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Prevention of ventricular fibrillation through de-networking of the Purkinje system

Proof-of-Concept Paper on the Substrate Modification of the Purkinje Network

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Abstract

Introduction: Sudden cardiac death from ventricular fibrillation (VF) remains a major health problem worldwide. Currently, there are limited treatment options available to patients who suffer from episodes of VF. Because Purkinje fibers have been implicated as a source of initiation of VF, we are presenting the first paper of a series highlighting the promising results of substrate modulation through "De-Networking" of the Purkinje system preventing VF in patients without an alternative ablation strategy.

Methods and Results: We studied 10 consecutive patients (two female) all but one implanted with an ICD with documented VF or fast polymorphic Ventricular tachycardia (VT) (five patients without history of structural heart disease, two with ischemic cardiomyopathy, one with hypertrophic obstructive cardiomyopathy, one with dilated cardiomyopathy, and one with aortic valve disease). After 3D electroanatomical mapping, the left bundle branch (LBB) and left ventricular Purkinje potentials were annotated creating a virtual triangle with the apex formed by the distal LBB and the base by the most distal Purkinje potentials. Linear radiofrequency catheter ablation at the base of the triangle was performed, followed by ablation within the virtual triangle sparing the LBB and both fascicles ("de-networking"). All patients were treated without complications. During 1-year follow-up, only 2/10(20%) patients experienced recurrence in form of a single episode of polymorphic VT/VF.

Conclusion: Catheter ablation of VF through "de-networking" of the Purkinje system in patients without overt arrhythmia substrate or trigger appears safe and effective and will require further study in a larger patient cohort.

KEYWORDS

ablation, Purkinje network, ventricular fibrillation, ventricular tachycardia

1 | INTRODUCTION

Ventricular fibrillation (VF) is a fatal cardiac arrhythmia in patients with cardiac and noncardiac diseases.[1,2] Currently, there are limited causal treatment options available to patients who suffer an episode of VF.[3,4] Purkinje fibers (PF) have been implicated as a source for VF initiation and a number of studies have shown their potential role in some cases of idiopathic VF.[5,6] Radiofrequency catheter ablation targeting premature ventricular contractions (PVC) emanating from the Purkinje network can effectively prevent recurrent VF.[7–11] The current case series is the first to describe substrate ablation of VF through "de-networking" of the Purkinje system in patients without overt arrhythmia substrate or VF trigger.

2 | METHODS AND RESULTS

The study included 10 consecutive patients (two female) with documented fast polymorphic VT or VF. No identifiable structural heart

disease was present in five, ischemic cardiomyopathy (ICM) in two, hypertrophic obstructive cardiomyopathy (HOCM) with bioprothetic aortic valve replacement in one, dilated cardiomyopathy (DCM) with bioprothetic aortic valve replacement in one, and mechanical aortic valve replacement in one patient, respectively. The mean age was 62.8 ± 17.6 years. The left ventricular (LV) ejection fraction (EF) was normal in seven patients. In two patients with ICM and one patient with DCM, the LV EF was 35%, 39%, and 35%, respectively. An ICD was implanted in eight patients for secondary prevention. One patient refused ICD implantation and in one patient ICD implantation was performed after the ablation procedure. A number of at least three appropriate shock deliveries had occurred in all ICD patients prior to the procedure.

The intervention was performed under sedation using propofol, midazolam, and fentanyl. After femoral access, three multipolar catheters were positioned at the bundle of His, the right ventricular apex and the coronary sinus for mapping and pacing. Left ventricular access was achieved via transseptal access using a steerable long sheath (Agilis® Long Curl, Abbott, USA). In all but one case, a multipolar high-density mapping catheter was used (PENTARAY®, Biosense Webster, USA [$n = 8$] or Advisor HD Grid Mapping Catheter, Abbott, USA [$n = 1$]). In one patient of this series, the 3D Map was performed by the ablation catheter solely (Navistar Thermocool, Biosense Webster, USA).

