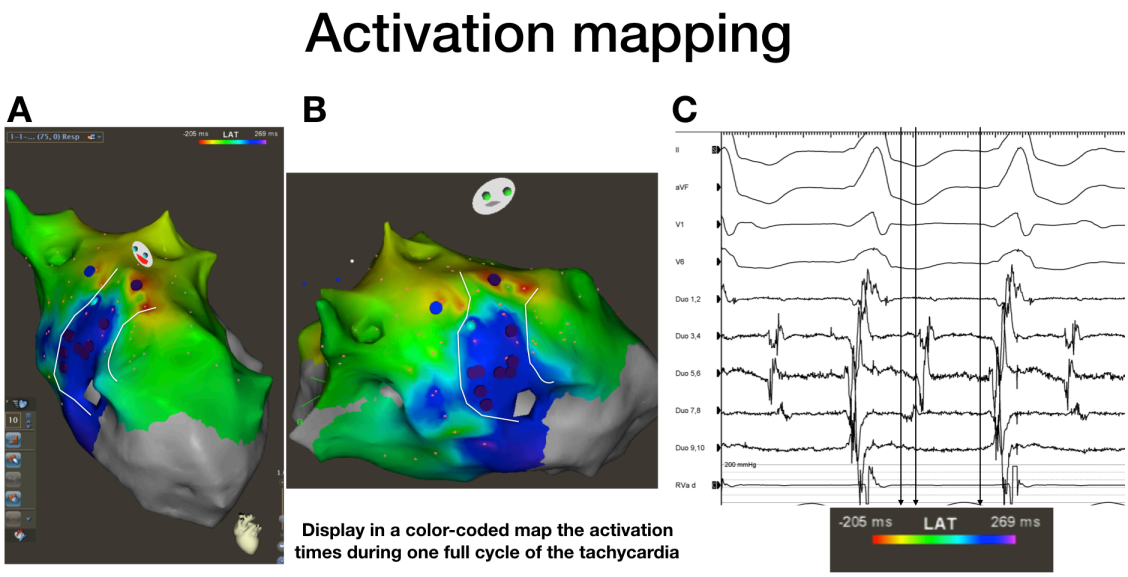

Figure 7. Activation mapping of ventricular tachycardia. Panel A and Panel B illustrate 2 views of the left ventricular endocardium of a patient with ischemic cardiomyopathy. Activation maps are color coded maps where each activation time during the tachycardia circuit is assigned a colour. Panel B illustrates diastolic electrograms obtained in the protected region of the reentrant circuit during VT.

e.ii. Pacemapping based strategies for VT ablation:

By means of stimulating at low output in areas of interest one can identify whether the morphology of the ECG resembles the one documented during VT. It is usually performed when identifying areas of abnormal EGMs and by creating a high number of points. With the aid of software that allows for an automated analysis of the correlation between the clinical and the pacemapped rhythm one can identify the circuits with reliable precision. Ablation in the area of interest renders de VT non inducible with good long-term outcomes. (81, 82).

e.iii. Substrate based strategies for VT ablation:

The main objetive of substrate-based strategies for VT ablation is to identify and eliminate all the areas that can be linked to the clinical VT (documented or induced) and possible future VTs without the need to be in sustained VT during the

procedure. The role of those signals identified during stable rhythm (fractionated EGM and late potentials) in the circuit of VT was documented in the first surgical resection series of patients treated for VT(83).

Several different strategies trying to eliminate all the possible culprits for sustaining VT have been developed. Those strategies involved identifying the area of low voltage and the small or fractionated or delayed electrograms that were considered to be involved in the VT circuit (84). A short summary of some of the most commonly used strategies is provided herein:

1) Linear ablation: The initial series of patients referred for VT ablation that had unmappable VT were treated with short or long lines of ablation across the substrate of VT or anchoring those lines of ablation to anatomical obstacles. Acute and long term success were reasonably good with that strategy (80, 85)
2) Identification of low-voltage area and homogenization of the abnormal EGM areas. This implies extensive delivery of radiofrequency to perform homogenization of the low voltage tissue to avoid recurrence of VT (86).
3) Identification of areas activated late in the low-voltage territory (late potentials). By creating a detailed map of the abnormal tissue in ICM patients one can identify areas with electrical activity ocurring several milliseconds after the whole activation of the chamber during a stable rhythm. Those EGMs are called late potentials and their elimination renders the VT non-inducible in the majority of cases with good long term results (79, 87, 88).
4) Isolation of the core of the scar area: In this strategy, identification of putative sites responsible for VT was guided by activation map if feasible or by pacemapping and the area of very low-voltage (below 0.5mV bipolar peak to peak) was targeted to produce exit block from it. Isolation of the core was an additional measure that

was accompanied by additional substrate modification in 61% of patients included (67).

5) Identification and ablation of local abnormal ventricular activation signals (LAVA): P Jaïs et al described this technique in 2012 that used the endpoint of eliminating all LAVA during the ablation procedure. Their strategy was successful in 70% of the cases and was a good predictor for VT freedom in the long term (89).

6) Scar dechanneling: Detailed mapping of the scar revealed that by eliminating the entry of the myocardial bundles that penetrate the substrate from the healthy areas a very high success rates can be obtained (90-92).

(Figure 8)

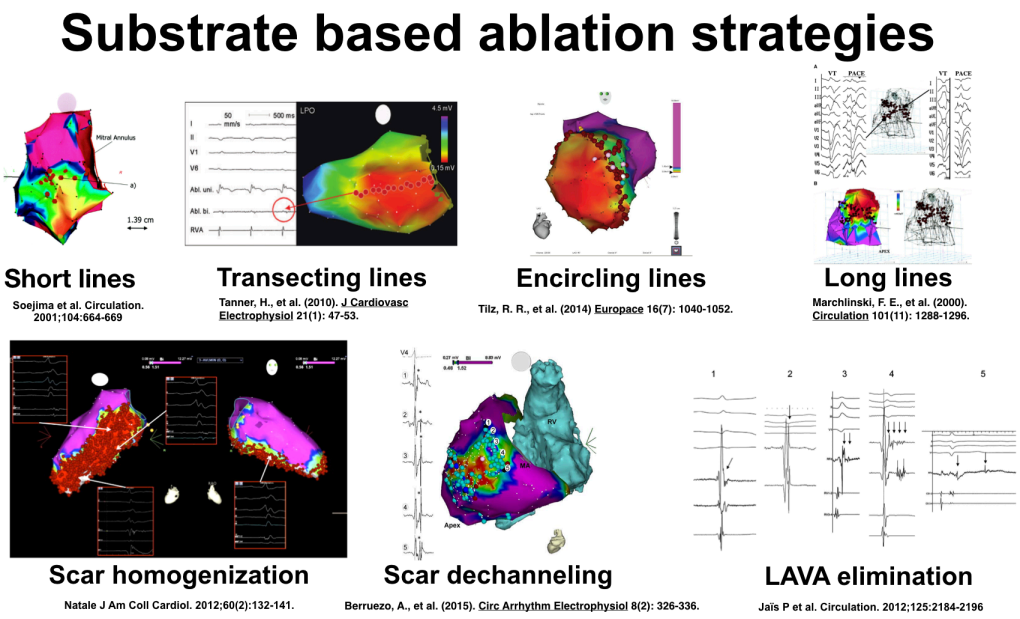

Figure 8. A summary of multiple substrate-based ablation strategies is depicted.

Head to head comparison with activation based mapping and ablation showed very minimal differences(93) and head to head comparison of substrate based

approaches has not been systematically performed but all of them show reasonable long term outcomes.

Although the success rates of those strategies were highly representative of an improvement in the technique, the lack of mechanistic and patophysiological insight into what was being ablated was one of the main concerns. Moreover, the definitions of what is an abnormal signal, or a LAVA or the core or dense scar area may vary from one rhythm to another and also from one catheter to another as the electrode spacing varies importantly thus affecting the characteristics of the signals being recorded. High density maps are more likely to encounter targets for ablation and this needs to be taken into account when analyzing data. Additionally, prolonged ablation procedures were linked to poor tolerance by the patients, many repeated induction protocols and shocks and there was evidence of poorer outcome if the procedure was prolonged (94). Hypothetically it could also happen that by targeting areas that play no role in the VT circuit (bystanders) new circuits could develop.

e.iv. The basis of functional mapping of the VT substrate:

The aim to move back to a more physiologically reproducible and mechanistic based VT ablation target was the seed for analyzing in depth the areas that led to unidirectional block and formed the isthmus of VT in patients that underwent endo-epicardial intraoperative mapping of VT. The description of the characteristics of the electrograms recorded at 4 time points (paced rhythm, extrastimulus rhythm and initiation of VT and during tachycardia) during the whole-heart in vivo mapping study and their spatio-temporal behaviour led to the definition of a decrement-evoked potential (95-97). The analysis of those VTs lead to the discovery of areas that displayed a delay in the time of activation between a stable rhythm and an extrastimuli. Those regions, called since then decrement-evoked potentials (DEEP) were closely correlated with the isthmus of the VT. Sensitivity and specificity for isthmus detection with DEEP mapping was better than with late

potentials that were not displaying decremental properties. We validated this analysis with mathematical modeling and elucidated the mechanism of decreased conduction velocity restitution as the mechanism underlying the participation of these potentials in the initiation and maintenance of VT(98).

The finding of DEEP potentials being better co-localized with the VT isthmus took us to plan, design, and execute a multicenter study that evaluated: 1. the feasibility of mapping DEEP potentials with the current electroanatomical mapping tools and 2. The possibility of those DEEPs being targeted as an ablation strategy.

The findings of that effort are reflected in the Part III of this thesis where the multicenter study of DEEP mapping is presented.

(Figure 9)

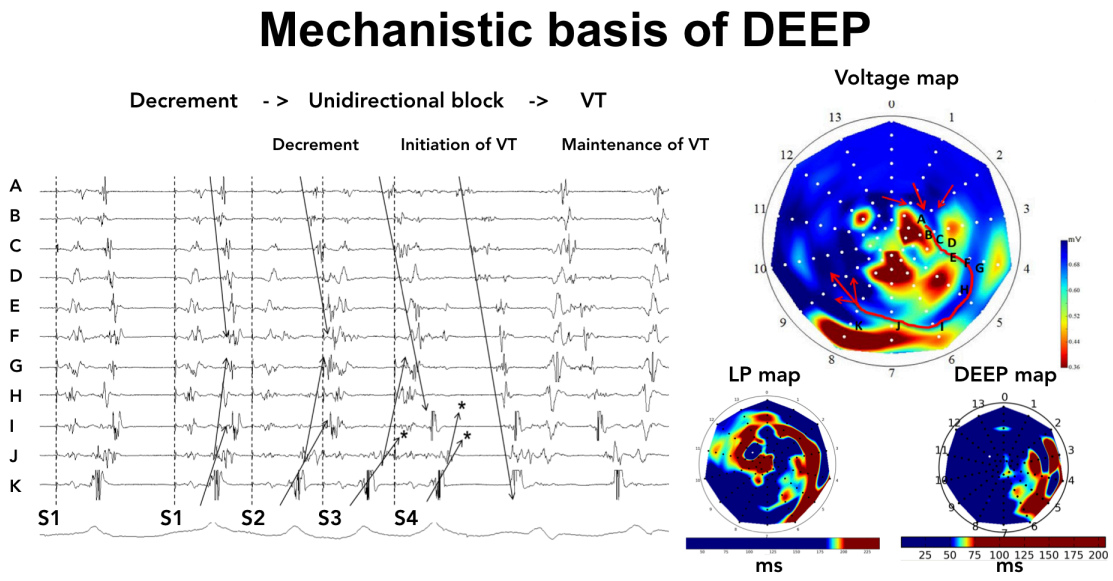

Figure 9. A set of recordings during the induction of ventricular tachycardia (VT) with S1 drive and S2/S3/S4 is displayed from an intra-operative mapping obtained with 112 bipolar electrodes. Late potentials are observed during S1 and bipoles from A to F show decremental properties that lead to unidirectional block and initiation of VT. Right panels highlight that the low voltage areas harbour the VT circuit but the area with late potentials is much wider than the area with decrement evoked potentials (DEEP). Adapted from Jackson N et al Circulation Arrhythmia and Electrophysiology 2015.

f. Part IV: Overcoming the directional dependency of bipolar electrograms with omnipolar methodology in a translational model of ventricular arrhythmia substrate.

The study of the health of the myocardial tissue is done by means of analyzing EGMs. Electrograms (EGM) are electrical signals obtained from solid electrodes in close proximity to the myocardial substrate. Cardiac electrograms are generated by the potential differences (voltage differences) created between two recording electrodes. All the EGMs are differential recordings between one source connected into the positive input of the recording amplifier and a second source that is connected to the negative input of it. If an exploring (roving) electrode is positioned in the heart and the second electrode is positioned very far from the heart (indifferent electrode) a unipolar signal is recorded. By convention, the exploring electrode is connected to the positive input of the amplifier and the morphology of the signal recorded depends on where the electrical wavefront is originating and whether it is being recorded at a site of origin of a rhythm (QS shape) or at a site where the electrical wavefront is passing through (RS pattern). The moment of the sharpest change in voltage as a function of time of the signal has been identified to be corresponding to the time when the action potential generated in the myocardium is passing beneath the recording electrode.

The major limitation of unipolar recordings is that they contain an important amount of far-field signal that is being generated by the activation (depolarization) of the tissue remotely from the exploring electrode. That is hardly an issue in areas of normal physiology of the electrical impulse but in areas with slowed conduction or where the tissue has been partially replaced by fibrosis a far field signal will obscure a small unipolar potential. That limitation led to the development of bipolar recordings. Bipolar EGMs are obtained by 2 electrodes that explore the area of interest and are connected to the signal amplifier. At each time point, the unipolar signal obtained by one of the electrodes is substracted from the inverted unipolar signal obtained by the other electrode. The fact that both electrodes

record a very similar amount of far-field signals allows for the elimination of them and that leaves the recording with only the local signal. In a homogeneously propagating tissue, the peak of the bipolar signal coincides in time with the depolarization beneath the recording electrodes(99).

(Figure 10)

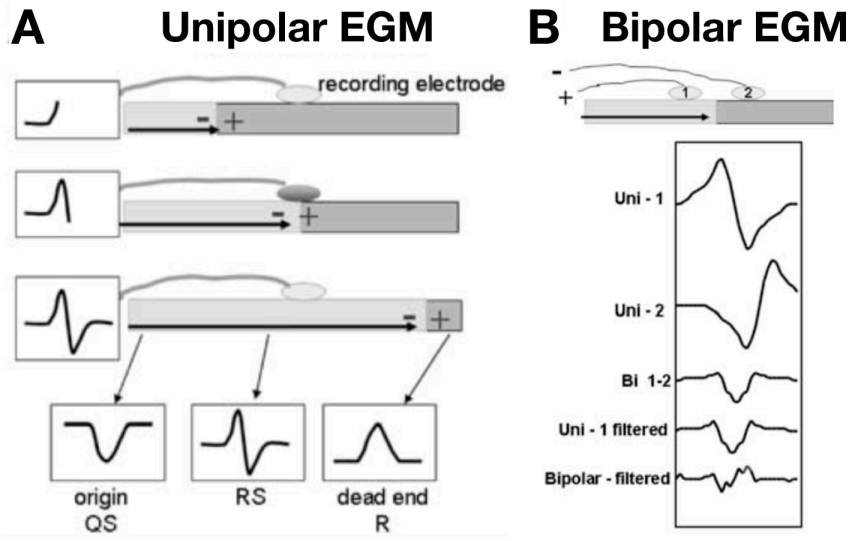

Figure 10. Panel A shows how a unipolar EGM is recorded with a single electrode. The shape of the unipolar EGM will be different depending on where in the wavefront the electrode is located. Panel B shows how a pair of electrodes record a bipolar EGM. Bipolar signals depict the local electrical activity with less far-field interference than the unipolar EGMs. Modified from Stevenson W, et al J Cardiovasc Electrophysiol 2005.

Bipolar EGM signals have been the standard for electrophysiological mapping. Unfortunately, the fact that the bipolar EGMs are obtained from 2 unipolar signals makes them extremely sensitive to the direction of the wavefront of electrical activation with respect to the orientation of the electrodes. For instance, if 2 electrodes are recording a signal that is propagating perpendicularly to the angle of the catheter position their bipolar signal will be null as the 2 unipolar signals will cancel each other. In contrast, when the electrical wavefront is propagating parallel

to the angle formed by the 2 recording electrodes the unipolar signals will have a remarkable time difference that will allow for a maximal bipolar recording. (100)
This is a very important issue as many decisions are taken based on the ability of the catheter to map the largest signal present in an area of interest. Moreover, the areas of interest –frequently targeted for ablation- are often located based on the criteria of the bipolar peak to peak voltage detection.
In vivo, it has been shown that defining the area of fibrosis based on the size of the electrogram recording has important limitations (101) and also it has been recognized that the interelectrode distance plays a very significant role on the size of the bipolar signal being recorded (102). Catheter design has evolved with time and currently many different interelectrode distances, small electrodes and multielectrode arrays have been designed to improve the efficiency of substrate mapping in daily practice. We have demonstrated *in silico* that the bipolar recordings are severely influenced by the configurations and sizes of the electrodes(103). In vivo there is compelling data about this issue that should always be taken into account when analyzing an EGM recording. That improvement has taken us into a new era of the high density of mapping with substantial benefits in terms of higher resolution of the substrate being mapped and potentially leading to better arrhythmia therapy. However, the challenge of the important directional influences in bipolar EGMs remains present and needs to be improved.
Those important limitations have triggered a novel interest in EGMs that could provide a more physiological and less ambiguous assessment of the myocardial activation. In that sense, the analysis of the wavefront of activation with a set of 3 or 4 electrodes by means of analyzing the 2D voltage loop created in the myocardial surface at the time of the depolarization of the cells leads to omnipolar EGMs (104, 105). Those omnipolar EGMs or OT-EGMs are void of directional influence, as the display of the signal could potentially be switched in 360 degrees to allow for mapping of the signal of interest (i.e. the signal across the wavefront of propagation or the signal along the wavefront of propagation or the miriad of signals in between). Several methodologies were used to validate the technology in

different settings including *in silico, ex vivo* and *in vivo* for simple patterns of wavefront propagation. One additional limitation of the bipolar EGMs is the reality that for chaothic rhythms such as atrial fibrillation the pattern of propagation changes from one beat to another. The determination of the direction of the wavefront of propagation in real time can allow for obtention of EGMs that are following a beat by beat consistent pattern. This can lead to more physiologically relevant voltage maps when the non-reliable areas are discarded as we have demonstrated in a canine model of atrial fibrillation(106).

(Figure 11)

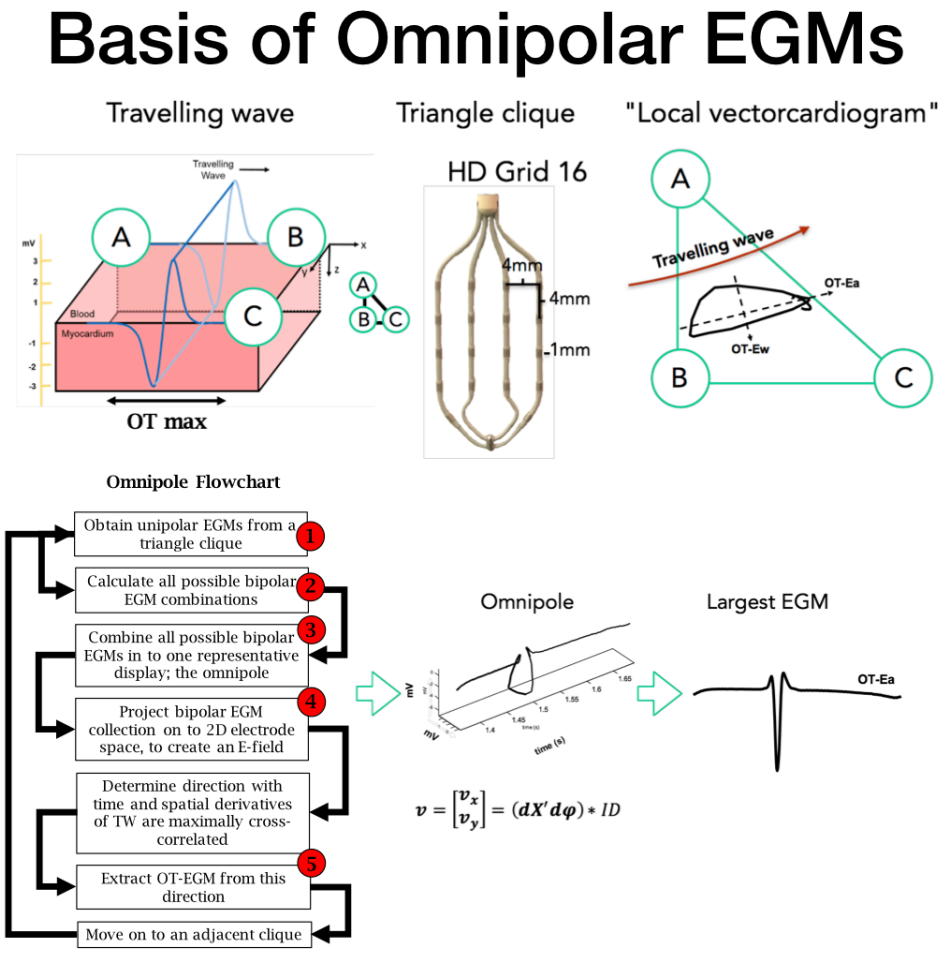

Figure 11. Omnipolar electrograms are obtained from a triangular set of electrodes that obtain the 3D voltage loop that a travelling wavefront generates when propagating through myocardial tissue. The largest EGM that is detected undeneath the mapping surface indicates the activation direction and can be then used to construct physiologically accurate maps without directional dependencies such as the ones faced by bipolar EGM. Adapted from Magtibay et al. JAHA 2017.

Ex vivo and *in silico* it has been proven that OT is able to determine in real time with independence of the surrounding local activation times the activation direction and conduction velocity (CV). This is due to the fact that for a travelling wave CV is the ratio of the time derivative to the spatial derivative in the direction of activation. This is a result independent from the waveform(105). This information

is of critical importance as high resolution activation time-based determinations of CV are showing that there is an important portion of the substrate of the VT sites that is confined to the areas of myocardium with steep gradients of slowing of conduction(107). This may play an important role also in other arrhythmic substrates such as the atrium where areas of slowing of CV may be central to anchoring drivers of atrial fibrillation(108).

Preclinical work has led to the implementation of the real time representation of OT-EGMs thus allowing for mapping in a research setup. The application of OT-EGMs in vivo would be of great interest to allow for a realistic and physiological and direction agnostic way of mapping. In Part IV of our work we applied the OT-EGM to a ventricular tachycardia substrate preclinical swine model. (Figure 12)

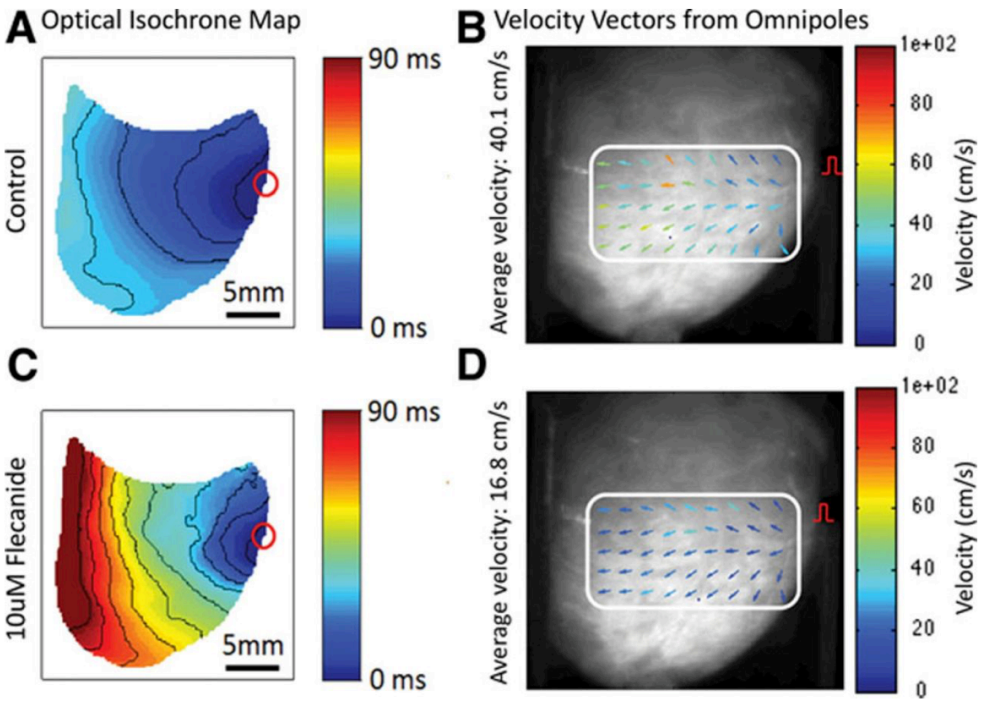

Figure 12. Omnipolar EGMs are able to depict in real time conduction velocity measures that are not dependent on local activation time measurements. Panel A shows the isochronal map of a rabbit heart at baseline with uniform propagation velocity seen in Panel B. Panel C illustrates how a Na+ channel blocker increases the activation times and how this is readily detected by decreased conduction velocity measured in real time by omnipolar mapping. Adapted from Massé S et al. Circulation Arrhythmia Electrophysiology 2016. (Figure 12)

Hypotheses and Objectives:

Part I: The impact of ICD therapies in a large population-based registry that includes secondary prevention patients.

- Hypotheses
  - Primary:
    - The presence of appropriate ICD therapies in patients with structural heart disease is an independent marker for increased mortality.
  - Secondary:
    - The risk of mortality associated with appropriate ICD therapies differs based on the indication for device implantation (primary prevention or secondary prevention).
- Objectives:
  - To describe the impact of ICD therapies on the mortality risk of patients treated with primary and secondary prevention indications.
  - To analyze the differential impact of ICD shocks vs ATP therapies on mortality.

Part II: Comparison of the clinical outcomes and healthcare costs of catheter ablation versus medical therapy for recurrent VT.

- Hypotheses:
    - Primary:
        - Patients with structural heart disease, poor LVEF and implanted ICD treated with catheter ablation for VT have less hospital admissions and emergency room visits compared to medically treated patients with the same baseline clinical characteristics.
    - Secondary:
        - Patients with structural heart disease, poor LVEF and implanted ICD treated with catheter ablation for recurrent VT have decreased healthcare-related costs compared to medically treated patients with the same baseline clinical characteristics.
        - Patients with structural heart disease, poor LVEF and implanted ICD treated with catheter ablation for recurrent VT have an improved survival compared to medically treated patients with the same baseline clinical characteristics.

- Objectives:
    - To evaluate in a cohort of patients treated with VT ablation due to recurrent ICD interventions:
        - The healthcare admissions of cardiovascular cause compared to a propensity-matched medically-treated cohort with the same clinical risk factors for mortality at baseline.
        - The costs of a strategy based on catheter ablation compared to medical treatment in a propensity-matched cohort with the same clinical risk factors for mortality at baseline.

- To evaluate the mortality rates in the cohort treated with catheter ablation as compared to the medically treated patients.

Part III: Introduction and validation of DEEP mapping as a novel strategy for a mechanistic VT ablation strategy.

- Hypotheses:
  - Primary:
    - A mechanistic based strategy that identifies areas of decremental conduction in patients suffering from recurrent VT is feasible with current electroanatomical mapping tools and identifies more accurately the critical regions of the VT circuit than identification of non-decremental late potentials.
  - Secondary:
    - A mechanistic based strategy targeting fundamentally areas that display decremental conduction properties in the myocardium has acute and chronic success rates that are similar to conventional substrate based strategies.
- Objectives:
  - To test the feasibility of detecting areas of decremental conduction and assess its accuracy in identifying the VT circuit in patients with structural heart disease experiencing recurrent VT and in need of a catheter based VT ablation.
  - To assess the acute and mid-term outcomes of an ablation strategy focused in the areas displaying decremental conduction properties.

Part IV: Overcoming the directional dependency of bipolar electrograms with omnipolar methodology in a translational model of ventricular arrhythmia substrate.

- Hypotheses:
  - Primary:
    - Real time mapping *in vivo* of a swine model of VT substrate with omnipolar electrograms provides substrate maps that detect larger voltages compared to bipolar electrograms.
  - Secondary:
    - Real time mapping *in vivo* of a swine model of VT substrate with omnipolar electrograms provides voltage maps that are more accurate that conventional bipolar maps with less beat to beat variability.
- Objectives:
  - To define the substrate of VT in a swine model with novel omnipolar electrograms.
  - To compare the results of assessing the myocardial substrate with omnipolar EGMs versus conventional bipolar EGMs.
  - To analyse the accuracy for the detection of myocardial scar with Omnipolar EGMs compared to late gadolinium enhancement areas on magnetic resonance imaging.

Main Publications:

a. Part I: The impact of ICD therapies in a large population-based registry that includes secondary prevention patients.

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Mortality Implications of Appropriate Implantable Cardioverter Defibrillator Therapy in Secondary Prevention Patients: Contrasting Mortality in Primary Prevention Patients From a Prospective Population-Based Registry

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***Background*—**We sought to examine the mortality impact of appropriate implantable cardioverter defibrillator (ICD) therapy between patients who received ICD for primary versus secondary prevention purposes.

***Methods and Results*—**From a prospective, population-based registry, we identified 7020 patients who underwent de novo ICD implantation between February 2007 and May 2012 in Ontario, Canada. The primary outcome was all-cause mortality. We used multivariable Cox proportional hazard modeling to adjust for differences in baseline characteristics and analyzed the mortality impact of first appropriate ICD therapy (shock and antitachycardia pacing [ATP]) as a time-varying covariate. There were 1929 (27.5%) patients who received ICDs for secondary prevention purposes. The median follow-up period was 5.02 years. Compared with those with secondary prevention ICDs, patients with primary prevention ICDs had more medical comorbidities, and lower ejection fraction. Patients who experienced appropriate ICD shock or ATP had greater risk of death compared with those who did not, irrespective of implant indication. In the primary prevention group, the adjusted hazard ratios of death for appropriate shock and ATP were 2.00 (95% CI: 1.72–2.33) and 1.73 (95% CI: 1.52–1.97), respectively. In the secondary prevention group, the adjusted hazard ratios of death for appropriate ICD shock and ATP were 1.46 (95% CI: 1.20–1.77) and 1.38 (95% CI: 1.16–1.64), respectively.

***Conclusions*—**Despite having a more favorable clinical profile, occurrence of appropriate ICD shock or ATP in patients with secondary prevention ICDs was associated with similar magnitudes of mortality risk as those with primary prevention ICDs. A heightened degree of care is warranted for all patients who experience appropriate ICD shock or ATP therapy. **(*J Am Heart Assoc.* 2017;6:e006220. DOI: 10.1161/JAHA.117.006220.)**

Key Words: cardiac arrhythmia • death • implantable cardioverter-defibrillator • sudden • ventricular arrhythmia • ventricular fibrillation

Implantable cardioverter defibrillators (ICD) are the mainstay for preventing sudden cardiac death in patients with structural heart disease and impaired left ventricular ejection fraction, as demonstrated in multiple randomized trials that employed ICD as either a primary or secondary prevention strategy.[1–3] On the other hand, occurrence of an appropriate ICD shock is associated with a subsequent 3- to 5-fold increased risk of death among patients with primary prevention ICDs.[4–7] Whether this association can be extended to patients with secondary prevention ICD is not well defined.

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Received March 27, 2017; accepted June 15, 2017.

Clinical Perspective

What Is New?

- The mortality implications of appropriate implantable cardioverter defibrillator (ICD) therapy between primary and secondary prevention patients is provided from a prospective registry of ≈7020 de novo ICD patients not in a clinical trial setting.
- Secondary prevention ICD patients have a lower clinical profile of risk with better left ventricular ejection fraction and fewer medical comorbidities, but have greater burden of ventricular arrhythmia and exhibit similar long-term mortality as their primary prevention counterparts following therapy.
- Appropriate ICD shocks for ventricular arrhythmia are associated with an adjusted ≈2-fold increase of death in primary prevention patients and a 46% increase in secondary prevention patients.
- Appropriate ICD antitachycardia pacing therapy for ventricular arrhythmia is associated with an adjusted 1.73-fold increase of death in primary prevention patients and a 38% increase of death in secondary prevention patients.

What Are the Clinical Implications?

- Ventricular arrhythmia treated by the ICD by means of shock or antitachycardia pacing is a marker of increased risk of death, irrespective of implant indication of primary or secondary prophylaxis.
- Strategies to prevent the occurrence of ventricular arrhythmia are warranted.

Since the frequency of appropriate ICD shock is 2 to 3 times greater among patients with secondary prevention ICD,[8] delineation of the association between appropriate ICD therapy and its subsequent impact on survival will have important implications for clinicians when communicating the expected outcomes of ICD therapy with these patients. Elucidating the mortality impact of ICD therapy in this population may enhance decision-making when allocating healthcare resources for this presumably high-risk patient subset, given their propensity for experiencing ventricular arrhythmias post-ICD implant.

To address this question, we analyzed data from a prospective, population-based registry of consecutive de novo ICD patients in Ontario, Canada in which healthcare costs are provided by a single payer. Clinical outcomes are ascertained by linkage with administrative databases. As this registry also collected data on all first appropriate ICD therapies (shock or antitachycardia pacing [ATP]), we were able to examine the association between ICD therapy (shock or ATP) and its impact on patients' subsequent survival in relation to their implant indication.

