New Insights Into the Mechanism and Treatment of Idiopathic Ventricular Arrhythmias

Leendert Jan de Vries

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Nieuwe inzichten in het mechanisme en de behandeling van idiopathische ventriculaire aritmieën

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"Accepter l'absurdité de tout ce qui nous entoure est une étape, une expérience nécessaire: ce ne doit pas devenir une impasse. Elle suscite une révolte qui peut être féconde"

(Accepting the absurdity of everything around us is one step, a necessary experience: it should not become a dead end. It arouses a revolt that can become fruitful)

- Albert Camus ("*Three Interviews*" in *Lyrical and Critical Essays; 1970*)

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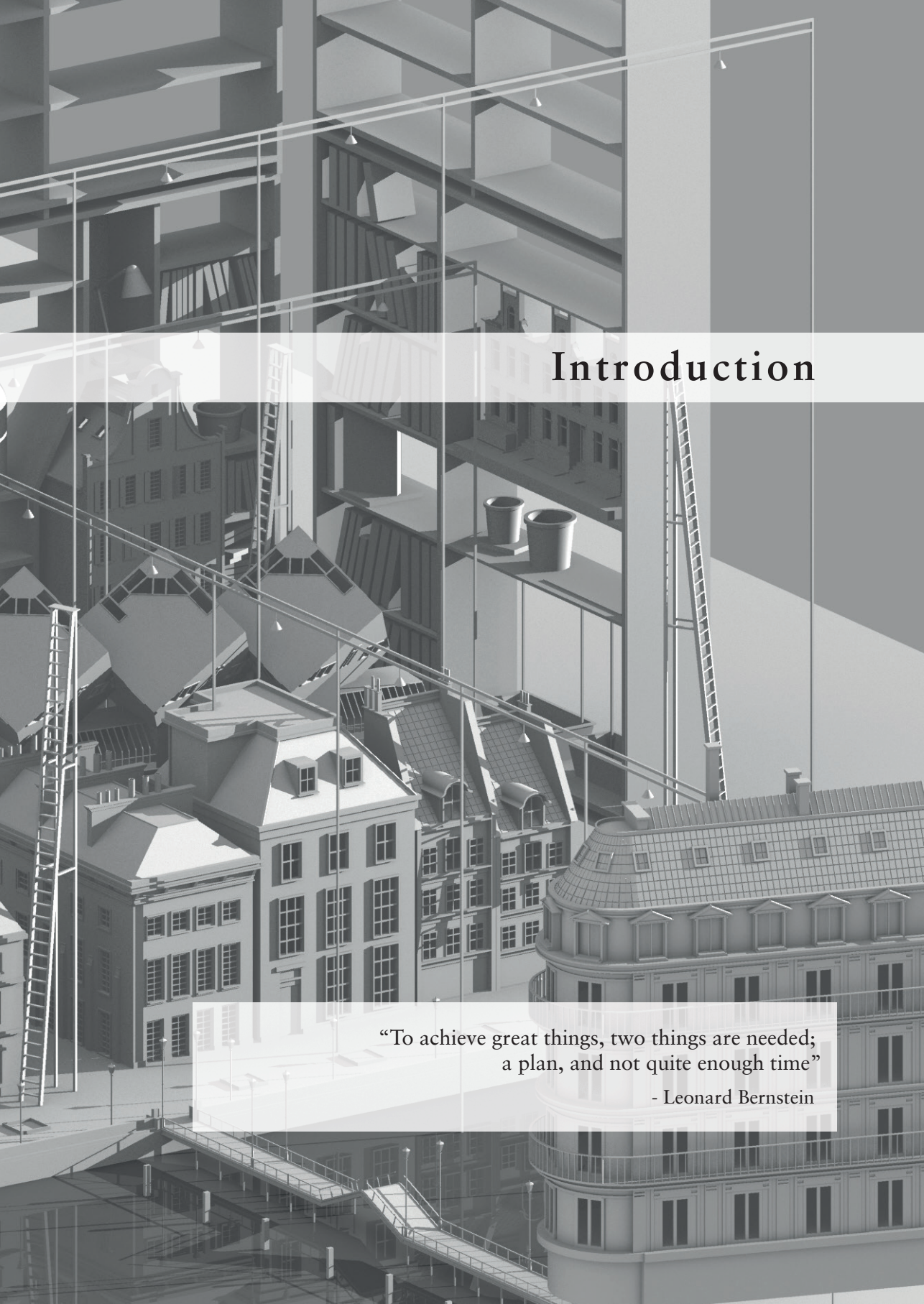

Introduction

"To achieve great things, two things are needed;
a plan, and not quite enough time"

- Leonard Bernstein

INTRODUCTION

Why do ventricular arrhythmias (VAs) occur in perfectly healthy people with a seemingly normal and potent heart? This question represents the main motive of this thesis. Not only does it represent the motive: the driving force behind most of the research described in this thesis, but also the *motif*: the recurrent theme that connects these studies. In the following chapters, a *motif* was also what we looked for in order to be able to explain the numerous intriguing clinical observations that we made or found in the literature. Oftentimes, mostly due to its repetitive nature, a *motif* is hard to overlook. Some patterns, however, may be more difficult to detect, for example due to the fact that we are unable to see past the dogmas in our frame of reference. In other occasions we may see a pattern where there actually is none, caused by our human brains' excellent, although in this case unfortunate, pattern recognition abilities. These issues may be overcome by creating our own frame of reference based upon fundamental research and by deliberately and explicitly looking for evidence contrary to our hypothesis, respectively. It is the difference between seeing a connection, and proving one.

A hint at where an answer may be found is already enclosed in the question itself, in the evocative phrase "seemingly normal", which suggests that these hearts actually may not be normal: the abnormality may just not have been uncovered or recognized yet. Therefore, in this thesis we aim to investigate and clarify the fundamental mechanisms behind IVAs and to gain new insights into their treatment. We pursue this by first reviewing the fundamental experimental research at the base of what is currently known in the literature about IVAs and continue to build upon this foundation by using this knowledge to conduct our own original research.

Definitions

First, we have to calibrate our definitions. Idiopathic ventricular arrhythmias (IVAs) are tachycardias or premature ventricular contractions (PVCs) arising from either one of the cardiac ventricles that occur in patients without the presence of any apparent structural heart disease[1]. The term "IVA" is a hypernym for all ventricular arrhythmias (VAs) that occur in patients with structurally normal hearts, varying from fascicular to papillary VAs. The subgroup that accounts for the largest share of IVAs, and that is at the center of this thesis, are the outflow tract (OT) IVAs, named after their referred location in the left- or right ventricular OT (LVOT or RVOT). They most frequently emerge from the RVOT[1]. Why this arrhythmia is commonly confined to this specific region is subject to discussion and may at the same time be an important clue regarding the underlying mechanism.

Epidemiology, clinical presentation and treatment

In the general population IVAs are not uncommon and, when screened for, may be seen in around 50% of people[2, 3]. Fortunately, the frequency of PVCs only rarely surpasses 50 beats per 24-hours (in 2-6%)[2,3]. Of all VA etiologies, IVAs are estimated to account for approximately 10%[4]. As mentioned earlier, the majority of this proportion consists of OT IVAs[1]. The occurrence of OT IVAs is generally not associated with a higher mortality rate, a higher rate of sudden cardiac death (SCD) or later development of structural heart disease[5-7]. Only in seldom cases they may be associated with a more malignant type of arrhythmia[8, 9]. Nevertheless, they can be highly symptomatic (with complaints ranging from palpitations to hemodynamic instability) and additionally may cause tachycardiomyopathy in patients that have a very high VA burden[10, 11].

One of the treatments for VAs that is increasingly being performed and is generally reported to have high success rates for both ventricular tachycardias (VTs) and PVCs is catheter ablation (CA)[1]. For OT IVAs, CA it is now considered a first choice therapy[1]. In our center nearly 70% of all performed VA CAs are of IVAs, and this number has been steadily increasing over the years. This rise is most likely caused by the constant improvement and increased safety of this technique, making it more and more suitable for safely treating arrhythmias that generally have a benign prognosis and that would previously have been treated more conservatively with anti-arrhythmic drugs out of fear for taking unnecessary risks in the form of CA related complications.

Curiously, although in general the success rate of OT IVA CA is considered high[1], when the literature is analyzed actually a broad range in success rates is reported (between 54 and 100%[12, 13]). This may partly be explained by differences in IVA locations, some of which are easier to reach than others. However, it is known among electrophysiologist that in practice, IVA OT CAs are often not as easy or as highly successful as the success rate of >95% reported in the European guidelines suggests[1]. This discrepancy between success rates could also reflect a gap of knowledge regarding the actual underlying arrhythmia mechanism of OT IVAs.

IVA etiology

Then what is the underlying arrhythmia mechanism of OT IVAs? Of the three basic arrhythmia mechanisms (automaticity, re-entry and triggered activity), a general mainstay classification for the mechanistic division of different cardiac arrhythmias, OT IVAs are considered to be caused by triggered activity (cyclic adenosine monophosphate (cAMP) mediated delayed afterdepolarizations (DADs))[14, 15]. This generally accepted assumption, however, is founded on a series of experiments in which

through deductive reasoning the IVA mechanism is concluded to be triggered activity based on the response of the arrhythmia on pacing maneuvers and on pharmacological interventions[14, 15]. This conclusion is reached based on the simplified hypothesis that only three basic mechanisms exist, by providing evidence that the two remaining mechanisms (automaticity and re-entry) as underlying causes can be excluded[14, 15]. If, however, we consider that other arrhythmia mechanisms may also exist, these assumptions are invalid and merely prove that the arrhythmia is not caused by these two mechanisms but by another. One that may share some common characteristics with the triggered activity mechanism but that does not necessarily have to be analogous to it. Additionally, this theory provides no satisfying answer to the question why these cAMP mediated DADs occur in the first place, as opposed to other triggered activity arrhythmias (such as catecholamine polymorphic ventricular tachycardia (CPVT) or digitalis induced VT) where the cause can be appointed to a specific receptor (ryanodine) or ion-exchanger (sodium-calcium), respectively. Moreover, these arrhythmias do not present as monomorphic VAs as is the case for OT IVAs. As mentioned earlier, the localized presentation of this arrhythmia in the OTs is also of interest. In contrast, the aforementioned arrhythmias that are similarly categorized into the triggered activity mechanism are not confined to a specific region in the heart. In other words: what is so special about the outflow tract region that would make them more prone to generate triggered-activity mediated VAs?

Finally, there are several other intriguing questions we could ask ourselves: why do atrioventricular nodal re-entry tachycardias (AVNRTs) often co-exist with OT IVAs? What is the significance of the simultaneous disappearance of OT IVAs after accessory pathway ablation? How can pacing from atrial tissue induce PVCs from the ventricular outflow tracts? What causes the conduction-tissue-like signals preceding idiopathic PVCs at the site of the ablation? Why do PVCs associated with the developmental heart disease non-compaction cardiomyopathy (NCCM) often emerge from the outflow tracts? Is there a *motif* behind these seemingly unrelated observations?

These are just some pieces of the puzzle regarding the OT IVA etiology, emphasizing the need to question the commonly accepted dogmas surrounding this arrhythmia and to explore alternative precipitating factors.

Aim of this thesis

Following the conclusions that have to be drawn from the abovementioned considerations, this thesis aims to investigate and clarify the fundamental mechanisms behind OT IVAs and to gain new insights into their treatment. To attain these objectives, we focus on the following subjects:

- Etiology, or: the role of the embryologic development of the heart and the cardiac conduction system in the occurrence of OT IVAs (Part I)
- New perspectives on arrhythmia mechanisms and precipitating factors of IVAs (Part II)
- Therapeutic challenges and future perspectives on the treatment of IVAs (Part III)

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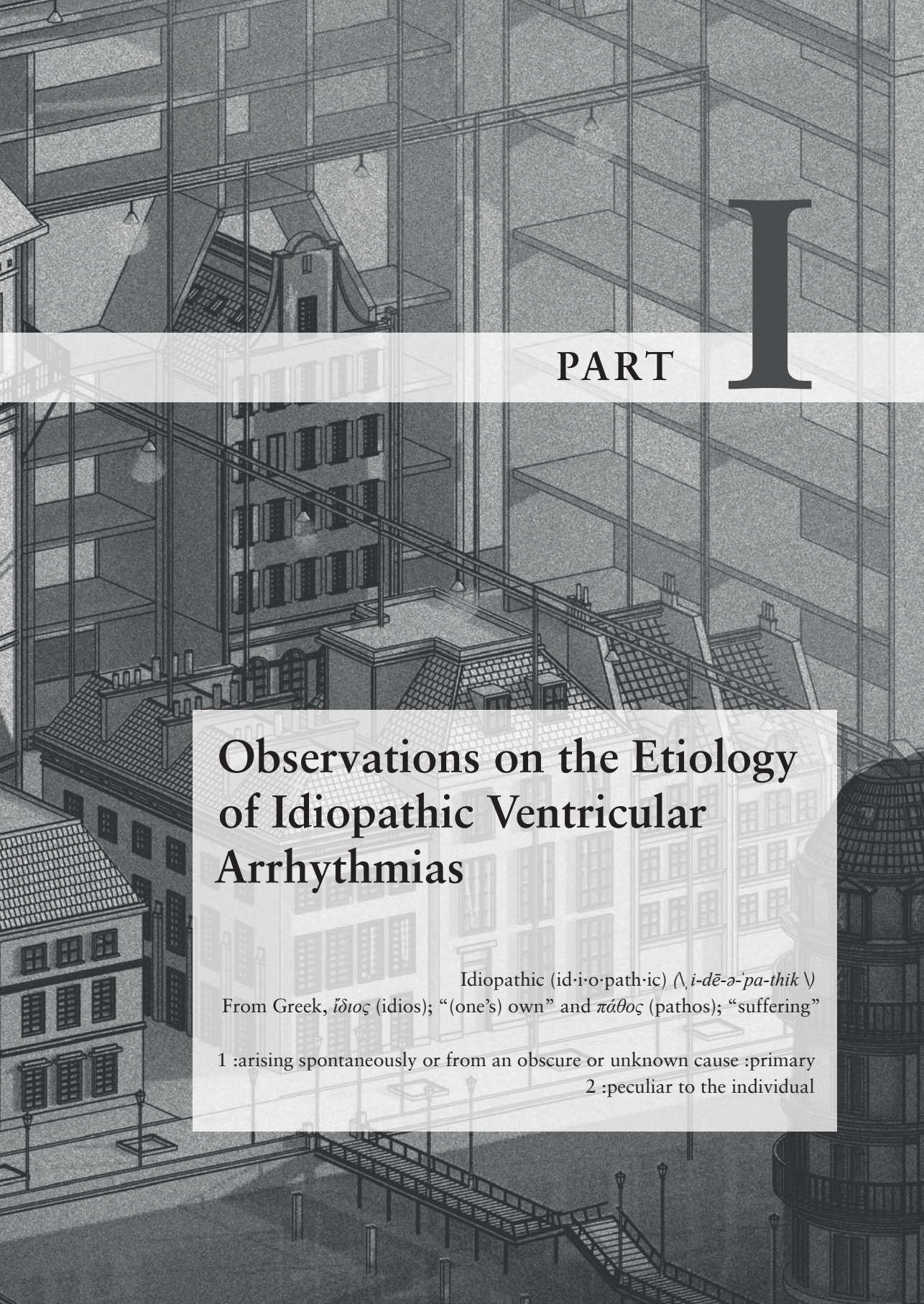

PART I

Observations on the Etiology of Idiopathic Ventricular Arrhythmias

Idiopathic (id·i·o·path·ic) /\ˌi-dē-ə-ˈpa-thik\/
From Greek, *ἴδιος* (idios); "(one's) own" and *πάθος* (pathos); "suffering"

1 :arising spontaneously or from an obscure or unknown cause :primary
2 :peculiar to the individual

Chapter 1

The "Dead-end tract" and its role in arrhythmogenesis

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ABSTRACT

Idiopathic outflow tract ventricular arrhythmias (VAs) represent a significant proportion of all VAs. The mechanism is thought to be catecholamine-mediated delayed after depolarizations and triggered activity, although other etiologies should be considered. In the adult cardiac conduction system it has been demonstrated that sometimes an embryonic branch, the so-called "dead-end tract", persists beyond the bifurcation of the right and left bundle branch (LBB). Several findings suggest an involvement of this tract in idiopathic VAs (IVAs). The aim of this review is to summarize our current knowledge and the possible clinical significance of this tract.

1. INTRODUCTION

During the development of the ventricular conduction system sometimes a so-called "dead-end tract" is seen in addition to the right and left bundle branch, fading out on the crest of the muscular ventricular septum[1,2]. Remnants of the developing conduction system have been linked to the occurrence of arrhythmias[3]. The frequently described co-existence of VAs from the outflow tracts, the area in which the dead-end tract may persist, and the presence of atrioventricular re-entry tachycardias in structural normal hearts could implicate a clinical significance of this tract in the form of a connection between these regions[4-8]. Outflow tract VAs without underlying structural heart disease can be found in a large part of the population and can be very symptomatic[9-16]. The mechanism behind these IVAs is not completely understood and could be explained by the dead-end tract. In this review we aim to summarize our current knowledge and the clinical significance of this tract.

2. THE DEAD-END TRACT IN THE DEVELOPING CARDIAC CONDUCTION SYSTEM

2.1. The Developing Heart

The developing heart consists of cardiomyocytes with distinctive combinations of automaticity, conduction and contraction regulated by Tbox transcription factors[17,18]. Growth of the heart is established not by the division of myocytes, but by the addition of cells from a pool of precursors who do not obtain a definitive identity until they reach their final destination[19-22]. The formation of the cardiac chambers is characterized by ballooning: proliferation and differentiation in specific locations of the primary heart tube[23]. In the atrial appendages, trabeculated myocardium in the finalized heart is acquired from the ballooned atrial chambers[23]. The smooth part of the atrial walls is shaped from the myocardium from the connecting veins and the atrial component of the primary heart tube[23-26]. In the outer curve of the heart tube lies the origin of the developing ventricles[27]. After initial proliferation of trabeculated myocardium, compact myocardium is formed by discontinuation of proliferation at the luminal side and an increase in proliferation at the pericardial side[28-30].

2.2. The Developing Conduction System

2.2.1. The Ring Theory

The ring theory, as proposed in earlier studies, states that four rings of specialized tissue precede the development of the conduction system[31]. Under normal circumstances these rings should, after fusing, lose their specialized quality or vanish by apoptosis.

In the fully developed heart the sinus node, AV node, His bundle and bundle branches are thought to originate from the remnants of these rings[31]. This theory has been a source of great discussion. However, Lamers et al. provided a conclusive evaluation after studying material from human embryos showing that the inlet component of the morphologically right ventricle forms from the ascending limb of the embryonic ventricular loop, and that the inlet and apical trabecular elements of the muscular septum are formed from the same primary ventricular septum[32].

2.2.2. Nodal Myocytes

When focusing specifically on the conduction system, the development starts in the early embryonic heart tube. Some early data on the development of the conduction of the heart came from studying avian embryos[33,34]. However, studies of human material were also available[32,35,36]. It is important to emphasize that during its development, the cardiac conduction system is not so much a single confined system as it is a composition of myocyte populations[37]. Although in the early embryonic stages ECGs resembling adult ones can be recorded, morphologically this arrangement of cells cannot be recognized[38,39].

Around Carnegie Stage 9–10 (19–23 days post fertilization), the first beats of the developing heart can be distinguished[40-42]. The first signs of the sinus node appear after five weeks of human development in the anteromedial wall of the right common cardinal vein[43,44]. This leading pacemaker at the most posterior part of the heart tube ensures a unidirectional peristaltic contraction wave. However, it is unclear how this pacemaker area remodels into a node distinct from the atrial neighboring myocardium. Due to the previously mentioned cardiomyocytes with their distinctive arrangement of characteristics, an adult-resembling ECG expressing the sequential activation of the atrial and ventricular chambers can now be acquired in the absence of electrical insulation or differentiated nodes and conduction system[45,46].

The slow conducting heart tube now evolves into separate atrial and ventricular myocardium segments characterized by higher conduction velocities[47-50]. At this time, in line with several observations, the heart tube itself is considered to be a conducting unit without a morphologically distinct conduction system complete with a pace-making sinuatrium, atrioventricular junctional tissue and an atrioventricular zone of slow conduction[51-54]. The transformation of this zone into a nodal structure starts to become visible from around five weeks of human development when the contrast of the primary nature of the nodal myocytes with the differentiating myocardium becomes more apparent over time[55,56]. The mechanism, similar to that of the transformation of the sinus node, remains unknown.

Responsible for the most distinctive trait of the early heart tube, varying slow- and fast-conducting areas, are the gap junctions enabling transfer of action potentials between myocytes[57]. The number and size of these gap junctions increase during development, however remain limited in the sinus- and atrioventricular node[43,58-61]. Composites of these membrane channels are the connexins of which five types are expressed in the human heart. Absent expression of these connexins, as is the case in nodal tissue, correlates with the absence of gap junctions and consequently with areas of slow conduction[62]. This characteristic has proven to be very helpful in distinguishing nodal from atrial cells[63,64].

2.2.3. The Ventricular Conduction System

Current knowledge suggests that the ventricular conduction system may largely originate from the trabecular component of the ventricle[47,52,53,55,56,65-80]. As previously reported, the ventricular conduction system, as the rest of the conduction system, is theorized to originate from a primary ring of specialized cardiac tissue undergoing a series of changes in topography through the different stages of cardiac development[2,31]. Originating from myocardium tracing the primary interventricular foramen, part of this ring will eventually surround the subaortic outlet of the ventricle and the right atrioventricular junction just above the annulus[2]. The other part, responsible for conducting depolarizing impulses to the ventricles (the His bundle and bundle branches), hangs from the ventricular crest tracing the luminal side of the ventricles[2]. At this point it is unknown which regulatory pathways are responsible for the remodeling of these parts of the conduction system. It is thought that over time, insulation between the atrial and ventricular myocardium is accomplished by melding of the tissues of the atrioventricular sulcus with the atrioventricular cushions and that further separation of the ventricular conduction system from the surrounding myocardium may be regulated by cell-surface molecules which regulate cell-cell interactions[81,82].

2.3. Experimental Pathologic Evidence of the Dead-End Tract during Development

A great diversity in the position of conduction system cells exists within human hearts[83,84]. Of special interest are additional and remnant ventricular conduction branches that have previously been described[1-3,85].

After apoptosis or loss of "special" function of the earlier discussed rings, remnants may persist in the developed heart[3]. Sometimes consisting of entire branches, these remnants could be origins for re-entry, non-re-entry or automatic triggered arrhythmias[3].

In 1974, Anderson et al. described an additional right atrioventricular ring bundle in fetal human hearts[85]. Remnants of this ring were seen in infant and adult hearts, localized mostly anterolateral adjacent to the tricuspid orifice[85]. It was speculated that in some cases this remnant tissue might form a substrate for ventricular pre-excitation in the form of accessory atrioventricular pathways[85].
In a report by Kurosawa et al., three cases were presented showing continuations of the conduction axis beyond the bundle branch bifurcation[1]. In this study two normal neonatal hearts and one with Fallot's tetralogy were analyzed[1]. An extension starting on the summit of the ventricular septum after the bifurcation of the bundle branches was seen in these three sectioned hearts[1]. In the two normal hearts this extension reached the aortic root and close to the muscular summit of the septum where it faded out[1]. In the other heart it disappeared in the substance of the left ventricular aspect of the trabecular septum[1]. In this paper the tract was named a "dead-end tract"[1]. Their findings suggested that this dead-end tract was the more direct continuation of the conduction axis, as opposed to the right bundle branch[1]. The fact that they did not find this tract in adult hearts (in a previous study of 15 hearts, in subjects varying from stillbirth to adult age[86]), led them to suggest that it might only be seen in the neonatal and infant period[1]. This would imply that it represents a developmental stage in the maturation of the cardiac conduction axis[1].
Wessels et al. also demonstrated the dead-end tract as previously described by Kurosawa et al.[1,2]. Their findings showed an anterior continuation of cardiac specialized tissue of the atrioventricular bundle originating from the summit of interventricular septum, reaching into the retro-aortic root branch[2]. They also refer to a publication showing this continuation persists in guinea-pigs after birth[87].
Cells resembling atrioventricular junctional cells that were found along the AV orifices in two other reports, might provide additional clues for the presence of this tract[88,89].

3. CLINICAL EVIDENCE OF THE DEAD-END TRACT

The arrhythmic potential of persistent embryonic tissue as discussed earlier may, in the case of the dead-end tract, become apparent in the form of idiopathic VAs. For example, the regularly seen co-existence of VA's from the outflow tracts and the presence of accessory pathways (APs) or atrioventricular re-entry tachycardias in structural normal hearts has been observed in several previous reports[4-8]. These coinciding findings suggest there is a connection between these anatomically distant regions, which could be explained by the dead-end tract when taking into account the above mentioned pathological and topographical characteristics (Figure 1)[4,90-92].

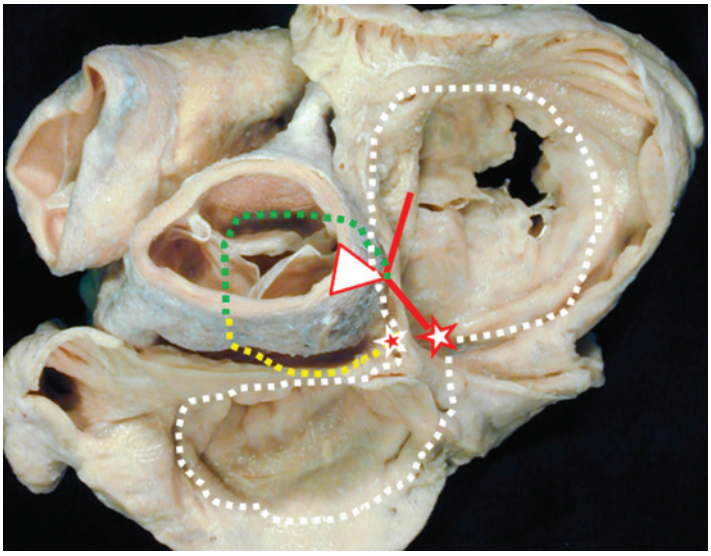

Figure 1. *Cardiac base as seen from the atrial aspect. White star, red borders: the atrioventricular node; Red line: the bundle of His; Green dotted line: the dead-end tract (the continuation of the atrioventricular conduction axis); Yellow dotted line: the retro-aortic ring branch; White dotted line: embryonic atrioventricular ring; Red star, white borders: the retroaortic node; This image was both provided and labelled by Professor Robert H. Anderson and reproduced with his kind permission. Professor Anderson retains his intellectual copyright in the original image.*

Another important clue comes from several case reports and studies reporting so-called pre- or presystolic potentials as a target during catheter ablation[93-107]. These potentials with low amplitude, occurring slightly before the major potential were seen at target sites for ablation (Figure 2). In these studies ablation of idiopathic outflow tract, ventricular summit or aortomitral continuity (AMC) VT's at the site of the pre-potentials was associated with a higher percentage of successful results. All of these structures lay within the route of the dead-end tract[1]. One study also reported a higher premature ventricular contraction (PVC) burden in patients with pre-potentials[93]. In most of these reports it was speculated that these pre-potentials could be caused by the presence of myocardial fibers, possibly representing the dead-end tract[93,97,98,100,102,104-107].

Exemplary for these studies is a report by Hachiya et al. in which successful ablation sites were located on the left or right coronary aortic sinus in 8.9% of outflow tract VAs[106]. In 9% of these cases a discrete pre-potential with a constant isoelectric interval was seen[106]. In all of these cases the site of successful ablation was at the pre-potential[106]. They described the pre-potential to be similar to that recorded between

the His bundle and ventricular electrogram by electrodes in the His bundle area[106]. In support of the dead-end tract theory was the finding that the potential, seemingly originating from the normal conduction system, was recorded just beneath the successful ablation site[106]. This serves as a clue because it is known that ablation in the coronary aortic sinus does not affect the valve tissue itself, but instead ablates the myocardium of the ventricular septum roof just inferior to the valve[108,109]. Another observation they made was that after successful ablation they saw a delayed potential similar in morphology to the previously seen pre-potential, suggesting a shift in timing after ablation[106]. They hypothesized that the pre-potential represented the activation of a tract connecting the arrhythmia focus to the ventricular myocardium[106].

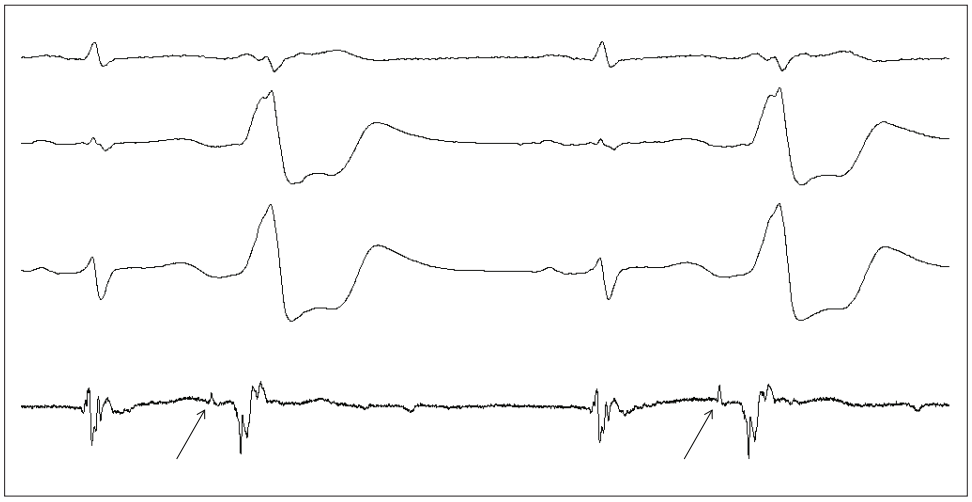

Figure 2. *Pre-potentials on Intracardiac ECG. Intracardiac ECG of a patient from our center during catheter ablation of a VA originating from the AMC. Shown are a sinus complex followed by a PVC, which is then repeated. The arrows indicate the pre-potentials representing conduction over some kind of tract with an isoelectric interval of 92 ms.*

Additionally, some studies on ECG characteristics of IVAs revealed a delta wave-like onset of the QRS complex, which might serve as another hint at a possible source of these arrhythmias[96,110]. Delta waves often represent APs with slowed conduction and essentially, the dead-end tract might have similar properties to a slow conducting AP. One report, in addition to observed pre-potentials, described this delta wave-like onset in all of their 35 patients presenting with mitral annulus VA[96]. Another report demonstrated the delta wave-like onset in six of 48 IVA patients, most of them originating in the right ventricular outflow tract (RVOT), negatively associated with ablation success[110].

4. DISCUSSION

4.1. Evidence

It is known that the occurrence of arrhythmias is related to certain preferential anatomical sites. As we have seen in the current report, persistence of embryonic remnants of the conduction system has been reported frequently[3,85,88,89]. More specifically, several pathological studies have demonstrated the dead-end tract in particular as a known anatomical entity[1,2,87]. These remnants could present a source of ectopic focal triggered activity and, provided that they are long enough to reach structures such as AMC or the outflow tracts, could contribute to re-entrant or non-reentrant circuits involving these regions.

4.2. Clinical Implications

IVAs can be found in 80% of the population[9,10], with 10% of all VT's accounting for idiopathic VT's, for the largest part originating from the outflow tracts[12]. Although generally considered benign, frequent ventricular arrhythmias can present a great burden on the patient and have been known to cause cardiomyopathy[12-16,111,112].
A higher quality of life and reversal of frequent ventricular arrhythmia associated cardiomyopathy has been accomplished after catheter ablation, making these arrhythmias an important target for treatment[13,113,114]. Since the mechanism behind these arrhythmias is not entirely clarified, other etiologies should be considered. When an anatomical substrate such as the dead-end tract can be targeted directly, this could theoretically improve ablation outcomes. As remarked earlier, targeting pre-potentials might provide higher success rates for these procedures.

4.3. Considerations and Limitations

Although many of the above-mentioned findings point to a possible role of and embryologic conduction tissue remnant as a cause for these arrhythmias, it is important to consider there is no direct evidence proving this involvement. The mechanism by which a remnant tract could cause outflow tract arrhythmias is not entirely clear. One should not rule out reentry as a possible mechanism. Furthermore, results suggesting involvement of the dead-end tract in the arrhythmia mechanism contain a significant amount of speculations. We do believe that for a better understanding and possible therapeutic improvements more basic research is needed. Even restudying the development of the human conduction system from the arrhythmogenesis point of view would be desirable. It seems that there is still a lack of consensus even on matters such as the timing of the appearance of the first morphological signs of the His bundle and bundle branches. Larger and more

detailed pathological studies regarding the exact location and course of the dead-end tract should be performed to see whether it is able to reach the outflow tracts and AMC. Also, dense pace-mapping studies should be carried out to prove involvement of a common tract in the etiology of outflow tract ventricular arrhythmias and to assess its conduction properties. Finally, to clarify the actual prevalence of this possible entity, more population-based data needs to be collected.

5. CONCLUSIONS

The dead-end tract is a known embryological remnant of the developing ventricular conduction system. Pathological studies have shown us its existence and localization. In several publications a possible association between this tract and the occurrence of idiopathic ventricular arrhythmias, a very common and often impairing disorder in the general population, has been considered. Additional circumstantial evidence for the existence of this tract and its role in arrhythmogenesis can be found in the coincidence of disappearing outflow tract PVCs after AP ablation and the encounter of pre-potentials and a delta wave-like QRS onset at IVA ablation sites and the association of pre-potentials with higher success rates. More efficient targeting of this possible origin of IVAs could help to further improve ablation outcomes.

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Chapter 2

Novel putative effectors identified in the arrhythmogenesis of idiopathic outflow tract ventricular arrhythmias: a novel concept beyond triggered activity

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ABSTRACT

Background. The arrhythmogenic mechanism of idiopathic ventricular arrhythmias (IVAs) from the outflow tracts (OTs) has been described to be triggered activity. However, it is incompletely understood why this focal mechanism would be confined to the OTs and what factors could precipitate it. Remnants of the embryologic AV conduction system in the periannular regions might serve as preferential pathways with a potential role in the genesis of OT-VAs.

Methods and results. Six patients referred for catheter ablation of OT-related PVCs were included in this study. During the electrophysiology study the patients exhibited a very low PVC frequency (≤1 PVC/3-5 min). Programmed atrial stimulation at the interatrial septum or within the coronary sinus was performed. Pacing at the AV annuli was capable of evoking OT-PVCs with an ECG-morphology identical to the clinical PVCs by presumably capturing specific fibers within the network of nodal-type tissue of the AV junctional sleeves. Based on the analysis of intracardiac electrograms the observed PVCs were indeed elicited as a result of prior atrial stimulation (co-incidental occurrence of spontaneous PVCs was excluded).

Conclusion. Our findings suggest that unique pathways (consisting of nodal-type tissue) might exist between specific periannular atrial locations and the OTs, the activation of which could result in triggering PVCs from the presumed "exit site" of these pathways in the OTs. These findings might facilitate the development of a novel ablation strategy, which might also include mapping of atrial locations, in order to identify and ablate the presumed "entry-sites" of these special "atrium-to-outflow-tract" pathways.

INTRODUCTION

The underlying arrhythmogenic mechanism of idiopathic ventricular arrhythmias (IVAs) originating from the ventricular outflow tracts (OT) (and adjacent anatomical structures like e.g. aortic sinuses of Valsalva, aorto-mitral continuity, atrioventricular annulae) has generally been accepted to be triggered activity induced by cAMP-mediated delayed afterdepolarization (DAD)[1-8]. However, despite significant research efforts in the field, it still remains elusive why this focal mechanism originates almost exclusively in the ventricular outflow tracts (and the above mentioned structures) in structurally normal hearts, and what specific factors can be held responsible for initiating arrhytmogenesis. The presumably more complex nature of the arrhythmogenic substrate in OT-related IVA is also supported by observations that describe the relative frequent co-existence of supraventricluar tachycardia (mainly AVNRT) with IVA[9-11]; along with others that suggest the involvement of preferential pathways of conduction tissue in arrhythmogenesis (based on observations of discrete prepotentials preceeding the ventricular signals within this region)[12-18]. Moreover, we recently reported on the abolishment of OT-related premature ventricular contractions (PVCs) that occurred in parallel with successful ablation of accessory pathways at the atrioventricular annuli of both the left and right side of the heart[19]. In the current case series we add yet another interesting piece to this puzzle, by describing the unique findings of the electrophysiology study of six patients with idiopathic VA. All of these patients were referred to our center for catheter ablation of symptomatic PVCs originating from the ventricular outflow tracts (or adjacent perivalvular structures). We demonstrate here that stimulation at specific atrial location in the vicinity of the atrioventricular annulae was capable to evoke OT-related PVCs with an electrocardiographical morphology virtually identical to the clinical PVCs. Based on these findings we hypothesize that specific pathways with preferential conduction might exist between certain atrial locations (e.g. periannular network of nodal-type tissue) and the OT regions, which might play a role in the genesis of OT-related IVA.

METHODS

Six patients were included in this study. All patients were referred to the cardiology department of the Erasmus MC for catheter ablation because of symptoms of palpitations and a significant PVC burden as detected by 24-hour Holter monitoring. A 12-lead surface ECG was performed to assess the possible anatomical origin of the PVCs (Figure 1.A.). Table 1 contains the demographic data of the patients and the findings of echocardiography and cardiac magnetic resonance imaging. Table 2

shows the individual PVC burdens as revealed by the Holter studies, together with the morphological analysis of all PVCs on the twelve-lead ECG (preprocedural and intraprocedural). A medical ethical committee of our institute (METC) approved the data collection as a prospective registry.

Table 1. *Patient characteristics and echocardiographic/cardiac-MRI findings*

	Age	Sex (m/f)	LV systolic function	Structural Heart Disease	Antiarrhythmic medication
Case 1	52	m	Mild dysfunction	None*	Beta-blocker
Case 2	57	f	Mild to moderate dysfunction	None*	Beta-blocker
Case 3	58	f	Normal	None	Calcium channel blocker
Case 4	57	f	Normal	None	Calcium channel blocker
Case 5	71	m	Moderate dysfunction	None*	Beta-blocker
Case 6	43	f	Normal	None	Beta-blocker

*LV = left ventricle; PVC = premature ventricular contraction. *As revealed by cardiac magnetic resonance imaging.*

Table 2. *ECG/Holter findings*

	PVC burden		PVC morphology			Possible PVC origin
	Percentage	>10.000 /24h	BBB pattern	Horizontal axis	Precordial transition zone	
Case 1	17%	yes	LBBB	Left inferior	V2-V3	outflow tract
Case 2	12%	yes	RBBB	Right inferior	none	aortomitral continuity/ superior mitral annulus
Case 3	16%	yes	LBBB	Horizontal	V3-V4	parahisian region
Case 4	16%	yes	LBBB	Left inferior	V1-V2	outflow tract
Case 5	19%	yes	LBBB	Left inferior	V2-V3	outflow tract
Case 6	18%	yes	LBBB	Inferior	V2-V3	outflow tract

PVC = premature ventricular contraction BBB = bundle branch block; LBBB = left bundle branch block; RBBB = right bundle branch block

All patients underwent standard preprocedural preparations: after vascular access had been established a radiofrequency ablation catheter (the type of ablation catheter was left at the operators discretion) was placed into the heart either alone (single-catheter approach) or together with a steerable decapolar diagnostic catheter (Inquiry, Abbott Laboratories, Abbott Park, Illinois, USA). The ablation catheter was guided either manually or with magnetic navigation (Stereotaxis Niobe Magnetic Navigation System; Stereotaxis, Inc., Saint Louis, MO, USA). Despite the fact that Holter monitoring revealed relatively high PVC burden, all patients included in this study, exhibited a fairly low frequency of spontaneous PVCs (not more than 1 PVC/3-

5 min) throughout the EP procedure (even after intravenous isoproterenol and/or atropine administration). Due to this low frequency of spontaneous PVCs activation mapping of the PVC origin was not attempted. Nevertheless, 3D anatomical maps of the outflow tract regions were created with the CARTO electroanatomic mapping system (Biosense Webster, Inc., Diamond Bar, CA, USA) in two out of the six cases (see right panel on Figure 2.A). After detecting this low occurrence rate of PVCs, the procedure was continued with programmed atrial stimulation (atrial burst pacing at several pacing cycle lengths between 350 ms and 600 ms), as part of the induction attempts to evoke PVCs possessing a morphology indicative of the clinical arrhythmia (outflow tract origin). Using either the ablation catheter or the decapolar diagnostic catheter, programmed atrial stimulation was performed at several distinct locations around the mitral annuli (within the coronary sinus in the latter case) and at the septal aspects of the tricuspid annulus. Atrial-pacing-induced PVCs were recorded and their morphology was compared with that of the spontaneous PVCs (as recorded by the EP-Workmate recording system and the pre-procedural 12-lead ECG; Figure 1). The specific sites from where PVCs with an OT-related morphology could be induced were marked on the fluoroscopic image (see example on Figure 2.)

RESULTS

All patients included in this study were referred to our EP department due to symptomatic VA with a relatively high PVC burden (12-19%; more than 10.000 PVC/24h in each case) despite antiarrhytmic medication (either beta-blocker or calcium channel blocker). Three patients had normal left ventricular systolic function, whereas three patients exhibited mild-to-moderate LV systolic dysfunction. However, cardiac MRI studies did not show any evidence for structural heart disease in these patients, hence all patients could be categorized into a diagnostic class of idiopathic ventricular arrhythmia. (Since the above mentioned MRI studies did not reveal any structural abnormalities for the latter three patients, they were diagnosed to have PVC-induced cardiomyopathy as the most feasible underlying condition for their LV dysfunction.)

Figure 1.A shows the morphology of the clinical PVCs of each patient as depicted on the preprocedural 12-lead ECG, and Table 2. summarizes the ECG characteristics of these PVCs. It can be appreciated that in five out of the six cases the clinical PVCs presented with a left-bundle branch morphology, and five clinical PVCs showed a clear inferior axis in the horizontal plane (except case 3, for which the axis was more horizontal). Based on these specific characteristics we concluded that the clinical PVCs either originated from the right or the left ventricular outflow tract regions

(depending on the location of the transition zones in the precordial leads); except for cases 2 and 3, where they originated from adjacent anatomical structures. In case 2 the focal activity arose from the superior mitral annulus/aorto-mitral continuity, whereas in case 3 the origin of the PVC was located in the parahisian region of the RV inflow tract (as also confirmed by the EP studies). Figure 1B. shows the relevant PVC morphologies as detected by the electrophysiology recording system (EP-Workmate) during the procedure at a recording speed of 100 mm/s. On Figure 1C we show representative images of atrial-pacing-induced PVCs. The morphology of these PVCs closely resembled that of the spontaneous PVCs (on Figure 1B.), i.e., the pacing-induced PVCs showed the same type of bundle-branch block morphology with the same axis in the horizontal plane and identical transition zones.

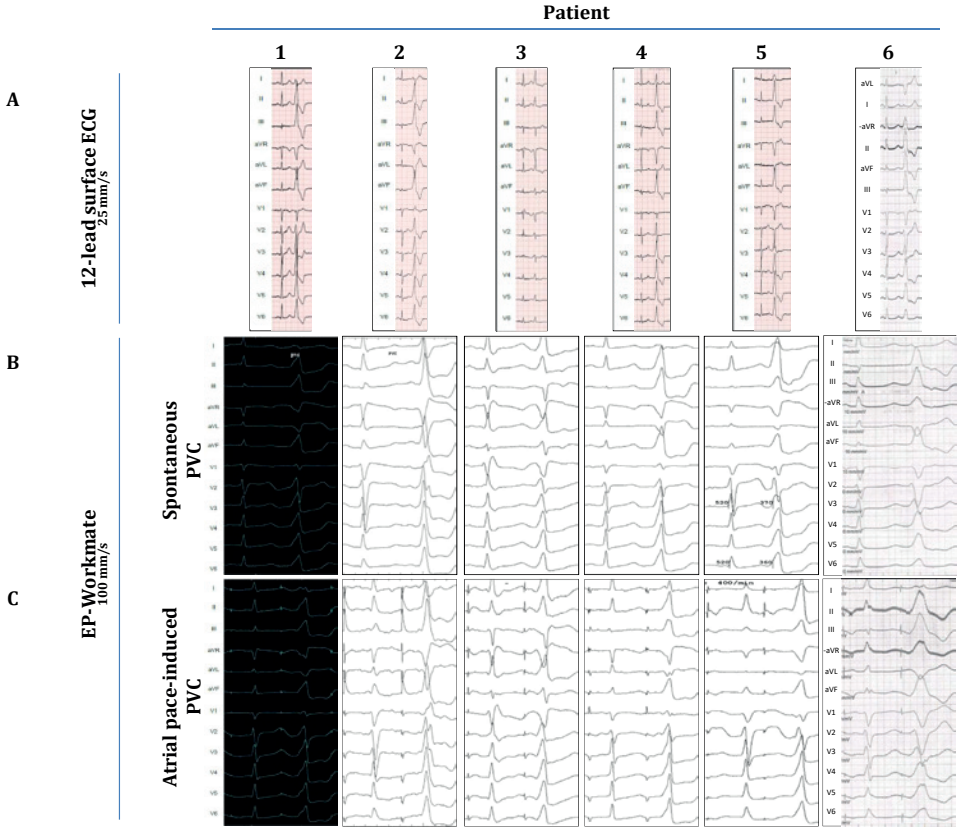

Figure.1. *Comparison of spontaneous and atrial-pace-induced PVCs in all patients. A) Spontaneous PVCs on pre-procedural 12-lead surface ECG. B) Spontaneous PVCs as recorded during the procedure by the EP-Workmate recording system. C) Atrial-pace-induced PVC as recorded during the procedure by the EP-Workmate system.*

It is also important to emphasize that these PVCs occured after apparent capture of the atrial myocardium, hence the elicited PVCs do not occur due to inadvertent capture of the ventricular myocardium. This fact is clearly demonstrated on Figure 2., which represents the intracardiac electrograms of the decapolar catheter (located in the coronary sinus) during the occurence of an atrial-pacing induced PVC (in the cases of patient 1 and patient 2). One can clearly appreciate that the atrial activation sequence on the CS electrodes (during pacing either from the electrode pair CS 9-10 in the case of patient 1 or from CS1-2 in the case of patient 2) occurs before the onset of the PVC. It is also evident that there is an isoelectric line between the atrial and ventricular local activation signals. In addition, a small pre-potential between the atrial and ventricular signals on the electrode pairs „Abl1-2" of the ablation catheter can be appreciated located at the spot of earliest ventricular activation in the case of patient 2 (see right panel of Figure 2.B).
Moreover, the „atrial-stimulus-to-PVC interval" (measured from the occurence of the atrial pacing stimulus till the onset of the PVC) was consistently shorter than the „atrial-stimulus-to-normal-QRS-interval" (measured from the occurence of the atrial pacing stimulus till the onset of the normal QRS complex) and the duration of this „atrial-stimulus-to-PVC interval" (together with local A-to-V intervals on the electrode pairs of the CS and the ablation catheters) remained essentially the same when consecutive PVCs were elicited with the same pacing cycle length (Figure 2.B).

Another interesting phenomenon was observed when PVCs were induced with progressively shorter atrial pacing cycle lengths. Figure 3. demonstrates an example of this observation. It can be seen that the coupling intervals of the PVCs became progressively shorter when the pacing cycle length was decreased from 500 ms to 400 ms. On the other hand decremental conduction was also observed (over the hypothetical preferential pathway between the atrium and the outflow tract), as the "atrial-stim-to-PVC interval" was consistently prolonging with progressively shortened cycle lengths; a phenomenon similar to the characteristic behavior of the normal AV conduction over the AV node (which can also be seen in the case of the "normally conducted" atrial pacing stimuli at the left sides of the panels on Figure 3.).

Based on these findings we concluded that peri-annular atrial pacing was capable to evoke outflow-tract related PVCs by possibly capturing the "atrial entry sites" of certain preferential pathways (between the atrium and the outflow tract). In addition,

due to the decremental behavior of this conduction it might also be plausible that these unique pathways consist of nodal-type tissue.

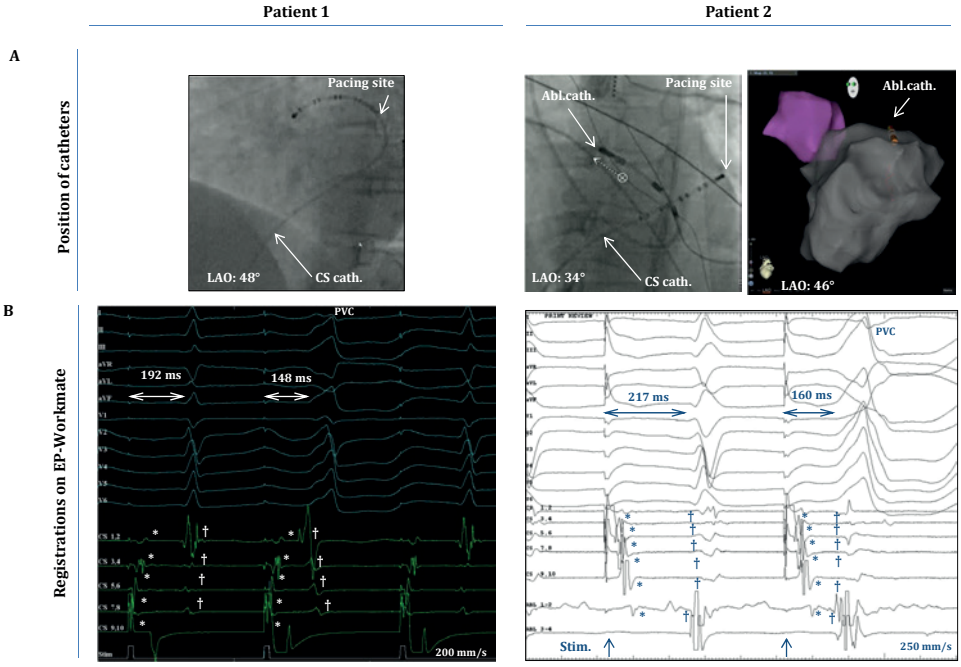

Figure 2. *Intracardiac electrograms (EGMs) during atrial-pace-induced PVCs in Patient 1. and 2.* **A**) *Position of the coronary sinus (CS) catheter and the ablation catheter (Abl) as depicted on fluoroscopy (left anterior oblique projection) and on the 3D anatomical map of the CARTO system (in Patient 2. on the right panel). In the case of Patient 1. the electrode pairs of the coronary sinus catheter are located in the distal part of CS and the great cardiac vein, and pacing occurs from CS9,10. In the case of Patient 2. the same diagnostic catheter is located more proximally in the coronary sinus (electrode pairs CS9,10 are located at the ostium of CS), and the ablation catheter is located at the superior mitral annulus/aorto-mitral continuity; and pacing occurs from CS1,2.* **B**) *Intracardiac EGMs (together with 12-lead EGMs) from the electrode pairs of the CS catheter and the ablation catheter (only for Patient 2. on the right panel) as recorded by the EP-Workmate recording system during the occurrence of an atrial-pace-induced PVC. The onset of the pacing stimulus is depicted at the bottoms of each panel. The "atrial-stimulus-to-normal-QRS time" (in ms) and the "atrial-stimulus-to-PVC time" was measured and depicted on the recordings. Note, that the duration of the "stimulus-to-PVC time" is shorter in both cases than that of the "stimulus-to-normal-QRS time". * represent the atrial activation signals and † designate the ventricular activation signals on both panels.*

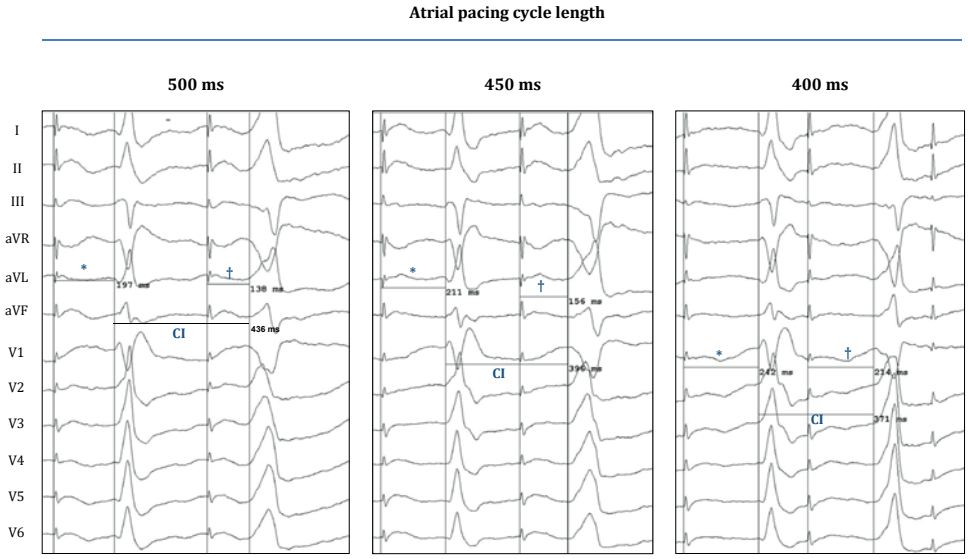

Figure 3. *12-lead surface electrograms during atrial-pace-induced PVCs. Surface EGMs (recorded by the EP-Workmate recording system) are depicted at three different atrial pacing cycle lengths (CL) at the occurrence of an atrial-pace induced PVC in Patient 3. "Stimulus-to-normal QRS time" and "stimulus-to-PVC time" are labelled with * and †, respectively; and the corresponding time durations are depicted on each panel. The coupling intervals are labelled with "CI" and these intervals are also depicted on the electrograms. Shortening pacing CL results in a progressive shortening of the coupling interval of the PVCs, whereas it also causes a prolongation in the duration of both the "stimulus-to-normal-QRS time" and that of the "stimulus-to-PVC time". The latter phenomenon could suggest the decremental conduction property of the putative preferential pathway between the atrial and ventricular locations (entry and exit sites) analogous to the decremental properties of the atrioventricular conduction over the AV node.*

DISCUSSION

Although OT-VAs are generally considered to follow a benign clinical course, there have been reports on *i)* clinical cases with more malignant subtypes of OT-VA, capable of causing syncope and even sudden cardiac death), and *ii)* incessant forms accounting for tachycardia-induced cardiomyopathy and/or PVC-induced cardiomyopathy[2-4]. In addition, high PVC/non-sustained VT burden can render many patients highly symptomatic and therefore significantly lower their quality of life. Thus, according to current guidelines, therapy is recommended in symptomatic cases and in asymptomatic individuals for whom LV dysfunction is suspected to be attributed to PVC-/tachycardia-induced cardiomyopathy[2-4, 20]. In most cases this means eventual catheter ablation, since pharmacological therapy often has limited efficacy[4]. In fact, all of the patients included in this report were referred for catheter

ablation due to a high PVC burden with symptoms not amenable to medical therapy and 50% of these patients were suspected to have LV dysfunction due to PVC-induced cardiomyopathy.

