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Ventricular Arrhythmias Involving the His-Purkinje System in the Structurally Abnormal Heart

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Abstract

His-Purkinje related ventricular arrhythmias are a subset of ventricular tachycardias that use the specialized cardiac conduction system. These arrhythmias can occur in various different forms of structural heart disease. Here, we review the basic science discoveries and their analogous clinical observations that implicate the His-Purkinje system as a crucial component of the arrhythmia circuit. While mutations serve the molecular basis for arrhythmias in the heritable cardiomyopathies, transcriptional and post-translational changes constitute the adverse remodeling leading to arrhythmias in acquired structural heart disease. Additional studies on the electrical properties of the His-Purkinje network and interactions with the surrounding myocardium will improve the clinical diagnosis and treatment of these arrhythmias.

Keywords

Ablation; Animal Studies; Electrophysiology - Basic; Electrophysiology - Clinical; VT

Introduction

Perturbation of the His-Purkinje system can lead to life-threatening ventricular arrhythmias, including ventricular tachycardia (VT) or ventricular fibrillation (VF). These arrhythmias can be idiopathic, as reviewed recently,[1] or they can occur in the context of structural heart disease. This review will highlight the molecular understanding and clinical features of His-Purkinje-related arrhythmias in the structurally abnormal heart.

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Author Contributions

P.B. conducted literature review and wrote the section on basic science studies. M.S. conducted literature review and wrote the section on ventricular tachycardia/fibrillation in ischemic heart disease and healed infarct. B.J.H. edited the manuscript, conducted literature review, and wrote the section on His-Purkinje derived arrhythmias including bundle branch reentry, inter-/intra-fascicular reentry, and focal tachycardias.

Purkinje fiber remodeling in structural heart disease and heart failure (HF)

Numerous ion channels and their function are altered in cardiac cells from the failing human/animal heart. The well described increase in action potential duration (APD) in HF ventricular myocytes as well as Purkinje cells (PCs) could easily underlie early afterdepolarization (EAD) dependent focal activations (Figure 1).[2] This loss of repolarization reserve is secondary to decreases in both cardiac K^+ (I_K) and L type Ca^{2+} currents ($I_{Ca,L}$).[3] Changes in these currents reset the AP plateau voltages. Slow conduction observed in mapping studies may exist due to loss of function in the cardiac Na^+ current (SCN5A) where density of the cardiac Na^+ channels is decreased and Na^+ channel inactivation is defective also leading to the prolonged APD. Additionally, downregulation and intense phosphorylation of connexin 43 (Cx43) proteins lead to decreased function in HF cell pairs to alter cell-to-cell conduction.[4]

Enhanced Purkinje focal activations in the failing heart could also be due to changes in channel expression of the I_f current (the so-called pacemaker current). Most studies have been completed by providing evidence of I_f expression and its enhancement in ventricular cells of HF hearts.[5] Concomitant with enhanced I_f expression, there is a reduced expression of the I_{K1} channel and elevated beta-adrenergic stimulation in HF myocytes. While remodeled Purkinje cells isolated from failing hearts have been studied,[6] I_f current changes were not mentioned.

However, just as important to the substrate for initiation of arrhythmias, are the marked changes in intracellular Ca^{2+} handling, which can enhance the development of delayed afterdepolarizations (DADs)[7] in PCs from HF hearts. DADs are relatively easily induced in hypertrophied ventricular cells[8] and failing ventricular trabeculae.[9, 10] In some cases, a role for I_{TI} and Ca_i has been implicated. Traveling Ca^{2+} waves have been illustrated in isoproterenol stimulated cells[11] and trabeculae from the failing rat heart.[10]

Evidence provided by epicardial and endocardial mapping of ex vivo failing human hearts suggests that VTs arise in a substrate exhibiting slowed conduction. Premature stimulation produces progressive conduction delay and the first beat initiating VT is from the subendocardium.[12, 13] Mapping studies in the rabbit model of HF revealed a similar location of initiating impulses consistent with non-reentrant, focal activations from Purkinje laden myocardium.