Methods

Study Population

The Ontario ICD registry was a population-based, prospective, multicenter registry that included all patients who underwent de novo ICD implant in the province between February 2007 and May 2012. Design, implementation, and maintenance of the Ontario ICD database have been previously published elsewhere.[9] All patients referred for evaluation of ICD implantation were enrolled into the registry. The Ontario Ministry of Health and Long-Term Care mandated this registry. This study was approved by the Institutional Review Board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada) and complies with the Declaration of Helsinki.

All patients ≥18 years old and residents of Ontario were enrolled if they underwent de novo ICD implantation between February 2007 and May 2012, and informed consent was waived because it was a mandatory registry. The database accrued patients at the time of arrhythmia clinic assessment. For the purposes of this study, the date of implantation served as the index date ("time zero") for the analysis. Patients were followed until death or until the end of the prespecified follow-up period on March 31, 2015. Patients were excluded from this analysis if 1 of the following conditions was met: <18 years old; non-Ontario residency or death before implant (n=19); received a secondary prevention ICD for an inherited arrhythmia syndrome, hypertrophic cardiomyopathy, or complex congenital heart disease (n=243); or if they had missing covariates for the multivariate analysis (n=587).

Data Sources

ICD data source

Trained personnel collected ICD data from all implantation centers in the province. Data included baseline clinical characteristics, ICD implant indications, and subsequent ICD therapies. Details on first appropriate ICD shocks and ATP were collected from patients' ICD follow-up visits, and they were adjudicated by electrophysiologists with high interobserver agreement.[8] Primary prevention patients were defined as those who received ICD on a prophylactic basis without a prior history of sudden cardiac death, cardiac arrest, or sustained ventricular arrhythmia. Secondary prevention patients were defined as those who experienced resuscitated sudden cardiac death, cardiac arrest, or sustained ventricular arrhythmia before ICD implantation. Standardized programming was not mandated in this study given its observational design. Further details pertaining to data collection and quality assurance have been described elsewhere.[9]

Outcome data source

The primary outcome was all-cause mortality, which was collected using each patient's unique, encoded health card number where ICD data were linked to Ontario provincial administrative databases for vital statistics, namely, the Registered Persons Database for death events. Vital statistics information was ascertained in all study patients until the end of study follow-up. Database linkage using unique encoded identifiers was performed at the Institute for Clinical Evaluative Sciences in Ontario, Canada.

Statistical Analysis

We reported serum creatinine with median (interquartile range), and the Kruskal–Wallis test was used to compare the values. The other continuous variables were reported using mean±SD and comparisons were performed using ANOVA test. Categorical variables were reported as proportions and were compared using the χ^2 statistic. There were 2 main exposures of interest in this study. First, we were interested in comparing outcomes between patients who received primary versus secondary prevention ICD. Second, we compared outcomes between patients who experienced ICD shock or ATP versus those who did not during study follow-up. The primary analysis was a comparison of the rates of death between patients who experienced appropriate ICD therapy (shock or ATP) versus those who did not. Furthermore, we examined whether the rates of death differed between primary versus secondary prevention ICD patients who experienced appropriate shock or ATP. In order to conduct these analyses, we performed multivariable Cox proportional hazard modeling in which the occurrence of appropriate ICD therapy (shock or ATP) was analyzed as a time-varying covariate. The date of the ICD implantation was assigned as the date of start of follow-up and the end of the follow-up was death or March 31, 2015, whichever happened first. When the cumulative incidence function curves were plotted, death was considered as a competing event, and the end of the follow-up was death date or appropriate shock/ATP date or March 31, 2015, whichever happened first.

The evaluation of appropriate ATP was performed separately from the analysis of ICD shock. According to the design of the Ontario ICD Database, only the first appropriate ATP was recorded, and ATPs were not recorded if there was a preceding appropriate ICD shock. We included the following covariates in the model: implant indication (primary versus secondary), left ventricular ejection fraction, and the individual components of a validated mortality prediction score for ICD patients that we previously published (age, ischemic heart disease, previous revascularization procedure, previous heart failure hospitalization, New York Heart Association status III–IV, pre-existing permanent pacemaker system, systolic blood pressure, diabetes mellitus, smoker, chronic obstructive lung disease, home oxygen therapy, cancer, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment, creatinine, serum sodium, and hemoglobin).[10] To examine whether the risk of death differed between primary and secondary prevention ICD patients, we added an interaction term between the occurrence of appropriate ICD therapy (shock or ATP) and implant indication. Statistical measures of significance were reported with hazard ratios (HR) with exact 95% CI. For all analyses, a 2-sided $P<0.05$ was considered to be statistically significant. All analyses were performed with SAS 9.4 (Cary, NC, USA).

Results

Baseline Clinical Characteristics

Our study cohort consisted of 7020 patients and there were 5091 (72.5%) and 1929 (27.5%) patients who received primary and secondary prevention ICD, respectively (Table 1). Compared with those with secondary prevention ICDs, patients in the primary prevention group had lower left ventricular ejection fraction, higher New York Heart Association class, were more likely to have heart failure or diabetes mellitus, and more likely to receive cardiac resynchronization therapy. The use of heart failure medications was more frequent in the primary prevention group compared with the secondary prevention. On the other hand, amiodarone use at baseline was 4 times more common in the secondary group than the primary group. The median follow-up period of the entire cohort was 5.02 years (interquartile range: 3.8–6.3 years).

Appropriate ICD Therapy

In the primary prevention group, 395 (8.4%) patients experienced appropriate ICD shock and 617 (12.1%) patients had appropriate ATP during follow-up. In the secondary prevention group, 310 patients experienced appropriate ICD shock (16.1%) and 445 patients (23.1%) received ATP. The cumulative incidence of shock at 1, 2, 3, and 4 years of follow-up was (primary prevention versus secondary prevention): 4.5% versus 11.3%; 6.3% versus 14.3%; 7.4% versus 15.7%; and 7.7% versus 16.0% ($P<0.001$ for all comparisons). The cumulative incidence of ATP at 1, 2, 3, and 4 years of follow-up was (primary prevention versus secondary prevention): 7.5% versus 17.2%; 10.4% versus 20.9%; 11.7% versus 22.5%; and 12.1% versus 22.9% ($P<0.001$ for all comparisons).

The rate of first occurrence of appropriate ICD shock was 1.7 per 100 person-years in the primary prevention group and

Table 1. Baseline Patient Characteristics by ICD Indication

	Primary Prevention N=5091	Secondary Prevention N=1929	*P* Value
Demographics			
Male, n (%)	4037 (79.3)	1560 (80.9)	0.143
Age at ICD implant date, n (%)	64.51±11.93	65.47±12.58	0.003
Cardiomyopathy details			
Ischemic, n (%)	4738 (93.1)	1712 (88.8)	<0.001
Ischemic+previous revascularization, n (%)	3320 (65.2)	1377 (71.4)	. . .
Previous heart failure, n (%)	1886 (37.0)	439 (22.8)	<0.001
Device details			
Cardiac resynchronization-defibrillator, n (%)	1678 (33.0)	178 (9.2)	<0.001
Dual-chamber ICD, n (%)	1311 (25.8)	831 (43.1)	. . .
Single-chamber ICD, n (%)	2100 (41.2)	918 (47.6)	. . .
Medical comorbidities			
Atrial fibrillation, n (%)	1506 (29.6)	609 (31.6)	0.105
Diabetes mellitus, n (%)	1571 (30.9)	472 (24.5)	<0.001
Current cigarette smoking, n (%)	751 (14.8)	325 (16.8)	0.03
Hypertension, n (%)	2900 (57.0)	1209 (62.7)	<0.001
Stroke or transient ischemic attack, n (%)	184 (3.6)	87 (4.5)	0.082
Peripheral vascular disease, n (%)	514 (10.1)	219 (11.4)	0.124
COPD, n (%)	636 (12.5)	219 (11.4)	0.192
Clinical variables			
Reported NYHA class			
III or IV	1778 (34.9%)	283 (14.7%)	. . .
Systolic blood pressure, mean±SD	121.46±19.91	124.62±20.08	<0.001
Mean QRS duration, mean±SD	132.93±35.62	122.47±33.18	<0.001
Testing			
Serum creatinine, median (IQR)	96.00 (80.00–120.00)	95.00 (80.00–117.00)	0.092
Hb <110 g/L, n (%)	385 (7.6)	422 (21.9)	<0.001
LVEF			
LVEF ≤20, n (%)	1033 (20.3)	201 (10.4)	<0.001
LVEF: 21 to 30, n (%)	2695 (52.9)	471 (24.4)	<0.001
LVEF: >30, n (%)	1208 (23.7)	1079 (55.9)	<0.001
Medications			
β-Adrenoreceptor antagonist, n (%)	4388 (86.2)	1616 (83.8)	0.01
ACEI, n (%)	3614 (71.0)	1273 (66.0)	<0.001
ARB, n (%)	904 (17.8)	253 (13.1)	<0.001
Spironolactone, n (%)	1556 (30.6)	287 (14.9)	<0.001
Loop diuretics, n (%)	3144 (61.8)	753 (39.0)	<0.001
Digoxin, n (%)	1202 (23.6)	238 (12.3)	<0.001
Amiodarone, n (%)	499 (9.8)	696 (36.1)	<0.001
Statin, n (%)	3632 (71.3)	1386 (71.9)	0.673
Aspirin, n (%)	3012 (59.2)	1376 (71.3)	<0.001
Clopidogrel, n (%)	915 (18.0)	586 (30.4)	<0.001

Baseline characteristics of subjects. Patients with ICDs for primary prevention had lower LVEF, had more previous history of heart failure, higher prevalence of ICM and diabetes mellitus, and were more likely to have a cardiac resynchronization therapy defibrillator than the secondary prevention group and more frequently on heart failure medications. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association.

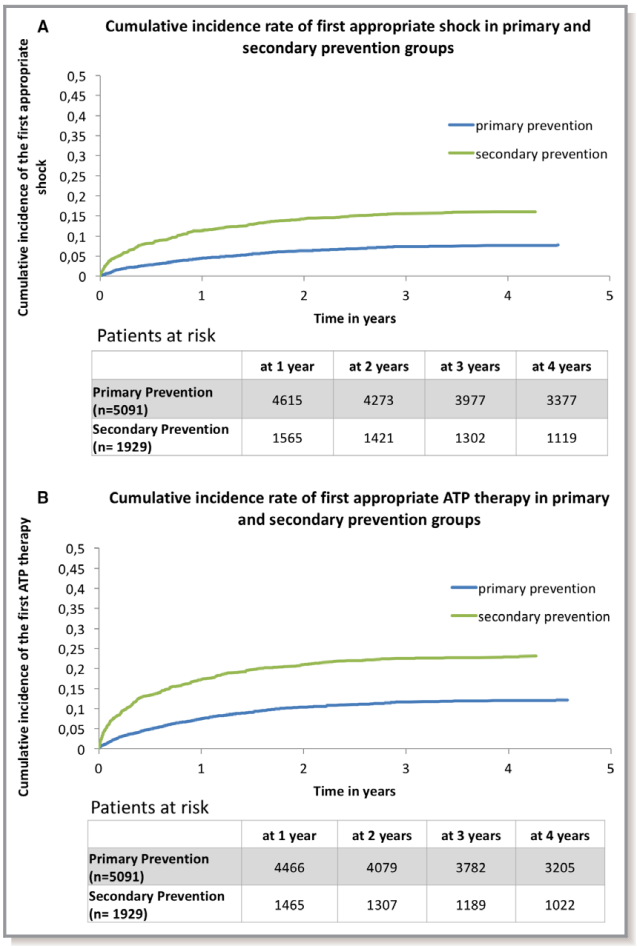


Figure 1. A, Cumulative incidence rate of first appropriate shock in primary and secondary prevention groups. B, Cumulative incidence rate of first ATP in primary and secondary prevention groups. ATP indicates anti-tachycardia pacing.

4.0 per 100 person-years in the secondary prevention group (P<0.001) (Figure 1). On univariable analysis, patients in the primary prevention group who received an ICD shock were more likely male, had history of atrial fibrillation, had lower left ventricular ejection fraction, and were more frequently treated with loop diuretics and digoxin compared with those who did not receive an ICD shock (Table 2). On univariable analysis, patients in the secondary prevention group who experienced appropriate ICD shock were more likely to be male, had a history of peripheral vascular disease, chronic obstructive pulmonary disease, and had higher baseline hemoglobin levels (Table 3). In this group, the rate of amiodarone use at baseline was similar between patients with or without appropriate ICD shock.

Mortality Rates

In the overall cohort, 2360 (33.6%) patients died. There were 1697 (33.3%) patients who died in the primary prevention group and 663 (34.4%) patients died in the secondary prevention group. The unadjusted incidence rate of death was 6.87 per 100-person years in the primary prevention group and 7.31 per 100-person years in the secondary prevention group (P=0.178) (Figure 2).

Table 2. Clinical Characteristics of Primary Prevention ICD Patients With and Without Appropriate Shock

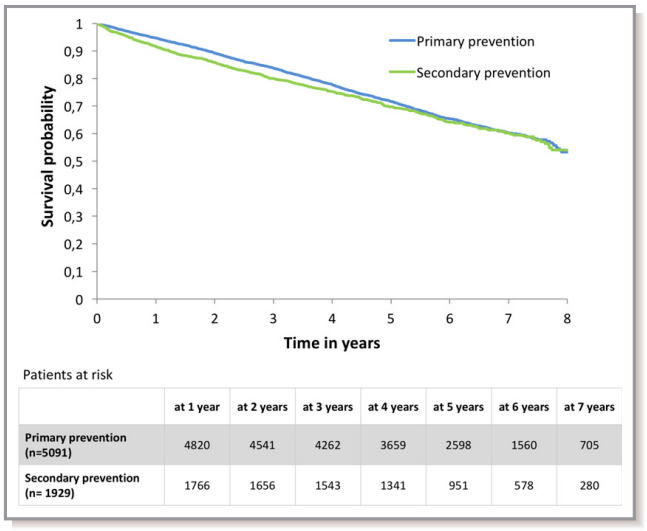
	No Appropriate Shock N=4696	Appropriate Shock N=395	*P* Value
Demographics			
Male, n (%)	3691 (78.6)	346 (87.6)	<0.001
Age, y, mean±SD	64.59±11.93	63.61±12.01	0.118
Cardiomyopathy details			
Ischemic, n (%)	4360 (92.8)	378 (95.7)	. . .
Ischemic+previous revascularization, n (%)	3066 (65.3)	254 (64.3)	0.044
Previous heart failure, n (%)	1726 (36.8)	160 (40.5)	0.138
Device details			
Cardiac resynchronizator-defibrillator, n (%)	1553 (33.1)	125 (31.6)	0.876
Dual-chamber ICD, n (%)	1204 (25.6)	107 (27.1)	. . .
Single-chamber ICD, n (%)	1937 (41.2)	163 (41.3)	. . .
Medical comorbidities			
Atrial fibrillation, n (%)	1355 (28.9)	151 (38.2)	<0.001
Diabetes mellitus, n (%)	1459 (31.1)	112 (28.4)	0.262
Current cigarette smoking, n (%)	683 (14.5)	68 (17.2)	0.151
Hypertension	2690 (57.3%)	210 (53.2%)	0.112
Stroke or transient ischemic attack, n (%)	169 (3.6)	15 (3.8)	0.839
Peripheral vascular disease, n (%)	479 (10.2)	35 (8.9)	0.396
Any cancer, n (%)	397 (8.5)	35 (8.8)	0.792
COPD, n (%)	590 (12.6)	46 (11.6)	0.596
Clinical variables			
Reported NYHA class			
III or IV, n (%)	1638 (34.9)	140 (35.4)	
Systolic blood pressure, mean±SD	121.62±19.90	119.64±19.98	0.058
QRS duration in ms, mean±SD	132.77±35.44	134.86±37.72	0.265
Testing			
Serum creatinine, median (IQR)	96.00 (80.00–120.00)	100.00 (84.00–122.00)	0.017
Hb <110 g/L, n (%)	353 (7.5)	32 (8.1)	0.177
LVEF			
LVEF ≤20, n (%)	935 (19.9)	98 (24.8)	0.02
LVEF: 21 to 30, n (%)	2484 (52.9)	211 (53.4)	0.842
LVEF: >30, n (%)	1133 (24.1)	75 (19.0)	0.021
Medications			
β-Adrenoreceptor antagonist, n (%)	4046 (86.2)	342 (86.6)	0.815
ACEI, n (%)	3318 (70.7)	296 (74.9)	0.072
ARB, n (%)	842 (17.9)	62 (15.7)	0.264
Spironolactone, n (%)	1420 (30.2)	136 (34.4)	0.082
Loop diuretics, n (%)	2875 (61.2)	269 (68.1)	0.007
Digoxin, n (%)	1075 (22.9)	127 (32.2)	<0.001
Amiodarone, n (%)	458 (9.8)	41 (10.4)	0.687
Statin, n (%)	3359 (71.5)	273 (69.1)	0.308
Aspirin, n (%)	2798 (59.6)	214 (54.2)	0.036
Clopidogrel, n (%)	852 (18.1)	63 (15.9)	0.275

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 3. Clinical Characteristics of Patients With Secondary Prevention Indication by Presence or Absence of Shock

	No Appropriate Shock N=1619	Appropriate Shock N=310	*P* Value
Demographics			
Male, n (%)	1291 (79.7)	269 (86.8)	0.004
Age, mean±SD	65.40±12.69	65.82±12.00	0.589
Cardiomyopathy details			
Ischemic, n (%)	1437 (88.8)	275 (88.7)	. . .
Ischemic+previous revascularization, n (%)	1163 (71.8)	214 (69.0)	0.491
Previous heart failure, n (%)	366 (22.6)	73 (23.5)	0.717
Device details			
Cardiac resynchronizator-defibrillator, n (%)	146 (9.0)	32 (10.3)	0.82
Dual-chamber ICD, n (%)	700 (43.2)	131 (42.3)	. . .
Single-chamber ICD, n (%)	771 (47.6)	147 (47.4)	. . .
Medical comorbidities			
Atrial fibrillation, n (%)	510 (31.5)	99 (31.9)	0.88
Diabetes mellitus, n (%)	419 (25.9)	53 (17.1)	<0.001
Current cigarette smoking, n (%)	271 (16.7)	54 (17.4)	0.769
Hypertension, n (%)	1018 (62.9)	191 (61.6)	0.673
Stroke or transient ischemic attack, n (%)	71 (4.4)	16 (5.2)	0.546
Peripheral vascular disease, n (%)	172 (10.6)	47 (15.2)	0.021
Any cancer, n (%)	133 (7.4)	33 (9.4)	0.195
COPD, n (%)	173 (10.7)	46 (14.8)	0.035
Clinical variables			
Reported NYHA class			
III or IV, n (%)	237 (14.6)	46 (14.8)	. . .
Systolic blood pressure, mean±SD	124.60±19.98	124.70±20.66	0.94
QRS duration in ms, mean±SD	121.91±33.63	125.37±30.59	0.095
Testing			
Serum creatinine level, median (IQR)	95.00 (79.00–117.00)	95.00 (81.00–117.00)	0.763
Hb <110 g/L, n (%)	360 (22.2)	62 (20.0)	0.004
LVEF			
LVEF ≤20, n (%)	162 (10.0)	39 (12.6)	0.174
LVEF: 21 to 30, n (%)	400 (24.7)	71 (22.9)	0.498
LVEF: >30, n (%)	913 (56.4)	166 (53.5)	0.355
Medications			
β-Adrenoreceptor antagonist, n (%)	1353 (83.6)	263 (84.8)	0.579
ACEI, n (%)	1059 (65.4)	214 (69.0)	0.218
ARB, n (%)	218 (13.5)	35 (11.3)	0.299
Spironolactone, n (%)	245 (15.1)	42 (13.5)	0.473
Loop diuretics, n (%)	631 (39.0)	122 (39.4)	0.9
Digoxin, n (%)	198 (12.2)	40 (12.9)	0.741
Amiodarone, n (%)	574 (35.5)	122 (39.4)	0.19
Statin, n (%)	1163 (71.8)	223 (71.9)	0.971
Aspirin, n (%)	1160 (71.6)	216 (69.7)	0.482
Clopidogrel, n (%)	494 (30.5)	92 (29.7)	0.77

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.



Patients at risk

	at 1 year	at 2 years	at 3 years	at 4 years	at 5 years	at 6 years	at 7 years
Primary prevention (n=5091)	4820	4541	4262	3659	2598	1560	705
Secondary prevention (n= 1929)	1766	1656	1543	1341	951	578	280

Figure 2. Kaplan–Meier survival curve showing occurrence of all-cause mortality in primary vs secondary prevention groups.

Impact of Appropriate ICD Shock on Mortality

In the overall cohort, the crude mortality rate was higher among patients who received appropriate ICD shock when compared with those who did not (9.33 versus 6.72 deaths per 100-person years, $P<0.001$). The crude mortality rate was higher among primary prevention ICD patients who experienced appropriate shock when compared with secondary prevention ICD patients who had appropriate ICD shock (13.02 versus 9.94 deaths per 100 person-years, $P=0.0187$). The median post-ICD shock follow-up periods for the primary and secondary prevention groups were 4.16 and 4.48 years, respectively.

Impact of ATP Therapy on Mortality

Patients who experienced appropriate ATP had higher crude mortality rates when compared with those who did not (8.56 versus 6.69 deaths per 100-person years, $P<0.001$). Survival rates were similar between primary and secondary prevention patients who experienced appropriate ICD shocks (10.58 versus 9.95 deaths per 100 person-years, $P=0.52$).

Risk of Death After Appropriate ICD Shock or ATP

After an appropriate ICD shock, the unadjusted HR of death was 1.96 (95% CI 1.68–2.27, $P<0.001$) in the primary prevention group and 1.42 (95% CI 1.17–1.72, $P<0.001$) in the secondary prevention group. After appropriate ATP, the unadjusted HR of death was 1.60 (95% CI 1.40–1.82, $P<0.001$) in the primary prevention group and 1.48 (95% CI 1.25–1.75, $P<0.001$) in the secondary prevention group.

After adjustment of baseline differences with multivariable regression, patients who had an appropriate ICD shock had a 74% increase in their risk of death relative to those who did not have an ICD shock (HR 1.74, 95% CI 1.54–1.96, $P<0.001$) in the overall cohort. In the primary prevention group, patients who experienced appropriate ICD shock had a 2-fold increase in their risk of death when compared with those who did not have appropriate ICD shock (adjusted HR 2.00, 95% CI 1.72–2.33, $P<0.001$) (Figure 3A). Patients who experienced appropriate ICD shock in the secondary prevention group had a 46% increase in their risk of death when compared with those who did not have ICD shock (adjusted HR 1.46, 95% CI 1.20–1.77, $P<0.001$) (Figure 3A). We did not observe a statistically significant interaction between implant indication (primary versus secondary) and occurrence of appropriate ICD shock on mortality ($P=0.13$). This suggested that the impact on mortality of an appropriate ICD shock did not differ based on the implant indication.

In the primary prevention group, patients who experienced appropriate ATP had a 73% increased risk of death when compared with those who did not have ATP (adjusted HR 1.73, 95% CI 1.52–1.97, $P<0.001$) (Figure 3B). In the secondary prevention group, patients who experienced appropriate ATP had a 38% increase in their risk of death

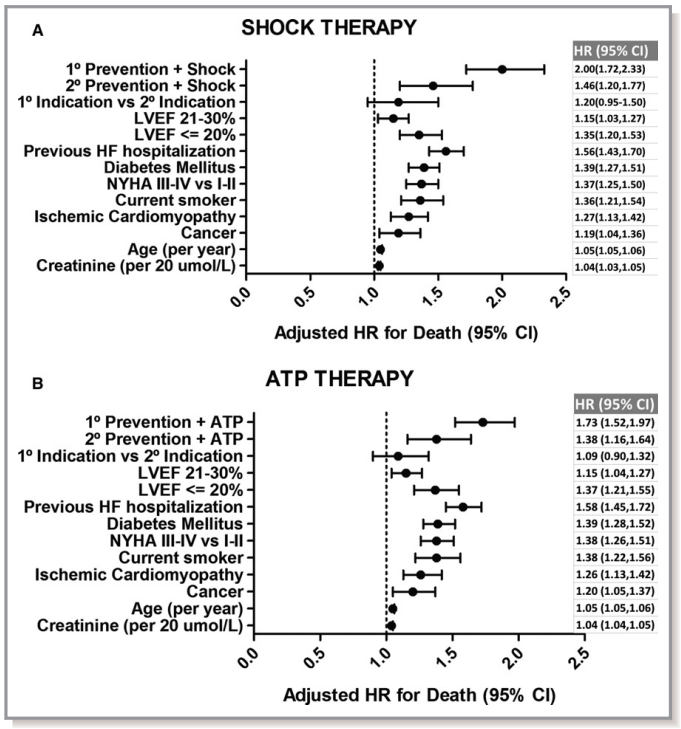


Figure 3. Forest plot with adjusted hazard ratios of death of variables included in the Cox model. A, HR of risk of death in patients with shock therapy vs no shock therapy. B, HR of risk of death in patients with antitachycardia therapy (ATP) therapy vs no ATP therapy. HF indicates heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

when compared with those who did not have ATP (adjusted HR 1.38, 95% CI 1.16–1.64, $P<0.001$) (Figure 3B). We did not observe a statistically significant interaction between implant indication (primary versus secondary) and occurrence of appropriate ATP on mortality ($P=0.4$).

Discussion

There are 3 main findings from this prospective, population-based registry of ≈7020 patients who underwent de novo ICD implantation in Ontario, Canada with long-term follow-up. First, we observed that the incidence of first appropriate shock or ATP was twice as common in patients with secondary prevention ICD relative to those with primary prevention ICD. Second, occurrence of either an appropriate ICD shock or ATP was associated with a substantial increase in patients' subsequent risk of dying irrespective of implant indication. Third, despite having twice as much appropriate ICD therapies, patients in the secondary prevention group had similar survival rates as those with primary prevention ICDs.

Incidence of Appropriate ICD Therapy

The incidence of shocks was higher in the secondary prevention population compared with primary prevention patients, and this is in keeping with the findings of previous smaller registries.[11,12] It is indeed not surprising that patients who receive an ICD after symptomatic ventricular arrhythmia are at higher risk of experiencing an appropriate shock from their devices than those who receive it prophylactically. Our data suggest that treatment measures to avoid ICD therapies in the secondary prevention group are of paramount importance since both ATP and shocks carry a significant mortality risk in a population otherwise thought to exhibit a lower risk profile.

Mortality Analysis

The fact that the adjusted mortality of primary and secondary prevention patients after receiving a shock or ATP is similar could be interpreted as somewhat unexpected. One would expect that therapies in the primary prevention population reflect a much sicker myocardium since the baseline characteristics of patients showed a significantly higher risk profile. In contrast, patients with a secondary indication seem to exhibit a better clinical profile at the time of implant and for instance should not exhibit the same long-term mortality. One possible hypothesis is that secondary prevention patients have higher rates of ventricular arrhythmia during follow-up and that probably has an impact on their mortality. Other authors' data have also shown similar findings.[13]

The negative impact on mortality of ventricular tachycardia or ventricular fibrillation needing shocks has been consistently seen in different primary prevention clinical trials.[6,7] Studies to define predictors of shocks and mortality have been done in primary prevention patients with aims to shift clinicians' focus toward mitigating such risks.[10,14] Although it has been consistently demonstrated that secondary prevention patients have higher incidence of shocks, there is not a large amount of comparative data[11–13,15] with primary prevention patients' outcomes. In that respect, only left ventricular ejection fraction <35% as a cut point as a predictor for secondary prevention has been highlighted in meta-analysis of major secondary prevention trials.[1] However, the largest secondary prevention trial—AVID[16]—randomized more than 1000 patients and in those patients, ICD shocks were not associated with increased mortality,[17] although findings in that population may be because of important differences of baseline characteristics from subjects in our registry.

With regard to ATP therapies, recent data suggest increased mortality risk in patients who experience ATP therapies,[18] and our findings also point in that direction. This is in contrast with previous data from subanalysis of MADIT-RIT,[19] where ATP had a neutral effect in mortality risk. Our population of patients is different from the MADIT-RIT population in a few aspects: (1) It is larger; (2) It has a longer follow-up period; (3) It includes primary and secondary prevention patients; and (4) It has a higher occurrence of primary outcome in patients treated with ATP. Comparability of both studies is arguable based on these facts. Our findings indicate that experiencing arrhythmia that merits treatment from the ICD is an independent marker of risk of death no matter how the device treats it.

Our study with a larger number of patients and a longer follow-up in a real-world setting provides clinicians caring for ICD patients information that could potentially benefit them if strategies could be developed to mitigate the increased risk.

Clinical Implications

The clinical implications of our study are as follows. The first implication is that prophylaxis of shocks and ATP by recommending a strategy that mitigates the likelihood of ventricular arrhythmia in patients with ICDs may have mortality implications. Two randomized trials have evaluated the effect of prophylactic ventricular tachycardia catheter ablation as an addition to ICD in the ischemic cardiomyopathy population.[20,21] Although the findings of those trials cannot be extrapolated to our population, one could hypothesize that decreasing the burden of shocks or delaying the appearance of ventricular arrhythmia could translate into a better survival. The second clinical implication of our study is that patients presenting with an appropriate shock or ATP whether they received an automatic implantable cardioverter/defibrillator for primary or secondary indication has mortality implications. It is a novel finding that there is increased mortality both in primary and secondary prevention even in patients with a less severe cardiomyopathy in terms of LV dysfunction but with greater probability of therapy in the secondary prevention group. Consideration for advanced heart failure therapies or antiarrhythmic drugs or ventricular tachycardia ablation should be taken and optimization of heart function treatment should be done accordingly.

Limitations

Programming strategies for primary prevention patients were not standardized in the implanting centers, but previous reports of our group have shown that the shocks and ATP incidence rates were similar to the contemporary studies with delayed detection therapy groups,[22,23] so an impact on mortality risk based on this is very unlikely. The score used to control for baseline differences was designed and validated on a sample derived from a primary prevention cohort and was extended to the secondary prevention sample in the analysis.[10] Our analysis was focused on assessing outcome after a single ICD shock or ATP and did not evaluate multiple shocks or ATPs. We did not pursue analysis of repeated therapies because during the study follow-up, changes in device programming may occur and were not standardized[24–26] and so will antiarrhythmic drugs and utilization of catheter ablation. We believe that the first ICD therapy is the one with the highest impact in the management of patients and that analyzing further therapies includes several possible biases that would be extremely difficult to account for in the analysis of the data. Inappropriate ICD therapies and the specific type of mortality were not analyzed in our study and are beyond the scope of this prospective registry. This analysis is especially pertinent to the ischemic cardiomyopathy patients because nonischemic cardiomyopathy patients only

comprised a very small minority of the group studied. The use of antiarrhythmic drugs and their possible impact on the mortality of patients who received shocks has not been analyzed in this study.

Conclusion

The implant indication of primary versus secondary prevention did not have a differential impact on mortality following ICD therapies irrespective of the worse baseline clinical profile in the primary prevention group. Though the ICD shock aborted sudden death in the secondary prevention patient who had malignant arrhythmia and had ICD implantation on this basis, this study highlights an unrecognized patient issue that suggests that event has mortality implications. The issue highlighted by this work is that, though the ICD therapy in the secondary prevention patient achieved its goal of aborting sudden death, the work of the clinician is not complete. Strategies should be implemented for caring for these patients even after a single appropriate ICD therapy, and the impact of such strategies on altering survival will require further characterization.

Acknowledgments

The opinions, results and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. Parts of this material are based on data and information compiled and provided by the Canadian Institute of Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI.

Sources of Funding

Dr Porta-Sánchez's collaboration was partially funded via a 'la Caixa' Foundation grant, Barcelona (Spain). Dr Austin is supported in part by a Career Investigator Award from the Heart and Stroke Foundation of Canada (Ontario Office). Dr. Nanthakumar laboratory was supported by an operating grant (CIHR MOP 142272). Dr Lee is the Ted Rogers Chair in Heart Function Outcomes. This Ontario ICD Database was supported by an operating grant (CIHR MOP 111150) and a Foundation Grant (FDN 148446) from the Canadian Institutes of Health Research, and an operating grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). This study was supported by Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Disclosures

None.

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b. Part II: Comparison of the clinical outcomes and healthcare costs of catheter ablation vs medical therapy for recurrent VT.

Canadian Journal of Cardiology 35 (2019) 169–177

Clinical Research

Health Care Utilization After Ventricular Tachycardia Ablation: A Propensity Score-Matched Cohort Study

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See editorial by Nery et al., pages 147–149 of this issue.

ABSTRACT

Background: Catheter ablation of ventricular tachycardia (VT) can reduce the burden of ventricular arrhythmia (VA) but its effect on health care utilization and costs after such therapy is poorly known. We sought to compare the rates of cardiovascular (CV)-related hospitalizations, survival, and health care costs in patients with recurrent VT treated either with VT ablation or with medical therapy.

Methods: One-hundred implantable cardioverter-defibrillator patients with structural heart disease who underwent VT ablation were included. Propensity score-matched patients with recurrent VT treated with medical therapy were identified from a prospective registry of approximately 7000 *de novo* implantable cardioverter-defibrillator patients. Outcomes and costs were ascertained using health administrative databases.

Results: Among patients who underwent VT ablation, the cumulative rates of VA-related hospitalizations were lower in the 2 years after their

RÉSUMÉ

Contexte : L'ablation par cathéter du foyer de tachycardie ventriculaire (TV) peut réduire le fardeau de l'arythmie ventriculaire (AV), mais les effets de cette intervention sur l'utilisation et les coûts des soins de santé ultérieurs sont mal connus. Nous avons voulu comparer les taux d'hospitalisation liée à un problème cardiovasculaire, la survie et les coûts des soins de santé requis chez les patients présentant une TV récidivante ayant été traités soit par une ablation, soit par une prise en charge médicale.