Patients referred to catheter ablation of idiopathic VA represent a significant population in the field of invasive electrophysiology (EP), accounting for around 10% of all referrals to EP centers[21]. The reports on the procedural outcome of OT-VA ablations have been somewhat conflicting with regards to acute success rates and long-term recurrence rates: some studies claim that the acute and long-term success would approximate nearly 100%[22-24], while others report on more humble outcome rates[20, 25-29]. These varying success rates might reflect differences in follow-up methods, definitions of success and also inclusion bias, but it has to be acknowledged that ablation failure-rate in an unselected clinical population is far from being negligible and that there is still plenty of room for further improvements in the field. Technical issues, such as 1) non-inducibility of tachycardia in the operating room, 2) arrhythmia foci near critical cardiac structures (e.g. coronary artery), 3) epicardial origin; might account for a significant part of ablation failures[4]; however another important aspect to consider is our limited understanding of the actual arrhythmia substrate underlying IVA.

Delayed afterdepolarization (DAD)-mediated Ca^{2+} overload and subsequent triggered activity (from a focal source in the OT) has generally been accepted to represent the underlying substrate for OT-VA[1-8]. However the exact underlying etiology leading to cAMP increase and subsequent Ca^{2+} accumulation is not well understood. Moreover, an even more confusing issue that remains to be resolved is why the outflow tracts would contain the foci of triggered activity in around 80% of the cases of IVA[20]. What is so special about them (compared to other areas of the ventricles) that would make them more prone to generate triggered-activity mediated PVCs/VTs?

Abnormal β-adrenergic signaling (increased sympathetic activation or selective dysregulation of β-receptors within these regions) has been implicated to play a crucial role in the pathomechanism[1, 5]. Other studies report on subtle structural abnormalities of the RVOT in patients with OTVA, suggesting a possible link to arrhythmogenic right ventricular cardiomyopathy (ARVC). In contrast, Lermann et al. found no evidence for such structural abnormalities and they suggest that the unique embryological development of the OT would account for their arrhythmogenic potential. According to this theory the adult OT is formed by the incorporation of embryonic OT into the working myocardium of the ventricles, which possesses characteristics resembling that of the primary myocardium (slow conduction, spontaneous depolarization), therefore non-matured remnants of this

embryonic phenotype in the adult OT would represent foci with nodal-tissue-like electrical properties, thereby forming the basis for arrhythmogenesis[5, 30-32].

Intriguingly, such nodal-tissue-like remnants in the OT have also been suggested by others to derive from the embryologic atrioventricular conduction system. Conduction-tissue-specific immuno-markers have been described to be abundantly expressed in the OTs during the early stages of cardiac development[33]. Several reports suggest the possible involvement of remnants of this primitive conduction system in the generation of OT-related IVA; based on the observations that discrete pre-potentials occur within the OT (or adjacent structures, e.g. aortic sinuses of Valsalva), which precede the local activation signal when recorded at the spot of the earliest ventricular activation[12-15, 17, 18]. These reports implicate that preferential pathways (insulated from the surrounding myocardium) might exist within these regions, which could connect the origins of the ventricular arrhythmia with their presumable exit/breakout site(s) within the outflow tracts. These studies hypothesize that the anatomical basis for the existence of such insulated pathways (with slow-conduction and possible decremental properties) could be conduction tissue that fails to regress during the maturation process of the AV conduction system.

In fact, the entire AV conduction system has been shown to develop from a specialized interventricular ring, and during further steps of the early developmental stages this primitive conduction tissue would encircle both the junctions of the developing ventricles at the AV orifices (designated as e.g. right atrioventricular ring bundle), as well as the roots of the great arteries (designated as septal branch, a.k.a. "dead-end-tract"; and subaortic root branch). In the later phases of the maturation process these segments around the AV junctions and the great arteries eventually disappear, giving rise to the mature conduction system which only consists of the AV node, the His bundle and the bundle branches[33]. However, in case any part of the above mentioned structures fails to regress completely, this remnant conduction-tissue could represent an arrhythmogenic focus at any of the above locations (including the OTs).

Remarkably enough, other studies even describe sleeves of nodal-type tissue around the tricuspid and the mitral annuli in the normal adult heart, which are also believed to represent remnants of the primitive conduction system[34]. This AV junctional network of nodal-type tissue exhibits histological characteristics similar to those of atrial tissue, but their cellular electrophysiology rather resembles the characteristics of nodal tissue (action-potential and conduction properties, adenosine response, relative lack of gap-junctional protein connexin-43). Although their actual function remains rather elusive, studies have shown that certain parts of these AV junctional sleeves can be electrically dissociated from the surrounding atrial tissue; therefore they might be insulated from the atrial myocardium. Moreover, the posterior

approaches of this system towards the AV node have been implicated to be the actual substrate of the slow AV nodal pathway, which represents the essential component of the re-entry circle in AVNRT[34]. Interestingly enough, some studies report on the relatively frequent co-existence of AVNRT and OT-VAs[9-11]. Even more intriguing is what Kautzner et al. describe in three of their series of seven patients with co-existent AVNRT and OT-VA. In these patients AVNRT was observed to initiate runs of OT-VT spontaneously and repeatedly. Moreover, in one of their patients, termination of RVOT-VT during RF application led to an abrupt transition into typical AVNRT[10]. Is it therefore conceivable that the above mentioned network of AV junctional tissue is interconnected with conduction tissue remnants in the outflow tract, and that these conduction tissue remnants (originating from the same embryologic structure) would represent the anatomical substrate for both of these disease entities?

We recently published a case-series, which reported on the unique electrophysiological findings of patients with co-existent WPW syndrome and OT-PVCs. The successful ablation of accessory pathways (APs) at the atrioventricular annuli simultaneously abolished the occurrence of the concomitant PVCs originating from the OT regions[19]. These remarkable observations suggested that during the ablation of the APs we might have also ablated parts of the above mentioned network of nodal-type tissue within the AV junctional sleeves; thereby involuntarily disrupting the possible "entry"-sites of those preferential pathways (of conduction tissue remnants) that have been suggested to have their exit sites in the OTs. A similar explanation might also account for the unique results that Garcia et al. present in their report, which describes (for the first time in the literature) the approach of idiopathic VA ablation from the right atrium. The authors suggest that the feasibility of targeting specific PVCs (arising from the posterior-superior-process of the left ventricle) from the right atrium lies in the fact that these structures are in close proximity to each other [35]. However, an alternative explanation for these remarkable findings could be the ablation of the "entry"-sites of the above mentioned specific pathways in the AV junctional network at the tricuspid annulus (especially if we consider the relatively large versatility of the presented PVC morphologies, which could indicate that they might arise from an area wider than the posterior-superior-process of the left ventricle). Based on these findings we hypothesized that this network of nodal-type tissue around the AV annuli could be interconnected with the conduction tissue remnants in the OT, provided that insulation defects could exist at certain locations between the atria and the ventricles.

Following the logic of this hypothesis in the current report we show that atrial pacing around the AV annuli was capable of evoking OT-PVCs (Figures 1-3) by presumably capturing specific fibers within the network of nodal-type tissue of the AV junctional

sleeves. Although these OT-PVCs did not follow each atrial pacing stimulus, they occurred relatively frequently during consecutive drivetrains of pacing at certain locations in the periannular regions. Based on our recordings it was evident that the PVCs did not occur due to an inadvertent capture of the ventricular myocardium, but instead after apparent atrial activation by pacing (Figures 1-2). Although the possibility for the concomitant occurrence of *spontaneous* PVCs during the pacing episodes may not be excluded unambiguously, the following characteristics argue for a causative interrelation between atrial pacing and the induction of OT-PVCs: 1) The selected patients exhibited a fairly low frequency (1-2 PVC/3-5 min) of spontaneous PVCs throughout the whole course of the EP study (as mentioned above in the Methods section), whereas with atrial pacing we could reproducibly induce PVCs (and hence significantly enhance their frequency of occurrence). 2) The duration of the "atrial-stimulus-to-PVC interval" remained relatively constant when pacing with the same cycle-length. 3) Subtle morphological differences could indeed be detected between spontaneous and pace-induced PVCs (compare the panels on Figure 2B and C). 4) The coupling intervals of the pace-induced PVC (measured from the preceding normal QRS complex) showed a progressive shortening with decreasing pacing cycle lengths, whereas we observed a fairly constant (fixed) coupling interval (at a certain range of heart rate) in the case of spontaneous OT-PVCs (current observations, and previous unpublished results). Taken together all these observations argued that the observed PVCs were indeed elicited as a result of prior atrial stimulation and that co-incidental occurrence of spontaneous PVCs during this atrial pacing protocol might be excluded.

We therefore speculate that unique (and yet undescribed) connections (consisting of conduction tissue remnants) might exist between specific atrial locations and the OTs of the ventricles, the activation of which could result in triggering PVCs (or repetitive ventricular activation) from the presumed exit point of these pathways in the ventricular OTs. In the presence of insulation defects, such special "atrium-to-outflow-tract" pathways could represent the pathophysiological substrate of OT-related ventricular arrhythmia. Since this premature conduction-tissue-network has previously been indicated: i) to be partially insulated from the surrounding (atrial) myocardium and ii) to possess distinct conduction properties, it is plausible to assume that they could serve as preferential pathways between the outflow tract and the atria; and once excited (either spontaneously or by pacing) their activation wave-front might be able to occasionally "leak out" towards the outflow tract regions, and exit there in the form of an OT-PVC. The above mentioned subtle morphological differences between the spontaneous and the pace-induced PVCs in our study might be explained by the existence of multiple adjacent exit points for the network of

these conduction fibers, located within close proximity to each other within the same region of the outflow tracts, and activated somewhat differently during pacing than during a spontaneous PVC .

The importance of our present report lies in the fact that (together with previous observations) it could have the potential to transform our current approach of catheter-ablation of OT-VA; since it might have the potential to introduce a novel strategy for extending our mapping efforts into the atria, in order to identify and ablate the presumed "entry-sites" of these special "atrium-to-outflow-tract" pathways.

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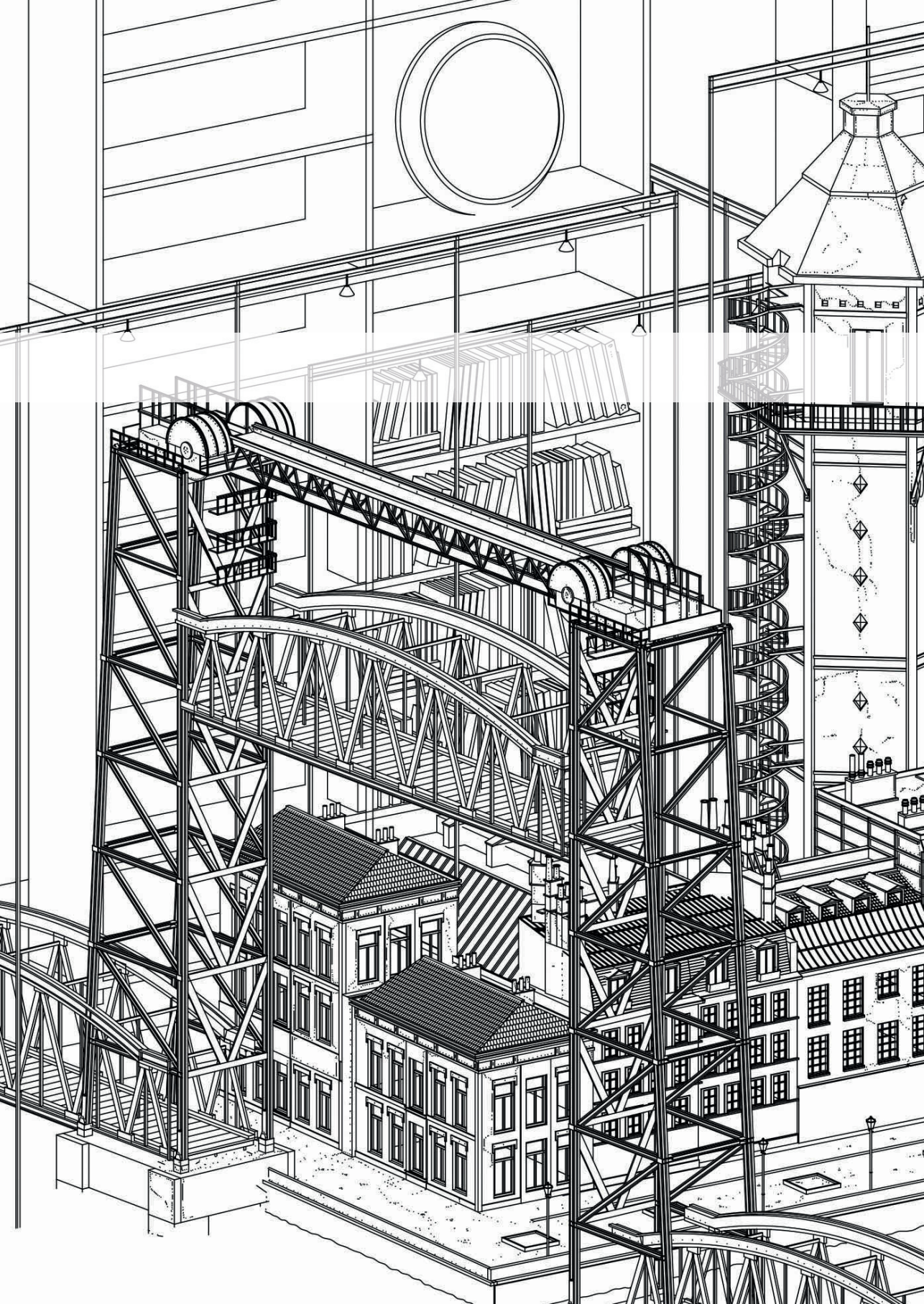

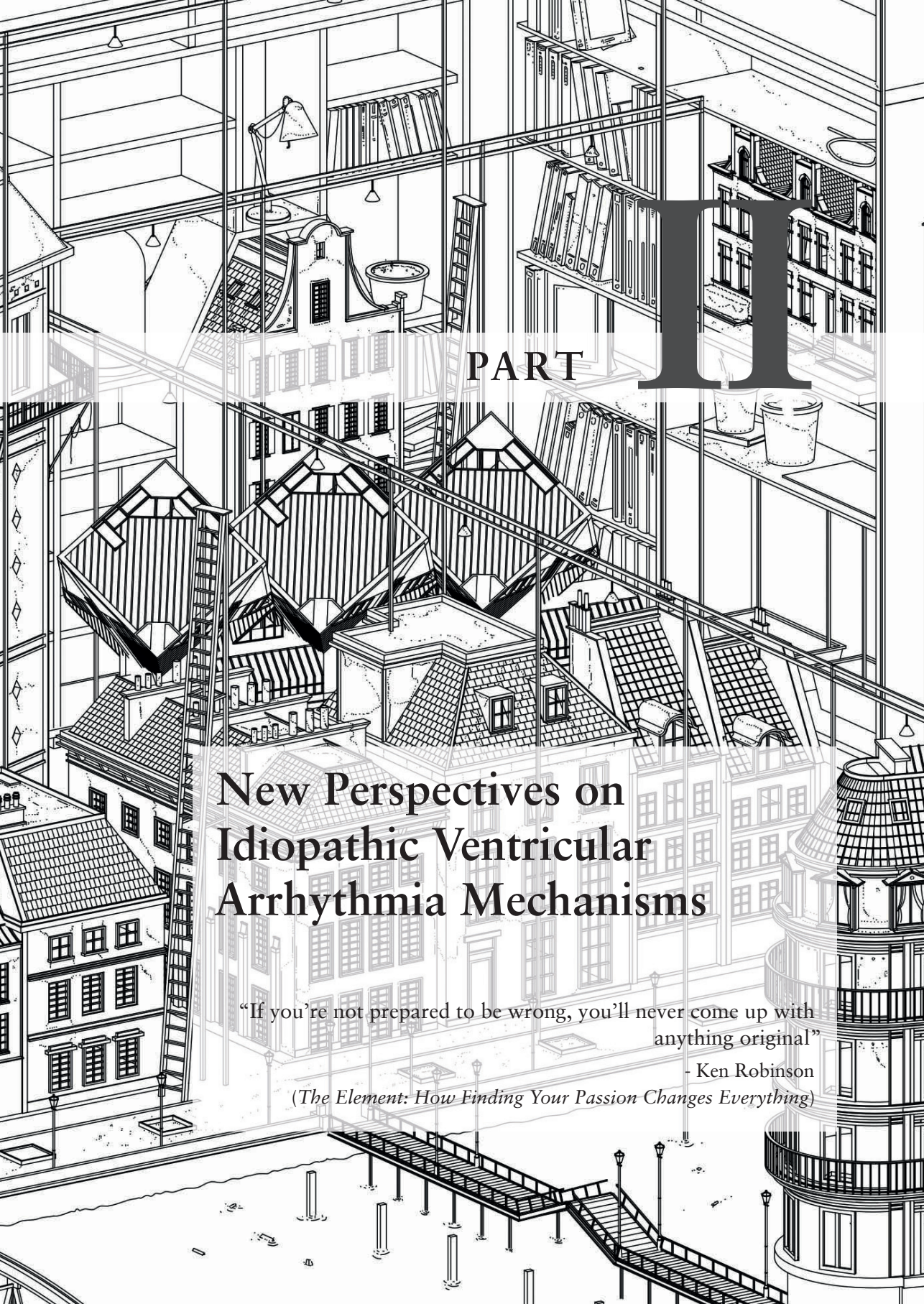

PART II

New Perspectives on Idiopathic Ventricular Arrhythmia Mechanisms

"If you're not prepared to be wrong, you'll never come up with anything original"

- Ken Robinson

(*The Element: How Finding Your Passion Changes Everything*)

Chapter 3

Disappearance of idiopathic outflow tract premature ventricular contractions after catheter ablation of overt accessory pathways

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ABSTRACT

Background. Multiple mechanisms have been proposed for idiopathic premature ventricular contractions (PVCs) originating from the outflow tracts (OTs). Recent observations such as the coexistence of these arrhythmias with atrioventricular nodal reentrant tachycardias and the association between discrete prepotentials and successful ablation sites of ventricular arrhythmias (VAs) from the OTs suggest a common link.

Objective. In this case series we draw attention to a unique association between accessory pathways (APs) and idiopathic PVCs from the OTs, disappearing after AP ablation.

Methods. We identified 6 cases in collaboration with several international electrophysiology centers, which presented with pre-excitation in association with OT, and in 1 case inflow tract (IT), PVCs on 12-lead surface ECG.

Results. Six cases displayed pre-excitation and PVCs, in 5 cases originating from the right ventricular outflow tract (RVOT) and in 1 case from the right ventricular inflow tract (RVIT). In all patients, PVCs were monomorphic and had fixed coupling intervals, in 3 cases presenting in bigeminy. Catheter ablation of the AP led to the simultaneous disappearance of PVCs in 5 of 6 cases. The sites of ablation were remote from the OTs in all these cases. In most cases, the occurrence of OT PVCs was closely associated with the presence of pre-excitation.

Conclusion. The coexistence of pre-excitation and PVCs from the OTs and the fact that in 5 of 6 cases PVCs disappeared after AP ablation suggests a common mechanism for arrhythmia genesis.

INTRODUCTION

Idiopathic ventricular arrhythmias (VAs) arising from the outflow tracts (OTs) and the aorto-mitral continuity (AMC) are considered to have a focal origin[1-3]. The most likely mechanism is considered to be catecholamine-mediated delayed afterdepolarizations and triggered activity[1-3]. However, some recent observations such as the coexistence of OT premature ventricular contraction (PVCs) with pre-excitation or perinodal arrhythmias, such as atrioventricular nodal reentrant tachycardia (AVNRT), or others reporting an association between discrete prepotentials and successful ablation sites of VAs, might indicate a novel putative mechanism responsible for arrhythmia genesis and challenge our current understanding of the pathogenesis of outflow tract arrhythmias (OTAs)[4-10]. Based on the above-mentioned observations a subset of patients may have an unconventional arrhythmia substrate that could even connect arrhythmic origins of anatomically distant regions. In this case series we present a unique finding suggesting an alternative mechanism for arrhythmia genesis mainly in patients with OT associated PVCs.

METHODS

The first patient, the index case, was referred to the cardiology department of the Erasmus Medical Center with palpitations and a combination of pre-excitation and PVCs from the RVOT documented on 12-lead ECG (see index case and Fig. 1). Intriguingly, radiofrequency (RF) ablation of the AP led to the simultaneous complete disappearance of the PVCs. Several international collaborating centers were contacted regarding these findings and multiple similar cases were identified.

After the index case, 5 more patients from international collaborating centers were included. Demographic data of the patients are listed in Table 1. Table 2 contains the findings of the electrophysiological studies. The AP location was determined by electrophysiological study. The effect of the ablation on PVCs was assessed based on 24-hour Holter data before and after the ablation, if available, or otherwise based on ECG or reported symptoms. Data collection was performed respecting the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule.

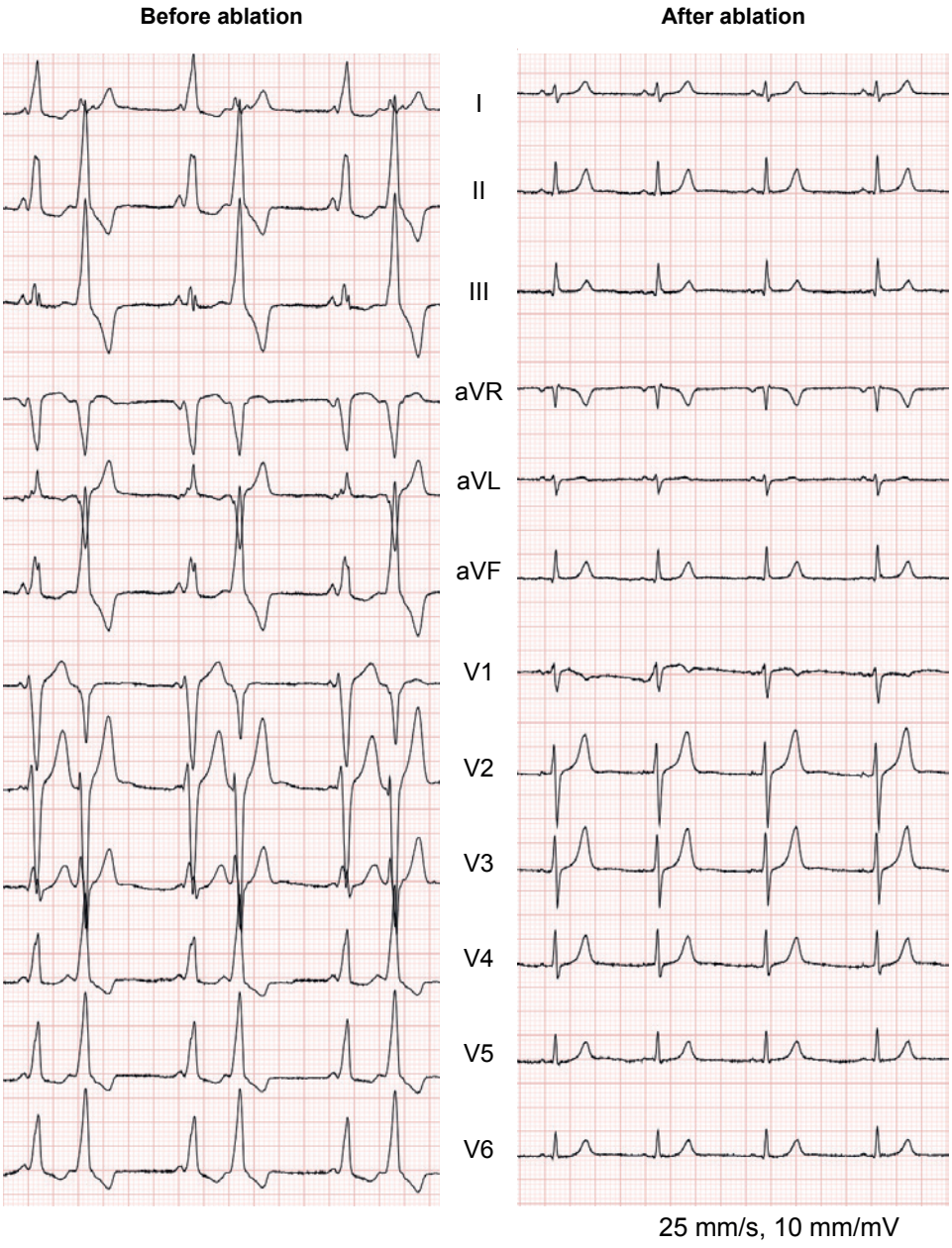

Figure 1. *Twelve-lead surface ECGs of the index case prior to and after ablation. Pre-ablation ECG shows pre-excited QRS complexes followed by PVCs of RVOT origin in a bigeminal pattern. Postablation ECG reveals that the termination of the AP conduction led to the simultaneous abolishment of PVCs.*

Table 1. *Patient demographics*

	Age (years)	Sex (m/f)	Echo/MRI findings	Symptoms
Case 1	27	Female	Normal	Palpitations/dizziness
Case 2	15	Male	Normal	Asymptomatic
Case 3	31	Male	Normal	Palpitations
Case 4	59	Male	Reduced LV systolic function (LVEF 44%)	Palpitations
Case 5	31	Female	Normal	Palpitations
Case 6	54	Female	Normal	Palpitations

LVEF = left ventricular ejection fraction.

Table 2. *ECG/Electrophysiological findings*

	Bigeminy	PVC morphology	PVC origin	Fixed coupling interval	AP location	PVC dis-appearance post AP ablation
Case 1	Yes	Monomorphic	RVOT	Yes	Right free wall	Yes
Case 2	Yes	Monomorphic	RVOT	Yes	Right free wall	Yes
Case 3	No	Monomorphic	RVOT	Yes	Left lateral	Yes
Case 4	Yes	Monomorphic	RVIT	Yes	Right posteroseptal	No
Case 5	No	Monomorphic	RVOT	Yes	Left lateral	Yes
Case 6	No	Monomorphic	RVOT	Yes	Left anterolateral	Yes

In case 4 a successful AP ablation was performed however, PVCs persisted. RVIT = right ventricular inflow tract, RVOT = right ventricular outflow tract.

RESULTS

Index Case: RF Ablation of AP Abolished the Occurrence of Simultaneous RVOT PVC

A 27-year-old woman without a cardiac history was referred to our clinic because of palpitations associated with dizziness. She never experienced syncope. The 12-lead surface ECG revealed a sinus rhythm with pre-excitation and PVCs in bigeminy pattern with a fixed coupling interval (Fig. 1). The PVCs had a typical configuration consistent with RVOT origin. Twenty-four-hour ECG monitoring revealed monomorphic PVCs in bi- or trigeminy pattern in 12% (14,000 per 24 hour) of the total number of heart beats. During exercise testing pre-excitation did not disappear. Echocardiography and magnetic resonance imaging (MRI) did not show any structural heart disease. Genetic testing revealed no mutations in genes encoding for catecholaminergic polymorphic ventricular tachycardia or arrhythmogenic right ventricular cardiomyopathy. Electrophysiological study identified a right-sided

free wall AP. Its location was very remote from the RVOT. A PVC map confirmed the diagnosis of an RVOT extrasystole that was localized at its anteroseptal side. Ablation of the AP was performed using a contact force guided RF catheter. With 7 applications and a total ablation time of 240 seconds the conduction of the AP was terminated. Additionally, we observed the simultaneous disappearance of PVCs. Moreover, after the successful ablation of the AP neither pre-excitation nor PVCs were recorded again and symptoms did not recur during the follow-up period of 18 months.

Cohort of Patients with Similar Findings: 5 Additional Patients Were Identified Exhibiting Similar ECG/Electrophysiological Characteristics as the Index Case

All patients presented with a combination of pre-excitation and monomorphic VAs with fixed coupling intervals on 12-lead ECG (Fig. 2). All patients had structurally normal hearts (Table 1). Bigeminy was seen in 3 patients. In 5 cases the PVCs originated from the RVOT and in 1 case from the RVIT. Locations of the APs varied from right free wall to left lateral. In 5 of 6 cases catheter ablation of the AP led to simultaneous disappearance or significant decrease of PVCs (Fig. 3), demonstrated by a reduced PVC burden on follow-up Holter when available (Table 3) or significant reduction of symptoms. The site of ablation in these cases was remote from the OTs. In cases 1 and 2 the ablation site was in the right free wall, in cases 3 and 5 it was left lateral, in case 4 right posterolateral and in case 6 it was left anterolateral (Table 2). In most cases, the occurrence of OT PVCs was closely associated with the presence of pre-excitation.

Table 3. *PVC Burden on Pre- and Post-Ablation Holter*

	PVC Burden Pre (%)	PVC Burden Post (%)	Months Post
Case 1	-	-	-
Case 2	35%	1.2%	3
Case 3	0.8%	-	-
Case 5	3.9%	0.18%	6
Case 6	1.2%	0.005%	15

Available Holter data for the 5 patients showing simultaneous disappearance of PVCs after AP ablation.

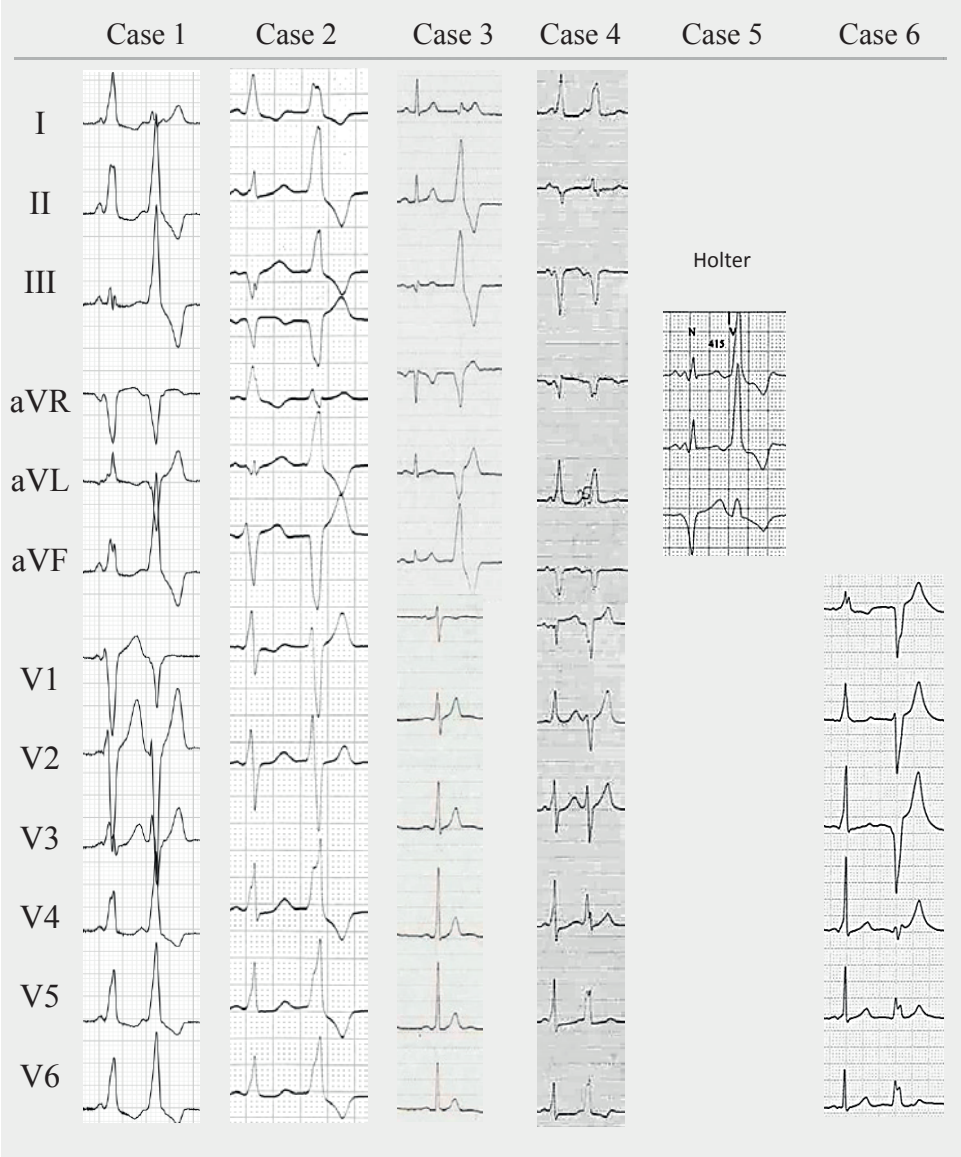

Figure 2. *Pre-ablation surface ECGs of all patients. A common characteristic of all cases is the presence of pre-excitation followed by PVCs.*

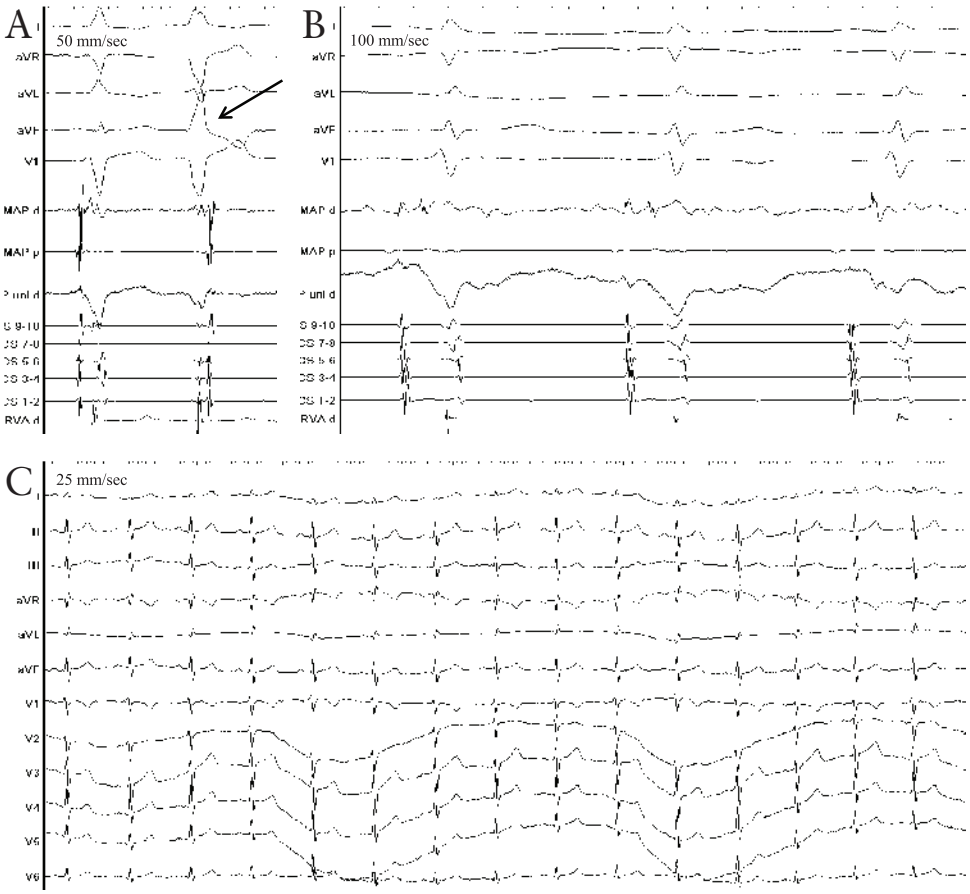

Figure 3. *Disappearance of pre-excitation and PVCs. A: Pre-ablation electrogram displaying, at a speed of 50 mm/second as indicated in the upper left corner, the last PVC of the patient before RF ablation is turned on. The PVCs present in a bigeminy pattern. Of note: the sinus QRS and the PVC complex have a similar axis. The activation sequence is consistent with a right free wall AP (late activation on al CS electrodes and early signals on the ablation catheter (MAP) placed on the high lateral tricuspid valve). During the PVC, the ventricular signal on the ablation catheter is late, consistent with a remote origin of the PVC relative to the AP. The arrow indicates the PVCs. Panel (B) shows the ECG and intracadiac electrograms during ablation, with complete absence of AP conduction and PVCs. Panel (C) shows the electrogram 20 minutes after ablation. MAP d = ablation catheter distal; MAP p = ablation catheter proximal; CS = coronary sinus; RVA d = right ventricle distal.*

DISCUSSION

We present a case series of overt pre-excitation and concomitant monomorphic idiopathic outflow tract PVCs appearing with fixed coupling intervals. The major

finding of this study is that AP ablation resulted in simultaneous disappearance or significant reduction of PVC burden in 5/6 cases.

Mechanism of Idiopathic Ventricular Arrhythmias

A major subgroup of idiopathic VAs are the OTA, for the largest part originating from the RVOT[11]. Other common OT sites include the LVOT, the aortic sinuses of Valsalva, the AMC, the superior basal septum near the His bundle and the epicardial surface of the OTs. This disease entity is characterized by the occurrence of frequent PVCs and/or monomorphic VTs, and is assumed to be benign in the majority of cases[11], although reports on LV dysfunction and occurrence of malignant VTs in some patients seem to question the obligate benign nature of these arrhythmias[12-17]. In general, OTAs are considered to be treatable with high success rates using catheter ablation[18-20]. However, there have been studies in the literature that reveal a significant (up to 20–30%) failure rate for ablation of OTAs[21]. A possible explanation for ablation failure might be the epicardial origin of some VAs. In addition, of the approximate 20% of OTAs originating outside the RVOT, a considerable number arise from special anatomical structures (e.g., AMC, aortic sinus cusp and structures around the pulmonic valve), which could make mapping and ablation procedures difficult. Although a number of reports in the literature describe the electrocardiographical and electrophysiological characteristics of VAs originating from these unique locations[8,22-24], the exact nature of the arrhythmogenic substrate still remains unknown in several cases. Therefore, we believe that, beside technical considerations associated with difficult anatomical locations, a significant number of ablation failures might also be attributed to incomplete understanding of the underlying arrhythmogenic mechanisms. In addition, we hypothesize that a considerable number of OTAs are caused by more complex and unconventional arrhythmia substrates. Some recent studies start to shed more light on such novel mechanisms.

Alternative Mechanisms and Coexistence of WPW and PVCs

Mulpuru et al. describe a special reentrant circuit involving muscle sleeves and fibrous tissue between the cusps of the pulmonary valve, which in turn creates a fairly unconventional substrate for RVOT arrhythmia[9]. Even more interesting is the observation that in some cases OTAs can occur in parallel with supraventricular arrhythmias. Kautzner et al. is among the first to report on patients who exhibit coexisting OTAs and atrioventricular nodal reentrant tachycardia (AVNRT)[4]. Another study described a significantly higher prevalence of idiopathic VAs in

patients with AVNRT compared to patients with APs (11% vs. 0.76%)[10]. Chen et al. describe the characteristics of VAs originating from the AMC or fibrous trigone (a fibrous structure that consists of the aortic annulus and the anterior side around the mitral annulus[25]). Intriguingly, some patients in the latter study population show AMC-related VT/PVC and AVNRT simultaneously[23]. It remains to be elucidated whether there is a causative association between these arrhythmias that are generally considered to be caused by 2 separate underlying mechanisms: triggered activity and reentry. Assuming that this phenomenon is more than just a coincidence, one could speculate the presence of a novel and more complex arrhythmia mechanism, which in turn could explain the occurrence of both OTA and AVNRT. Hai et al. suggests the possible involvement of conduction tissue remnants in the genesis of VAs arising from the fibrous AMC[8]. The study identifies prepotentials (PPs) at the AMC preceding the ventricular electrogram in a major subgroup of patients who underwent successful OTA ablation at that specific site. In addition, patients with PPs at the AMC have a higher PVC burden and shorter V-H intervals. Moreover, a strong positive correlation has been demonstrated between V-H interval and QRS duration among those with PPs. Therefore, the occurrence of these PPs and their association with His-bundle activation time suggests that islets of residual cells (located within the fibrous trigone) that once originated from the conduction system and failed to regress during maturation might be actively involved in the genesis of VAs originating from this region. Similar findings have been described in several reports[5-7,22-24,26-35].

The observations of our present study highlight the potential existence of another unique and complex mechanism for arrhythmia genesis. In this case series, we present 6 patients with simultaneous occurrence of pre-excitation and OT, and in 1 case inflow tract, PVCs with fixed coupling intervals. To the best of our knowledge this unique combination of a focal, nonreentrant trigger and an accessory pathway representing a potential route for reentrant circuits has never been described before in the literature. Naturally, it remains to be clarified whether there is a causative association between these 2 types of arrhythmia, which are considered to have 2 distinct arrhythmogenic substrates. But the simultaneous disappearance of the OT PVCs in 5 of 6 successful AP ablations (at a site that according to electrophysiological mapping was fairly remote from the focus of these PVCs) might be suggestive of a common pathway. Additionally, the fact that RVIT PVCs did not disappear after ablation indicates this is a different mechanism from the other cases.

An even more intriguing question is whether a common link exists between the phenomenon described in our study and the one in the above-mentioned reports on coexisting AVNRT and AMC-related OTAs. Can we identify a mutual mechanism,

which could be held responsible for these similar phenomena, and which could represent a more complex arrhythmia mechanism than the ones previously described in the literature?

Dead-End Tract: Is it the Common Link?

We hypothesize that a possible explanation for both of the abovementioned phenomena could lie in the embryonic development of the atrioventricular conduction system. During maturation the left and the right bundle branches, as well as a third septal branch, develop from a specialized interventricular ring[36]. This ring initially encircles the junction of the developing ventricles at both AV orifices. The third, "nonbranching" bundle moves into the smooth septal surface of the left ventricle and encircles the aortic root as the so called "dead-end-tract," first described by Kurosawa et al. in 1985[37]. It is thought that under normal circumstances, the third branch disappears at maturity; however, sometimes it persists as a remnant of the atrioventricular conduction system. Studies have shown that conduction tissue that fails to regress could become arrhythmogenic later in life[38-40]. While anatomical studies have not been able to demonstrate the presence of ventricular muscle cells within the AMC, McGuire et al. have identified certain cell groups that histologically and electrophysiologically resembled the atrioventricular junctional cells[38]. Furthermore, the previously mentioned PPs could represent conduction through the 'dead-end tract,' consequently resulting in VAs from the tracts' presumed endpoint in the AMC[26]. It is therefore plausible that if this remnant of the conduction structures extends into the AMC (or other possible locations in the proximity of the OTs), it could serve as a potential substrate for a certain subgroup of idiopathic VTs and might also have the potential to contribute to reentrant arrhythmias involving the AMC[40].

Limitations of the Study

Although a connection between the above-presented findings is apparent, the amount of cases included in this series is too small to distinguish between coincidence and commensuration. A larger international registry will be necessary to make this qualification and to clarify the incidence and prevalence of this association in an idiopathic VA population. It also remains unclear whether these results are just part of a more general finding in patients with idiopathic VAs or if they actually indicate a specific entity, namely "dead-end tract" associated arrhythmia. Finally, because of the retrospective nature of this paper and the fact that Holter monitoring is not routinely performed before and after WPW ablations, it was not possible to provide a complete overview of the PVC burden pre- and postablation.

In conclusion, the coexistence of pre-excitation and PVCs from the OTs and the fact that in some cases PVCs disappear after AP ablation, together with several previous related observations, suggests there may be an alternative common mechanism for this arrhythmia.

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Chapter 4

The predictive value of discrete presystolic potentials in catheter ablation of outflow tract arrhythmias

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(submitted)

ABSTRACT

Background. Despite general perception, inconsistency exists in the reported success in ablation of idiopathic ventricular arrhythmias. This may suggest that other possible mechanisms than triggered activity or abnormal automaticity may play a role in the development of outflow tract ventricular arrhythmias (OT-VAs). Recently, discrete prepotentials (DPPs) at the ablation site have been described during successful ablation of OT-VAs. The aim of this study was to investigate the presence and predictive value of DPPs in OT-VA ablation.

Methods. Twenty-six patients were included in this study who underwent radiofrequency catheter ablation for OT-VA. All mapping points at the ablation sites were re-analyzed to determine the presence of DPP. The following parameters were collected: demographic data, procedural data, procedural success, recurrences and/or repeat procedures. The data and outcome were correlated to the presence of DPP. Results. In 10 (38%) of 26 patients, a DPP was identified. There was no difference in acute procedural success between patients with and without a DPP (60% versus 88%, p = NS). The presence of a DPP was associated with a higher recurrence rate (70% versus 19%, p = 0.015) and more repeat procedures (40% versus 6%, p = 0.009) during a median follow-up duration of 18 months.

Conclusion. DPPs in patients undergoing ablation of OT-VAs are common. In the current study the presence of DPPs are associated with more VA recurrences. Their presence may suggest the involvement of the conduction system and based on its location possibly the so-called dead-end tract.

INTRODUCTION

Radiofrequency (RF) ablation for outflow tract ventricular arrhythmias (OT-VAs) is an established treatment.[1,2,3] Despite general perception, inconsistency exists in the reported (long term) ablation success of idiopathic ventricular arrhythmias that ranges from 34 - 96%[4,6]. Cyclic AMP-mediated triggered activity is thought to be the most common mechanism of idiopathic OT-VA[6,7], however, other mechanisms involving varying conduction properties of the OT have been proposed.[8] In recent reports, discrete prepotentials (DPPs) have been described during successful ablation of ventricular arrhythmias at the site of elimination of the ventricular extrasystole (VES) and ventricular tachycardia (VT) [8, 9 10,11], but their exact significance remains unclear. This may suggest involvement of a remnant of the embryonic conduction system or the conduction system itself. Purkinje fibers are known to be involved in left sided OT-VA, involvement of the conduction system in right sided OT-VA is less often described.[12] The aim of this study was to investigate the value of the presence of DPPs during catheter ablation of OT-VA in relation to acute and long-term outcome of the procedure.

METHODS

Study population and data collection

Consecutive patients who underwent ablation in our center for ventricular arrhythmias from the OT - including patients with either VT or VES - between January 2014 and April 2015 were included in this study. All data was collected prospectively except for the analysis of DPPs. Informed consent was obtained from all the patients prior to electrophysiology study. The patient information was de-identified.

Preprocedural protocol

All catheter ablation procedures were performed in accordance with institutionally approved local medical treatment protocols of the Erasmus MC, Rotterdam, the Netherlands. Anti-arrhythmic drugs were discontinued for at least 3 half-lives prior to the procedure. The use of amiodarone was an exclusion criteria.

Procedural protocol

The procedures were performed under local anesthesia with a single exception. The following mapping /ablation catheters were utilized in this study: Navistar Thermocool, Navistar Thermocool Smarttouch (Biosense Webster, Inc), St Jude

Tacticath (St Jude Medical Inc.). The catheters were advanced via percutaneous access through a femoral vein or artery to the RVOT and/or aortic sinus of Valsalva for mapping the outflow tracts. When the OT-VA originated in the left OT, the distal great cardiac vein and aortic cusps were also mapped and a decapolar deflectable coronary sinus catheter was inserted into the coronary sinus as deeply as possible to map within the great cardiac vein and the anterior interventricular cardiac vein. All procedures were performed using either EnSite NavX 3D (St. Jude Medical Inc., St. Paul, MN) mapping or the CARTO system (Biosense Webster, Inc., Diamond Bar, California). Intracardiac bipolar electrograms filtered at 30 to 500 Hz were recorded by a computerized electrophysiological recording system (EP-WorkMate system, Inc., St Jude Medical). For irrigated catheters, the electrode-tip temperature limit was usually set at 43°C, with a power ranging from 35 to 45 W, and irrigation flow of 20-30 mL/min. The ablation time was usually 60 seconds, depending on the location and effect. The catheter selection was dependent on clinical judgment of the operator.

Analyses of DPPs

All procedural recordings were re-reviewed by 2 independent electrophysiologists. All available OT electrograms for the OT-VA were analyzed during sinus rhythm and after a ventricular extrasystole, or ventricular pace. DPPs were defined as sharp, high-frequency potentials with an obvious iso-electric line between the potential and the onset of the QRS complex (Figure 1). The DPPs were recorded at different remote areas of the OT region.

Post-procedural protocol

For 48 hours after the procedure there was continuous rhythm monitoring and a resting 12 lead electrocardiogram, laboratory tests and chest radiograph were acquired. All patients were seen for regular follow up at 3 months after the ablation. A 24-hour Holter recording was scheduled for the 3-months follow-up visit, thereafter only when symptomatic.

Outcome definitions

We used the following outcome parameters: acute procedural success, VA recurrences and repeat ablations during follow-up. Acute procedural success was defined as disappearance of the clinical VA. VA-recurrence is defined as less than 95% reduction of VES on Holter compared to pre-ablation beats per 24 hours. In case of VT recurrence is defined as any VT recorded during follow-up.

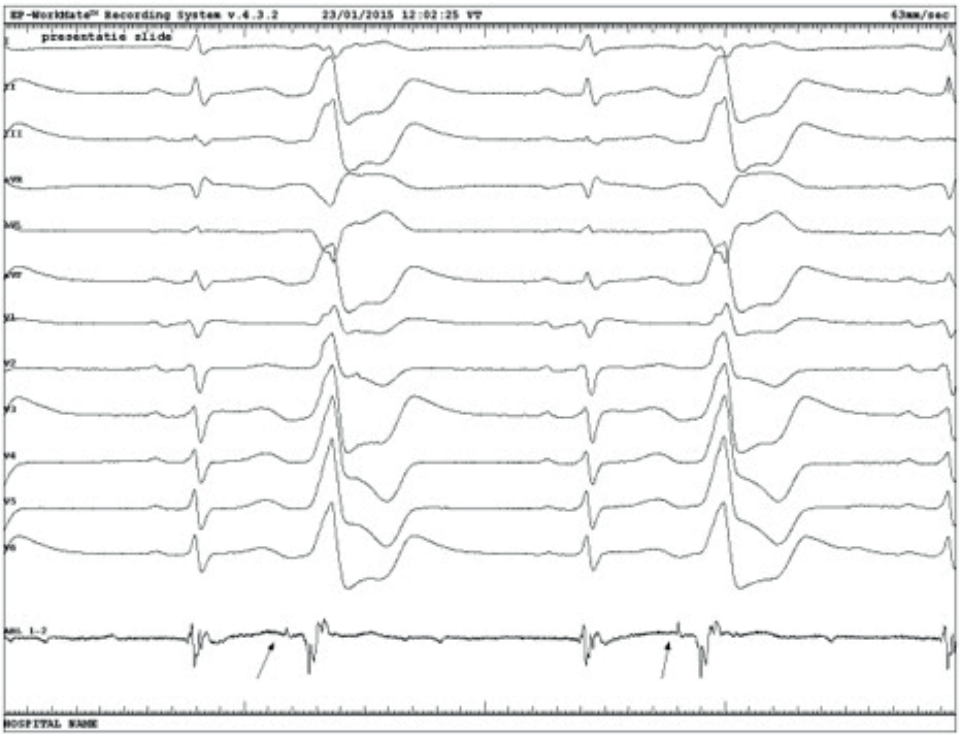

Figure 1. *Discrete prepotential. At the location of the ablation catheter a discrete prepotential with a constant coupling interval of 90 ms is seen before the ectopic beats. RV - right ventricle. ABL - ablation catheter*

Statistical analysis

Data were analyzed using SPSS 15.0 (SPSS INC., Chicago, IL, USA). Descriptive statistics for categorical data were expressed in absolute numbers and percentages. Student t test, chi-square test, and Fisher exact test were used to compare differences across groups. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Median and interquartile ranges (IQR) were computed for continuous variables with non-normal distribution, and the Mann-Whitney U test to compute statistical significance. A two sided p-value of < 0.05 (two tailed) was considered significant.