Purkinje fiber remodeling post myocardial infarction (MI)

From endocardial mapping studies of the ex vivo healed infarcted human heart, a majority of VT episodes have been observed where endocardial activation preceded epicardial activation. It seemed that a majority of VTs were due to reentrant activity. Some studies showed that initial focal activations spread from small areas to remaining tissues.[14] These authors concluded that endocardial APs were relatively normal and that the recorded fragmented extracellular electrograms were due to complex anatomical heterogeneities such as the observed increased fibrosis. Sustained monomorphic VTs post MI in the human heart appeared to be due to focal activation that arose in the subendocardium or intramural reentry from the subendocardium as well as epi- and mid-myocardium.[14]

In hearts of large animals, acute coronary artery occlusion results in rapid ventricular arrhythmias (VT or VF), as reviewed previously.[15] It is unlikely that chronic or persistent changes in ion channel function in cells of substrate underlie these acute arrhythmias. Over the following 24–48 hrs during the subacute phase post occlusion, delayed spontaneous ventricular arrhythmias originating from the subendocardial Purkinje fibers occur in both experimental models and humans. During the healing phase (days, weeks) or healed (months) infarct phase, sustained VTs are inducible with programmed stimulation, suggesting that a reentrant substrate is present. The sites of origin of the ventricular arrhythmias in these hearts depend on the location of the surviving cells overlying the infarcted region.

Mechanisms for some of these ventricular arrhythmias can be understood in terms of the alterations in cellular electrical activity (remodeling) in specific regions of the heart post MI. Generally, by 24–48 hrs after total coronary artery occlusion, the APs of the subendocardial border zone Purkinje fibers show reduced resting potentials and maximal AP upstroke velocity ($\dot{V}max$), as well as an increase in the total time of repolarization (Figure 2).[16] It is likely that there is a net decrease in potassium permeability of the sarcolemma in Purkinje cells with reduced resting potentials. This is consistent with a decrease in the density of both the transient outward K^+ current (I_{to}) and inward rectifying K^+ current, I_{K1}.[17, 18] By virtue of the loss in resting potential, there would be a predictable change in $\dot{V}max$ of the subendocardial Purkinje myocytes that survive in the infarcted myocardium. While the Na^+ channel protein/function is not yet altered, the expression of its adapter protein Ankyrin-G is still robust and increases.[19] Gap junctional proteins (Cx40 and Cx43) are altered in assembly but have not yet redistributed along sarcolemma by 48hrs post occlusion in PCs.

Importantly, peak L type Ca^{2+} current density is significantly reduced in subendocardial Purkinje myocytes dispersed from 48 hr infarcted heart.[20] The loss in Ca^{2+} channel function could contribute to the depressed and triangular plateau phase of the prolonged APs of these arrhythmogenic Purkinje myocytes (Figure 2).[16] Despite reduced Ca^{2+} currents, PCs post MI show an increase in travelling Ca^{2+} waves which by activating the sodium-calcium exchanger (NCX), cause DADs and triggered activity.[21] Purkinje fibers also show variable degrees of automaticity as well as exit block (Figure 3). Slowed and inhomogeneous conduction particularly at rapid rates, within the subendocardial Purkinje fibers of this substrate may be due to marked changes in Cx43 location and function in pairs as is found in the 5 day epicardial border zone surviving cells.[22–24] However, segments of the intercalated Purkinje to Purkinje discs appear no different from those of normal subendocardium.[25]

About 2 months post coronary artery occlusion, the process of ion channel reverse remodeling of the cardiac cell is ongoing. The APs of the subendocardial PCs that were arrhythmogenic 24–48 hrs post occlusion period have improved considerably. Resting potentials, $\dot{V}max$ and action potential amplitude have returned to near control levels. The time course of APD changes is illustrated in Figure 2.[16, 26] The most significant change that occurs in the post MI healed animal heart is the replacement of ventricular myocytes with fibrosis tissue. Thus, the subendocardial layer of PCs that survive are anatomically “isolated” becoming a 2D sheet.

Purkinje fibers in heritable cardiomyopathies

Several groups have described the genetic basis of an inherited but rare arrhythmogenic disorder, catecholamine polymorphic ventricular tachycardia (CPVT), as an autosomal dominant mutation in the cardiac ryanodine receptor (RYR2)[27, 28] or homozygous and heterozygous missense mutations in the calsequestrin 2 (CASQ2) gene.[29] These genes control levels of proteins critical for proper Ca^{2+} handling in Purkinje myocytes. While a mutation in a stated gene will affect function in all cardiomyocytes, cardiac PCs from one mouse model of CPVT (RyR2 R4496C) showed enhanced sensitivity to the Ca^{2+} dysregulation caused by the gain of function of the mutated RyR2 protein, so called Ca^{2+} leak.[27, 30, 31] Thus triggered focal activations preceding any VTs/VF in these hearts are highly likely to be Purkinje related.