Méthodologie : Cent patients porteurs d'un défibrillateur cardioverteur implantable et atteints d'une cardiopathie structurelle qui avaient subi une ablation de TV ont été inclus dans l'étude. Des patients appariés en fonction de leur coefficient de propension dont la TV récidivante avait été traitée par une prise en charge médicale ont été repérés dans un registre prospectif recensant environ 7000 personnes porteuses d'un défibrillateur cardioverteur implanté *de novo*. Les résultats des

Among patients with structural heart disease and left ventricular dysfunction, catheter-based ablation of ventricular tachycardia (VT) has been shown to effectively reduce the recurrence of VT in this population.[1-4] Despite the positive finding, the effect of VT ablation of clinical outcomes such as mortality, heart failure (HF) events, and health care utilization remains uncertain, because published trials are not specifically designed and powered to assess such end points.[5] To justify the continued growth of VT ablation, it is imperative for researchers to show that it can positively affect outcomes, which have a direct effect on our health care systems. This is particularly pertinent in the current era, because cost containment and cost-effectiveness justification are increasingly demanded and expected by health payers. These issues are germane to VT ablation, an invasive complex therapy with high associated procedural costs and morbidity.[6] It is conceivable that reduction of VT burden via ablation might reduce patients' subsequent downstream health care utilization by reducing hospital admissions or emergency

Received for publication July 17, 2018. Accepted October 15, 2018.

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See page 177 for disclosure information.

https://doi.org/10.1016/j.cjca.2018.10.011

ablation procedure compared with the year before (rate ratio, 0.3; 95% confidence interval [CI], 0.22-0.43). Rates of CV-related hospitalization and hospitalization because of VA post index date were similar between the VT ablation and medical therapy groups (hazard ratio [HR], 0.94; 95% CI, 0.57-1.54 and HR, 1.04; 95% CI, 0.57-1.91, respectively). Health care costs in the VT ablation patients were not increased post-ablation compared with the medical management group. The risk of all-cause mortality was lower among patients in the VT ablation group relative to the medical therapy group (HR, 0.64; 95% CI, 0.4-0.99).

Conclusions: Patients who underwent VT ablation experienced a significant reduction in their rate of VA-related hospitalizations. Patients treated with VT ablation had similar rates of CV-related hospitalization compared with those treated with medical therapy without increased health care-related costs.

traitements et les coûts ont été établis à partir de bases de données administratives sur la santé.

Résultats : Parmi les patients dont la TV avait été traitée par ablation, les taux cumulatifs d'hospitalisation liée à l'AV ont été plus bas au cours des 2 années suivant l'ablation que durant l'année précédant cette intervention (rapport des taux, 0,3; intervalle de confiance [IC] à 95 %, 0,22-0,43). Les taux d'hospitalisation liée à un problème cardiovasculaire et d'hospitalisation en raison de l'AV après la date index étaient comparables chez les patients traités par ablation et chez ceux traités par une prise en charge médicale (rapport des risques instantanés [RRI], 0,94; IC à 95 %, 0,57-1,54 et RRI, 1,04; IC à 95 %, 0,57-1,91, respectivement). Les coûts des soins de santé dans le groupe traité par ablation n'ont pas augmenté après l'intervention comparativement au groupe ayant fait l'objet d'une prise en charge médicale. Le risque de mortalité toutes causes confondues était plus faible dans le groupe traité par ablation que chez les patients ayant fait l'objet d'une prise en charge médicale (RRI, 0,64; IC à 95 %, 0,4-0,99).

Conclusions : Chez les patients dont la TV a été traitée par ablation, une réduction marquée du taux d'hospitalisation liée à l'AV a été observée. Les patients traités par ablation ont affiché des taux d'hospitalisation liée à un problème cardiovasculaire comparables à ceux du groupe ayant fait l'objet d'une prise en charge médicale, sans augmentation des coûts en matière de soins de santé.

department (ED) visits. Recent data have suggested that VT ablation could result in a decrease in health care costs but no control arm was present in one of the reports[7] and probably it only applies for patients receiving amiodarone at baseline as per subgroup data from the Ventricular Tachycardia Ablation vs Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease (VANISH) trial.[8] As such, better delineation of the relationship between VT ablation and patients' subsequent downstream health care utilization is important, because it might be a strong driver of health policy outcomes for this therapy.[9]

Using clinical and administrative health databases from Ontario, Canada, we sought to examine if VT ablation has a positive effect on patients' subsequent health care utilization by comparing the rates of cardiovascular (CV)-related hospitalizations, CV mortality, all-cause mortality, and costs between VT ablation patients and a propensity score-matched cohort of patients with recurrent VT treated with medical therapy.

Methods

This study was approved by the institutional review board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada) as well as by the Review Ethics Board at University Health Network (Toronto, Ontario, Canada).

Study populations

VT ablation cohort. From a single institution (University Health Network, Toronto, Ontario, Canada), 103 consecutive patients with an implantable cardioverter-defibrillator (ICD) and structural heart disease, depressed left ventricular ejection fraction (LVEF) < 40%, recurrent symptomatic VT refractory to antiarrhythmic drug therapy, and with more than 1 appropriate ICD shock who underwent catheter-based VT ablation were identified between April 2008 and September 2015.

Selection of the medical management cohort. VT patients treated with medical therapy alone were obtained from a cohort of approximately 7000 subjects in the ICD database, which prospectively collected data from all 10 ICD implantation centres in Ontario, Canada from February 2007 to May 2012. The design, implementation, and maintenance of the Ontario ICD database have been previously detailed elsewhere.[10] In brief, all patients referred for evaluation in ICD clinics were enrolled into a prospective registry with detailed clinical data collection at enrollment and with subsequent clinical follow-up and documentation of ICD therapies. The Ontario Ministry of Health and Long-Term Care mandated this registry. As a prescribed entity under Ontario's health information privacy legislation, we were able to collect data on all patients in this registry without the need for written informed consent.

All 10 institutions (see the *Participating Centers in the Ontario ICD Database* section of the Supplementary Material) where patients were followed-up are tertiary centres that have the capability of deciding to perform VT ablation procedures and performing guideline-directed treatment thus avoiding clustering effects in the treatment depending on the institution and providing for a similar threshold for VT ablation. For this analysis, selection of subjects into the medical therapy (control) group was restricted to all institutions except University Health Network to mitigate potential selection bias. Inclusion criteria into the control group were the following: presence of structural heart disease, LVEF < 40%, and an ICD; at least 1 appropriate shock with at least 1 subsequent ventricular arrhythmia (VA)-related hospitalization; and without a VT ablation procedure (Table 1).

Propensity score-matching schemes

Propensity score-matching was used to match each subject in the VT ablation cohort with a similar subject in the medical therapy cohort. Variables present and measured at baseline that have been previously shown to affect mortality in ICD patients[10] were used for inclusion in the propensity score model: age, sex, LVEF groups (≤ 20%, 21%-30%, > 30%), diabetes, creatinine levels, and type of cardiomyopathy (ischemic or nonischemic). Subjects were matched on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score.[11] We did not include antiarrhythmic drug usage in the main analysis because time points for the collection of these data were different in each group (Table 2).

Additionally, with the objective of better classifying our 2 groups of patients and to account for the variability in the VT burden and the antiarrhythmic drug usage pre-index date a secondary propensity matching scheme was studied by adding those 2 variables to the matching scheme. Antiarrhythmic drug usage was obtained from the Ontario Drug Database (Table 3).

Follow-up of the study population

VT ablation patients. The index date (and time at which follow-up started) for these patients was the date of the VT ablation procedure. Antiarrhythmic drug usage data were collected at the time of the ablation procedure. Follow-up was up to the earliest date of death or March 31, 2017.

Medical management patients. The index date (and time at which follow-up started) for the control patients was the date of the rehospitalization for VA after a first shock had occurred. This date was elected to mitigate lead-time bias because those patients at the time of recurrent VA readmission could have undergone a VT ablation procedure but continued medical therapy according to physician preference. Antiarrhythmic drug usage data were collected at the time of ICD implantation. Follow-up for hospital admissions and ED visits was up to the earliest date of death or March 31, 2017. Causes of death were analyzed until December 2014 according to administrative data availability.

Data sources

Mortality data were collected using each patient's unique, encoded health card number where ICD data were linked to administrative databases for vital statistics, namely the Registered Persons Database for death events. Vital statistics information was ascertained in all study patients. CV death was determined using the Ontario Registrar General Database. Information about CV hospitalizations before and after the procedure or after the recurrent shock was identified via the Canadian Institute for Health Information Discharge Abstract Database using the International Classification of Diseases Tenth Revision, Canada (ICD) coding system. Codes used for HF were I50, for ischemic heart disease (IHD) I20-I25, and for VA I459-I461, I469-I472, I479, I4900, and I4901. Drugs prescribed at the time of index admission were obtained from the Ontario Drug Benefit Database. These data sets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. Accuracy of the most responsible diagnosis for detection of VT was assessed according to ICD logs of VT therapies being the gold standard. The sensitivity of hospitalization for VT to detect ICD-logged VT was calculated to be 95.5% for accurately classifying patients who experienced VT as assessed in the ICD logs.

Outcomes and comparisons

The primary outcome in this study was the occurrence of nonelective hospitalizations and ED visit for CV reasons including HF, VA, or IHD. Secondary outcomes included: all-cause mortality and CV mortality. Those outcomes were compared using 2 strategies: (1) rates of events 1 year pre-VT ablation vs 2 years post-VT ablation among patients who underwent the procedure; and (2) propensity-matched medical management patients vs VT ablation patients followed for 2 years after the index date (Fig. 1).

Cost analysis

For matched patients in the VT ablation cohort and the medical therapy cohort, any health care costs occurred during 1 year before and after the index date were calculated in 2015 Canadian dollars. The health costs included all types of costs, such as hospital services (inpatient, same-day surgery, rehabilitation, complex and continuing care, and long-term care), drug claims recorded in Ontario Drug Benefit, home care services, or health services covered by the Ontario Health Insurance Plan. Those costs were compared: (1) within each cohort; the costs 1 year before and after the index were compared; and (2) the expense occurred in the

Table 1. Baseline characteristics of patients before propensity score matching

	Medical management (n = 211)	Catheter ablation group (n = 103)	Standardized difference
Age	65.39 ± 12.40	62.25 ± 14.05	0.2367
Male sex	178 (84.4)	93 (90.3)	0.179
LVEF groupings			
≤ 20	33 (15.6)	28 (27.2)	0.2843
20%-30%	80 (37.9)	45 (43.7)	0.1177
> 30%	82 (38.9)	30 (29.1)	0.2066
Missing	16 (7.6)	0 (0.0)	0.4051
Diabetes mellitus	41 (19.4)	15 (14.6)	0.1299
Creatinine level, μMol/L	117.81 ± 89.10	112.53 ± 43.32	0.0753
Amiodarone use	63 (29.9)	79 (76.7)	1.0633
Ischemic cardiomyopathy	140 (66.4)	66 (64.1)	0.0477

Data are presented as mean ± SD or n (%).
LVEF, left ventricular ejection fraction.

Table 2. Baseline characteristics of patients after baseline propensity score-matching

	Medical management (n = 100)	Catheter ablation group (n = 100)	Standardized difference
Age	63.18 ± 13.67	62.97 ± 13.43	0.0155
Male sex	92 (92.0)	90 (90.0)	0.0699
LVEF groupings			
≤ 20	27 (27.0)	28 (28.0)	0.0224
20%-30%	40 (40.0)	42 (42.0)	0.0407
> 30%	33 (33.0)	30 (30.0)	0.0646
Diabetes mellitus	11 (11.0)	15 (15.0)	0.1192
Creatinine level, μMol/L	120.17 ± 100.98	113.20 ± 43.60	0.0896
Ischemic cardiomyopathy	68 (68.0)	65 (65.0)	0.0636

Data are presented as mean ± SD or n (%).
LVEF, left ventricular ejection fraction.

same period were compared between matched medical management patients and VT ablation patients.

Statistical analysis

In the intragroup analysis among patients who underwent VT ablation a Poisson regression model estimated using generalized estimating equations methods was applied to compare event rates pre- and post-VT ablation. In the between groups analysis, the similarity of measured baseline covariates was assessed between the VT ablation patients and the medical therapy patients using standardized differences, before and after matching.[12] In the matched sample, the effect of the intervention (VT ablation) was determined by using a cause-specific hazard model to regress the cause-specific hazard of the outcome on an indicator variable denoting treatment status.[13] The time to outcomes was calculated as time to first event. Importantly, a large percentage of ED visits led to unplanned hospital admissions (90% of HF ED visits, 81% of IHD ED visits, and 87% of VA-related ED visits). In these cause-specific models, death was accounted for as a competing risk (in the model in which all-cause mortality was used, a conventional Cox model was used).[14] A robust variance estimator was used to account for the matched nature of the sample.[15] Median costs were compared using a signed rank test. All analyses were performed using SAS version 9.4.5 (SAS Institute, Inc, Cary, NC).

Results

Baseline clinical characteristics and procedural data of the matched cohort

Between April 2008 and September 2015, we identified 100 patients in the VT ablation group. From a cohort of approximately 7000 patients who received *de novo* ICDs, we identified 211 patients for inclusion in the pool of potential controls who received medical management (Table 1). The final cohort consisted of 100 matched pairs of patients and their baseline characteristics are shown in Table 2. Notably, 35% of patients had a nonischemic etiology. The total follow-up duration for patients in the VT ablation and medical management group was 353 person-years and 362 person-years, respectively. See the *Procedural Characteristics of the VT Ablation Treatment* section of the Supplementary Material for details.

Health care utilization rates

VT ablation group. In the year before VT ablation, the overall rate of unplanned CV hospitalizations (because of VA, HF, or IHD) was 144.7 admissions per 100 person-years. It decreased to 48.6 admissions per 100 person-years in the 2 years after VT ablation (rate ratio [RR], 0.35; 95% confidence interval [CI], 0.26-0.47; $P < 0.001$). The cumulative rate of ED visits because of CV causes (because of VA, HF, or IHD)

Table 3. Sensitivity analysis propensity score matching

	Medical management (n = 66)	Catheter ablation group (n = 66)	Standardized difference
Age	63.68 ± 13.58	62.21 ± 14.72	0.1038
Male sex	60 (90.9)	58 (87.9)	0.0985
LVEF grouping			
≤ 20	13 (19.7)	14 (21.2)	0.0376
20%-30%	25 (37.9)	25 (37.9)	0
> 30%	28 (42.2)	27 (40.9)	0.0307
Diabetes mellitus	8 (12.1)	9 (13.6)	0.0452
Creatinine level, μMol/L	111.05 ± 81.0	105.85 ± 31.27	0.0848
Ischemic cardiomyopathy	41 (62.1)	40 (60.6)	0.031
Number of VT hospitalizations within 1 year before the index date	0.76 ± 0.84	0.76 ± 0.8	0
Patients receiving antiarrhythmic drugs on the index date	25 (37.9)	23 (34.8)	0.063

Baseline characteristics of patients after the secondary propensity score matching that included age, etiology of cardiomyopathy, previous diabetes, antiarrhythmic medication use, along with the quadratic term of age, and interaction terms between LVEF group with other variables. Data are presented as mean ± SD or n (%).
LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.

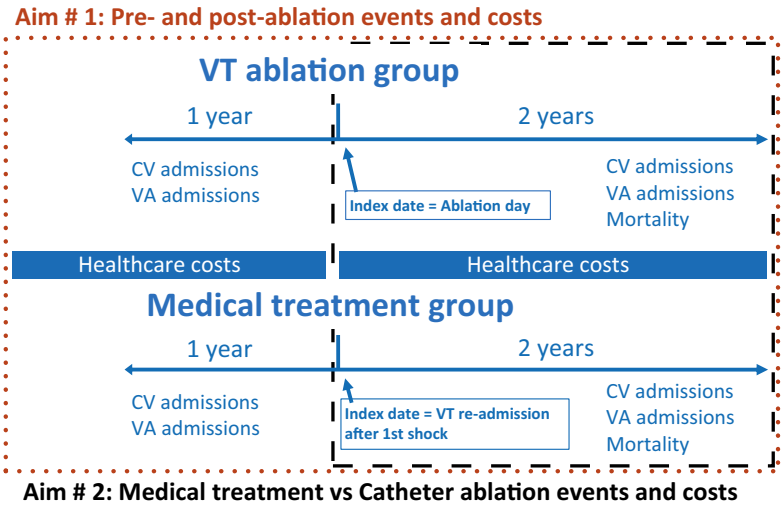

Figure 1. Study design and aims. **Dotted red line** indicates the timeline of the pre- and post-ventricular tachycardia (VT) ablation event rate study. Index time is the day of the VT ablation procedure. **Black interrupted line** indicates the medical treatment vs VT ablation comparison with index time in the medical treatment group being the day of a subsequent readmission for VT after having experienced a previous appropriate implantable cardioverter-defibrillator shock for VT (recurrent VT). CV, cardiovascular; VA, ventricular arrhythmia.

was 139.8 visits per 100 person-years in the year before VT ablation. This rate decreased to 54.6 visits per 100 person-years in the 2 years after VT ablation (RR, 0.41; 95% CI, 0.30-0.56; $P < 0.001$). Reduction in the number of VA-related unplanned hospitalizations and ED visits was the primary driver of the overall reduction in hospitalization and ED visit rates. In the year before VT ablation, the cumulative rate of unplanned CV hospitalizations because of VA was 114.6 admissions per 100 person-years, which decreased to 33.8 admissions per 100 person-years in the 2 years after VT ablation (RR, 0.30; 95% CI, 0.22-0.43; $P < 0.001$). Similarly, the cumulative rate of ED visits because of VA was 95.1 visits per 100 person-years in the year before VT ablation, which decreased to 27.9 visits per 100 person-years in the 2 years after VT ablation (RR, 0.31; 95% CI, 0.21-0.46; $P < 0.001$; Table 4).

Medical management group. In the year before experiencing a recurrent appropriate ICD shock, patients treated medically had an overall rate of unplanned CV hospitalizations (because of VA, HF, or IHD) of 53.0 admissions per 100 person-years. After experiencing the index recurrent shock the rate was 55.9 admissions per 100 person-years (RR, 1.10; 95% CI, 0.76-1.60; $P = 0.597$). The cumulative rate of ED visits because of CV causes (because of VA, HF, or IHD) was 75.0 visits per 100 person-years in the year before a recurrent appropriate ICD shock. This rate was 60.6 visits per 100 person-years in the 2 years after the index

Table 4. Outcomes and measures of association 12 months before VT ablation vs 24 months after VT ablation among patients who underwent the procedure

	Event rate per 100 person-years			
Outcome	12 months before VT ablation (reference)	24 months after VT ablation	Rate ratio (95% CI)	*P*
Unplanned hospital admissions				
HF	20.39	12.46	0.66 (0.33-1.34)	0.2516
VA	114.56	33.81	0.30 (0.22-0.43)	< 0.0001
IHD	9.71	< 5	0.24 (0.08-0.77)	0.016
Cardiovascular hospitalization (HF + VA + IHD)	144.66	48.64	0.35 (0.26-0.47)	< 0.0001
ED visits				
HF	32.04	18.39	0.60 (0.32-1.12)	0.1067
VA	95.15	27.88	0.31 (0.21-0.46)	< 0.0001
IHD	12.62	8.30	0.68 (0.33-1.42)	0.3077
Cardiovascular ED visit (HF + VA + IHD)	139.81	54.58	0.41 (0.30-0.56)	< 0.0001

CI, confidence interval; ED, emergency department; HF, heart failure; IHD, ischemic heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia.

Table 5. Outcomes and measures of association 12 months before recurrent VT vs 24 months after recurrent VT among patients who were medically managed after experiencing recurrent appropriate ICD shocks for VT

Outcome	Event rate per 100 person-years		Rate ratio (95% CI)	*P*
	12 Months before earliest recurrent VT arrhythmia (reference)	24 Months after earliest recurrent VT arrhythmia		
Unplanned hospital admissions				
HF	28.00	26.98	1.02 (0.61-1.70)	0.9514
VA	16.00	23.69	1.52 (0.78-2.95)	0.2175
IHD	9.00	5.27	0.58 (0.21-1.62)	0.3007
Cardiovascular hospitalization (HF + VA + IHD)	53.00	55.94	1.10 (0.76-1.60)	0.597
ED visits				
HF	34.00	32.91	1.07 (0.62-1.84)	0.8081
VA	25.00	20.40	0.81 (0.45-1.47)	0.4926
IHD	16.00	7.24	0.46 (0.22-0.96)	0.0386
Cardiovascular ED visit (HF + VA + IHD)	75.00	60.55	0.83 (0.56-1.22)	0.344

CI, confidence interval; ED, emergency department; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia.

recurrent shock (RR, 0.83; 95% CI, 0.56-1.22; $P = 0.344$; Table 5).

Comparison of health care utilization of patients treated with medical therapy vs VT ablation

Event rates of first unplanned hospitalization and first ED visit for the VT ablation and medical therapy groups are presented in Table 6. On the basis of the reported hazard ratios (HRs), the instantaneous rates of unplanned hospitalizations, and ED visits because of HF, VA, or IHD were similar between the 2 groups. Notably, during the year before the index date the burden of VA was much higher in the VT ablation group (Table 5).

Costs of health care utilization of patients treated with medical therapy vs VT ablation

Analysis of total health care-related costs is summarized in Table 7. Among patients who underwent VT ablation a significant increase in the median costs was seen in the year after the index procedure. In contrast, patients who continued medical therapy had similar costs after their repeated admission for recurrent appropriate ICD shocks for VT. Patients treated with VT ablation had a baseline 1 year preablation cost that was slightly higher than the medically treated cohort although no statistically significant difference was seen. Post VT ablation costs remained similar for the VT ablation cohort compared with the medical treatment group.

Mortality

Rates of CV mortality were similar between the VT ablation and medical therapy group (HR, 0.75; 95% CI, 0.38-1.48; $P = 0.41$). Patients in the VT ablation group had lower all-cause mortality rates compared with those treated with medical therapy (HR, 0.63; 95% CI, 0.40-0.998; $P = 0.0489$; Table 6).

Sensitivity analysis

In an additional analysis patients were matched according to the number of admissions for VA and the presence of antiarrhythmic drug usage at the time of the index date (sotalol or amiodarone). Sixty-six pairs of patients were found with a well balanced matching scheme (Table 3). In this analysis VT ablation was shown to be linked to a decreased number of visits to the ED for VA during follow-up (HR, 0.53; 95% CI, 0.28-0.97). There were no other differences in the outcomes although a trend toward better survival was also

Table 6. Outcomes (calculated using time to first event) and measures of association between groups (VT ablation vs medical treatment group)

Outcome	Event rate per 100 person-years (follow-up person-years)		Hazard ratio (95% CI)	*P*
	VT ablation group (n = 100)	Medical treatment group (n = 100)		
Unplanned hospital admissions				
HF	5.21 (326)	9.5 (305)	0.68 (0.34-1.33)	0.26
VA	12.63 (253)	12.65 (261)	1.04 (0.57-1.91)	0.89
IHD	1.46 (343)	3.22 (342)	0.31 (0.09-1.11)	0.07
Cardiovascular hospitalization (HF + VA + IHD)	19.14 (230)	22.13 (230)	0.94 (0.57-1.54)	0.79
ED visits				
HF	7.42 (296)	9.41 (298)	0.84 (0.44-1.59)	0.58
VA	10.78 (278)	12.38 (259)	0.88 (0.47-1.62)	0.68
IHD	3.4 (323)	4.18 (335)	0.50 (0.18-1.38)	0.18
Cardiovascular ED visit (HF + VA + IHD)	21.77 (221)	22.37 (223)	0.86 (0.54-1.38)	0.54
Cardiovascular mortality	8.09 (284)	9.14 (328)	0.75 (0.38-1.48)	0.41
All-cause mortality	12.45 (353)	16.84 (362)	0.63 (0.40-0.998)	0.049

CI, confidence interval; ED, emergency department; HF, heart failure; IHD, ischemic heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia.

Table 7. Analysis of health care-related costs: primary analysis of costs within and between VT ablation and medical treatment patients

	Median (IQR) costs within 1 year before index procedure/admission (in 2015 CAD$)	Median (IQR) costs within 1 year after the index procedure/admission (in 2015 CAD$)	*P* for signed rank test within groups
VT ablation patients (n = 100)	39,600.00 (21,751.50-64,367.50)	40,707.00 (22,240.50-88,830.50)	0.0460
Medical treatment patients (n = 100)	28,376.00 (7345.00-60,108.00)	34,338.50 (15,324.00-67,585.00)	0.2703
P for signed rank test between groups	0.1053	0.0514	

IQR, interquartile range; VT, ventricular tachycardia.

seen (HR, 0.65; 95% CI, 0.39-1.09; $P = 0.1$; Table 8). Further details are shown in Supplemental Table S1.

Discussion

There are 4 major findings in our study. First, patients with structural heart disease and impaired LVEF who underwent VT ablation experienced a significant reduction in their number of unplanned hospital admissions and ED visits because of VA thus indicating the effectiveness of the treatment strategy undertaken. Second, we observed that VT ablation patients had comparable rates of health care utilization and major adverse cardiac events compared with a matched cohort of medically treated patients. Third, our analysis suggests improved survival for patients who underwent VT ablation relative to those treated with medical therapy. Fourth, health care-related costs were not significantly increased after VT ablation compared with medical treatment. Taken together, these results suggest that when VT ablation is performed in a carefully selected population of patients with advanced cardiac dysfunction and VAs, a meaningful reduction in their subsequent health care utilization can be achieved without compromising their safety or survival, however, a decrease in their health care costs is not to be expected.

Effect of VT ablation on VA-related hospitalizations

Previous studies had shown that VT ablation reduces VT burden.[2] However, these studies were neither designed nor powered to address whether reduction of VT burden using ablation could reduce mortality or unplanned hospitalizations/ED visits because of VA. Elucidating the potential effect of VT ablation on such outcomes is critical if the overarching goal is to influence health policy. In this respect, our study is novel because it focuses on the downstream health care utilization effect of VT ablation in a medically compromised population of patients with VT. Among patients in the VT ablation group, we observed high rates of unplanned hospitalizations and ED visits because of VA, at approximately 1.5 admissions and approximately 1.4 ED visits per person-year in the 12 months before ablation. Remarkably, we noted a threefold decrease in the cumulative rates of VA-related hospitalizations and ED visits for these patients within the 2 years after VT ablation.

The favourable findings of VT ablation on health care utilization are restricted to our intragroup analysis. When we compared the rates of unplanned hospitalization and ED visits between patients who underwent VT ablation with a matched cohort of VT patients who were medically treated only (ie, not ablated), we observed comparable outcomes. These findings were consistent with the VANISH trial in terms of cardiac hospitalization outcomes.[5] However, in our study, in the 12 months before the start of study follow-up, the cumulative rates of unplanned VA-related hospitalizations and ED visits were markedly greater in the VT ablation group (10-fold and 5-fold, respectively) than the medical therapy group. This suggested that patients in the VT ablation group might represent a higher arrhythmic risk group than the medical treatment group (more VA-related admissions despite being matched for many other prognostic markers). Our finding that the postprocedural rates of hospital admission and ED visits of patients who underwent VT ablation were similar to a matched cohort of medically treated VT patients actually might favourably reflect the effect of VT ablation on patients' subsequent arrhythmic risk. Moreover, even when matching patients with the same antiarrhythmic drug usage and number of VA-related admissions in the year before the index date we

Table 8. Sensitivity analysis: outcomes (calculated using time to first event) and measures of association between groups (VT ablation vs medical treatment group) using the propensity score that includes AAD usage and number of VA-related admissions

	Event rate per 100 person-years (follow-up in person-years)			
Outcome	VT ablation group (n = 66)	Medical treatment group (n = 66)	Hazard ratio (95% CI)	*P*
Unplanned hospital admissions				
HF	< 5 (235)	5.95 (235)	0.74 (0.33-1.68)	0.471
VA	9.01 (200)	9.26 (194)	0.97 (0.49-1.90)	0.917
IHD	< 5 (249)	< 5 (245)	0.50 (0.18-1.35)	0.170
Cardiovascular hospitalization (HF + VA + IHD)	14.47 (180)	16.34 (184)	0.83 (0.49-1.41)	0.496
ED				
HF	7.06 (213)	6.89 (232)	0.91 (0.43-1.93)	0.811
VA	7.45 (215)	14.5 (172)	0.53 (0.28-0.97)	0.041
IHD	< 5 (244)	< 5 (240)	0.72 (0.28-1.86)	0.495
Cardiovascular ED visit (HF + VA + IHD)	16.67 (174)	22.12 (158)	0.75 (0.47-1.22)	0.246
Cardiovascular mortality	7.44 (202)	10.72 (224)	0.61 (0.30-1.24)	0.171
All-cause mortality	9.78 (256)	14.35 (258)	0.65 (0.39-1.09)	0.099

AAD, antiarrhythmic drug; CI, confidence interval; ED, emergency department; HF, heart failure; IHD, ischemic heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia.

confirmed very similar results. Notably, a decrease in VA-related visits to the ED in the VT ablation group was seen. This could translate into a decrease of unplanned hospitalizations that is not detected in our model because it is driven by time to first event and patients very frequently visit the ED before having an unplanned hospitalization. Our findings raise the tempting possibility that VT ablation can potentially assuage the risk of a previously highly arrhythmic patient cohort to a more stable clinical state. Larger-scale, prospective, multicentre studies with a focus on the real-world health care utilization outcomes of VT ablation vs medical therapy are required to formally address this hypothesis.

Effect of VT ablation on HF outcomes

A bidirectional relationship exists between HF and VAs, making them two closely linked entities. It is not uncommon for HF to serve as an important trigger for VAs among patients with left ventricular dysfunction. However, onset of sustained VAs can exacerbate HF in some patients. The role of VT ablation in preventing subsequent HF onset is scarcely addressed in published VT ablation trials. Neither VANISH nor Thermocool observed differences in HF event rates between the VT ablation and medical therapy groups.[5,16] No data on HF outcomes were reported by the **S**ubstrate **M**apping and **A**blation in **S**inus Rhythm to **H**alt **V**entricular **T**achycardia (SMASH-VT) and the **V**entricular **T**achycardia **A**blation in **C**oronary **H**eart Disease (VTACH) trials.[17,18] Moreover, there is a theoretical risk that patients' HF status might be worsened by VT ablation when the already-compromised myocardium is ablated and destroyed. This consideration is particularly relevant in the current era when extensive substrate ablation is advocated by some groups worldwide.[19,20] In this respect, our results provide reassurance to clinicians on the effect of VT ablation on patients' subsequent HF outcomes if an activation mapping and late potential elimination strategy is followed.

Effect of VT ablation on mortality

Our results suggest that patients who underwent VT ablation had lower all-cause mortality compared with those who were medically treated. However, no difference in the risk of CV mortality was observed between the two groups. Because of the retrospective and nonrandomized design of our study, these findings are hypothesis-generating and should be interpreted with caution. However, there were recent data suggesting that VT ablation could be associated with improved survival in the sickest HF patients.[21] Without randomized trial data, it is not possible to conclude whether VT ablation can reduce mortality even if it is performed in the sick, high-risk patients at the present juncture. In addition, our sensitivity analysis adding the antiarrhythmic drug usage and the VA burden before the index date did not show a survival benefit for the VT ablation group. Accordingly, clinicians must rely on studies that focus on other clinically relevant outcomes (eg, health care utilization, VT recurrence, quality of life) to decide on whether VT ablation should be offered to their patients.

Effect of VT ablation on health care costs

VT ablation is a procedure with very high costs as it pertains to advanced electroanatomical mapping systems, expensive catheters, multiple physicians, prolonged hospital stay, etc. One could hypothesize that if there were large benefits to be expected in terms of downstream cost savings after the procedure this would be a cost-effective strategy. Interestingly, pre-index date costs showed no significant differences between groups although a trend toward higher costs in the VT ablation group was seen, which could well be a reflection of a higher number of hospitalizations and ED visits in this group. Additionally, our analysis suggests that there was no comparative increase in costs after the VT ablation procedure compared with medically treated patients with recurrent VT. Although the higher VA-related admissions burden in the VT ablation group pre-procedure might suggest that their health care consumption would keep increasing if the procedure was not performed, our analysis was not designed to assess this hypothesis. A large randomized trial with real-world cost analysis would be needed to answer this question and recent data from the VANISH trial have shown that the decrease in health care-related costs might be limited to patients with VT refractory to amiodarone usage.[8]

Limitations

Our study has a number of important limitations. It was a retrospective, single-centre experience of VT ablation outcomes and it is subject to the usual limitations of observational research in terms of selection bias and overall generalizability. Outcomes were ascertained using administrative databases. Our findings need to be validated with larger-scale, preferably prospective studies. Second, although we use 2 propensity scores to match key baseline characteristics of patients treated with ablation vs medical therapy, residual unmeasured confounding might still persist. Yet, even if there was residual confounding that could not be accounted for using our statistical methods, we did incorporate variables that are known to be strongly associated with adverse outcomes in the ICD and HF population in our propensity score.[22] In addition, it should be pointed out that the presence of survival and lead-time bias could exist in the VT ablation group, which would potentially bias our findings away from the null. However, most of our outcomes were similar between the VT ablation and medical therapy groups. Therefore, even if the VT ablation group is affected by survival and lead-time bias, their potential effects on our results is, at best, uncertain. Furthermore, in the 12 months before the start of follow-up, patients in the VT ablation group had considerably higher rates of HF- and VA-related hospitalizations and ED visits than those in the medical therapy group. In this respect, survival and lead-time bias did not appear to be important factors in selecting a subgroup of lower-risk VT ablation patients in our comparative analysis.