Results

Clinical characteristics

Table 1 shows the baseline characteristics. DPPs were identified in 10 of 26 patients (38%). Patients with DPP more often had a VT as the index arrhythmia (30% versus

0%, p = 0.046) in comparison to patients without DPP. In the presence of DPP in 50% the origin of arrhythmia was ablated in the in the LVOT, and in the absence of DPP 35% (p = NS). There were no differences in age, sex, previous OT-VA ablation procedure, use of antiarrhythmic drug therapy (Table 1). Structural heart disease varied from congenital heart disease (2 cases), arrhythmic right ventricular cardiomyopathy (1 case) and LV dysfunction (7 cases). None of the patients' voltage maps showed areas of low voltage.

Table 1. *Baseline characteristics*

	DPP absent	DPP present	p-value
Number of procedures	16	10	
Male	8/16 (50%)	8/10 (50%)	0.218
Median age [IQR]	49 [20-60]	48 [37-54]	0.159
Structural heart disease	7/16 (44%)	3/10 (30%)	0.683
VT	0/16 (0%)	3/10 (30%)	0.046
VES	16/16 (100%)	7/10 (70%)	0.046
RVOT	10/16 (65%)	5/10 (50%)	0.412
Aortic cusps	2/16 (13%)	1/10 (10%)	1.000
Index procedure is a repeat procedure	4/16 (25%)	2/10 (20%)	1.000
Median duration of follow-up (months) [IQR]	18 [17 -22]	17 [15 - 21]	0.408
Beta blocker	5/16 (31%)	4/10 (40%)	0.692
Verapamil	3/16 (19%)	3/10 (30%)	0.644
Sotalol	0/16 (0%)	1/16 (10%)	0.385
Flecainide	3/16 (19%)	4/10 (40%)	0.369

AMC - aortomitral cusps. LVOT - left ventricular outflow tract, DPP - discrete prepotentials, VES - ventricular extrasystole. VT - ventricular tachycardia

DPP and the characteristics

In 10 procedures DPPs were observed, in 8 procedures during PVC, 1 during sinus rhythm only and in 1 during both sinus rhythm and PVC. The DPP-PVC interval ranged from 25 to 90 ms. In 9 out of 10 procedures the DPP was observed at the site of ablation. The DPP was located in the RVOT in 5 out of 10 procedures. In two of the right side procedures the DPPs were located in the septum. Two were localized in the high posterior RVOT and 1 in the low posterior RVOT near the pulmonary valve. In 2 left sided procedure the site of the DPP was near the aortic valve, of which 1 near the left coronary cusp and 1 in the subvalvular septum. In the other 2 left sided procedures a DPP was found septally. In one procedure the exact localization of the DPP remained unclear (Figure 2A and B).

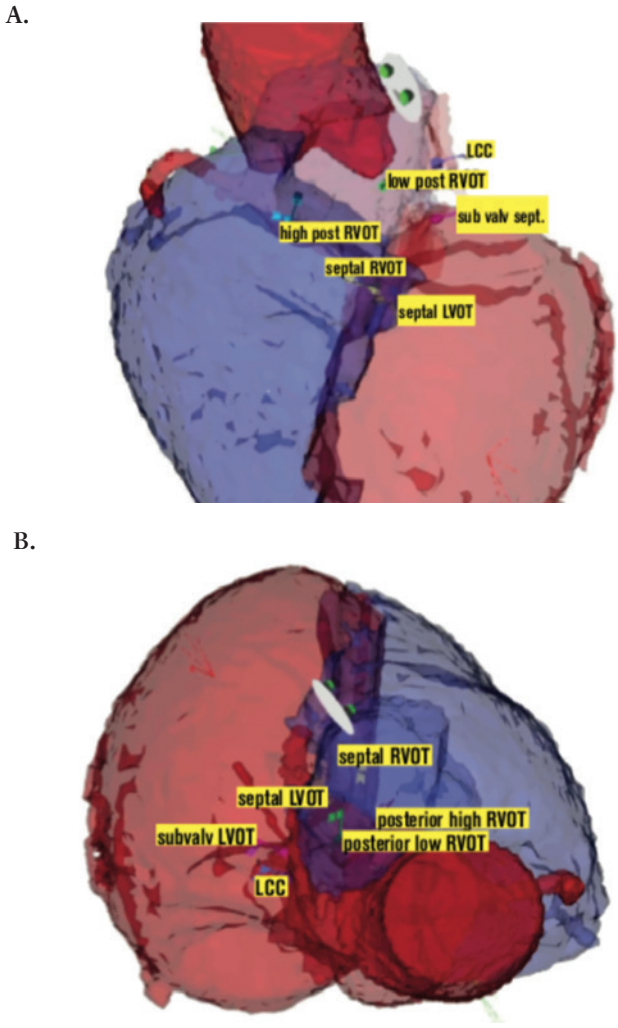

Figure 2. *Localization of discrete prepotential in different procedures. (A) LAO view of the outflow tracts, (B) superior view of the outflow tracts. The DPP was located in the septal RVOT (2), high posterior RVOT (2), low posterior RVOT, septal LVOT, LCC and subvalvular septal LVOT (2). In the 9 illustrated procedures, the ablation was done at the site of the DPP. DPP = discrete prepotential; LCC = left coronary cusp; LVOT = left ventricular outflow tract; PROX = proximal; RVOT = right ventricular outflow tract; SUB VALV = subvalvular.*

Mapping and ablation data

The target of ablation was identified by activation mapping and in the minority of cases in the absence of PVC under isoprenalin, pace mapping. Pace map based ablation only was used in one case in the DPP present group and in 3 cases in the DPP

absent group. In 9 of the 10 cases the earliest site of the DPP was ablated. Procedural time 140 [105-205] minutes, application number 6.5 [4 – 17], application time 10 [3–21] minutes and fluoroscopy time 21 [13-37] minutes were not significantly different between the groups.

Procedural outcome

Seventy-seven percent of the procedures were successful (table 2). There was no difference in acute procedural success between patients with and without a DPP (60% versus 88%, p = NS) (Figure 3A).

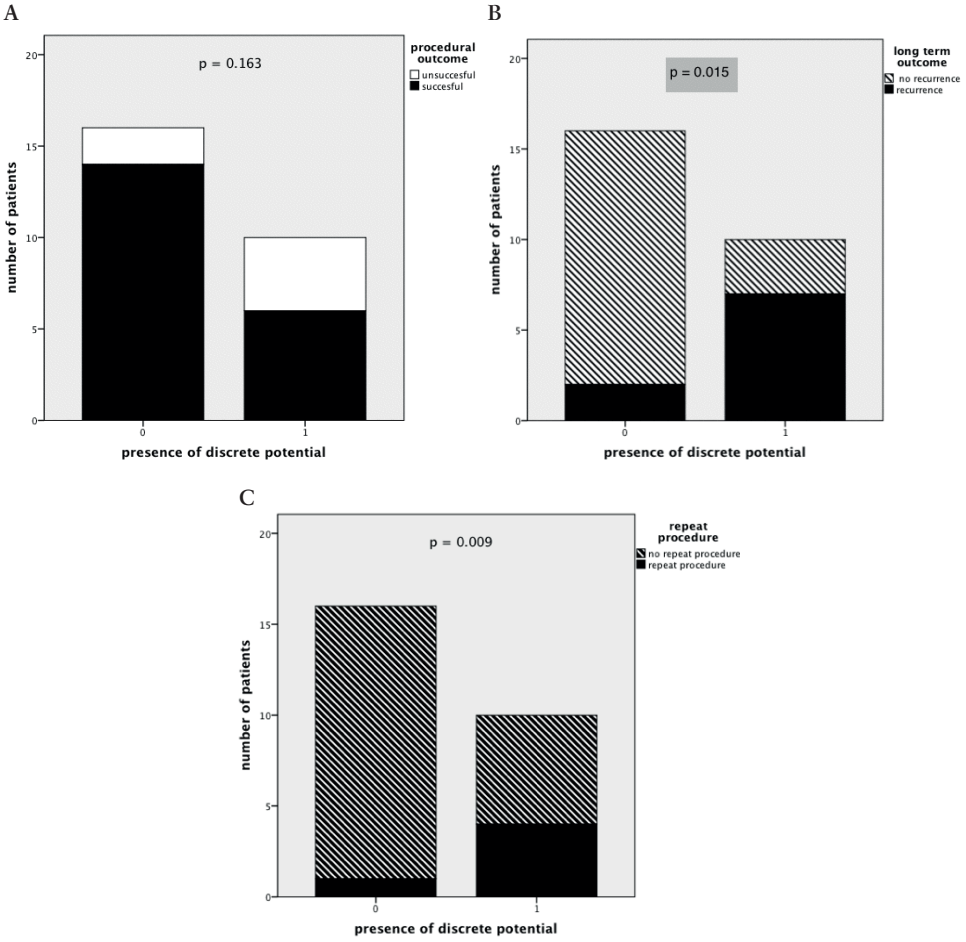

Figure 3A - C. *Presence versus absence of discrete prepotential and procedural outcome (A) long-term outcome (B), repeat ablation (C).*

Table 2. *Procedural outcome*

	absence DPP	presence DPP	p-value
Success	14/16 (88%)	6/10 (60%)	0.163
Recurrence	3/16 (19%)	7/10 (70%)	0.015
Repeat procedure	1/16 (6%)	4/10 (40%)	0.009

Recurrence and repeat procedure

After a median follow-up of 18 [16-21] months, 62% of the patients were free of VA recurrence (Figure 3B). The DPP patient group had a higher VA recurrence rate (70% versus 19%, P=0.015) and needed more repeat procedures (40% versus 6%, p = 0.009) (Figure 3C). Two patients with an early recurrence were free of recurrence at 6 months.

DISCUSSION

The major finding of this study is that the presence of DPP is associated with a higher recurrence rate in OT-VA ablation. In our study, 38% of the patients referred for the ablation of OT-VA had DPPs. Hachiya[10] and his group found a similar percentage of DPPs (26%) in patients with coronary cusp ventricular arrhythmias. In the current study, recurrences occurred in 38%, consistent with the existing literature (5-52% during various follow-up periods).[13]

Conflicting results for the value of DPPs in OT ablation

Recent publications described the DPP to be an indicator of a successful ablation site when using the discrete potential as a target.[8, 9, 10,11] Mulpuru et al. associated mid diastolic signals in 3 cases with atypical RVOT VA with slow conduction zones of the myocardial sleeves near the pulmonic valve.[8] DPP in outflow tract arrhythmia have been correlated with low voltage areas as shown by intracardiac high density contact mapping suggesting a substrate-related mechanism.[14] Successful acute and long-term ablation of the arrhythmia was linked to inability of conduction back to the RVOT in case of termination of the arrhythmia.[8] To target the arrhythmia in our study, conventional pace and activation mapping was used. Using this approach the presence of a DPP led to significantly higher recurrences on follow-up compared to its absence. The appearance of the DPP may suggest involvement of the conduction system. Idiopathic ventricular arrhythmias in fact may be subjected to a different arrhythmogenic mechanism than commonly thought.

Electrophysiology studies and ablation of the DPP

Entrainment of the coupling interval between the DPP and QRS complex of the VT was possible in a case of idiopathic RVOT tachycardia.[14] They showed a relation between the cycle length of the VT and the V-DPP interval. Further increasing the pacing interval gradually resulted in prolongation of the stimulus to DPP interval until a 2:1 block occurred.

In a report by Hachiya et al.[10] a DPP was demonstrated in 9-15% of the OT-VAs located on the coronary cusps. The OT-VAs all had a constant coupling interval between the preceding ventricular activation and DPP during sinus rhythm. The target for ablation in the coronary cusp VA was inferior alongside the valve, located in the myocardium of ventricular septal roof.[16] The DPP, recorded just beneath the successful ablation site, seemingly originated from the normal conduction system. Interestingly, after successful ablation a few patients showed delay of discrete potential following the terminal portion of the QRS during sinus rhythm. This suggest that timing of the DPP had shifted to a later time. This could represent the activation of a tract connecting the arrhythmia focus to the ventricular myocardium.

Origin of the DPP

Several studies have observed DPPs during ablation of OT-VAs, especially VA from the aortic mitral continuity, coronary cusps and left sinus of Valsalva. [8,9,10,11, 15,17] Apart from these localizations we found 50% of the DPP to be localized in the septal and posterior RVOT. A few characteristics of the DPP stand out: a His-like morphology [10], a relation to sinus rhythm[17], a constant coupling interval between the DPP and the QRS [10], entrainment of the V-DPP interval[15], decremental properties of the DPP[15], and a shift in timing after ablation.[10] All before-mentioned characteristics suggests an origin of the DPP in the conduction system.

His-like morphology and the decremental properties suggests involvement of the conduction system. Long intervals between the preceding QRS and the DPP and between the DPP and following ectopic ventricular activation demonstrates there is also slow conduction. In case of a DPP in a tachycardia slow conduction is reflected by long intervals between successive ventricular activations and the interposed DPP. The sharp deflection indicates fast conduction. The combination of properties suggests that the conduction system involved has both fast conducting and slow conducting components. A constant interval of the DPP to sinus rhythm implies that the supraventricular stimulus is conducted to the focus where the DPP originates from, and that the DPP is not an automatic focus. The constant and in case of VT an entrainable DPP-QRS coupling interval suggests a causal relationship. Finally, a shift

in timing after ablation advocates modification of an activating pathway connecting the arrhythmia focus to the ventricular myocardium.

A possible explanation for the pathway that gives rise to the DPP might be a remnant of the atrioventricular conduction system[10,17], the so-called "dead-end-tract".[18-20] Kurosawa et al.[20] described a dead-end-tract persisting beyond the bifurcation of the right and left bundle branch in 3 sectioned hearts of neonates and infants. In one case the tract extended into the aortic root and in the other two cases the tract disappeared close to the muscular summit of the septum. We hypothesize that when the dead-end tract persists and is extensive enough to reach structures such as the OT, it may contribute to the initiation of arrhythmias. Judging by its location, a structure as such may be difficult to reach and might therefore explain why patients with OT-VA and DPP have more recurrences after catheter ablation. The current study emphasizes that a different approach to arrhythmias presenting with discrete prepotentials is needed. However in order to prove a theory as such, future investigation is necessary.

Limitations of the study

This is an observational study of a limited number of patients. The median duration of follow-up was 18 months. Generally most recurrences are seen within the first follow-up visits[21], whereas late recurrences have more to do with non-procedural related factors.[22] A relatively large amount of patients had structural heart disease. Therefore the present study may not be representative when extrapolated to the general idiopathic VA population. Yet in the presence of DPP, structural heart disease was not more often the underlying condition. The ablation was not DPP guided, however in 9 of the 10 cases the earliest site of the DPP was ablated. These observations are retrospective in nature and should be interpreted with caution.

Conclusions

The presence of DPPs is common (38%) in patients referred for OT-VA ablation. The presence of DPPs is associated with a significantly higher VA recurrence rate. Characteristics of the DPPs suggest involvement of the conduction system, and may be linked to the so-called dead end tract. Portions of the dead-end tract may be remote from the ablation catheter tip, surviving and perpetuating outflow tract arrhythmia.

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Chapter 5

Sleep medications containing melatonin can potentially induce ventricular arrhythmias in structurally normal hearts: a 2-patient report

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ABSTRACT

Idiopathic ventricular arrhythmias (IVAs) are relatively common in the general population and usually have a good prognosis. However, frequent PVCs can lower quality of life (in symptomatic cases) and can cause cardiomyopathy and sudden cardiac death. In this report, we demonstrate a novel trigger for IVAs. Melatonin use for treating sleep-disorders has increased significantly in recent years. We provide here the first human evidence of its pro-arrhythmic effect by presenting two patients (with normal myocardium) with symptomatic PVCs, while on melatonin. Discontinuation of melatonin stopped PVCs in both patients. Our findings highlight the importance of identifying precipitating factors for IVAs.

INTRODUCTION

Even in patients with structurally normal heart symptomatic PVCs are relatively common. The majority originate in the ventricular outflow tracts (OTs). Although it is well-known that triggered activity is the main underlying mechanism of arrhythmogenesis, precipitating factors for this focal activity remain largely undetected[1].

Here we report on the pineal hormone melatonin (which normally regulates the body's circadian rhythms and sleep-wake cycles) being capable of mediating OT PVCs in the absence of structural heart disease. Melatonin is widely-used as a prescription-/over-the-counter-drug to treat sleep disorders. Based on its pharmacological effect of alleviating sleeping problems it is rather expected to protect against arrhythmias, because of the association between arrhythmias and sleep deprivation. In our patients, however, we observed a clear association between melatonin use and the occurrence of PVCs from the OT. As OT arrhythmias represent more than 10% of overall referrals for electrophysiological studies, our present findings highlight the importance of identifying pharmacons that can mediate OT-PVC-generation, because refraining from these drugs is safer and more cost-effective than trying to treat the disease with antiarrhythmic medication or catheter ablation[1].

CASE SERIES

Two patients referred to our department because of palpitations were included in this report. Both patients used melatonin for sleeping problems. Holter and/or implantable loop recorder (ILR) registrations demonstrated PVCs as a cause for their symptoms. The origin of the PVCs was specified either through electrophysiological study or based on QRS morphology on 12-lead ECG. Patient characteristics are listed in Table 1. A comprehensive literature search in several electronic databases for relevant studies published until January 2017 was conducted. Informed consent was obtained from both patients. Data collection was performed respecting the Health Insurance Portability and Accountability Act 1996.

Case 1

The first patient was a 72-year-old male with an uneventful cardiac history (except for a short episode of paroxysmal SVT in 1980). In August 2014 he was referred to our outpatient clinic because of palpitations despite being on beta-blocker therapy. Other medication used by the patient included: sitagliptin (oral anti-hyperglycaemic), atorvastatin (statin), candesartan (angiotensin II receptor blocker) and metformin

(oral anti-hyperglycaemic). The patient also used melatonin (1 mg once daily, sublingual) due to problems falling asleep.

Table 1. *Patient characteristics*

	Case 1	Case 2
Gender	Male	Male
Age (y)	72	63
BMI (body mass index)	25	22
LVEF	Normal	Normal
Cardiac history:		
Arrhythmic	Paroxysmal SVT	AVRT, AT, AF, AFl
Ischemic	No CAD	No CAD
Melatonin dosage	1 mg once daily, sublingual	1 mg once daily, per os

LVEF = left ventricular ejection fraction; AVRT = atrioventricular re-entry tachycardia; AT = atrial tachycardia; AF = atrial fibrillation; AFl = atrial flutter; SVT = supraventricular tachycardia; CAD = coronary artery disease.

Holter tracings revealed more than 2000 multiform PVCs per 24 hours and ILR registration (Medtronic Reveal LINQ) confirmed PVCs as the cause for the palpitations. 7.5 mg bisoprolol was ineffective. The dominant morphology of the PVCs was suggestive of an OT origin on a 12-lead ECG (Figure 1). An exercise test showed only occasional PVCs, both during exercise and recovery phase, and without symptoms of angina or ST-segment alterations. A normal LV function was seen on echocardiogram. CT-angiography showed no coronary artery disease with a calcium-score of zero. Subsequently, 150 mg flecainide was given in combination with 2,5 mg bisoprolol, but without any effect. In September and November 2014 he discontinued melatonin resulting in complete cessation of symptoms. In March 2015, after completely abstaining from melatonin, the patient became free from any symptoms. Complete disappearance of PVCs was also confirmed with ILR registration (Figure 2).

Case 2

In May 2012 a 63-year-old male presented with recurrent palpitations after a prior cardiac history of catheter ablation of a left anterolateral accessory pathway, a focal atrial tachycardia and atrial fibrillation (successful catheter ablation in 2011). He also used melatonin (1 mg once daily, *per os*) because of difficulties falling asleep. Other medications included: acetylsalicylic acid (platelet aggregation inhibitor), formoterol (long-acting β_2 agonist, 12 µg 2 times daily), fluticasone and ciclesonide (glucocorticoids).

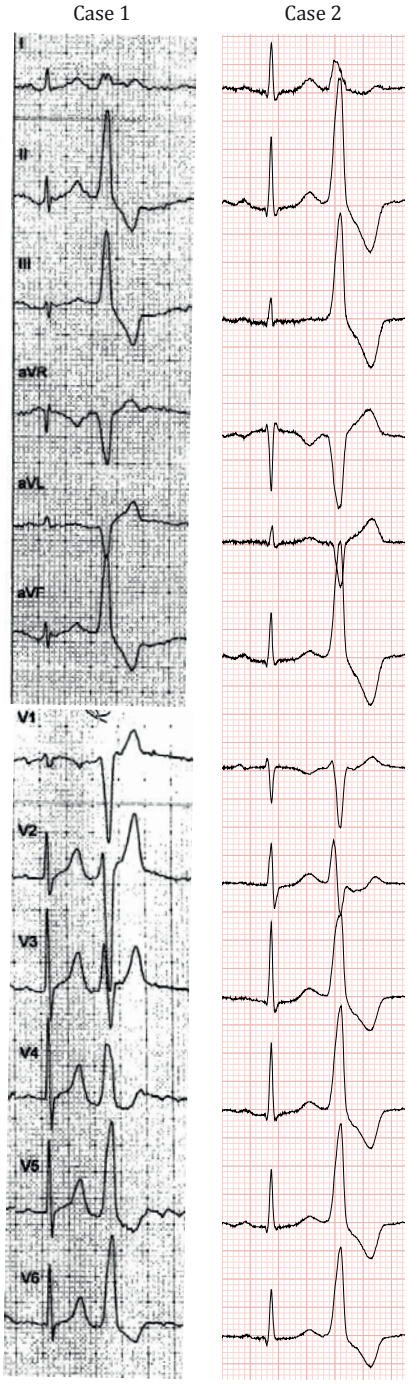
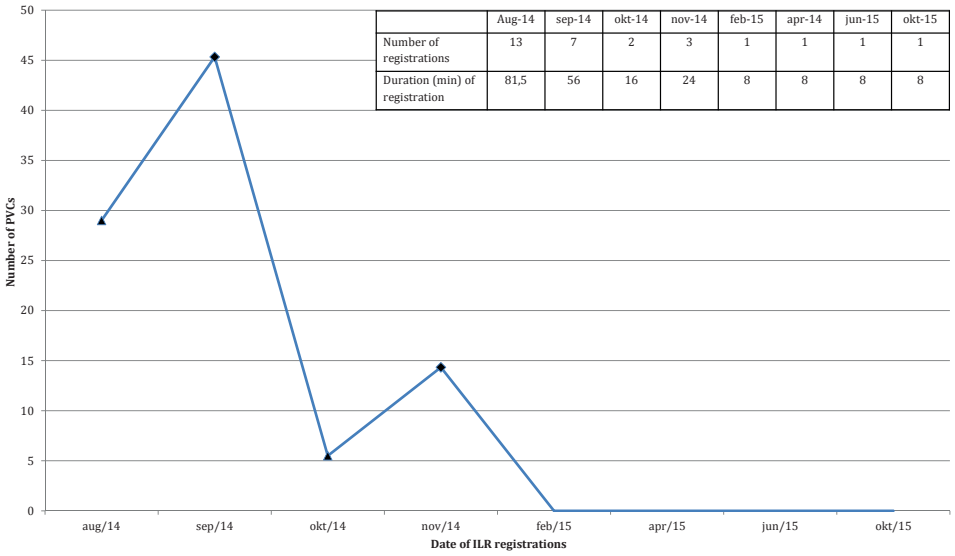


Figure 1. *The ECGs of both patients showing PVCs originating from the outflow tracts.*

At follow-up, in July 2012 a five-day Holter was performed, revealing multiple symptomatic PVCs and non-sustained VTs with a morphology suggestive of an OT origin (Figure 1). A coronary angiogram ruled out an ischemic cause for the arrhythmia. Echocardiogram showed a normal LVEF without any other structural abnormalities In October 2012, unsuccessful PVC ablation, targeting an RVOT origin, was performed. After a 24-hour Holter revealed a PVC-burden of 6% in May 2015, the patient was suggested to stop using melatonin (based on our previous experience with the patient from case 1). A follow-up 24-hour Holter registration showed a complete cessation of PVCs (0% PVC-burden), and additionally, the patient became free from any symptoms.



	Aug-14	sep-14	okt-14	nov-14	feb-15	apr-14	jun-15	okt-15
Number of registrations	13	7	2	3	1	1	1	1
Duration (min) of registration	81,5	56	16	24	8	8	8	8

Figure 2. *Mean PVC number/registration period with ILR. Mean PVC number during registration period is depicted for each month of ILR use. All registrations were patient-activated. Triangles: (re)start of melatonin, rhombuses: discontinuation of melatonin. Embedded table shows the total number and total duration of recordings during one month.*

DISCUSSION

This is the first report in the literature that describes evidence for a possible association between melatonin use and the occurrence of idiopathic VAs in humans. Discontinuation of melatonin in two patients with OT VAs led to a complete suspension of symptoms and the disappearance of arrhythmias on Holter/ILR registrations.

In the absence of structural heart disease VAs most commonly arise in the RVOT. Focal triggered activity mediated by delayed afterdepolarizations (DADs) is believed to account for the generation of these VAs. DADs can be evoked in the presence of various pathological factors (myocardial ischemia, genetic disorders of intracellular Ca^{2+}-handling, *etc.*), which can cause intracellular Ca^{2+}-overload in myocytes. However in the absence of such disorders the mechanism of DAD-mediated arrhythmogenesis is less well understood. Increased sympathetic influence seems to play a role in the generation of DADs in normal myocardium in a cAMP-mediated fashion[2].

Several "extrinsic factors" have also been implicated to cause VAs in structurally normal hearts: extensive alcohol caffeine or tobacco use, electrolyte imbalance (hypokalaemia) and certain medications represent the main examples. β-receptor-activators (catecholamines and synthetic β-agonists) can cause DAD-induced VAs through the elevation of cAMP levels and digitalis causes Ca^{2+} accumulation and subsequent DADs through the inhibition of the Na^{+}-K^{+} exchange[2].

Based on our observations, melatonin could also belong to the group of mediators that have the potential to precipitate VAs in structurally normal myocardium. In recent years the clinical use of melatonin has increased significantly. In the US, its use more than doubled between 2007 and 2012[3], and a similar (or even more significant) increase has been reported in Scandinavian countries[4]. In Europe the availability of melatonin as prescription- *vs*. over-the-counter drug varies from country to country. In the US, melatonin is classified as dietary supplement and therefore available over-the-counter. Melatonin content of such dietary supplements is not controlled by the Food and Drug Administration (FDA), and therefore concerns may arise regarding the actual melatonin dose of these preparations.

Reports in the literature mainly argue for a protective effect of melatonin against arrhythmias. This putative anti-arrhythmic effect has been implicated to occur through indirect mechanisms. As a sleep medication it might be able to alleviate "sleep-deprivation-induced arrhythmias". In addition, by reducing the sympathetic tone, melatonin can also reduce arrhythmia burden caused by sympathetic predominance. A study that analysed the effect of melatonin in canines on the repetitive extrasystole threshold of the vulnerable period of the ventricular myocardium, showed that this threshold was increased by melatonin, thus arguing for a protective effect against arrhythmias[5]. The authors proposed that this effect may be achieved by the inhibition of the flow of 'arrhythmogenic' sympathetic nerve traffic from the CNS to the heart[5]. Moreover, through its antioxidant activity melatonin has also been shown to significantly reduce ischemia/reperfusion-induced VAs [6, 7].

Recent studies describe the expression of melatonin receptors in cardiac tissue[8]. The three known melatonin receptors are: MT1, MT2 and MT3[9]. Of these, MT1 and MT2 have been detected in the cardiovascular system[8, 10]. Through these two G-protein-coupled receptors melatonin might be able to alter the function of key players in the Ca^{2+}-handling machinery (*e.g.* L-type Ca^{2+}-channel, ryanodine receptor, SERCA). Although a pro-arrhythmic mechanism has never been reported before, a presumable direct effect on the myocardium through its receptors could provide the functional basis for a pro-arrhythmic effect. However, (although less likely) indirect pro-arrhythmic effects of melatonin should also not be excluded. For instance, a seemingly paradoxical effect of melatonin is the reduction of deeper sleep[11]. Through the altered sleep structure melatonin might exert an indirect pro-arrhythmic effect. Another side-effect of melatonin reported in literature is hypothermia[11], which in turn is thought to be a pro-arrhythmic condition. This pro-arrhythmic effect, however, is usually reported in the context of therapeutic hypothermia (between 32-36°C). The temperature-drop associated with melatonin has been reported to be only 0,28°C after a dose of 5 mg, which therefore represents an unlikely mechanism for arrhythmogenesis in the patients in our current report.

The ultimate effect of melatonin (pro- *vs.* anti-arrhythmic) might depend on the balance between its indirect *vs.* direct effects, which in turn might be determined by several factors: *e.g.* melatonin dosage in different preparations (especially in dietary supplements), differences in bioavailability, and genetically defined inter-individual differences in receptor-expression and receptor-activity. For instance, it has been shown that there is a substantial person-to-person variability in bioavailability (with up to 25-fold variations in areas under the curve of a single dose in five subjects in one study)[12]. Time to maximum melatonin levels and half-life elimination may range between 40 – 90 minutes and 50 – 120 minutes, respectively[13, 14]. Hence, our patients might represent a certain population, the members of which might either show greater susceptibility to the pro-arrhythmic effects of melatonin, or possess an altered pharmacokinetics and different bioavailability of this drug. Both of these conditions could lead to the development of symptomatic VAs in response to this medication.

When taking into consideration other possible triggers of PVCs, it is noteworthy to mention that the patient from Case 2 used formoterol, which is known to have the potential to cause palpitations. However, the use of this long-acting β_2 agonist was constant pre-, peri- and post-melatonin use. In addition, considering the fact that these patients did not have any drug in common on their list of medications (not even one from the same group) drug-drug interactions causing the pro-arrhythmic effect of melatonin seemed unlikely, as well.

Although idiopathic VAs are believed to follow a benign clinical course, some patients can be highly symptomatic (especially the ones with high PVC/nsVT-burden) and in rare cases life-threatening VAs can occur. In addition, frequent PVCs/nsVT can precipitate a potentially reversible form of cardiomyopathy (even in asymptomatic patients). Therapy is only warranted for symptomatic patients or asymptomatic individuals with signs of decline of LV systolic function, attributable to frequent PVCs/nsVTs. Medical therapy has proven to have limited efficacy. Catheter ablation, however, is a more effective treatment; although procedural success as well as complication rates may be highly dependent on the site of origin; with lower efficacy and higher complication rates reported for more uncommon sites of origin (LVOT, aortic cusps)[1]. Still, lower success rates may also be attributed to incomplete understanding of the arrhythmia mechanism and lack of knowledge on possible precipitating factors. Therefore our findings highlight the importance of the awareness of the potential for melatonin to cause VAs, and should prompt physicians to specifically search for melatonin use in patients with symptomatic PVCs or with high PVC-burden on Holter; as melatonin use might often be unreported by many patients (especially in countries where it is available over-the-counter). In addition, these observations should initiate further studies aiming to identify other possible precipitating factors for VAs in a normal myocardium, and to clarify the underlying mechanisms of their effects. In our opinion, this approach would reduce the costs as well as increase the safety of the clinical treatment of patients with idiopathic ventricular arrhythmias; because, although the complication rates of ablation procedures are reported to be low, they are nevertheless not negligible (especially for foci located outside the RVOT) and include major complications such as tamponade, stroke and coronary artery damage. Therefore identifying reversible causes (similar to melatonin medication) for idiopathic VAs would enable clinicians to offer better treatment strategies and avoid unnecessary and potentially harmful therapy.

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As native English speaker, R. Alloway revised the manuscript for language.

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Chapter 6

Coupling interval variability of premature ventricular contractions in patients with different underlying pathology: an insight into the arrhythmia mechanism

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ABSTRACT

Purpose: Coupling interval (CI) variability of PVCs is influenced by the underlying arrhythmia mechanism. The aim of this study was to compare CI variability of PVCs in different myocardial disease entities, in order to gain insight into their arrhythmia mechanism.

Methods: Sixty-four patients with four underlying pathologies were included: idiopathic (n=16), non-ischemic dilated cardiomyopathy (NIDCM) (n=16), familial cardiomyopathy (PLN/LMNA) (n=16) and post-MI (n=16) associated PVCs. The post-MI group was included as a reference, on account of its known re-entry mechanism. On Holter registrations, the first 20 CIs of the dominant PVC morphology were measured manually after which median ΔCI and mean SD of CI/√R-R (= CI of PVC corrected for underlying heart rate) were obtained. Two observers independently measured PVC CIs on pre-selected Holter registrations in order to determine inter- and intra-observer reliability.

Results: The largest ΔCI was seen in the PLN/LMNA group (220 ms (120-295)), the lowest in the idiopathic group (120 ms (100-190)). The ΔCI in the PLN/LMNA group was significantly larger than the post-MI group (220 ms (120-295) *vs* 130 ms (105-155), p = 0.023). Mean SD of CI/√R-R in the PLN/LMNA group was also significantly higher than in the post-MI group (p = 0.044). Inter- and intra-observer reliability was good (ICC = 0.91 *vs* 0.86 and 0.96 *vs* 0.77, respectively).

Conclusions: Low ΔCI and SD of CI/√R-R of idiopathic and NIDCM PVCs suggest that the underlying arrhythmia mechanisms might be re-entry or triggered activity. Abnormal automaticity or modulated parasystole are unlikely mechanisms. High CI variability in PLN/LMNA patients suggests that re-entry and triggered activity are less likely mechanisms in this group.

INTRODUCTION

Premature ventricular contractions (PVCs) are common both in patients with and without structural heart disease (SHD)[1]. Even in the population without apparent SHD the incidence of PVCs is estimated to lie between 4 - 50%[2-5]. Although the independent prognostic importance of the PVC burden regarding adverse cardiac events (e.g. VT, sudden cardiac death, heart failure, etc.) has not been clarified unambiguously, symptomatic PVCs can significantly reduce the quality of life (QoL) in both patient populations, and frequent PVCs can result in tachycardiomyopathy even in the absence of overt SHD[1, 6, 7]. It is therefore important to emphasize that the treatment of symptomatic and/or frequent PVCs can lead to a significant improvement of the QoL[6] and to the preservation/improvement of left ventricular function[7]. Catheter ablation (CA) has become a highly efficient alternative to medical therapy and is now in many cases being applied as a treatment of first choice[8]. However, a broad range of success rates have been reported in the literature, varying from 69%[9] to as high as 90%[8]. Incomplete understanding of the main underlying mechanisms of these arrhythmias may play a key role in this discrepancy.

One of the basic ECG characteristics of PVCs is the coupling interval (CI), which is defined as the distance between the onset of the preceding sinus QRS and that of the premature beat. An important feature of PVCs described in the literature is the variability of the CI. Although the determinants of CI variability and their clinical implications are not completely understood yet, early studies describe an association between higher CI variability and the incidence of VT and SHD among PVC patients[10, 11]. In addition, a relation between CI variability and the efficiency of antiarrhythmic medical therapy has also been implicated[10]. Moreover, a recent publication has shown that CI variability might be able to discriminate between the precise anatomic origins of PVCs within the outflow tracts in patients with idiopathic ventricular arrhythmias (VAs) [12].

Although the variability of CIs is influenced by several factors (*e.g.* variation of the preceding cycle length, fluctuations in rhythmic distribution patterns, intermittent parasystole and precipitancy of another ectopic source[13, 14]) their major determinant is believed to be the underlying arrhythmia mechanism. When PVCs have fixed CIs then re-entry and triggered activity are among the most probable mechanisms. On the other hand when PVCs exhibit variable CIs, then increased/abnormal automaticity or parasystole are more likely to be the source of rhythm disturbances [10, 15-17].

By describing the CI variability of PVCs in four distinct pathophysiological groups of myocardial disease, this study aims to shed more light on their underlying arrhythmia mechanisms. As the arrhythmogenic substrate for PVCs in patients with prior myocardial infarction (post-MI group) is well-described as being scar-related

re-entry with a fixed CI (in cases of monomorphic PVC/VT) this group of patients served as a control in our analyses. The arrhythmogenic substrates in structurally normal hearts and in non-ischemic myocardial disorders are less well-understood; therefore we assessed the CI variability of PVCs in the following three groups: (i) patients with idiopathic VAs (idiopathic group), who exhibited PVCs in the absence of apparent SHD; (ii) patients with non-ischemic dilated cardiomyopathy (NIDCM group); and (iii) patients with familial dilated cardiomyopathy due to mutations in the genes encoding lamin A/C or phospholamban (PLN/LMNA group).

METHODS

Patients

A database containing all performed CAs in our center was screened for patients undergoing VA ablation. Out of 345 VA ablations performed in our center between 2007 and 2015, 16 consecutive idiopathic VA patients, 16 NIDCM patients and 16 post-MI patients were selected based on availability of Holter registrations. Sixteen PLN/LMNA cardiomyopathy patients from the inherited channelopathy and cardiomyopathy database were selected based on the same criteria. Selection of Holter registrations was based on the amount of PVCs recorded. A cut-off of 20 monomorphic PVCs of the dominant morphology was applied for selection, or otherwise the recording with the highest amount with a minimum of 4. All patient data was acquired from medical records by a trained physician. Pediatric patients were defined as younger than the age of 18 years. Arrhythmia origin was derived from electrophysiological studies, when available. We distinguished right ventricular outflow tract (RVOT), left ventricular outflow tract (LVOT), which includes coronary cusps and aorto-mitral continuity, and other (such as; ventricle walls, fascicular or His region). Demographic data are presented in Table 1. Data collection was performed respecting the Health Insurance Portability and Accountability Act 1996.

Measurement and determination of CIs

For every patient, PVC CIs were taken from a single 24-hour Holter recording. Individual rhythm strips (depicting a certain time frame within the 24-hour recording period, which usually encompassed approximately 10-60 seconds) were selected by designated Holter analyst, either manually or with the help of computer software that generates an automatic event summary. These rhythm strips had been collected (and saved within the electronic documentation of each patient) based on their relevance with regard to the clinical inquiry posed by the referring physician. For the purpose of our analysis we selected PVCs (and corresponding R-R intervals) without regard

to the actual time periods these rhythm strips were depicting (throughout the 24 hour registration period); thereby ensuring that comparable numbers of day-or nighttime registrations have been included. The first 20 PVC CIs of the dominant morphology were measured by hand with an accuracy of 20 milliseconds. Additionally, the corresponding sinus R-R intervals preceding the selected PVC CIs were measured in order to correct the CIs for heart rate variability (as described below). The dominant PVC morphology was established by reviewing all the individual rhythm strips of the full 24-hour Holter registrations. Distinct morphologies were then identified and grouped accordingly. Subsequently the number of PVCs in each distinct group was determined and the morphology which belonged to the group with the highest PVC count (thus the most frequently occurring morphology) on the analyzed rhythm strips was considered the dominant morphology.

VTs were not included in this study. Two methods were used for assessing CI variability: (i) delta (Δ) CI (defined as the maximum minus the minimum CI duration) was defined for each patient, and the median and 25th and 75th percentiles of ΔCIs were presented for each group; (ii) the SD of CI/√R-R (the CI of each PVC corrected for the underlying heart rate) for each patient was defined, after which the SD of CI/√R-R per group was presented as mean with SD. The first step of the latter methodology was analogous to Bazett's formula, which is used to correct the QT-interval by taking into consideration the underlying heart rate [18]. In our calculations of CI/√R-R the R-R interval of the preceding sinus beat was used.

The monomorphic or polymorphic nature of PVCs and the amount of each morphology was determined subsequently (as described above). The monomorphic or polymorphic nature of PVCs was defined as possessing only one morphology or two or more morphologies on Holter, respectively.

Inter- and intra-observer reliability

To determine inter- and intra-observer reliability, agreement and bias for CI measurements first two observers, both physicians, independently measured PVC CIs on pre-selected Holter registrations from 32 patients (the idiopathic and NIDCM groups). When there was a discrepancy in the amount of CIs measured by the observers, this was discussed and a consensus decision was made. After good reliability of the measurement method was established, one observer analyzed the two remaining groups.

Statistics

The normality of distribution was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as mean ± SD for continuous variables if normally distributed,

or otherwise as median with 25th and 75th percentiles, where appropriate. Data were compared by one-way ANOVA or median test, as appropriate. The median test was used because equal variances between the groups were not assumed. Categorical data were expressed as percentages and compared with the Chi-squared test. Intraclass correlation coefficients (ICC) were used to describe inter- and intra-observer reliability. Additionally, a Bland-Altman plot was used to assess the agreement between the two observers and to detect any bias. Statistical analysis was performed using SPSS version 21 (IBM Corp., Somers, NY). Statistical significance was defined as $p < 0.05$ (two-tailed).

RESULTS

Patients and demographics

Patient demographics are presented in Table 1. Patients in the post-MI group contained more men (93.8%, p = 0.028), they were older (55 years (53-63), p = 0.042) and had a higher BMI (28 ± 3, p = 0.026). Digoxin was used more often in the PLN/LMNA group (37.5%, p = 0.006). Left ventricular ejection fraction (LVEF) was significantly different among the groups (p < 0.001): most patients (93.8%) in the idiopathic group had a normal LVEF and most patients (50%) in the PLN/LMNA group had severe LV dysfunction. All VAs in the post-MI group originated in the LV and none of them in the outflow tracts, whereas most of the VAs in the idiopathic group originated in the RV (75%), predominantly in the RVOT (75%). In the NIDCM group, the etiology was unknown (idiopathic) in 68.7% of the patients. The remaining etiologies included; SCN5A mutation, structural congenital heart defects and limb-girdle muscular dystrophy.

Coupling intervals

In 4 cases there was a discrepancy in the amount of CIs measured by the observers, which was discussed followed by a consensus decision. Overall, the largest median ΔCI was seen in the PLN/LMNA group (220 ms (120-295)) and the lowest in the idiopathic group (120 ms (100-190))(Figure 1). The ΔCI in the PLN/LMNA group was significantly larger than in the post-MI group (220 ms (120-295) *vs* 130 ms (105-155), p = 0.023) (Figure 1). Mean SD of CI/√R-R was as follows: post-MI 47 ± 15 ms, idiopathic 47 ± 20 ms, NIDCM: 52 ± 25 ms and PLN/LMNA 65 ± 31 ms (Figure 2). Mean SD of CI/√R-R in the PLN/LMNA group was significantly higher compared to the post-MI group (p = 0.044) (Figure 2). The median amount of CIs measured was equal between the groups (p = 0.485). In the idiopathic group there were no patients with polymorphic PVCs, in the PLN/LMNA most patients (94%) had polymorphic PVCs (p <0.001)(Table 1).

Table 1. *Patient Demographics*

	Post-MI	Idiopathic	NIDCM	PLN/LMNA	P-value
Total Pts	16	16	16	16	
Age (years)	55 (53-63)	45 (40-61)	54 (38-60)	52 (40-57)	0.042
Pediatric (%/n)	0% (0)	0% (0)	6.2% (1)	6.2% (1)	0.559
Sex (%male/n)	93.8% (15)	50% (8)	56.2% (9)	50% (8)	0.028
Length (m)	1.78 ± 0.1	1.76 ± 0.1	1.76 ± 0.1	1.71 ± 0.1	0.296
Weight (kg)	88 ± 15	82 ± 15	83 ± 21	71 ± 14	0.029
BMI	28 ± 3	27 ± 3	27 ± 5	24 ± 3	0.026
Any anti-arrhythmic drugs	93.8% (15)	56.2% (9)	68.8% (11)	62.5% (10)	0.102
- Class I	0% (0)	12.5% (2)	0% (0)	0% (0)	0.103
- Beta blockers	81.2% (13)	37.5% (6)	43.8% (7)	56.2% (9)	0.064
- Class III	25.0% (4)	12.5% (2)	43.8% (7)	25.0% (4)	0.252
- Class IV	6.2% (1)	6.2% (1)	6.2% (1)	0.0% (0)	0.789
- Digoxin	6.2% (1)	0% (0)	6.2% (1)	37.5% (6)	0.006
LVEF					<0.001
- Normal (>55%)	6.2% (1)	93.8% (15)	18.8% (3)	31.2% (5)	
- Mild dysfunction (45-54%)	31.2% (5)	6.2% (1)	37.5% (6)	6.2% (1)	
- Moderate dysfunction (30-44%)	18.8% (3)	0% (0)	18.8% (3)	12.5% (2)	
- Severe dysfunction (<30%)	43.8% (7)	0% (0)	25.0% (4)	50.0% (8)	
Monomorphic PVCs	13% (2)	100% (16)	44% (7)	6% (1)	<0.001
Polymorphic PVCs	88% (14)	0% (0)	56% (9)	94% (15)	<0.001
Ventricle of origin					<0.001
- Left	100% (16)	25.0% (4)	50.0% (8)	n.a.*	
- Right	0% (0)	75.0% (12)	37.5% (6)	n.a.*	
- Both	0% (0)	0% (0)	12.5% (2)	n.a.*	
Arrhythmia focus				n.a.*	<0.001
- RVOT	0% (0)	75.0% (12)	31.2% (5)	n.a.*	
- LVOT	0% (0)	25% (4)	25% (4)	n.a.*	
- Other	100% (16)	0% (0)	43.8% (7)	n.a.*	
PVC characteristics (of dominant morphology)					
- LBBB + superior axis	n.d.#	n.d.#	n.d.#	18.8% (3)	
- RBBB + superior axis	n.d.#	n.d.#	n.d.#	18.8% (3)	
- LBBB + inferior axis	n.d.#	n.d.#	n.d.#	25% (4)	
- RBBB + inferior axis	n.d.#	n.d.#	n.d.#	37.5% (6)	

*Descriptive statistics are presented as mean ± SD for continuous variables, if normally distributed, or otherwise by median with (25th and 75th percentile). BMI = body mass index, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, LVOT = left ventricular outflow tract, RBBB = right bundle branch block, RVOT = right ventricular outflow tract. (*Not applicable: no ablation was done in this group of patients therefore the exact origin of the PVCs was not determined by electroanatomical mapping; PVC characteristics, indicative of PVC foci, are presented as a surrogate. #Not displayed: In case electroanatomical mapping is available no PVC characteristics are displayed.)*

Inter-and intra-observer reliability

The inter-observer reliability in a two-way mixed effects model was very good for the idiopathic group (ICC = 0.91) and good for the NIDCM group (ICC = 0.86) (Supplementary Figure 1). The Bland-Altman plots for both groups show the observers were in good agreement regarding CI measurements (Supplementary Figure 1).

The intra-observer reliability in a one-way random effects model was very good for the idiopathic group (ICC = 0.96) and good for the NIDCM group (ICC = 0.77) (Supplementary Figure 2). The Bland-Altman plots for both groups show good agreement and no bias regarding CI measurements (Supplementary Figure 2).

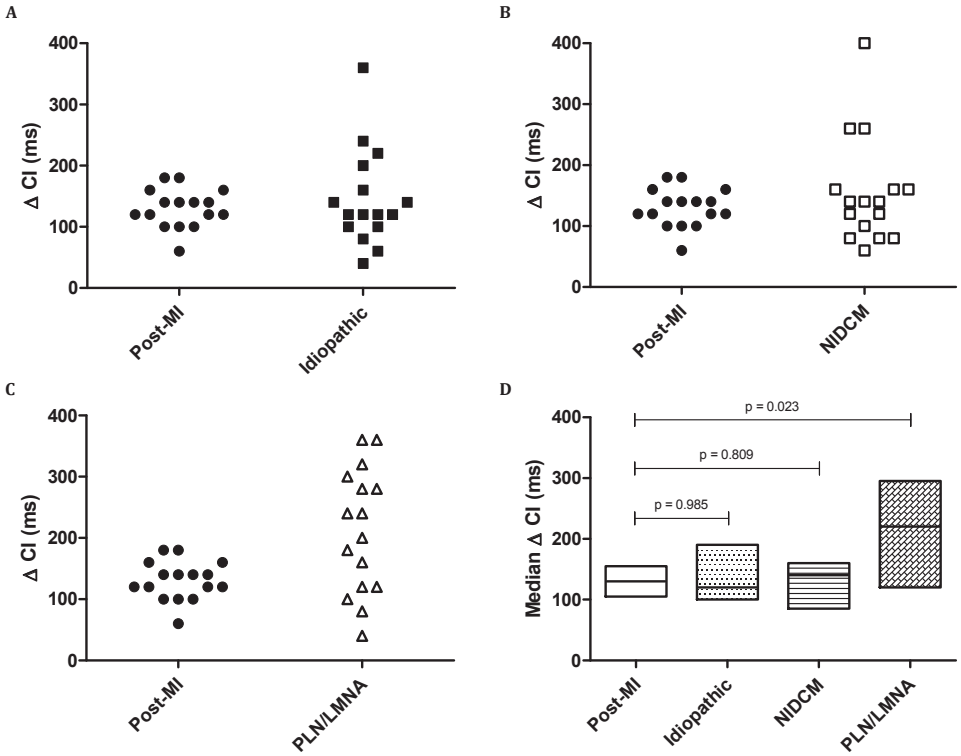

Figure 1. *ΔCI compared to post-MI group. Median ΔCI per patient for post-MI group versus (a) idiopathic PVCs, (b) NIDCM PVCs and (c) PLN/LMNA PVCs. The median ΔCI with 25th and 75th percentiles per group is shown in panel d.*

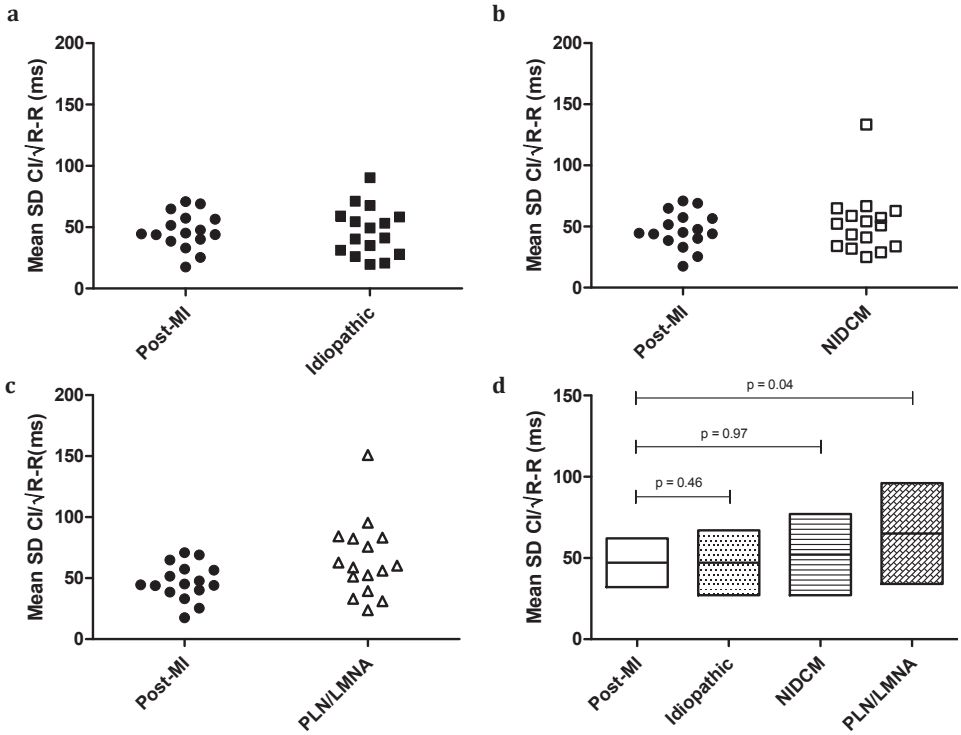

Figure 2. *Mean SD of CI/√R-R compared to post-MI group. Mean SD of CI/√R-R per patient for post-MI group versus (a) idiopathic PVCs, (b) NIDCM PVCs and (c) PLN/LMNA PVCs. The mean SD of CI/√R-R with standard deviation per group is shown in panel d.*

DISCUSSION

To the best of our knowledge, this is the first study in the literature that analyses the CI variability of PVCs in several distinct subgroups of patients with VAs, in order to provide further insights into the underlying mechanisms of arrhythmogenesis related to different cardiac pathophysiology. The main findings of this study are the following: 1) although the underlying arrhythmia mechanisms might differ between the post-MI population and the idiopathic VA population (scar-related macro-re-entry *versus* focal triggered activity) the CI variability of these groups were essentially identical, which indicates a similarly stable CI (fixed CI) for both re-entry and triggered activity within these pathophysiological subgroups. 2) The majority of the patients in the NIDCM group exhibited similar CI variability as the patients of the post-MI and idiopathic VA groups, which suggests that (despite a rather heterogeneous etiological background), the main mechanisms for arrhythmogenesis

might essentially be similar to the ones of the previous groups, namely: scar-related micro/macro re-entry or focal triggered activity with fixed CIs. 3) The patients of the familial dilated cardiomyopathy group (PLN/LMNA mutation group) exhibited high CI variability, which indicates that a mechanism different from re-entry or triggered-activity might be responsible for PVC-generation in this group. This mechanism may be abnormal automaticity, parasystole or another more complex mechanism. Since a considerable portion of patients (10 out of 16) from this group were on either digoxin or class III anti-arrhythmic drug therapy, we additionally compared the CI variability of the subgroup of patients on these AADs with their counterparts not using these medications. We found no significant differences between the CI variability of these subgroups of patients (data not shown), implicating that although these AADs might be able to alter the PVC frequency, they might not have any effect on the underlying arrhythmia substrate (however, the numbers in each subgroup were considerably small with regards to statistical relevance, therefore a firm conclusion from the results cannot be drawn).