An anatomical and bipolar voltage map of the left ventricle was created in sinus rhythm with a setting of 0.5-1.5 V to distinguish normal from abnormal tissue. The left bundle branch (LBB) and Purkinje potentials (PP) were marked as colored tag points. Thereafter, a virtual triangle was created with its apex formed by the proximal LBB and its base by the most distal PP. The anterior and posterior fascicles were marked as the margins of the triangle (Figure 1). None of the patients demonstrated clinically relevant spontaneous PVCs before or during the procedure—including isoproterenole infusion. While eight patients had no demonstrable endocardial scar, two patients with ICM had scaring at the basal lateral wall and the basal inferior wall. In these two patients, catheter ablation of residual scar channels and late potentials was performed before Purkinje network substrate modulation.

It should be noted, that in all cases presented in this study, we were able to map LBB-potentials and at least 3-4 distal Purkinje potentials. In cases where the Purkinje fiber potentials are not recognized, ventricular pacing with extra stimuli or pacing with high and low output should be considered.

After detailed mapping of the LV, the multipolar high-density mapping catheter was replaced for a irrigated tip bidirectional D/F curve ablation catheter (SmartTouch®, Biosense Webster or FlexAbility™, Abbott, USA). First, linear ablation at the base of the triangle was performed with subsequent ablation perpendicular to the base following the axis of symmetry of the virtual isosceles triangle sparing the LBB and both fascicles. Ablation was performed over 30-40 s using 30-35 W of power. In seven patients, contact force measurements were used during ablation. The accepted contact force range was 10-40 g. The average 1900.5 ± 1436.8 points were mapped in LV. Total average procedural time, fluoroscopy time, and ablation time amounted to 109.6 ± 35.9 min, 9.8 ± 5.4 min, and 694.7 ± 243.2 sec, respectively.

During the electrophysiology study, fast polymorphic VT or VF was mechanically induced in four patients, with programmed stimulation in two patients while no arrhythmia was inducible in four patients. In three patients, sustained VT/VF required defibrillation using a 200 J shock. All patients underwent catheter ablation without significant complications. One patient developed an intraventricular conduction delay. No VT/VF was inducible after the ablation procedure. The hospital stays composed 2.1 ± 2.4 days. Amiodarone was administered in all patients for a 3-month period to prevent arrhythmias due to inflammation caused by the ablation procedure. After a 1-year follow-up period only 2/10 (20%) patients experienced a single episode of recurrent VT. One patient with idiopathic VT/VF who had suffered from multiple VT/VF episodes prior to ablation had only one episode of fast polymorphic VT. The patient remained free of recurrent ventricular arrhythmias on beta blocker therapy, which has not been effective prior to the intervention, in the subsequent 2 years. Another patient with HOCM and bioprothetic aortic valve replacement had also only one episode of fast polymorphic VT. After installation of amiodaron, which failed to be efficient prior to Purkinje De-networking, no further episode of VT/VF has been documented.

3 | DISCUSSION

3.1 | Clinical findings

Clinical outcome of Purkinje "de-networking" in the first 10 patients is promising. We used this technique in patients without overt trigger or arrhythmia substrate accounting for fast VT or VF. It seems to be effective in patients with and without structural heart disease. The development of this method was based on clinical observations in concordance to existing anatomical, experimental, and preliminary clinical data. In the very first patient from the group presented in this article, we found no endocardial scar or spontaneous PVCs during the mapping procedure. The patient had frequent VT/VF runs, which were induced mechanically or during programmed ventricular stimulation. Using the PentaRay mapping catheter (Figure 2), rapid PF activation was observed which was isolated from ventricular activation and demonstrated a "figure-of-eight" (when transferred to an anatomical surface) irregular propagation pattern through the Purkinje network. The faster the activation, the faster the tachycardia and, once the PF activation disappeared, the tachycardia slowed and terminated. This finding was reproducible several times and inspired us to modulate the PF network. The result was distinctly positive: no PF activation was recorded after ablation and no VT/VF induction was possible.

3.2 | Anatomy of the left ventricular conduction system

Knowledge of the anatomy and physiology of the conduction system and the myocardium can help to develop potentially useful therapies for some forms of cardiac arrhythmia, particularly VF.