Conclusions

After VT ablation, patients experienced a significant decrease in their rates of unplanned hospitalizations and ED visits because of VA relative to their preablation state. Patients who underwent VT ablation had a higher burden of VA-related admissions pre-procedure and experienced comparable health care utilization outcomes and costs after the procedure compared with those who were medically managed. There was no significant difference in costs

among the two treatment strategies although patients treated with VT ablation seemed to experience lower overall mortality rates.

Funding Sources

Dr Porta-Sánchez' collaboration was partially funded via a "la Caixa" Foundation fellowship grant, Barcelona (Spain) and by the Miriam Burnett Fellowship program at University Health Network (Toronto, Ontario, Canada). Dr Austin is supported in part by a Career Investigator Award from the Heart and Stroke Foundation of Canada (Ontario office). Drs Lee and Nanthakumar are investigators of the Heart and Stroke Foundation, and Dr Lee is the Ted Rogers Chair in Heart Function Outcomes.

This Ontario ICD Database was supported by an operating grant from the Canadian Institutes of Health Research (MOP 111150), a Foundation grant from the Canadian Institutes of Health Research (FDN 148446), and the Ontario Ministry of Health and Long-Term Care.

The Institute for Clinical Evaluative Sciences is supported in part by a grant from the Ontario Ministry of Health and Long-Term Care. The opinions, results, and conclusions are those of the authors and no endorsement by the Ministry of Health and Long-Term Care or by the Institute for Clinical Evaluative Sciences is intended or should be inferred. Parts of this material are on the basis of data and information compiled and provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors, and not necessarily those of the Canadian Institute for Health Information.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.10.011.

c. Part III: Introduction and validation of DEEP mapping as a novel strategy for a mechanistic VT ablation strategy:

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 4, NO. 3, 2018

PUBLISHED BY ELSEVIER

Multicenter Study of Ischemic Ventricular Tachycardia Ablation With Decrement-Evoked Potential (DEEP) Mapping With Extra Stimulus

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ABSTRACT

OBJECTIVES The authors conducted a multicenter study of decrement-evoked potential (DEEP)-based functional ventricular tachycardia (VT) substrate modification to evaluate if such a mechanistic and physiological strategy is feasible and efficient in clinical practice and provides reduction in the VT burden.

BACKGROUND Only a fraction of the myocardium targeted in current VT substrate modification procedures is involved in the initiation and perpetuation of VT. The physiological basis of the DEEP strategy for identification of areas of initiation and maintenance of VT was recently established.

METHODS We included 20 consecutive patients with ischemic cardiomyopathy. During substrate mapping, fractionated and late potentials (LPs) were tagged, and an extra stimulus was performed to determine which LPs displayed decrement (DEEPs). All patients underwent DEEP-focused ablation: elimination of DEEP + further radiofrequency (RF) if VT was still inducible. Patients were followed during 6 months.

RESULTS Patients were predominantly male (95%), and their mean age was 64.6 ± 17.1 years. Mean left ventricular ejection fraction was 33.4 ± 11.4%. Mean ablation time was 30.6 ± 20.4 min. Specificity of DEEPs to detect the isthmus of VT was better than that of LPs (0.97 [95% confidence interval [CI]: 0.95 to 0.98] vs. 0.82 [95% CI: 0.73 to 0.89]), without significant differences in terms of sensitivity (0.61 [95% CI: 0.52 to 0.69] vs. 0.60 [95% CI: 0.44 to 0.74], respectively). Fifteen of 20 (75%) patients were free of any VT after DEEP-RF at 6 months of follow-up and there was a strong reduction in VT burden compared to 6 months pre-ablation.

CONCLUSIONS In a multicenter prospective study, DEEP substrate mapping identified the functional substrate critical to the VT circuit with high specificity. DEEP-guided VT ablation, by its physiological nature, may enable greater access to focused ablation therapy for patients requiring VT treatment. (J Am Coll Cardiol EP 2018;4:307-15)

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received October 19, 2017; revised manuscript received December 7, 2017, accepted December 11, 2017.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2017.12.005

ABBREVIATIONS AND ACRONYMS

DEEP = decrement-evoked potential

EGMs = electrograms

ICD = implantable cardioverter defibrillator

ICM = ischemic cardiomyopathy

LAT = local activation time

LP = late potentials

NICM = nonischemic cardiomyopathy

RF = radiofrequency

S1 = stimulus 1

S2 = stimulus 2

VERP = ventricular effective refractory period

VT = ventricular tachycardia

Contemporary substrate-based approaches for ventricular tachycardia (VT) ablation targets abnormal potentials and late potentials, and can result in large areas of viable myocardium being ablated that may or may not be linked to the mechanisms of initiation and/or maintenance of VT (1,2). An alternative ablation strategy would be to identify which of those potentials actually participate in the initiation and maintenance of VT as targets for VT ablation. We have recently shown which of these many abnormal and late potentials actually initiate and/or maintain VT. In our previous study, regions that displayed decremental behavior evoked during right ventricular (RV) pacing with extra stimuli (decrement-evoked potential; DEEP), colocalized with the regions of the initiation and diastolic circuit of VT more accurately than those areas displaying nondecremental late potentials (LPs) (3).

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This mechanistic physiological demonstration, where decrement precedes unidirectional block, allowed us to identify the region of diastolic path of VT by delivering extra stimulus and evoking the delay of the electrogram (EGM) so that the hidden mechanistic substrate could manifest itself. This obviates the need for VT induction for identifying the critical component of the circuit. This physiological substrate deduction comes from patients who underwent intraoperative global mapping of substrate and activation of VT including the moment of initiation of VT. That study provided the mechanistic basis of DEEP in substrate ablation of VT, allowing VT ablators to identify regions that are responsible for the mechanism of VT without inducing VT. However, that study did not test the practical use and feasibility in the catheterization laboratory. More importantly, it was not established whether DEEP-guided substrate ablation could be adapted to contemporary clinical practice and could be implemented by other operators and sequential mapping systems.

To address these issues, as a follow-up to our original mechanistic study, we designed a multicenter prospective observational study to: 1) establish if the methodology for DEEP mapping with extra stimulus to identify mechanistic substrate is implementable using contemporary 3-dimensional (3D) electroanatomic mapping systems in the catheterization laboratory; and 2) describe the initial results of a multicenter DEEP-guided ablation strategy for reducing VT burden using this focused ablation strategy in the ischemic substrate.

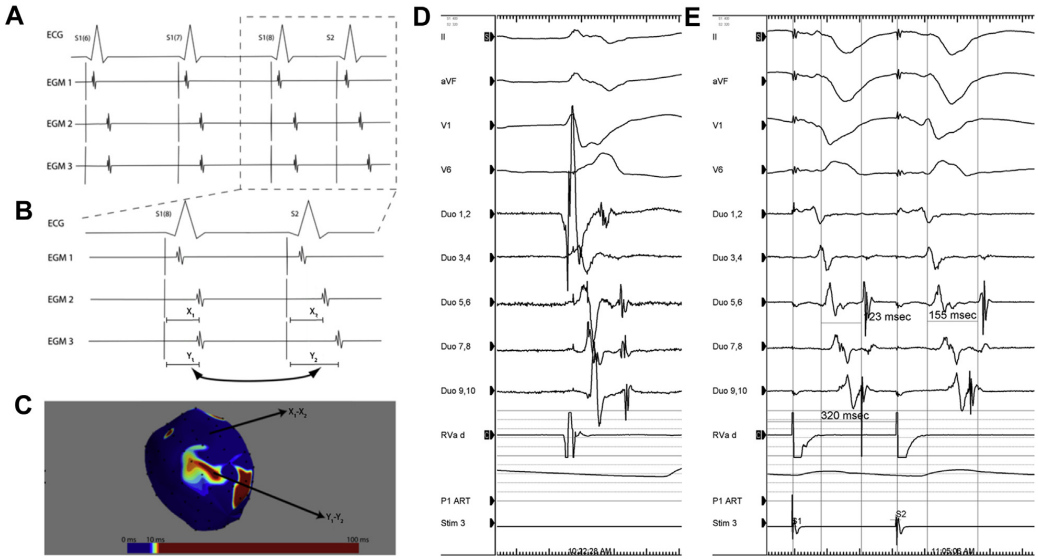
METHODS

PATIENTS. Consecutive patients with ischemic cardiomyopathy (ICM) and recurrent episodes of VT despite medical therapy listed for VT ablation at 4 different institutions (Toronto General Hospital, Ontario, Canada; John Hunter Hospital and Lake Macquarie Private Hospital, Newcastle, Australia; and Århus University Hospital, Skejby, Denmark) were evaluated for participation in the study. The protocol of the study was reviewed and approved by the research ethics boards at all institutions and complies with the Declaration of Helsinki; all patients provided informed consent. All patients underwent DEEP mapping (n = 20) and the ablation strategy focused on eliminating DEEP sites and perform further radiofrequency (RF) if VT was still inducible.

DEEP MAPPING. Substrate maps were created in sinus rhythm or during RV pacing. Access to the left ventricular endocardial surface was achieved with a retroaortic (n = 13) or transseptal approach (n = 7). In 16 patients, multielectrode catheters were used for substrate mapping (Decanav in 9 patients, Pentarray in 6 patients [Biosense Webster, Diamond Bar, California], and Orion in 1 patient [Boston Scientific, Marlborough, Massachusetts]). The rest of patients (n = 4) underwent mapping with a 3.5-mm irrigated tip ablation catheter (Thermocool SF catheter, Biosense Webster). LPs (potentials with complex high frequency or multicomponent after or at the QRS offset either present in sinus rhythm or seen during RV pacing) were identified and annotated either as location tags or as local activation time (LAT) maps by manually annotating onset of the delayed bipolar EGM.

For all the points showing LPs, a systematic assessment for local decrement was performed with a drive train (S1) from the RV at 600 ms with a single extra stimulus (S2, coupled at 20 ms above the ventricular effective refractory period [VERP]). If the difference in the time interval measured from surface ventricular far field signal onset to the local LP bipolar EGM during the S1 drive compared to the same interval measured immediately after the S2 was >10 ms, the LP was defined as a DEEP (**Figure 1**). The same strategy was used for multicomponent EGMs from which DEEP were identified if their components split by >10 ms after S2. All DEEP and non-DEEP-LPs (hereafter referred as LPs) were given a different annotation marker in the substrate map. Care was taken to map the areas of interest with the same

FIGURE 1 Diagram Illustrating the Concept of Decrement-Evoked Potential Versus Nondecremental Late Potential



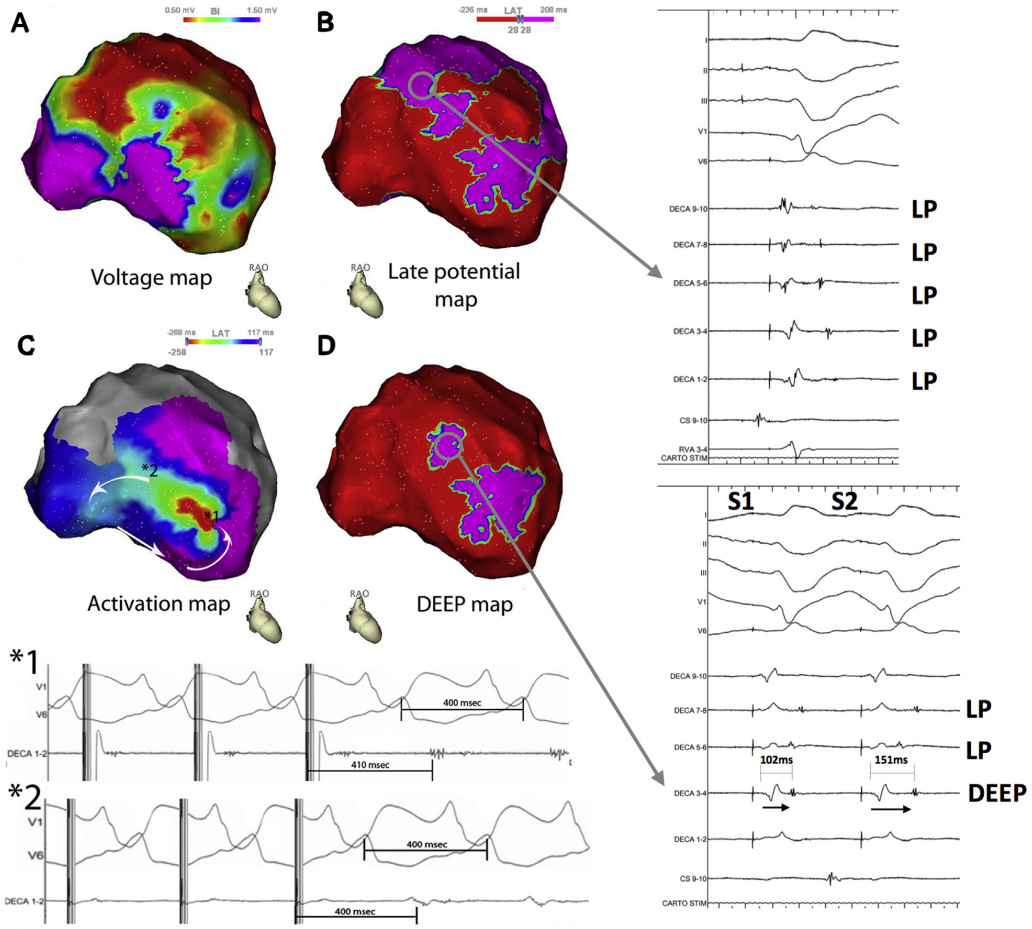
(A) Schematic representation of an isolated late potential recorded by bipoles 1, 2, and 3 during a drive and an extra stimulus (S1/S2). **(B)** Zoom and measurement of timing of the late potential after stressing the myocardium with S2. There is a lack of difference between X1–X2 indicating a non-decremental potential and the difference in timing between Y1–Y2 indicating decremental conduction (DEEP). **(C)** Schematic representation of an LV endocardial LAT map where **blue** represents areas with late activation but nondecremental (X1–X2 ≤10 ms) and **red** depicts areas with decrement of >10 ms (Y1–Y2). **(D)** Mapping during sinus rhythm. Signals obtained with a DecaNav catheter showing an initial far field ventricular component followed by a near field sharp late potential (LP) in D 1,2, D 5,6, D 7,8, D 9,10. **(E)** RV pacing S1/S2 (600/320 ms) showing a change of more than 10 ms in the distance between the far field signal and the local LP during S1 compared to the same distance after S2 in D 5,6, thus identifying a region with decremental conduction properties, whereas in D 9,10 the timing between the far field signal and the LP is unchanged after S2, thus indicating a nondecremental LP. DEEP = decrement-evoked potential; Duo = DecaNav signals; ECG = electrocardiogram; EGM = electrogram; LAT = local activation time; LP = late potentials; LV = left ventricle; P1 ART = invasive blood pressure recording; RVad = right ventricular apical distal bipole; Stim = stimulus.

density of points to avoid over-representation of the DEEP or LP areas. Analysis of areas of DEEPs and LPs could also be performed by creating an LAT map during RV pacing annotating the onset of the bipolar sharp delayed component for timing of LPs/DEEPs (Figure 2). LAT maps could only be created either in sinus rhythm or during RV pacing, but never together to allow for a correct interpretation of activation times. The threshold of 10 ms for local decrement was chosen based on the intraoperative mapping data and to reduce interobserver disagreement from small variations in measurements (3). Percentage area of LPs and DEEPs was calculated based on the number of LP tags and DEEP tags compared to the total number of points for patients who had >290 points in their maps (above the median of our study) (n = 14). Supplemental information on the procedure can be found in the Methods section of the Online Appendix.

IDENTIFICATION OF THE VT CIRCUIT. In those patients with hemodynamically tolerated VT with high density activation maps (arbitrarily defined as >100 points; n = 13 VTs) the diastolic path of the VT was identified via an LAT map and used to delineate the re-entrant circuit including exit sites as per the classical criteria (4,5). The channel containing all mid-diastolic and pre-systolic signals was identified as the path of VT and used for comparison to the LP and DEEP regions to derive their diagnostic accuracy measures (sensitivity and specificity); points located <5 mm from the mid-diastolic path were considered to be in the re-entrant circuit during VT (Figures 2 to 4).

ABLATION STRATEGY AND PROCEDURAL ENDPOINTS. Ablation was performed with either an SF Navistar irrigated-tip catheter (Biosense Webster) or a Smart-Touch Navistar irrigated-tip catheter

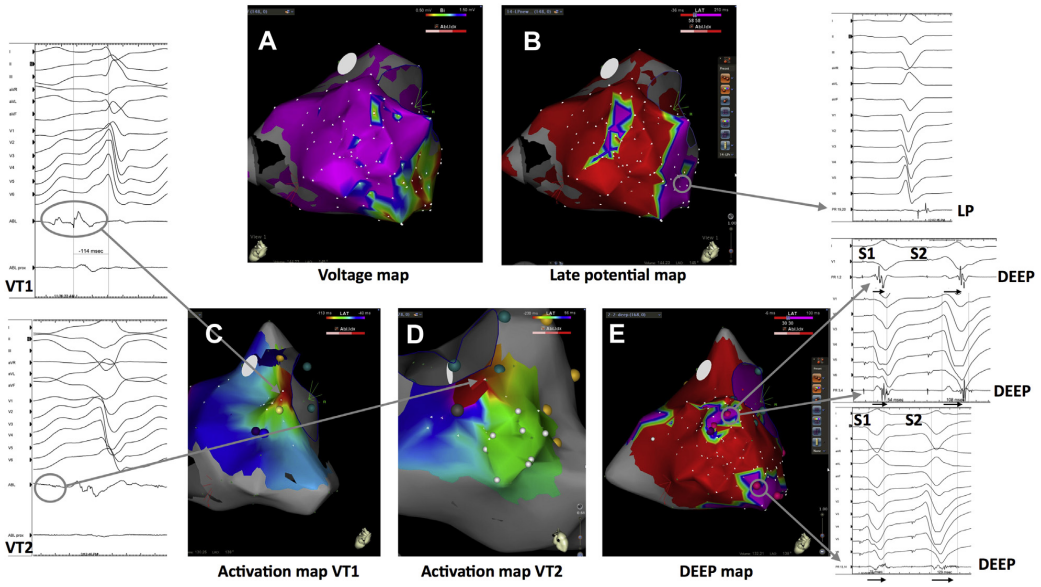
FIGURE 2 Example 1 of Decrement-Evoked Potential Mapping to Guide Ventricular Tachycardia Ablation



Right anterior oblique (RAO) view of the LV endocardial maps of a patient with ischemic cardiomyopathy. The points of EGM acquisition are shown. **(A)** Voltage map showing area of scar in **red** and healthy myocardium in **purple** (thresholds <0.5 mV for dense scar, 0.5 mV to 1.5 mV for borderline zone, and >1.5 mV for healthy tissue). **(B)** Late potential map: LAT map during RV pacing showing the area of late activation after QRS offset in **purple** and the rest of the ventricle in **red** with examples of the EGMs identified in the **purple** area. **(C)** Activation map: LAT map during VT showing the entire VT cycle length and the diastolic path located in the apical to mid-septal region of the LV mainly in the scar border zone. Entrainment is performed at 2 separate points: the isthmus entry **(*1)** and at the isthmus exit **(*2)** to prove a re-entrant mechanism and define the isthmus as shown in the EGM recordings below. **(D)** DEEP map: LAT map showing the 2 areas with DEEP potentials, collocating with the diastolic path of the VT (entry and exit sites). Carto stim = stimulation channel; CS = coronary sinus; deca = DecaNav catheter signals; RVA = right ventricular apex; S1 and S2 = drive train and extra stimulus; VT = ventricular tachycardia; other abbreviations as in Figure 1.

(Biosense Webster) or an IntellaNav open-irrigated catheter (Boston Scientific). Areas with DEEPs were ablated first, and inducibility of the clinical tachycardia was assessed after targeting DEEP areas only. Acute success of the ablation was defined as achieving noninducibility of all clinical tachycardias. If the patient was inducible and became noninducible after DEEP-RF, the procedure was terminated. If the patient was noninducible at the beginning of the case, no further reinductions were performed.

FIGURE 3 Example 2 of Decrement-Evoked Potential Mapping to Guide Ventricular Tachycardia Ablation



Oblique views of left ventricular endocardial maps of a patient with ischemic cardiomyopathy. The points of EGM acquisition are shown. **(A)** Voltage map showing area of scar in **red** and healthy myocardium in **purple** (thresholds <0.5 mV for dense scar, 0.5 mV to 1.5 mV for borderline zone, and >1.5 mV for healthy tissue). **(B)** Late potential map: LAT map during sinus rhythm, showing in **purple** the area of late activation after QRS offset, and the rest of the ventricle in **red**. **(C)** Activation map of VT1: LAT map during VT showing the endocardial breakthrough of VT1 in the anterolateral basal region close to the mitral ring, where EGMs preceding the QRS onset were identified (exit site) as shown in EGM recordings. **(D)** Activation map of VT2: Inferior and lateral view: Entire VT cycle length and the diastolic path located in the inferobasal region of the LV close to the mitral valve where low voltage prolonged fractionated mid-diastolic signals were identified during VT as shown in EGM recordings. **(E)** DEEP map: LAT map showing the 2 areas with DEEP potentials collocating with the exit sites of both VT1 and VT2. ICM = ischemic cardiomyopathy; other abbreviations as in Figures 1 and 2.

If the tachycardia was still inducible, further RF was performed at the discretion of the operator. Details on the RF strategies used, procedural end-points, and follow-up after ablation can be found in the Online Appendix.

STATISTICAL ANALYSIS. Statistical analysis of data was performed with the aid of a biostatistician (C.L.) using STATA (StataCorp, 2013, Stata Statistical Software: Release 13, StataCorp LP, College Station, Texas). For continuous variables with normal distribution, mean ± SD or ranges are reported. For those with non-normal distribution, median and interquartile range (IQR) is expressed. For comparisons of continuous variables, a Student *t* test was used if data were normally distributed and a sign-rank test was used for non-normally distributed variables. Categorical data was compared with the Fisher exact test or chi-square test as needed.

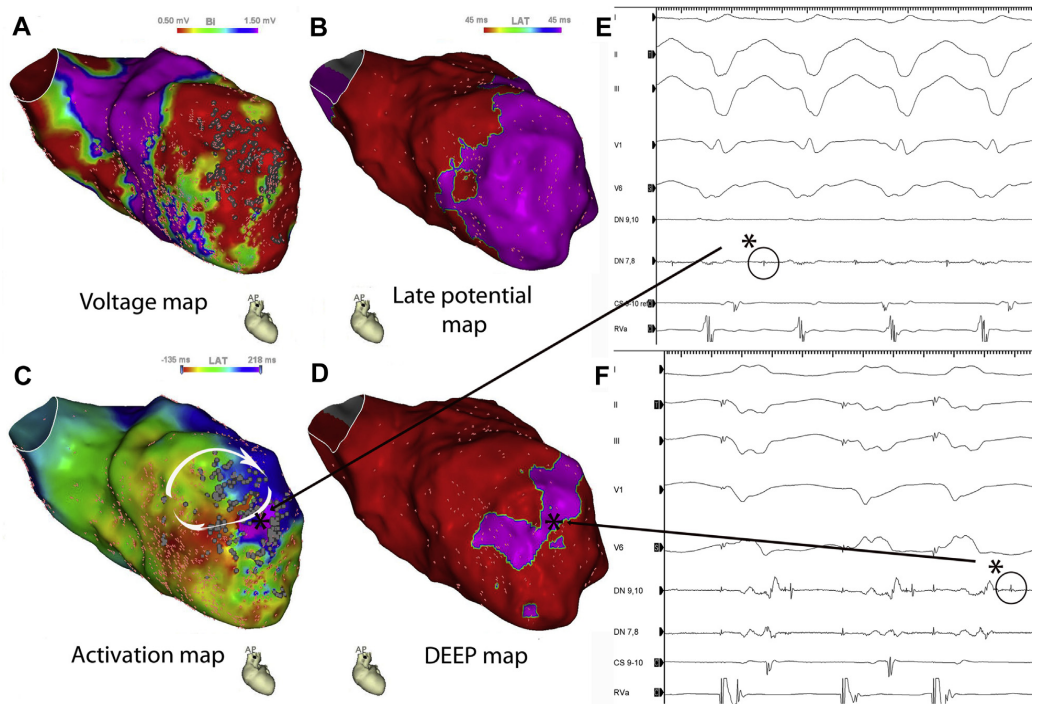
A bivariate mixed-effects regression model was used to calculate summary statistics for sensitivity and specificity, as well as to construct a hierarchical summary receiver operator curve (ROC) of DEEP and LP for the diagnosis of the isthmus of VT.

RESULTS

PATIENT CHARACTERISTICS. Twenty patients were prospectively enrolled. Their baseline characteristics are summarized in Table 1. The location of scar (bipolar voltage <1.5 mV) was inferior in 12 patients, anterior in 9 patients, lateral in 3 patients, and septal in 1 patient. Procedural details are available in the Online Appendix.

LP AND DEEP MAPS. Points with LPs accounted for a median area of 16.8% (IQR: 8.9% to 73.7%) of the myocardium mapped. The median area with DEEP

FIGURE 4 Example 3 of Decrement-Evoked Potential Mapping to Guide Ventricular Tachycardia Ablation



(A) Substrate map of the LV endocardium of a patient with a previous anteroseptal myocardial infarction (voltage threshold of <0.5 mV for dense scar, 0.5 mV to 1.5 mV for border zone, and >1.5 mV for healthy tissue). **(B)** Area with late activation during RV pacing where late potentials are identified after QRS offset. **(C)** High-density LAT map during VT delineating the re-entrant circuit. **(D)** DEEP potentials maps, identifying a much more circumscribed area of the LV during S1/S2 pacing thus providing a more accurate delineation of the VT circuit than LP. **(E)** Presystolic EGM **(*)** during VT in the area of successful termination during RF. **(F)** S1/S2 maneuver to identify a DEEP-EGM **(*)** that accurately colocalizes with the area of the isthmus of VT identified on the LAT map. RF = radiofrequency; other abbreviations as in Figures 1 and 2.

points was 4.8% (IQR: 2.2% to 25.7%) of the myocardium mapped ($p < 0.001$ compared to LP area). Examples of maps are shown in Figures 2 to 4.

ABLATION ENDPOINTS. All patients had VT inducible at the beginning of the procedure; the majority (n = 16, 80%) became noninducible after DEEP-focused RF. Further RF on those patients who were still inducible did not achieve noninducibility in any of them. The RF time was 30.6 ± 21.4 min.

VT BURDEN BEFORE AND AFTER DEEP-GUIDED ABLATION. The median (IQR) number of VT episodes 6 months pre-procedure was 11 (IQR: 5 to 25) and the median number of shocks was 1.5 (IQR: 0 to 4.5); this decreased to 0 (IQR: 0 to 2) for VT episodes and to 0 (IQR: 0 to 0) shocks 6 months post-procedure ($p = 0.02$ and $p = 0.03$, respectively). Fifteen of 20 patients (75%) were free of any VT after DEEP-RF at 6 month of follow-up (Online Figure).

RELATIONSHIP BETWEEN LPs AND DEEPs AND DIASTOLIC SIGNALS IN VT. The diagnostic performance of DEEP and LPs was analyzed in only those VTs mapped where a detailed LAT map was created (13 VTs in 9 patients) with a median number of activation points of 485.5 (IQR: 352 to 890 points). Areas with DEEPs performed better than LPs at colocalizing within the region of the diastole of VT with a sensitivity of 0.61 (95% confidence interval [CI]: 0.52 to 0.69) and a specificity of 0.97 (95% CI: 0.95 to 0.98) with an ROC area under the curve of 0.86 (95% CI: 0.82 to 0.88) compared to LPs sensitivity of

TABLE 1 Baseline Characteristics (N = 20)

Age (yrs)	64.55 ± 17.1
LVEF (%)	33.4 ± 11.4
Male	19 (95)
ICM	20 (100)
NYHA functional class I to II	18 (90.0)
NYHA functional class III to IV	2 (10.0)
Hypertension	6 (30.0)
Stroke	1 (5.0)
Diabetes mellitus	8 (40.0)
Chronic renal disease	11 (55.0)
Amiodarone as single AAD	7 (35.0)
2 or more AAD	8 (40.0)
VT storm	6 (30.0)

Values are mean ± SD or n (%).

AAD = antiarrhythmic drug; DEEP = decrement-evoked potential; ICM = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RF = radiofrequency; VT = ventricular tachycardia.

0.60 (95% CI: 0.44 to 0.74) and a specificity of 0.82 (95% CI: 0.73 to 0.89) with an ROC area under the curve of 0.79 (95% CI: 0.75 to 0.82) (Online Figure).

DISCUSSION

The primary findings from this multicenter prospective observational study of ischemic VT ablation are: 1) identification of critical myocardial regions for VT maintenance with decremental conduction properties (DEEP mapping) by extra stimulus is feasible using contemporary 3D mapping systems; 2) targeting the DEEP regions, which is a physiological assessment of the substrate, deems VT noninducible in the majority of cases; 3) areas of DEEPs are localized more frequently in the diastolic pathway of the VT than LPs; and finally, 4) mid-term outcomes of this limited focused mechanistic ablation strategy using extra stimulus are in keeping with the current ablation outcomes described in the published data.

The insight that decrement precedes unidirectional block is observable in atrial tissue sections in studies undertaken by Lammers et al. (6). This has also been shown later in modeling studies as well as in experimental models and in humans (7–9). We have shown previously the sequence of decrement preceding unidirectional block leading to re-entry in patients with VT, and the unique clinical finding of improved sensitivity, specificity, and accuracy of DEEP over LP mapping for identifying the initiating regions and diastolic pathway of VT using a tightly coupled S2 (VERP + 20 ms) (3). The results described in this paper prove clinical feasibility and act as a validation of the findings from the derivation cohort. With the inherent limitations of a catheter-based sequential mapping approach available currently, we have been able to identify regions with decremental conduction (DEEP) properties, and we found that they frequently colocalize to the areas that initiate and maintain VT, providing a functional and mechanistic target for ablation.

Conventional substrate mapping currently involves high-density mapping during sinus rhythm or during ventricular pacing to identify and target areas with fractionated EGMs, double potentials, LPs, or all abnormal EGMs in the case of substrate homogenization. Identification of those targets is subject to interobserver variability and will not always identify circuits that are involved in VT initiation or maintenance and can be linked to ablating a very large area of myocardium. Additionally, ablating abnormal tissue that is not actively participating in VT perpetuation could potentially create new areas of block/decrement that may predispose to new VT circuits.

Our work builds on our previous study in identifying which of the abnormal EGMs are involved in initiation and maintaining VT and provides a mechanistic ablation strategy for substrate modification. This is an alternative strategy to targeting all abnormal potentials. Even when LPs are easily identifiable beyond the end of the QRS, they could represent fixed delayed conduction through bundles of viable myocardium inside the scar (10). In contrast with those fixed-delayed LPs, DEEPs display decremental conduction properties, allowing the time for blocked regions to recover excitability and potentially initiate re-entry. It has also been shown that regions with the latest activation during sinus rhythm are infrequently linked to successful ablation sites, whereas the slowly conducting regions that actually propagate into the latest zone of activation are more likely to correlate with the critical isthmus of a VT (11). Additionally, with recent high-resolution mapping tools, there is growing evidence about the importance of functional block in the critical areas that sustain re-entry (12).

Current substrate modification procedures targeting an extensive substrate with scar homogenization are associated with long procedural times with broad ablation targets in some series and outcomes after VT ablation are influenced by procedural length (13). In our current study, although the methodology is to use a focused ablation strategy, for purposes of proving the concept it was important to identify the critical isthmus in VT with activation mapping, pacing maneuvers, and often multiple VT inductions and

that leads to procedural times that are similar to other contemporary series (2). Furthermore, annotation of the DEEP points is not automated at present and must be performed manually. For these reasons, this study was unlikely to show shorter procedure times than contemporary substrate-based ablation studies. We postulate that automation of DEEP mapping could lead to a decrease in procedure times. When implemented, the combination of the focused DEEP mapping, automated annotation, and limited ablation would make VT ablation procedures less cumbersome and therefore accessible to more patients; this is our goal for future development of DEEP.

There are numerous VT substrate-based strategies with individual merit that include RF transection of the scar (14) or scar "dechanneling" with (15) or without the use of RV pacing and extra stimuli to identify the origin of channels of slow conduction near the low voltage areas (16). These methodologies are weighted towards the anatomic/structural channels and are essentially challenged by the physiological/functional block and channels that are claimed to be significant by Josephson (17) and others (18). Although some reports have suggested the lack of incremental value of mechanistic strategy compared to substrate homogenization (19), the fundamental problem of identifying whether the myocardium being ablated is part of initiation and maintenance of the VT circuit and ablating such regions of myocardium is the focus of this paper.

Recurrence rates after a DEEP-guided ablation were similar to what has been seen in the literature with a similar reduction in the VT burden and the follow-up time for our study was limited to 6 months to focus on the feasibility aspect of the mapping technique. Additionally it has been recently described that VT recurrences occurring after 6 months from the procedure have limited impact on outcomes (20).