PVCs: general symptomatology and treatment

Symptomatic PVCs can present a considerable burden to patients, even with a structurally normal heart[6]. In addition to the significant impact of symptomatic PVCs on QoL, frequent PVCs can cause LV dysfunction and in a minority of patients they are also reported to initiate malignant VAs with a potential to cause sudden cardiac death. These outcomes should not be trivialized, especially when structural heart disease is present[7, 8, 19, 20].

Treatment of symptomatic and/or frequent PVCs can be challenging. More often than not, medical drug therapy is either inadequately effective, or its adverse side-effects ensure that the cure becomes worse than the disease[8, 21]. Moreover, anti-arrhythmic drugs have not been demonstrated to reduce all-cause mortality in patients with or without structural heart disease[22]. On the other hand, although randomized trials of PVC suppression have not been performed, multiple studies indicate the high efficacy of PVC ablation [1]. In addition, technological advancements, such as magnetic navigation, have increased the safety of these procedures significantly[23]. Abolishment of frequent PVCs has been shown to reverse LV dysfunction in PVC-induced cardiomyopathy and improve QoL in patients with structurally normal heart[6, 7]. CA of some specific VA entities (such as e.g. idiopathic RVOT VAs or left posterior fascicular VAs) are reported to have very high success rates (>95%)[8] and CA is increasingly being performed as a first choice therapy in these select cases. However, CA of certain other VA etiologies shows a much lower success rate in terms of arrhythmia termination[8]. The relatively wide range of success rates reported

in the literature can at least be partially attributable to the different sites of VA origin[24] (i.e. technically challenging locations for the ablation procedure as e.g. epicardial sites), and/or they might also be influenced by publication bias. On the other hand, incomplete understanding of the underlying arrhythmia mechanisms of VAs occurring in the presence of distinct cardiac diseases could represent another key contributing factor to the failure of CA procedures.

Correlation of CI variability with arrhythmia mechanisms in different myocardial diseases

In order to further dissect the possible mechanisms that generate PVCs in different myocardial disease states we analyzed the CI of PVCs in different patient populations. Although there is limited data available in the literature about the characteristics of CIs and their clinical significance, some reports suggest a connection between short CI duration (<300 ms), a low prematurity index (<0.73) and the potential of these parameters to indicate an increased risk for malignant VAs[25-27]. An earlier report of Komatsu et al. describes the variability of CIs as a characteristic that might have the potential to discriminate between groups of patients with low *vs.* high risk for VT[10]. Additionally, their report suggests that higher CI variability has a tendency to occur in patients with organic heart disease, whereas patients with frequent PVCs in the absence of SHD tend to have a more fixed CI. Moreover they also describe a correlation between CI variability and the efficacy of antiarrhythmic drug therapy. Intriguingly, the characteristics of fixed and variable CIs that we describe in our study correspond well with the results of Komatsu et al.: *i.e.* the mean SD of CI/√R-R of the post-MI group (47 ms), the idiopathic VA group (47 ms) and that of the NIDCM group (52 ms) all approach a range (35.4 ± 14.1 ms) that has been identified in their report as fixed CI and the mean SD of CI/√R-R of the PLN/LMNA group (65 ms) fits well with the measures of their variable group (74.1± 28.6 ms).

In general, the following underlying mechanisms have been described in the literature to account for the generation of VAs: re-entry, abnormal automaticity, triggered activity, parasystole and other more complex mechanisms involving such entities as e.g. an arrhythmogenic milieu created by genetically defected ion channels and abnormal regulatory protein functions. Although it is not completely understood what determines the length and variability of CIs and there is limited data on their association with the above mentioned basic arrhythmia mechanisms, it is generally presumed that re-entry and triggered activity have a rather fixed CI, whereas abnormal automaticity, parasystole and other more complex mechanisms tend to result in CIs of higher variability[10, 15]. Hence analyzing these interval changes might give us a good hint about the underlying mechanisms in different myocardial disorders.

From the four different disease entities included in our study, the arrhythmogenic substrate for VAs is best described and understood in post-MI patients. Unidirectional block and slow conduction in areas within myocardial scar tissue represent the pathological basis for the re-entry mechanism, which then gives rise to PVCs with a fixed CI (in case PVCs with the same morphology are taken into consideration, which of course represent the same underlying re-entry circuit with an identical exit site)[28]. Our results from the post-MI group indeed demonstrated low CI variability, hence this group served as a control for the other three groups. One of them is the idiopathic VA group (patients with VAs in the absence of SHD). Most idiopathic VAs have their origin in one of the outflow tracts. Focal mechanisms have been described to account for this type of idiopathic VAs, which are usually localized in the RVOT (other less common sites include the LVOT and the aortic sinuses of Valsalva). Triggered activity secondary to cAMP-mediated delayed afterdepolarization is believed to be mainly responsible for this focal activity, but micro-re-entry, abnormal automaticity and modulated parasystole have also been implicated to account for this focal activity[29-33]. Our results showed a relatively low CI variability in this group (similar to post-MI patients), which in turn suggests that triggered activity and/or micro-re-entry are the most likely mechanism for PVCs from the outflow tracts. However, as demonstrated by the three "outliers" in this group with a ΔCI above 200 ms (Figure 1a) it is conceivable that in a small subset of patients different mechanisms might also play a role. A recent report of Bradfield et al. identified a subset of patients with outflow tract VAs, who exhibited more variable CIs than the majority of patients in this group. They postulated that the arrhythmia mechanism might be modulated parasystole in these patients and that the occurrence of this rather unusual mechanism might be related to the fact that the focal activity originates in more unique anatomic locations within the outflow tract (e.g. aortic sinus of Valsalva)[12]. However we did not observe such a correlation, as all three patients exhibited PVCs with a common RVOT origin.

Since the patients in the NIDCM group represent a population with heterogeneous etiological backgrounds (in most cases the underlying etiology remains unknown, other etiologies include valvular heart disease, hypertension, sarcoidosis, etc.), a high CI variability would be expected in this group. Intriguingly, our data shows the opposite: PVCs with fixed CIs. In contrast to post-MI patients the electrophysiological VA substrate in this group is not clearly defined. Although scar-related macro re-entry seems to account for the majority of monomorphic VTs, PVCs are believed to initiate primarily from the subendocardium by a focal mechanism without evidence of macro re-entry. The exact nature of the focal mechanism remained unknown so far, but our results might suggest that triggered activity and/or micro-re-entry might

be the most likely candidates. However, similarly to the previous subgroup of patients with idiopathic VAs, we identified several 'outliers' in the NIDCM group ΔCI as well (see Figure 1b), who exhibited higher CI variability, which could indicate the presence of different underlying arrhythmogenic substrates (abnormal automaticity or modulated parasystole). Correlations between the higher CI variability and clinical outcomes were beyond the scope of our present study.

The last group of patients in our present study was the group of familial dilated cardiomyopathy patients (PLN/LMNA group) who had a genetic disorder affecting the genes LMNA and PLN [34]. The LMNA gene encodes for two splice variants of proteins: lamin A and C that are members of the intermediate filament class of cytoskeletal proteins[35]. Phospholamban (gene product of PLN) is a calcium regulating protein in the sarcoplasmic reticulum [36]. Intriguingly, we found that the CI of PVCs was highly variable in this group of patients, unlike that of the other three groups. This could suggest that common mechanisms such as re-entry and triggered activity are not likely to play a role in the genesis of VAs in this population. Other potential mechanisms could involve abnormal automaticity or modulated parasystole but more complex mechanisms cannot be excluded either. Especially if we consider that phospholamban plays an important role in intra-myocardial Ca^{2+}-handling, it seems plausible that the gene-alteration of such a regulatory protein might be able to create an arrhythmogenic milieu, which enables the generation of PVCs. How the altered intracellular ionic concentrations can specifically affect the mechanism of arrhythmogenesis and result in PVCs with variable CIs remains to be elucidated in future studies.

Outcome implications and clinical significance

In an optimal case scenario the treatment strategy of VAs should target the underlying arrhythmia mechanism. With CA this mechanism can be targeted directly. For instance, in case of macro re-entry as the underlying mechanism (*e.g.* fascicular VAs), abolishment is accomplished simply by interrupting the re-entry circuit[37]. For VAs with a triggered activity related mechanism (*e.g.* RVOT VAs) ablation of a focal target is required[38], as it is the case for automaticity. VAs precipitated by myocardial scar-related re-entry (*e.g.* post-MI VAs) should be targeted by substrate based ablation[28]. Therefore, it is of importance that the underlying mechanism of the arrhythmia to be treated is clarified before deciding on a therapeutic strategy. Determination of CI variability could be a relatively easy and non-invasive method for aiding in the identification process. A better understanding of the arrhythmia mechanism could assist physicians in selecting optimal patient-tailored care and to determine the appropriate medical therapy. For instance, instead of beta-blockers,

class III anti-arrhythmic drugs may be prescribed when the arrhythmia mechanism is found to be re-entry. Interestingly, ranolazine (originally intended as an antianginal drug) has recently been shown to reduce triggered PVCs based on its suppression of early- or delayed afterdepolarizations[39, 40]. Additional studies are required to clarify whether this drug might be useful for the treatment of VAs for which the underlying mechanism is thought to be triggered activity.

Limitations of the study

Although we tried to minimize any form of bias through our meticulous methodology, including (but not limited to) the assessment of inter-and intra-observer reliability of the measurement method, some limitations should be mentioned. Firstly, the use of Holter registrations with a registration speed of 25 mm/sec for our CI measurements could introduce a minimal lack of precision. Secondly, the amount of PVC CIs that were counted per patient and the number of included patients was relatively small. The total patient count per group was limited by the amount of patients in the NIDCM group, upon which we matched the amount of included patients in the other groups. An automated CI measurement program counting PVC amounts of above 1000 per patient would be ideal. Additionally, inter-and intra-observer reliability was assessed with measurements from patients in the idiopathic and NIDCM group and not from patients in the two other groups. Finally, for patients from the PLN/LMNA group EP studies were not available to confirm the clinical PVC origin or to invasively measure CIs. More basic studies are needed to clarify arrhythmia mechanisms, in order to improve our understanding of different types of ventricular arrhythmias and to optimize their treatment strategies.

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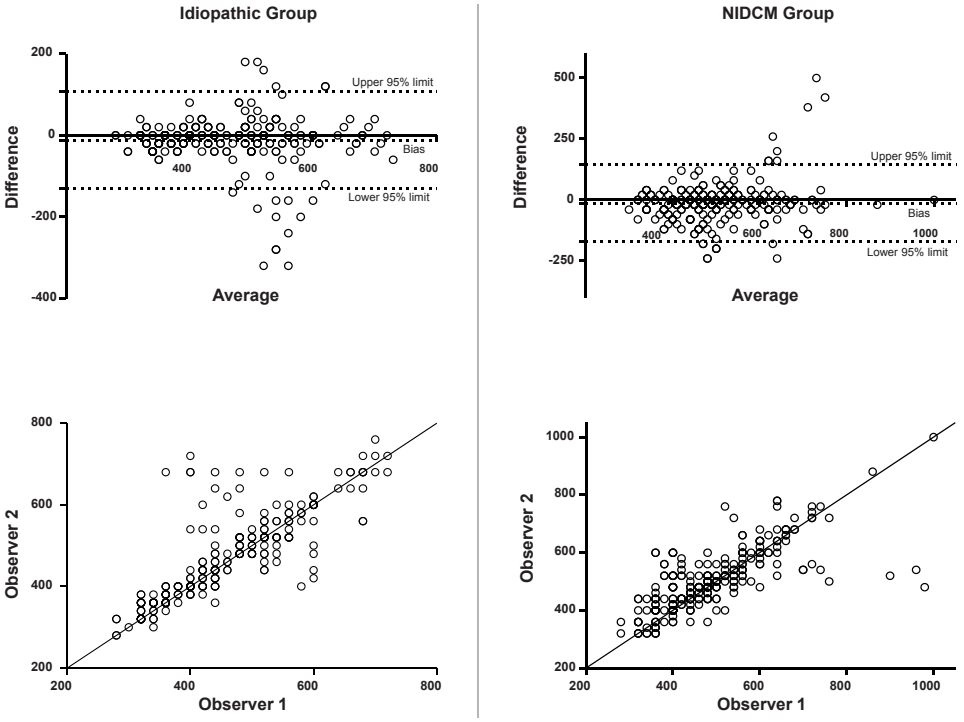
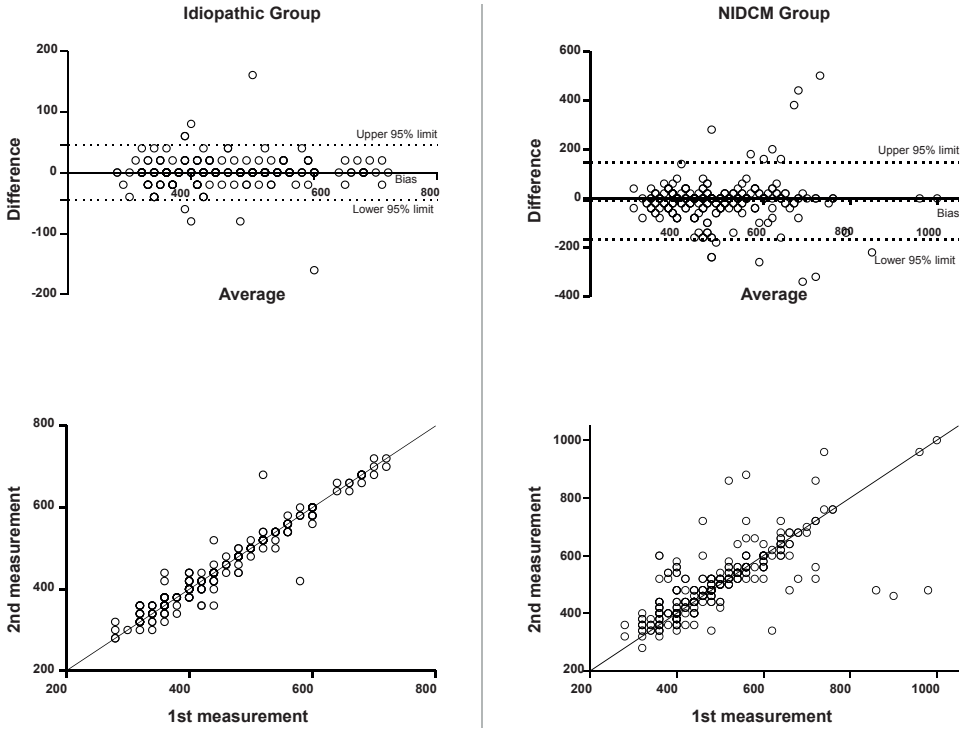
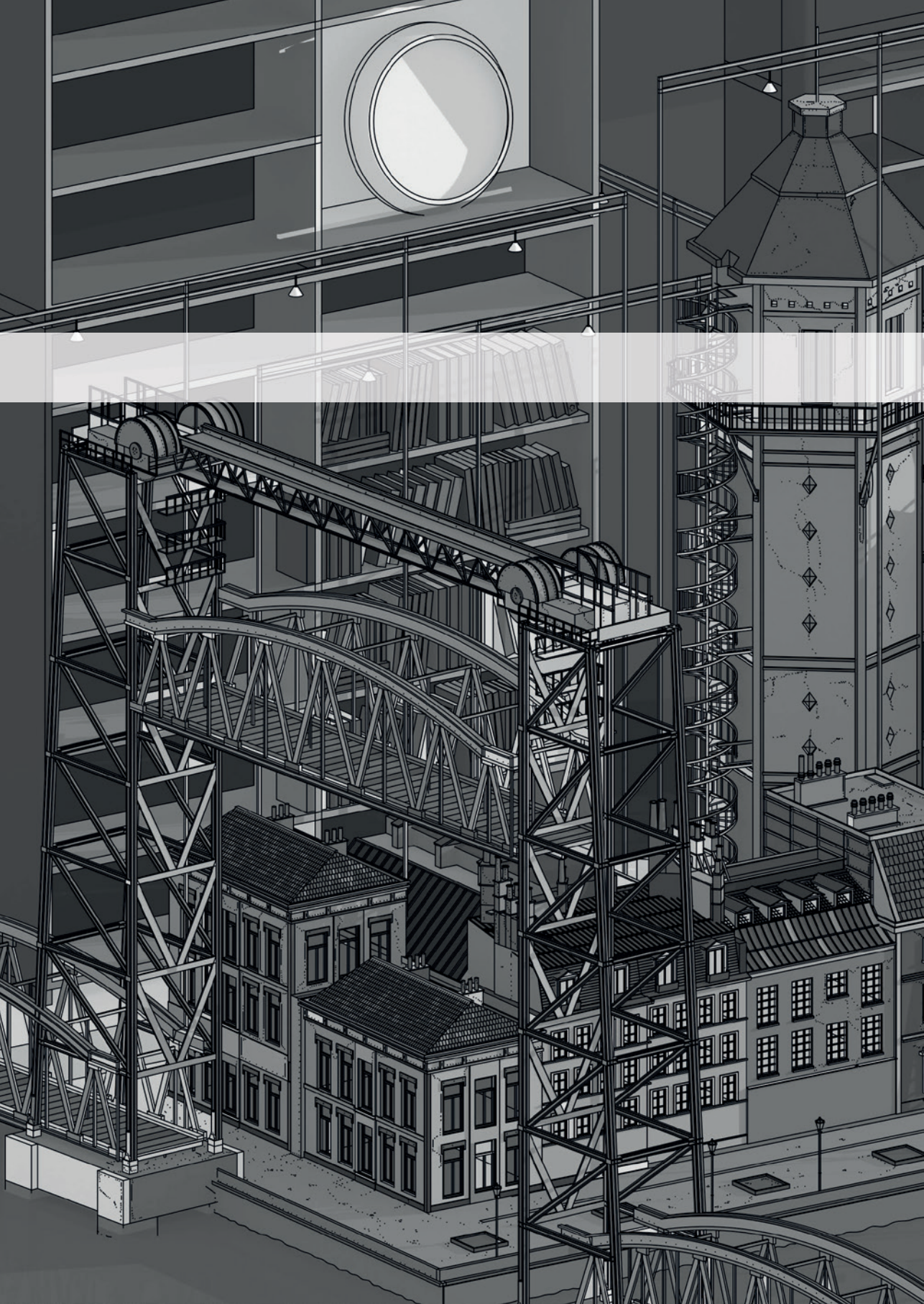
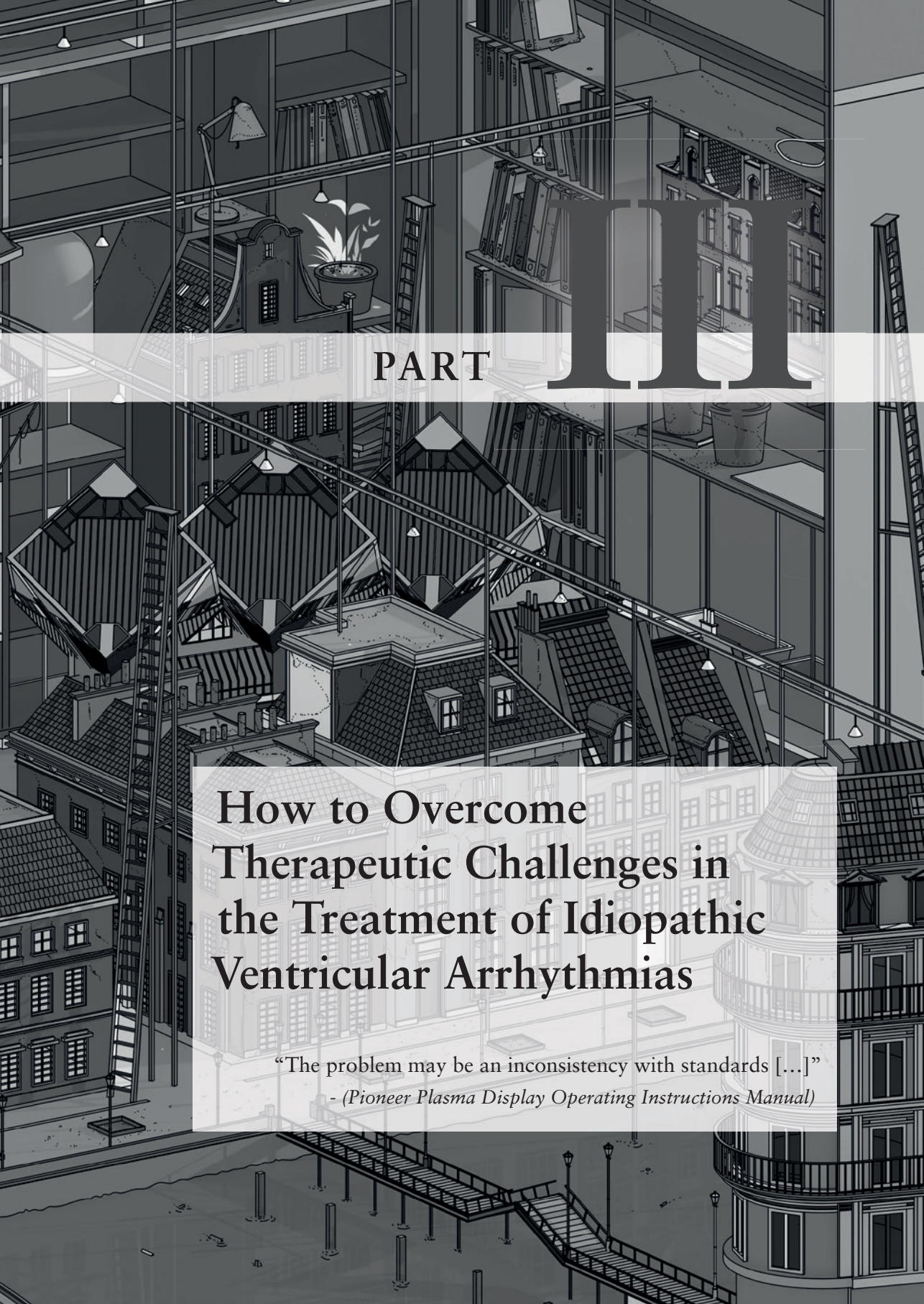


Supplementary Figure 1. *Bland-Altman plot and correlation for inter-observer reliability. Demonstrating good agreement between the observers for both groups (ICC for idiopathic group = 0.91, ICC the NIDCM group = 0.86). The dotted lines in the Bland-Altman plot represent the upper and lower limits of agreement and the bias.*



Supplementary Figure 2. *Bland-Altman plot and correlation for intra-observer reliability. Demonstrating good agreement between the first and repeated measurements by observer 1 for both groups (ICC for idiopathic group = 0.91, ICC the NIDCM group = 0.86). The dotted lines in the Bland-Altman plot represent the upper and lower limits of agreement and the bias.*





PART III

How to Overcome Therapeutic Challenges in the Treatment of Idiopathic Ventricular Arrhythmias

"The problem may be an inconsistency with standards [...]"

- (Pioneer Plasma Display Operating Instructions Manual)

Chapter 7

Sudden cardiac death and idiopathic ventricular arrhythmias

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ABSTRACT

Ventricular arrhythmias (VAs) in patients without structural heart disease can be found in a significant portion of the general population. The prognosis of patients with idiopathic VA is usually favorable and patients are often asymptomatic. However, sudden cardiac death (SCD) as a consequence of idiopathic VA has been reported. The aim of this review is to present an overview of the association between idiopathic VA and SCD.

INTRODUCTION

Premature ventricular contractions (PVCs) and ventricular tachycardias (VTs) that are observed in patients without overt structural heart disease are considered idiopathic ventricular arrhythmias (VA). Idiopathic VA usually originates from the outflow tract region[1]. These arrhythmias are generally considered benign, although in some cases they can lead to severe symptoms and/or cardiomyopathy[2-8]. It is important to rule out conditions which may be associated with malignant VA originating from the outflow tract, such as arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome or catecholaminergic polymorphic VT. After excluding these potential malignant causes of VA, some patients with idiopathic VA are at risk of SCD (although this risk is low). In this review we aim to summarize the association between idiopathic VA and SCD.

Malignant idiopathic VA

The most common form of idiopathic VA is an outflow tract VT which usually originates from the right ventricular outflow tract (RVOT). Most forms of outflow tract VTs are adenosine-sensitive and are thought to be mediated by catecholamine-induced, delayed after depolarizations (DADs)-induced triggered activity[9-11]. Although the prognosis of outflow tract ectopy is considered to be good[12-17], rapid polymorphic VT (PVT) and/or ventricular fibrillation (VF) are occasionally initiated by RVOT PVCs[18,19].

There is a growing body of evidence that very short coupled PVC's may initiate idiopathic VF[19,20]. These close coupled beats fall in the vulnerable phase of ventricular activation and usually originate from the distal Purkinje system. Haissaguerre et al. described a case series of 27 patients with idiopathic VF initiated by a short-coupled PVC[21]. Most patients had initiating PVCs from the distal Purkinje conduction system. However, 4 patients had PVCs originating from the RVOT, which is interesting because ventricular ectopy from the RVOT is usually considered benign. The sources of the Purkinje beats were approximately equally distributed between both ventricles. Patients with VF initiated from the Purkinje system were older and had more episodes of VF and polymorphic beats, and 26% had a familial history of SCD. Other groups have also described RVOT PVCs initiating PVT/VF[18,19]. The exact incidence of malignant idiopathic VA is not known. Most cases are described in case reports or case series with a highly selected population (i.e. patients undergoing electrophysiologic study for treatment of PVCs initiating idiopathic VF). One report demonstrated a prevalence of 16% of spontaneous PVT/VF in patients referred for radiofrequency catheter ablation of VA arising from the RVOT[18]. This reflects referral bias, as patients with PVT are more likely to be referred for catheter ablation.

Recognizing malignant idiopathic VA

In general, the coupling interval of PVCs triggering malignant VT or VF is shorter than PVC's triggering benign VT[19]. Especially in those with idiopathic VF, the initiating PVC usually falls on the peak of the T-wave[21]. In the study of Viskin et al., the coupling intervals of the initiating PVC in those with idiopathic VF, malignant RVOT VT, and benign RVOT VT was 300 ± 40 ms, 340 ± 30 ms, and 427 ± 76 ms, respectively[19]. However, considerable overlap exists and there is not a clear cutoff value that could differentiate malignant and benign PVCs. Igarashi et al. suggested that a prematurity index (the coupling interval divided by the QT interval of the preceding sinus complex) <0.73 can identify malignant PVCs with a sensitivity of 91% and a specificity of 44%[22].

Noda et al. described the clinical characteristics of 16 patients with RVOT PVCs initiating VF and/or polymorphic VT (PVT)[18]. Interestingly, the coupling interval of the PVCs triggering PVT/VF was long, which is in contrast with the short-coupled Purkinje system related PVCs as described earlier. Furthermore, 11 patients (69%) showed pre-syncope or syncope as the first symptom, the remaining patients had only palpitations due to PVCs or monomorphic VT as a first symptom. In comparison to patients with benign RVOT VT, patients with VF/PVT more often had a history of syncope (69% versus 18%) and shorter cycle length of non-sustained VT on previous Holter recordings (245 ± 28 ms versus 328 ± 65 ms). This highlights the necessity of careful follow-up of patients with a history of syncope and frequent RVOT PVC's.

Another study compared patients with benign and malignant outflow tract VTs[23]. Patients with malignant outflow tract VT were defined as having syncope, aborted SCD or VF. On analysis of non-sustained VT in these patients, the second coupling interval of NSVT beats was significantly shorter in the malignant group (313 ± 58 ms versus 385 ± 83 ms), whereas the first coupling interval of NSVT was similar between groups. Furthermore, the malignant group frequently had more than 1 focus of VT, whereas the benign group showed only a single focus. Thus a short second coupling interval of NSVT or demonstration of multiple VT origins may help identify the malignant form of outflow tract VT[23].

Management of malignant VA

Successful radiofrequency catheter ablation of PVCs initiating idiopathic VF has been described by multiple groups[22,24-27]. Knecht et al. reported one of the largest series of patients with idiopathic VF treated with radiofrequency catheter ablation[27]. Thirty-eight patients from 6 different centers underwent ablation of idiopathic VF initiated by short coupled PVCs. PVCs arose from the right Purkinje system in 16

patients, the left Purkinje system in 14 patients, from both the left and right Purkinje system in 3 patients, and in the myocardium in 5 patients (80% RVOT). During a median follow-up of 63 months, 18% of patients experienced VF recurrence. A majority of these patients underwent repeated ablation without any recurrence. Thus, radiofrequency catheter ablation seems to be effective in the management of patients with idiopathic VF initiated by short coupled PVCs.

Noda et al. performed radiofrequency ablation in 16 patients with RVOT PVCs initiating spontaneous PVT/VF[18]. Ablation was successful in 13 patients and partially successful in 3 patients. During a follow-up of 54 months there were no recurrences of syncope, VF or cardiac arrest in this group.

CONCLUSION

Idiopathic VA, usually RVOT ectopy, is common and has a benign prognosis. However, RVOT ectopy may cause rapid polymorphic VT/VF in rare cases, potentially leading to SCD. Appropriate efforts should be made to rule out conditions known to be associated with malignant VA from the outflow tract, especially ARVC and Brugada syndrome. Early radiofrequency catheter ablation should be offered to patients with high risk factors such as history of syncope, very fast VT (>230 bpm), and PVCs with short coupling interval.

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Chapter 8

Procedural and long-term outcome after catheter ablation of idiopathic outflow tract ventricular arrhythmias: comparing manual, contact force and magnetic navigated ablation

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ABSTRACT

Aims: Currently, comparative data on procedural and long-term clinical outcome of outflow tract (OT) idiopathic ventricular arrhythmia (IVA) ablation with manual (MAN), contact force (CF) and magnetic navigation system (MNS) ablation are lacking. The aim of this study was to compare the procedural and long-term clinical outcome of MAN, CF and MNS ablation of OT IVAs.

Methods: Seventy-three patients (31 MAN, 17 CF and 25 MNS patients; consecutive per group) with OT IVA who underwent catheter ablation in our center were analyzed. Procedural success rates (success at the end of the procedure), procedural data and long-term follow-up data were compared.

Results: Baseline patient demographics were comparable. Procedural success rates were similar (MAN 81%, 71% CF and MNS 92%; p = 0.20). Median fluoroscopy time was shorter in the MNS group: MAN 29 (16-38), CF 37 (21-46) and MNS 13 (10-20) minutes (p = 0.002 for MNS vs CF and MAN). The overall complication rate was: MAN 10%, CF 0% and MNS 0% (p = 0.12). Median follow-up was: MAN 2184 (1672-2802), CF 1721 (1404-1913) and MNS 3031 (2524-3286) days (p <0.001). Recurrences occurred in MAN 46%, CF 50% and MNS 46% (p = 0.97). Repeat procedures were performed in MAN 20%, CF 40% and MNS 33% (p = 0.32).

Conclusion: Procedural and long-term clinical outcome of OT IVA ablation are equal for MAN, CF and MNS. MNS has a favorable procedural safety profile due to the shorter fluoroscopy time compared to MAN and CF.

INTRODUCTION

Idiopathic ventricular tachycardias (VTs) account for approximately 10 percent of all VTs[1]. Additionally, depending on the measurement duration and the method of detection, premature ventricular contractions (PVCs) in patients without structural heart disease can be found in about 4 to 50% of the population [2, 3]. They are commonly located in one of the cardiac outflow tracts (OT)[1]. Idiopathic ventricular arrhythmias (IVAs) generally have a benign course[1]. However, they can be highly symptomatic and frequent arrhythmias can result in the development of tachycardiomyopathy[1]. Therefore, it is important to consider that treatment with catheter ablation leads to a better quality of life and reversal of tachycardiomyopathy [4, 5]. Catheter ablation of VTs is an important and increasingly performed treatment and has a high procedural succes rate for both VTs and PVCs [1, 6]. Recent technological advances have been made to increase the safety and efficacy of this treatment. The use of a magnetic navigation system (MNS) has been shown to result in higher procedural success rates and a better safety profile compared to manual (MAN) ablation due to the flexible nature of the MNS catheters [7, 8]. Additionally, contact force (CF) sensing ablation catheters have been developed to reduce cardiac perforations and have been shown to enhance lesion formation in ablation of atrial fibrillation [9]. Data on IVA ablation with CF are sparse and there are very few comparative studies on long-term clinical outcome of these techniques. The aim of this study is to compare the procedural and long-term clinical outcome of MAN, CF and MNS OT IVA ablation.

METHODS

Patients

This prospective registry included 73 patients, consecutive per group, who underwent catheter ablation for OT IVAs either with MAN, CF or MNS ablation before 2014. A total of 31 patients were included in the MAN group, 17 in the CF group and 25 in the MNS group. There are 2 separate electrophysiology laboratories at our center: one equipped with the MNS system and one without. For all patients the index procedure was a first procedure. Pediatric patients were defined younger than the age of 18 years. A medical ethical committee, the METC, approved data collection as prospective registry.

Electrophysiology studies - ablation strategy

The procedures were performed by the same group of senior electrophysiologists and with the assistance of 2 fellows over the entire study duration. In our center,

all operators are equally trained in both manual and remote MNS ablation. All ablation procedures were performed in accordance with institutionally approved local medical treatment protocols from the Erasmus MC, Thoraxcenter, Rotterdam. Informed consent was obtained from all patients before the ablation procedure. Within 48 hours post-procedure, a resting 12-lead ECG, laboratory tests, a chest X-ray, and 2-dimensional echocardiography were obtained from all patients. Standard peri-procedural medication protocols were followed in all patients. Patients were instructed to discontinue antiarrhythmic drugs (except amiodarone) for a period of at least 4 half-lives prior to the planned ablation procedures. After a successful procedure the use of antiarrhythmic drugs was halted. The procedures were performed during a fasting state, with use of local or general anesthesia. As clinically indicated at the discretion of the operator, market-approved diagnostic and ablation catheters were used. Left-sided access was achieved via retrograde aortic route or transseptal puncture based on the operators' preference and the exact location of the arrhythmia. All procedures were performed using a 3-dimensional mapping system. Standard ablation and mapping techniques were applied based on the operators' preference. For induction, programmed stimulation was performed using up to triple extra-stimuli pacing from the right ventricular apex, right ventricular outflow tract (RVOT) or left ventricle. Isoproterenol was administered in a dosage ranging between 1.3 µg/min and 2.7 µg/min. As a first step usually an activation map was created. This was then followed by pace mapping (the site with a paced 12-lead QRS morphology identical to an inducible monomorphic VT was assumed to be the exit site of that particular VT) for verification. There were no differences between ablation strategies in the MAN, CF or MNS ablation groups. Crossovers were excluded from the study. The following definitions of endpoints of procedural success were applied: if the VT was inducible, noninducibility was the endpoint; if only PVCs were present, then the complete termination of clinical PVCs or presence of <5 PVCs per hour from different locations was required. The presence of a pacemaker (PM) or implantable cardioverter defibrillator (ICD) was not considered a contraindication for MNS guided ablation procedures, which is consistent with the product labeling for the MNS [8].

MNS-guided ablations

The procedures in the MNS group were performed with the Stereotaxis Niobe Magnetic Navigation System (Stereotaxis, Inc., Saint Louis, MO, USA) in an EP lab equipped with a Siemens Axiom Artis (Siemens, Erlangen, Germany) fluoroscopy system. All patients were treated with a NaviStar RMT ThermoCool catheter (Biosense Webster, Inc., Diamond Bar, CA, USA). Electroanatomical mapping was

performed using the CARTO RMT (Biosense Webster, Inc., Diamond Bar, CA, USA) system [8].

Manual-and CF-guided ablations

The manual catheter ablation procedures took place in an EP lab equipped with a Philips Allura Xper (Philips, Eindhoven, the Netherlands) fluoroscopy system. Electroanatomical mapping was performed either with the EnSite NavX system (St. Jude Medical, Inc.) or CARTO (Biosense Webster Inc.). The ablation catheters that were used included the following: Biosense Webster Navistar Thermocool D and F curve and St. Jude Cool Path Duo [8].

CF ablation was performed in the same lab using the same equipment as mentioned for MAN ablation. Ablation catheters that were used included the following: Thermocool Smarttouch CF (Biosense Webster Inc., Diamond Bar, California, USA) and TactiCath (Endosense/St Jude Medical, St Paul, Minnesota, USA). A target contact force of between 10-20 grams was pursued for all ablations.

Data collection and analysis

The parameters that were analyzed for all groups include the following: procedural success rate, fluoroscopy time, procedure time, total radiofrequency (RF) application time, RF application number, and major and minor procedure related complications. The procedural success rate was assessed based on the conclusions in the procedural reports. At follow-up, recurrences and repeat procedures were assessed. Fluoroscopy time was recorded from the fluoroscopy system in both rooms. Procedure time was specified as the interval between subcutaneous injection of lidocaine to the groin and removal of catheters from the patients' body, including a 30-minute waiting period for every case. Any adverse event registered by the operator during the procedure, by the attending cardiologist prior to hospital discharge or by the general physician during follow-up was examined by a trained electrophysiologist and was considered as a complication if the event could be ascribed to the procedure. Major complications were defined as pericardial effusion and/or tamponade, permanent AV block, PM/ICD damage requiring device or electrode replacement, stroke, major bleeding or death. Minor complications were defined as minor bleeding, transient ischemic attack, new permanent bundle branch block, transient ST-elevation, pericardial effusion without the need for intervention, an audible steam pop without consequences and temporary AV block [8].

Follow-up

Routine follow-up visits were scheduled at the outpatient clinic of our department for all patients 3 months after the procedure and subsequently every 6 months. 24-hour Holter recordings were employed during these visits for documentation of recurrent arrhythmias. For long-term follow-up, patient records were analyzed and all patients were contacted by phone and interviewed concerning recurrences and/or repeat ablation procedures (performed in other institutions).

Statistics

The normality of distribution was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as mean ± SD for continuous variables if normally distributed, or otherwise as median with 25th and 75th percentiles, where appropriate. Data were compared by one-way ANOVA, Kruskal-Wallis test or Mann-Whitney test, as appropriate. Categorical data were expressed as percentages and compared with Fisher's exact test. Statistical analysis was performed using SPSS version 21 (IBM Corp., Somers, NY). Statistical significance was defined as $p < 0.05$ (two-tailed).

RESULTS

Demographics and procedural results

Baseline characteristics including age, gender distribution, number of pediatric patients, medication use and left or right OT VA did not significantly differ between the three groups, except for beta-blocker use which was higher in the CF group compared to the MNS group ($p = 0.007$) (Table 1). There was no significant difference in procedural success rates between the groups (Table 2). Fluoroscopy time was significantly shorter in the MNS group compared to the MAN and CF group ($p = 0.002$ for MNS vs MAN and CF). Procedure time, application time, number of applications and hospital stay were equal in all three groups (Table 2). The application time was not significantly different between MAN and CF (499 [128-870] vs 200 [120-270] sec.; $p = 0.57$) or MAN and MNS (499 [128-870] vs 291 [183-431] sec.; $p = 0.15$).

Complications

The complication rates are reported in Table 2. There were no significant differences in overall, minor or major complication rates. In total one major complication (tamponade after perforation, with full recovery after pericardiocentesis) occurred which was in the MAN group. Minor complications occurred in 2 patients (7%),

both from the MAN group (Table 2). In both instances an audible steam pop occurred without consequences and a normal CT afterwards.

Table 1. *Demographic data*

	MAN	CF	MNS	p-value
Patient total (n)	31	17	25	
Patient age (y)	48 ± 16	45 ±18	49 ± 13	0.72
Sex (male)	18 (58%)	8 (47%)	10 (40%)	0.40
Pediatric	2 (7%)	2 (12%)	0 (0%)	0.25
ASA	4 (13%)	3 (18%)	3 (12%)	0.86
Acenocoumarol	2 (7%)	0 (0%)	0 (0%)	0.25
AADs:				
- Class III	5 (16%)	0 (0%)	1 (4%)	0.10
- Beta blocker	15 (48%)	12 (71%)	7 (28%)	0.024*
VA origin:				0.51
- RVOT	23 (74%)	15 (88%)	20 (80%)	
- LVOT	8 (26%)	2 (12%)	5 (20%)	

*Patient characteristics and comparison of ablation results between the MAN and MNS groups. Descriptive statistics are presented as mean ± SD for continuous variables. AADs; antiarrhythmic drugs, ASA; acetylsalicylic acid, VA; ventricular arrhythmia, RVOT; right ventricular outflow tract, LVOT; left ventricular outflow tract. * p < 0.05 for MNS vs CF.*

Long-term follow-up

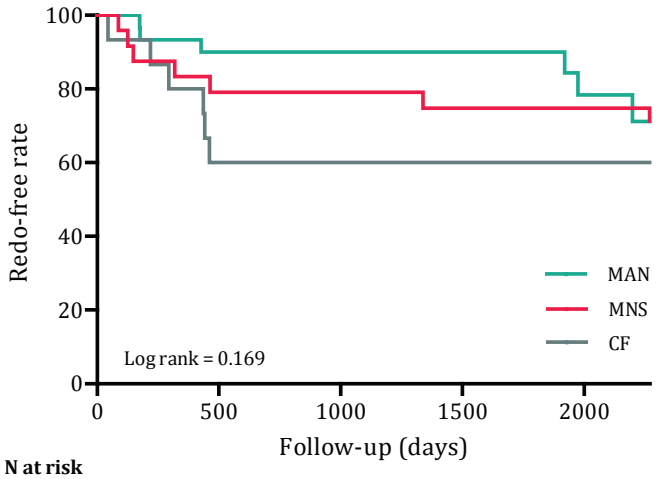
Median follow-up was 2184 (1672-2802) days for the MAN group, 1721 (1404-1913) days for the CF group and 3031 (2524-3286) days for the MNS group (p <0.001). In total, 5 patients were lost to follow-up. In the MAN group 1 patient was unable to answer our telephone inquiry due to Alzheimer's disease. In the CF group 2 patients were lost to follow-up; both patients did not respond to our efforts to contact them. In the MNS group 2 patient were lost to follow-up; 1 patient due to loss of contact after emigration and 1 patient deceased because of acute myeloid leukemia. The number of recurrences and repeat procedures were equal in the three groups (Table 2, Figure 1 and Figure 2). Six patients had an early recurrence during the admission period after a reported successful procedure. Of those, 3 patients were in the MAN group, 1 was in the CF group and 2 were in the MNS group. Repeat procedures were successful in 67% (4 out of 6) of patients in the MAN group, 83% (5 out of 6) of patients in the CF group and 100% (8 out of 8) of patients in the MNS group. The ablation technique used for the repeat procedures was MAN in 28% (5/18), CF in 39% (7/18), MNS in 28% (5/18) and cryoablation

in 6% (1/18). Of two repeat procedures the ablation technique was not reported. Repeat procedures with MAN were successful in 80% (4/5) of procedures, with CF in 86% (6/7), with MNS in 100% (5/5) and with cryoablation also in 100% (1/1) of procedures. Overall, there were no major complications during repeat procedures. During repeat procedures one minor complication (post-ablation pericarditis) occurred after a CF procedure. In two repeat procedures occurrence of complications was not reported.

Table 2. *Procedural data*

	MAN (n = 31)	CF (n = 17)	MNS (n = 25)	p-value
Procedural success	25 (81%)	12 (71%)	23 (92%)	0.20
Ablation data				
Approach (% of group total):				0.55
- Antegrade	22 (71%)	15 (88%)	20 (80%)	
- Transseptal	1 (3%)	1 (6%)	0 (0%)	
- Retrograde	7 (23%)	1 (6%)	5 (20%)	
- Epicardial	1 (3%)	0 (0%)	0 (0%)	
LVOT: below/above aortic valve	5 (63%)/3 (38%)	1 (50%)/1 (50%)	3 (60%)/2 (40%)	0.95
Application Number	11 (4-21)	7 (3-17)	7 (4-9)	0.35
Application Time (sec)	499 (128-870)	200 (120-270)	291 (183-431)	0.46
Fluoroscopy Time (min)	29 (16-38)	37 (21-46)	13 (10-20)	0.001†
Procedure Time (min)	175 (123-221)	165 (146-180)	150 (120-173)	0.31
Hospital Stay (days)	3 (2-5)	3 (2-4)	2 (2-3)	0.51
Complications				
- Overall	3 (10)%	0 (0%)	0 (0%)	0.12
- Minor	2 (7%)	0 (0%)	0 (0%)	0.25
- Major	1 (3%)	0 (0%)	0 (0%)	0.50
Long-term follow-up				
- Follow-up time (days)	2184 (1672-2802)	1721 (1404-1913)	3031 (2524-3286)	<0.001
- Recurrences	12 (46%)	5 (50%)	10 (46%)	0.97
- Repeat procedures	6 (20%)	6 (40%)	8 (33%)	0.32

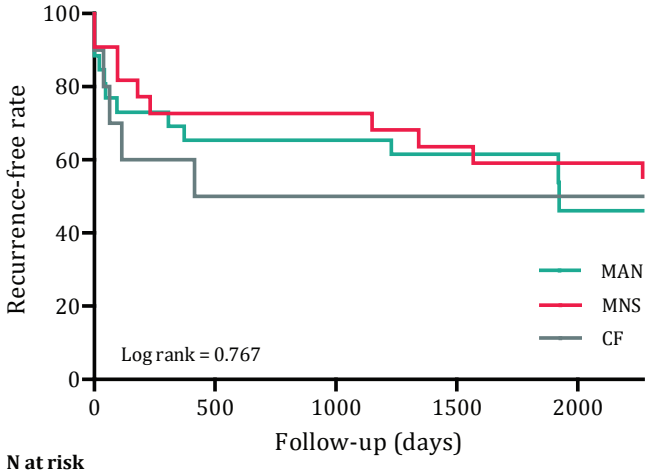
Comparison of ablation results between the MAN, CF and MNS groups. Descriptive statistics are presented median with (25th and 75th percentile). † *$p < 0.05$ for MNS vs MAN and CF.*



N at risk				
MAN	28	28	25	14
MNS	20	19	18	17
CF	10	10	8	3

Figure 1. *Repeat procedure-free rate*

Repeat procedure-free rate and time to repeat procedure.



N at risk				
MAN	18	18	14	6
MNS	17	17	15	14
CF	6	6	6	3

Figure 2. ***Recurrence-free rate***

The recurrence-free rate and time to recurrence.

DISCUSSION

This is the first study directly comparing the long-term clinical outcome of exclusively OT IVA ablation between MAN, CF and MNS catheter ablation. The major findings of this study are that there are no significant differences in procedural or long-term success rates between these three groups and that fluoroscopy time is shorter for MNS compared to MAN and CF.

Manual catheter ablation success rates and complications

In literature, conflicting success rates are reported for manual catheter ablation of IVAs. Procedural success rates between 54% and 100% have been reported [10, 11]. Reported mid-term success rates also vary, ranging between 55% and 100% [12, 13]. In our present study, the procedural success rate of manual catheter ablation was 81%. These varying success rates may reflect differences in follow-up methods, definitions of success and inclusion bias. Additionally, it may also demonstrate the heterogeneity in IVA presentation, from easily accessible and frequently seen locations such as the RVOT to more complex regions like the aortic cusps.

Minor complications during manual catheter ablation are reported in literature to be between 0 and 20% [13, 14], while major complications occur in 0 to 6% [11, 15]. In our study, minor complications occurred in 7% of the MAN group and major complications in 3%.

Contact force ablation

A recent innovation regarding manual catheter ablation is the use of contact force sensing catheters. These catheters were designed to improve catheter – tissue contact by providing direct and quantified feedback to the operators of the applied pressure on the endo- or epicardium in order to enhance lesion formation and to simultaneously improve safety by guarding against excessive applied force. The advantage of CF ablation is the additional force information that is obtained during the ablation. A disadvantage, however, is the increased stiffness of CF catheters. A recent meta-analysis comparing 19 studies showed that for ablation of atrial fibrillation, the use of CF catheters versus non-CF MAN catheters resulted in a significantly lower occurrence of acute pulmonary vein reconnections and recurrences as well as a reduced major complication rate and improved procedure parameters during 1 year follow-up [9]. However, very few data exist on CF ablation of VAs. One study from our center demonstrated that CF ablation of idiopathic VAs in general showed no improvement on complication rate, acute success rate or recurrence rate during long-term follow-up compared to MAN or MNS ablation [16].

In the current study, we found no improvement of procedural success or recurrences and repeat procedures when we compared CF to MAN or MNS ablation. Additionally, the CF group complication rate was equal compared to MAN ablation.

MNS ablation

One of the main advantages of MNS over MAN ablation reported in literature is safety. Upon publication, not a single myocardial perforation during ablation with the MNS has been reported, which is due to the soft and flexible quality of the catheter. Furthermore, after completion of an initial learning curve, the use of MNS most likely shortens procedure time, which in turn may prevent operator fatigue, shortens fluoroscopy time (as supported by the data in this report) and helps to reach less easily accessible areas in the heart during mapping [7, 17]. Another advantage during mapping is the fact that the flexible catheter rarely induces mechanical PVCs, which makes identifying focal localizations of ventricular arrhythmias less challenging [18]. A report on endocardial voltage maps for the diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) comparing MAN and MNS acquired maps, showed MNS maps were more accurate because of better defined low voltage regions and higher surface areas and volumes of the RV [19]. Emphasis on procedural safety is important in general, but even more so in the treatment of usually non-lethal conditions such as IVAs. The ratio of treatment benefit versus treatment risk in these cases needs to be weighed extra carefully. This makes a system like the MNS particularly useful for treating IVAs. Additionally, as noted in the literature and again demonstrated in this study, most IVAs are ablated in the RVOT which is a vulnerable area due to a relatively thin wall and neighboring structures such as the bundle of His, the left main coronary artery, the left anterior descending artery and the right and left coronary ostia [1, 20]. Precision steering and reproducibility of mapping sites by using stored vectors helps to avoid these structures and to navigate back to previously determined safe and effective ablation targets [17].

Clinical outcome

Our data did not show a significant difference in procedural success rates between the three groups. As mentioned earlier, apart from a study which showed no significant differences between MAN and CF regarding acute and long-term success of idiopathic VA ablation in general [16], very few data exist on CF ablation of VAs. A recent randomized controlled study comparing MAN and MNS ablation of RVOT arrhythmia in 30 patients similarly showed no significant difference in procedural success [21]. One report comparing MAN and MNS ablation for all VT entities, which

included a subgroup of IVA, did show a significant difference in procedural success (MAN 62% vs MNS 84%), although the IVA subgroups were unevenly distributed in number (21 vs 49) and included a variety of both OT and non-OT VT locations [8]. Our report did not show any significant differences in long-term clinical outcome; recurrences and repeat procedures were similar in all three groups.

Limitations of the study

This study is not a randomized trial and contains a relatively small patient cohort. Nonetheless, it should be taken into account that for the studied population of idiopathic VA patients this sample size is very reasonable. Additionally, follow-up was long and consecutive patients were included in both groups in compensation of the non-randomized nature of this study.

CONCLUSION

Procedural and long-term clinical outcome of IVA ablation are equal for MAN, MNS and CF. MNS has a favorable procedural safety profile due to the shorter fluoroscopy time compared to MAN an CF. To confirm our conclusions, more prospective and randomized studies with larger patient cohorts should be performed.