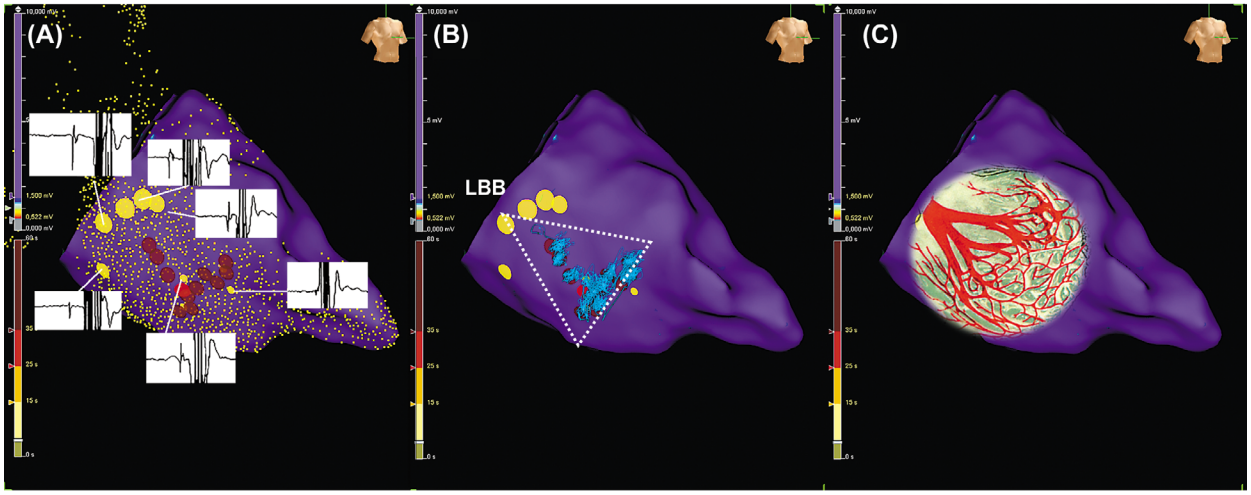

FIGURE 1 3D mapping (RAO projection) with the EnSite Precision system using the Advisor HD-Grid mapping catheter (Abbott, USA). The yellow points depict the LBB (large diameter) and Purkinje potentials (small diameter), as well as the ablation lesions (red points). A, High-density map with illustration of the LBB and PF potentials. B, Virtual triangle with LBB at the apex and the base formed by the most distal Purkinje potentials. The anterior and posterior fascicles represent the margins of the triangle. Linear ablation along the distal part of the virtual triangle and within the body of the triangle. C, Modified schematic picture of the Purkinje network *(from Tawara S. Das Reizleitungssystem des Säugetierherzens. Jena: Gustav Fischer, 1906)* to illustrate the ablation target