STUDY LIMITATIONS. This is a nonrandomized cohort of 20 patients. A randomized study with a comparator control is needed to further confirm its clinical value. The validity of this strategy in VT ablation in nonischemic or patchy scar patterns must also be established as the use of DEEP in this population remains to be proven. Identification of DEEP points was performed with RV apical pacing. Whether our findings would be reproducible and/or perform better with pacing from other regions of the myocardium is currently under investigation. Previous work from Baldinger et al. (21) has shown that RV pacing could also preclude the identification of a significant proportion of LPs by creating a wider QRS; for that reason our work has not restricted the identification of LPs to sinus rhythm or RV pacing, but has used both strategies to increase the sensitivity of mapping. In rare instances during DEEP mapping, VT was induced with S1/S2, usually requiring us to use a longer coupling interval for S2 to characterize LPs as DEEP. In patients with incessant VT and/or extremely easy inducibility of VT DEEP, mapping could become cumbersome and is not feasible. We also acknowledge the limitations of not creating an ultra high-density map and performing entrainment maneuvers systematically to define the re-entry circuits which has been reported to define smaller or larger sizes of the isthmus respectively (22) and we limited our analysis to proximity between LPs and DEEPs to the shortest path of diastolic EGMs during VT. Furthermore, whether the calculations of the diagnostic performance of DEEPs were influenced by VT stability and circuit characteristics is unknown, but our initial study by Jackson et al. (3) showed that when the whole VT circuit is mapped with a nonsequential mapping system, DEEPs perform better at identifying the isthmus of VT than nondecremental LPs.

CONCLUSIONS

In this prospective multicenter study, we have evaluated the feasibility of a mechanistic physiological approach to identify functional substrate modification for VT therapy by targeting limited regions of the diseased myocardium that are involved in the initiation and maintenance of VT. DEEP mapping with an extra stimulus can be implemented using contemporary 3D mapping systems with a meaningful reduction in VT burden. Initial results of catheter ablation guided solely by this technique are encouraging, with the majority of patients rendered noninducible for clinical VT. Automation of the DEEP technique will allow for rapid identification of DEEP potentials enabling further validation of such a strategy in a randomized study.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Patients with unstable, nonmappable VT may have an extensive substrate in which only a small proportion participates in VT. It is by no means mechanistic to eliminate or practically strategize to eliminate all of the substrate by RF ablation. A mechanistic-focused strategy such as DEEP mapping can provide a physiologically relevant ablation target and yield the same results as extensive and tedious substrate modification.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Electrophysiologists performing VT ablation could adopt this DEEP technique in cases where VT is noninducible or nonmappable due to hemodynamic instability. The diagnostic performance of areas of the substrate with DEEP properties provides higher specificity than late potentials and similar sensitivity for detection of critical isthmuses of VT as shown in our multicenter study.

TRANSLATIONAL OUTLOOK: This multicenter prospective experience is a validation of our previous mechanistic work that showed the concept that decrement in the region of the diastolic circuit and critical isthmus precedes unidirectional block, and that unidirectional block precedes VT using global endocardial mapping in patients. This current study translates those mechanistic findings and proves their applicability with the currently available electro-anatomic mapping technologies in the electrophysiology laboratory for the benefit of patients undergoing VT ablation.

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KEY WORDS catheter ablation, mapping, myocardial infarction, nonischemic cardiomyopathy, substrate ablation, ventricular tachycardia

APPENDIX For supplemental text and a figure, please see the online version of this paper.

d. Part IV: Overcoming the directional dependency of bipolar electrograms with omnipolar methodology in a translational model of ventricular arrhythmia substrate.

ESC European Society of Cardiology

Europace (2019) **0**, 1–9
doi:10.1093/europace/euy304

BASIC SCIENCE

Omnipolarity applied to equi-spaced electrode array for ventricular tachycardia substrate mapping

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Received 28 August 2018; editorial decision 26 November 2018; accepted 4 December 2018

Aims Bipolar electrogram (Bi_{EGM})-based substrate maps are heavily influenced by direction of a wavefront to the mapping bipole. In this study, we evaluate high-resolution, orientation-independent peak-to-peak voltage (Vpp) maps obtained with an equi-spaced electrode array and omnipolar EGMs (OT_{EGMs}), measure its beat-to-beat consistency, and assess its ability to delineate diseased areas within the myocardium compared against traditional Bi_{EGMs} on two orientations: along (AL) and across (AC) array splines.

Methods and results The endocardium of the left ventricle of 10 pigs (three healthy and seven infarcted) were each mapped using an Advisor™ HD grid with a research EnSite Precision™ system. Cardiac magnetic resonance images with late gadolinium enhancement were registered with electroanatomical maps and were used for gross scar delineation. Over healthy areas, OT_{EGM} Vpp values are larger than AL bipoles by 27% and AC bipoles by 26%, and over infarcted areas OT_{EGM} Vpp values are 23% larger than AL bipoles and 27% larger than AC bipoles ($P < 0.05$). Omnipolar EGM voltage maps were 37% denser than Bi_{EGM} maps. In addition, OT_{EGM} Vpp values are more consistent than bipolar Vpps showing less beat-by-beat variation than Bi_{EGM} by 39% and 47% over both infarcted and healthy areas, respectively ($P < 0.01$). Omnipolar EGM better delineate infarcted areas than traditional Bi_{EGMs} from both orientations.

Conclusion An equi-spaced electrode grid when combined with omnipolar methodology yielded the largest detectable bipolar-like voltage and is void of directional influences, providing reliable voltage assessment within infarcted and non-infarcted regions of the heart.

Keywords Electroanatomic mapping • Omnipolar • Bipolar • Unipolar • Voltage • Electrogram • Myocardial infarction • Porcine

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What's new?

- Bipolar EGMs (Bi_{EGM}) are significantly influenced by direction of the propagating wavefront to recording bipolar axis, especially in diseased myocardium.
- The new methodology of Omnipolar EGMs (OT_{EGMs}) when coupled to a fixed equi-spaced array provides for voltage measurements that are physiological and have been validated *ex vivo* previously. Omnipolar voltage assessment can be visualized in real time and is void of directional influences and in this manuscript has been validated *in vivo* in diseased myocardium.
- Here, we demonstrate that *in vivo* substrate mapping of a swine model of myocardial infarction with OT_{EGMs} provides higher peak to peak voltages than Bi_{EGMs} and more consistent measurements with less beat-to-beat variability.
- Those findings may indicate their ability to detect surviving bundles of myocardial tissue and may be an important tool for VT substrate assessment.

Introduction

The directional dependency of bipolar electrograms (Bi_{EGMs}) and voltage assessment for detection of non-healthy myocardium have been recently highlighted in multiple publications.[1–4] An orientation agnostic voltage assessment would allow for a consistent physiological description of the myocardium being interrogated. Recently, Deno *et al.*[5] introduced the concept of omnipoles which are bipolar-like EGMs that are catheter-orientation independent and could potentially alleviate the limitations of traditional direction-dependent bipolar recordings. Omnipolar methodology (OT) determines the direction of a traveling wave (TW) along the myocardial plane by interrogating its electric field (E-field).[6] Another advantage of omnipoles is that it can survey all possible bipolar electrode orientations without the need for catheter rotation. Previous *ex vivo* studies by Massé *et al.*,[6] Haldar *et al.*,[7] and Magtibay *et al.*[8] in isolated animal and human hearts introduced omnipolar EGM (OT_{EGM}), an OT_{EGM} with the largest voltage peak-to-peak (Vpp), an OT_{Vmax}, value along the myocardial plane which was used to create consistent, physiologically relevant voltage maps of the myocardial substrate both in healthy and diseased conditions. However, especially in the endocardium, substrate evaluation *in vivo* with OT_{EGM} has not been undertaken.

Previously, it has been shown that within diseased areas, surviving myocardial tracts produces heterogeneous scar substrates.[9] Omnipolar EGM could provide the largest Vpp value along the maximal bipole direction independent of catheter orientation which could potentially better reflect the physiological condition of the near field myocardium.

We conducted *in vivo* studies to generate electroanatomical maps of the left ventricle (LV) of infarcted pigs using both OT_{EGMs} and Bi_{EGMs} along two orientations within a grid catheter of 16 equally spaced electrodes. The objectives of our work are as follows: (i) evaluate orientation-independent OT_{EGM}-based voltage maps compared with traditional Bi_{EGM}-based voltage maps, along two bipole orientations; (ii) assess mapping densities of OT_{EGM}-based voltage maps; (iii) measure beat-to-beat consistency of Vpp values from both Bi_{EGM} and OT_{EGM}; and finally, (iv) assess OT's capability to delineate infarcted areas within the myocardium. Thus, we hypothesize that an equi-spaced electrode array coupled with OT could provide higher resolution, physiologically relevant, and consistent voltage maps of the endocardium.

Methods

Swine infarct model

Animal procedures were approved by the Animal Care Committee at Sunnybrook Health Sciences Centre and at University Health Network, both in Toronto, Ontario, Canada. Details are provided in the Supplementary material online, *File*.

Cardiac magnetic resonance imaging

Approximately 3 weeks following myocardial infarction (MI), each pig underwent cardiac magnetic resonance imaging with late gadolinium enhancement (LGE). Details of the imaging protocol used in this study were described by Ghugre *et al.*[10] elsewhere and are detailed in the Supplementary material online, *File*.

Electroanatomic mapping procedure

Endocardial mapping was performed 4 weeks after MI using an Advisor™ HD grid (*Figure 1A*) and a research version of EnSite Precision™ mapping system (Abbott Laboratories, St Paul, MN, USA). A quadripolar catheter was advanced in to the right ventricular apex and another within the inferior vena cava for electrical unipolar reference. Surface electrocardiograms (ECGs) were used for timing reference. Initially a 3D volume was created with the Advisor™ HD grid of both the aortic root and the LV endocardium with care in reconstructing the entire LV surface. Local activation time (LAT) maps were also created during sinus rhythm and during right ventricular pacing with annotation based on absolute $+dV/dt$ (Supplementary material online). Post-procedure, MRI-segmented surfaces, as described above, were registered with the electroanatomical 3D surface using anatomical landmarks that included the LV apex, the aortic root and the mitral ring, which was available for two pigs. Macrohistology was available for two post-MI hearts. After inclusion in formaldehyde, 5 mm cuts were used to grossly correlate the areas of MI and fibrosis with our electroanatomical maps and MRI findings (Supplementary material online). No precise electroanatomical comparison measures of healthy vs. infarcted tissue was done with histology due to the change in size of the cardiac surfaces after formaldehyde inclusion (*Figure 2*).

Bipolar voltage mapping with Advisor™ HD grid

Bipolar electrograms were filtered at 30–300 Hz and were measured from two orientations within the Advisor™ HD grid: along- (AL) and across (AC) splines as shown in *Figure 1A*. Bipolar electrogram Vpp values were plotted at the centre of a hypothetical line segment between adjacent electrodes of each bipolar orientation. For each mapped area, there were a total of 24 Bi_{EGM} Vpp values, 12 from each orientation. Voltage cut-off used to define low voltage was <1.5 mV. These values were minimally interpolated to create continuously coloured voltage maps of the LV using a triangular-mesh-based interpolation method available within the EnSite Precision™ mapping system.

Omnipolar voltage mapping with Advisor™ HD grid

Technical details of OT have been previously described by Deno *et al.*[5] The method for derivation of OT_{EGMs} used for voltage mapping has also

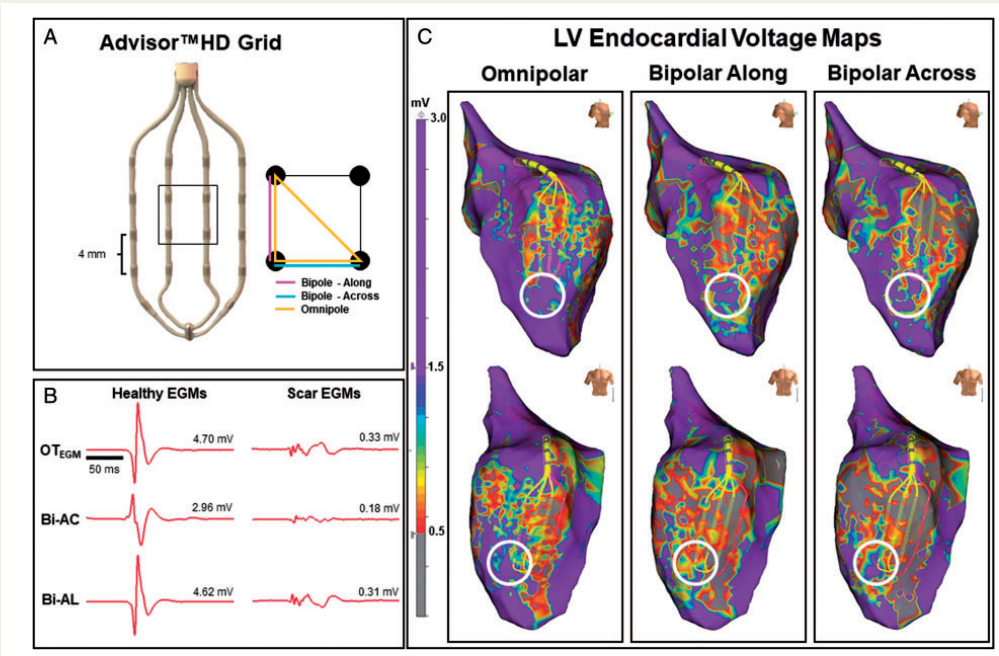

Figure 1 Voltage mapping with Advisor™ HD grid. (*A*) The specifications of an Advisor™ HD grid as well as the configuration of the bipoles and omnipoles are shown. Each electrode along and across the splines of the catheter are 4 mm apart, unrestricted. Bipoles were calculated AL and AC the splines while omnipoles (OT_{Vmax}) were derived from a right triangle clique. Within a square area, we can derive four OT_{Vmax} values and two bipolar AL and two bipolar AC values. Constituent bipoles and omnipoles were matched later for analysis. (*B*) Sample EGMs calculated using OT and its paired bipolar electrode splines over healthy and scarred areas are shown. Sensitivity of bipoles to electrode orientation is clearly shown between the two bipoles calculated within an area. OT_{EGMs} exhibits an EGM with the largest Vpp which is similar—but larger—to the largest measurable traditional bipole. This is true for both healthy and scarred areas. (*C*) The comparison of resultant voltage maps from OT_{Vmax}, bipolar AL, and bipolar AC is shown. Electrode orientation dependence of bipoles is exacerbated when translated in to maps providing different low-voltage zone map profiles. Omnipolar maps, on the other hand, provides voltage maps with larger voltages as well as better defined boundaries. White circles highlight the specific differences in the voltage maps between bipolar AL and AC and OT_{Vmax}. AC, across; AL, along; EGM, electrograms; LV, left ventricle; OT, omnipolar methodology; OT_{EGMs}, omnipolar electrograms; Vpp, voltage peak-to-peak.

been previously described by Haldar *et al.*[7] and Magtibay *et al.*[8] In brief, OT is derived from the E-field of a uniform TW that is sensed by at least three closely spaced unipolar electrodes (cliques) lying along the plane of the myocardium. In this work, we used in real-time right triangle cliques within the Advisor™ HD grid which allowed for relatively higher resolution mapping as an alternative to the originally proposed square cliques[5] (36 vs. 9 mapping points). Omnipolar EGMs were filtered at 30–300 Hz. As with previous works, Vpp of OT_{EGMs} (OT_{Vmax}) were mapped at the centre of each triangle clique and projected on to previously made LV endocardial geometry to create voltage maps. Similar to bipolar voltage mapping, standard voltage cut-offs used to define low voltages was <1.5 mV. OT_{Vmax} values were interpolated using triangular-mesh-based interpolation method available within the EnSite™ Precision™ mapping system.

Quantitative analysis

For each pig, voltage data were collected over both healthy and infarcted areas identified using MR-LGE images as described above. Time segments during sinus rhythm were qualified for analysis only when the HD grid™ is close to the surface of the LV endocardial shell (<4 mm), when EGMs are time stable for at least 10 beats, and when the Advisor™ HD grid splines are unrestricted so that the interelectrode distances AL and AC the catheter splines are similar and consistent between the two bipolar orientations. Furthermore, OT_{EGM} and OT_{Vmax} values from each clique were paired with their constituent Bi_{EGM} and Bi_{EGM} Vpp values from both AL and AC orientations.

Voltage mapping with bipolar electrograms vs. omnipolar electrograms

First, to illustrate the dependence of Bi_{EGM} Vpp values on electrode orientation, we quantified the mean absolute difference of Vpp values between Bi_{EGM} Vpps from AL and AC orientations. Second, we calculated how much the mean absolute difference OT_{Vmax} values are larger than measured traditional Bi_{EGM} Vpp values to demonstrate its orientation independence and its potential for more accurate physiological

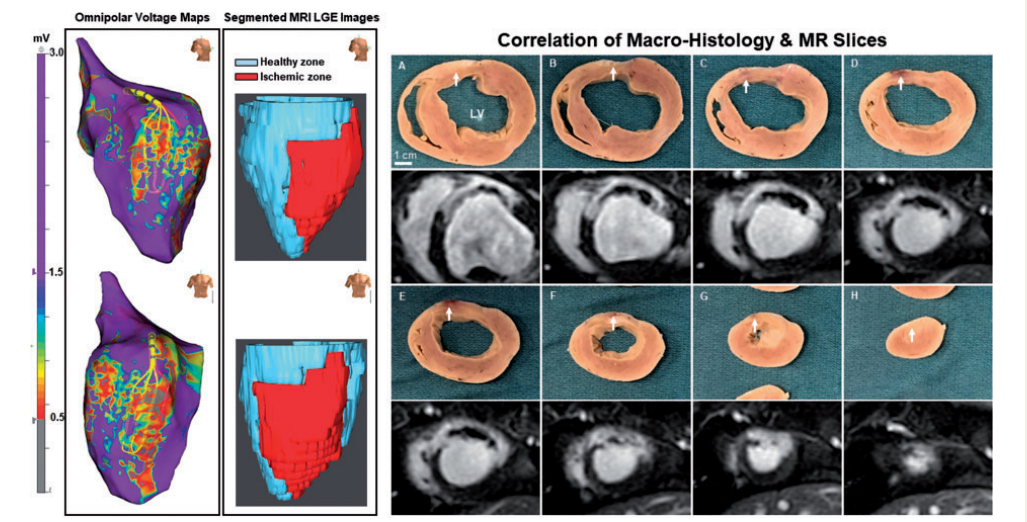

Figure 2 Omnipolar voltage map comparison to LGE-MR images. This figure shows the comparison of the detected low-voltage areas in an omnipolar voltage map compared with the segmented shells of MR images with LGE taken from a sample infarcted porcine heart. LGE shows the general areas of no-reflow and intramyocardial haemorrhage frequently seen in 3–4-week-old myocardial infarction following a patchy pattern. For reference, we show the general location of the infarcted zones within an LV with respect to the location of the low-voltage areas in an omnipolar substrate map using segmented portions of the MR-LGE images coloured in red. We verify the location of the infarcted zones by comparing the macro-histological slices of the whole heart. White arrows point to the infarcted zones as shown from *A* (base) to *H* (apex), respectively. LGE, late gadolinium enhancement; LV, left ventricle; MR, magnetic resonance.

measurement. Third, we measured how similar and how much larger the mean absolute difference of OT_{Vmax} values were compared with the largest measurable Bi_{EGM} Vpp from either AL or AC orientations (Max-Bi). Furthermore, for a single beat, we calculated for the correlation of OT_{Vmax} and Max-Bi values and the morphologies of their corresponding EGMs, OT_{EGM} vs. Max-Bi_{EGM}, for all pigs.

Voltage mapping density: omnipolar vs. bipolar voltage maps

We defined mapping density as the number of points per square centimetre (pts/cm^2). In order to quantify the mapping density of both omnipolar and bipolar voltage maps, random areas within the LV endocardial shell were chosen and were enclosed with an arbitrary surface polygon with areas readily calculated by the EnSite Precision™ system. Within these areas, the number of OT_{Vmax} values and Bi_{EGM} Vpp values projected on to the shell were counted. It is important to note that there was no repetition of points within a 3 mm radius of each point. We then divided the counted points with the area of the arbitrary surface polygon to obtain mapping density values for each mapping method.

Beat-by-beat consistency between omnipoles and bipoles

We calculated beat-by-beat variations between OT_{Vmax} and Bi_{EGM} Vpp values by measuring their coefficient of variation (CoV) over 10 beats, while the catheter array was in a stable position. CoV values that approach one and above are not consistent throughout beats, while CoV values that approach values near 0 have better consistency throughout beats.

Comparison of low-voltage areas from electroanatomical maps and infarcted areas from magnetic resonance late gadolinium enhancement images

After registration, previously calculated surface areas of the infarcted regions of the endocardial LV based off MR-LGE images were compared with the low-voltage areas (<1.5 mV) of voltage maps generated from both bipolar orientations, AL and AC, and OT_{Vmax} for two pigs. We referred to the MR-LGE images as reference and surface areas were calculated as described above. The surface area of low-voltage areas from all three substrate map types were readily obtained from EnSite Precision™ mapping system.

Results

Bipolar maps are qualitatively but not quantitatively sensitive to electrode orientation

Bipolar voltage maps created from AL and AC bipolar orientations differ visually from each other for all pigs from both healthy and

Table 1 Summary of quantitative analysis of voltage mapping data

	Healthy	Infarcted
A. Vpp of bipoles		
AL (mV), avg ± std err	4.87 ± 0.95	0.53 ± 0.09
AC (mV), avg ± std err	4.94 ± 0.95	0.51 ± 0.09
Δ |AL − AC| (mV), p (HME)	0.07 ± 0.23, NS	0.02 ± 0.06, NS
B. Vpp of omnipoles		
OT_{Vmax} (mV), avg ± std err	6.64 ± 0.95	0.69 ± 0.09
Δ |OT_{Vmax} − AL| (mV), p (HME)	1.77 ± 0.23, S	0.17 ± 0.06, S
Δ |OT_{Vmax} − AC| (mV), p (HME)	1.70 ± 0.23, S	0.19 ± 0.06, S
C. OT_{Vmax} vs. maximal (AL or AC) bipole Vpp		
Correlation − r (avg)	0.99	0.99
Max-Bi (mV), avg ± std err	5.99 ± 0.95	0.64 ± 0.08
Δ |OT_{Vmax} − Max-Bi| (mV), p	0.65 ± 0.23, S	0.06 ± 0.06, NS
D. Beat-by-beat variation (CoV)		
Bipole, avg ± std	0.32 ± 0.16	0.31 ± 0.13
OT_{max}, avg ± std	0.17 ± 0.12	0.19 ± 0.11
P-value (paired *t*-test)	$P < 0.01$	$P < 0.01$

Section A shows the average and standard error of both bipolar types, AL and AC and their absolute difference, within the Advisor™ HD Grid in both healthy and infarcted areas of the left ventricle. Although, there is no quantitative difference between the bipolar voltage values from two different orientations their corresponding maps shown in *Figure 1C* that orientation is a determining factor for voltage map profiles. *Section B* shows the average and standard error of OT_{Vmax} and its difference to both bipolar voltage from AL and AC orientations in both healthy and infarcted areas. OT_{Vmax} provides larger voltage values compared with any bipolar voltage values from any orientations as shown in their absolute differences. *Section C* illustrates that even obtaining the bipolar voltage with the largest value from any orientation, OT_{Vmax} still provides larger values than any bipolar values as shown by the absolute difference of their average and standard error. *Section D* shows that OT_{Vmax} values have greater temporal consistency compared with traditional bipolar values as shown by their contrasting CoV. We used a HME with Random Intercept (RI) model test for Sections A–C to determine statistical significance of the absolute differences of voltage values. **S** indicates that there is a statistically significant difference between voltage values while **NS** indicates that there is not. For Section D, we used a standard paired *t*-test to assess the statistical difference between the CoV values of bipolar and omnipolar values with a 95% confidence interval. Comparisons with *P*-values that were below 0.05 ($P \leq 0.05$) have significant differences.
AC, across; AL, along; CoV, coefficient of variation; HME, hierarchical mixed effect; OT_{Vmax}, omnipolar voltage values; std err, standard error; Vpp, voltage peak-to-peak.

infarcted areas. Absolute Vpp difference between bipolar AL (4.88 ± 0.95 mV) and bipolar AC (4.94 ± 0.95 mV) was calculated as (0.07 ± 0.23 mV) over healthy areas. Absolute Vpp difference between bipolar AL (0.53 ± 0.09 mV) and bipolar AC (0.52 ± 0.09 mV) was calculated as (0.02 ± 0.06 mV) over infarcted areas. Although the numerical differences between bipolar AL and AC Vpps for both comparisons were statistically non-significant, *Figure 1B* and *C* illustrates sample bipolar AL and AC EGMs over healthy and scar area as well as the visual differences between voltage maps created with bipolar AL and AC configuration, i.e. maps obtained with different bipolar configurations with identical electrode spacing will look different from each other despite mapping the exact same substrate. *Table 1* (Section A) shows a summary of the numerical findings.

OT_{Vmax} provide higher voltage peak-to-peak values than traditional bipoles

OT_{Vmax} substrate maps have larger Vpp values than the substrate maps individually derived from AL and AC bipolar orientations over both healthy and infarcted areas for all pigs. Over healthy areas, OT_{Vmax} Vpp values are larger than AL bipoles by 27% (6.64 ± 0.95 mV vs. 4.87 ± 0.95 mV) and AC bipoles by 26% (6.64 ± 0.95 mV vs. 4.94 ± 0.95 mV). Over infarcted areas, OT_{Vmax} Vpp values are also larger than AL bipoles by 23% (0.69 ± 0.08 mV vs. 0.53 ± 0.08 mV) and AC bipoles by 27% (0.69 ± 0.08 mV vs. 0.51 ± 0.08 mV). Numerical differences between bipolar AL and AC Vpps and OT_{Vmax} were determined to be statistically significant within a 95% confidence interval which shows that OT_{Vmax} values do provide higher Vpp values than traditional bipoles. Sample EGMs for both OT and bipoles are shown in *Figure 1B* and their corresponding voltage maps in *Figure 1C*. A summary of the numerical results are shown in *Table 1* (Section B).

OT_{Vmax} values are larger and correlated to Max-Bi

OT_{Vmax} Vpp values are highly correlated with Max-Bi obtained from either AL or AC configurations, for all pigs. Correlations between OT_{Vmax} Vpp values and Max-Bi Vpp values were calculated as 0.99 over both healthy and infarcted areas as shown in *Table 1* (Section C). Importantly, OT_{Vmax} Vpp values are still larger than Max-Bi Vpp values over healthy areas by 10% (6.64 ± 0.95 mV vs. 5.99 ± 0.95 mV) and over infarcted areas by 8% (0.69 ± 0.08 mV vs. 0.64 ± 0.08 mV). Scatter plots for both myocardial conditions as shown in *Figure 3* illustrates this relationship.

Omnipoles provide better beat-to-beat voltage consistency than traditional bipoles

During sinus rhythm for an average of 10 beats from all pigs, mean CoV values of omnipoles are lower than those of bipoles by 47% in healthy areas (0.17 ± 0.12 vs. 0.32 ± 0.16, $P < 0.01$) and by 39% in infarcted areas (0.19 ± 0.10 vs. 0.31 ± 0.13, $P < 0.01$) as shown in *Figure 4* and *Table 1* (Section D). This indicates that OT_{Vmax} exhibit more consistent beat-to-beat Vpp values than traditional bipoles.

Substrate maps derived from omnipoles are denser than substrate maps from along and across bipoles

Recorded mapping segments have an average duration of 37.7 ± 9.3 min. Within each pig and for same mapping duration, OT_{Vmax} substrate maps are denser compared to traditional bipolar substrate maps. OT_{Vmax} maps are denser by 36.7% than bipolar maps (32.74 ± 5.24 points/cm^2 vs. 20.71 ± 4.72 points/cm^2) for all pigs as shown in *Figure 5*. This finding is inherent to the number of mapping points obtained in each acquisition during mapping.

Omnipolar substrate maps better delineate infarcted areas maps than bipolar substrate maps

Table 2 summarizes the comparison between the measurements of the surface area of infarction from MR-LGE images and low-voltage areas of substrate maps created from both bipolar orientations, AL and AC, and OT_{Vmax} for two pigs. We show that low-voltage areas from OT_{Vmax}-based substrate maps were closer in value with the surface area of endocardial infarction based on MR-LGE images compared with either bipolar substrate maps in both pigs. These results indicate that OT_{Vmax}-based substrate maps could better delineate infarcted areas within the endocardium compared with traditional orientation-dependent bipolar substrate maps which could overestimate the span of infarction and hence produce larger low-voltage areas. Supplementary material online, *Figure S3* illustrates the concept and the ability of OT_{Vmax} to detect surviving endocardial bundles.

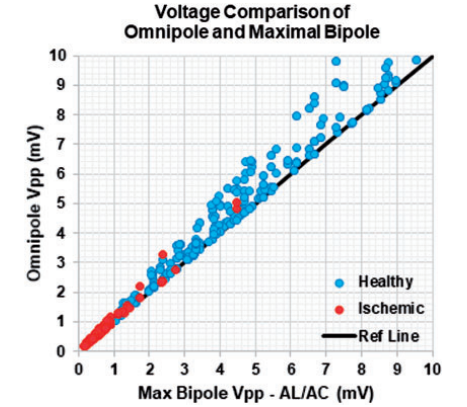

Figure 3 Relationship of OT_{Vmax} and Max-Bi. A scatter plot shows the correlation between OT_{Vmax} values and the Max-Bi values from any orientation, AL or across AC, within the Advisor™ HD Grid over both healthy and infarcted areas. As shown in *Table 1*, Section C, that OT_{Vmax} still offers an advantage (by over 10% on healthy areas and 8% on infarcted areas) over traditional bipolar voltage values even if the Max-Bi was chosen for mapping. AC, across; AL, along; Max-Bi, maximum bipolar; Vpp, voltage peak-to-peak.

Discussion

Our main findings from *in vivo* porcine studies using OT with an equispaced catheter array are as follows: (i) OT_{Vmax} has larger Vpp values compared with conventional Bi_{EGM} along any direction; (ii) beat-by-beat, OT_{EGMs} and OT_{Vmax} are more consistent than Bi_{EGMs} and Max-Bi; (iii) OT_{Vmax}-based substrate maps have higher mapping point densities, hence greater mapping resolution, than Bi_{EGM}-based substrate maps from any orientation; and lastly, (iv) OT could potentially provide better estimation of the span of endocardial infarcted areas compared to traditional bipolar mapping.

Novel omnipolar vs. traditional bipolar mapping

Bipolar-electrograms have been shown to be extremely susceptible to the angle of incidence of a wavefront with respect to recording electrodes while OT_{EGMs} have been previously shown to provide catheter/wave orientation-independent measurements. The key difference between conventional Bi_{EGMs} and OT_{EGMs} lies in the fact that OT takes advantage of the local E-field generated along the endocardial surface using equally spaced electrodes to obtain physiologically reproducible measurements. OT generates information similar to an ECG QRS vectorcardiogram only it is specific and local to areas within the myocardium.

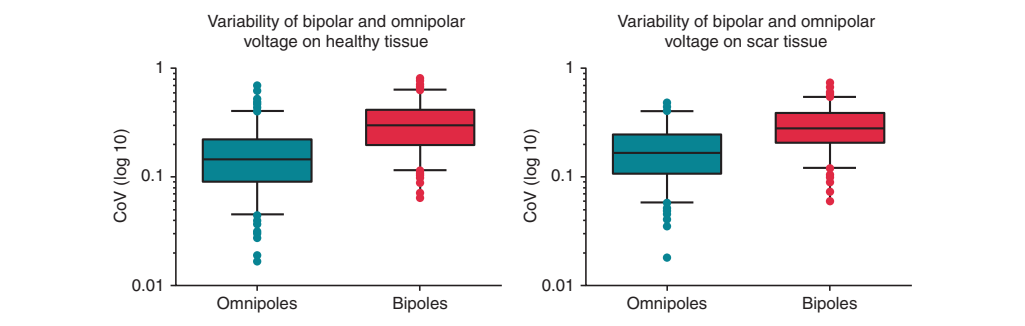

Figure 4 Beat-by-beat value of OT_{Vmax} is less variable compared with traditional bipoles. Boxplots showing comparison of the CoVs for OT_{Vmax} and traditional bipolar voltage values from any orientation for over 10 beats over healthy and infarcted areas. OT_{Vmax} offer less variable values over time compared with traditional bipoles which we have previously shown to be greatly influenced by catheter orientation. CoV, coefficient of variation.

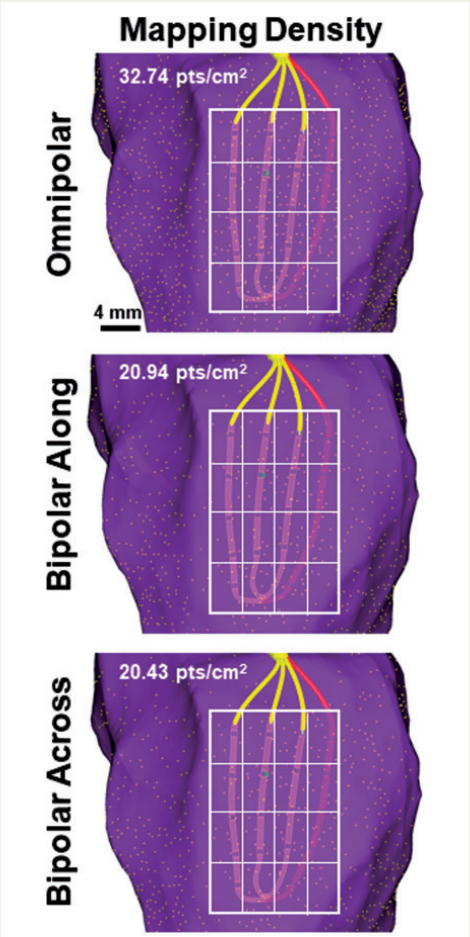

Figure 5 Omnipolar methodology provides denser voltage maps compared with traditional bipoles using the Advisor™ HD Grid. Over the same mapping areas and the same mapping time, compared to traditional bipoles, omnipoles provides greater number of mapping points availing denser voltage maps which could give extra details about the myocardium being mapped. On average, omnipolar maps provide 36% denser maps than both bipolar maps, from either direction using the Advisor™ HD Grid. Bipoles from any direction only uses a maximum of 12 mapping points while omnipoles could provide a maximum of 36 mapping points because of the clique arrangements within the catheter grid.