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Chapter 9

Beyond catheter tip- and radiofrequency lesion delivery: the role of robotics in ablation of ventricular tachycardias

Editorial comment

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Catheter ablation of ventricular tachycardia (VT) has become an important and increasingly performed treatment[1]. The use of remote magnetic navigation (RMN) for this procedure has been shown to have several advantages compared with manual catheter navigation (MCN)[2]. Since RMN was introduced in 2003 the most obvious advantage of RMN when compared with MCN is safety. Increased safety for both operators and patients is achieved by shortening fluoroscopy time and by reducing complications due to catheter flexibility[3]. So far, there has not been a single report of myocardial perforation. Additionally, after an initial learning curve has been completed, the use of RMN most likely shortens procedure time[4], may prevent operator fatigue and helps to reach the parts of the heart that are less easily accessible during mapping.

In the current issue of the Netherlands Heart Journal, Wu et al.[5] present their meta-analysis on RMN vs. MCN for the ablation of VT. They included four non-randomised studies and conclude that acute and long-term success rates for VT ablation are equal between RMN and MCN. However, complication rates, procedure and fluoroscopy times are favourable for RMN.

Their conclusion adds to the aforementioned findings of improved safety and at least a non-inferior success rate. In fact, the only limitation of RMN that remains in experienced teams is the cost of the equipment which can be up to 2 million €[6]. However, the long-term benefits of this installation should be taken into account when assessing these expenses[6].

Looking at success rate, the authors have been cautious in their interpretation. Several studies have in fact demonstrated a better outcome compared with MCN in VT ablation[4,7]. What could be a possible explanation for this variable outcome?

As RMN is a relatively new and evolving method, procedural outcomes can be further improved when sufficient experience is obtained. Only a limited group of operators could acquire the appropriate level of skill due to the cost of the system and a consequently limited availability. This could potentially result in an operator-dependent success rate variability and also brings up another point related to the financial aspect. Most of the centres able to afford the installation are academic centres, dealing with a very specific patient population. This means the procedures performed with RMN will be those in patients with a more complex pathology, which in turn may result in an underestimation of treatment success. Finally, because of the limited availability of RMN technology, present studies are mostly non-randomised. Non-significant trends in success rates favourable to RMN, as seen in Dinov et al.[8], may in the future prove significant in randomised trials.

Notably, the papers by Bauernfeind et al. and Szili-Torok et al., both used in the current report, showed superiority to MCN in acute success rates in structurally

normal hearts but equal results in structural heart disease[4,7]. This raises the issue of how RMN can improve success rates. Is it related to the improved manoeuvrability of the catheter tip: tip delivery, or due to the constant type of tissue tip contact which improves radiofrequency lesion formation: lesion delivery? The data from of the above-mentioned manuscripts as well as this meta-analysis indirectly suggest that tip delivery efficiency may be superior using RMN while lesion delivery should be equally good when compared with MCN. RMN is theoretically more suitable for reaching difficult locations because of the flexible nature of the catheter in combination with the possibility of more accurate positioning.

What are the future perspectives? An important step that could definitively make RMN favourable to MCN will be the utilisation of contact force measuring ablation catheters for magnetic navigation and ablation. Optimal electrode—tissue contact has been previously demonstrated to be of great importance for lesion formation[9] and has already been shown to improve clinical outcome in the treatment of atrial fibrillation[10]. When this technique becomes available for RMN and reaches its full potential (new combined parameters, involvement of cardiac imaging for real time visualisation of lesion formation) it might revolutionise treatment of ventricular and supraventricular arrhythmias with RMN and might prove pivotal in achieving long-term success in VT ablation.

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Chapter 10

Optimizing contact force during ablation of atrial fibrillation: available technologies and a look to the future

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SUMMARY

In a select atrial fibrillation population, catheter ablation is considered first-line therapy. Prevention of early reconnection of the isolated pulmonary veins is an important goal for a successful treatment. Here, adequate catheter–tissue contact is crucial. One of the most promising new advances, therefore, is contact force (CF) sensing technology. The aim of this review is to provide an overview of innovations regarding catheter ablation of atrial fibrillation with a special focus on CF optimization. Both experimental and human studies show how CF sensing catheters lead to a reduction of fluoroscopy time, increased procedural safety and a better clinical outcome. Possible future developments include new parameters combining real-time ablation data, direct visualization of lesion formation and incorporation of robotics.

BACKGROUND

Despite rapidly developing advances in treatment techniques, atrial fibrillation (AF) remains the most common arrhythmia[1]. In a selected patient population, it has been established that catheter ablation is the best treatment, superior to antiarrhythmic drugs[2-4]. Prevention of early reconnection of the isolated pulmonary veins due to insufficient transmurality of the applied lesions has been one of the most important goals for a successful treatment[5,6]. To accomplish this, adequate catheter–tissue contact is crucial[7-14]. However, it has been demonstrated that even highly experienced operators cannot accurately judge catheter contact by tactile feedback alone[15]. Consequently, one of the most promising new advances in ablation of AF to help overcome this issue is the use of contact force (CF) sensing technology. In this review, we aim to present an overview of the developments regarding this technique.

Biophysics of radiofrequency lesion formation & contact influence

To fully understand the importance of CF technology, it is important to be familiar with the basic biophysics of radiofrequency (RF) ablation. The current used for catheter ablation is alternating, delivered at cycle lengths of 300–750 kHz[16]. The primary mechanism of destruction of the tissue in contact with the electrode relies on resistive heating, although electrical injury may be a contributing factor[17,18]. It is well known that achievement of adequate lesion formation depends on several parameters and processes. These include CF (for which catheter stability, impedance drop, temperature rise and electrogram attenuation previously served as surrogates); the distribution of RF energy among blood, myocardium and patient; tissue heating; coagulum formation; electrode impedance and electrical and thermal response from the electrode[8].

Looking at the distribution of energy during RF ablation, it is important to realize that a considerably larger amount of power will be delivered to the surrounding blood than to the cardiac tissue due to better conduction and contact between blood and electrode. Also, power is lost in the surrounding structures of a patient's body depending on the relationship between patient and interface impedance. Assuming good contact between electrode and cardiac tissue, less than 10% of total power will be delivered to the endocardium when accounting for the difference in impedance and surface contact between blood and tissue[8]. Thus, with varying tissue contact (i.e., CF), the ratio between power delivery to the tissue and the surrounding environment will greatly differ due to changes in impedance and varying electrode–blood/tissue contact. When electrode–tissue contact doubles, this would result in a twofold increase in tissue heating. This is one of the reasons why CF is a major contributor to lesion size.

Tissue heating, a second important process in lesion formation, can be divided in direct resistive heating and heat conduction to the surrounding myocardium[19-25]. During resistive heating, most of the total power delivered to the endocardium is absorbed within the first millimeter from the electrode surface. Heat conduction is responsible for heating the rest of the tissue, although this is a relatively slow reaction compared with resistive heating. Accordingly, for achieving an adequate lesion an RF application of at least 30–60 s is desired[26].

Continuing with tissue and electrode temperatures, cooling of the electrode by blood flow and the variation in electrode–tissue contact both cause large temperature differences between electrode and endocardium. Good tissue contact improves power transfer to the tissue and low blood flow reduces electrode cooling and thus temperature difference between electrode and endocardium. A target electrode temperature may in these cases be reached at a relatively low power level, which means that the combination of power and electrode temperature rise may be a better parameter for lesion size than electrode temperature alone[8].

Another factor in lesion formation is electrode impedance. Because electrode impedance increases with the square of distance from the center, changes in impedance that occur further away from the center of the electrode will only minimally affect electrode impedance but changes more nearby can be relevant for the quality of tissue contact[8]. When the contact area is small, very little RF current will pass through the endocardium and the temperature of the surrounding blood in contact with a larger part of the electrode will remain low. A change in electrode impedance caused by heating therefore will not be significant. A significant drop in impedance during ablation has been shown to have good correlation with tissue heating and lesion size[27].

CF: experimental evidence in tissue & animal studies

The importance of CF for creating effective lesions was first demonstrated in various tissue and animal studies in which CF and lesion size were shown to be significantly correlated[7-14,28-30], but for long could not be measured directly. One of the first studies to look at the relationship between tissue contact and lesion size using CF technology in combination with saline-irrigated RF ablation was a study by Yokoyama et al., in which canine thigh muscle was used to compare CF with the previously mentioned surrogate markers and lesion size[7]. While maintaining a constant power and ablation time, varying CF was delivered and the effect on the aforementioned parameters was measured. Tissue temperature at depths of 3–7 mm, lesion depth, diameter and volume all significantly increased with increasing CF. Larger lesions were produced with lower power and greater CF compared with higher power and lower CF. No increase in electrode or electrode–tissue interface temperature was seen due to the irrigated RF catheter. Higher CF did, however, show an increase in steam pop (a sudden venting of steam after intramural boiling during RF ablation, potentially causing perforation or tamponade[31]) and thrombus, which only occurred at a CF above 20 g. By measuring CF before an RF application, this risk may be minimized by adjusting RF power and application time[7].

Other experimental studies all show a similar relationship among electrode–tissue contact, the surrogate markers and lesion size[8-10,13,28-30]. In a study by Shah et al., these parameters were examined in a beating heart simulation model, mimicking the variations in contact during systole and diastole[5]. With a fixed RF power constant (20 g all through), variable (between 10 and 20 g) and intermittent (between 0 and 20 g) contacts were applied to a bovine skeletal muscle placed on a ground plate and a force–time integral ([FTI] in gram–seconds), the area under the CF curve, was evaluated (Figure 1). In this setup, constant contact models the characteristics of the fibrillating heart chamber, the other models represent other rhythms. The FTI correlated linearly to lesion volume and was highest in the constant contact group, intermediate in the variable contact group and lowest in the intermittent group. It was therefore proposed that applying a clinical strategy of achieving a variable contact pattern without exceeding safe peak force values may allow for more effective and predictable lesion formation[5].

All above-mentioned findings have led to the use of steerable sheaths to optimize electrode–tissue contact[32,33] and more importantly to the development of two different types of CF measuring catheters. One type computes CF by measuring microdeflections of a spring connecting the ablation tip electrode to the catheter shaft (ThermoCool SmartTouch CF, Biosense Webster Inc., CA, USA) (Figures 2 & 3)[34].

The other type uses optical fibers to measure microdeflections of a deformable body in the catheter tip (TactiCath, Endosense/St Jude Medical, MN, USA) (Figure 4)[35].

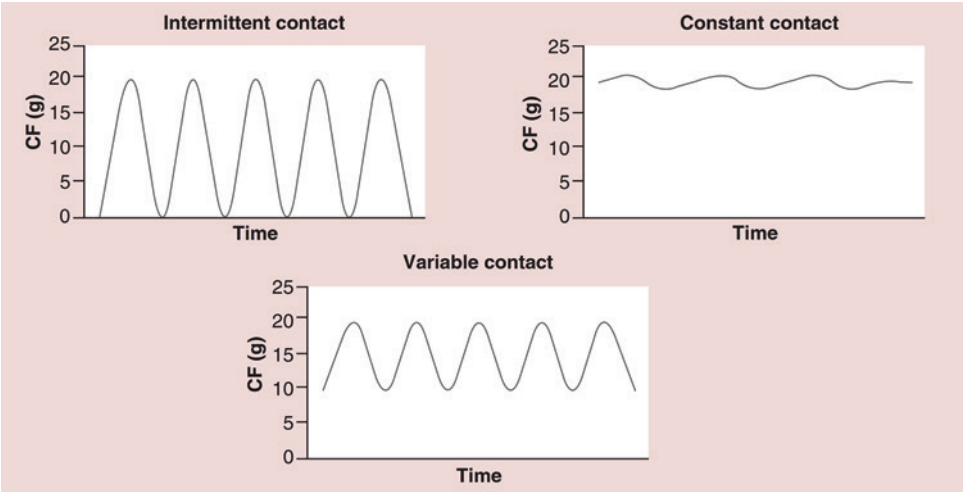

Figure 1. *Fixed radiofrequency power with intermittent, constant and variable contact force. CF: Contact force, g: grams.*

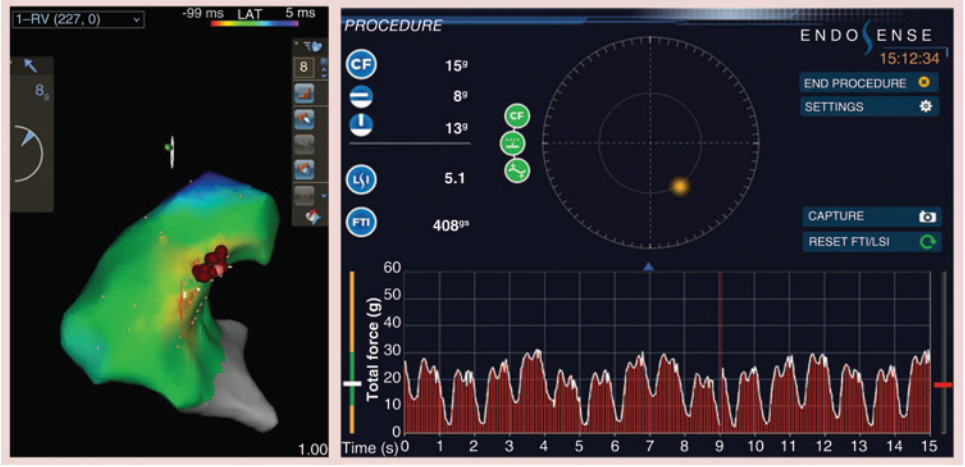

Figure 2. *ThermoCool SmartTouch interface. Left panel: ThermoCool SmartTouch (Biosense Webster Inc., CA, USA) interface. The arrow in the left upper corner indicates the force vector with the amount of CF in grams. Right panel: TactiCath (Endosense/St Jude Medical, MN, USA) interface. Perpendicular and parallel CFs are indicated separately and combined. The orange dot represents the force vector with the color indicating the amount of force. CF: Contact force; FTI: Force–time integral; LSI: The LSI index is an algorithm combining radiofrequency power, ablation time and contact force applied to the tissue in order to estimate lesion formation in real time.*

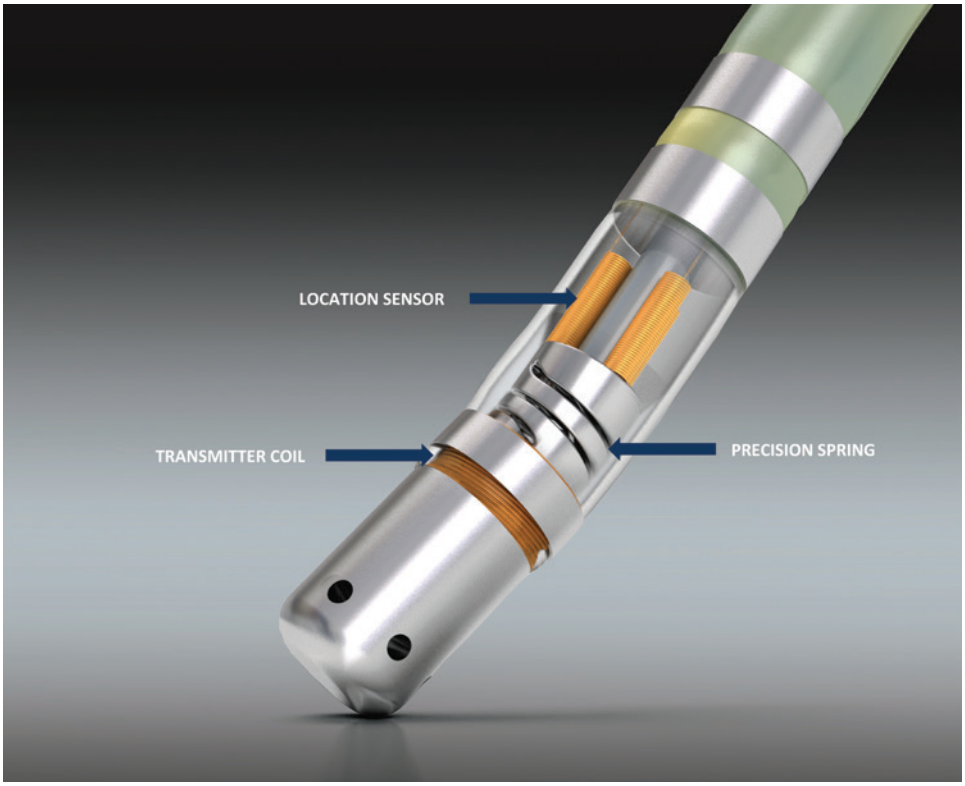

Figure 3. *ThermoCool SmartTouch contact force (Biosense Webster Inc., CA, USA). The transmitter coil sends location reference signal. The precision spring provides consistent movement in response to contact force. The location sensor detects micromovement of the transmitter coil.*

Two new but indirect techniques for assessing CF are the IntelliSense force sensing system, which is used in combination with the electromechanic robotic system Sensei (Hansen Medical, Inc., CA, USA) and the EnSite Contact system (St Jude Medical). IntelliSense determines CF by measuring friction in the catheter shaft and calculating the amount of perpendicular force in grams applied to the tissue[36]. Results from studies comparing IntelliSense measurements with direct CF measurements from the TactiCath catheter show that direct measurement is preferable to this system[37,38]. This is most likely because IntelliSense effectively only measures perpendicular force, whereas with TactiCath both perpendicular and parallel forces can be measured.
The EnSite Contact system calculates CF using impedance measures from the electrode–tissue interface isolated by a three-terminal circuit. A measure called the electrical coupling index is then acquired which should represent electrode–tissue contact[39]. In a study with animal models by Holmes et al., it was proposed that

this additional measure may provide valuable feedback regarding lesion formation[40]. However, although impedance drop shows good correlation with lesion size, it remains an indirect parameter for CF. Additionally, because the system relies on impedance changes, the presence of scars or already ablated tissue can cause inaccurate readings. This property could make the system more useful for tissue characterization, but less useful for CF assessment.

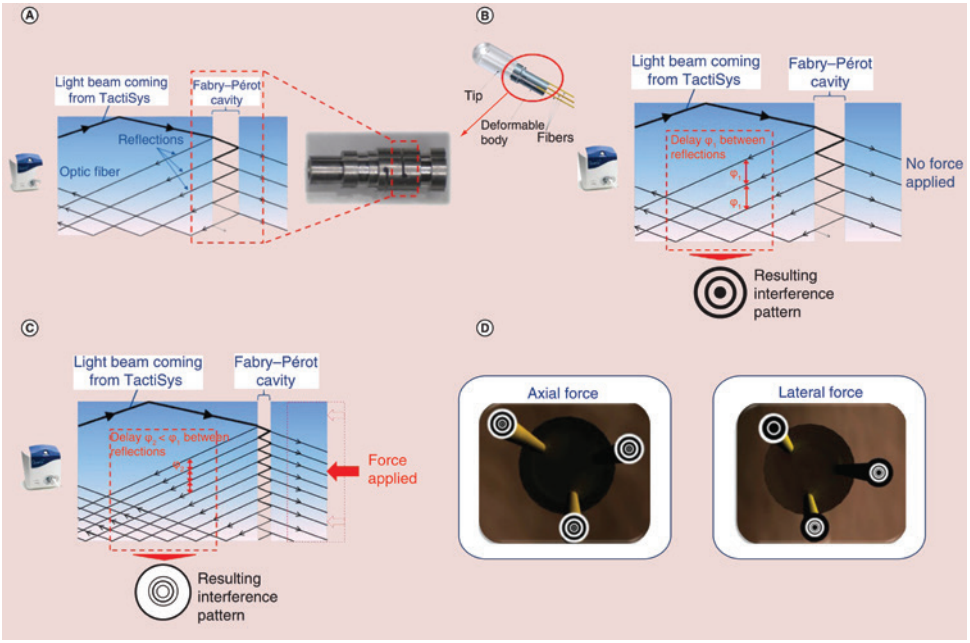

Figure 4. *TactiCath (Endosense/St Jude Medical, MN, USA). Cavity made of two semireflective mirrors in parallel with air in between. Light emitted by the catheter and passing through the cavity is reflected back and forth (***A***). The resulting beams have different path lengths and interfere with one another creating interference patterns (***B***). The interference patterns are sensitive to the light path lengths and when force is applied, the cavity length changes and so does the interference pattern (***C***). Interferences based on the signals returned by the three optic fibers are analyzed by the TactiSys™ Quartz system. Analysis of the interference pattern determines the length of the three cavities and the exact computation of both magnitude and orientation of the contact force (***D***).*

Evidence from human studies

Following the results from these experimental studies, CF catheters became available for human studies. The first clinical study on the use of a CF catheter in humans was the TOCCATA study. As part of this multicenter trial, Kuck et al. first evaluated the device- and procedure-related safety of this new catheter[15]. In a population of

77 patients, they looked at a right-sided supraventricular tachycardia (SVT) group and an AF group. During mapping, CF values were blinded to assess the CF that the operator would apply during standard mapping and RF ablation, during the ablation phase CF measures were available. In both groups, the incidence of serious adverse events (SAE) was well below the predetermined safety rate, confirming device and procedure safety. In the right-sided SVT group, SAE incidence was 2%, in the AF group 12% (with a predetermined rate of 11.4 and 16.8%, respectively) at procedure and 3-month follow-up[15]. One patient (3%) experienced tamponade and fully recovered after pericardiocentesis, another patient (3%) experienced sinusbradycardia and recovered within a week[15]. A third patient (3%) had a groin bleeding that resolved in 3 days, and a fourth patient (3%) suffered a stroke not related to the study device but by a difficult transseptal puncture under low anticoagulation[15].

They found that the CF catheter was as safe as conventional irrigated RF catheters and proposed that it might increase both the safety and effectiveness of RF ablation by preventing the use of inappropriately high CF, not just during ablation but also during manipulation, and by allowing better control of the RF lesion size[15]. Also, by assessing the blinded mapping contact data, they once more demonstrated the marked interand intra-investigator variability as previously mentioned with mean CF per operator ranging from 2 to 21 g and standard deviations per operator ranging from 5 to 281, again underlining the importance of real-time CF[15].

The improvement of procedural safety was further demonstrated by Akca et al., who evaluated the reduction of cardiac perforations (as primary end point) and other major complications (as secondary end point) with CF catheters and also compared this to the safety offered by magnetic navigation system (MNS)[41]. In this prospective registry data from 1517 ablation procedures with either CF catheters, non-CF (NCF) catheters or MNS was analyzed[41]. The four subgroups analyzed were AF, SVT, ventricular tachycardia and patients with congenital heart defects. It was found that CF catheters could reduce the risk of cardiac perforation compared with conventional ablation catheters, mostly due to a reduction of perforations in the AF subgroup (CF: 0.0 vs NCF: 3.3%)[41]. CF procedures had an equal amount of other major procedure-related complications. During AF and SVT ablations, more fluoroscopy was required for CF procedures compared with NCF procedures, presumed by the authors to be due to the complicated nature of academic patients and the use of the new systems operators needed to grow accustomed to[41]. Another potential factor explaining this finding could be the need to learn the orientation of the catheter and the catheter shaft by fluoroscopy in order to increase contact in the CF group. Independent predictors for major complications were NCF catheters,

transseptal approach and epicardial approach. CF ablation offered equal safety compared with MNS procedures[41].

Another study looking at the safety and efficacy of CF ablation is the SMART-AF trial[42]. In this prospective, multicenter, nonrandomized study, 122 patients enrolled at 21 sites with drug-refractory symptomatic paroxysmal AF underwent pulmonary vein isolation (PVI). The results showed that the 12-month effectiveness success rate was 74% with no unanticipated device-related adverse events. When operators stayed within the selected CF range in ≥80% of the time during ablation, there was a significantly higher success rate. Also, there was a marked improvement in quality of life and AF symptoms and severity[42].

In addition to safety, the TOCCATA study also assessed clinical outcome. In a one-arm prospective study, the relationship between CF measurements and clinical outcome in a group of 34 patients referred for PVI was investigated[43]. Live CF parameters were available during PVI for the operator, but without guidelines on CF at ablation. A success group was defined as no AF recurrence (absence of AF for >30 s) or AF recurrence but with confirmed durable PVI during a repeat ablation procedure. Acute PVI success was 100%. The results revealed that CF was low (<10 g) in 35% of all ablation lesions and also intermittent (reaching 0% during diastole) during 10% of these ablation lesions and that low CF correlated with increased clinical recurrences.

The largest variability in the topographical distribution of CF was found especially in the left anterior inferior ridge, the right inferior and the right anterior superior wall. Thus, in these sites CF may have an important additional role. All patients treated with an average CF of <10 g experienced AF recurrences and 80% of patients treated with a CF of >20 g had none. Clinical recurrence rate was also predictable on the basis of the number of applications with a CF of <5 g. When there were ≥2 low CF applications, the success rate at 12 months was 40%; when there were 0–1 low CF applications, this amounted to 75%[43].

Recently, in another multicenter study (EFFICAS I), the relationship between CF measurements during PVI and the incidence of isolation gaps at 3-month follow-up was studied[44]. In 46 patients with AF PVI was performed. During the procedure the operator was blinded to CF data. An interventional diagnostic procedure was performed at followup to assess gap formation. The end point was the correlation between the CF measurements (ablation parameters, CF and FTI from all index procedure ablations) and either gap formation or successful ablation after 3 months. At follow-up 65% of the patients had PV reconnections. There was a trend for better ablation results in segments with a higher average CF and FTI. But the best measures for isolation versus gap formation were minimum CF and FTI per segment. In each

segment, the 3-month outcome was only as effective as the minimum FTI of any RF application in that segment, especially when FTI was below 400 gs. This study also showed that most gaps were found in the left anterior segment. Based on their results, Neuzil et al. recommend a target CF of 20 g with a minimum of 10 g and a minimum FTI of 400 gs per application[44].

One of the latest published studies on the relationship between CF and clinical outcome, and the first to look at medium-term outcome, is a multicenter retrospective case–control study by Jarman et al.[45] They included 600 patients undergoing first-time RF AF ablation in four hospitals, matched 1:2 CFS and non-CFS ablation. Three AF types were defined: paroxysmal, persistent and long-lasting persistent. In all CF procedures, fluoroscopy time was significantly reduced and in paroxysmal AF ablation, a significantly higher procedure success rate was seen. CF catheter use (and severity of mitral regurgitation) was the only independent predictor of 11-month outcome. This did not apply to the nonparoxysmal AF types, which can be explained by different mechanisms that are of importance in nonparoxysmal AF as opposed to paroxysmal AF, for instance, the fact that more progressed atrial substrate may cause fibrillation in the presence of intact lesions[45].

In a small study by Kimura et al., a CF- and an NCF-guided PVI population were compared for procedure parameters and outcome[46]. Thirty-eight patients were included and randomized to a CF group and an NCF group, both consisting of 19 patients. In the CF group, CF values between 10 and 20 g were kept, whereas in the NCF group CF information was blanked while using the same catheter. In each application, RF current of 30 W in the anterior and 25 W in the posterior left atrial wall was applied for 20–25 s. In the CF group, a significantly shorter procedure time, a higher mean CF and a smaller total number of conduction gaps than the NCF group were demonstrated. There were no major complications in both groups. After the 6-month follow-up period, there was no difference in AF recurrence[46].

Sizeable studies like the EFFICAS II, focusing on limiting of low FTI applications by applying guidelines derived from the EFFICAS I, and the forthcoming TOCCASTAR study, focusing on safety, should offer further insight and confirmation of CF impact and may provide guidelines for the use of this evolutionary or revolutionary advance in technology[47]. A first look at the TOCCASTAR results shows that operators provided with real-time CF data achieved higher average CF, fewer low CF ablations and a lower incidence of ablations with low FTI (<400 gs) compared with the TOCCATA data, all of which are determinants of long-term success[48].

Results from the EFFICAS II trial showed that limiting of low FTI applications by applying guidelines derived from the EFFICAS I led to more durable PVI in catheter ablation of paroxysmal AF[49]. Compared to the EFFICAS I, where CF guidelines were

not used, 85% of PVs remained isolated instead of 72% when assessed by remapping after 3 months[49]. Also, narrower distribution of CF and FTI in the EFFICAS II, indicating better catheter control, was demonstrated to lead to a reduction of the number of RF applications by 15% compared with the EFFICAS I[49]. The study also showed that when the continuity index (a new parameter indicating the number of positions the catheter tip has moved over, when subsequent RF applications were delivered in nonadjacent positions) remained low, the isolation rate significantly increased even further up to 98%[49].

A minor disadvantage of the first generation of CF catheters is that they are more rigid compared with NCF catheters. This inconvenience can easily be compensated by acquiring more user experience and by the use of steerable sheaths.

Not much is known about the differences in outcome or procedural data between CF ablation and one-shot ablation techniques like cryoballoon ablation or nMARQ. A study by Jourda et al. compared CF ablation with second-generation cryoballoon therapy in 150 consecutive patients with paroxysmal AF[50]. They found no differences in mid-term clinical outcome or procedural complications; however, procedure duration, fluoroscopy and X-ray time were all significantly lower in the CF group[50]. In this study, a minimal CF value of 10 g was set, a lower cutoff point then proposed by the EFFICAS I trial, which could have led to insufficient transmurality of lesions in the CF group, leading to an underestimation of the clinical outcome[44,50]. Procedural times, on the other hand, should be observed with some caution as this was a center highly experienced in RF ablation and procedure time with RF ablation is more likely to be influenced by the operators' experience level than with cryoballoon ablation[50].

A recent study comparing CF with nMARQ ablation by Rosso et al. also shows comparable success rates in the treatment of AF after a mean follow-up of 11 months of 86 patients[51]. The end point of elimination of all PV potentials was reviewed with a second circular catheter inside the PV[51]. In four patients (11%) from the nMARQ group elimination could not be achieved and was completed using the CF catheter[51]. Data on procedure or fluoroscopy time are not mentioned in the abstract of this yet to be published study.

CONCLUSION & FUTURE PERSPECTIVE

The implementation of CF sensing technology has a great impact on optimizing lesion formation. The development of this technology has come a long way, from creating different ways of improving electrode–tissue contact to CF measuring techniques. Now that these advances have been made, the next logical step will be to

compare the different available technologies head-to-head in order to reach optimal results with maximum safety.

However, our understanding and therefore our approach to deliver appropriate lesions is far from being perfect. Possible tools that in the near future may help to enhance catheter ablation results include new parameters combining CF data with RF current and ablation duration that will provide real-time information about lesion growth. But until direct visualization of lesion formation will be achieved, CF will to some extent remain an indirect value.

During the process of developing the ultimate method, an important factor to take into account will be the targeted chamber wall thickness. One possible way of doing this may be by integrating imaging techniques, such as myocardial contrast echocardiography, which as previously demonstrated could potentially allow for real-time assessment and direct visualization of the applied lesions[52].

Another possibility could be the use of unipolar signal modification, as shown by Bortone et al. to be a very useful end point for RF delivery in patients with paroxysmal AF[53]. By targeting these reversed unipolar atrial electrograms with a positive–negative morphology and eliminating the negative component of these signals, they achieved a decrease of the total ablation time compared with conventional AF ablation and a substantial rate of sinus rhythm maintenance after PVI[53]. This strategy could be useful in acquiring more information about the location of the targeted tissue.

In the future, when all of these essential parameters will be accessible and can be combined, it could theoretically be possible to develop a so-called 'closed-loop' system that can automatically regulate lesion growth. A system like this would then in turn open the road for including robotic technologies[54,55]. Another application in which CF technology could play a significant role is the development of superior multipolar mapping catheters. When creating high-density voltage maps for substrate-based ablation, catheter–tissue contact is crucial in obtaining accurate voltage measurements: insufficient contact can produce false low-voltage areas or lead to gaps in the electroanatomic map[56,57]. Additionally, during epicardial mapping inadequate direction of the catheter away from the myocardium, which can be seen in almost half of the mapping points in a study by Jesel et al., is often related to higher CF[57]. This study also showed that the use of CF catheters helped to improve catheter–tissue contact in ventricular mapping[57]. When comparing accuracy and density of ventricular maps created with either a multipolar catheter (PentaRay®, Biosense Webster) or a quadripolar ablation catheter (NaviStar®, Biosense Webster), Berte et al. showed the former to be superior[56]. Anter et al. demonstrated multielectrode mapping catheters improved mapping resolution within areas of low voltage and

scar in the atrial substrate as well[58]. Incorporating CF technology in multielectrode mapping catheters therefore could prove a useful future development.
Finally, there is another important issue that should be solved. Although knowledge on RF ablation is excellent, the same level of awareness in competing technologies like cryo-, laser-, microwave- and ultrasound ablation has not yet been reached. Many of these techniques have so far failed to fulfill expectations due to incomplete understanding of their lesion profile. Improving this knowledge could provide the means for new innovative technology and for a more patient-tailored treatment of AF.

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Chapter 11

Clinical outcome of manual and magnetic navigated ablation of idiopathic outflow tract ventricular arrhythmias: a systematic review and meta-analysis

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ABSTRACT

Background: Radiofrequency (RF) catheter ablation of idiopathic ventricular arrhythmias (IVA) from the outflow tracts (OTs) can be performed with either manual (MAN) or, since 2003, magnetic (MNS) navigated ablation. The aim of this report is to compare the procedural and 1 year, or greater, outcomes of MAN and MNS ablation of OT IVA.

Methods: This review was conducted in accordance with the PRISMA and MOOSE guidelines. Six bibliographic electronic databases were searched for relevant studies published until March 29, 2017. Studies in English describing procedural outcome and with a mean follow-up of at least 12 months after OT IVA RF ablation with either MAN or MNS were selected.

Results: Twenty-six studies (with 3009 patients in total) were included. The overall procedural success rate of MAN was 90% (95% confidence interval (CI): 0.87 – 0.92), of MNS this was 94% (95% CI: 0.92 – 0.96). The overall long-term success rate for MAN was 83% (95% CI: 0.78 – 0.87), of MNS this was 89% (95% CI: 0.86 – 0.92). There was no significant difference in procedural or long-term success between MAN and MNS ($p = 0.32$ and $p = 0.41$, respectively). Complication rates were low (ranging from 0.6% to 5.6%), no major complications occurred with MNS or resulted in death. Heterogeneity between studies could be explained by follow-up method and geographical location of the study.

Conclusions: OT IVA catheter ablation has high procedural and moderately high long-term success rates for both MAN and MNS. Our data suggests that MNS may have a favorable safety profile. More RCTs are needed to confirm these findings.

1. INTRODUCTION

Idiopathic ventricular arrhythmias (IVA) are a common finding in the general population and represent about 10% of all ventricular arrhythmias (VA) in patients presenting on the outpatient clinic[1-3]. Around 90% of IVAs have their origin in one of the outflow tracts (OT), mainly the right ventricular outflow tract (RVOT)[4-7]. Manual radiofrequency (RF) catheter ablation has become an increasingly performed therapeutic option for this arrhythmia, showing variable but usually high success procedural rates ranging from 76 to 100%[8-10]. The magnetic navigation system (MNS) has proven to be a useful tool in improving the safety and in some cases the efficacy of catheter ablation for various arrhythmias, including IVAs[11-13]. However, current guidelines (from 2015) on IVA ablation are outdated and the most recent guideline recommendations on VA ablation with magnetic navigation (from 2009) are based on the former lack of clinical experience and comparative studies between these two approaches[8,14]. The aim of this systemic review and meta-analysis was to compare the procedural and 1 year, or greater, outcomes of manual (MAN) and MNS ablation of OT IVA.

2. METHODS

2.1 Data sources and search strategy

This review was conducted using a predefined protocol and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Appendix A and B). An extensive literature search in six electronic databases (Ovid Medline, EMBASE, Cochrane Central, Web of Science, Core Collection and Google Scholar) was conducted with the help of a medical librarian on March 29th 2017. The strategy combined terms for idiopathic ventricular arrhythmia with terms for intervention ablation and searched for cohort, follow-up and longitudinal studies or trials. The search results were limited to English language articles, without restriction on publication dates. The detailed search methodology is provided in Appendix C. Reference lists of selected studies and reviews identified on the topic were searched to identify additional publications.

2.2 Study selection and eligibility criteria

Studies were eligible if they (i) were observational studies and clinical trials and (ii) reported the procedural success (the immediate success of the procedure) and at least 12 month outcome data (long-term success and/or recurrence) of patients after MAN

or MNS RF ablation of OT IVAs. Studies enrolling less than 8 patients, or in which the outcome data of OT IVA ablation was not clearly distinguishable from other VA origins or etiologies were excluded. Articles focusing on VA ablation outcome of patients with structural or other heart diseases were excluded as well. Furthermore, individual case reports, editorials, review articles and meeting abstracts were not included. Two independent reviewers screened the titles and abstracts of all initially identified studies according to the selection criteria. Full texts were retrieved from studies that satisfied all selection criteria. Any disagreement was resolved through consensus or consultation with a third independent reviewer.

2.3 Data extraction

Data was extracted by two independent reviewers on qualitative aspects of the studies (date and country of publication, study design, number of included patients, median follow-up, definition of procedural success and follow-up method), participant characteristics (patient age, gender and VA origin (RVOT or left ventricular outflow tract (LVOT)), information on the reported exposure/outcome (type of ablation, RF application time, number of RF applications, procedural time, fluoroscopy time, complications) and procedural and long-term success rate.

2.4 Assessing the risk of bias

Study quality of observational studies was assessed by two independent reviewers based on the nine-star Newcastle–Ottawa Scale (NOS) using three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Studies that received a score of nine stars were judged to be of low risk of bias; studies that scored seven or eight stars were considered at medium risk; those that scored six or less were considered at high risk of bias (Appendix D). The Cochrane Collaboration's tool was used for assessing the risk of bias for randomized controlled studies (Appendix E).

2.5 Statistical analysis

Narrative synthesis and construction of descriptive summary tables were performed for the included studies. For this meta-analysis, we measured proportions of subjects recovered after a MAN or MNS intervention and 95% confidence intervals (CIs), to assess the procedural and long term success rate of MAN or MNS. The inverse variance weighted method was used to combine summary measures using random-

effects models to minimize the effect of between-study heterogeneity[15]. Heterogeneity was assessed using the Cochrane $\chi 2$ statistic and the I^2 statistic and was distinguished as low (I^2 ≤25%), moderate (I^2 >25% and <75%), or high (I^2 ≥75%)[16]. Follow-up period (12-20, 20-40 or >40 months), follow-up method (with routinely performed Holter, or Holter only performed when symptoms were reported), year of publication (2010 and before, or 2011 and after) and geographical location in which the study was performed (Europe, United States, Asia, South America or Africa) were pre-specified as characteristics for assessment of heterogeneity, and were evaluated using stratified analyses and random effects meta-regression for the meta-analysis that included 5 or more studies[17]. Publication bias was evaluated through funnel plots and Egger's regression symmetry tests[18]. All tests were 2-tailed; p-value ≤0.05 was considered statistically significant. Stata release 14 (StataCorp) was used for all analyses.

3. RESULTS

3.1 Identification of relevant studies

After removing duplicates, the search strategy identified 2135 citations, out of which, following initial screening based on titles and abstracts, full-texts of 181 articles were evaluated further. Of these we included 23 articles on MAN catheter ablation and 3 articles on MNS catheter ablation (with a total of 3009 patients) discussing the procedural and >12-month ablation success rates in patients with OT IVAs in the final analysis (Figure 1).

3.2 General characteristics of the included studies

The main characteristics of the included studies are summarized in Table 1 and 2. In total, 3009 patients with OT IVAs were included in this review. Out of the 26 included studies, 10 were prospective studies and 16 were retrospective studies. Three randomized controlled trials (RCT) and 23 observational studies were included. Out of the 26 studies, 1 multi-center and 25 single-center studies were analyzed. The follow-up method and intensity differed among the studies (supplementary table 1). Definitions of procedural success are summarized in supplementary table 2.

Table 1. *MAN ablation study characteristics*

Publication	Country of publication	Study type	Number of OT IVA patients	Median follow-up time (months)	Median patient age (years)	Patient gender (% male)	Quality score (NOS)
Chinushi 1997[19]	Japan	Single center, retrospective	13	28	48	15	4
Chung 2014[20]	Taiwan	Single center, retrospective	220	35.2	43.2	36.4	3
Corrado 2008[21]	Italy	Single center, prospective	27	41	33.9	55.6	4
Darrieux 2007[9]	Brazil	Single center, prospective	30	14.5	40	16.7	3
Dubner 2016[22]	Argentina	Single center, prospective	16	15†	48†	50†	3
Ge 2012[23]	China	Single center, retrospective	52	12.9	60.6	30.8	6
Gumbrielle 1997[24]	UK	Single center, retrospective	10	16	45	30	4
Hayashi 2017[25]	USA	Single center, retrospective	130	36	50	37.6	7
Krittayaphong 2006[26]	Thailand	Single center, retrospective	144	72.2	42	22.9	3
Latchamsetty 2015[27]	USA	Multicenter, retrospective	1185	20.2	52	45	4
Ling 2014[10]	China	Single center, prospective, randomized	165	12	52.6	28.5	‡
Miyamoto 2010[28]	Japan	Single center, prospective	63	21	52†	49†	4
Munclinger 1998[29]	South Africa	Single center, retrospective	11	13.7	47.8	27.2	3
Noda 2005[30]	USA	Single center, retrospective	16	54	39	43.7	4
O'Donnell 2003[31]	UK	Single center, retrospective	33	54	39	33	6
Petrač 2002[32]	Croatia	Single center, prospective	20	56	34	50	4
Rørvik 2016[33]	Norway	Single center, retrospective	34	130.8	56.3	47	3
Stec 2012[34]	Poland	Single center, prospective, randomized	50	48	47	40	†
Tsai 1997[35]	Taiwan	Single center, retrospective	51	29.2	38	65.6	7
Ventura 2007[36]	Germany	Single center, retrospective	71	135	39	42	3
Vestal 2003[37]	Taiwan	Single center, retrospective	86	56	49	36	4
Wen 1998[38]	Taiwan	Single center, retrospective	79	41	38	54	4
Zhang 2013 (2)[39]	Singapore	Single center, prospective	136	36.2	41.6	39.7	4

IVA = idiopathic ventricular arrhythmia; MAN = manual catheter ablation; NOS = Newcastle Ottawa Scale; OT = outflow tract; UK = United Kingdom; USA = United States of America; † = not available for OT IVA only; ‡ = for quality score see Appendix E Cochrane Collaboration's Tool for randomized studies

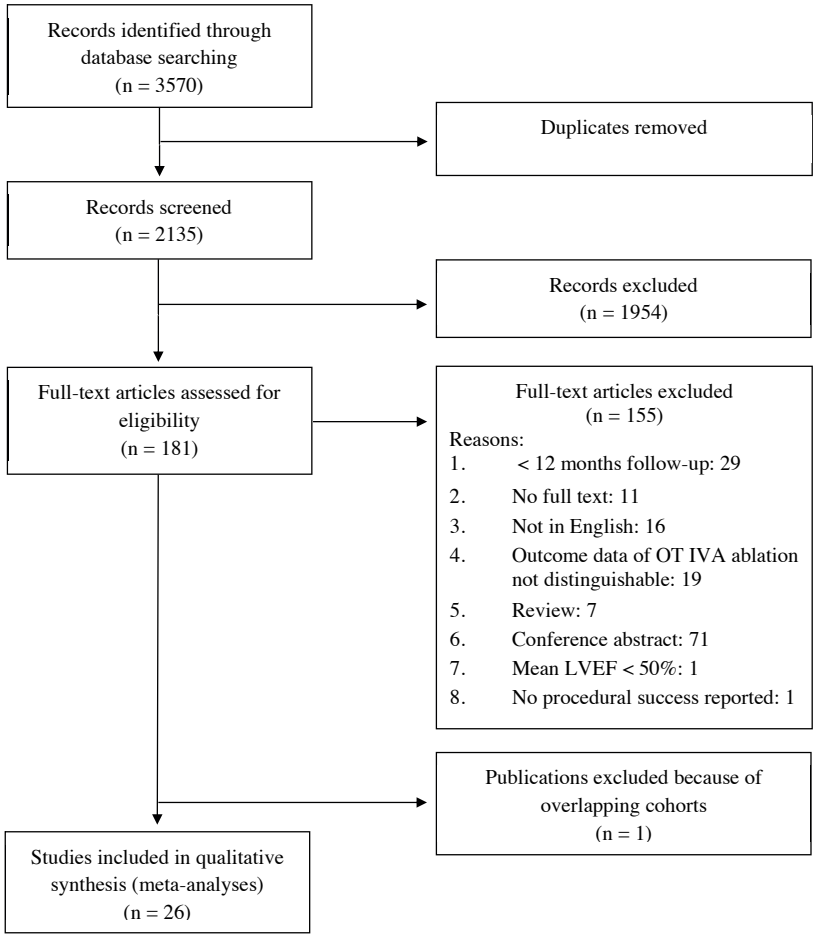

Figure 1. *Flowchart of studies for outcome of manual or magnetic navigated ablation of idiopathic ventricular arrhythmia*

Table 2. *MNS ablation study characteristics*

Publication	Country of publication	Study type	Number of OT IVA patients	Median follow-up time (months)	Median patient age (years)	Patient gender (% male)
Kawamura 2016[40]	USA	Single center, retrospective	51 (22 MNS)	26	45/49 (MAN/MNS)	55/32 (MAN/MNS)
Thornton 2006[41]	The Netherlands	Single center, prospective	8	12	44	75
Zhang 2013 (1)[42]	Singapore	Single center, prospective, randomized	30 (15 MNS)	22,1	46.5/41.7 (MAN/MNS)	26.6/26.6 (MAN/MN)

IVA = idiopathic ventricular arrhythmia; MAN = manual catheter ablation; MNS = magnetic navigation system; USA = United States of America; OT = outflow tract

3.3 MAN ablation: procedural success rates and sensitivity analysis

Procedural success rates were available for all studies (Table 3). The pooled success rate was 90% (95% CI: 0.87 - 0.92) (Figure 2). Evidence for heterogeneity between studies was found (I^2 = 99.8%).

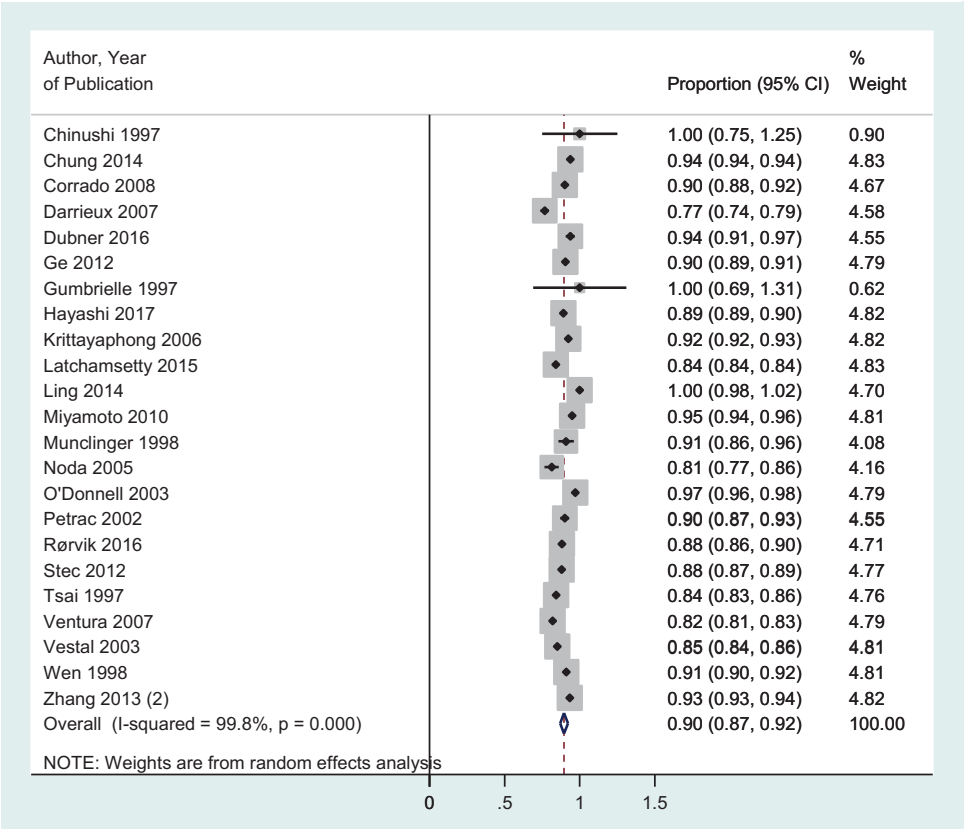

Figure 2. *Forest plot of procedural success of MAN studies*

The 10 studies from Asia showed the highest overall procedural success rate of 93% (95% CI: 0.93 - 0.93; I^2 = 98.8%). The one study from Africa reported a procedural success rate of 91% (95% CI: 0.86 - 0.96). The 7 European studies reported an overall 89% (95% CI: 0.89 - 0.90; I^2 = 98.5%) success rate and the 2 studies from South-America reported an overall success rate of 85% (95% CI: 0.83 - 0.87; I^2 = 98.5%). Finally, the 3 studies from the USA reported an overall success rate of 84% (95% CI: 0.84 - 0.84; I^2 = 99.6%). Evidence for influence on heterogeneity between groups was found (p = 0.016).

Table 3. *MAN procedural data*

Publication	RVOT/LVOT	Procedural success (%)	Long-term success (%)	RF time (min+SD)	RF applications (number+SD)	Procedure time (min+SD)	Fluoroscopy time (min+SD)
Chinushi 1997[19]	RVOT	100	92	-	8 ± 5.5	-	-
Chung 2014[20]	RVOT	93.8	68.3	-	-	-	-
Corrado 2008[21]	RVOT	90	62.9	-	23 ± 18	-	-
Darrieux 2007[9]	RVOT	76.7	80	-	8 ± 5.5	98 ± 37	3 ± 1.7
Dubner 2016[22]	RVOT‡	93.7	81	-	-	186 ± 30†	37 ± 9.5†
Ge 2012[23]	LVOT	90.4	95.7	4.3 ± 1.2	-	73.6 ± 26.7	10.1 ± 4.1
Gumbrielle 1997[24]	RVOT	100	90	-	4.1 ± 2	-	33.3 (SD N/A)
Hayashi 2017[25]	RVOT/LVOT	89.2	86.1	-	-	-	-
Krittayaphong 2006[26]	RVOT	92.4	88.9	-	11.8 ± 12.8	130 ± 67.6	32.5 ± 29.7
Latchamsetty 2015[27]	RVOT/LVOT	84	71	12 ± 11	-	198 ± 115	30 ± 24
Ling 2014[10]	RVOT	100	80.6	-	-	82 ± 35	13.5 ± 9.8
Miyamoto 2010[28]	RVOT	95	100	-	7 ± 5†	-	24 ± 12†
Munclinger 1998[29]	RVOT/LVOT	90.9	90.9	-	11.8 ± 6.4	-	-
Noda 2005[30]	RVOT	81.3	75	-	9 ± 4	-	-
O'Donnell 2003[31]	RVOT	97	95	-	8 ± 3	-	-
Petrač 2002[32]	RVOT/LVOT	90	90	-	10 ± 4	-	-
Rørvik 2016[33]	RVOT	88.2	91.2	-	-	-	-
Stec 2012[34]	RVOT/LVOT	88	88	-	-	-	-
Tsai 1997[35]	RVOT/LVOT	84.3	88.2	-	5 ± 4	-	-
Ventura 2007[36]	RVOT	82	39	-	-	-	-
Vestal 2003[37]	RVOT	85	77	-	-	-	-
Wen 1998[38]	RVOT/LVOT	91	88.6	-	-	158.9 ± 49.3	38.0 ± 20.4
Zhang 2013 (2)[39]	RVOT	93.4	86.8	-	4.4 ± 5.5	169.4 ± 67.8	12.2 ± 13.2

IVA = idiopathic ventricular arrhythmia; LVOT = left ventricular outflow tract; MAN = manual catheter ablation; min = minutes; N/A = not available; OT = outflow tract; RVOT = right ventricular outflow tract, SD = standard deviation; † = not available for OT IVA only, ‡ = 2 LVOT patients were included but not ablated.

The pooled long-term success rate was 83% (95% CI: 0.78 - 0.87) (Figure 3). Evidence for heterogeneity between studies was found (I^2 = 99.9%, p <0.001).