However, PCs can be sources of other ventricular arrhythmias (e.g. short coupled torsades de pointes) in hearts that exhibit loss in function mutations in RYR2 protein.[32–34] This loss in function occurs because the mutated RyR2 protein is hypoactive and does not release large amounts of Ca^{2+} from the SR due to decreased and changed inactivation time course of the L type Ca^{2+} current. This could prolong luminal Ca^{2+} activation. The resultant prolonged Ca^{2+} release is hypothesized to lead to EADs and potentially a premature ventricular contraction (PVC) at a short coupling interval.[33] Others have described probands with similar ECGs that were found to have gain of function mutations of KCNE5 (encoding for MiRP 4 beta subunit), a regulatory subunit, on the function of the cell's voltage dependent transient outward current (I_{to1}).[35] Adult PCs have a large I_{to1} and thus a considerable "notch" in the AP.[17] Subsequently, mutations in two other regulatory proteins, DPP6 (dipeptidyl peptidase like 6) and DPP6T, affect the magnitude of I_{to1} in PCs resulting in an arrhythmogenic substrate.[36, 37]

Long and short QT intervals

Genetically based long QT (LQTS) or short QT (SQTS) syndromes can occur with mutations in several K^+ and Na^+ channels and clearly would affect both PCs and myocytes. However, as shown in a study using LQTS Type 3 mice (delta KPQ),[38] the PC repolarization phase is more sensitive to these mutations than that of ventricular cells and are probable sources of EAD or DAD induced arrhythmias.

Shortened QT intervals and poor rate adaptation are hallmarks of SQTS. Gain of function mutations in K^+ channels (e.g. KCNH2, encoded by *hERG*, I_{Kr}) as well as RYR2 gene (see above) have been identified in patients. In the first example, the SQTS *hERG* mutation has a dramatic effect on Purkinje AP when studied under AP voltage clamp conditions.[39] The amount of mutated I_{Kr} is increased in the PC as well as in ventricular cells, thus significantly altering AP repolarization. Additionally, the mutated *hERG* channel augments the current associated with early premature stimuli, thus increasing the vulnerability to PVCs.

Conduction slowing/block

Heritable conduction slowing and/or block in His-Purkinje system can be caused by ion channel mutations that change the Purkinje AP and/or the coupling between PCs. Well known are the loss-of-function mutations in the alpha subunit of the sodium channel $Na_V1.5$,

encoded by SCN5A. These can lead to forms of conduction disease and/or hyper excitable Purkinje fiber bundles. For example, there is a SCN5A mutation with net gain of function of the Na^+ channel particularly in the −80 to −40 mV range. A new syndrome MEPPC, Multiple ectopic Purkinje related premature depolarizations, has been defined.[40] EP studies revealed that all premature beats originated from Purkinje tissues. A similar gain of function SCN5A mutation (a shift in the "window" current) was found associated with a large kindred with dilated cardiomyopathy (DCM) and PVCs.[41] In these individuals, a history of palpitations preceded the DCM diagnosis suggesting that the DCM may have resulted from the Purkinje ectopy and enhanced Na^+ influx.

Important modifiers of the cardiac sodium channel, the beta1 subunits, can themselves be mutated and decrease $Na_V1.5$ function and lead to conduction slowing/bundle branch block in the absence of SCN5A mutations.[42] However these EP changes rarely end in VT. Recently, idiopathic bundle branch reentrant VT has been described in some patients where mutations in either SCN5A or LMNA (for lamin A and C proteins) have been described.[43] In this case, SCN5A mutations would be consistent with loss of function of the Na^+ channel leading to a decrease in peak I_{Na} and reduced "window current" late I_{Na}. Lamins are important for the integrity of the nuclear membrane. Their dysfunction often leads to DCM and conduction disease.

Arrhythmias Involving the Purkinje System in Patients with Ischemic Cardiac Disease

The role of the Purkinje system in the geneses of ventricular arrhythmias in animal models of ischemic heart disease has been discussed above. This section will focus on the clinical counterpoints of these observations as they relate to either acute ischemia or healed MI.