Specific to this work, the overall differences in Vpp between the AC and AL Bi_{EGMs} were found to be non-significant which may be counterintuitive. The reason for this is as follows. In an ideal case, where a catheter has a fixed position and senses a wavefront along a specific direction, Bi_{EGM} Vpps AL and AC will give different values, as has been shown with mathematical models by Beheshti *et al.*[11]; however, when mapping an entire heart chamber with catheter positions always changing with respect to a wavefront, the population of AL and AC Bi_{EGMs} Vpp measurements will be similar to each other yielding non-statistically significant difference.

The importance of having OT_{EGMs} and OT_{Vmax} is underscored by the following observations made on Bi_{EGM} maps derived from AL and AC. Highlighted in *Figure 1* are specific areas in which Bi_{EGM} Vpps greatly differ. Bi_{EGMs} at one orientation could erroneously indicate that certain areas of the substrate are diseased but if examined at another orientation they are not. This, coupled with the ever-changing position of catheters within a heart chamber, could produce highly inconsistent substrate maps. Therefore, interpretation of such maps and a clinician's treatment strategy could be heavily influenced by catheter orientation. Omnipolar EGMs, and its corresponding OT_{Vmax} values, could aid to improve substrate mapping by providing physiologically relevant and consistent measurements independent of catheter orientation. This is supported by the fact that on the same areas of the OT_{EGM}-based substrate maps, only the higher Vpp values are mapped, if not the highest. We validate this claim by presenting Max-Bi_{EGM}, a directly measured Bi_{EGM} with the largest Vpp, Max-Bi, from any orientation to be maximally correlated to both OT_{EGMs} and OT_{Vmax}. This type of an approach could help identify channels of conduction into the dense scar critical for sustaining VT. Furthermore, beat-to-beat consistency of OT_{Vmax} values ensure that substrate map profiles are maintained.

OT was originally introduced by Deno *et al.*[5] to utilize four-electrode cliques within the Advisor™ HD Grid to provide a total of nine measurement points at particular areas at any time. This is to establish the theoretical concept of OT with a model of a uniform TW. However, we proposed the use of three-electrode cliques to maximize the use of catheter grid arrays under the OT paradigm, providing a total of 36 measurement points. This is a still valid approach since the examination of a 3D E-field requires a minimum of three points. This allowed us to significantly increase the mapping resolution of OT used with an equi-spaced electrode array, completely mapping the endocardium in less time compared to its four-electrode clique version and its linear catheter counterparts.

Another traditional tool for substrate analysis is a LAT map which allows for global tracking of wave propagation within the heart chamber. Here, we provide additional comparison of LAT maps generated from Bi_{EGMs} and OT_{EGMs} LAT maps generated using traditional Bi_{EGMs}, when compared with LAT maps generated with OT_{EGMs} show similar profiles as shown in Supplementary material online, *Figure S2*. This is because OT_{EGMs} are bipole-like EGMs, that they provide local information only they are orientation independent. Unlike unipolar EGMs, which are also orientation-independent, OT_{EGMs} are more resilient to far-field noise which could greatly influence the creation of unipole-based LAT and substrate maps.[12–15] The ability of OT_{EGMs} to depict the 3D intramural structure of the scar remains to be proven at this time as the normal projection of the E-field to perform such task needs further testing and validation *ex vivo* first and then *in vivo* thoroughly.

Table 2 Area comparison between low-voltage areas from electroanatomical maps and MR-LGE images of infarcted areas maps

	Total endocardial scar area (cm^2)	Total low-voltage area from OT (cm^2)	Total low-voltage area from Bi-AL (cm^2)	Total low-voltage area from Bi-AC (cm^2)
Pig 1	18.8	23.0	30.2	32.9
Pig 2	7.7	12.6	17.0	16.7

The total measured area of endocardial scars from segmented MR images are closer in value with the measured low-voltage area from orientation independent, OT-based voltage maps compared with those from any of the two orientations of bipolar-based voltage maps for both sample pigs.
AC, across; AL, along; LGE, late gadolinium enhancement; MR, magnetic resonance; OT, omnipolar methodology.

Multi-electrode vs. linear mapping catheters

A wide variety of linear mapping catheters are currently used in cardiac mapping practice with different electrode and shaft configurations, electrode spacing, and electrode size. It has been shown in a number of studies[11,16–18] that bipolar electrode spacing and electrode size could greatly influence substrate mapping profiles, hence the interpretation of the substrate and corresponding appropriate treatment strategies.[19] The authors attempted to minimize this effect by representing conventional linear mapping catheters with a spline within the Advisor™ HD Grid array. This ensures that the Bi_{EGM} and OT_{EGM} measurement comparisons are fair such that electrode size and electrode spacing are consistent across all studies.

Electrode spacing and detection of low voltage

Within the Advisor™ HD Grid array there are four orientations along which Bi_{EGMs} can be derived: AL, AC, and two opposite diagonals in-between splines. In our study, we limited our analysis only between OT_{EGMs} and AL and AC Bi_{EGMs} and their corresponding Vpp values to maintain a consistent electrode spacing (4 mm, centre-to-centre). We have not used the 'HD wave' software for any of our analysis. We did not include the Bi_{EGMs} from the two opposite diagonals in-between splines since their interelectrode spacing is different. It is important to note that OT measurements are based on E-fields, which are in the units of mV/mm and are scaled by average interelectrode distances among the bipolar electrode pairs within a clique as previously introduced by Haldar *et al.*[7] and Magtibay *et al.*[8]

Re-examination of the Bi_{EGM} Vpp threshold for determining diseased areas within the ventricular myocardium as many new types of catheters (multielectrode or linear, large or small electrodes) are created is of importance. The case of Advisor™ HD Grid array with the OT methodology is no different. Magtibay *et al.*[8,20] attempted to adopt a new voltage threshold specifically for OT_{Vmax} values derived from a 56-channel (2-mm interelectrode spacing) grid array used in *ex vivo* fixed epicardial mapping of isolated porcine hearts. They came up with OT_{Vmax} values ≥2.0 mV for healthy tissues, between 1.5 mV and 2.0 mV for tissues at the scar border, and ≤1.5 mV for dense scar. However, the authors followed the standard <1.5 mV voltage threshold for this *in vivo* study since a voltage threshold for a 4-mm equi-spaced grid array has not been previously determined. Using this threshold value, we showed that an OT_{Vmax}-based substrate map depicts a closer representation of the endocardial span of the infarcted areas compared with the traditional Bi_{EGM}-Vpp-based substrate maps from any orientation.

Limitations

As with any multielectrode catheter, tissue-electrode contact could be an issue with the Advisor™ HD Grid array. However, in keeping with *ex vivo* findings where catheter contact was standardized the *in vivo* findings of this work still show the same results. As for the derivation of OT in this case, it is robust such that OT_{Vmax} retains its maximal value since the interelectrode distances within an OT clique is taken in to consideration when measuring E-field parameters. We did not pursue analysis of the normal projection of the E-field for 3D mapping capabilities of OT in this manuscript.

Correlations between MR-LGE images of scar and substrate maps were calculated only from two out of the seven pigs with MI mapped. Majority of the MR data collected from pigs were not sufficient for proper registration with corresponding electroanatomical maps since they lacked robust landmarks (i.e. aortic root and/or valves). Furthermore, a histological examination of the MI was not performed as a trade-off to maintain the size and shape of the heart slices so that they are comparable and easily matched with their corresponding MR-LGE image slices. Future *in vivo* studies should involve detailed histological analysis of the MI substrate to detect surviving myocardial tissues within diseased areas to compare with areas of OT_{Vmax}- and Bi_{EGM}-Vpp-based substrate maps.

Conclusions

In an *in vivo* pig infarct model, substrate mapping with OT using an equi-spaced electrode grid array produces local, orientation-independent, physiologically relevant electrograms which may improve delineation of diseased areas and aid to optimize treatment strategies for ventricular arrhythmias.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

The authors would like to thank Antonio Berruezo and Lluis Serra for the help provided by analyzing our MRI data with ADAS VT.

Funding

This work was funded by Abbott Laboratories, St. Paul, MN, USA.

Conflict of interest: D.C.D. is an employee of Abbott Laboratories. K.N. and S.M. have received consultant honoraria from Abbott Laboratories and Biosense Webster. M.L. is one of the owners of BlueRock Therapeutics. A.P.S. has received consultant honoraria from Abbott Laboratories. K.M, S.N., A.B., P.F.H.L., C.L., B.Q., R.R., H.M., L.B., and N.G., have no disclosures.

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Discussion:

a. General aspects:

This work has provides novel findings in several aspects of the management of patients with ventricular arrhythmia. With a truly translational perspective it was possible to answer important clinical questions regarding: 1) The clinical outcome of patients suffering from VT treated with an ICD. 2) The healthcare usage and clinical outcome of matched patients suffering from recurrent VT being treated with 2 strategies: VT ablation or medical management. 3) The development of a substrate mapping strategy with a mechanistic approach. 4) The improvement of the knowledge of novel orientation independent electrograms and its use in a preclinical model of VT substrate.

The main findings of our work are the following:

1. In a population based registry, patients treated with secondary prevention ICDs showed an increased mortality rate after receiving appropriate ICD therapies (ATP or shocks).
2. Patients suffering from recurrent VT experienced a significant decrease in the VT burden following catheter ablation compared to pre-ablation. The rate of cardiovascular admissions and healthcare costs were the same among patients who were treated with catheter ablation than that observed in a cohort matched for clinical characteristics and treated medically.
3. A mechanistic substrate mapping strategy identifying decrement evoked potentials (DEEP) is highly specific for depiction of the critical isthmus of VT.
4. Orientation independent EGM (Omnipolar EGM) yield the largest detectable bipolar-like voltage *in vivo* and provides a reliable way of mapping the substrate in a swine model of VT substrate.

b. Part I: The impact of ICD therapies in a large population-based registry that includes secondary prevention patients.

Experiencing an ICD shock is one of the greatest fears of patients after implantation of the device and is linked to not only morbidity and mortality but also significant effects on mental wellbeing of our patients. Strategies to minimize ICD shocks have led to very important reductions in inappropriate ICD therapies which could have severe psychological consequences in for example young patients. Probably because ICD shocks were considered a life-saving intervention in the early days very little data was collected to illustrate the impact on mental status of our patients.

It was soon after the large datasets of ICD recipients were analyzed when the first dramatic publications of the long term impact on mortality that receiving ICD shocks had. The data was really compelling particularly among patients included in primary prevention RCTs and large registries of primary prevention. (24, 43, 51, 109).

The aim of our study was to use a large population-based registry (the Ontario ICD registry) that includes all patients treated with *de novo* ICD implants and follows them up in the long term capturing their clinical evolution and mortality. Due to the lack of good quality data in the literature we aimed at exploring the secondary prevention population that had been not represented in the pivotal RCT studies.

In our study there were several important findings: Firstly, patients who receive any appropriate ICD therapy, either shock or ATP, have increased mortality no matter what the initial indication as highlighted by increased hazard ratios for all cause mortality: (HR, 95% CI 2 (1.72-2.33) for shocks in primary prevention and 1.46 (1.20-1.77) for shocks in secondary prevention and 1.73 (1.52-1.97) for ATP in primary prevention and 1.38 (1.16-1.64) for ATP in secondary prevention. Secondly, patients receiving an ICD for secondary prevention indication have a twofold risk of experiencing appropriate therapies from the device compared to primary prevention patients. Thirdly and perhaps most importantly, the risk of

subsequent death after experiencing ICD therapy was identical between primary and secondary prevention patients. This finding was of interest and surprising since patients in the primary prevention cohort had more comorbidities including diabetes mellitus and hypertension, were older and had more advanced heart failure and worse LVEF compared to the secondary prevention patients. This finding is in keeping with the idea that having a higher burden of ventricular arrhythmia warranting ICD interventions impacts very significantly the risk of death in the secondary prevention population as shown in other studies (51).

Our data on ATP is of great interest since there are conflicting findings regarding the impact on mortality of such therapies. Previous data from a subanalysis of the MADIT-RIT study showed that ATP had a neutral effect on mortality(110). Our study differs in several aspects but has the strength of including more patients and a large secondary prevention population.

The main strengths of the manuscript is the large number of patients included and the long term follow-up of approximately 5 years and that it is able to track granular data in all patients. In addition, the the assessment of ICD therapies was performed by electrophysiologists in a core lab. The main limitations of the work is the lack of information on the strategies followed after the patient had received an ICD intervention and whether the patient received further interventions during the follow-up. Importantly, data on the exact cause of death was not available so it is not known if patients died because of pump failure, lethal arrhythmia or electromechanical dissociation. Another important limitation of our work is that the effects of inappropriate shocks were not assessed in our population. Moreover, we do not know which patients suffered them and their impact is unknown.

Thus the paradox is clear in the case of appropriate ICD therapies: they are life-saving but at the same time they highlight the fact that the patient is at a higher risk for mortality. Physicians dealing with patients suffering from ICD interventions need to be aware of the importance that this finding has independently of the baseline condition of the patient as it is clear that even with a better clinical profile

at the time of implant, secondary prevention patients will experience a similar mortality as their primary prevention counterparts.

It has been shown that strategies that minimize ICD therapies with either long detection times before treatment is delivered or those requiring higher heart rates to start intervening may be linked to better survival(111). Some of them include the evaluation of multiple parameters detected via home-monitoring of the device (112-115). The evidence in the literature seems to point towards deletereous effect of ICD shocks of any cause. Current programming strategies have minimized significantly the rate of inappropriate ICD interventions. (116) (Figure 13)

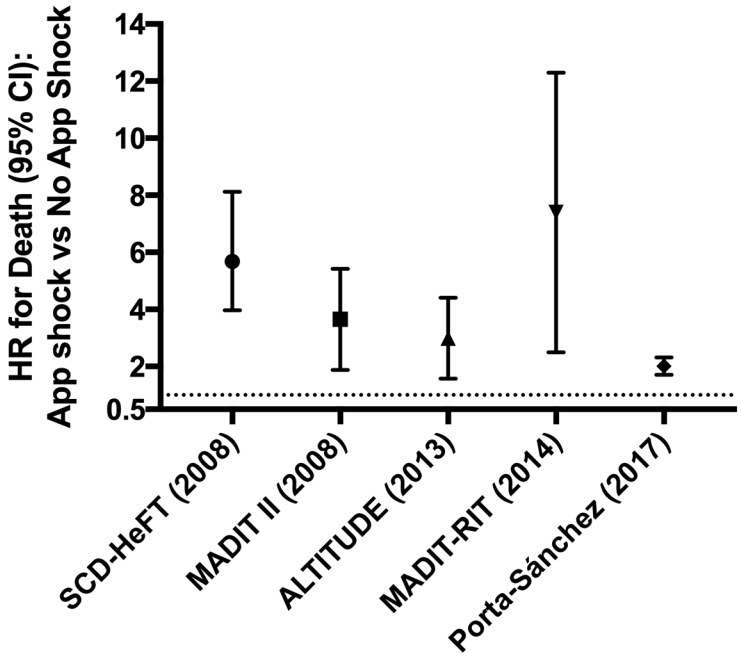


Figure 13. Forest plot showing Hazard Ratios and 95% CI for different studies analyzing the risk associated with experiencing appropriate ICD shocks versus not experiencing them. A consistent effect is seen in the literature regarding the increased risk of death associated with experiencing appropriate ICD shocks.

All clinicians are aware of what to do when identifying a risk factor for increased mortality such as diabetes mellitus, tobacco use, hypertension or coronary artery disease. It is unclear what to do with the risk factor that has been identified in our secondary prevention population that is receiving ICD interventions. Several

studies of strategies to reduce the burden of ventricular arrhythmia have shown an important decrease in VT episodes(63, 64, 117) and there is evidence that patients that are VT free after catheter ablation have improved outcomes(27). However, prospective evaluations of head to head comparisons with medical management in patients suffering VT have failed to prove improved survival with catheter ablation(26, 65). An alternative to an invasive treatment strategy would be risk stratify those patients that are more likely to experience ICD interventions during the follow-up by means of risk markers of arrhythmic death. Some of them are based on tissue characterization by late gadolinium enhanced sequences on cardiac MRI(118), others focus on virtual EP testing by means of computer modeling(119), microvolt T wave alternans (120, 121) and QRS duration or high resolution ECG (122) or signal averaged ECG (123, 124). Small studies have tested the usefulness of non-invasive EP study to identify patients at higher risk of interventions after ICD implant(125) and it seems very clear that using LVEF as the only marker for high risk of sudden death is a very imprecise situation as highlighted by the fact that after 4 years of follow-up the majority of ICD recipients have not received any intervention from it. Future research should try to identify those patients that benefit most from an invasive ablation strategy if they are at high risk for developing lethal ventricular arrhythmias.

Clinically, the increase in mortality seen after ICD interventions should be regarded by the treating physician as a marker of an unstable situation. When analyzing our data, ICD shock is harbouring more risk than for example an LVEF of less than 20% or being in a NYHA functional class III-IV and a similar risk to having had a previous admission because of heart failure. As soon as the risk factor for death is indeed identified, strategies to prevent it and treat it will at some point show improved survival.

c. Part II: Comparison of the clinical outcomes and healthcare costs of catheter ablation vs medical therapy for recurrent VT.

A difficult clinical scenario is the one reflected in part II of this thesis. A patient that has an ICD implanted is experiencing recurrent life-saving interventions for ventricular arrhythmia. We clinicians need to decide whether an invasive management is warranted or antiarrhytmic drugs are enough to treat this critical condition. Catheter ablation of VT has evolved importantly in the last decades and it now implies a percutaneous access to the heart, detailed mapping with steerable catheters and high resolution mapping systems and then delivery of radiofrequency energy at the sites where the VT is thought to be located. Safety and efficacy of the procedure is proven but currently it still requires a high level of expertise, the procedure is complex and prolonged and it is costly. All those reasons justified the approach of our study to compare an invasive vs non-invasive management of patients suffering recurrent VT due to ICM and NICM. Since the demonstration of mortality benefit with catheter ablation has been so far elusive our objective was to focus on other clinically relevant variables that may be able to guide policymaking and also clinical decision-taking such as healthcare usage and costs of each treatment strategy.

The main findings of our propensity-score matching scheme between ICD patients experiencing recurrent VT with a similar clinical risk profile treated medically or with VT ablation are the following: 1) An important reduction in the burden of VT episodes quantified as VT admissions is seen compared to the pre-ablation state in the catheter ablation group. 2) Catheter ablation patients displayed a similar rate of health care usage and major adverse cardiac events compared to medically treated patients. 3) There is a trend towards better overall survival in patients treated with catheter ablation compared to medical therapy. 4) Health care related costs were not different between the 2 treatment strategies.

Data from large registries has proven that catheter ablation for recurrent VT is linked to a significant decrease in the burden of VT. Treatment efficacy is critical to be able to prove a survival benefit in this setting since it has been clearly demonstrated that being free of VT after catheter ablation is associated with better survival even if the baseline conditions are very unfavourable (27, 58, 62, 126, 127). (Figure 14)

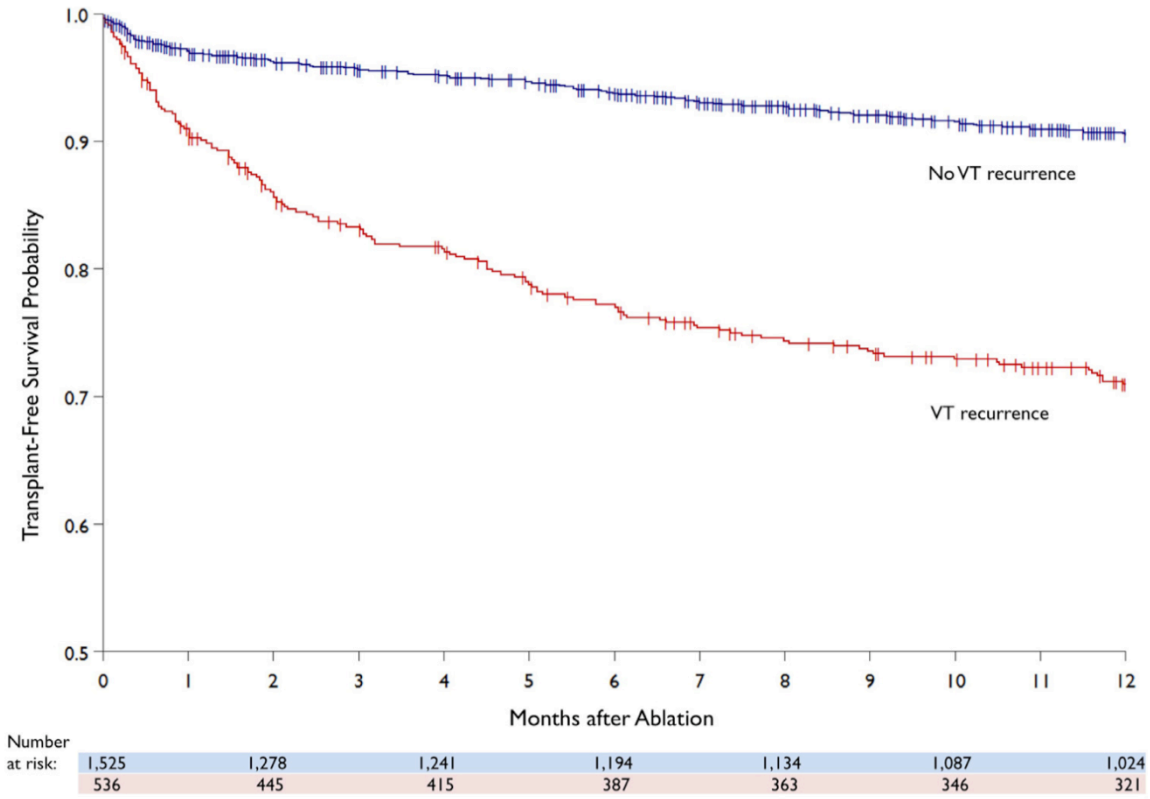


Figure 14. Kaplan-Meier survival plots comparing patients that were free of recurrent VT vs those who were not in the international ventricular tachycardia registry. Tung et al, Heart Rhythm 2017

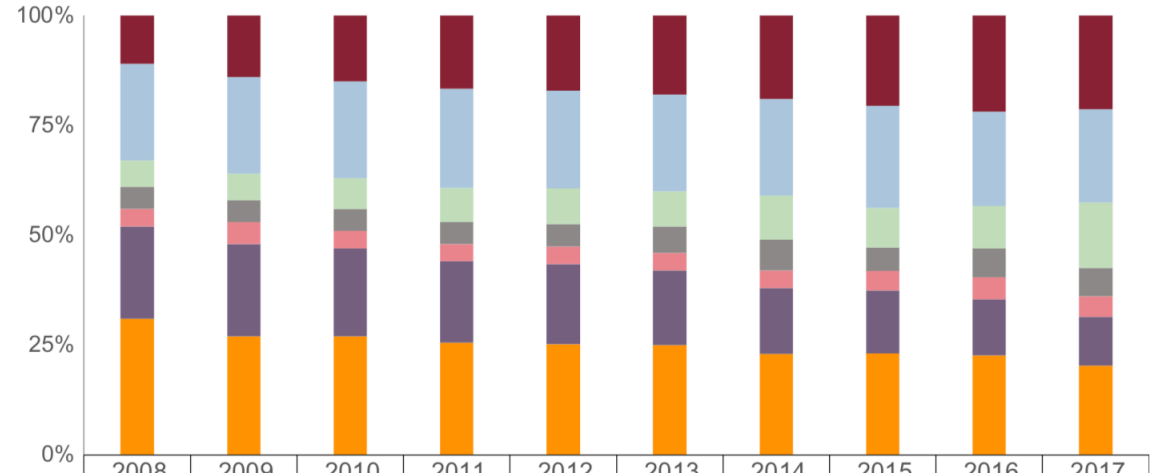
Analysing in depth the registries and prospective series clinicians often may perceive that catheter ablation of VT could be linked to improved survival. However, when RCTs have compared the efficacy of catheter ablation vs medical management with antiarrhythmic drugs they have failed to show a mortality benefit in the invasive treatment strategy even when dealing invasively with the VT

substrate in a prophylactic fashion (26, 65). Recurrence of VT after the ablation may be linked to failure to create effective and durable lesions or to identify the entire substrate or to disease progression or proarrhythmic effects of the ablation lesions themselves. Moreover, recurrence of VT early after an ablation has a severe impact on the long term mortality (128).

Our study by aligning the most important risk factors for death in a propensity-matched population of patients adds to the body of evidence that patients referred for catheter ablation benefit from a reduction in unplanned admissions due to breakthrough ventricular arrhythmia episodes after they were experiencing a high VT burden before the ablation. Importantly the rate of cardiovascular admissions as a whole was similar between the 2 groups after the treatment was established. The fact that their clinical conditions were similar but the catheter ablation group was experiencing a higher burden of ventricular arrhythmia and this becomes similar after the procedure makes it plausible that thanks to the procedure they return to a more stable state in their disease.

Due to the known impact of the pre-ablation antiarrhythmic drug usage we also stratified that variable in a subgroup of patients as a sensitivity analysis. There was clear demonstration that the main results of the study were identical even when stratifying for amiodarone or sotalol usage and the pre-ablation VT burden.

One additional issue is the non-ischemic substrates causing VT. It has been shown that catheter ablation in this subgroup of patients is less effective and this has led to systematically excluding those patients from RCT thus creating a biased perception of VT ablation as being neutral to mortality but rather this may not hold true if NICM patients would have included in the trials. Despite those findings, a constant increase in the number of VT catheter ablations in several registries -including the Spanish one(129)- has been seen. In our study there was a 35% proportion of patients with NICM that could undermine the benefits of catheter ablation. (Figure 15)



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
FA	11	14	15	17	17	18	19	21	22	23
ICT	22	22	22	23	22	22	22	23	21	23
TV	6	6	7	8	8	8	10	9	10	16
TA	5	5	5	5	5	6	7	5	7	7
NAV	4	5	4	4	4	4	4	4	5	5
VAC	21	21	20	19	18	17	15	14	13	12
TIN	31	27	27	26	25	25	23	23	23	22

Figure 15. Column graph highlighting the increase over time in the number of structural VT ablation procedures performed in Spain. Data is collected yearly and published in the Rev Española de Cardiologia.

When focusing on the cost calculation aspect of our paper the limitation that this is not a RCT is of paramount importance. Our findings are novel in the sense that they show that catheter ablation has a favourable health economic profile because the strategy is not associated to increased costs.

Importantly, our work has other important limitations: 1) Despite the propensity score analysis being able to match for several key clinical variables, being a non-RCT, our study will always have confounding variables in the background that may influence some of the results. 2) This series has a limited number of patients with its limitations. 3) Ventricular arrhythmia-related admissions were higher in the catheter ablation group in the pre-treatment period, which may introduce some bias in the data against catheter ablation strategy. 4) The catheter ablation strategy used is focused in eliminating the substrate by using activation mapping guided ablation with limited radiofrequency delivery and rendering the induced VTs non-inducible, meaning that extensive ablation strategies with substrate

homogenization or core isolation were not used in our cohort. Therefore, our results may not apply if that strategy is to be used.

Lastly, our work has important strengths: 1) Including real-world patients with ICM and NICM etiologies leading to high VT burden. 2) Detailed propensity-matching for variables known to significantly affect outcomes. 3) Lack of missing data regarding admissions or mortality. 4) Precise cost-analysis which is key in public healthcare systems.

d. Part III: Introduction and validation of DEEP mapping as a novel strategy for a mechanistic VT ablation strategy.

Several different VT substrate modification strategies have been described in the literature. The usefulness of identifying the VT substrate has been thoroughly proven and acceptable clinical outcomes have followed the ablation strategies that targeted different areas of the substrate thought to be responsible for the VT circuits. The need for ablating the substrate was mainly initially driven by the fact that activation mapping had several limitations, most importantly the poor hemodynamic tolerance of most induced VT. Elegant work was able to demonstrate the correlation between the isolated late potentials identified during sinus rhythm or right ventricular pacing and the VT circuit identified during activation mapping (79, 130-132). Those findings led to a widespread use of the isolated late potentials as targets for ablation in patients in whom the VT was not mappable or non-inducible. The definition of isolated late potentials was clear cut in both studies: "potentials that are separated from the ventricular electrogram by an isoelectric segment of > 20ms" in Bogun et al. work(130) and "electrograms recorded in the scar tissue showing double or multiple components separated > 50 ms" in Arenal et al. work(79). Attempts at improving ablation outcomes detailed different ways of ablating those signals by linear lesions, short lesions or focal lesions to achieve non inducibility. It was not until 2012 when Jaïs et al presented the somewhat difficult and long definition of local abnormal ventricular activation (LAVA): "sharp high-frequency ventricular potentials, possibly of low amplitude, distinct from the far field ventricular electrogram occurring anytime during or after the far-field ventricular electrogram in sinus rhythm (…) that sometimes displayed fractionation or double or multiple components separated by very-low-amplitude signals or an isoelectric interval and were poorly coupled to the rest of the myocardium"(89). This broader definition allowed for a more extensive ablation of the substrate. Yet one further step in the simplification of the definition of the VT substrate was used "ablation was empirically extended throughout the entire scar

(homogenization of the scar)" in Di Biase et al. work(133). At that time, VT ablation was moving from a purely mechanistic ablation strategy -the circuit needed to be identified in order to proceed with the ablation- to a purely anatomical non-mechanistic ablation strategy –the abnormal areas of the electroanatomical map being identified to proceed with the ablation without the need to have mappable sustained VT.

Several groups tried to move the field towards a more in-depth analysis of the substrate by identifying which of the signals seen during stable rhythms were more specific to detect the components of the VT circuit without the need of inducing VT. Markers of protected channels such as EGM Shannon entropy were characterized (134) and other groups advanced in the modeling work of the isthmus sites characterized while in sinus rhythm (135). Our approach was to focus on the analysis of the whole heart activation maps that were obtained intraoperatively with a non-sequential mapping system. The importance of the data was that signals were obtained with instrumented bipolar electrodes separated by 1.5mm with a reasonably high density of 112 points per chamber, during sinus rhythm, at the time of VT induction and during VT, allowing for a detailed analysis of the VT circuit before the onset of VT and during it. This analysis highlighted the importance of the decrement evoked potential (DEEP) regions to localize the VT isthmus by stressing the cardiac tissue (98). The characteristics of the signals showed that those near-field late potentials that displayed decrement (i.e. delayed activation) with extrastimuli colocalized better with the isthmus of the VT than non-decremental late potentials.

In this thesis, our multicenter study of DEEP mapping included 20 consecutive patients in which precise delineation of the VT circuit was possible in 13 different VT of 9 patients. The main findings of the work were as follows: 1) Identifying DEEP regions in the myocardium is possible, 2) targeting these regions with RF deemed VT non-inducible in the majority of patients, 3) areas of DEEPS identified the critical components of the VT circuit more precisely than conventional LPs and,

4) a limited ablation strategy targeting DEEPs led to mid-term outcomes similar to other substrate based strategies.

This work included a typical population of patients referred for VT ablation with the majority being treated already with antiarrhythmic drugs and a third presenting with VT storm and with poor LVEF. We rendered the VT non-inducible in 80% of our patients by targeting only the DEEP areas and further ablation was not useful in rendering the rest of patients non-inducible.

Our work is one of the pioneers to the growing interest in identifying the substrate that may be prone to unidirectional block or the so-called functional substrate sometimes even located in normal voltage areas that can be linked to anatomical channels of conduction. It has been proven by other groups that the functional substrate identified by means of stressing the myocardium with extrastimuli has led to improved VT ablation outcomes compared to historical cohorts (92, 136). Other tools to identify areas that are predisposed to fractionation or slowed conduction during extrastimulation have been developed recently by refining previous concepts and adding them to the current electroanatomical mapping tools (137, 138).

Further work on the behaviour of the late potentials has been 3D-modeled *in silico* by our group. This has allowed for an accurate depiction on how the influence of the pacing site and the configuration of the scar channels can change importantly the amount of decrement the surviving tissue has. Notably, pacing adjacent to the excitable tissue but from the opposite site of the entry to the channel will give rise to the longest decremental response and the protected channels in the scar were characterized by important decrement compared to the unprotected channels (139). The wide recognition that unidirectional block is responsible for the initiation of reentry in most of the arrhythmias has been proven to be of help in identifying atrial tissue at risk for complex atrial reentrant circuits (140).