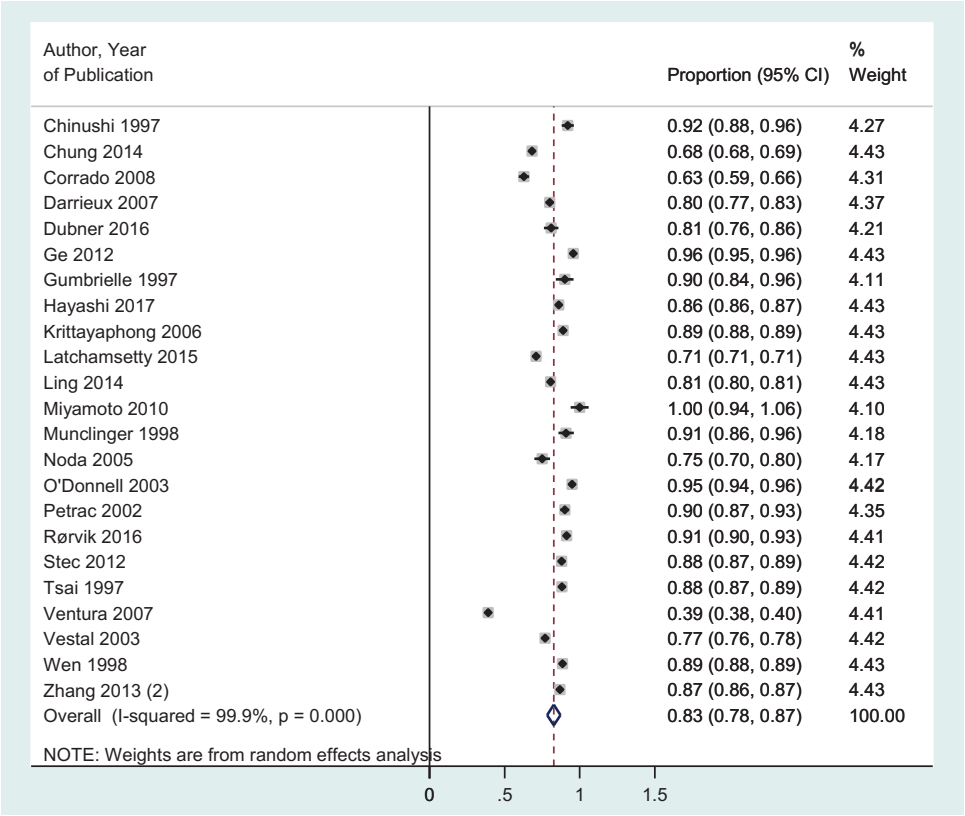

Figure 3. *Forest plot of long-term success of MAN studies*

The highest long-term success rates were found in studies with short and long-term follow-up (12-20 months and >40 months): 85% (95% CI: 0.84 - 0.85; I^2 = 99.6%) and 85% (95% CI: 0.85 - 0.85; I^2 = 99.8%), respectively. The long-term success rate in mid-term follow-up length studies was 72% (95% CI: 0.72 - 0.72; I^2 = 99.9%). P for heterogeneity was 0.40.

When long-term success rates were stratified by follow-up method, studies without routinely performed Holter registrations but only when symptoms were reported showed the highest overall success rate of 89% (95% CI: 0.89 - 0.89; I^2 = 99.1%). The overall reported long-term success rate of studies routinely performing Holter registrations during follow-up was 72% (95% CI: 0.72 - 0.72; I^2 = 99.9%). Evidence was found for heterogeneity between groups: p = 0.006.

Studies performed in 2010 or before reported an overall long-term success rate of 85% (95% CI: 0.85 - 0.85; I^2 = 99.8%). Studies from 2011 or after had an overall long-term success rate of 72% (95% CI: 0.72 - 0.72; I^2 = 99.9%). P for heterogeneity is 0.89.

The one study from Africa reported the highest long-term success rate of 91% (95% CI: 0.86 - 0.96). The 10 studies from Asia reported an overall long-term success rate of 82% (95% CI: 0.82 - 0.82; I^2 = 99.9%). The 2 studies from South-America reported an overall success rate of 80% (95% CI: 0.78 - 0.83; I^2 = 0%). The 7 European studies reported an overall 78% (95% CI: 0.77 - 0.79; I^2 = 99.9%) success rate and finally, the 3 studies from the USA reported an overall long-term success rate of 71% (95% CI: 0.71 - 0.71; I^2 = 99.9 %). P for heterogeneity is 0.58.

3.4 MNS ablation: procedural and long-term success rates

Success rates were available for all studies (Table 4). The overall procedural success rate in the MNS studies was 94% (95% CI: 0.92 - 0.96)(Figure 4). No evidence for heterogeneity between studies was found (I^2 = 0%). The pooled long-term success rate was 89% (95% CI: 0.86 - 0.92)(Figure 5). No evidence for heterogeneity between studies was found (I^2 = 34.1%).

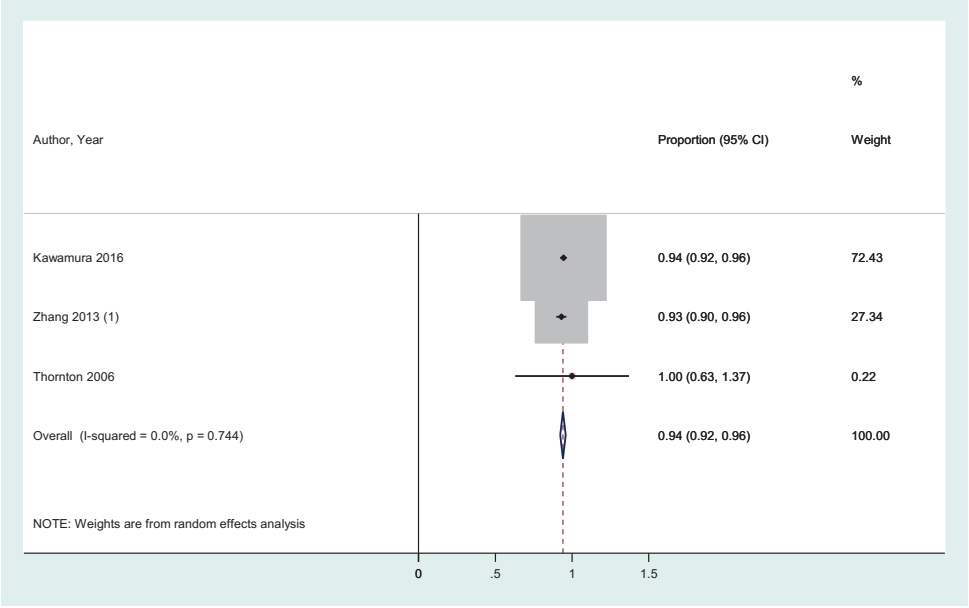

Figure 4. *Forest plot of procedural success of MNS studies*

Table 4. *MNS procedural data*

Publication	RVOT/LVOT	Procedural success (%)	Long-term success (%)	RF time (min+SD)	RF applications (number+SD)	Procedure time (min+SD)	Fluoroscopy time (min+SD)
Kawamura 2016[40]	RVOT/LVOT	94	91	-	14 ± 8 (MAN); 11 ± 8 (MNS)	168 ± 72 (MAN); 152 ± 71 (MNS)	34 ± 2 (MAN); 19 ± 14 (MNS)
Thornton 2006[41]	RVOT	100	88	4.7 ± 2.6	5.4 ± 2.6	151 ± 35	12.5 ± 5.8
Zhang 2013 (1)[42]	RVOT	93	87	1.2 ± 0.6 (MAN); 1 ± 0.5 (MNS)	-	115.1 ± 27.4 (MAN); 131.8 ± 19.4 (MNS)	10.5 ± 5.0 (MAN); 5.2 ± 2.6 (MNS)

LVOT = left ventricular outflow tract; MAN = manual catheter ablation; MNS = magnetic navigation system; min = minutes; RVOT = right ventricular outflow tract; SD = standard deviation

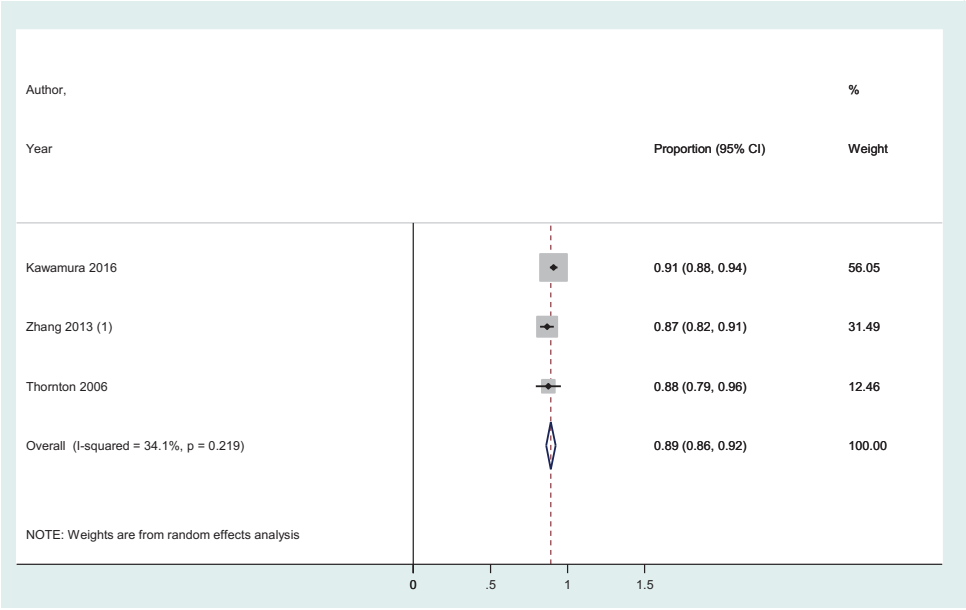

Figure 5. *Forest plot of long-term success of MNS studies*

In the two studies comparing MNS and MAN procedures, procedural success rates of RVOT ablations were higher for MNS (Kawamura 2016[40]: MNS 93% (95% CI: 0.90 – 0.97) *vs* MAN 63% (95% CI: 0.51 – 0.74) and Zhang 2013 (1)[42]: MNS 93% (95% CI: 0.90 - 0.96) *vs* MAN 67% (95% CI: 0.61 – 0.73)). Long-term success was similar in the study by Kawamura et al.[40]: MNS 91% (95% CI: 0.88 – 0.94) *vs* MAN 90% (95% CI: 0.88 – 0.92). In the study by Zhang et al.[42] it was higher for MAN: MNS 87% (95% CI: 0.82 – 0.91) *vs* MAN 100% (95% CI: 0.79 – 1.21).

3.5 Success rates MAN versus MNS

There was no significant difference in procedural or long-term success rates between MAN and MNS studies (p = 0.32 and p = 0.41, respectively).

3.6 Overall Complications

Meta-analysis was not performed on complication outcomes due to many studies reporting rates of 0%. Overall complication rates were low, with minor complications reported in 9 studies (two including MNS procedures) ranging from 0.5 to 26%. The highest minor complication rate of 26% occurred in the MAN arm of the study by Zhang 2013 (1)[42]. The complications consisted of 4 patients with mechanically induced right bundle branch block that normalized during

follow-up. Major complications were found in only 5 studies (ranging from 0.6 to 5.6%), none of which included MNS procedures. Reported major complications included: tamponade, major groin hematoma, femoral arterio-venous fistula, deep vein thrombosis and pulmonary embolism, atrioventricular block and VF. None of these complications resulted in death.

3.7 Quality evaluation

Of the non-randomized studies, 3 were judged to be of medium risk of bias based on the NOS. The remaining studies were considered at high risk of bias (Appendix D). Quality evaluation of the randomized studies with Cochrane Collaboration's tool is provided in Appendix E.

3.8 Publication bias

Visual examination of Begg's funnel plots for the analysis on the procedural and long-term success rate was asymmetrical, therefore providing evidence for publication bias. This was further supported by the results of Egger's test which was significant for both outcomes (p = 0.026 and 0.009, respectively). Studies reporting negative outcomes are underrepresented according to these data.

4. DISCUSSION

The main finding of this systematic review and meta-analysis is that procedural and long-term success rates of OT IVA catheter ablation are generally high and equal for both MAN and MNS, and that MNS ablation seems to have a better safety profile.

4.1 Comparison to previous systematic reviews

To the best of our knowledge, this is the first study thoroughly evaluating and comparing clinical outcome studies of catheter ablation of IVAs with either manual or magnetic navigation. Additionally, by only analyzing OT IVAs we have attempted to provide a comparison of outcomes in a homogenous patient population. One previous study compared manual and magnetic navigation of VAs of any etiology, a meta-analysis by Wu et al.[43] The study compared the acute and long-term success of MAN versus MNS ablation. Only studies comparing these two techniques were included. This resulted in the inclusion of four studies analyzing various types of VAs. Overall, they found no significant difference in acute success (72.3% *vs* 83.8%, MAN/MNS) or recurrence rate (35.2% *vs* 25.5%, MAN/MNS) with a follow-up between 13 and 22 months. Similarly to the present study, they found MNS to be associated with less complications (2.9% *vs* 12.0%, OR 0.279, 95 % CI: 0.092 -

0.843, p = 0.024). There was significant heterogeneity between the four studies, however, the source of heterogeneity was not accounted for.
One study analyzed by Wu et al.[43] was also found in the present study. The remaining three studies were not included in our analysis due to unavailability of separate OT IVA data.

4.2 Success rates, sensitivity analysis and safety

Overall, procedural and long-term success rates of MAN and MNS ablation of OT IVAs were not significantly different in the current analysis. However, in the two included studies comparing MAN and MNS, MNS did have higher procedural success rates. Although a difference in procedural success was found in the present study (MAN 90% *vs* MNS 94%), there was a lack of statistical significance which may be caused by the low number of included MNS studies.
Sensitivity analysis showed that the heterogeneity of procedural success of MAN studies could be explained by the geographical location where it was performed. The 10 studies performed in Asia showed the highest overall procedural success rate (93%), whereas the 3 studies from the USA showed the lowest overall success rate (84%). The discrepancy in the amount of studies per geographical location, however, is apparent. Additionally, in one of the studies from the USA, the study by Noda et al., 3 of 16 patients had a "partially successful" ablation which could arguably be considered "successful" as this was defined as complete termination of the target VA but incomplete termination of other VAs[30].
The long-term success rates of MAN and MNS were equal according to our data. Although differing rates were seen (MAN 83% *vs* MNS 89%), the discrepancy was not statistically significant possibly due to the low number of MNS studies included. The heterogeneity found in the long-term success of MAN studies could be explained by the follow-up method that was used. In studies where follow-up Holter was not routinely performed, higher long-term success rate were reported. This could indicate that in many cases, reported long-term success is overestimated. Furthermore, this shows that a routinely performed Holter during follow-up is important in order not to miss asymptomatic VAs.
Although safety regarding complications could not be analyzed due to many studies reporting complication rates of 0%, MNS was not involved in any of the reported major complications. This confirms the reliable safety profile that is found for MNS ablation of several arrhythmias[13,45-47]. However, only 3 studies evaluated the MNS approach in 89 patients so further studies are required to confirm its safety profile. Another advantage of MNS regarding safety, for both patients and operators, is the shortening of fluoroscopy time[48]. Although this was not analyzed in the present

study due to incomplete reporting of procedural data in the included studies (Table 3 and 4), the two studies comparing MAN and MNS both show a significantly lower fluoroscopy burden in favor of MNS[40,42]. In the study by Zhang et al., fluoroscopy time for both patients and operating physicians was reduced with 50.5% and 68.6%, respectively[42]. The importance of this advantage is clearly illustrated in a recent study that compared health problems among personnel staff working in interventional cardiology or cardiac electrophysiology and performing fluoroscopically guided cardiovascular procedures to a non-exposed control group[49]. A significantly higher prevalence of disease that was potentially associated with occupational exposure to radiation was seen in the exposed group (OR of 9.0; 95% CI, 2–41 for cataract and OR of 4,5; 95% CI, 0.9–25 for cancer, in highly exposed *vs* unexposed subjects), with the highest prevalence among the personnel staff reported in electrophysiologist and interventional cardiologists, followed by nurses and technicians (69% *vs* 22% and 9%, respectively), with a clear unfavorable correlation with length of history of work[49].

4.3 Strengths and limitations

This is the first systemic review presenting an overview of all the available studies analyzing and/or comparing clinical outcome of MAN and MNS ablation of OT IVAs only. Previous studies have looked at the very heterogeneous group of idiopathic VAs, which includes entities such as OT IVAs to, for instance, fascicular VAs. Arrhythmia mechanisms are very different for each of these IVAs. This heterogeneity produces a distorted image of the real-world clinical outcome of the idiopathic VAs we see most in our daily practice; the OT IVAs. Our search method ensured that we included only the most relevant articles in our review, enrolling over 3000 patients. Nonetheless, there are some limitations of this study that have to be taken in account. In spite of our meticulous attempt to create a comprehensive search of the published literature, we are unable to exclude the possibility of publication bias due to the underreporting of negative outcomes. Additionally, inclusion of studies that may potentially be poorly conducted may be a limitation of the present review. Furthermore, many studies reported incomplete procedural data (*i.e.* ablation time, number of RF applications, fluoroscopy time, etc.) which therefore could not be analyzed, although instead is summarized in the supplementary material. More high quality and highly powered RCTs with standardized long-term follow-up are needed to accurately assess long-term success rates and other clinical outcome comparisons between MAN and MNS ablation.

4.4 Clinical significance

Due to the homogenous group of patients analyzed in this systematic review, the data and conclusions presented here are clinically well applicable and representative for the VA patients that are seen most in daily practice. Because of the unavailability of high quality and highly powered comparative studies, the present study might provide a useful oversight assisting physicians in clinical decision making regarding this ever-growing group of patients.

Although the complication rate could not be analyzed, the reason for this makes apparent the overall safety of OT IVA ablation. Even more so with use of MNS, major complications only rarely occur and usually do not lead to permanent damage or death. In light of the generally benign prognosis of OT IVAs, it is of special importance that the safety of the treatment of this arrhythmia is paramount. In this respect, MNS ablation, when available as an option, could be the preferred therapeutic strategy. Of course, this is not the only consideration that plays a role in choosing this utility. An important limitation that remains for MNS is the cost of the equipment, which is around two million euros[50].

Currently, catheter ablation is recommended as a treatment of first choice for RVOT IVAs and failure of anti-arrhythmic drug therapy is no longer a requirement[8]. This recommendation, in combination with the expanding experience among operators and the increasing safety of ablation procedures, has led to a significant rise in performed OT IVA ablation procedures which will in future most likely only grow. For instance, in our center, the rate of IVA ablations has risen from 7.7% of all ablations in 2008 to over 10% in 2015. With this perspective in mind, even when taking in to account the significant financial burden of the equipment, MNS might become a feasible option to more centers in the near future.

5. CONCLUSIONS

OT IVA catheter ablation is a treatment that can be safely performed and that has high procedural and moderately high long-term success rates for both MAN and MNS. The heterogeneity of procedural success rates of the MAN studies included in this review could be explained by their geographical location. The heterogeneity found in the long-term success of MAN studies was influenced by the follow-up method that was used (*i.e.* with – or without routine Holter). Additionally, our data suggests that MNS ablation may have a more favorable safety profile compared to MAN ablation. More RCTs comparing these techniques are needed to confirm these findings.

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SUPPLEMENTAL MATERIAL

Appendix A PRISMA guidelines
Appendix B MOOSE checklist
Appendix C Detailed search methodology
Appendix D NOS
Appendix E The Cochrane Collaboration tool for assessing risk of bias

Supplementary table 1: follow-up method description of included studies
Supplementary table 2: definitions of procedural success of included studies

Supplementary figure 1: publication bias funnel plots
Supplementary figure 2: Sensitivity analysis forest plots of MAN studies (procedural success by year of publication)
Supplementary figure 3: Sensitivity analysis forest plots of MAN studies (procedural success by geographical location of study)
Supplementary figure 4: Sensitivity analysis forest plots of MAN studies (long-term success by follow-up category)
Supplementary figure 5: Sensitivity analysis forest plots of MAN studies (long-term success by year of publication)
Supplementary figure 6: Sensitivity analysis forest plots of MAN studies (long-term success by geographical location of study)
Supplementary figure 7: Sensitivity analysis forest plots of MAN studies (long-term success by follow-up method)

Appendix A. *PRISMA guidelines*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2, 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, 7, Appendix 4 and 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Appendix A. *PRISMA guidelines (Continued)*

Section/topic	#	Checklist item	Reported on page #
METHODS			
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, 14, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1, 2, Appendix 4 and 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-17, Fig 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17, Suppl Fig 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-17, Suppl fig 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17, 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

Appendix B. *MOOSE checklist*

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Radiofrequency (RF) catheter ablation of idiopathic ventricular arrhythmias (IVA) from the outflow tracts (OTs) is an increasingly performed therapeutic strategy. This treatment is mostly performed with manual catheter ablation (MAN). Since 2003, however, the magnetic navigation system (MNS) is available for these procedures. Currently, studies comparing the clinical outcome of OT IVA ablation between these techniques are lacking.
√	Hypothesis statement	The use of MNS will lead to improved procedural and 1 year, or greater, outcomes of OT IVA ablation.
√	Description of study outcomes	Studies were eligible if they reported procedural and at least 12 month outcome data of patients after MAN or MNS RF ablation of OT IVAs.
√	Type of exposure or intervention used	Two type of catheter ablation techniques were assessed: MAN and MNS RF ablation
√	Type of study designs used	Eligible study designs included randomized controlled trials (RCTs), cohort, case-control studies.
√	Study population	Only studies carried out in adults (>18 years old) without structural heart disease were included.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators are indicated in the authors list on the title page.
√	Search strategy, including time period included in the synthesis and keywords	The search strategy and corresponding time periods are detailed on page 5 of the manuscript and in Figure 1. The full search strategy is available in Appendix 3.
√	Databases and registries searched	Ovid Medline, EMBASE, Cochrane Central, Web of Science, Core Collection and Google Scholar
√	Search software used, name and version, including special features	We did not employ search software. Endnote was used to merge the retrieved citations and to eliminate duplications.
√	Use of hand searching	Bibliographies of retrieved systematic reviews and meta-analysis were hand searched for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are presented in the flow chart (Figure 1). Citations for the included studies are included in the text and in table 1. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We restricted our search to studies published in English.
√	Method of handling abstracts and unpublished studies	Abstracts and unpublished studies were not included.
√	Description of any contact with authors	The authors of included studies were contacted to retrieve missing full texts and to identify any missing studies.

Appendix B. *MOOSE checklist (Continued)*

	Criteria	Brief description of how the criteria were handled in the meta-analysis
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the methods section.
√	Rationale for the selection and coding of data	To extract the relevant information from the included full texts, a predesigned data extraction form was prepared. The list included questions on qualitative aspects of the studies (such as author, date of publication, country, design, period, setting, area, sample size, follow-up), participant characteristics (such as age and sex) and information on the reported exposure/outcome (such as catheter ablation type (MAN or MNS), and procedural and long-term success rate
√	Assessment of confounding	We performed qualitative analyses to evaluate differences between studies.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review. For randomized controlled studies we used The Cochrane Collaboration Tool.
√	Assessment of heterogeneity	The data were pooled visually and statistically.
√	Description of statistical methods in sufficient detail to be replicated	Narrative synthesis and construction of descriptive summary tables were performed for the included studies. For this meta-analysis, we measured proportions of subjects recovered after a MAN or MNS intervention and 95% confidence intervals (CIs), to assess the procedural and long term success rate of MAN or MNS. The inverse variance weighted method was used to combine summary measures using random-effects models to minimize the effect of between-study heterogeneity. Heterogeneity was assessed using the Cochrane $\chi 2$ statistic and the I^2 statistic and was distinguished as low (I^2 ≤25%), moderate (I^2 >25% and <75%), or high (I^2 ≥75%). Follow-up period (12-20, 20-40 or >40 months), follow-up method (with routinely performed Holter, or Holter only performed when symptoms were reported), year of publication (2010 and before, or 2011 and after) and geographical location in which the study was performed (Europe, United States, Asia, South America or Africa) were pre-specified as characteristics for assessment of heterogeneity, and was evaluated using stratified analyses and random effects meta-regression for the meta-analysis that included 5 or more studies. Publication bias was evaluated through funnel plots and Egger's regression symmetry tests. All tests were 2-tailed; p-value ≤0.05 was considered statistically significant. Stata release 14 (StataCorp) was used for all analyses.
√	Provision of appropriate tables and graphics	We included 5 main figures, 4 main tables, 5 appendices and 4 supplements

Appendix B. *MOOSE checklist (Continued)*

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2-5
√	Table giving descriptive information for each study included	Tables 1-2
√	Results of sensitivity testing	Supplemental Fig. 2
√	Indication of statistical uncertainty of findings	95% confidence intervals or SD's were presented if available
Reporting of discussion should include		
√	Quantitative assessment of bias	NA
√	Justification for exclusion	We excluded studies that had no, unclear or non-applicable definition of outcome, or data extraction was not feasible.
√	Assessment of quality of included studies	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review and The Cochrane Collaboration Tool for randomized controlled studies
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Due to the lack of standardisation of follow-up, it is difficult to provide unifying statements within a larger number of manuscripts hampered by large levels of heterogeneity. This is also true for procedural success definitions and definition of IVAs.
√	Generalization of the conclusions	The generalizability of our findings has been enhanced by including international data. Additionally, we looked at a very homogenous patient population.
√	Guidelines for future research	More RCTs comparing these two techniques are needed to confirm our findings.
√	Disclosure of funding source	Nothing to disclose.

Appendix C. *Detailed search methodology*

Search date: 29th of March 2017
catheter ablation idiopathic ventricular arrhythmia

embase.com	1829	1799
Medline ovid	851	110
Web of science	618	118
Cochrane	28	0
Google scholar	244	108
Total	3570	2135

Embase.com

(((‘heart ventricle arrhythmia’/exp OR ‘heart ventricle tachycardia’/de OR ‘monomorphic ventricular tachycardia’/de OR ‘heart ventricle extrasystole’/de) AND (‘idiopathic disease’/de OR ‘heart left ventricle outflow tract’/de OR ‘heart right ventricle outflow tract’/de)) OR (((idiopath* OR outflow-tract* OR rvot OR summit* OR ((without NEAR/3 (structural-heart-disease* OR shd)) OR ((magnet* OR robot*) NEAR/6 navigat*))) AND ventric* NEAR/3 (arrythm* OR arrhythm* OR tachyarrythm* OR tachyarrhythm* OR tachycard* OR extrasystole* OR ectopic-beat*)) OR ((RVOT OR idiopath* OR outflow-tract*) NEAR/3 (VT OR va)) OR iva OR (prematur* NEAR/3 ventric* NEAR/3 (contraction* OR complex*)) OR pvc OR pvcs):ab,ti) AND (‘catheter ablation’/exp OR ‘ablation catheter’/de OR ‘ablation device’/de OR ‘radiofrequency ablation device’/de OR ‘radiofrequency ablation’/de OR ‘ablation therapy’/de OR (ablation OR rfa):ab,ti) AND (‘observational study’/exp OR ‘cohort analysis’/exp OR ‘longitudinal study’/exp OR ‘retrospective study’/exp OR ‘prospective study’/exp OR ‘epidemiological data’/de OR ‘case control study’/de OR ‘cross-sectional study’/de OR ‘correlational study’/de OR ‘major clinical study’/de OR ‘multicenter study’/de OR ‘comparative study’/de OR ‘follow up’/de OR ‘clinical study’/de OR ‘clinical article’/de OR ‘clinical trial’/exp OR ‘randomization’/exp OR ‘intervention study’/de OR ‘open study’/de OR ‘community trial’/de OR ‘review’/exp OR ‘systematic review’/exp OR (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/3 (stud* OR survey)) OR (health* NEAR/3 survey*) OR ((case OR cases OR match*) NEAR/3 control*) OR (cross NEXT/1 section*) OR correlation* OR multicenter* OR multi-center* OR follow-up* OR followup* OR clinical* OR trial OR random* OR review* OR meta-analy*):ab,ti) AND [english]/lim

Medline ovid

((((idiopath* OR outflow-tract* OR rvot OR summit* OR ((without ADJ3 (structural-heart-disease* OR shd)) OR ((magnet* OR robot*) ADJ6 navigat*))) AND ventric* ADJ3 (arrythm* OR arrhythm* OR tachyarrythm* OR tachyarrhythm* OR tachycard* OR extrasystole* OR ectopic-beat*)) OR ((RVOT OR idiopath* OR outflow-tract*) ADJ3 (VT OR va)) OR iva OR (prematur* ADJ3 ventric* ADJ3 (contraction* OR complex*)) OR pvc OR pvcs).ab,ti.) AND ("Catheter Ablation"/ OR (ablation OR rfa).ab,ti.) AND ("observational study"/ OR exp "Cohort Studies"/ OR exp "Epidemiologic Studies"/ OR "multicenter study"/ OR "comparative study"/ OR exp "clinical study"/ OR "Random Allocation"/ OR "review"/ OR (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) ADJ6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR ((case OR cases OR match*) ADJ3 control*) OR (cross ADJ section*) OR correlation* OR multicenter* OR multi-center* OR follow-up* OR followup* OR clinical* OR trial OR random* OR review* OR meta-analy*).ab,ti.) AND english.la.

Cochrane

((((idiopath* OR outflow-tract* OR rvot OR summit* OR ((without NEAR/3 (structural-heart-disease* OR shd)) OR ((magnet* OR robot*) NEAR/6 navigat*))) AND ventric* NEAR/3 (arrythm* OR arrhythm* OR tachyarrythm* OR tachyarrhythm* OR tachycard* OR extrasystole* OR ectopic-beat*)) OR ((RVOT OR idiopath* OR outflow-tract*) NEAR/3 (VT OR va)) OR iva OR (prematur* NEAR/3 ventric* NEAR/3 (contraction* OR complex*)) OR pvc OR pvcs):ab,ti) AND ((ablation OR rfa):ab,ti)

Web of science

TS=(((((idiopath* OR outflow-tract* OR rvot OR summit* OR ((without NEAR/3 (structural-heart-disease* OR shd)) OR ((magnet* OR robot*) NEAR/6 navigat*))) NEAR/10 ventric* NEAR/2 (arrythm* OR arrhythm* OR tachyarrythm* OR tachyarrhythm* OR tachycard* OR extrasystole* OR ectopic-beat*)) OR ((RVOT OR idiopath* OR outflow-tract*) NEAR/2 (VT OR va)) OR iva OR (prematur* NEAR/2 ventric* NEAR/2 (contraction* OR complex*)) OR pvc OR pvcs)) AND ((ablation OR rfa)) AND ((((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/5 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/2 (stud* OR survey)) OR (health* NEAR/2 survey*) OR ((case OR cases

OR match*) NEAR/2 control*) OR (cross NEAR/1 section*) OR correlation* OR multicenter* OR multi-center* OR follow-up* OR followup* OR clinical* OR trial OR random* OR review* OR meta-analy*))) AND LA=(english)

Google scholar

First 200:
"idiopathic ventricular arrythmia|arrhythmia|tachycardia|arrythmias|arrhythmias|tachycardias" ablation|rfa
First 100:
allintitle:"ventricular arrythmia|arrhythmia|tachycardia|arrythmias|arrhythmias|tachycardias" ablation|rfa

Appendix D. *Newcastle Ottawa Scale (NOS)*

Study	Selection	Comparability	Exposure	Total
Chinushi 1997[19]	2	0	2	4
Chung 2014[20]	2	0	1	3
Corrado 2008[21]	2	0	2	4
Darrieux 2007[9]	2	0	1	3
Dubner 2016[22]	2	0	1	3
Ge 2012[23]	4	0	2	6
Gumbrielle 1997[24]	2	0	2	4
Hayashi 2017[25]	4	0	3	7
Kawamura 2016[40]	4	0	3	7
Krittayaphong 2006[26]	2	0	1	3
Latchamsetty 2015[27]	2	0	2	4
Miyamoto 2010[28]	2	0	2	4
Munclinger 1998[29]	1	0	2	3
Noda 2005[30]	2	0	2	4
O'Donnell 2003[31]	3	0	3	6
Petrač 2002[32]	2	0	2	4
Rørvik 2016[33]	2	0	1	3
Thornton 2006[41]	2	0	2	4
Tsai 1997[35]	4	0	3	7
Ventura 2007[36]	2	0	1	3
Vestal 2003[37]	2	0	2	4
Wen 1998[38]	2	0	2	4
Zhang 2013 (2)[39]	2	0	2	4

Appendix E. *The Cochrane Collaboration tool for assessing risk of bias*

Publication	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other Bias
Ling 2014[10]	Low risk *("A computer-generated list of random numbers was used for randomization")*	Low risk *("Allocation concealment was safeguarded by ensuring that allocation was obtained by computer output after the patients had consented")*	High risk *(AAD vs RF ablation)*	Unclear for recurrence/ number of PVCs/ PVC burden *(not mentioned)* Low risk for LVEF *("analyzed by an expert analyst blinded to patient status"*	High risk *(5 missing; 1 RF ablation group, 4 AAD group. No reason mentioned)*	Low risk *(all mentioned endpoints in method reported)*	
Stec 2012[34]	Low risk *("… patients were randomized…")*	Unclear *(Not mentioned)*	High risk *("physicians were not blinded to the patients' therapy")*	High risk *("physicians were not blinded to the patients' therapy")*	Low risk *("All patients completed long-term follow-up")*	Low risk *(all mentioned endpoints in method reported)*	
Zhang 2013 (1)[42]	Low risk *("Randomization was Performed using a random number generator, with sealed envelopes opened on the day of procedure")*	Low risk *("… sealed envelopes opened on the day of procedure")*	High risk *(MNS vs MAN)*	Unclear	Low risk *(all patients completed follow-up)*	Low risk *(all mentioned endpoints in method reported)*	*"The investigators had prior knowledge of the primary endpoints in the conduct of this study" "…type I error..."*

Supplementary table 1. *Definitions of procedural success of included studies*

MAN studies:

Publication	Procedural Success Definition
Chinushi 1997[19]	Complete disappearance of spontaneous VT after ablation as assessed by electrocardiographic monitoring. When VTwas induced by programmed electrical stimulation, the efficacy was judged by electrophysiological study at the end of ablation and two weeks later. For VT induced by isoprenaline infusion or a treadmill exercise test before ablation, or both, ablation was judged to be successful when VT was rendered non-inducible by these interventions
Chung 2014[20]	Elimination of RVOT IVAs
Corrado 2008[21]	If VA was abolished during ablation, remained absent for at least 30 min after ablation, and was not re-induced by either programmed ventricular stimulation or isoproterenol infusion
Darrieux 2007[9]	End-of-procedure criterion was the complete disappearance of RVOT-PVC, even after 30 minutes of isoproterenol infusion (immediate success)
Dubner 2016[22]	Total abolishment for at least 30 min of the spontaneous PVCs/VT or the reduction greater than 99%
Ge 2012[23]	When PVCs disappear or when sporadic PVCs (≤1 beats/min)/VT cannot be induced after radiofrequency ablation and when close observation for 30 min after operation reveals a reduction of the total number of PVCs to less than 10
Gumbrielle 1997[24]	Monitored for 30 minutes to detect recurrence of spontaneous tachycardia or ectopic activity. If no arrhythmia occurred, programmed ventricular stimulation and infusion of isoproterenol were repeated
Hayashi 2017[25]	Complete suppression of the VAs and no recurrence after a waiting period of at least 20 minutes and with a stimulation protocol that included ventricular and/or atrial pacing and intravenous isoproterenol infusion (average dose 6.2 ± 5.6 μg/minute)
Krittayaphong 2006[26]	Complete elimination of spontaneous or inducible VAs with and without isoprenaline infusion at least 30 min after successful ablation
Latchamsetty 2015[27]	Elimination of the targeted PVCs at the termination of the procedure at least 30 min after the last ablation
Ling 2014[10]	The absence of PVCs with similar morphology during a 30-minute observation period
Miyamoto 2010[28]	The endpoint of ablation for sustained VT was VT termination, subsequent non-inducibility of VT for focal VT, and non-inducibility for non-sustained focal VT and PVC
Munclinger 1998[29]	N/A
Noda 2005[30]	If the PVCs and/or VT including the target VT were completely eliminated and were not induced at all
O'Donnell 2003[31]	The absence of any inducible tachycardia at the end of the ablation procedure using both programmed stimulation and isoprenaline

Supplementary table 1. *Definitions of procedural success of included studies (Continued)*

MAN studies:

Publication	Procedural Success Definition
Petrač 2002[32]	If no sustained VT, non-sustained VT, or PVCs similar in configuration to clinical arrhythmia were induced or observed
Rørvik 2016[33]	The elimination of spontaneous clinical VT or PVCs via isoproterenol administration and non-inducibility of the clinical ventricular arrhythmias was the procedural endpoint
Stec 2012[34]	N/A
Tsai 1997[35]	Complete ablation of PVCs during programmed electrical stimulation and intravenous infusion of isoproterenol
Ventura 2007[36]	Abolishment of the RVOT VT
Vestal 2003[37]	1) Complete disappearance of spontaneous, or non-inducibility by programmed stimulation on and off isoproterenol of, sustained or non-sustained VT, or 2) Complete disappearance of ectopy on and off isoproterenol immediately (at least 20 minutes) during the observation period post ablation
Wen 1998[38]	Inability to induce VT by programmed stimulation with and without isoproterenol infusion
Zhang 2013 (2)[39]	If the VT or PVCs was eliminated during ablation and/or became non inducible with programmed electrical stimulation and use of isoproterenol infusion

MNS studies:

Publication	Procedural Success Definition
Kawamura 2016[40]	Absence of any VA with the same morphology of the targeted VA after a 30-min waiting period after the final ablation and was defined as at least 80 % reduction of PVCs in the 24-h Holter recording
Thornton 2006[41]	Absence of clinical VAs during monitoring and non-inducibility of arrhythmia using isoprenaline and burst pacing. Maneuvers were repeated after a 30-minute waiting period. All patients underwent continuous 24-hour monitoring after the procedure, and acute success was defined only if no ventricular ectopy was observed during this period
Zhang 2013 (1)[42]	If the VT or VPC was eliminated during ablation and/or became non inducible with programmed electrical stimulation and isoproterenol infusion

Supplementary table 2. *Follow-up method description of included studies*

MAN studies:

Publication	Follow-up Method
Chinushi 1997[19]	Outpatient clinic visit at least once, after 1 month in a drug free state. Recurrence of tachycardia was identified based on symptoms and confirmed by Holter
Chung 2014[20]	On outpatient clinic with 12-lead ECGs, 24-hour Holter and echocardiography after ablation every 3 months for the first year and then 6 months thereafter. Telephone contact for patients unable to travel to outpatient clinic, for recurrent symptoms and recurrent arrhythmias. These patients were advised to visit affiliated institutions to complete follow-up screening. The medical reports were obtained from these affiliated institutions
Corrado 2008[21]	N/A
Darrieux 2007[9]	Outpatient clinic visits at 30, 60, and 120 days, and for up to 1 year of follow-up. 12-lead ECGs, 24-hour Holter (at least 3 times) and exercise stress test (at least 2)
Dubner 2016[22]	Every 15/30 days (first 2 months) and every 4 months thereafter with routinely clinical controls, ECG and 24-hour Holter during the first year after the procedure
Ge 2012[23]	Patient re-examination once in 3 months using echocardiogram and dynamic ECG to estimate the long-term effect. During this period, all administration of anti-arrhythmia drugs was ceased. Further and timely consultation for any special condition alterations during outpatient follow-up. Archival of each patient. Patients were followed up by telephone in 6, 12, and 18 months after the ablation procedure. ECG and 24-hour ECG monitoring were performed whenever the patient had symptoms suggestive of recurrence of PVCs/VT
Gumbrielle 1997[24]	N/A
Hayashi 2017[25]	Telemetry monitoring immediately after the procedure. Patients were routinely evaluated at 4–8 weeks after ablation and then at 3- to 6-month intervals. For patients not followed at our institution, the referring cardiologists were contacted and ECG/Holter monitoring strips were reviewed to assess for arrhythmia recurrence. Telephone interviews were performed at 6- and 12-month intervals with patients or family members to confirm the absence of arrhythmias symptoms.
Krittayaphong 2006[26]	Outpatient clinic visit every 3 months for 1 year after the procedure. Patients were instructed to return to the clinic whenever they had recurrent symptoms, to determine whether they had recurrent arrhythmia
Latchamsetty 2015[27]	Clinical success was evaluated at centers where 24- to 48-h Holter monitoring was performed routinely during follow-up and was defined as at least an 80% decrease in PVC burden. Holter monitoring was performed 3 to 6 months post-ablation and further monitoring was performed at the discretion of the clinician based on symptom recurrence or finding of PVCs on an electrocardiogram (ECG)
Ling 2014[10]	Routine 12-lead Holter monitoring was performed at the 1st, 3rd, 6th, and 12th month, and echocardiography was performed at the 3rd and 6th months. When patients reported symptoms of palpitations, dizziness, or syncope during follow-up, they were advised to contact their doctors immediately for evaluation of vital signs, 12-lead ECG, and 12-lead 24-hour Holter monitoring

Supplementary table 2. *Follow-up method description of included studies (Continued)*

MAN studies:

Publication	Follow-up Method
Miyamoto 2010[28]	Outpatient clinic visit 1 week, 1 month, and 3 months after the procedure, and every 6 months thereafter. Holter ECG monitoring was performed if the patient reported any symptoms
Munclinger 1998[29]	N/A
Noda 2005[30]	N/A
O'Donnell 2003[31]	Follow-up at 1, 6 and 12 months, then yearly. At each review, patients completed standardized questionnaires regarding symptoms and underwent a standard 12-lead electrocardiogram, 48-h ambulatory electrocardiographic recordings and transthoracic echocardiography. Results of implantable cardioverter defibrillator interrogations, unscheduled outpatients appointments and hospital admissions were also collected
Petrač 2002[32]	Outpatient clinic visit every 6 months with ECG, physical exam and a Holter every 10 months
Rørvik 2016[33]	In-house questionnaire comprising a self-evaluation score. The patients were asked to report on all symptoms commonly experienced from these arrhythmias. They also rated their overall general health perception as a consequence of their arrhythmia on a scale from 1 (poor) to 4 (excellent), as well as their fitness to work on a scale from 1 (incapacitated) to 5 (full time employment) prior to RFA, immediately after treatment with RFA and at long-term FU. The antiarrhythmic drugs were listed in the questionnaire. All patients were contacted by telephone and given sufficient information to avoid any misinterpretation of the self-evaluation scores. A qualitative assessment of the patients' medical records was also performed. A 12-lead ECG recording was performed in patients who were able to sustain an outpatient examination, either in the ambulatory clinic at our hospital or at their local hospital. All follow-ups and ECG were conducted at long-term FU, 10 years after the RFA procedure.
Stec 2012[34]	Control Holter ECG monitoring > 4 weeks after ablation or prolonged pharmacological therapy as well as during the last follow-up visit. Patients were followed up at an outpatient clinic every 6–12 months or by telephone to assess their clinical status and current therapy.
Tsai 1997[35]	At 1 month, 2 months and then every 6 months after discharge from hospital. Long-term follow-up information was also obtained in all the patients from the referring physicians and through telephone interviews with the patients. Recurrences of VT after antiarrhythmic drugs or successful ablation were assessed by clinical symptoms, follow-up Holter recorder, cardiac event recorder, or repeated electrophysiological study

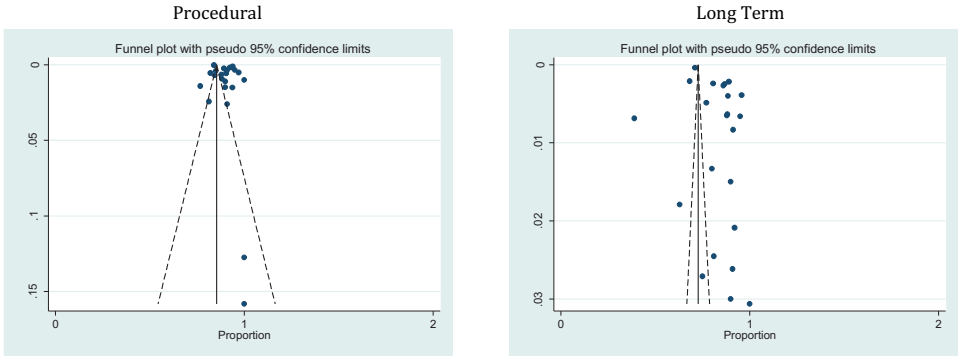
Supplementary table 2. *Follow-up method description of included studies (Continued)*

MAN studies:

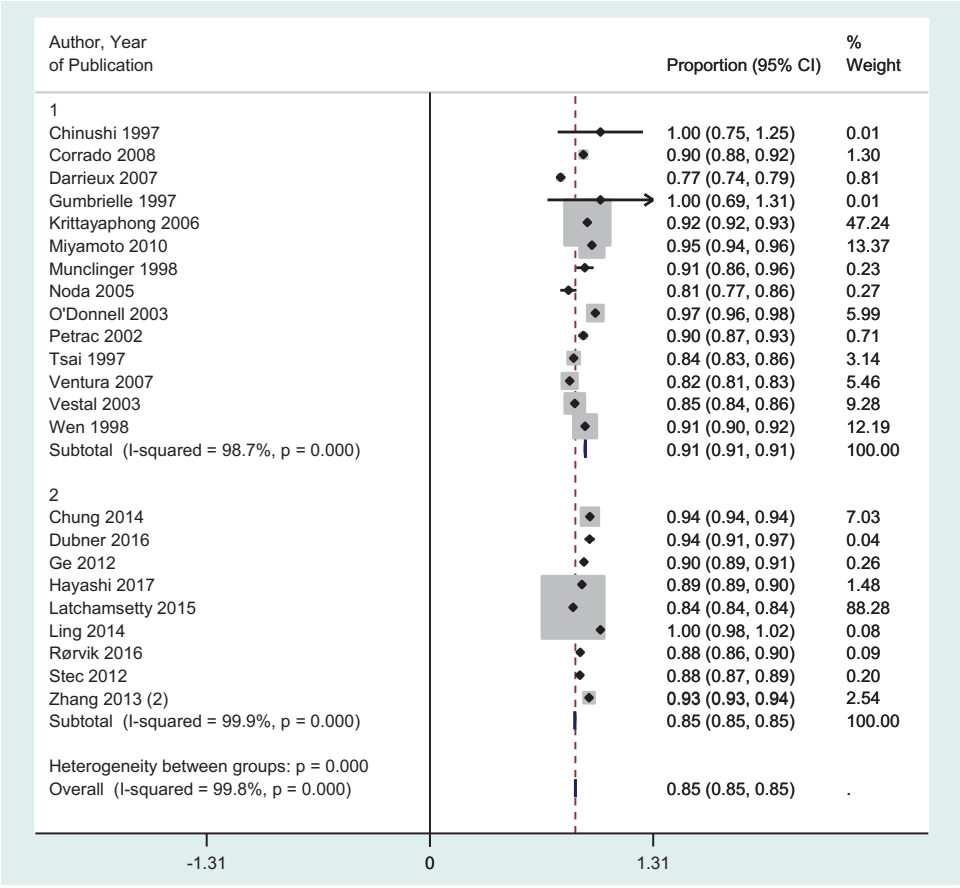
Publication	Follow-up Method
Ventura 2007[36]	All study patients were contacted over telephone and asked about the entire clinical history. When a patient was not reachable or died, relations or family physicians were inquired. All patients were invited to undergo a follow-up screening at the outpatient clinic including complete physical examination, 12-lead ECG, laboratory analysis, 24 h Holter recording, exercise testing, and transthoracic two-dimensional echocardiography. The follow-up assessment was aimed to compare parameters obtained at the time of the first diagnosis of RVOT-T and that of long-term follow-up. Patients, who could not be successfully invited to visit the institution, were encouraged to undergo a similar follow-up screening in another institution and to send to the medical reports. Thereafter, referring cardiologists were contacted in order to collect eventually lacking data.
Vestal 2003[37]	All patients were followed up regularly in the outpatient clinic in an antiarrhythmic drug-free state. Serial 24-hour ambulatory Holter monitoring, event recording, treadmill exercise test, and resting ECGs were performed during follow-up upon recognition of symptomatic recurrence and routinely 1 day, 1-2 months post ablation, and every 6 to12- month interval thereafter. Repeat electrophysiological study was performed on some patients with frequent symptoms in whom noninvasive diagnostic evaluation (serial resting, event recording and ambulatory ECGs and treadmill exercise) failed to document any arrhythmia
Wen 1998[38]	Electrocardiographic recording, 24-hour ambulatory Holter monitor, and treadmill exercise test were performed at the time of recurrent palpitation; otherwise, they were performed routinely 1 day, 1 to 2 months, and then at 3- to 6-month intervals after ablation. A follow-up electrophysiological study was conducted 2 months after ablation or thereafter in patients with an electrically inducible, isoproterenolol provocable or spontaneous recurrent VT who consented to a repeat study
Zhang 2013 (2)[39]	No antiarrhythmic agents were administered in the absence of arrhythmia recurrence. Patients had monthly clinic reviews for first 3 months and then 6-month follow-up, with a 12-lead ECG and 24-hour Holter monitoring performed at each visit

MNS studies:

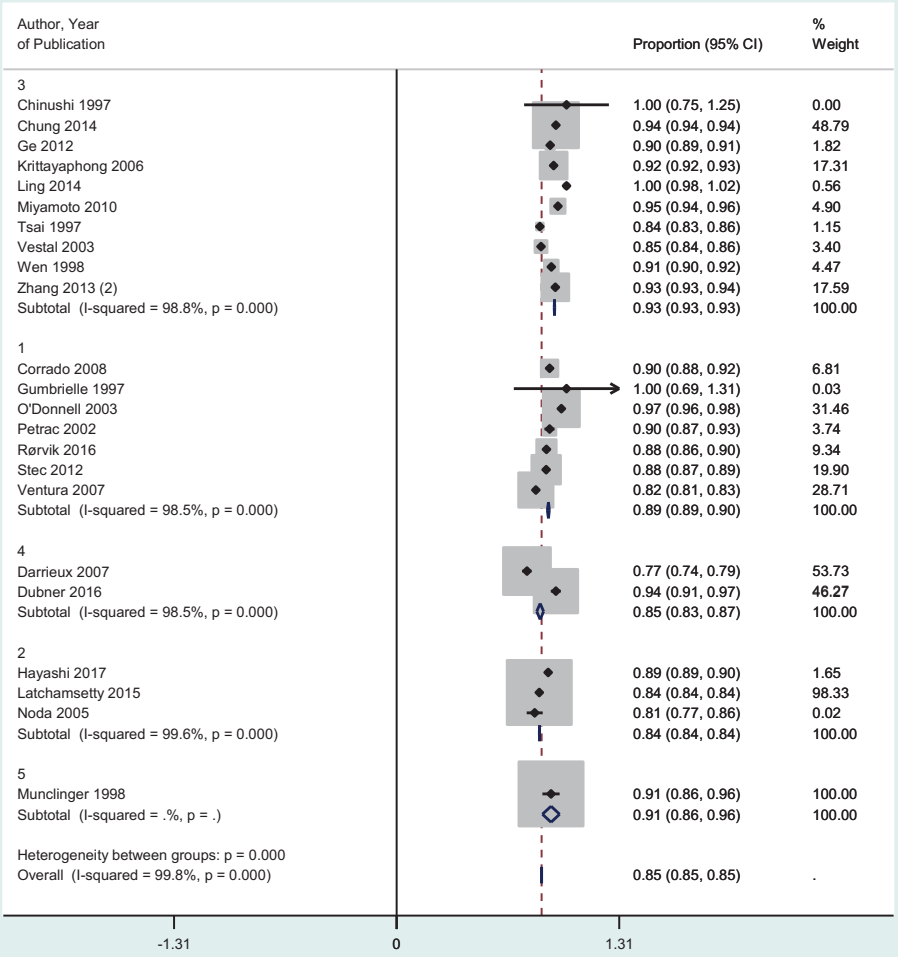
Publication	Follow-up Method
Kawamura 2016[40]	Every 3–6 months in an outpatient clinic after the ablation procedure. The follow-up 24-h Holter recording was performed within 6 months of ablation
Thornton 2006[41]	24-hour Holter ECG was recorded 6 weeks after ablation. All patients were followed clinically for at least 9 months after the procedure
Zhang 2013 (1)[42]	Antiarrhythmic medications were not restarted after ablation. All patients were reviewed monthly after the procedure for the first 3 months, followed by 6 monthly visits. During each clinic visit, a 12-lead ECG and 24-hour Holter monitoring were performed