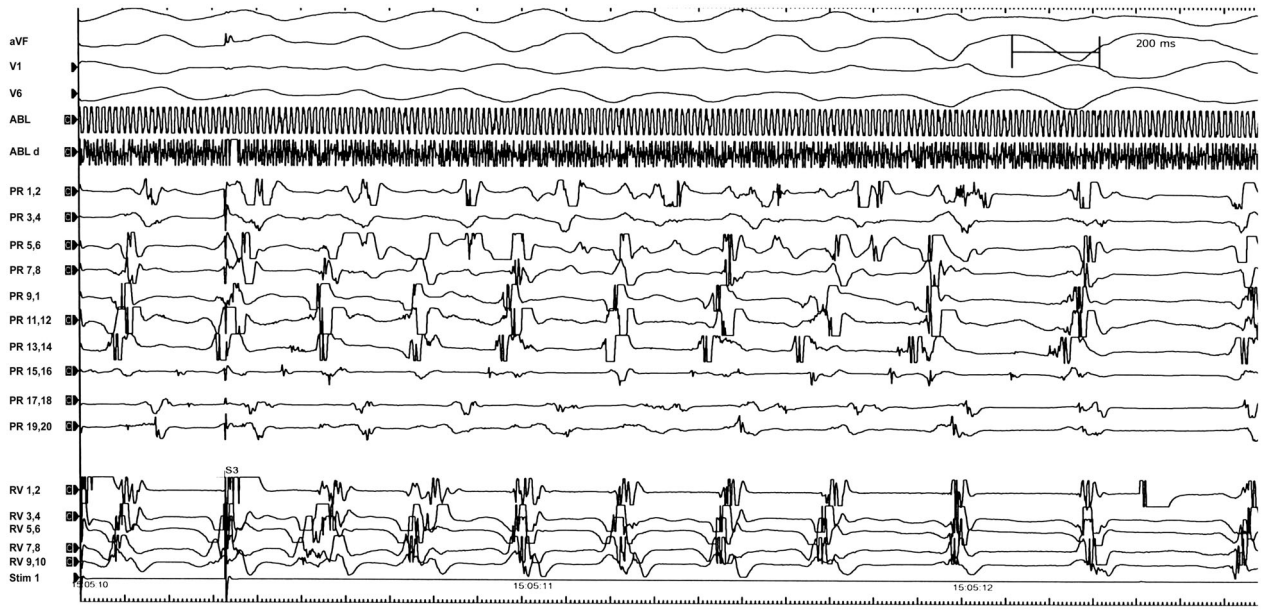

FIGURE 2 A tracing from the PENTARAY® mapping catheter, Biosense Webster, USA. Purkinje network activation—the sharp small potentials on channels PR11-PR20 (see text for details)

The bundle of His penetrates the right fibrous trigone, and then divides into a left and right bundle branch. The proximal part of the LBB is longer than its right counterpart. The LBB originates below the commissure between the right and noncoronary cusps of the aortic valve. The LBB descends through the sub-endocardial interventricular septum surrounded by connective tissue—the fibrous sheath, which isolates the LBB from the muscular tissue. Only at the distal ramifications of the bundle branches do the fibrous sheaths disappear, allowing continuity with the ventricular myocardium through the Purkinje network.[12] In humans, the left branch is typically divided into three fascicles with extensive intercommunication. These fascicles become ramified in the ventricular apex. More distally, it is almost impossible to trace the ramifications of the Purkinje fibers.[12–14] It is important to know that intramural branches of the Purkinje network have not been demonstrated in the human heart.[12,15–17] The Purkinje fibers differ from the working myocytes in several aspects: they have a dissimilar anatomic distribution, connexin proteins, action potentials, resting potentials, sodium and calcium currents. They are susceptible to the development of early and delayed after-depolarization and can show normal and abnormal automaticity.[15,18–22]

3.3 | Ventricular fibrillation—experimental data

Ventricular fibrillation occurs as a primary or secondary event and is a terminal cardiac dysrhythmia in patients with cardiac and noncardiac diseases.[1,2] Purkinje fibers have been implicated as a source for VF initiation. A number of studies have shown that they may play a role in some cases of idiopathic VF.[5,6] Studies using a canine heart model showed that the PF system may play an integral role in the maintenance of long-duration VF (LDVF).[23] Although the refractory period for Purkinje fibers in sinus rhythm is longer than those for myocardial cells. PF accommodate so that their refractory period shortens more than myocardial cells when activated rapidly.[24] The rapid activation during the LDVF is because the PF are more resistant to the global ischemia caused by the lack of perfusion during VF compared to working myocardial cells.[25–29] This may be due to the increased metabolic load required for the contractions of the myocardial cells and to the increased glycogen stored in the PF.[30,31] Compared with other mammals—in dogs, as well as in humans, the PF are near the endocardium so that they are less ischemic than the working myocardium because of the diffusion of oxygen from the nearby LV cavity.[32,33] Huang et al hypothesized that if the Purkinje system plays an important role during VF, more wave fronts propagating from the endocardium to the epicardium should exist in dogs (PFs are endocardial—like in the human heart) as opposed to pigs (intramural propagation of PFs), and Purkinje activation should precede or be faster than myocardial activation during LDVF. The results of the study showed that the transmural gradient in activation frequency occurred in dogs but not pigs after 2 min of LDVF. The canine endocardial layer activated faster than mid and epicardial layers during LDVF, while in pigs, rapid activation occurred in all three layers, thus, no significant activation frequency transmural gradient was observed. During LDVF, extracellular recording sites with Purkinje activation complexes had significantly faster mean working myocardium (WM) activation rates than extracellular sites without Purkinje activation complexes. Moreover, after 5 min of LDVF in intracellular endocardial recordings, the mean Purkinje activation rate was significantly faster than the mean WM activation rate.[18] Jackson et al examined myocardial activation patterns in short duration ventricular fibrillation and LDVF in myopathic Langendorff-perfused human hearts. The study demonstrated a greater resistance to ischemia and a greater capacity for continued 1:1 capture of PF compared with ventricular myocardium. Sharp Purkinje potentials during unipolar mapping became more prominent on the endocardium as VF progressed, whereas on the epicardium, the local cycle length slowed, and signals had a lower frequency. The authors concluded that human LDVF is characterized by an endocardial to epicardial activation frequency gradient created by focal endocardial activations with mid-myocardial wave break. Reentry is an uncommon mechanism in human LDVF; instead, focal endocardial activations originate most commonly from the PF. Rapid activations during early VF may mediate focal activity in LDVF and facilitate its maintenance.[34] Dosdal et al demonstrated that chemical ablation of the Purkinje system in dogs caused the VF activation rate to slow significantly after 2 min of VF. Ablation of the Purkinje system led to spontaneous termination of VF significantly earlier than in the control group.[11] Recently, Livia et al published a study that targeted the PF in an experimental model of canine hearts with irreversible electroporation. Abolishing Purkinje signals was associated with a decreased window of vulnerability toward VF induction.[35] All of these findings suggest that the Purkinje system is important for the maintenance of VF. As such, catheter ablation of PF is a promising approach and requires further study for the treatment of VF.