High resolution activation mapping in preclinical models of VT has also allowed for depiction of the propagation velocity of the wavefront in critical sites of the circuit and compare them with the patterns of propagation during sinus rhythm. It

is of great interest that the areas showing an important slowing of propagation correlated better with the critical isthmus sites than the presence of late activation patterns (107). This is in keeping with our findings pointing towards the relevance of the functional components of the circuit of VT. (Figure 16)

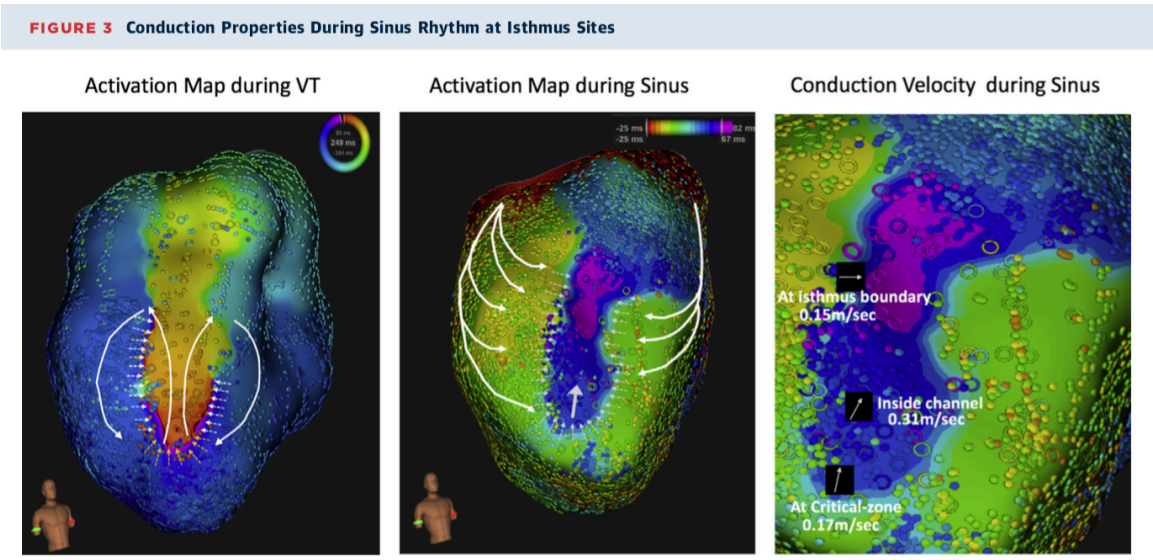


Figure 16. Left ventricular endocardial maps of a swine model of ventricular tachycardia substrate. The ultrahigh density maps allow for a careful depiction and precise calculation of conduction velocity changes in the propagation of the cardiac impulse by using local activation times and distances travelled by them. The illustration clearly shows that the areas that identify the VT isthmus are those that show slowing of propagation during sinus rhythm. Adapted from Anter E et al. JACC EP 2018.

Our work has several important limitations including the fact that it was not randomized, it lacked a control group and it did not systematically perform in all patients multielectrode mapping with small interelectrode spacing. This approach has been shown to detect signals that are less prone to far-field detection. Additionally, the DEEP mapping strategy is currently not automated and it did not allow for delivery of extrastimuli in the complete substrate as done in our intraoperative maps. This could have led to missing areas harbouring DEEPs and it was also associated with similar procedure times as the ones seen in the literature. The main strength of our work was the multicenter and prospective nature of it and the fact that it refines the area of the substrate to be ablated. Currently more and more patients are undergoing VT ablation and the concept of not ablating the entire

substrate may be of great importance as most of it is not -and will never be- part of any VT circuit.

e. Part IV: Overcoming the directional dependency of bipolar electrograms with omnipolar methodology in a translational model of ventricular arrhythmia substrate.

Electrograms are the most important tools used in the complex electrophysiological procedures being performed nowadays. All types of cases, even simple cases or the most challenging cases, timing, morphology, location and responses to perturbations to the EGMs are the only tools that are used to guide our ablation procedures.

During the evolution of mapping it was first seen that the use of unipolar electrograms had a local component but was contaminated by large signals that were not actually happening in the mapped tissue but in the remote regions of the heart (far field recordings). Despite the believe that their recordings were direction independent recent data has challenged this concept (141) and their characteristics are influenced by a miriad of factors including tissue thickness as well as propagation speed and obviously catheter size and distribution of the non-conductive tissue with respect to the depth of the tissue (142).

To increase the yield of the recordings the subtraction of the inverse unipolar signal has led to bipolar recordings. Much more agnostic to the influence of the far-field signals they allow for a clear depiction of the wavefront being mapped between two electrodes but they have the caveat that the signal size will be heavily influenced by the angle of wavefront propagation (direction-dependency) with regards to the electrode-pair orientation. This limitation is well known since the 90s ex vivo (99) and has been also proven to have a significant impact in vivo (101).

To overcome the main limitation of the directional-dependency of bipolar EGMs the omnipolar EGMs were developed. We used this new tool for mapping with an equi-spaced electrode array (Advisor HD grid ™) in a porcine model of established myocardial infarction confirmed by late gadolinium enhancement on pre-procedural MRI. The main findings of our *in vivo* validation of OT-EGMs for the assessment of ventricular substrate are the following: 1) OT detected maximum

peak to peak voltages was larger than bipolar voltages obtained in any electrode directions. 2) beat by beat, OT EGMs were more consistent than bipolar EGMs with less coefficient of variation. 3) The mapping point densities were higher with OT EGMs than bipolar EGMs and 4) OT-EGM may be linked to a better estimation of the extent of diseased myocardium. (Figure 17)

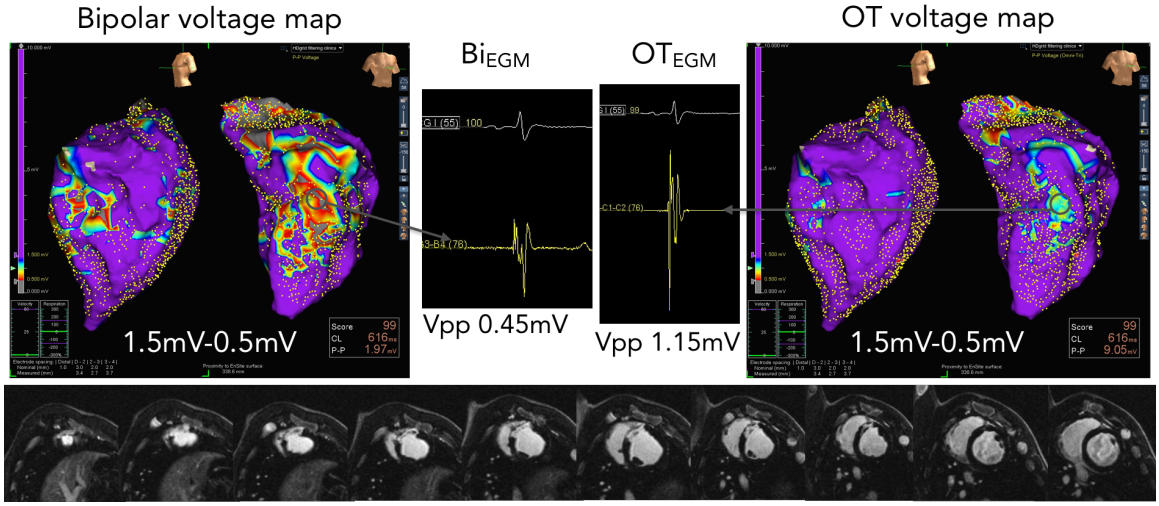


Figure 17. Swine model of ventricular tachycardia substrate. The maps illustrate the differences in the voltage detected by a conventional bipolar EGM configuration and Omnipolar EGM configuration. EGMs analyzed with omnipolar methodology detect smaller areas of low voltage. The co-localization with cardiac Magnetic Resonance imaging is shown at the bottom. Adapted from Porta-Sánchez A et al Europace 2018.

Originally introduced by Deno et al(105), OT-EGMs take advantage of the local electrical field (E-field) being generated underneath 3 electrodes that are scanning the wavefront of activation in a 3D fashion. Coupled with an equi-spaced electrode array the utility of OT EGMs has been highlighed. When obtaining the pattern of activation between those 3 electrodes a "local vectorcardiogram" is computed and the voltage loop is available for its use. This means we can theoretically select the minimum EGM depicted in the area and also the maximal one (OTVmax)(143). This finding is of key importance as it provides near-field accuracy of the recordings which are unaffected by the angle of influence of the wavefront.

It could be argued that if a high-resolution map of a myocardial substrate is to be taken with multiple direction catheters the issue of the direction dependency of the recordings could be solved. This is not the case as it has been elegantly highlighted in recent preclinical works (144).

Moreover, not only the concept of a local voltage loop is visually appealing but also there are further wavefront properties that can be assessed by means of OT-EGMs which include conduction velocity and activation direction based on real time measurements and without the need to collect LAT data to measure them as it has been proven thoroughly ex-vivo and in-silico (104). These concepts may allow for further characterization of the myocardial tissue with its complexities. Additionally, the availability of activation direction could provide a more reliable tool when mapping the most complex existing rhythm which is atrial fibrillation as supported by our previous preclinical work (106). In the field of complex atrial tachycardias, it has recently been shown that coupling information on conduction propagation with LAT based activation direction calculations may yield to better assessment of complex atrial tachycardias (145) and that the speed of the impulse propagation could be critical when assessing areas of interest harbouring arrhythmic circuits. (146)

(Figure 18)

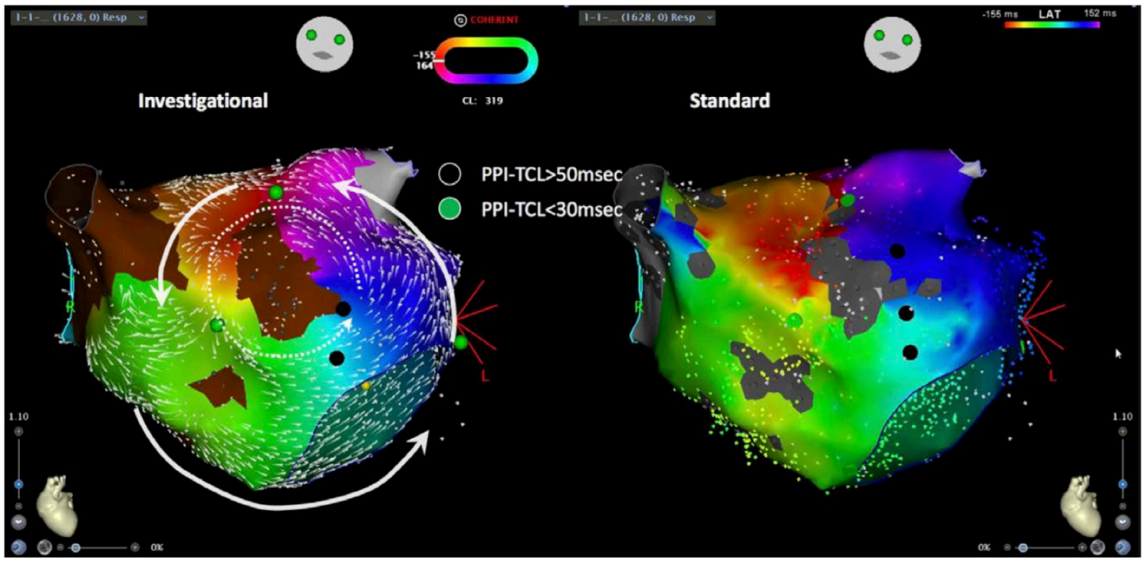


Figure 18. Activation maps of a complex arrhythmia: Left atrial macroreentrant tachycardia. Directionality of the wavefront is assessed by new tools (i.e. coherent mapping) -left- and cmpared with traditional bipolar activation maps -right-. The additional information provided by those newer tools has been systematically assessed by Anter E et al. Circulation: Arrhythmia and Electrophysiology 2018 with promising results.

Which tool should we use for omnipolar mapping is one of the other questions that remains open. It has been recognized in several works including ours that bipolar electrograms are heavily influenced as well by the interelectrode spacing and its size (103, 147). In vivo work has shown that to be able to detect accurately an MRI-identified myocardial scar an interelectrode spacing of 4mm must be used as it yielded high sensitivity and specificity (102) which makes our findings reliable and physiologically sound. There is also evidence on the different assessments of the substrate as judged by peak to peak voltage amplitude by using large electrode tips. This is in combination with the underestimation of small conducting channels that penetrate the scar which may be unrecognized (148). Randomized data has shown elegantly the differences between 2 mapping tools when detecting late activating areas (149). One of the main findings when comparing large tip electrodes with closely spaced electrodes of small size is that the latter allows for the detection of surviving bundles of tissue inside the scar. A logical way of thinking may be that small spaced electrodes recognize better the activation underneath the catheter. However, modeling work and experimental work has shown that for the same

wavefront propagating in the same tissue with the same electrode size, peak to peak bipolar voltage will be smaller with smaller electrode spacing. (Figure 19) A logical explanation for this could be that a small electrode pair used for mapping is more often able to sit along the activation wavefront than the larger electrode spacing configurations. This is due mainly -in our opinion and based on our data- to the directional influences of the bipolar recordings and OT-EGMs may prove to be able to solve the issue.

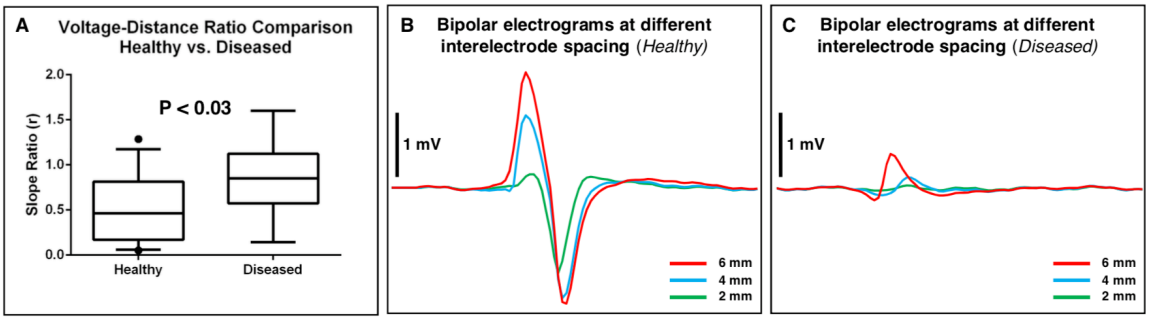


Figure 19. Modeling data allows for the recreation in-silico of an infinite number of combinations of variables. In this case, Behesti M et al (Comp Bio Med 2018) compared the different bipolar EGM signals obtained in different myocardial tissues. It is clearly demonstrated that smaller interelectrode spacing yields a smaller voltage peak to peak in the bipolar signal. This finding emphasizes the role played by the resulution and directional influences when mapping with smaller electrodes. A huge modification of the substrate can be seen when changing the interelectrode distances.

Our work has important limitations in the sense that *ex vivo* 3D histology with preserved volume was not performed to allow for an MRI histological reconstruction of the LGE-CMR regions and correlate them to our electroanatomical maps for increased accuracy. Also, the porcine model used has important histological differences compared to humans that include the distribution of the Purkinje fibers and also the fact that the substrate is not as evolved in time as in humans.

The main strength of the manuscript is the fact that it was the first preclinical series of an equi-spaced array as an *in vivo* mapping tool and that it confirmed that OT-EGM is able to produce near-field, orientation independent bipolar-like recordings

that may be of great use when delineating the physiological properties of the wavefront being mapped.

Conclusions:

In this translational thesis we have been able to provide a panoramic view of unanswered questions in the management of VT patients that include population based data, an intervention vs medical management group, a new tool for substrate mapping and ablation of VT in humans and a preclinical work bringing to the stage omnipolar electrograms for the assessment of VT.

This work highlights the bench to bedside philosophy of research and it has contributed to enrich the current knowledge on the impact of VT and to find a way for possible better outcomes in the future.

In summary, we have shown that:

1. In patients with ICD that experience a life-saving ICD intervention there is an increased risk of mortality that is independent of the implant indication.
    a. Secondary prevention ICD patients experience a twofold risk of receiving life-saving ICD interventions and experience the same long-term mortality as the primary prevention patients, despite having a more favourable clinical profile at the time of ICD implant.
    b. A single appropriate ICD therapy warrants careful clinical evaluation because of the increased mortality that is associated with it.
2. In a propensity-matched analysis of patients suffering recurrent VT episodes, those treated with invasive catheter ablation experience a significant decrease in the number of ventricular arrhythmia related admissions during follow-up compared to those treated medically.
    a. Total cardiovascular admissions and heart failure episodes were not different between the catheter ablation or medical therapy patients.
    b. There is no significant difference in the healthcare costs of patients treated with an invasive strategy compared to those treated medically.
    c. These results hold true even after stratifying for the types of antiarrhythmic drugs used.

3. A prospective-multicenter study has shown the feasibility and clinical efficacy of a mechanistic VT ablation strategy that focuses on identifying areas with decrement evoked potentials (DEEP) and their ablation.
    a. In patients with mappable VTs, DEEPs demonstrated higher sensitivity and specificity than conventional late potentials to identify the critical sites of VT with extrastimulus pacing.
    b. Ablation of DEEP regions only yield the vast majority of VTs non-inducible with mid-term follow up success rates comparable to previously published substrate based ablation techniques.
4. The use of an equi-spaced electrode array allows for *in vivo* mapping of VT substrate with omnipolar EGMs.
    a. Omnipolar EGMs allow for a local, orientation independent and physiologically relevant bipolar-like map that provides less beat by beat variability compared to bipolar EGMs.
    b. Omnipolar EGMs provide larger peak to peak voltages compared to bipolar EGMs both in diseased and healthy myocardium which may help reflect better the true nature of the VT substrate.

Supplementary material:

a. Ethical aspects:

The highest ethical standards were applied for all parts of the studies. In keeping with the regulation of the Declaration of Helsinki and the regulations of Canada at the time of the studies. The authors' conflicts of interests are disclosed in each article. The funding sources are described in each article. The author has no individual conflicts of interest to declare regarding the research performed in this thesis.

Part I

In this study the need for informed consent from the patients was waived as it pertains to a mandatory registry from the Ministry of Health of Ontario. The ethics approval for the project was obtained from the Ethics committee of Sunnybrook Health Sciences in Toronto (Ontario).

Part II

This study was based on a retrospective collection of patients data regarding VT ablation procedures. Informed consent was waived due to the retrospective nature of the study. No ethical concerns apply to this study since there was no intervention mandated by the protocol. The study protocol was approved by the Ethics Board at University Health Network, Toronto (Ontario). The information from the medical treatment group was obtained from the Ontario ICD registry database (Institute for Clincal Evaluative Sciences, ICES).

NOTIFICATION OF REB RENEWAL APPROVAL

Date: January 30, 2017

To: Kumaraswamy Nanthakumar
Room 3R414-17; 3rd Floor, Room 3R414-17, Max Bell Research Centre; Toronto General Hospital; 200 Elizabeth St., M5G 2C4; Toronto, Ontario, Canada

Re: 13-6278
Outcomes of Ventricular Tachycardia Ablation

REB Review Type:	Delegated
REB Initial Approval Date:	February 11, 2015
REB Renewal Approval Effective Date:	February 11, 2017
Lapse In REB Approval:	N/A
REB Expiry Date:	February 11, 2016

The University Health Network Research Ethics Board has reviewed and approved the Renewal (13-6278.2) for the above mentioned study.

Best wishes on the successful completion of your project.

Sincerely,
Marina Mikhail
Ethics Coordinator, University Health Network Research Ethics Board

For: Alan Barolet
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.

Part III

This was a prospective study that was approved by the Ethics Board at University Health Network, Toronto (Ontario) and at each participating site (Åarhus University Hospital, Åarhus (Denmark); John Hunter Hospital, Newcastle (Australia)). Informed consent was obtained for each of the patients treated and screening of candidates was performed following the study protocol. Given the fact that the best VT substrate mapping approach is controversial and considering that the endpoint of the procedure is non-inducibility of any VT there is no ethical concern regarding the intervention. Patients were followed in the outpatient clinic post-procedure as part of their rutine clinical care.

NOTIFICATION OF REB AMENDMENT APPROVAL

Date: January 27, 2017

To: Kumaraswamy Nanthakumar
Room 3R414-17; 3rd Floor, Room 3R414-17, Max Bell Research Centre; Toronto General Hospital; 200 Elizabeth St., M5G 2C4; Toronto, Ontario, Canada

Re: 14-7464
DEEP Novel Mapping Technique to Identify Ventricular Tachycardia Circuit

REB Review Type:	Delegated
REB Initial Approval Date:	November 6, 2014
REB Amendment Approval Date:	January 27, 2017
REB Expiry Date:	November 6, 2017

Documents Approved:

Document Name	Version Date	Version ID
Summary of Changes	December 12, 2016	

The University Health Network Research Ethics Board has reviewed and approved the Amendment (14-7464.3) for the above mentioned study.

The UHN REB approves this Amendment as specified under "Amendment Description".

Best wishes on the successful completion of your project.

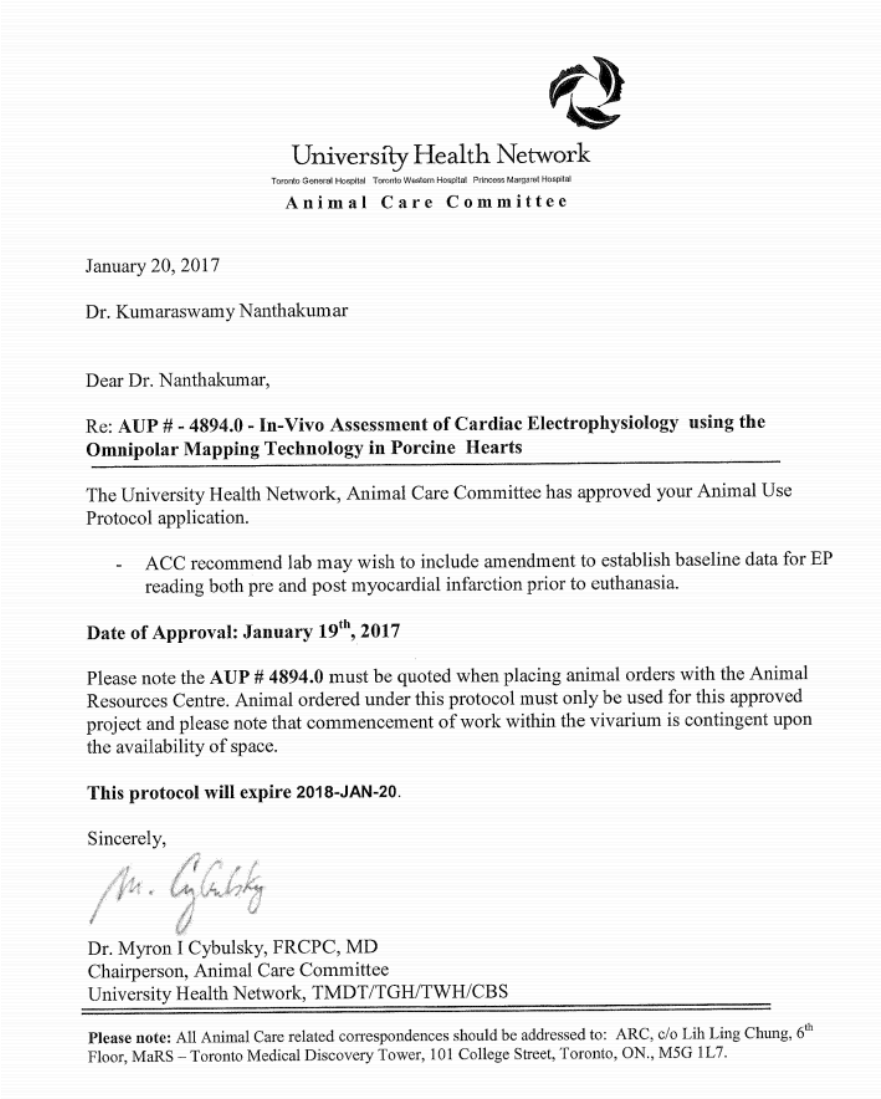
Sincerely,
Svetlana Tzvetkova
Ethics Coordinator, University Health Network Research Ethics Board

For: Alan Barolet
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.

Part IV

In this porcine model of myocardial infarction the approval from the Animal Unit at Toronto General Hospital Research Institute (TGHRI) was obtained (Toronto, Ontario). In the protocol, the rational and ethical use of animals was detailed, taking into account the legislatory regulations in place and the highest veterinary care standards for the animals. The three "R" concept: Reduce, reuse and recycle was applied. During the follow-up and the procedures the well being of the animal was an essential part of the management and was taken care by expert veterinarians. All procedures were done under deep sedation and animals that showed signs of suffering that were not responding to conventional symptomatic management were euthanized.



University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

Animal Care Committee

January 20, 2017

Dr. Kumaraswamy Nanthakumar

Dear Dr. Nanthakumar,

Re: **AUP # - 4894.0 - In-Vivo Assessment of Cardiac Electrophysiology using the Omnipolar Mapping Technology in Porcine Hearts**

The University Health Network, Animal Care Committee has approved your Animal Use Protocol application.

- ACC recommend lab may wish to include amendment to establish baseline data for EP reading both pre and post myocardial infarction prior to euthanasia.

Date of Approval: January 19th, 2017

Please note the **AUP # 4894.0** must be quoted when placing animal orders with the Animal Resources Centre. Animal ordered under this protocol must only be used for this approved project and please note that commencement of work within the vivarium is contingent upon the availability of space.

This protocol will expire 2018-JAN-20.

Sincerely,

Dr. Myron I Cybulsky, FRCPC, MD
Chairperson, Animal Care Committee
University Health Network, TMDT/TGH/TWH/CBS

Please note: All Animal Care related correspondences should be addressed to: ARC, c/o Lih Ling Chung, 6th Floor, MaRS – Toronto Medical Discovery Tower, 101 College Street, Toronto, ON., M5G 1L7.

b. Additional publications related to the topic:

i. Jackson N, Gizurarson S, Viswanathan K, King B, Massé S, Kusha M, **Porta-Sánchez A**, Jacob JR, Khan F, Das M, Ha A, Pashaei A, Vigmond E, Downar E, Nanthakumar K. Decrement Evoked Potential (DEEP) Mapping: The Basis of a Mechanistic Strategy for Ventricular Tachycardia Ablation. Circ Arrhythm Electrophysiol 2015 Dec; 8(6)1433-42.

ii. King B, **Porta-Sanchez A**, Massé S, Zamiri N, Balasundaram K, Kusha M, Jackson N, Haldar S, Umapathy K, Nanthakumar K. The Effect of Spatial Resolution and Filtering on Mapping Cardiac Fibrillation. Heart Rhythm 2017;14:608-615. doi:10.1016/j.hrthm.2017.01.023.

iii. Jackson N, Gizurarson S, Azam MA, King B, Ramadeen A, Zamiri N, **Porta-Sánchez A**, Al Hesayen A, Graham J, Kusha M, Massé S, Lai PFH, Parker J, John R, Kiehl TR, Kumar Nair GK, Dorian P, Nanthakumar K. Effects of Renal Artery Denervation on Ventricular Arrhythmias in a Postinfarct Model. Circ Cardiovasc Interv. 2017; 10:e004172 [doi: 10.1161/CIRCINTERVENTIONS.116.004172].

iv. Magtibay K, Massé S, Asta J, Kusha M, Lai PFH, Azam MA, **Porta-Sánchez A**, Haldar S, Malebranche D, Labos C, Deno DC, Nanthakumar K. Physiological Assessment of Ventricular Myocardial Voltage Using Omnipolar Electrograms. J Am Heart Assoc. 2017;6:e006447. June 2017. DOI: 10.1161/JAHA.117.006447.

v. Haldar S, Magtibay K, **Porta-Sánchez A**, Massé S, Mitsakakis N, Lai PFH, Azam MA, Asta J, Kusha M, Dorian P, Ha ACT, Chauhan V, Deno DC, Nanthakumar K. Resolving Bipolar Electrogram Voltages during Atrial Fibrillation using Omnipolar Mapping. Circ Arrhythm Electrophysiol 2017 Sep;10(9). doi: 10.1161/CIRCEP.117.005018.

vi. Beheshti MA, Nayyar S, Magtibay K, Massé S, **Porta-Sánchez A**, Haldar S, Bhaskaran A, Vigmond E, Nanthakumar K. Quantifying the Determinants of Decremental Response in Critical Venticular Tachycardia Substrate. Computers in Biology and Medicine. [in press, May 2018. doi: 10.1016/j.compbiomed.2018.05.025].

vii. Beheshti MA, Magtibay K, Massé S, **Porta-Sánchez A**, Haldar S, Bhaskaran A, Nayyar S, Glover B, Deno DC, Vigmond EJ, Nanthakumar K. Determinants of Atrial Bipolar Voltage: Inter-electrode Distance and Wavefront Angle. Computers in Biology and Medicine. [in press, July 2018. doi: 10.1016/j.compbiomed.2018.07.011].

viii. Bhaskaran A, Gizurarson S, **Porta-Sánchez A**, Massé S, Nair K, Nanthakumar K. Atrial Decremental Evoked Potentials Accurately Determine the Critical Isthmus of Intra-atrial Re-entrant Tachycardia. Europace. [in press, July 2018. doi: 10.1093/europace/euy164].

ix. Bhaskaran A, Nayyar S, **Porta-Sánchez A**, Haldar S, Bokhari M, Massé S, Liang T, Zehra N, Talha F, Downar E, Nanthakumar K. Exit Sites on the Epicardium Rarely Subtend Critical Diastolic Path of Ischemic VT on the Endocardium: Implications for Non-Invasive Ablation. J Cardiovasc Electrophy [in press, Jan 2019].

x. Suszko AM, Nayyar S, **Porta-Sánchez A**, Das M, Pinter A, Crystal E, Tomlison G, Dalvi R, Chauhan V. Quantification of Abnormal QRS Peaks Predicts Response to Cardiac Resynchronization Therapy and Tracks Structural Remodeling. PLoS One. 2019 Jun 6;14(6):e0217875. doi: 10.1371/journal.pone.0217875. eCollection 2019.

xi. Romagnuolo R, Masoudpour H, **Porta-Sánchez A**, Qiang B, Barry J, Laskary A, Qi X, Massé S, Magtibay K, Kawajiri H, Wu J, Valdman Sadikov T, Rothberg J, Panchalingam K, Titus E, Li RK, Zandstra PW, Wright GA, Nanthakumar K, Ghugre NR, Keller G, Laflamme MA. Human Embryonic Stem Cell-Derived Cardiomyocytes Regenerate the Infarcted Pig Heart but Induce Ventricular Tachyarrhythmia. Stem Cell Reports. 2019 May 14;12(5):967-981. doi: 10.1016/j.stemcr.2019.04.005. Epub 2019 May 2.

c. Abstract presentations related to the topics:

As presenter:

i. **Porta-Sánchez A**, Magtibay K, Massé S, Nayyar S, Bhaskaran A, Deno DC, Nanthakumar K. Equi-Spaced Electrode Array for Orientation Independent Bipolar Substrate Mapping. Oral moderated Poster presentation at EHRA Europace, Barcelona (Spain), March 2018. Featured in the highlights of the congress.

ii. **Porta-Sánchez A**, Magtibay K, Massé S, Deno DC, Nanthakumar K. Solving the Josephson dilemma: Equi-spaced Electrode Array for Direction-Independent Bipolar Substrate Mapping. Oral abstract presentation at 12th Annual VT Symposium, Philadelphia (US), Oct 2017. 1st Mark Josephson Innovation Award nominee.

iii. **Porta-Sánchez A**, Haldar S, Magtibay K, Massé S, Kusha M, Azam MA, Asta J, Lai PFH, Deno DC, Nanthakumar K. Assessment of transmurality during lesion formation with electrograms. Oral abstract presentation at EHRA Europace/Cardiostim 2017, Vienna (Austria), June 2017.

iv. **Porta-Sánchez A**, Haldar S, Magtibay K, Massé S, Kusha M, Azam MA, Asta J, Lai PFH, Deno DC, Nanthakumar K. Bipolar electrograms directed across wavefronts provide greater physiological accuracy. Poster presentation at EHRA Europace/Cardiostim 2017, Vienna (Austria), June 2017.

v. **Porta-Sánchez A**, Jackson NM, Lukac P, Kristiansen SB, Nielsen JM, Gizurarson S, Massé S, Kusha M, Ha ACT, Viswanathan K, King BJ, Downar E, Nanthakumar K. Multicenter Observational Study of Mechanistic VT Ablation with DEEP Mapping. Oral abstract presentation at 38th Heart Rhythm Society Scientific Sessions, Chicago, USA. May 2017. Young Investigator Awards nominee.

vi. **Porta-Sánchez A**, Ha ACT, Almehmadi F, Wang X, Fischer H, AlQubbany A, Chemello D, Austin PC, Nip S, Lee DS, Nanthakumar K. Does catheter-based ventricular tachycardia ablation worsen heart failure outcomes?

Findings from a propensity score matched analysis. Moderated poster presentation at 38th Heart Rhythm Society Scientific Sessions, Chicago, USA. May 2017.

vii. Almehmadi F, **Porta-Sánchez A**, Fisher H, Wang X, Ha A, Austin P, Lee D, Nanthakumar K. The Prognostic Impact of Appropriate Implantable Cardioverter Defibrillator Shock Based on Implant Indication: Insights from a Prospective, Population-based Registry in Ontario, Canada. Oral abstract presentation at American Heart Association Scientific Sessions, New Orleans, USA. November 2016.

viii. **Porta-Sánchez A**, Jackson N, Gizurarson S, AlQubbany A, Massé S, Kusha M, Nair K, Ha A, Downar E, Nanthakumar K. Decrement Evoked Potential (DEEP) Mapping: Clinical Validation of Limited Substrate Ablation Strategy for Ventricular Tachycardia. Oral abstract presentation at 37th Heart Rhythm Society Scientific Sessions, San Francisco, USA. May 2016.

ix. **Porta-Sánchez A,** Massé S, Magtibay K, Deno C, Nanthakumar K. The Basis of a Wavefront Method to Map Ventricular Tachycardia in Humans: Omnipolar Mapping. Poster presentation at 37th Heart Rhythm Society Scientific Sessions, San Francisco, USA. May 2016.

x. **orta-Sánchez A**, Jackson N, AlQubbany A, Massé S, Kusha M, Viswanathan K, King B, Downar E, Nanthakumar K. Decrement Evoked Potential (DEEP) Mapping: Mechanistic and Limited Substrate Ablation for Ventricular Tachycardia. Canadian Journal of Cardiology, Vol. 31(10):S287 October 1, 2015. Oral abstract presentation at Canadian Cardiovascular Conference.

xi. As collaborator:

xii. Bhaskaran AP, Nayyar S, **Porta-Sánchez A**, Massé S, Liang T, Magtibay K, Aukhojee P, Tung R, Jons C, Kawada S, Downar E, Nanthakumar K. The Forgotten Mapping Space: Intra-Mural Circuits in Ischemic Ventricular Tachycardia. Poster presentation at Heart Rhythm Scientific Sessions 2019, San Francisco (USA). May 2019.

xiii. Magtibay K, Bhaskaran A, **Porta-Sánchez A**, Massé S, Laflamme M, Deno DC, Nanthakumar K. Identifying Surviving Myocardial Tracts Within Infarcted Regions in an In-vivo Swine Model Using Omnipolar Methodology. Poster presentation at Canadian Cardiovascular Congress, Toronto, Canada. October 2018.

xiv. Bhaskaran A, Magtibay K, Massé S, **Porta-Sánchez A**, Laflamme M, Deno DC, Nanthakumar K. Drag and Map Strategy for Dynamic Detection of Diseased Myocardium: Innovative Omnipolar Application with Advisor HD Grid. Poster presentation at Canadian Cardiovascular Congress, Toronto, Canada. October 2018.