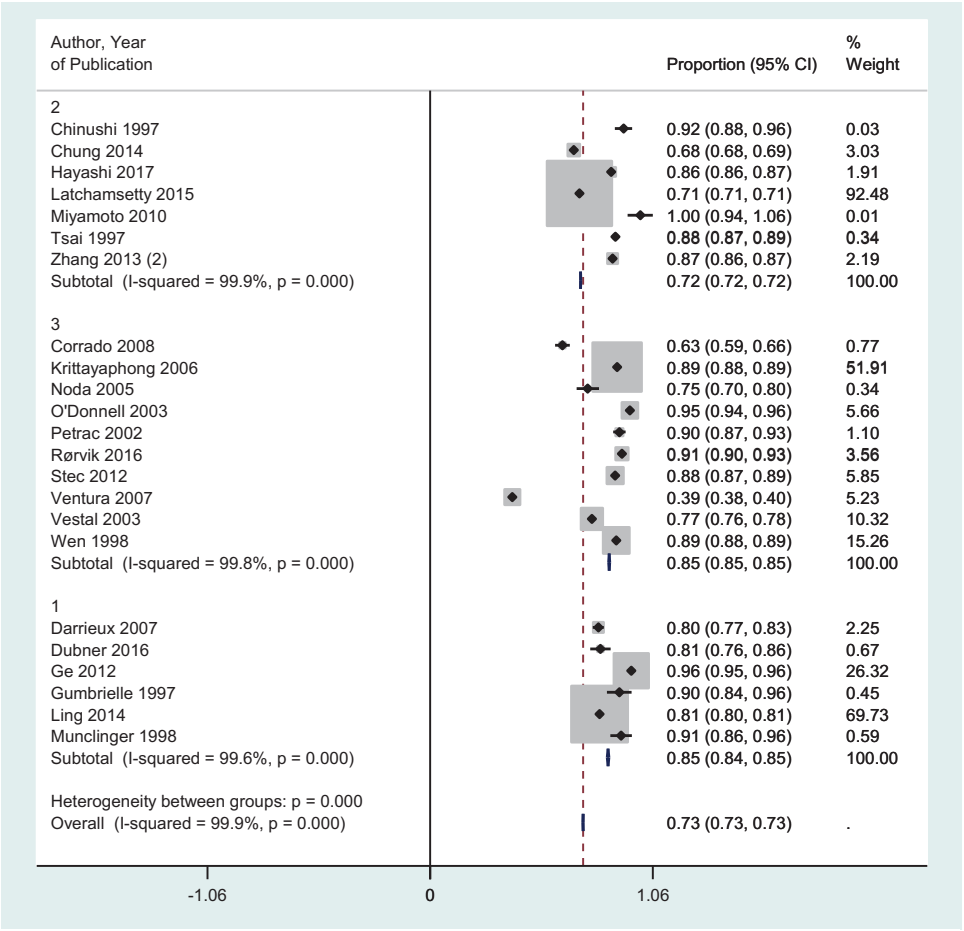
Supplementary figure 1. *Publication bias funnel plots*



Supplementary figure 2. *Sensitivity analysis forest plots of MAN studies (procedural success by year of publication)*
Categories: 1 = ≤ 2010; 2= ≥ 2011, p for heterogeneity = 0.31

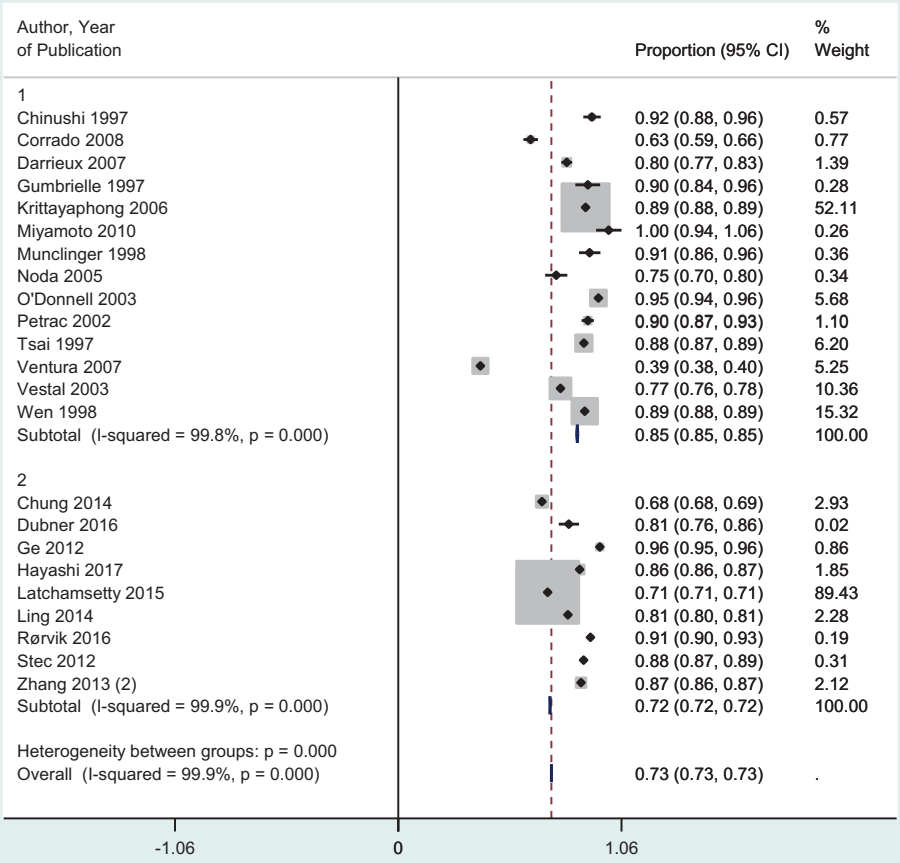


Supplementary figure 3. *Sensitivity analysis forest plots of MAN studies (procedural success by geographical location of study)*
Categories: 1 = Europe, 2 = USA, 3 = Asia, 4 = South America, 5 = Africa, p for heterogeneity = 0.016

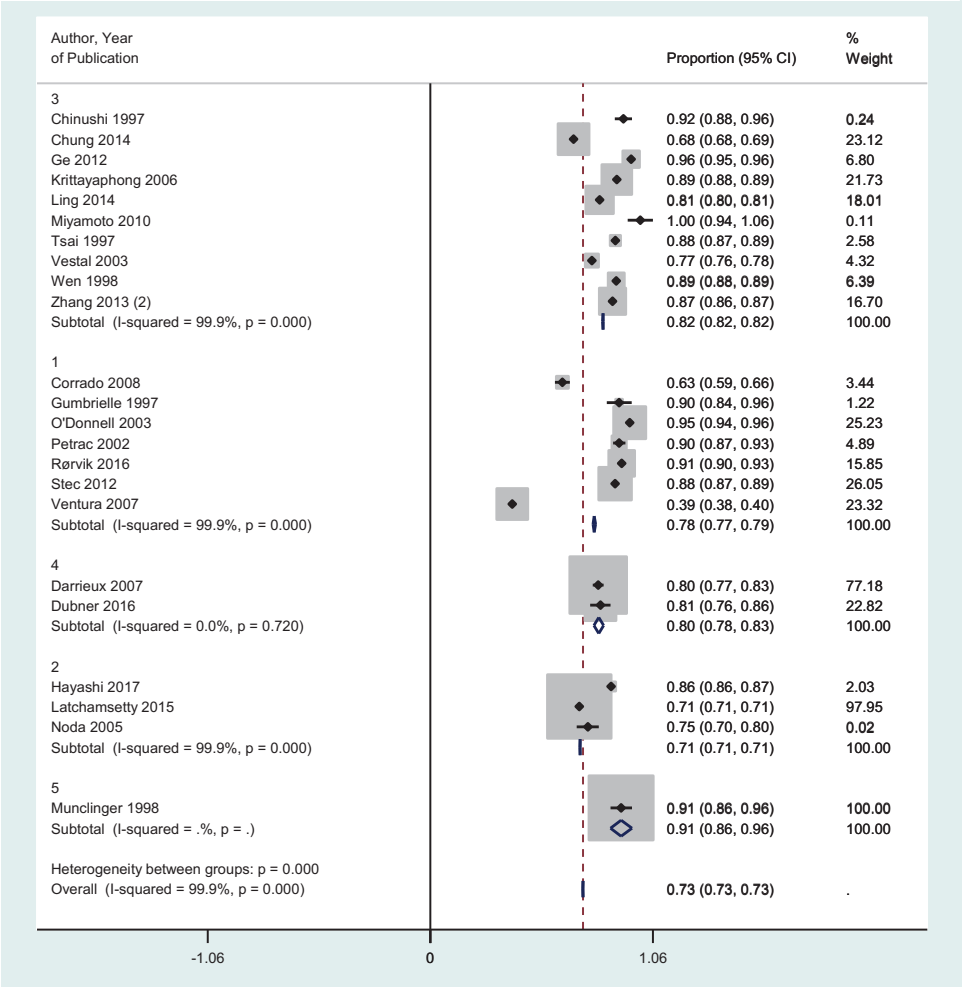


Supplementary figure 4. *Sensitivity analysis forest plots of MAN studies (long-term success by follow-up category)*

Categories: 1 = 12-20; 2 = 20-40; 3 = >40, p for heterogeneity = 0.40

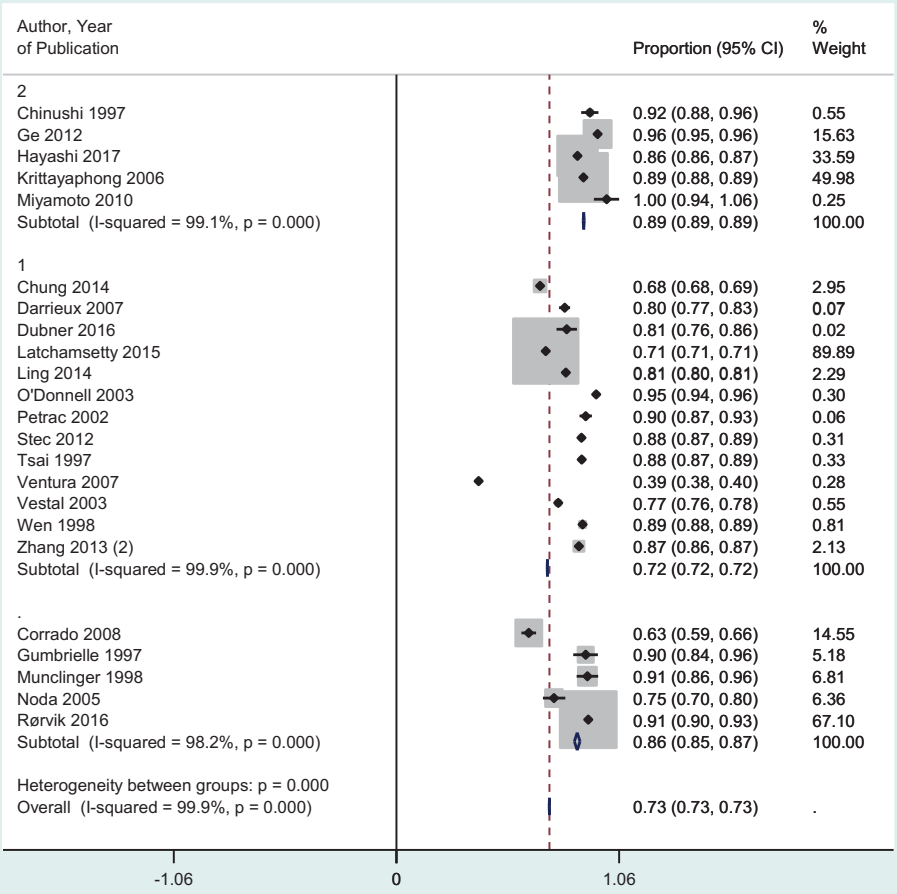


Supplementary figure 5. *Sensitivity analysis forest plots of MAN studies (long-term success by year of publication)*
Categories: 1 = ≤ 2010; 2= ≥ 2011, p for heterogeneity = 0.89



Supplementary figure 6. *Sensitivity analysis forest plots of MAN studies (long-term success by geographical location of study)*

Categories: 1 = Europe, 2 = USA, 3 = Asia, 4 = South America, 5 = Africa, p for heterogeneity = 0.58



Supplementary figure 7. *Sensitivity analysis forest plots of MAN studies (long-term success by follow-up method)*

Categories: 1 = FU with routine Holter; 2 = FU Holter only performed when symptoms reported, p for heterogeneity = 0.006

Chapter 12

Remote magnetic navigation versus manually controlled catheter ablation of right ventricular outflow tract ventricular arrhythmias: a retrospective study

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ABSTRACT

Background. Remote magnetic navigation (RMN) is an alternative to manual catheter control (MCC) radiofrequency ablation of right ventricular outflow tract (RVOT) arrhythmias. The data to support RMN approach is limited.

Objective. We aimed to investigate the clinical and procedural outcomes in a cohort of patients undergoing RVOT PVCs/VT ablation procedures using RMN vs. MCC.

Methods. Data was collected from two centers. 89 consecutive RVOT PVCs/VT ablation procedures were performed in 75 patients; RMN: 42 procedures and MCC: 47 procedures. CARTOXP™ or CARTO3 (Biosense Webster) was used for endocardial mapping in 19/42 (45%) in RMN group and 28/47 (60%) in MCC group; EnSite™ NavX™ (St. Jude Medical) was used in the rest of the cohort. Stereotaxis platform (Stereotaxis Inc, St. Louis, MO) was used for RMN approach.

Results. Procedural time was 113±53 min in the RMN group and 115±69 min in MCC (p=0.90). Total fluoroscopic time was 10.9±5.8 vs 20.5±13.8 (p<0.05) and total ablation energy application time 7.0±4.7 vs 11.9±16 (p=0.67) accordingly. There were 2 complications in RMN group and 5 in MCC (p=0.43). Acute procedural success rate was 80% in RMN vs 74% in MCC group (p=0.46). After a median follow up of 24 months (IQR 13-34), the success rate remained 55% in the RMN group and 53% in MCC (P=0.96).

Conclusion. RVOT arrhythmia ablations were performed using half of fluoroscopic times with Stereotaxis platform RMN compared to manual approach. Acute and chronic success rates as well as complication rates were not significantly different.

BACKGROUND

Catheter ablation of ventricular tachycardia or premature extra systole (VT/PES) originating from the right ventricular outflow tract (RVOT) has been emerging as an effective alternative to drug therapy[1-4]. Ablation of these arrhythmias requires high mapping precision. Mapping and ablation can be challenging for multiple reasons (difficult catheter manipulation, catheter induced arrhythmias, sporadic arrhythmia behavior) but nonetheless, a high rate of success in elimination of the arrhythmia was reported in several studies[1, 2, 5]. Remote magnetic navigation (RMN) has been introduced as an alternative to manual catheter control (MCC) ablations. This technology utilizes a magnetic field to manipulate specially designed ablation catheters. The catheter tip aligns with the magnetic vector produced by the system, allowing the operator to navigate the catheter from its distal tip. The RMN system also allows the operator to store the catheter location and reapply. RMN catheters are designed with greater flexibility than manual catheters and are not limited by fixed curves as manual catheters are. Thus, they may reach areas which are challenging such as the outflow tract. Ablation procedures using RMN navigations were shown to be effective and safe in arrhythmias such as atrial fibrillation[6, 7] and VT[8-10]. Studies in atrial flutter and SVT have shown that RMN is safe and feasible and decrease fluoroscopy exposure for both patients and operators [11] and radiofrequency times.
The aim of this study was to evaluate the clinical efficacy and safety of RVOT PVCs/VT ablation procedures using RMN vs. MCC. In addition, we compared the radiation, ablation and total procedural times between these technologies.

METHODS

Patient selection

The study retrospectively included consecutive ablation procedures of patients who had idiopathic RVOT PVCs or VT. The procedures were performed at Sunnybrook hospital (Toronto, Canada) and Erasmus Medical Center (Rotterdam, Netherlands) between November 2007 and July 2014. Patients who were found to have an arrhythmia that was originated in the left ventricular outflow tract, left ventricular or right ventricular body were excluded. Patients' characteristics and pre procedural data were retrieved from the patient files, 24-hour Holter monitoring and echo or magnetic resonance imaging (MRI) exams. Patients with known structural heart disease including coronary artery disease were excluded from the analysis. Respective local ethics boards had the study approved.

Procedure

Ablation procedures were performed using either RMN technology or manual approach according to the discretion of the operators. Endocardial mapping was performed using CARTOXP™ or CARTO3 (Biosense Webster) or with EnSite™ NavX™ (St. Jude Medical) system. Stereotaxis platform (Stereotaxis Inc, St. Louis, MO) was used for RMN approach. Total procedure time, total fluoroscopic time and total ablation time were compared between RMN and manual approach groups. The total ablation time was defined as the sum of times of each radiofrequency application. The rate of success was compared immediately post procedure and at follow up. Acute success was defined as the elimination of PVCs or VT during the procedure without the ability to reinduce. The amount and severity of procedure complications was compared between the two groups. Major complications were defined as tamponade, stroke or the need for a pacemaker. Minor complications were defined as groin hematoma, arterio-venous (AV) fistula, or minor conduction abnormalities.

Follow up

The data for long term success was retrieved from the patients' follow up visits records and 24-hour Holter monitoring. Long term success was defined as the lack of reported symptoms as well as PVC burden <2% on repeat Holter monitoring or lack of documented PVC/VT on repeat stress test for patients whose initial referral was due to PVC on exercise.

Statistics

Categorical variables were compared with the *chi*-squared test or Fisher's exact test. Continuous variables were compared using Student's t-test. Normality of distribution was assessed using Independent samples Kolmogorov-Smirnov test. Descriptive statistics are presented as mean ± SD for continuous variables if normally distributed (or otherwise as median with 25th and 75th percentiles, where appropriate). Statistical significance was defined as $P < 0.05$ (two-tailed).

RESULTS

Eighty nine procedures performed in 75 patients were included in the analysis. 42 procedures were performed using remote magnetic navigation and 47 using manual catheter control. Among the patients 45 were men and 44 women, and their mean age was 49±16. Patients' characteristics are presented in table 1. Holter results prior to the procedure were available in 57 cases (64%). PVC burden was 16±14 and 50

(56%) patients had documented VT. No significant difference was found between the groups. The indication for ablation was high PVC burden in 39 patients, VT in 50 patients and exercise induced PVCs/VT in 16 patients. Endocardial mapping using CARTOXP™ or CARTO3 (Biosense Webster) was performed in 19 procedures (45%) in RMN group and 28 (60%) in MCC group (p=0.18); EnSite™ NavX™ (St. Jude Medical) system was used in the rest of the cohort.

Table 1. *Patient characteristics*

	RMN (42)	MCC (47)	p-value
Age (years)	50±14	48±18	0.92
Gender (male/females)	21/21	24/23	0.92
Weight (kg)	80±14	79±18	0.99
Height (cm)	173±8	174±12	0.61
LVEF (%)	56±9	51±10	0.13
RVEF (%)	56±6	51±9	0.10
Syncope (%)	16 (38%)	14 (30%)	0.45
PVC burden (%)	18±9	15±14	0.58
Patients with stress induced PVC	9 (21%)	7 (15%)	0.42
Patients with VT (%)	26 (62%)	24 (51%)	0.65
Patients on BB/CCB (%)	28 (66%)	30 (63%)	0.6

Continuous variables are presented as mean±SD. Categorical variables as counts and percentage. RMN: Remote magnetic navigation. MCC: Manual catheter control. LVEF: Left ventricular ejection fraction. RVEF: Right ventricular ejection fraction. PVC: Premature ventricular complex. BB: beta blockers. CCB: Calcium channel blockers.

Table 2. *Procedure parameters and clinical outcomes*

	RMN (42)	MCC (47)	p-value
Carto/ESI	19/23	28/19	0.18
Total procedure time (min)	113±53	115±69	0.87
Ablation time (min)	7.0±4.7	11.9±16	0.67
Fluoroscopic time (min)	10.9±5.8	20.5±13.8	<0.05
Acute success (%)	34 (80%)	35 (74%)	0.46
Long term success (%)	23 (55%)	25 (53%)	0.96
Complications			
Total	2 (4%)	5 (10%)	0.46
Tamponade	0	2	
Right Bundle Branch Block	1	1	
Groin hematoma	1	1	
AV fistula	0	1	

Continuous variables are presented as mean±SD. Categorical variables as counts and percentage. AV block: Atrioventricular block. AV fistula: Arteriovenous fistula.

Mean procedural and clinical outcome is presented in table 2. Mean procedural time was 113±53 min in the RMN group and 115±69 min MCC (p=0. 87). Total fluoroscopic time was 10.9±5.8 min in RMN vs. 20.5±13.8 in MCC group (p<0.05). Total ablation energy application time was 7.0±4.7 min in RMN vs. 11.9±16 min in MCC (p=0.67). There were 2 major and 3 minor complications in the MCC group whereas in the RMN group there were 2 minor complications. (p=0.43) (Figure 1). Complications in the MCC group were two perforations, one AV fistula, one groin hematoma and one right bundle branch block (RBBB). In the RMN group there were one groin hematoma and one RBBB. Acute procedural success rate was 80% in RMN vs 74% in MCC group, (p=0.46) (Figure 1). Long term follow up of six months or longer was available for 79 of the 89 procedures. Median follow up time was 25 months (IQR 13-34). The success rate at follow up was 55% in the RMN group and 53% in MCC (P=0.96).

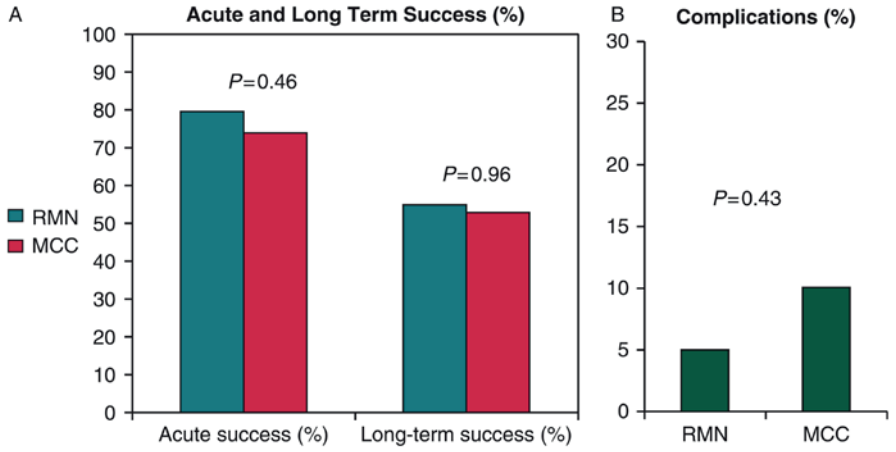

Figure 1. *A. Acute and long term success at median follow up of 25 (IQR 13-34) months. B. Complication rate in both groups.*

DISCUSSION

In this study we compared procedures using RMN technology to those performed with manual control in RVOT PVC/VT arrhythmia ablations. The main finding is that RMN ablation is as effective as manual ablation for RVOT PVCs, without increment in ablation or total procedural time. RMN allows reduction of fluoroscopy time, which was roughly half than that in the manual control group. No perforations occurred with RMN versus 2 in 47 manual procedures.

These results support those from a previously published randomized controlled study comparing these technologies in RVOT ablations[9]. RMN has some advantages over manual mapping and ablation of RVOT, namely easier catheter maneuvering and stability; it is less proarrhythmic and it is more precise in inner shell acquisition on 3D mapping system. A potential disadvantage of RMN may be limited contact force at the ablation site. The retrospective nature of the study does not allow us to look at any specific component of total procedural time and to characterize which of the above mentioned factors determined the total procedural time.

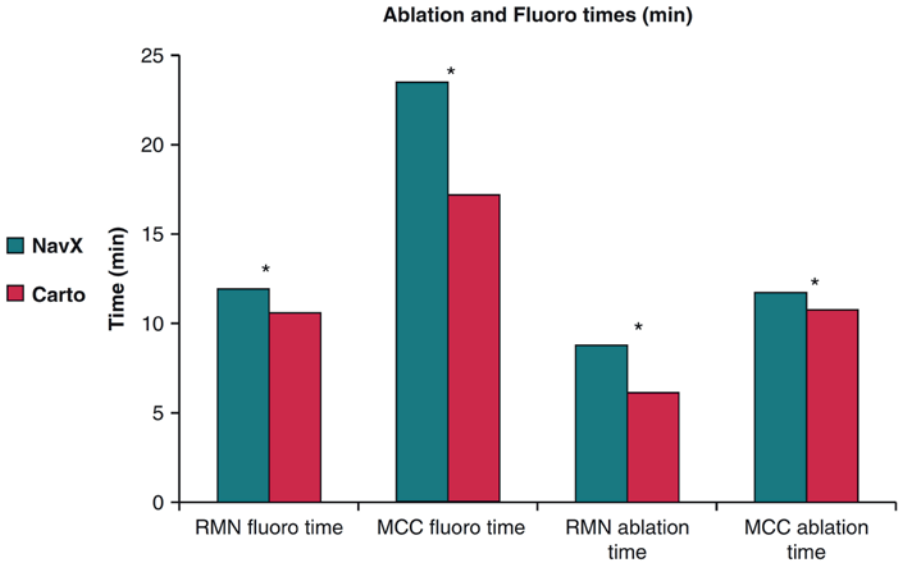

Figure 2. *Ablation and fluoroscopic times according to 3D system.*
** = non-significant.*

Why does radiation exposure for patients decrease using RMN technology? It was suggested that the reduction in fluoroscopic time may be due to operator perception that the soft tip is less likely to cause myocardial trauma, resulting in increased operator comfort in maneuvering the catheter without using continuous fluoroscopy. Furthermore, because of improved catheter stability, there may be less operator concern for catheter dislodgment, which may reduce the perceived need for fluoroscopy to confirm tip location during the ablation phase[12]. We compared the mean fluoroscopic time between the two groups by the year. We observed that in the last five years fluoroscopic times were decreasing over time in both groups likely due to more proficient 3D mapping systems use, but remained shorter in RMN group. We

compared the ablation and fluoroscopic times between the two 3D systems (figure 2) and found no statistically significant difference between these technologies. The acute success rate in our cohort was 80% and 74% in the RMN and manual control groups, respectively, and 55% and 53% of the patients were free of the arrhythmia in the long term. Together with other published data[8, 9] these results further support RMN as an efficient technology in comparison with manual control.

One of the greatest concerns in RVOT ablations is the risk of perforation due to its thin wall, resulting in tamponade or mediastinal bleeding. In our cohort two patients in the manual control group had perforations versus none in the RMN group. The catheters used when perforation occurred were manual irrigated non-contact force catheters. Although the difference in complication rate did not reach statistical difference, the lack of perforation using RMN in our cohort as well as in other studies adds to the accumulating data regarding the overall safety of this technology[10, 13, 14].

Limitations

Due to the retrospective nature of this study some biases are unavoidable such as different operators' experience. Due to lack of specific time measurements we could not adjust for left ventricular outflow tract mapping times.

CONCLUSIONS

Remote magnetic control navigation significantly reduces the fluoroscopy times in RVOT arrhythmias ablation procedures. Complication rate and acute and long term success are not significantly different from manual control approach.

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Chapter 13

The effect of intensified post-procedural follow-up on reported success rates in patients undergoing catheter ablation for idiopathic ventricular arrhythmias

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ABSTRACT

Background. Catheter ablation (CA) success of idiopathic ventricular arrhythmias (IVAs) is generally considered high. However, in the literature a wide range of procedural success rates are reported. The aim of this report was to analyze the influence of follow-up methodology on reported success rate by comparing standard follow-up based on the procedure reports with intensified follow-up utilizing continuous ECG monitoring.

Methods. We analyzed clinical data of 215 patients who underwent CA for IVAs. The following data were collected and compared: demographic data, acute procedural success (defined based on the reported procedural success), recurrences during admission and at 3 months after the procedure, and ablation techniques, locations and approaches. Intensified follow-up was defined as follow-up using continuous ECG monitoring during the full admission period, based on which the intensified post-procedural success rate was acquired. Mid-term success was assessed at 3 months after the procedure with 24-hour Holter registration. All parameters were additionally compared between the following subgroups: ablation techniques (manual vs contact force and magnetic navigated procedures), ablation location (RVOT vs LVOT and outflow tract vs other locations) and ablation approach (transseptal vs retrograde).

Results. Overall, the acute procedural success rate was 75%. Applying intensified follow-up resulted in a lower success rate (67%; $p < 0.05$). Mid-term success showed no further significant decline compared to intensified post-procedural success (63%). There were 11 patients (5%) without acute procedural success with mid-term success. Baseline characteristics did not differ between ablation technique groups, patients with LVOT ablations location were older compared to RVOT locations (54 ± 14 vs 46 ± 16 years; $p = 0.006$), more patients with a transseptal approach were on class I anti-arrhythmic drugs (AADs) compared to a retrograde approach (40% vs 5%; $p = 0.004$) and on class III AADs (60% vs 16%; $p = 0.02$). All success rates were equal between subgroups. Overall, intensified post-procedural success was a better prognostic parameter for mid-term success than acute success (AUC acute success 0.69 (95% CI: 0.62 - 0.76) vs. intensified post-procedural success 0.80 (95% CI: 0.73 - 0.86); $p = 0.004$).

Conclusion. Our data suggests that mainly relying on reported acute success as a guide for mid-term success will result in overestimation of the success of IVA CA procedures. We recommend an intensified in-hospital follow-up methodology with continuous ECG monitoring in order to accurately predict mid-term success of IVA CA.

INTRODUCTION

The success rate of catheter ablation (CA) of idiopathic ventricular arrhythmias (IVAs) is generally considered high[1]. Nevertheless, in the literature a wide range of procedural success rates of IVA ablation are reported, varying from 54% to 100%[2, 3]. This may in part be caused by actual differences in procedural success, that for instance may be dependent on the high variability of IVA ablation targets, some of which are easier to reach (e.g. the right ventricular outflow tract (RVOT)) than others (e.g. the aortic sinuses of Valsalva or epicardial locations)[1]. However, this variability may also be attributed to additional factors such as differences in the definition of ablation success and inadequate follow-up methods that may cause over-reporting of success rates. In most IVA CA studies procedure success is only assessed directly after the ablation procedure, without continuous ECG monitoring during post-procedure admission. The availability of continuous ECG monitoring during the full admission period, however, is important for detecting early (and sometimes asymptomatic) recurrences of IVAs after ablation. Another indirect indication that CA of IVAs in practice may not be as successful as is often reported in literature, is the fact that new ablation methods and techniques are still being developed[4-8]. This could be interpreted as a sign that the efficacy of the current ablation techniques is not completely satisfactory, especially for longer term CA outcome. The aim of this report was to compare standard follow-up (with success assessment directly after ablation, without continuous ECG monitoring during post-procedure admission: acute procedural success) with intensified follow-up (with success assessment after continuous ECG monitoring during post-procedure admission: intensified post-procedural success) of IVA CA and to analyze their relation to mid-term success (at 3 months, determined with 24-hour Holter registration).

METHODS

Patients

This registry included consecutive patients who underwent CA for IVAs in the Erasmus Medical Center between January 2008 and June 2017. A total of 215 patients were included. For all patients the index procedure was a first procedure. Pediatric patients were defined as younger than the age of 18 years. A medical ethical committee, the METC, approved data collection as a registry.

Ablation techniques and strategy

Techniques that were used for the included procedures involved manual radiofrequency (RF) and cryoablations (MAN), as well as contact force (CF) and magnetic navigated (MNS) RF ablations.

The procedures were performed in accordance with the institutionally approved local medical treatment protocols from the Erasmus Medical Center. We obtained informed consent from all patients before every ablation procedure. Within 48 hours post-procedure a 12-lead resting ECG, routine laboratory tests, a chest X-ray and 2-dimensional echocardiography were obtained from all patients, as part of our routine follow-up. Continuous ECG monitoring was performed during the entire admission period. In all patients routine peri-procedural medication protocols were followed. Antiarrhythmic drugs (except for amiodarone) were discontinued for a period of at least 4 half-lives prior to the planned ablation. If the procedure was successful, the use of antiarrhythmic drugs was not resumed. Ablations were performed during a fasting state with use of local or general anesthesia. At the discretion of the operator and as clinically indicated, market-approved diagnostic and ablation catheters were used. When left-sided access was appropriate, this was achieved either via the retrograde aortic route or transseptal puncture based on the preference of the operator and the exact location of the arrhythmia. Every ablation was guided by a 3-dimensional mapping system. Based on the operators' preference, the type of arrhythmia and the number of premature ventricular contractions (PVCs), the following mapping and ablation techniques were applied: activation-, voltage-, or pace-mapping and a combination of those. Programmed stimulation was performed for induction, using up to triple extra-stimuli pacing from the right ventricular apex, the RVOT or the left ventricle if necessary. Isoproterenol was dispensed in dosages ranging between 1.3 and 2.7 μg/min.

The first step of the procedure was usually creating an activation map, which was then followed by pace mapping (the site with a paced 12-lead QRS morphology identical to an inducible monomorphic VA was assumed to be the origin of that particular VA) for confirmation. There were no differences between ablation strategies in any of the applied techniques (i.e. manual RF- or cryoablation, CF and MNS ablation). Crossovers were excluded from this study. The definitions of endpoints of acute success were the following: if the VT was inducible, noninducibility was the endpoint; if only PVCs were present, then complete cessation of clinical PVCs or presence of <5 PVCs per hour from different locations was required.

Data collection and analysis

The following parameters were analyzed and compared: demographic data, acute procedural success (based on the conclusions in the procedural reports), recurrences during admission and at 3 months after the procedure, ablation techniques, approaches and locations. We defined standard follow-up as the assessment of success based on acute procedural success only. Intensified follow-up was performed using continuous ECG monitoring during the full admission period, based on which the intensified post-procedural success rate was acquired (defined as freedom of symptoms and arrhythmia during admission). Mid-term success was assessed at 3 months after the procedure and was defined as freedom of symptoms and arrhythmia on 24-hour Holter registration (Figure 1). These parameters were also analyzed for the following subgroups: ablation techniques (MAN, consisting of RF- and cryoablations, versus CF and MNS ablations), ablation locations (RVOT versus left ventricular outflow tract (LVOT) and outflow tracts (OTs) versus other locations) and ablation approach (transseptal versus retrograde aortic approached procedures).

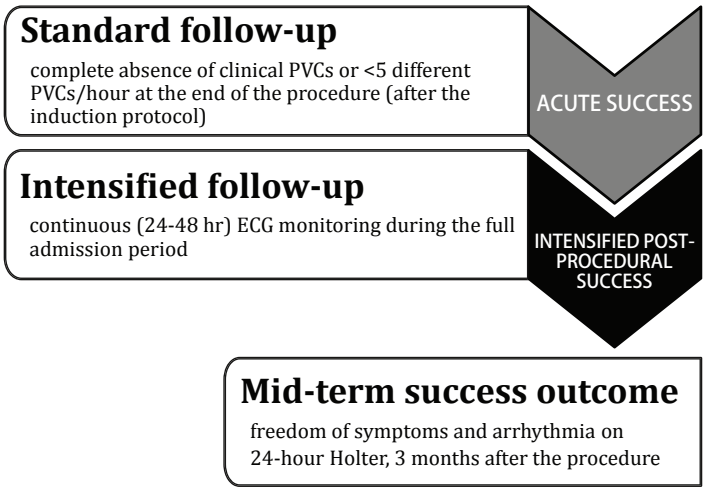

Figure 1. *Follow-up methodology definitions*

Statistics

The normality of distribution was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as mean ± SD for continuous variables if normally distributed, or otherwise as median with 25th and 75th percentiles, where appropriate. Data were compared by the independent t-test, or Mann-Whitney U test, as appropriate. Categorical data were expressed as percentages and compared with Fisher's exact

test or Cochrane's Q test, as appropriate. Statistical analysis was performed using SPSS version 21 (IBM Corp., Somers, NY). MedCalc Statistical Software version 17.6 (MedCalc Software bvba, Ostend, Belgium) was used for comparing the area under the curve (AUC) in receiver operating characteristic (ROC) curves using the Hanley and McNeil method for dependent groups[9]. Statistical significance was defined as $p < 0.05$ (two-tailed).

RESULTS

Patients

The overall and per ablation technique group baseline characteristics including age, gender distribution, number of pediatric patients and medication use are listed in Table 1. The demographics per ablation technique did not significantly differ (Table 1). The targets of ablation overall and per ablation technique are listed in Table 2.

Overall success results

Overall, the acute procedural success rate was 75%, the intensified post-procedural success rate 67% and the mid-term success rate 63% (Figure 2). Acute procedural success was significantly higher than both intensified post-procedural and mid-term success (Figure 2)($p = 0.02$ and 0.01, respectively).

Table 1. *Demographic data*

	Overall	MAN	CF	MNS	P-value
Total pts	215	53	56	106	
Patient age (y)	49 ± 16	48 ± 15	47 ± 18	51 ± 16	0.40
Sex (male)	108 (50%)	31 (59%)	28 (50%)	49 (46%)	0.35
Pediatric	14 (7%)	3 (6%)	6 (11%)	5 (5%)	0.33
Cryoablation	4 (2%)	4 (8%)	-	-	
ASA	29 (14%)	7 (13%)	10 (18%)	12 (11%)	0.51
Acenocoumarol	5 (2%)	2 (4%)	2 (4%)	1 (1%)	0.42
AADs:					
- Class I	19 (9%)	7 (13%)	6 (11%)	6 (6%)	0.25
- Beta blocker	87 (41%)	20 (38%)	22 (39%)	45 (43%)	0.83
- Class III	33 (15%)	8 (15%)	9 (16%)	16 (15%)	0.99
- Class IV	22 (10%)	5 (9%)	3 (5%)	14 (13%)	0.29
Digoxin	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0.22

Presented as mean ± SD or number and percentage in brackets. AADs; antiarrhythmic drugs, ASA; acetylsalicylic acid. P-values refer to between group (MAN, CF and MNS) comparisons.

Table 2. *Targets of ablation per subgroup*

Origin	Overall	MAN	CF	MNS
RVOT	118 (55%)	31 (59%)	37 (66%)	50 (47%)
LVOT	20 (9%)	5 (9%)	5 (9%)	10 (9%)
Papillary muscle	13 (6%)	1 (2%)	0 (0%)	4 (4%)
Fascicular	12 (6%)	2 (4%)	3 (5%)	7 (7%)
AMC	12 (6%)	2 (4%)	1 (2%)	2 (2%)
RV	8 (4%)	1 (2%)	1 (2%)	6 (6%)
LCC	5 (2%)	2 (4%)	4 (7%)	6 (6%)
Via CS	5 (2%)	2 (4%)	0 (0%)	2 (2%)
Moderator band	4 (2%)	1 (2%)	1 (2%)	0 (0%)
MV	4 (2%)	0 (0%)	1 (2%)	3 (3%)
Para-Hisian	3 (1%)	1 (2%)	0 (0%)	2 (2%)
RVOT+LVOT	3 (1%)	1 (2%)	1 (2%)	1 (1%)
RCC	3 (1%)	0 (0%)	0 (0%)	3 (3%)
LV	2 (1%)	3 (6%)	2 (4%)	8 (8%)
RVOT+LCC or NCC	2 (1%)	0 (0%)	0 (0%)	2 (2%)
Fascicular+RVOT	1 (1%)	1 (2%)	0 (0%)	0 (0%)

MAN = manual; CF = contact force; MNS = magnetic navigated; RVOT = right ventricular outflow tract; LVOT = left ventricular outflow tract; LCC = left coronary cusp; LV = left ventricle; AMC = aorto-mitral continuity; CS = coronary sinus; RV = right ventricle; MV = mitral valve; RCC = right coronary cusp; NCC = non-coronary cusp.

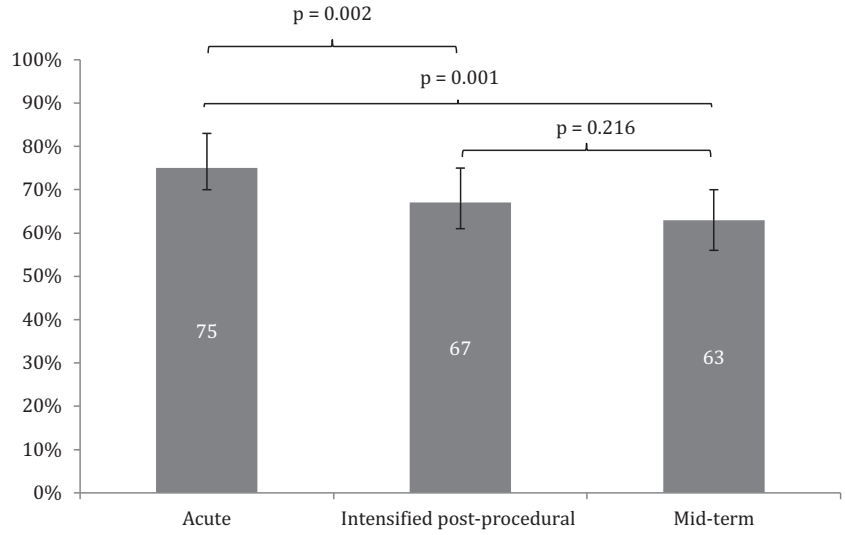

Figure 2. *Overall ablation success rates*

Overall ablation success rates with 95% confidence intervals. Overall: p < 0.001.

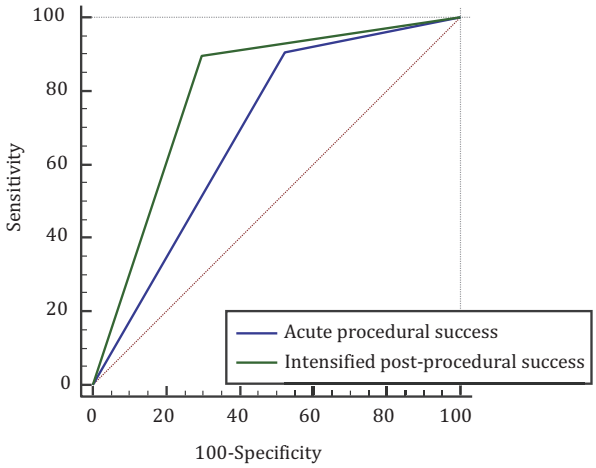

Figure 3. *ROC curves of overall acute- and intensified post-procedural success*

Discriminating power for mid-term success of acute and intensified post-procedural success, expressed as the AUC of the ROC curves: AUC acute success 0.69 (95% CI: 0.62 - 0.76) vs. intensified post-procedural success 0.80 (95% CI: 0.73 - 0.86); p < 0.004.

Table 3. *Contingency table acute vs. mid-term success*

		Mid-term success		
		No	**Yes**	**Total**
Acute success	No	32	11	43
	Yes	35	105	140
	Total	67	116	183

Sensitivity: 90.5% Specificity: 47.8% Positive predictive value: 75% Negative predictive value: 74.4%

Table 4. *Contingency table intensified post-procedural vs. mid-term success*

		Mid-term success		
		No	**Yes**	**Total**
Intensified post-procedural success	No	47	12	59
	Yes	20	104	124
	Total	67	116	183

Sensitivity: 89.7% Specificity: 70.1% Positive predictive value: 83.9% Negative predictive value: 89.7%

With an AUC of 0.69 (95% CI: 0.62 – 0.76), overall acute procedural success was a poorly discriminating parameter for mid-term success. The AUC of 0.80 (95% CI: 0.73 – 0.86) for overall intensified post-procedural success indicates that its discriminating power for mid-term success was good, moreover, it was significantly

better than overall acute procedural success (p = 0.004)(Figure 3). In the contingency tables (Table 3 and 4) sensitivity, specificity and other characteristics for acute and intensified post-procedural success vs. mid-term success are listed.

Subgroup results

Ablation techniques

Figure 4 shows the success rates per ablation technique, where no significant differences were found.

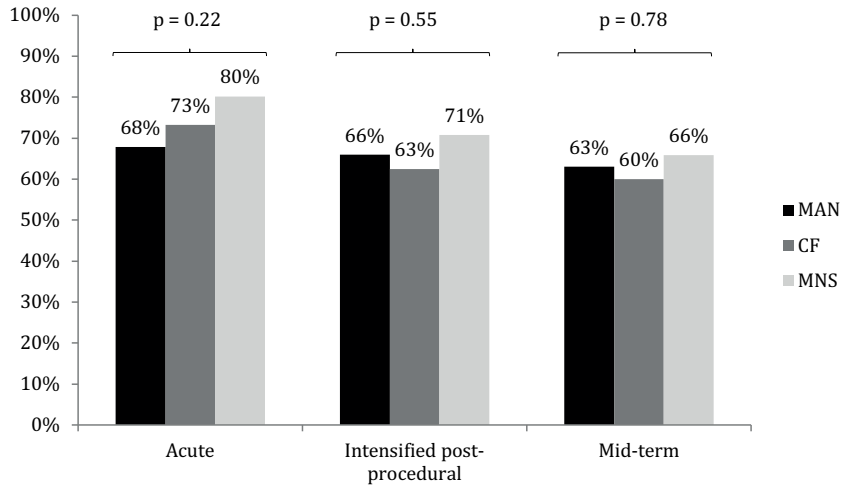

Figure 4. *Success rates per ablation technique*
MAN = manual; CF = contact force; MNS = magnetic navigated

When analyzed per ablation technique, the intensified post-procedural success was only better in discriminating for mid-term success in the CF group (AUC acute success: 0.67 (95% CI: 0.53 - 0.79) vs. intensified post-procedural success: 0.86 (95% CI: 0.74 - 0.94); p = 0.008). For the MAN group this was: 0.73 (95% CI: 0.57 – 0.85) vs. 0.76 (95% CI: 0.61 – 0.87); p = 0.34, and for the MNS group: 0.69 (95% CI: 0.58 – 0.78) vs. 0.78 (95% CI: 0.67 – 0.86); p = 0.19.
For the analysis of the following subgroups procedures with multiple ablation targets were not included (including 3 RVOT + LVOT procedures, 1 RVOT + left coronary cusp procedure, 1 RVOT + non-coronary cusp procedure and 1 fascicular + RVOT procedure).

RVOT versus LVOT ablation locations

There were 119 procedures targeting the RVOT and 40 targeting the LVOT. Patients with LVOT ablations location were older compared to RVOT locations (54 ± 14 vs 46 ± 16 years, respectively; p = 0.006). Success rates did not significantly differ for RVOT versus LVOT ablation locations (acute success 79% vs 73%; p = 0.40, intensified post-procedural success 71% vs 70%; p = 0.86 and mid-term success 69% vs 58%; p = 0.23). The LVOT group included coronary cusp and aorto-mitral continuity ablation locations.

OTs versus other ablation locations

Baseline characteristics did not differ between the groups. Success rates did not significantly differ for OT (n=158) versus other ablation locations (n=52)(acute success 77% vs 75%; p = 0.74, intensified post-procedural success 71% vs 62%; p = 0.21 and mid-term success 66% vs 61%; p = 0.52).

Transseptal versus retrograde aortic approach

For left sided ablations 5 procedures were performed with a transseptal approach and 62 procedures with a retrograde aortic approach. More patients with a transseptal approach were on class I anti-arrhythmic drugs (AADs) compared to patients with a retrograde aortic approach (40% vs 5%; p = 0.004) and on class III AADs (60% vs 16%; p = 0.02). Success rates did not significantly differ for transseptal or retrograde approach (acute success 100% vs 74%; p = 0.36, intensified post-procedural success 80% vs 68%; p = 0.67 and mid-term success 60% vs 58%; p = 0.97).

Delayed success

There were 11 (5%) patients without acute success who did have mid-term success. Four of them were in the MAN group (8% of group), 3 in the CF group (5% of group) and also 4 were in the MNS group (4% of group)(p = 0.46). Of these 11 patients, 3 had intensified post-procedural success (27% of delayed success group). Seven were ablated in the RVOT (64% of delayed success group), 2 in the LVOT (18%), 1 in both RVOT and LVOT (9%) and 1 in the epicardial aspect of the outflow region via the coronary sinus (CS) (9%).

DISCUSSION

The main finding of this study is that if intra-admission follow-up for IVA CA is performed without continuous ECG monitoring, thus relying on acute success as a

guide for mid-term success, this will result in overestimation of the success of the procedure.

Factors of success rate variability

As we pointed out earlier a wide range of success rates of IVA CA is reported in literature, even though success rates are generally thought to be high[1]. In this report we focus on the discrepancy between acute-, intensified post-procedural- and mid-term success and the role of follow-up methodology as a source of this variability. There are several factors in measuring ablation success that may introduce bias.

Firstly, the success of an ablation procedure may be determined at different time intervals: (i) immediately after the procedure with the patient still on the operating table, (ii) after the full admission period for the ablation procedure or (iii) 3 months after the procedure. It seems obvious that the more time passes between the ablation and the determination of the success of the procedure, the higher the chance a recurrence will have occurred. Additionally, factors such as ablation scar edema may affect the occurrence of recurrences by masking ablation lesions that will later on prove insufficient when the edema has dissolved, which is one of the reasons for the "blanking period" after atrial fibrillation ablation[10].

Secondly, the method of success determination may differ. For acute success different stimulation protocols may be followed with varying intensity or length (also dependent on the operator), for establishing post-procedural admission success only single ECGs or alternatively continuous ECG monitoring may be used and for mid-term success 24-hour Holter may or may not be performed. Early recurrences during admission may be missed without continuous ECG monitoring (especially when asymptomatic), likewise for later recurrences at mid-term success determination if no Holter is performed. In our center, a very strict definition is used for determination of PVC ablation success (as described in the methods section).

These differences in success definitions and follow-up methods ensure that acute success rates reported in literature are often not suitable for comparison and may cause overestimation of the actual success of the procedure. In an analysis of the literature, we found that in only 14% of studies on IVA CA, intensified follow-up was the method that was used.

Another explanation for the success rate variability that needs to be considered is the role of the arrhythmia location. This role is twofold: firstly some locations are harder to reach than others which can make ablation of these areas more challenging (for example in applying enough contact force), secondly some locations may be too close to vulnerable structures thus preventing thorough ablation because of fear of complications. The threshold for an unfavorable risk-benefit ratio may especially

be lower for IVA ablations compared to other types of VA considering its generally benign prognosis. Interestingly, in our study we found no differences in success rate for different locations.

Predictors of early recurrence

In the current study we show that overall, intensified post-procedural success is a better prognostic parameter for predicting mid-term success than acute success. Because intensified post-procedural success incorporates early intra-admission recurrences recorded with continuous ECG monitoring, the use of this parameter will provide a more reliable estimation of the actual success of the procedure at mid-term.

Subgroups

Although intensified post-procedural success was shown to be a better discriminating parameter for mid-term success overall, when we analyzed this per ablation technique the only significant difference we found was in the CF group, similarly in favor of intensified post-procedural success. Seeing as though we did not find a statistically significant difference in discriminating power in our largest group, the MNS procedures (even though numerically there was a difference), the overall results should be interpreted with some caution.

In this report the acute success rate of MNS ablations was statistically not significantly higher than in the two other ablation technique subgroups (MNS 80%, MAN 68% and CF 73%, MNS vs MAN; $p = 0.09$). This may be caused by the relatively small (in statistical terms) group of patients included in this study, although for IVA study populations the current study size is considered very decent. A higher success rate has previously been shown compared to MAN ablation in other studies[11, 12]. The reason for this may be one of the following characteristics of the magnetic navigation system. It has been suggested before that the tip delivery (the maneuverability of the catheter tip) with MNS is superior to that of manual ablation[11, 12]. This may be caused by the ability to position the catheter more accurately due to its flexible nature, eliminating the need for preformed catheter curves[13-15]. Another feature of MNS which may allow for more effective ablation is the possibility of re-navigating to magnetic vectors stored during the procedure, making it easier to relocate areas of interest[15].

As mentioned earlier, interestingly enough we found no differences in ablation success rates between RVOT and LVOT locations, even though in literature RVOT ablations are considered more effective[1]. We also found no differences when

comparing OT versus other ablation locations. A possible explanation could be that the operators are more experienced with challenging ablation locations because of the higher number of these procedures performed in our center. Also, a large part of procedures is performed with MNS, which as explained earlier may provide better tip-delivery.

Additionally, we found no differences in success rates between procedures with transseptal versus retrograde aortic approaches for left sided ablations, although it has to be taken into consideration that the number of transseptal procedures was very low. Nevertheless, these similar success rates between approaches may also be explained by our comprehensive experience with transseptal procedures and transseptal puncture methods[16].

An interesting group, and certainly not negligible (comprising 5% of all patients in this study), are the patients with so-called "delayed success". These patients underwent an unsuccessful procedure, but nevertheless proved to be free of symptoms and arrhythmias at mid-term follow-up. This may illustrate well the sometimes elusive source of certain IVAs and may also be an indication that even nowadays there is still a lack of understanding of some of the underlying mechanisms of this arrhythmia.

Limitations of the study

Because this study is not a randomized trial but a retrospective registry, bias that usually accompanies this study design may apply. However, patients were included consecutively per ablation technique group in compensation of the non-randomized nature of this study. Although the total number of patients is relatively small in statistical terms, this sample size for an IVA population is considered very decent and thus, in our opinion, warrants clinical significance.