The role of the Purkinje system for triggering VF in patients with structurally normal hearts was first described by Haïssaguerre et al.[44] They discovered that triggered PVCs emanating from Purkinje tissue could cause VF and that these patients could be cured by ablation of these triggers. This observation was first extended to patients with recent MI with recurrent episodes of VF by Bänsch et al.[45] These authors described four patients with electrical storm following an acute MI, which proved refractory to drug therapy (including intravenous amiodarone and beta-blockers) or acute revascularization, and were found to have PVCs that served to trigger VF or Polymorphous VT. In each patient, a Purkinje potential preceded the QRS in sinus rhythm and was present before the triggering PVC. This potential preceded the QRS during VT prior to development of VF (Figure 4). In each patient, the trigger PVC had a RBBB with superior or inferior axis compatible with a fascicular origin. Of note, the Purkinje to QRS interval during sinus rhythm was 23–25 ms in front of the QRS and preceded the QRS during VT by 126–160 ms. These potentials were always found at the anatomic border zone of the infarct (similar to that found in animal models of acute ischemia). They found that multiple applications of radio frequency energy (6–50) were necessary to abolish the local Purkinje potentials (as well as the trigger PVCs) suggesting involvement of a broad area of diseased fibers. This procedure proved effective in abolishing VT or VF in all treated patients and provides clinicians with an important tool for management of critically ill patients.

The role of the Purkinje system for patients with healed MI

Marrouche et al[46] were the first to systematically describe the role of the Purkinje system in eight patients with electrical storm, which occurred approximately 11 months after an acute MI. These patients proved refractory to medical management and underwent detailed electrophysiological studies as well as electroanatomic mapping. In each, a Purkinje potential was recorded, both during sinus rhythm as well as during the trigger PVC from the anatomic border zone, as determined from the 3-dimensional map. In five patients, PVC mapping was possible because of high density PVCs while in three patients, Purkinje like potentials were empirically ablated in the infarct border zone. After ablation, there was no recurrence of VT storm, but one patient had recurrence of a single episode of VF while another had sustained monomorphic VT, which was successfully ablated. These observations highlight the role of the Purkinje system for those with well healed MI. These observations together with those described in the Bänsch study suggest that the Purkinje system acts as a trigger for either triggered rhythms or possibly micro reentrant rhythms involving the Purkinje system.

On the other hand, Bogun et al[47] described the importance of the Purkinje system for those with macro reentrant VT circuits in patients with healed MI. They described nine patients with sustained monomorphic VT and a QRS duration < than 145ms who were studied a mean of 4.7 years after MI. Most (8 of 9) suffered an inferior MI while one had an anteroseptal MI. Most showed a RBBB with superior axis. All underwent anatomic as well as entrainment mapping. They used the following criteria for proof the Purkinje system was part of the circuit: 1) the presence of concealed entrainment at sites where the Purkinje potential was recorded and matching Purkinje potential to QRS with stimulus to QRS during VT; 2) changes in the Purkinje discharge rate preceded changes in the VT cycle length; and 3) a pace map that matched the VT configuration from the site showing a Purkinje potential in sinus rhythm (Figure 5). Moreover, they excluded bundle-to-bundle reentry (absence of a His deflection during VT) as well as fascicular reentry (ability to entrain muscle far from site of Purkinje potential recording). A schema showing the putative circuit for most of their patients is shown in Figure 6. They found a Purkinje potential that preceded the QRS by 13 ± 16 ms in each of the patients. They used radio frequency applications to the exit site showing the Purkinje potential in 7 patients and to another site in the VT circuit in 2 patients. During follow up, VT was no longer present in the patients although several were maintained on their previous antiarrhythmic drug (Sotalol). The authors nicely demonstrated the role of diseased Purkinje tissue in the geneses of macro reentrant VT in those with healed MI.

Others have also described involvement of the Purkinje system post MI.[48–50] In most, the mechanism was related to bundle-to-bundle reentry or fascicular reentry, which are discussed next. Other reports likewise describe fascicular tachycardia either due to reentry[50] or abnormal automaticity.[49]

His-Purkinje derived VTs

Both macro-reentry and focal VTs involving the His-Purkinje system have been implicated in structural heart disease. His-Purkinje related VTs were found in 20 of 234 patients with

VT in a single center, retrospective series.[49] The majority of these patients (55%) had ischemic cardiomyopathy, and 60% of these patients also had inducible scar-related VT. Three varieties of His-Purkinje related VTs were identified including bundle branch reentry, which was by far the most common, and the less frequent types of interfascicular reentry and focal fascicular tachycardia. While all the His-Purkinje related VTs were amenable to catheter ablation, there was high grade AV block in 30% of patients, and treatment required concomitant antiarrhythmic therapy and/or implantable defibrillator.