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Resumen en castellano:

Introducción:

Cada año centenares de miles de personas sufren un paro cardíaco. De hecho, se estima que en países cómo los EEUU ocurren unos 350000 episodios al año de parada cardíaca(1). La mayor parte de ellos se producen por la aparición de arritmias malignas, siendo éstas la taquicardia ventricular (TV) y la fibrilación ventricular (FV). Dichas arritmias suelen afectar de manera más frecuente a los pacientes con una miocardiopatía establecida y con defectos estructurales (fibrosis ventricular) de causas variadas. Actualmente, uno de los principales tratamientos en los pacientes afectos de miocardiopatía que han presentado un episodio de paro cardíaco recuperado o bien presentan criterios de alto riesgo de sufrirlo (principalmente valorado a través de la función sistólica ventricular) uno de los tratamientos principales es el desfibrilador automático implantable (DAI). Así, la combinación de los avances en el tratamiento de las miocardiopatías, tanto a nivel médico como mediante DAI, se ha traducido en una tendencia a la mejoría en la supervivencia de los pacientes que las padecen, en los cuales la aparición de las arritmias malignas (TV y FV) constituye uno de los problemas más graves.

En caso de aparición de TV o FV, el DAI realiza una valoración rápida (intervalo de pocos segundos), con la que identifica el ritmo y administra un tratamiento, bien en forma de choque de alta energía (descarga), o bien en forma de terapias de estimulación antitaquicardia (más conocidas por su acrónimo inglés Anti-Tachycardia Pacing –ATP-). A pesar de la rapidez con la que el DAI identifica y trata estos episodios, su ocurrencia y la consecuente descarga provocan un empeoramiento en la calidad de vida de los pacientes. Además, en ocasiones, pueden acompañarse de episodios sincopales, con consecuencias impredecibles.

Actualmente existen datos de que la ocurrencia de episodios de FV y TV tratados a mediante descargas del DAI se relacionan con un incremento en la mortalidad a largo plazo, en comparación con pacientes que no los han padecido(24, 41). Cabe destacar que dicha evidencia proviene de subanálisis en pacientes que han participado en ensayos clínicos controlados y aleatorizados. Dado que los pacientes tratados en los ensayos clínicos no siempre reflejan con exactitud la

práctica clínica diaria, resulta de gran importancia verificar que los hallazgos de ensayos clínicos son también reproducibles en registros de práctica clínica. Existen además, escasos datos sobre el papel que juegan las descargas en los pacientes a los que se les ha implantado un DAI tras la recuperación de un episodio de muerte súbita (DAI en prevención secundaria), ya que no existen ensayos clínicos aleatorizados contemporáneos.

Uno de los tratamientos disponibles para mejorar los síntomas derivados de las arritmias ventriculares malignas es la ablación con catéter de TV mediante radiofrecuencia (57). En la actualidad, en ensayos clínicos aleatorizados, se ha demostrado un impacto significativo en cuanto a la disminución de episodios de TV en el seguimiento de pacientes con miocardiopatía isquémica. Sin embargo, no existe ningún ensayo clínico que haya demostrado que la ablación con catéter de TV se acompañe de una reducción en la mortalidad, así como tampoco existen ensayos aleatorizados que hayan incluido de forma extensa a pacientes con miocardiopatía de origen no isquémico. En los procedimientos de ablación de TV se realiza ablación con radiofrecuencia en ocasiones extensa dada la complejidad del sustrato que da origen a la reentrada ventricular. Así pues, existe la necesidad de asegurar que la terapia de ablación con catéter no es dañina y su influencia en las tasas de reingresos hospitalarios para los pacientes respecto a otras estrategias de tratamiento menos invasivas (médicas), incluyendo también subgrupos de pacientes con miocardiopatía no-isquémica en los que hay escasos datos.

Se han descrito diferentes tipos de terapias invasivas de ablación de TV, todas ellas fundamentadas en 2 principios: 1) Identificación del circuito de la TV mientras ésta ocurre (mapa de activación y maniobras de encarrilamiento) y 2) Identificación de las zonas de miocardio dañado potencialmente relacionadas con el inicio y mantenimiento de la TV sin necesidad de que ésta ocurra (mapa de sustrato de TV). Aunque inicialmente las estrategias de ablación por catéter se centraron en mapas de activación, en la actualidad la mayoría de pacientes que requieren ablación de TV presentan mala tolerancia hemodinámica durante la arritmia, por lo que no es posible crear un mapa de activación y realizar maniobras de encarrilamiento (27).

En la última década han sido desarrolladas distintas estrategias de ablación de sustrato de taquicardia ventricular, todas basadas en la creación de un mapa electroanatómico en 3D donde se identifica el miocardio sano y las zonas de bajo voltaje que se corresponden con áreas de fibrosis miocárdica. Dichas zonas de fibrosis o cicatriz a nivel ventricular están implicadas en la iniciación y perpetuación de la TV. Mediante los mapas electroanatómicos de sustrato, se intenta identificar dentro de las zonas de fibrosis las fibras de miocardio supervivientes que permiten la reentrada que sustenta la TV. Las estrategias de ablación de sustrato son variadas, y algunas de ellas conllevan procedimientos muy prolongados para identificar y ablacionar todas las posibles zonas que supuestamente podrían estar implicadas en la génesis de TVs (66). Estos procedimientos prolongados tratan de eliminar todas las posibles zonas de conducción anormal sin realmente analizar si dichas zonas son realmente capaces de provocar y mantener las TVs. La identificación mediante mapa electroanatómico y maniobras electrofisiológicas de las zonas del sustrato que realmente se relacionan con las TVs podría ser una estrategia que permita una ablación más rápida y limitada que podría llevarse a cabo en más pacientes y con menor riesgo (98).

Otra de las limitaciones de los mapas de sustrato miocárdico es su resolución y frecuentemente la imposibilidad de eliminar mediante ablación las zonas que predisponen a la reentrada y ocasionan TV. Las limitaciones en la resolución de los catéteres vienen dadas por el hecho de que la información eléctrica se obtiene mediante electrodos bipolares. Dichos electrodos se encuentran sujetos a una gran variabilidad debido a que el voltaje y señal detectados dependen en gran medida de la dirección del frente de despolarización que estemos estudiando. De hecho, un simple cambio en el modo de estimulación durante el mapeo del ventrículo izquierdo da lugar a mapas de voltaje con grandes discrepancias (101). Existen estrategias de mapeo que pueden eliminar o reducir de forma muy significativa la dependencia de la dirección del frente de onda de estudio y dichas estrategias

podrían conllevar la creación de mapas de sustrato más reproducibles y con menor variabilidad pudiendo ser de gran ayuda (104).

En resumen, la TV es una arritmia maligna cuando se origina en pacientes con cardiopatía estructural y su ocurrencia parece relacionarse con un incremento de mortalidad, incluso pese a un tratamiento rápido y efectivo mediante un DAI. Las estrategias para su control incluyen, entre otras, la ablación con catéter, que a día de hoy se encuentra todavía sujeta a una parcial eficacia a largo plazo (27). Las limitaciones del procedimiento radican principalmente en la imposibilidad de mapear de forma íntegra el circuito y estudiar el comportamiento funcional del sustrato que las causa y mantiene.

Esta tesis se centrará en describir los efectos sobre la mortalidad de los episodios de TV tratados a través del DAI en pacientes de un registro poblacional, valorar los efectos de la ablación de TV comparado con tratamiento médico de la misma y explorar nuevas modalidades funcionales de estudio del sustrato de TV en humanos y en un modelo animal.

Hipótesis y Objetivos:

Parte I. Análisis del impacto de las terapias de DAI en pacientes de un registro poblacional incluyendo indicación en prevención secundaria.

- Hipótesis:
    - Primaria:
        - La ocurrencia de terapias apropiadas del DAI en pacientes con cardiopatía estructural es un marcador independiente de mortalidad.
    - Secundarias:
        - El riesgo de mortalidad asociado a las terapias apropiadas del DAI es diferente según la indicación de prevención primaria o prevención secundaria en el momento del implante.
- Objetivos:
    - Cuantificar el impacto de las terapias del DAI en el riesgo de mortalidad en pacientes tratados por prevención primaria y los tratados por prevención secundaria.
    - Analizar el impacto diferencial de las terapias antitaquicardia y las descargas de alta energía en la mortalidad.
    - Analizar la importancia de la indicación de DAI (primaria vs secundaria) en la mortalidad tras haber sufrido terapias de DAI.

Parte II. Comparación de la evolución clínica, ingresos y costes económicos de la ablación con catéter con respecto al tratamiento médico en pacientes con TV recurrente.

- Hipótesis:
    - Primaria:
        - Los pacientes con miocardiopatía, disfunción sistólica ventricular izquierda y portadores de DAI tratados con ablación con catéter por TV recurrente presentan menor tasa de ingresos comparado con los pacientes con el mismo perfil de riesgo tratados médicamente.
    - Secundarias:
        - Los pacientes con miocardiopatía, disfunción sistólica ventricular izquierda y portadores de DAI tratados con ablación con catéter por TV recurrente tienen un menor coste sanitario que los pacientes con el mismo perfil de riesgo tratados médicamente.
        - Los pacientes con miocardiopatía, disfunción sistólica ventricular izquierda y portadores de DAI tratados con ablación con catéter por TV recurrente tienen una tasa de mortalidad menor que los pacientes con el mismo perfil de riesgo tratados médicamente.

- Objetivos:
    - Evaluar en una cohorte de pacientes con un perfil clínico de riesgo similar con TV recurrente, miocardiopatía, disfunción sistólica ventricular izquierda y portadores de DAI:

        - La tasa de ingresos por causas cardiovasculares en los pacientes tratados con ablación con catéter comparado con los pacientes tratados médicamente.
        - Los costes sanitarios de una estrategia de tratamiento con ablación con catéter vs una estrategia de tratamiento médico.
    - Evaluar en una cohorte de pacientes con un perfil clínico de riesgo similar con TV recurrente, miocardiopatía, disfunción sistólica ventricular izquierda y portadores de DAI la tasa de mortalidad de una estrategia de tratamiento con ablación con catéter respecto al tratamiento médico.

Parte III: Evaluación y validación de una nueva estrategia para la ablación mecanística del sustrato de TV en humanos: DEEP mapping.

- Hipótesis:
    - Primaria:
        - La estrategia mecanística de mapeo de zonas de conducción decremental (DEEP mapping) en pacientes con TV recurrente por cardiopatía estructural es posible e identifica las zonas críticas del circuito de TV mejor que los potenciales tardíos no-decrementales.
    - Secundaria:
        - La estrategia mecanística de mapeo y ablación focalizada de zonas de conducción decremental (DEEP mapping y ablación) en pacientes con TV recurrente por cardiopatía estructural se acompaña de tasas de éxito agudo y a medio plazo comparables con otras estrategias contemporáneas de ablación de sustrato.

- Objetivos:

- Evaluar la viabilidad de realizar mapas de zonas de conducción decremental con los sistemas de navegación electroanatómicos y secuenciales y valorar su precisión en la detección de zonas críticas en el circuito de TV.
- Implementar una estrategia mecanística de ablación de TV focalizada en la eliminación de potenciales decrementales y valorar su eficacia aguda y a medio plazo.

Parte IV: Mejora de la influencia direccional en los electrogramas bipolares mediante los registros omnipolares en un modelo translacional de sustrato de TV.

- Hipótesis
  - Primaria:
    - El mapeo electroanatómico en tiempo real en un modelo animal de sustrato de TV con electrogramas omnipolares se asocia con la detección de mayores valores de voltaje comparado con los electrogramas bipolares.
  - Secundaria:
    - El mapeo electroanatómico en tiempo real en un modelo animal de sustrato de TV con electrogramas omnipolares se asocia a la creación de mapas de voltaje más precisos y con menor variabilidad latido a latido comparado con electrogramas bipolares.
- Objetivos
  - Definir con electrogramas omnipolares el sustrato de TV en un modelo animal.
  - Comparar los resultados del mapeo con electrogramas omnipolares con electrogramas convencionales bipolares en un modelo animal.

- Analizar la precisión en la detección de escara miocárdica detectada por resonancia magnética cardíaca de los electrogramas omnipolares en un modelo animal.

Resultados:

Parte I: Análisis del impacto de las terapias de DAI en pacientes de un registro poblacional incluyendo indicación en prevención secundaria.

Nuestra cohorte de estudio incluyó 7020 pacientes, siendo 5091 (72.5%) portadores de DAI en prevención primaria y 1929 (27.5%) en prevención secundaria. Comparados con los pacientes en prevención secundaria, los portadores de DAI en prevención primaria presentaban en el momento del implante una FEVI más deprimida, una clase funcional de la NYHA más avanzada, habían sufrido más ingresos hospitalarios por insuficiencia cardíaca en el pasado, tenían más prevalencia de diabetes y mayor proporción de DAI-TRC. Además, una mayor proporción de ellos estaba recibiendo fármacos para el tratamiento de la disfunción ventricular en mayor proporción, aunque muchos menos se hallaban en tratamiento antiarrítmico con amiodarona.

Durante el seguimiento (mediana de 5 años, rango intercuartil 3.8-6.3 años), la tasa acumulada de descargas apropiadas del DAI en los pacientes en prevención primaria fue del 8.4% y de terapias antitaquicardia (ATP) del 12.1%. Dichas tasas fueron el doble en los pacientes tratados en prevención secundaria: 16.1% de descargas y 23.1% de ATP ($p<0.001$). Las tasas de mortalidad fueron similares en ambos grupos: 6.87 por 100 personas-año en prevención primaria y 7.31 por 100 personas-año en prevención secundaria ($p=0.178$). Dichas tasas fueron superiores en los pacientes que recibieron descargas del DAI en prevención primaria que secundaria: 13.02 vs 9.94 muertes por 100 personas-año ($p=0.02$). En cuanto a las ATP, su impacto sobre la mortalidad fue similar en prevención primaria y secundaria (10.58 vs 9.95 muertes por 100 personas-año, $p = 0.52$). El riesgo ajustado de muerte tras haber sufrido descarga fue el doble en los pacientes con DAI en prevención primaria vs pacientes sin descargas (HR 2.00, IC 95% 1.72-2.33). Dichos hallazgos fueron similares en los pacientes con DAI en prevención secundaria, con un HR de 1.46, IC 95% 1.20-1.77). No hubo una interacción

estadísticamente significativa en la mortalidad entre la indicación del implante y haber sufrido descargas, lo que hace sugerir que el impacto de las descargas sobre la mortalidad es independiente de la indicación del DAI.

Los resultados respecto al ATP mostraron que en los pacientes con DAI en prevención primaria, sufrir ATP se asoció a un incremento de la mortalidad del 73% comparado con aquellos que no requirieron ATP (HR 1.73, IC 95% 1.52-1.97). Dicho riesgo fue menor para los pacientes en prevención secundaria (HR 1.38, IC 95% 1.16-1.64) con una interacción que no resultó ser estadísticamente significativa (p=0.4).

Parte II: Comparación de la evolución clínica, ingresos y costes económicos de la ablación con catéter con respecto al tratamiento médico en pacientes con TV recurrente.

Se incluyeron 100 pacientes de un único centro tratados con ablación con catéter de TV, todos ellos con cardiopatía estructural y portadores de DAI. Mediante un esquema de propensity-score matching, de un registro de aproximadamente 7000 pacientes con cardiopatía estructural y portadores de DAI se seleccionaron 100 controles con las mismas características basales clínicas (edad, género, FEVI, diabetes, niveles de creatinina en sangre, tipo de miocardiopatía) y que presentaban también terapias apropiadas repetidas del DAI e ingresos repetidos por arritmias ventriculares. Se estudió la evolución de los pacientes en cuanto a su tasa de ingresos y los motivos 1 año antes y 2 años después de la fecha índice. Como fecha índice se estableció el día del procedimiento de ablación en el grupo invasivo y la fecha de readmisión por TV en el grupo de tratamiento médico. Como análisis pre-especificado también se realizó un emparejamiento por el uso de fármacos antiarrítmicos y por el número de ingresos por TV en el año previo en dos grupos de 66 pacientes (invasivo versus médico).

En el grupo de manejo invasivo se observó una reducción significativa de la tasa de ingresos de causas cardiovasculares en los 2 años post-ablación respecto al año pre-ablación (145 ingresos vs 49 ingresos por 100 personas-año, RR 0.35, IC 95% 0.26-0.47) y de forma similar en cuanto a las consultas a los servicios de Urgencias de causa cardiovascular (140 visitas vs 55 visitas por 100 personas-año, RR 0.41, IC 95% 0.30-0.56). La reducción fue fundamentalmente a expensas del número de ingresos y visitas motivadas por arritmias ventriculares. Comparado con el grupo de tratamiento médico, no se observaron diferencias significativas en la tasa de ingresos por causa cardiovascular (RR 0,94, IC 95% 0.57-1.54) ni en la tasa de consultas a urgencias por causa cardiovascular (RR 0.86, IC 95% 0.54-1.38). En cuanto a la mortalidad de cualquier causa, se observó una menor mortalidad en el grupo de tratamiento invasivo respecto al médico (0.63, IC 95% 0.4-0.99).

Analizando los grupos invasivo (n=66) y médico (n=66) añadiendo el uso de fármacos antiarrítmicos y la carga de ingresos por TV previos como factores de emparejamiento, los resultados fueron superponibles.

En cuanto a los costes de ambas estrategias, se observó que no hubieron diferencias estadísticamente significativas entre los grupos (invasivo 40.707 CAD$ anuales vs médico 34.338 CAD$, p = 0.051).

Parte III: Evaluación y validación de una nueva estrategia para la ablación mecanística del sustrato de TV en humanos: DEEP mapping.

En este estudio se incluyeron de forma prospectiva y multicéntrica 20 pacientes con miocardiopatía isquémica. Las características clínicas basales eran típicas de una serie de pacientes con episodios de taquicardia ventricular: edad 65 años, FEVI 33%, mayoría de varones, NYHA III-IV en un 10%, DM2 en 40% y en tratamiento con amiodarona en 35% de los casos y con múltiples antiarrítmicos en 40% de los casos, así como un 30% en situación de tormenta arrítmica.

En los mapas de sustrato realizados se observó que la zona con potenciales tardíos ocupaba un 17% del miocardio mapeado (RIC 8.9% a 73.7%), mientras que la zona con conducción decremental (DEEP) ocupaba únicamente un 4.8% (RIC 2.2% a 25.7%), $p < 0.001$. Todos los pacientes presentaban TV inducible al inicio del procedimiento. Mediante una estrategia de ablación focalizada en los DEEP se consiguió la no inducibilidad de ninguna TV en el 80% de los pacientes.

La carga de TV valorada a través de los registros del DAI mostró una mediana de 11 episodios de TV por paciente (RIC 5 a 25) en los 6 meses pre-procedimiento y de 0 (RIC de 0 a 2) post procedimiento ($p=0.02$). En el 75% de los pacientes no hubo recurrencia de ninguna TV a los 6 meses.

El análisis de los mapas de activación detallados con respecto a los DEEP y potenciales tardíos pudo realizarse en 13 TVs en 9 pacientes. Las áreas con DEEP identificaron la región con potenciales meso-diastólicos durante TV con una sensibilidad de 0.61 (IC 95% 0.52 a 0.69) con una especificidad de 0.97 (IC 95% 0.95-0.98) y un área de la curva ROC de 0.86 (IC 95% 0.82 a 0.88). Estos resultados son comparativamente mejores a los de los potenciales tardíos con una sensibilidad de 0.60 (IC 95% 0.44 a 0.74) y una especificidad de 0.82 (IC 95% 0.73 a 0.89) con un área de la curva ROC de 0.79 (IC 95% 0.75 a 0.82), $p<0.05$.

Parte IV: Mejora de la influencia direccional en los electrogramas bipolares mediante los registros omnipolares en un modelo translacional de sustrato de TV.

En el modelo translacional de infarto de miocardio porcino se realizaron mapas electroanatómicos mediante el sistema EnSite NavX Precision ™ y con un catéter con 16 electrodos con espaciado inter-electrodo fijo (Advisor HD Grid ™) de 4mm mediante acceso percutáneo y retro-aórtico. Se estudiaron 10 animales (3 sanos, 7 post-infarto) mediante mapeo simultáneo con electrogramas convencionales bipolares registrados con pares de bipolos longitudinales (BL) o bipolos perpendiculares (BP) y electrogramas Omnipolares creados entre 3 polos.

Los mapas bipolares creados BL y BP no difirieron significativamente en cuanto a los valores de voltaje pico a pico medio (4.88 +/- 0.95mV vs 4.94 +/- 0.95mV), pero sí lo hicieron de forma cualitativa en el sistema de mapeo electroanatómico, enfatizando la importancia de la dirección del frente de onda en el EGM bipolar.

El omnipolo máximo (OTVmax) mostró un voltaje pico a pico mayor que el voltaje bipolar BL o BP (6.64 +/- 0.95 mV vs 4.88 +/- 0.95 mV o 4.94 +/- 0.95mV, $p<0.05$ para ambas comparaciones). Dichas diferencias se mantuvieron en zonas de escaso voltaje. Las cifras de voltaje máximo obtenido con OTVmax fueron siempre mayores que cualquier bipolo obtenido en la misma localización y presentaron una correlación lineal, con valores 10% mayores en la zona de miocardio sano y 8% mayores en la zona de miocardio con escara identificada mediante RMC.

En cuanto a las variaciones en el voltaje pico a pico durante cada latido se observó que el coeficiente de variación (CoV) en los OTVmax fue menor que para los EGM bipolares (0.17 +/- 0.12 vs 0.32 +/- 0.16, $p<0.01$) en zonas sanas y 0.19 +/- 0.10 vs 0.32 +/- 0.13, $p<0.01$) en zonas con infarto, indicando menor variación latido a latido en los EGM omnipolares.

En cuanto a la capacidad para identificar y localizar la presencia de cicatriz evaluada mediante RMC se observó que el área de bajo voltaje identificada por los OT-EGM fue más similar al área identificada por RMC de realce subendocárdico que el área identificada con los EGM bipolares.

Por último, la densidad de puntos obtenida en los mapas omnipolares fue mayor (en el mismo tiempo) que en los bipolares, indicando una homogeneidad mayor en el mapeo mediante el uso de omnipolos.

Discusión:

Aspectos generales:

Este trabajo aporta una visión translacional novedosa en diversos aspectos del manejo del paciente con miocardiopatía y arritmias ventriculares.

Parte I: Análisis del impacto de las terapias de DAI en pacientes de un registro poblacional incluyendo indicación en prevención secundaria.

Una de las situaciones más temidas por los pacientes tras el implante de un DAI es la posibilidad de experimentar una descarga del mismo. Se conocía ampliamente por estudios previos en la literatura que la evolución de los pacientes tras recibir una descarga del DAI empeoraba y su riesgo de mortalidad aumentaba(24, 40, 41). Sin embargo, dichos hallazgos nunca se habían confirmado en los pacientes portadores de DAI en prevención secundaria dado que los únicos datos disponibles mostraban un efecto nulo sobre la mortalidad (49). El registro de DAIs de la provincia de Ontario, Canada, ofrece la posibilidad del análisis de datos de gran calidad y se trata de una herramienta ideal para responder a la pregunta del impacto sobre la mortalidad que experimentan los pacientes con DAI en prevención secundaria tras experimentar una descarga o ATP apropiadas.

Nuestros datos muestran un claro incremento en la mortalidad para ambos grupos de pacientes (5091 en prevención primaria y 1929 en prevención secundaria) tras recibir ATP o descargas del DAI. Dichos hallazgos, combinados con el hecho de que los pacientes en prevención secundaria experimentan el doble de terapias apropiadas del DAI que los pacientes en prevención primaria, pueden explicar la interesante evolución de la mortalidad global. De forma muy llamativa, los pacientes con DAI en prevención secundaria tienen unos parámetros clínicos de menor riesgo en el momento del implante (mejor FEVI, más jóvenes, menor número de episodios de insuficiencia cardíaca previa). Sin embargo, a largo plazo,

la evolución en cuanto a tasas de mortalidad es similar a la de los pacientes sometidos a implante de DAI por prevención primaria.

La mejor estrategia a fin de disminuir las tasas de descargas de DAI para aumentar la supervivencia está aún por definir, dado que en los ensayos clínicos destinados a dicho fin no se ha observado ningún beneficio en cuanto a supervivencia de una estrategia invasiva de ablación con catéter del sustrato de TV (29, 63, 64). Nuestros resultados también ejemplifican la necesidad de seguir identificando marcadores de riesgo que detecten a los pacientes con riesgo aumentado de sufrir episodios de TV durante el seguimiento, para poder focalizar la atención en dichos casos. A nivel del manejo clínico de los pacientes, debe otorgarse una gran importancia a la presencia de terapias del DAI debe ser siempre valorada con gran importancia, dado que constituye un marcador de inestabilidad clínica, con un impacto en la mortalidad similar o mayor que otras variables que suelen captar antes nuestra atención como la FEVI menor al 20% o que el paciente se halle en una CF III-IV de la NYHA o haber requerido ingresos previos por insuficiencia cardiaca.

Parte II: Comparación de la evolución clínica, ingresos y costes económicos de la ablación con catéter con respecto al tratamiento médico en pacientes con TV recurrente.

Una situación de gran complejidad clínica es la que se refleja en la parte II de esta tesis: La decisión terapéutica de tratamiento invasivo con ablación con catéter en el paciente que está sufriendo descargas frecuentes del DAI o bien el tratamiento con fármacos. En nuestro estudio, mediante el esquema de propensity-score incluyendo las variables clínicas más importantes que determinan la evolución clínica, hemos evaluado el tratamiento médico o invasivo de este subgrupo de pacientes tan común, focalizando nuestra atención en el impacto no sólo sobre la mortalidad sino también en los ingresos y consultas a urgencias por causa cardiovascular y arrítmica y sobre los costes sanitarios. Esta evaluación es importante para contribuir a la construcción realista de expectativas del paciente

ante el tratamiento invasivo o médico. En este sentido, un tercio de pacientes incluidos en nuestro estudio estaban afectos de miocardiopatía no isquémica, tratándose este de un subgrupo escasamente representado en ensayos aleatorizados y por lo tanto con unas expectativas desconocidas hasta el momento. Por otra parte, nuestro análisis proporciona información de gran valor para la organización de sistemas sanitarios con cobertura universal como el español o canadiense.
Los resultados se hallan en consonancia con los del estudio aleatorizado VANISH donde el manejo invasivo no se asoció a mayor supervivencia (26). Además, se demuestra que mediante la ablación con catéter se consigue una reducción muy significativa de la tasa de ingresos en el grupo tratado aunque sin una clara diferencia respecto al tratamiento médico, sin incrementar los costes sanitarios con ninguna de las 2 estrategias. Todo ello indica que ambas estrategias pueden ser empleadas con seguridad y sin perjuicio de nuestros pacientes, incluidos aquellos con miocardiopatía no-isquémica. En el contexto de nuestro sistema sanitario, y teniendo en cuenta las cifras crecientes de empleo de ablación de TV en pacientes con cardiopatía estructural es importante que se analice de forma individualizada la situación de cada paciente al afrontar el manejo de esta patología con efectos tan devastadores.

Parte III: Evaluación y validación de una nueva estrategia para la ablación mecanística del sustrato de TV en humanos: DEEP mapping.

Múltiples estrategias para la ablación del sustrato de TV han sido descritas en la literatura. Desde las descripciones iniciales de la importancia de los potenciales tardíos y su correlación con el circuito de la TV (79, 130-132) hasta las estrategias más elegantes y recientes de bloqueo de la conducción a los canales de TV detectados mediante RMC y procesado de intensidad de señal en la cicatriz miocárdica(150). Sin embargo, otras estrategias han mostrado criterios muy laxos a la hora de definir las zonas de interés en la ablación de TV, es decir, el sustrato responsable de la aparición del circuito de la TV. Por ejemplo, trabajos como los

que ejemplifica una homogenización endo-epicárdica del sustrato de TV en el que toda la zona de voltajes bajos se debe eliminar con RF (66) o el aislamiento de todo el "núcleo" de la cicatriz miocárdica (67).

Tras el hallazgo en 2015 de la importancia de las zonas de conducción decremental (DEEP) en el sustrato de TV y su capacidad de correlacionar con el circuito reentrante o iniciador de la TV (98)se diseñó el estudio que presentamos en la parte III de este trabajo. Con el objetivo fundamental de identificar áreas del sustrato de TV susceptibles a ser parte del circuito de reentrada y de sostén de la TV mediante extraestimulación se diseñó una estrategia de ablación focalizada en dichas zonas con resultados agudos y a medio plazo concordantes con la literatura contemporánea. Dichos hallazgos se asemejan en gran medida a los de otros grupos contemporáneos que han aplicado técnicas muy similares para la identificación de sustrato "oculto" (92, 136, 137). Trabajos de nuestro grupo sobre sustrato atrial y sobre modelos *in silico* han demostrado también la utilidad de esta herramienta en la valoración del sustrato arritmogénico(139, 140). De forma paralela, en modelos animales de sustrato de TV se ha observado que las zonas que muestran enlentecimiento de la conducción durante ritmos estables son las que con más frecuencia co-localizan con el istmo de la TV, hallazgos que apuntan a la importancia del sustrato funcional y dinámico en la iniciación de los episodios de TV(107). La automatización de la identificación de las zonas de conducción decremental podría tener un interés importante en el futuro ya que facilitaría la rápida focalización de la ablación consiguiendo buenos resultados.

Parte IV: Mejora de la influencia direccional en los electrogramas bipolares mediante los registros omnipolares en un modelo translacional de sustrato de TV.

El avance de las herramientas de mapeo electroanatómico ha generado grandes mejorías en la precisión de nuestros procedimientos. Sin embargo, una de las limitaciones más importantes bien conocidas desde los años 80 es la gran

influencia que juega el ángulo del frente de onda con respecto al par de polos que integra al bipolo que registra la actividad.

Con el objetivo de eliminar dicha limitación, pero manteniendo la esencia de la detección local de los electrogramas bipolares, se ha validado *ex vivo* e *in vivo* durante ritmos simples la utilidad de los electrogramas omnipolares. Mediante el uso de un set de 3 electrodos formando un triángulo separado por distancias fijas, se obtiene el electrograma local en 3D que corresponde de forma simplificada a un vectorcardiograma local de la activación(104, 105). Dicha obtención del EGM desde 3 electrodos permite su valoración en todos los ángulos posibles y permite también identificar su dirección de propagación. Estas propiedades, ya previamente demostradas por nuestro grupo en modelo ex-vivo humano y preclínico de ritmos complejos(106, 143), quedaban todavía por validar in-vivo en modelo preclínico de sustrato ventricular. Con el objetivo de valorar su utilidad in vivo diseñamos la parte IV de este trabajo. En este trabajo hemos observado que la aplicación pre-clínica de un catéter multielectrodo con un set de electrodos equidistantes es una herramienta que, en combinación con los EGM omnipolares, permite la identificación de zonas de escaso voltaje con mayor facilidad que los electrogramas bipolares, en menor tiempo, con mayor densidad y con menor variación latido a latido. Todo ello abre la puerta a su uso a nivel clínico para conseguir resolver la problemática de la direccionalidad de los registros de los EGM bipolares.

Conclusiones:

El trabajo translacional de esta tesis muestra una visión panorámica que incluye registros poblacionales amplios, series de pacientes con abordaje invasivo de TV, nuevas herramientas clínicas para la ablación y nuevos conceptos preclínicos para avanzar en el conocimiento de la evolución de los pacientes, su sustrato y su mejor estrategia terapéutica.

Los hallazgos principales son los siguientes:

1. En un registro poblacional de 7020 pacientes con DAI, los pacientes tratados con DAI en prevención secundaria presentaron un incremento del riesgo de mortalidad tras sufrir terapias apropiadas del DAI (ATP o descargas).
2. Los pacientes que sufren TV recurrente experimentan una disminución significativa de los ingresos por TV tras ablación con catéter respecto al periodo pre-ablación. Sin embargo, no presentan tasas menores de hospitalización de causa vascular comparado con pacientes tratados médicamente con su mismo perfil de riesgo.
3. Una estrategia mecanística con DEEP mapping para evaluar y ablacionar el sustrato de TV es altamente específica para la identificación de los potenciales responsables de las zonas críticas de la TV sin requerir la inducción y mapeo de activación.
4. Los electrogramas independientes del frente de activación (Omnipolares) consiguen el máximo voltaje local registrado *in vivo* y es una herramienta fiable para identificar el sustrato arrítmico ventricular con precisión.

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