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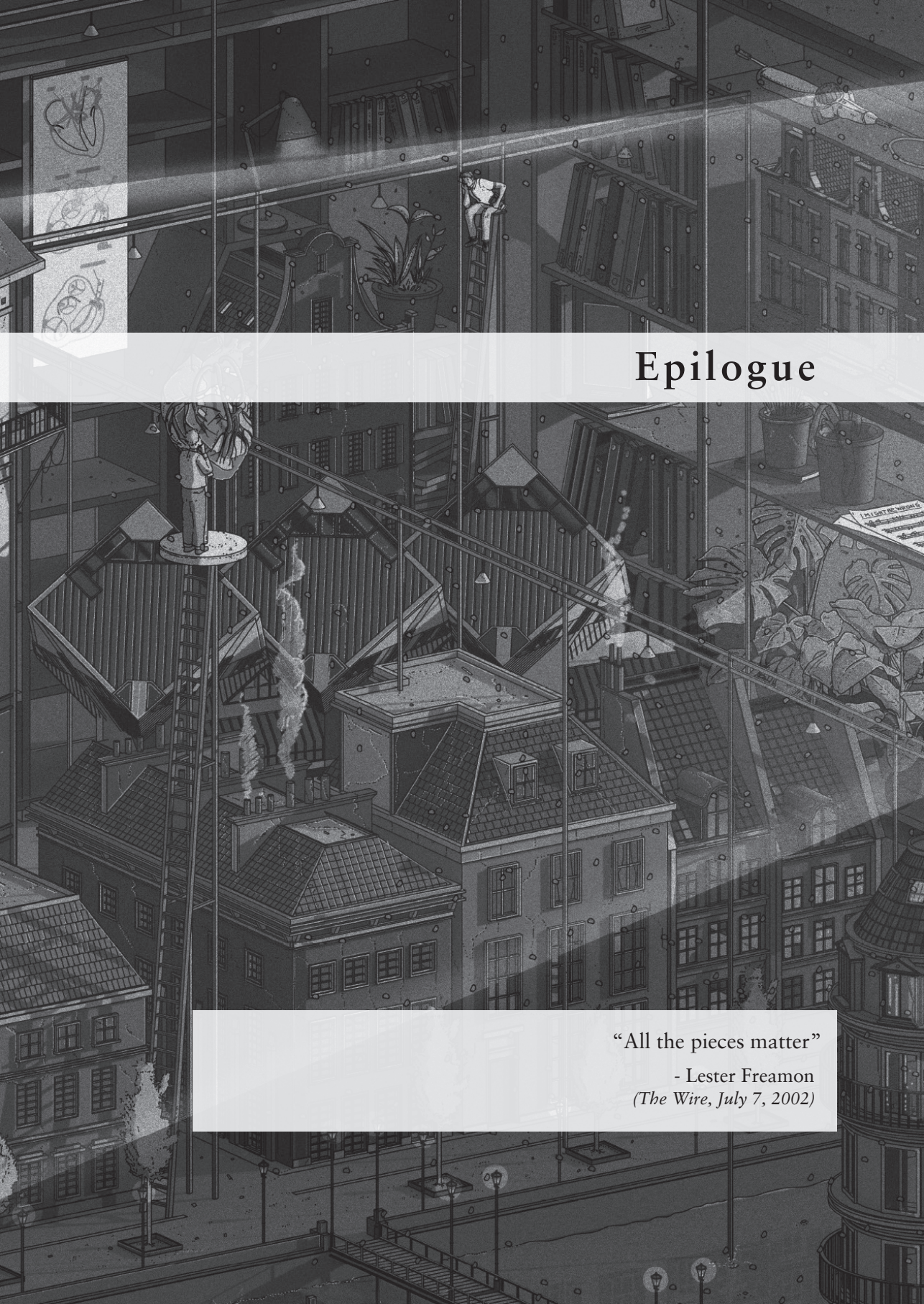

Epilogue

"All the pieces matter"

- Lester Freamon
(The Wire, July 7, 2002)

SUMMARY AND GENERAL DISCUSSION

Since idiopathic ventricular arrhythmias (IVAs) were first described in 1922[1], the implementation of IVA therapies has always preceded our understanding of the underlying arrhythmia mechanism. It took until 1986 before a mechanism of the most common subgroup of IVAs (the outflow tract (OT) IVAs) was proposed, *i.e.* triggered activity[2]. In the meantime anti-arrhythmic drug therapy was the mainstay for IVA treatment, although it never proved fully curative and has always posed the issue of significant side-effects. Alternatively, invasive treatment strategies were being developed that have evolved from extensive surgical treatment (ventricular aneurysmectomy and coronary bypass grafting) of drug-resistant ventricular arrhythmias (VAs) of ischemic origin in the 70's[3], via direct current (DC) trans-catheter ablation (CA) of both ischemic and idiopathic VAs in the 80's[4], finally to radiofrequency (RF) CA of IVAs in the 90's[5] and present. Currently, varying success rates of between 54% and 100%[6, 7] for IVA RF CA are reported in the literature. Interestingly enough, although OT IVAs have been classified into the triggered activity arrhythmia mechanism for over two decades now, unequivocal evidence for this classification still has not been established. When compared to the overwhelming success of the introduction of CA into the treatment of AV-nodal re-entry tachycardias (AVNRT) and Wolff-Parkinson-White (WPW) syndrome (showing consistent CA success rates of >95%)[8-11], of all the arrhythmias the two of which the underlying mechanism is most completely understood, the broad range in reported IVA CA success rates suggests that the current treatment strategies still fail to directly target the actual underlying cause of this arrhythmia.
In this thesis we aimed to investigate and clarify the fundamental mechanisms behind IVAs, with an emphasis on OT IVAs, and to gain new insights into their treatment.

Part I: Etiology of Idiopathic Ventricular Arrhythmias

To acquire a better understanding of OT IVAs and to consider alternative fundamental precipitating factors it could be of relevance to return to the basics of cardiac and cardiac conduction system development. Therefore, in the first part of this thesis, we attempted to understand these mechanisms from the context of the embryological development of the heart and the cardiac conduction system. In Chapter 1, we took a closer look at a proposed mechanism involving the so-called dead-end tract (an embryonic conduction branch) from this perspective by providing a comprehensive overview and summary of the most relevant publications regarding this subject. Additionally, we related this overview to several compelling clinical findings from the literature. Interestingly enough, we found that several studies

reported persistence of embryonic remnants of the conduction system. Moreover, we found several pathological studies demonstrating the dead-end tract as a known anatomical entity and linking this structure to the OT region[12]. Remnants of the developing conduction system have previously been linked to the manifestation of arrhythmias[13]. The clinical findings we summarized indicate that a possible association between this tract and the occurrence of OT IVAs should be considered. The importance of our findings lies in the identification of a possible anatomical substrate for OT IVAs, potentially enabling direct targeting and improvement of CA outcomes. As a response to this study, Anderson et al. published an editorial comment in which they discuss the relevance of our hypothesis and endorse our conclusions[14].

Informed by our previous findings, in Chapter 2 we aimed to evaluate the presence of the aforementioned hypothesized connection between atrial and OT tissue by way of pacing and capturing (sending and receiving) signals between these two regions. In patients undergoing CA for OT IVAs we performed pacing maneuvers around the atrioventricular annuli and analyzed if this resulted in precipitance of IVAs from the OT. In the patients included in this case presentation this was indeed achieved. The fact that pacing around the atrioventricular annuli subsequently led to the initiation of a corresponding OT PVC suggests that a connection between these two anatomically (and "electrically") distant regions is in place, possibly in the form of certain preferential pathways. This study further substantiates our assumptions on the involvement of the dead-end tract in OT IVA initiation, by serving as one of these preferential pathways between the atria and the OTs. When this connection is excited, the activation front might be able to "leak out" towards the OTs, and exit there in the form of an OT PVC. The importance of these findings lies in the fact that they show it may be necessary to re-evaluate our current approach of OT IVA CA. It could for example be beneficial to extend our mapping strategies into the atria, enabling identification and ablation of the entry sites of these preferential pathways.

Part II: New Perspectives on Idiopathic Ventricular Arrhythmia Mechanisms

After first establishing that there may be a gap-of-knowledge regarding the underlying arrhythmia mechanisms of IVAs, the next logical step was to explore new insights and perspectives on these precipitating factors. Therefore, in the second part of this thesis we focused on several clinical findings that shed a new light on the underlying causes of IVAs. The collated findings in the case series presented in Chapter 3 represent the first of several clinical observations that illustrate a possible connection between the OT region and a "higher up" region at the level of the atria, which in these cases was brought to light by a co-existing accessory pathway (AP).

In this study we showed 5 cases in which OT IVAs disappeared simultaneously after CA of an anatomically distant AP. This suggests that a connection between these regions was severed, leading to interruption of the arrhythmia circuit. When taking into account our knowledge on the course of the dead-end tract, we hypothesized that this rudimental conduction bundle may play a role in OT IVA initiation in these cases. This is the first publication suggesting a clinically relevant role of the persisting dead-end tract in relation to OT IVA precipitation.

This clinical relevance is further explored in Chapter 4, in which we set out to analyze the value of the presence of discrete prepotentials (DPPs) during OT IVA CA and the association with short and long-term procedural outcomes. We hypothesized that these DPPs that are seen during electrophysiological study and ablation may represent conduction through the dead-end tract, considering their conduction-tissue like electrophysiological properties and localization. DPPs were seen in 38% of patients undergoing OT IVA CA and their presence was associated with a significantly higher recurrence rate (70% versus 19% in patients without DPPs). An explanation for this higher rate could be that in these cases the dead-end tract is the precipitating source of the arrhythmia and that because of its concealed anatomical location it is more difficult to completely eradicate this IVA substrate. This study affirms that alternative CA strategies should be considered when treating patients with IVAs that present with DPPs.

A different perspective on OT IVA precipitance entirely, is covered in Chapter 5. As is the case for other arrhythmias, it should be noted that certain extrinsic factors may also take part in the initiation of OT IVAs. The main examples of such factors of which we know they play role include certain medications or excessive use of alcohol, caffeine or tobacco. In this study we showed that in two patients the use of medicinal melatonin (the pineal hormone that is responsible for modulating circadian rhythms) was also associated with the occurrence of OT IVAs that terminated after complete cessation of melatonin. This is the first documentation of a correlation between the use of medicinal melatonin and the occurrence of OT IVAs. Although the exact mechanisms through which melatonin exerts its influence on several bodily structures is incompletely understood, we hypothesized by way of a comprehensive summary and analysis of the literature that an unbalance between the direct effects (modulation of the Ca^{2+}-handling machinery through melatonin receptors present in cardiac tissue) and indirect effects (*e.g.* alleviation of "sleep-deprivation-induced arrhythmias", paradoxical reduction of deeper sleep, reduction of sympathetic tone, anti-oxidant activity) of melatonin on the heart may lead to OT IVA development. A cause for this unbalance may be found in the broad interindividual range in bioavailability of melatonin, differences in melatonin concentration per medical

preparation or in genetic variance in melatonin receptor expression. Our findings show that the use of medicinal melatonin should be added to the list of extrinsic factors initiating OT IVAs in order to create higher awareness among physicians and patients, especially in countries where melatonin is available without prescription. This is particularly important when considering that the use of medicinal melatonin has increased significantly in the past 5 years (more than doubled in the US and Scandinavian countries[15, 16]). Additionally, our observations should instigate further exploration of IVA precipitating factors and their underlying mechanisms. Through preventing the need for CA simply by discontinuing melatonin in these patients, a cost reduction as well as an increase in safety of IVA treatment can be accomplished.
A final viewpoint on alternative underlying arrhythmia mechanisms of IVAs was explored in Chapter 6. Here we analyzed and compared the variability of the distance between the onset of the preceding sinus QRS and that of the premature ventricular contraction (PVC), the coupling interval (CI), in different underlying cardiac pathologies. The variability of the CIs is dependent on the underlying arrhythmia mechanism and could therefore assist in gaining insights into these mechanisms. We compared CIs of idiopathic, non-ischemic dilated cardiomyopathy (NIDCM) and familial dilated cardiomyopathy (lamin A/C or phospholamban mutations; PLN/LMNA) related PVCs to a control group of post-myocardial infarction (MI) PVCs because of their known low CI variability on account of a well-known underlying re-entry mechanism. We found low variability of PVC CIs in the idiopathic and NIDCM group and high variability in the PLN/LMNA group. This suggest that re-entry or triggered activity are likely mechanisms for PVCs in the idiopathic and NIDCM groups and unlikely for the PLN/LMNA group. In this group abnormal automaticity or modulated parasystole are more likely mechanisms. These findings could potentially provide physicians with a non-invasive method to clarify the underlying arrhythmia mechanism before selecting an appropriate treatment strategy.

Part III: How to Overcome Therapeutic Challenges in the Treatment of Idiopathic Ventricular Arrhythmias

After evaluating the etiology and alternative underlying mechanisms of IVAs, it is important not to overlook the impact of this arrhythmia on the patient. Additionally, we have to ask ourselves the question: how can we achieve better treatment outcomes and higher procedural safety? In the final part of this thesis we try to address these questions and provide some answers and solutions.
Because the prognosis of IVAs is usually favorable and some patients can be nearly asymptomatic, the fact that in certain cases IVAs can take a more malignant course

is often disregarded. In Chapter 7 we emphasize the more malignant characteristics of some forms of IVAs in a comprehensive review of the literature. Moreover, we bring to attention that frequent IVAs can be highly symptomatic and may lead to a reduction in quality of life and can potentially lead to heart failure due to cardiac muscle overload. The importance of excluding any underlying cardiac disorder associated with IVAs is also underlined. Finally, this overview points out several red flags to reckon with when dealing with OT IVAs: a previous medical history of syncope, very fast IVAs (>230 bpm) or PVCs with very short CIs.

Because comparative data between different CA modalities are sparse for IVA ablations, in Chapter 8 we set out to compare the clinical outcomes of conventional manual CA (MAN), contact force (CF) sensing CA (the latest development in manual CA) and magnetic navigated CA (MNS) (where the catheter is controlled remotely by the operator from the adjacent control room). This is the first study comparing the long-term clinical outcome of OT IVA ablation between MAN, CF and MNS CA. We found equal procedural and long-term success rates for all CA techniques, however, a more favorable safety profile was found for the MNS group due to the shorter fluoroscopy time. The shorter fluoroscopy time compared to MAN and CF ablation can be explained by the fact that the operator is more confident of the catheter position inside the heart due to more accurate maps, easy navigation to predefined locations of interest and the fact that it is very unlikely to cause a perforation due to the flexible nature of the MNS catheter. These findings show that MNS combines equal efficacy with enhanced safety for ablation of OT IVA. An emphasis on procedural safety is especially important when treating usually non-lethal afflictions such as OT IVA, where the ratio of treatment benefit versus treatment risk needs to be weighed extra carefully. Therefore, MNS might be particularly useful for treating IVAs.

The advantages of MNS ablation are further explored in the context of VA treatment in Chapter 9, where we consider the place of MNS in daily practice and put the advantages in perspective with the high equipment costs and the initial learning curve for operators. After a brief comprehensive overview of the available literature, we surmise that aside from the enhanced procedural safety, treatment efficacy may also be increased by the improved “tip delivery” (the maneuverability of the catheter tip) that is achieved with MNS, while “lesion delivery” (radiofrequency lesion formation) remains equal compared to MAN ablation. The future developments discussed in this chapter could prove pivotal in assuring that MNS ablation will definitively be favorable over MAN ablation of VAs. In its full future capacity, MNS may have the potential to revolutionize VA therapy and could be essential for attaining long-term success.

In Chapter 10, in an effort to further detail the newest developments in the field of MAN CA, we presented an overview of the relevant literature regarding contact force (CF) ablation in the context of atrial fibrillation (AF). The studies we discussed in this review showed that the use of CF sensing catheters may lead to a reduction of fluoroscopy time, increased procedural safety and a better clinical outcome for AF ablation. These outcomes were achieved by better lesion formation due to higher applied average CF and more constant catheter-tissue contact and by lower incidence of perforations due to increased CF awareness among operators through the availability of real-time CF information during the procedure. This review of the literature should create awareness and increase knowledge among physicians about all the various aspects involved in optimal lesion formation, the newest developments and future perspectives regarding MAN CA and should encourage the execution of more comparative studies between the different available CA techniques.

On account of the lack of comparative studies between MAN and MNS CA of OT IVAs, we performed a systematic review and meta-analysis described in Chapter 11. We compared the short-term, >1-year clinical outcomes and influencing factors in an analysis of a total of 26 OT IVA CA studies (23 MAN and 3 MNS studies). This is the first study presenting an overview of all available studies analyzing and/or comparing clinical outcome of MAN and MNS ablation of OT IVAs only, thus providing a very homogenous patient comparison. We found that clinical outcome was equal, that the complication rate was low for both techniques and that the success rates reported in the literature are generally high (although we also describe a significant publication bias, showing studies reporting negative results are underrepresented). Interestingly, we also found that the study's geographical location affects the short-term success rate and that the follow-up methodology (whether or not 24-hour Holter monitoring was performed during routine follow-up) influenced the >1-year results. The influence of follow-up methodology could indicate that in a significant amount of studies reported long-term success rates are an overestimation and additionally shows that a routinely performed Holter during follow-up is important in order not to miss asymptomatic VAs that might still have the potential to either lead to deterioration of left ventricular function or in select cases to malignant VTs[17, 18]. Because of the lack of high quality and highly powered comparative studies, this chapter provides physicians with a valuable contemporary oversight of the literature assisting them in clinical decision making in this rapidly growing group of patients.

In Chapter 12 we confirm previous hypotheses and clinical findings regarding MNS ablation, in a comparison of MAN and MNS CA of RVOT IVAs (the most common subgroup of IVAs[19]). In this retrospective comparison of MAN and MNS RVOT

IVA ablation we found a marked decrease in x-ray exposure (as much as an 58% reduction) in favor of MNS, while preserving equal complication- and success rates. The decrease in x-ray exposure in patients is most likely explained by two factors: (i) the perception of the operator that the soft tip is less likely to cause myocardial trauma results in increased operator comfort in maneuvering the catheter without using continuous fluoroscopy. Moreover (ii), because of improved catheter stability, there may be less concern for catheter dislodgment, which likely reduces the perceived need for fluoroscopy to confirm tip location during the ablation. Our findings also showed that these advantages over MAN CA remained after the introduction of more proficient 3D mapping systems. The lack of perforations during CA when using MNS in this study, as well as in others, adds to the growing evidence for the overall enhanced safety of this technique.

In the final chapter of this thesis, Chapter 13, we highlighted the large range in reported success rates of IVA ablation and drew attention to the discrepancy between the different definitions of ablation success used in literature. In 215 patients who underwent CA for IVA we analyzed the influence of follow-up methodology on the success rate of the procedure by comparing the success rate after standard follow-up ("acute procedural success": based on the conclusions in the procedural reports, without continuous ECG monitoring during the admission period), to the success rate established after an intensified follow-up strategy ("intensified post-procedural success": freedom of symptoms and arrhythmia during admission assessed by continuous ECG monitoring during the full admission period) and related both these rates to the "mid-term success" assessed at 3 months after the procedure (defined as freedom of symptoms and arrhythmia on 24-hour Holter registration). We found that the overall acute procedural success rate was 75% and that applying intensified follow-up resulted in a significantly lower success rate (67%). Mid-term success showed no further significant decline compared to intensified post-procedural success (63%). Intensified post-procedural success was a better prognostic tool than acute procedural success for anticipating mid-term success. These findings are most likely explained by early recurrences occurring during admission that may be missed when continuous ECG monitoring is not performed (particularly if the patient is asymptomatic) and confirm our previous notions regarding the influence of follow-up methodology on success rates stated in chapter 12. Therefore, we caution that relying on acute procedural success as a guide for mid-term success will result in overestimation of the actual success of the ablation procedure and recommend the use of an intensified follow-up strategy instead. Finally, our data suggest that a more uniform definition of IVA CA success is needed to enable reliable assessment and comparison of true acute success rates between studies.

Conclusions and future perspectives

In conclusion, this thesis adds several fundamental puzzle pieces necessary to complete the full picture of the idiopathic outflow tract ventricular arrhythmia conundrum.

In short, we can state that (1) the cyclic adenosine monophosphate (cAMP) mediated delayed afterdepolarization (DAD) triggered activity mechanism may not fully envelop the OT IVA etiology based on the limitations of the deductive reasoning that led to this categorization, the absence of a satisfying explanation for the occurrence of these DADs in the first place, and based on the confinement of this arrhythmia specifically to the OT region (as opposed to other triggered activity arrhythmias). We may also state that (2), the origin of IVAs in this specific location may merely represent an exit/breakout site of emerging (and possibly branching) preferential pathways, after which the preserved nodal-tissue-like electrical properties of the OTs enable arrhythmogenesis. The concept of branching preferential pathways emerging in the OTs is supported by the finding that often multiple distinct PVC morphologies exist in OT IVAs, which in turn could explain a phenomenon that is often seen during OT IVA ablation; when elimination of one PVC morphology (*i.e.* exit site) based on earliest activation during mapping gives rise to another distinct type of ventricular ectopy that also seems to originate in the OT area but possesses a slightly different ECG morphology (*i.e.* utilizing other possible exit sites in the vicinity of the previously ablated site). Furthermore (3), we can state that these preferential pathways may have an entry site in the atria based on the finding of simultaneous disappearance of OT PVCs after accessory pathway ablation remotely from the PVC origin, the presence of sleeves of nodal-type tissue both around the tricuspid and the mitral annuli, the relatively frequent co-existence of AVNRTs and OT IVAs and the finding that atrial stimulation is capable of reliably and reproducibly evoking OT PVCs with a morphology almost identical to the clinical PVCs. Finally (4), we can state that a persisting dead-end tract (a rudimentary conduction bundle) might represent the underlying anatomical basis for one of these preferential pathways, forming a connection between the atrial tissue and the OTs. This is supported, among other things, by its anatomical course differentiating from the main conduction axis subsequently aligning the OTs and by the regularly observed thermal sensitivity (or: "warm-up" phenomenon) during ablation of OT IVAs and the presence of conduction-tissue-like potentials, both suggestive for involvement of conduction tissue in the precipitance of this arrhythmia.

In order to let all the pieces fall into place, continuing expansion of our knowledge regarding this arrhythmia in the future is crucial.

The first step towards a modernized therapeutic strategy for IVAs should be to synchronize our understanding of the arrhythmia mechanism with our current knowledge of treatment strategies and techniques. The sooner we will be able to directly target the underlying cause of this arrhythmia, the sooner we will be able to increase the efficacy of the current therapeutic strategies. In order to reach this goal, it is essential to re-evaluate the current dogmas regarding OT IVA etiology. Therefore, more basic research is needed regarding the arrhythmia mechanism and the precipitating factors of IVAs.

Optical mapping, a technique where voltage-sensitive dyes enable precise visualization of excitation wave propagation using a special photodetector, may provide researchers with a method to visualize dead-end tract/preferential pathway conduction in the whole heart in vivo[20, 21]. This could give us valuable information on the course of the dead-end tract and may be used to visualize preferential pathway conduction between atrial tissue and the OTs.

As discussed in Chapter 5 of this thesis, sympathetic activity has been proposed to play a role in the development of ventricular arrhythmias. Furthermore, a relationship between the sympathovagal balance and initiation of IVAs from the RVOT in patients without structural heart disease has previously been demonstrated[22]. This relationship could be further explored using noninvasive imaging of cardiac sympathetic innervation, which can be achieved with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy[23]. With this technique it would be possible to determine the expression of sympathetic innervation in the outflow tracts in patients with IVAs and compare this to a control group, to further clarify the role of sympathetic activity in this arrhythmia.

Furthermore, a large pathological study of structurally normal hearts from (young) adults could provide insights into the prevalence and exact course of a persisting dead-end tract or other preferential pathways. This would assist physicians in assessing the epidemiological scale of dead-end tract/preferential pathway associated OT IVAs and in creating a suitable and targeted treatment strategy for this arrhythmia.

In addition to this, we hypothesize that there may be a possibility to non-invasively assess the chance of a successful IVA CA for individual patients, by using signal averaged ECG (SAECG) to detect discrete pre-systolic potentials. As described in this thesis the presence of these potentials during CA, a possible indicator of conduction over a preferential pathway, are associated with a higher recurrence and repeat procedure rate after ablation. By using SAECG it may be possible to detect these potentials when the patient first presents on the outpatient clinic, before initiation of therapy, thus providing the physician with more tools to determine an early direction for the treatment strategy.

Finally, evolution of the currently available ablation techniques and strategies will be necessary to assist in increasing the efficacy and safety of IVA CA. Alternative strategies may include extending our mapping efforts into the atria in order to identify and target the "entry sites" of preferential pathways as described in Chapter 2 of this thesis, and targeting of discrete presystolic potentials during catheter ablation as shown in Chapter 4. Innovations regarding the formation of optimal ablation lesions and combined parameters that include information on catheter-tissue contact force and real-time visualization of lesion formation will provide operators with the necessary tools for a modernized approach to IVA catheter ablation.

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DUTCH SUMMARY | NEDERLANDSE SAMENVATTING

Idiopathische ventriculaire aritmieën, of: kamerritmestoornissen waarvan de oorzaak niet bekend is, zijn een veelvoorkomende kwaal in de algemene bevolking. Het betreft een overkoepelende term voor alle kamerritmestoornissen, met uitzondering van kamerfibrilleren of flutter, die voorkomen bij mensen met een ogenschijnlijk structureel normaal hart. In de meeste gevallen bevindt de bron van de ritmestoornis zich ergens in de uitmonding van ofwel de rechter- danwel de linker ventrikel, ook wel de "outflow tracts" genaamd. Bij vrijwel iedereen komen deze overwegend goedaardige ritmestoornissen weleens voor, weliswaar in verschillende mate. De hoeveelheid klachten die men hiervan kan ervaren varieert. Zowel mensen met zeer frequente, als mensen met relatief sporadische hartkloppingen kunnen hiervan een hoge ziektelast ervaren. Ook al heeft deze ritmestoornis meestal een gunstige prognose, een enkele keer kan het voorkomen dat deze maligne van karakter is doordat andere, wél levensbedreigende ritmestoornissen kunnen worden geïnitieerd. Tevens kan bij mensen met zeer frequente idiopathische hartritmestoornissen de hartspier zodanig worden belast dat zich op basis hiervan hartfalen ontwikkelt.
Gezien de bovengenoemde redenen is het van belang om in aanmerking te nemen dat er voor deze ritmestoornis verschillende behandelingen bestaan. De belangrijkste en tevens enige praktisch curatieve is katheter ablatie. Deze behandeling houdt in dat met een katheter die via een van de (slag)aders in de lies in het hart wordt gebracht, door middel van verhitting door radiofrequente energie de bron van de ritmestoornis gecontroleerd wordt weggebrand. Volledige genezing door zowel medicatie als katheter ablatie valt en staat echter bij het achterhalen van het mechanisme, de locatie en de oorzaak van deze aritmie, welke tot op heden onvoldoende wordt begrepen.
De doelstelling van dit proefschrift is als volgt samen te vatten: het ophelderen van de onderliggende oorzaken achter idiopathische ventriculaire aritmieën en het verkrijgen van nieuwe inzichten in haar behandeling.

Deel I: Observaties op de Etiologie van Idiopathische Ventriculaire Aritmieën

In het eerste deel van dit proefschrift richten wij ons op de etiologie van deze ritmestoornis en proberen we om onder andere vanuit het perspectief van de embryologische ontwikkeling van het hart en het geleidingssysteem enkele mogelijke oorzaken te belichten.
In Hoofdstuk 1 beschrijven we aan de hand van de embryologische ontwikkeling van het hart en het geleidingssysteem wat de mogelijke rol is van de zogenaamde "dead-end tract" bij het ontstaan van deze ritmestoornis en hebben wij de huidige

kennis over deze rudimentaire geleidingsbundel samengevat. Tevens schetsen we de mogelijke klinische implicaties van de aanwezigheid en het volharden van deze bundel. De “dead-end tract” werd als eerst beschreven in een publicatie uit 1985, waarin werd omschreven hoe deze geleidingsbundel zich vanuit de splitsing van de linker- en rechter bundeltak voortzet en zodoende de directe continuering vormt van de hoofd-geleidingsas. Uit deze en andere publicaties blijkt het verdere verloop van deze bundel richting de eerder genoemde “outflow tracts”, waar deze uiteindelijk uitdooft rond de oorsprong van de aorta. Hoewel wordt aangenomen dat deze bundel normaliter verdwijnt na de kinderleeftijd (op basis van de afwezigheid ervan in een pathologische studie van 15 harten van individuen in verschillende leeftijdscategorieën) zou de lokalisatie en de aanwezigheid van deze bundel op (jong) volwassen leeftijd een verklaring kunnen vormen voor het ontstaan van de betreffende ritmestoornis. Daarnaast beschrijven we enkele andere bevindingen uit de literatuur die verdere aanwijzingen vormen voor een verband met deze bundel, zoals de associatie tussen idiopathische “outflow tract” kamerritmestoornissen en de aanwezigheid van atrioventriculaire re-entry tachycardieën (wat een mogelijke connectie suggereert tussen deze twee anatomisch verafgelegen regio’s, mogelijk in de vorm van de “dead-end tract” gezien haar locatie), de aanwezigheid van zogenaamde pre-systolische potentialen tijdens katheter ablatie van “outflow tract” aritmieën (mogelijk afkomstig van de “dead-end tract”) en de aanwezigheid van een deltagolf-vormig QRS complex van sommige idiopathische kamerritmestoornissen (mogelijk wijzend op een vertraagde geleiding door de “dead-end tract”). Gezien de prominente plek die idiopathische kamerritmestoornissen tegenwoordig innemen in het elektrofysiologisch lab, concluderen we dat verheldering van het eigenlijke substraat hiervan, één die welllicht direct zou kunnen worden getarget, een verbetering teweeg zou kunnen brengen van de tot nu toe behaalde ablatie uitkomsten.

In Hoofdstuk 2 gaan we over op het actief opsporen en aantonen van de eerder beschreven mogelijke verbinding tussen de “outflow tracts” en de “dead-end tract”. Dit doen we door bij een serie patiënten die katheter ablatie ondergaan wegens idiopathische kamerritmestoornissen, een elektrisch signaal te verzenden vanuit één regio (rond de atrioventriculaire annuli) en deze proberen te registreren in de “outflow tracts” om zodoende een verbinding tussen deze twee anatomisch ver uiteenliggende regio’s aan te tonen. Als er na de gegeven impuls reproduceerbaar en met een constante tijdsinterval een ritmestoornis (of een enkele zogenaamde premature ventriculaire contractie (PVC)) ontstaat die morfologisch afkomstig lijkt uit de “outflow tracts”, wat bij deze patiënten daadwerkelijk werd bewerkstelligd, weten we dat er inderdaad een verbinding is tussen deze gebieden. Het belang van deze bevindingen is, naast het aantonen van een verbinding op zich, dat ze er op

wijzen dat het wellicht nodig is om de gebruikelijke ablatie methoden te herevalueren en om bijvoorbeeld onze mapping strategieën uit te breiden naar de atria om daar de mogelijke "entry site" van de betrokken verbinding(en) op te sporen om zodoende een meer efficiënte behandeling van deze aritmie te kunnen realiseren.

Deel II: Nieuwe Inzichten in de Mechanismen achter Idiopathische Ventriculaire Aritmieën

In het vervolg van dit proefschrift gaat onze aandacht uit naar het mechanisme achter idiopathische "outflow tract" kamerritmestoornissen. We bespreken hier verschillende klinische bevindingen die een nieuw licht werpen op de mogelijke onderliggende oorzaken.

In Hoofdstuk 3 beschrijven we een verzameling unieke klinische bevindingen in een serie patiënten afkomstig uit verschillende internationale ziekenhuizen. De zes beschreven patiënten lieten allen een combinatie van idiopathische aritmieën zien met daarbij de aanwezigheid van een zogenaamde accessoire bundel (een extra geleidende verbinding tussen de atria en ventrikels). Bij katheter ablatie van de accessoire bundel bleek dat bij 5 van de 6 patiënten gelijktijdig ook de kamerritmestoornissen verdwenen. Bij deze 5 patiënten waren de aritmieën afkomstig uit de rechter ventrikel "outflow tract", bij de andere patiënt was dit niet het geval. In de discussie van dit hoofdstuk brengen we deze observaties in verband met de eerder genoemde klinische bevindingen uit de literatuur en tonen we de mogelijke associatie met de aanwezigheid van de "dead-end tract". We illustreren hoe deze rudimentaire bundel mogelijk een verbinding vormt tussen de "outflow tracts" en de accessoire bundel: via de accessoire bundel bereikt het elektrische signaal mogelijk de "dead-end tract", welke op haar beurt de nabijgelegen "outflow tract" prikkelt aldus leidend tot de idiopathische kamerritmestoornissen. Onze hypothese is dat in het geval van ablatie van de accessoire bundel deze connectie wordt verbroken, waarna de kamerritmestoornissen verdwijnen. Dit is de eerste publicatie die de mogelijke klinische relevantie van een persisterende "dead-end tract" illustreert met betrekking tot het initiëren van "outflow tract" aritmieën.

Hoofdstuk 4 beschrijft de observatie dat tijdens elektrofysiologische studies van "outflow tract" kamerritmestoornissen vaak een zogenaamd pre-systolische potentiaal, zoals ook eerder benoemd in Deel I van dit proefschrift, wordt gezien ter plaatse van het ablatie target. Bij 26 patiënten die "outflow tract" ablatie ondergingen keken we naar de aanwezigheid van deze pre-systolische potentiaal en de uitkomst van de ablatie procedure. In 38% van de gevallen werd een potentiaal gedetecteerd. Een significant groter deel van de patiënten bij wie een dergelijk potentiaal werd gezien kreeg later opnieuw ritmestoornissen en moest opnieuw worden behandeld

vergeleken met de patiënten bij wie dit potentiaal niet werd gezien. We beschrijven hier de morfologie van het pre-systolische potentiaal en hoe deze verband houdt met de mogelijke etiologie en de associatie met het geleidingssysteem. Uiteindelijk concluderen we dat deze potentialen tijdens ablatie van "outflow tract" aritmieën vaak voorkomen en dat de aanwezigheid hiervan is geassocieerd met een hoger aantal terugkerende aritmieën. Tevens is de morfologie van de potentiaal suggestief voor een origine in het geleidingssysteem en op basis van de locatie mogelijk de eerder beschreven "dead-end tract". Dit zou op zijn beurt weer een verklaring kunnen zijn voor het hogere aantal terugkerende aritmieën, omdat praktisch gezien het eigenlijke substraat van de aritmie (de "dead-end tract") niet is behandeld, maar alleen het "exit point" van de aritmie.

Een heel ander mechanisme voor het ontstaan van idiopathische kamerritmestoornissen komt in Hoofdstuk 5 aan bod, waarin we voor het eerst een associatie tussen het gebruik van het pijnappelklierhormoon melatonine (normaal gesproken van invloed op verschillende licht gereguleerde slaap-waakcycli in het lichaam) en deze ritmestoornis beschrijven. We presenteren twee patiënten die beiden regelmatige "outflow tract" kamerritmestoornissen hadden, die na het staken van melatonine geheel zijn verdwenen. De verschillende in de literatuur beschreven (indirecte) effecten van melatonine (zoals het verhelpen van slaapproblemen, het remmende effect op het sympathische zenuwstelsel en de antioxiderende werking) zouden in theorie vooral van gunstige invloed moeten zijn op ritmestoornissen. Van ongunstige invloed op aritmieën echter zou de directe inwerking van melatonine op de in het hart aangetoonde melatonine receptoren kunnen zijn, welke verschillende hoofdrolspelers in de calcium huishouding van de hartspiercel beïnvloeden. Enkele andere ongunstige effecten van melatonine worden tevens genoemd, waarna we uiteindelijk concluderen dat een disbalans tussen deze verschillende indirecte en directe effecten mogelijk leidt tot het ontstaan van de ritmestoornis. Deze disbalans kan op zijn beurt worden veroorzaakt door verschillen in de dosis melatonine per preparaat, de grote variatie in bio-beschikbaarheid en in genetisch bepaalde verschillen van melatonine receptor expressie en activiteit per individu. Deze resultaten laten zien dat medicinale melatonine zou moeten worden opgenomen in de lijst van extrinsieke factoren (naast o.a. alcohol, cafeïne en tabak gebruik) die mogelijk "outflow tract" kamerritmestoornissen kunnen veroorzaken, om zo meer bewustwording te creëren bij zowel behandelend artsen als patiënten. Dit is met name van belang in ogenschouw nemend dat het gebruik van melatonine in de afgelopen 5 jaar significant is toegenomen (zelfs meer dan verdubbeld in de Verenigde Staten en Scandinavië). Bovendien zou door het simpelweg stoppen van dit middel kunnen worden voorkomen dat patiënten een ablatie moeten ondergaan (met alle gevolgen

van dien) wat zowel een verbetering van de veiligheid als een vermindering van de kosten van de behandeling zou betekenen.
In het laatste hoofdstuk van Deel II, Hoofdstuk 6, analyseren we de variabiliteit van het PVC koppelingsinterval (de tijdsspanne tussen een normale kamercontractie en een bijbehorende PVC) van patiënten met verschillende onderliggende (of ontbrekende, in het geval van idiopathische kamerritmestoornissen) cardiale pathologie om zodoende te proberen inzicht te krijgen in het onderliggende aritmie mechanisme. Het aritmie mechanisme is namelijk één van de belangrijkste factoren die van invloed zijn op deze variabiliteit. Drie patiëntengroepen werden vergeleken met een controle groep bestaande uit patiënten met PVC's vanuit littekenweefsel veroorzaakt door een eerder hartinfarct, waarvan we weten dat het onderliggende mechanisme "re-entry" is (een mechanisme met een lage koppelingsinterval variabiliteit). De drie groepen bestonden uit patiënten met idiopathische, niet-ischemische gedilateerde cardiomyopathie en familiaire gedilateerde cardiomyopathie (lamine A/C of phospholamban mutaties) gerelateerde PVC's. Na vergelijking van de PVC koppelingsinterval variabiliteit in deze groepen concluderen we dat de lage variabiliteit die werd gevonden bij idiopathische en niet-ischemische gedilateerde cardiomyopathie PVC's suggestief is voor een onderliggend "re-entry" dan wel "triggered activity" mechanisme en dat "abnormale automaticiteit" of "gemoduleerde parasystole" onwaarschijnlijke onderliggende mechanismen zijn. De hoge PVC koppelingsinterval variabiliteit die werd gevonden bij familiaire gedilateerde cardiomyopathie PVC's maakt "re-entry" en "triggered activity" als onderliggende aritmie mechanismen in deze groep juist onwaarschijnlijk. Het belang van deze bevindingen ligt in het feit dat dit behandelend artsen zou kunnen voorzien van een non-invasief middel om het onderliggende aritmie mechanisme te identificeren om zodoende een geschikte therapeutische strategie te kiezen.

Deel III: Hoe Therapeutische Uitdagingen van Idiopathische Ventriculaire Aritmieën te Overwinnen

In het laatste deel van dit proefschrift focussen we ons op de uitdagingen van de behandeling en op de prognose van idiopathische kamerritmestoornissen. Hierbij kijken we onder andere naar nieuwe ablatie technieken, nieuwe behandelingsstrategieën en herzien we de huidige behandelpaden en follow-up methoden.
In Hoofdstuk 7 bespreken we de prognose van deze aritmie en geven wij een overzicht van de huidige kennis over de associatie tussen deze ritmestoornis en plotse hartdood. We brengen hier onder de aandacht dat ondanks de over het algemeen goede prognose van deze aandoening, er niet moet worden vergeten dat zij in sommige gevallen zeer symptomatisch kan zijn met een afname van levenskwaliteit tot gevolg,

kan leiden tot hartfalen door overbelasting van de hartspier en een trigger kan zijn voor potentieel fatale hartritmestoornissen. Tevens beschrijven we het belang van het uitsluiten van onderliggende aandoeningen die geassocieerd zijn met de maligne uiting van "outflow tract" kamerritmestoornissen, zoals aritmogene rechter ventrikel cardiomyopathie (ARVC) en het Brugada syndroom. We concluderen dat katheter ablatie eerder moet worden overwogen bij patiënten met risicofactoren zoals: een voorgeschiedenis van plots bewustzijnsverlies, zeer snelle kamerritmestoornissen (>230 bpm) of PVC's met een zeer kort koppelingsinterval.
De behandeling van deze kamerritmestoornis door middel van katheter ablatie analyseren we in Hoofdstuk 8, waarin we de uitkomsten van de drie meest gebruikte ablatie technieken met elkaar vergelijken. We beschrijven hierin de korte- en lange termijn uitkomsten van conventionele handmatige ablatie, handmatige ablatie met "contact force" (waarbij de druk die men met de ablatie katheter uitoefent op het hartspierweefsel wordt gemeten en direct weergegeven, ten behoeve van het creëren van adequate ablatie laesies en het tegengaan van complicaties zoals perforaties) en magneet gestuurde ablatie (waarbij de ablatie katheter van afstand wordt bestuurd met behulp van een magnetisch veld). Onze bevindingen bevestigen dat het korte- en lange termijn succes van deze drie technieken gelijk is, maar dat magneet gestuurde ablatie veiliger is door het optreden van minder complicaties en de verminderde blootstelling aan röntgenstraling voor zowel patiënt als operateur (o.a. vanwege de mogelijkheid de katheter van afstand te besturen en de mogelijkheid tot het maken van gedetailleerdere 3-D kaarten van het hart waardoor het gebruik van röntgenstraling voor katheter lokalisatie significant kan worden verminderd).
Hoofdstuk 9, in reactie op een meta-analyse waarin de ablatie van kamerritmestoornissen in het algemeen met conventionele handmatige en magneet gestuurde ablatie met elkaar werd vergeleken, beschrijft de verschillende overwegingen voor het gebruik van magneet gestuurde ablatie in de dagelijkse praktijk. We wegen de toegenomen veiligheid van de behandeling door deze techniek, het verkorten van de behandelingstijd en het toenemen van de bereikbaarheid van bepaalde anatomische structuren af tegen de initiële leercurve voor operateurs en de kosten van de apparatuur. Ook behandelen we hier de toekomstige toepassingen en de mogelijke verdere ontwikkelingen van magneet gestuurde ablatie.
In Hoofdstuk 10 geven we een overzicht van de huidige ontwikkelingen op het gebied van een andere, eerder genoemde, relatief nieuwe ablatie techniek namelijk "contact force". Ditmaal doen we dit in het kader van de behandeling van een andere veelvoorkomende ritmestoornis: atriumfibrilleren. Het isoleren van de pulmonaal venen van de rest van het linker atrium door middel van ablatie is de hoeksteen van de behandeling van deze aritmie. Een veelvoorkomend probleem

van deze behandeling echter, is dat door inadequate ablatie laesies (de fysieke manifestaties van de toegediende radiofrequente energie) opnieuw een connectie kan ontstaat met het atrium weefsel waardoor de ritmestoornis weer kan terugkeren. In dit hoofdstuk beschrijven we de natuurkundige basisprincipes achter het creëren van een effectieve ablatie laesie op basis waarvan we de rol van "contact force" in dit proces uiteen zetten. Ook worden hier de voor de ontwikkeling van deze techniek belangrijkste studies in zowel dieren als mensen samengevat en beschrijven we de meest gebruikte manieren van "contact force" registratie. De eerste studies in mensen naar de veiligheid en effectiviteit van "contact force" ablatie komen hier tevens aan bod, waarna de toekomstperspectieven en nog te nemen drempels verder worden besproken. Met deze review hopen we meer bewustwording en kennis te bewerkstelligen bij behandelend artsen met betrekking tot de fundamentele principes achter het formeren van een optimale laesie, de laatste ontwikkelingen op het gebied van katheter ablatie en hopen we meer vergelijkend onderzoek aan te moedigen tussen de verschillende ablatie technieken.

Hoofdstuk 11 beschrijft de verzameling en vergelijking van alle relevante in de literatuur gevonden studies naar de behandeling van "outflow tract" kamerritmestoornissen door middel van conventionele handmatige dan wel magneet gestuurde katheter ablatie. In deze systematische review en meta-analyse vergelijken we de korte termijn en >1-jaars resultaten van deze twee technieken en analyseren we verschillende factoren die van invloed kunnen zijn op deze uitkomsten. In deze vergelijking van in totaal 26 studies (waarvan 23 conventionele handmatige, en 3 magneet gestuurde ablatie studies) vonden wij geen verschillen in korte termijn en >1-jaars succes tussen de twee technieken en concludeerden we dat de in de literatuur gerapporteerde succes percentages van ablatie over het algemeen hoog zijn. Wel beschrijven we hierbij ook dat studies met negatieve resultaten in de literatuur ondervertegenwoordigd zijn, zoals blijkt uit de publicatie bias analyse. Verder laten we zien dat het aantal complicaties van deze procedure bij beide technieken laag ligt, met mogelijk een iets gunstiger veiligheidsprofiel voor magneet gestuurde ablatie (ook verminderde röntgenstraling belasting in acht nemend). We beschrijven verder dat de geografische locatie van de behandeling van invloed is op de korte termijn uitkomsten van conventionele handmatige ablaties, en dat voor >1-jaars uitkomsten de methode van follow-up (het al dan niet routinematig uitvoeren van een 24-uurs Holter registratie bij controle) van invloed is. Bij afwezigheid van grote en kwalitatieve studies op het gebied van (magneet) ablatie van "outflow tract" aritmieën, verschaft dit hoofdstuk de behandelend arts van een waardevol en compleet overzicht van alle op dit moment beschikbare literatuur, om zodoende te assisteren in de klinische besluitvorming aangaande de optimale behandeling van deze snel groeiende groep patiënten.

Hoofdstuk 12 gaat verder in op het gebruik van magneet gestuurde ablatie voor het behandelen van "outflow tract" kamerritmestoornissen, specifiek die uit de rechter kamer "outflow tract". In deze retrospectieve vergelijking tussen conventionele handmatige en magneet gestuurde ablatie bevestigen we nogmaals een afname in blootstelling aan röntgenstraling (in dit geval van wel 58%) bij het gebruik van deze techniek, terwijl gelijke complicatie- en succespercentages worden behouden. Tevens laten onze bevindingen zien dat dit voordeel ook na de introductie van nieuwe en verbeterde 3D mapping systemen in stand blijft. We zetten in dit hoofdstuk verder kort onze veronderstellingen uiteen over de mogelijke redenen achter deze afname van röntgenstraling belasting (zowel voor de patiënt als de operateur).
In het laatste hoofdstuk van dit proefschrift, Hoofdstuk 13, constateren we dat er sprake is van een hoge mate van variabiliteit tussen de in de literatuur gerapporteerde succespercentages van de ablatie van idiopathische kamerritmestoornissen en stellen wij de discrepantie tussen de verschillende in de literatuur gebruikte definities van ablatie succes en de invloed van de follow-up methodologie (al dan niet met continue ECG monitoring) op het succes van deze procedure aan de kaak. Hiervoor analyseren we drie gehanteerde succes definities in een groep van 215 patiënten die een idiopathische ventriculaire aritmie ablatie hebben ondergaan. We analyseren procedure succes (direct na de ablatie, na het stimulatie protocol en de wachttijd, met de patiënt nog op de operatietafel), geïntensiveerd post-procedure succes (vrijheid van aritmieën op de laatste dag van de opname, gemeten door middel van continue ECG monitoring) en middellange termijn succes (vrijheid van aritmieën 3 maanden na ablatie, gemeten met 24-uurs Holter registratie). Tevens vergelijken we de voorspellende waarde van procedure- en geïntensiveerd post-procedure succes ten opzichte van het uiteindelijke middellange termijn succes na 3 maanden. We laten zien dat het procedure succespercentage significant hoger ligt dan het geïntensiveerd post-procedure en middellange termijn succespercentage en dat geïntensiveerd post-procedure succes een beter discriminerende parameter voor middellange termijn succes is dan procedure succes. Het niet uitvoeren van continue ECG monitoring tijdens de opname kan leiden tot het missen van het vroeg terugkeren van de aritmie (met name als de patiënt hierbij asymptomatisch is). We concluderen dat het gevolg van het alleen rapporteren van procedure succes is dat dit zal leiden tot een overschatting van het succes van de ablatie procedure en dat om meer betrouwbare en beter vergelijkbare analyses van succespercentages tussen studies mogelijk te maken een meer uniforme definitie van succes nodig is.

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PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student:	L.J. de Vries	PhD period:	April 2015 – January 2018
Erasmus MC Department:	Cardiology/ Electrophysiology	Promotor:	F. Zijlstra
Research School:	COEUR	Co-promotor:	T. Szili-Torok

1. PhD training

	Year	Workload (ECTS)
General academic skills		
- Systematic Literature Retrieval (PubMed 1)	2015	0.1
- Systematic Literature Retrieval (PubMed 2)	2015	0.1
- Systematic Literature Retrieval (other databases)	2015	0.1
Research skills		
- NIHES Biostatistical Methods I: Basic Principles	2016	5.7
- Research Integrity	2016	0.3
In-depth courses (e.g. Research school, Medical Training)		
- MolMed: Basic Introduction Course on SPSS	2015	1.0
- Fundamental Critical Care Support (FCCS)	2017	4.0
Presentations		
- Journal Club: VT or not VT	2015	1.0
- Journal Club: Safety and Efficacy of Exercise Training in Patients With an Implantable Cardioverter-Defibrillator: A Meta-Analysis	2016	1.0
International conferences		
- February 21-23: 5th International Symposium on Advances in Arrhythmias, Rotterdam, the Netherlands	2011	0.9
- May 3-7: Heart Rhythm Society (HRS) 37th Annual Scientific Sessions, San Francisco, USA (*Oral presentation*)	2016	2.0

	Year	Workload (ECTS)
- June 7-10: Cardiostim 2016, Nice, France (*Moderated poster*)	2016	1.6
- October 20-21: Society for Cardiac Robotic Navigation (SCRN), Inaugural Meeting, Amsterdam, the Netherlands	2016	0.6
- November 3: The Netherlands Society of Cardiology (NVVC) Autumn Congress, Papendal, the Netherlands	2016	0.3
- November 12-16: American Heart Association (AHA) Scientific Sessions 2016, New Orleans, USA (*Poster*)	2016	1.8
- August 26-30: European Society of Cardiology (ESC) Congress, Barcelona, Spain (*Moderated poster*)	2017	1.9
- October 19-20: Society for Cardiac Robotic Navigation (SCRN), 2nd Annual Meeting, Lisbon, Portugal (*Invited oral presentation*)	2017	1.1
Seminars and workshops		
- May 29: COEUR day	2015	0.3
- June 4: PhD day	2015	0.3
- September 11: COEUR Seminar Cardiovascular Interventions in the Elderly	2015	0.2
- September 25: Electrophysiology Basics: Diagnostics and Ablation of Tachyarrhythmias for Medical Professionals	2015	0.3
- October 3: NVVC Juniorkamerdag: Cardiovascular Imaging	2015	0.3
- December 14: Innovations in Cardiovascular Pharmacotherapy Symposium	2015	0.3
- January 28-29: COEUR Arrhythmia Research Course	2016	1.5
- February 12: COEUR Heart Failure Symposium	2016	0.2
- March 17-18: International Workshop on Supra Ventricular Tachycardia	2016	0.5
- November 11: Innovations in Cardiovascular Medicine Symposium	2016	0.1
- April 5-6: International Workshop on Supra Ventricular Tachycardia	2017	0.5

	Year	Workload (ECTS)
Didactic skills		
- Reviewing paper	2016	0.1

2. Teaching activities

Supervising practicals and excursions		
- Supervising 2nd year medical students in writing a systemic review	2015-2016	6.0
	TOTAL	34.1

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ABOUT THE AUTHOR | CURRICULUM VITAE

Leendert Jan de Vries was born on September 26th 1986, in Utrecht, the Netherlands. After graduating high school (Johan de Witt Gymnasium, Dordrecht), he studied Biomedical Sciences at the University of Utrecht for one year after which he started medical school at the Erasmus University in Rotterdam. During his study he followed a research internship at the cardiology/electrophysiology department of the Erasmus Medical Center, Rotterdam. After acquiring his Medical Doctor's degree, he started working as a resident (ANIOS) at the department of cardiology at the Amphia Ziekenhuis, Breda. In 2015, he started with the research project described in this thesis: "New Insights Into the Mechanism and Treatment of Idiopathic Ventricular Arrhythmias", supervised by Dr. Tamas Szili-Torok and Prof. Dr. Felix Zijlstra at the Erasmus Medical Center, Rotterdam. During this project, he had the opportunity to present his work on several international conferences and to publish manuscripts in international peer reviewed medical journals. As of February 2018, Lennart is working as a resident at the department of cardiology at the Erasmus Medical Center, Rotterdam.

Why do ventricular arrhythmias occur in perfectly healthy people with a seemingly normal and potent heart? This question lies at the core of this thesis. In the general population these so-called idiopathic ventricular arrhythmias (IVAs) are common and present in varying degrees of severity. The subgroup that accounts for the largest share of IVAs are the outflow tract IVAs, named after their referred location. They can be highly symptomatic with complaints ranging from palpitations to hemodynamic instability and can cause tachycardia-induced cardiomyopathy. Fortunately, however, they usually have a good prognosis. For the past decades, it has been generally accepted that the underlying mechanism of this arrhythmia is triggered activity. Curiously enough, other than providing a mechanistic classification, this categorization does not elucidate the actual underlying etiology, the distinctive localized nature or many other key characteristics of this arrhythmia. In this thesis, we aim to clarify these aspects in order to provide new insights into the mechanism and treatment of IVAs.