Currently, there is no cure for VF, with only limited treatment options available for patients. Thus, sudden cardiac death from VF remains a major health problem worldwide.[3,4]

In select cases, this lethal arrhythmia may be amenable to radiofrequency catheter ablation targeting VF triggers such as PVCs emanating from the Purkinje tissue.[7–11] This current proof-of-concept paper is the first to describe substrate ablation of VF in patients without an overt VF trigger by means of "de-networking" the Purkinje system of the human heart. The Purkinje network that we targeted for substrate modification in this series does not include the moderator band, right ventricular exits, or the so-called "dead-end tracts", which are seen in addition to the right and left bundle branch, fading out on the crest of the muscular ventricular septum. Their potential role as a substrate for an arrhythmogenesis role was recently discussed.[36,37]

As such, our method describes a partial Purkinje de-networking, which provides modest but significant results. On the other hand, the LV septal section of the Purkinje network is the largest section of the total network. It is always located in the same place, and is invariably shaped like a triangle.[38] Therefore, the mapping and creation of a virtual triangle is easy—even if we have a minimal number of targets (eg, LBB potential or Purkinje potential).

Moreover, according to some experimental data from the animal Purkinje fiber model, there are differences between the left and right-sided Purkinje fibers. For example, the left ventricular Purkinje fibers' spontaneous rates are faster than those from the right ventricle in canine hearts. These results are in agreement with the messenger ribonucleic acid differences between the left and right Purkinje fibers, as well as the earlier findings pertaining to the mink-related peptides (MiRP1) in the Purkinje fibers in rabbit hearts.[39–42] Nevertheless, during the next stage of our investigation, we feel it would be prudent to clarify whether or not the additional mapping and ablation of the right-sided exits and "dead-end tracts" increase the success rates of the treatment.

In reflection, it is also interesting that the role of the subendocardial Purkinje network in triggering torsade de pointes has been confirmed in vivo in long QT syndrome.[43] The ablation strategy we have presented might also be considered in patients with long QT syndrome and intractable episodes of Torsade-de-Pointes tachycardia (TdP).

4 | CONCLUSION

Substrate modulation in VF and fast polymorphic VT through "de-networking" of the Purkinje system is feasible and appears safe and highly effective in patients without overt trigger or arrhythmia

substrate. The presented ablation technique is relatively easy to perform and contains no increased complication risk and might be a "rescue approach" in patients with otherwise untreatable fast VT or VF.

5 | STUDY LIMITATIONS

While the number of patients reported is small, this report can function as a preliminary proof-of-concept that can potentially be further explored via a multi-centered approach, or at least provide fodder for further clinical reports.

In this study, we did not provide a quantitative assessment of the thresholds in the induction of ventricular fibrillation and ventricular defibrillation before and after ablation. This topic should be addressed in the next series.

Strong measures were not taken to evaluate dyssynchrony (between endo- and epicardial sides) before and after ablation in this case series. During the next step of this process, we plan to use the coronary sinus branches to look at the simultaneous differences between the epicardium and endocardium during VT/VF, both before and after ablation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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