Bundle Branch Reentry Tachycardia in Structural Heart Disease

Bundle branch reentry tachycardia utilizes a macro-reentry circuit, typically using the right bundle branch as the antegrade limb and the left bundle branch/fascicles as the retrograde limb (Figure 7A). Atypical bundle branch reentry employs the right bundle branch as the retrograde limb. Typical bundle branch reentry results in tachycardia with a LBBB morphology and conventional intracardiac findings of His recording preceding the QRS, HV interval equal or exceeding that during sinus rhythm and HH interval preceding change in VV interval (Figure 7B). These findings were initially described in an early clinical series which detailed 20 consecutive patients with sustained bundle branch reentry from a single center.[51] The authors found that 95% (19 of 20 patients) had DCM and more than half (11 of 20 patients) had a predominant nonischemic etiology and left ventricular dysfunction; one patient had an aortic valve prosthesis for severe aortic regurgitation. These patients were combined into a later published series[52] to include a total of 48 patients with inducible bundle branch reentry tachycardia, again the vast majority of which were LBBB morphology. Interestingly, two induced tachycardias had an interfascicular mechanism, described in more detail below.

Like all macro-reentry circuits, bundle branch reentry relies on relative conduction delays, in this case, within a diseased His-Purkinje system and diseased transseptal myocardial conduction tissue. Therefore, bundle branch reentry tachycardias typically occur in the setting of cardiomyopathy because a normal conduction system cannot sustain this type of tachyarrhythmia. Likewise, complete bundle branch block would also not allow reentry to occur, which serves the basis for catheter ablative therapy of the right bundle[51–53] or the left bundle.[54] The latter study described electroanatomic mapping in four patients with bundle branch reentry tachycardia and LBBB morphology. In all four patients, there was no conduction in the anterior fascicle and slow conduction in the posterior fascicle. Left ventricular activation in two of the four patients was via slow conduction through the left posterior Purkinje fibers and via passive transseptal propagation in the other two patients. The authors speculated that the absence of conduction in the anterior fascicle is secondary to its susceptibility to ischemic injury. More recent recognition of bundle branch reentry tachycardia in structurally normal hearts[43] suggests that genetic mutations may result in conduction delay, which serves as a substrate for bundle branch reentry.

Interfascicular and Intrafascicular Tachycardia in Structural Heart Disease

One of the first case reports on successful ablation for interfascicular reentry tachycardia was described in a patient who previously had an inferior wall MI.[55] The QRS morphology during tachycardia was identical to that during sinus rhythm, that is, RBBB with LPFB.

Electrophysiology study demonstrated that the antegrade limb was the anterior fascicle and the retrograde limb the posterior fascicle (Figure 8). The fascicular potential to fascicular potential variations in this tachycardia drove changes in VV intervals. The HV interval during tachycardia was shorter than that during sinus rhythm, excluding bundle branch reentry.

Fascicular injury as the basis for monomorphic VT has also been described in nonischemic cardiomyopathy. In a series of six patients, five with nonspecified DCM and one with polymyositis, three different mechanisms of VT involving the left anterior fascicle were proposed.[56] Electroanatomic mapping identified a low-voltage area on the left ventricular septum, the border of which had diastolic and presystolic potentials that were targeted for ablation. These signals of slow conduction occurred either at the anterobasal to anterolateral septum close to the exit site of the left anterior fascicle or more distal at the mid to inferior septum. Two of the patients had involvement of both anterior and posterior fascicles to allow interfascicular tachycardia. Other proposed mechanisms included intrafascicular tachycardia within the left anterior fascicle and fascicular ventricular reentry tachycardia involving the Purkinje fibers and surrounding myocardium.

The aforementioned slow conduction properties of the left posterior fascicle allow for reentry between the branches of the fascicle, described in four patients post-MI.[50] While the left anterior fascicle is anatomically vulnerable to ischemic injury, the posterior fascicle, being anatomically broader, seems resistant.[57] The conduction system appeared preserved in the majority (three out of four) of these patients as evidenced by normal HV interval. During tachycardia, changes in the Purkinje to Purkinje potential intervals, as opposed to HH intervals, drove change in VV intervals. HV intervals were variable, -2 ± 43 ms, and fascicular potential preceded His potential. Other electrophysiologic properties, namely the presence of presystolic (in all four patients) and diastolic (in three out of four) potentials as well as entrainment with overdrive pacing, support macro-reentry where the antegrade limb were decremental Purkinje fibers and retrograde limb the posterior fascicle. Collectively, these properties were similar to idiopathic, verapamil sensitive left ventricular tachyarrhythmia.

Page et al described a case report of scar-mediated VT presenting with narrow QRS morphology similar to sinus rhythm.[48] They propose the mechanism as micro-reentry based on 1) initiation with programmed stimulation, 2) reproducible entrainment, and 3) presence of a low amplitude, mid-diastolic signal at the site of ablation, suggesting involvement of a critical isthmus. This site of ablation was at the basal septum of the left ventricle, where notably, there was no pre-systolic Purkinje potential.

Focal Tachycardia

Focal tachycardia involving the His-Purkinje system is rare. In a series of 234 patients with recurrent VT in context of heart disease, there were only two patients found with focal tachycardia from the specialized conduction system, one in the left bundle branch and one in the right.[49] The electrophysiologic features are similar to propranolol sensitive autonomic VT.[58] These tachycardias were induced by isoproterenol and not induced by programmed extrastimulation. They show transient response to adenosine but are not responsive to

verapamil. Ablation targeted the interventricular septum at a site where there was the earliest Purkinje potential, and this induced a flurry of ectopic beats and was successful at terminating the tachycardia. These tachycardias are not always responsive to ablation. In a retrospective study of 8 patients with fascicular arrhythmia of various etiologies, catheter ablation was successful in 2 out of 5 attempted cases; the other 3 patients responded to either verapamil or encainide.[59] The majority of these patients had preserved left ventricular systolic function, and of the 3 patients who had a cardiomyopathy, 2 patients did not undergo EPS, and 1 patient had multiple fascicular arrhythmias and failed ablation.

Distinguishing Tachycardia Mechanism

The differentiation of tachycardia mechanism is challenging. We currently use a technique that a number of recent authors have proposed,[60] namely retrograde aortic insertion of a multi polar electrode catheter along the posterior or anterior fascicle, whichever is thought to be the culprit. Another catheter is then introduced via a transseptal route for mapping and ablation. For non-reentrant or focal fascicular VT, the putative fascicle involved is identified in sinus rhythm as showing an anterograde activation pattern. Entrainment is not possible when pacing from then RV apex or from the atrium. Nogami and colleagues found that during VT a retrograde fascicular activation pattern was discerned and the site of successful ablation was at the longest fascicle to V interval.[60] For those with reentrant fascicular VT, a two catheter technique is employed as described above, and we employ entrainment pacing from the RV apex to prove a reentrant mechanism. If the patient is stable during tachycardia the left ventricle is mapped using a 3D imaging system to best delineate the tachycardia circuit. For the more common reentrant fascicular tachycardia, the ablation is carried out over the diastolic potentials or P1 area if this can be identified. Otherwise, we use the earliest fascicle to V or the insertion site of P1 into P2.

It is important to distinguish between a fascicular potential from isolated muscle potential. The key is to position the catheter over the fascicle in question and record the anterograde activation pattern in sinus rhythm. Once this is defined, we see whether these potentials precede the QRS during tachycardia. For the non-reentrant fascicular tachycardia, the earliest fascicular potential to QRS has been reported at 25±16 ms.[60]

Finally, arrhythmias arising from the papillary muscles are important potential confounders because the fascicles are anchored to these muscles. The surface ECG is key. Papillary muscle VT is broader than fascicular VT and will show a qR rather than a rR’ pattern in V1. Intracardiac echocardiography is always used in order to best define the boundaries of the papillary muscles during ablation. Fascicular potentials may be recorded either just before or with in the QRS.

Conclusions

His-Purkinje related arrhythmias can occur in various different forms of structural heart disease. The site of injury to the conduction system translates into molecular changes at that location and gives rise to substrate for arrhythmia. There are common cellular mechanisms underlying these arrhythmias, including slow conduction allowing for reentry, triggered activity, and enhanced automaticity. Our understanding and treatment approach for these

arrhythmias will continue to evolve with advances in both cellular and clinical electrophysiological studies.

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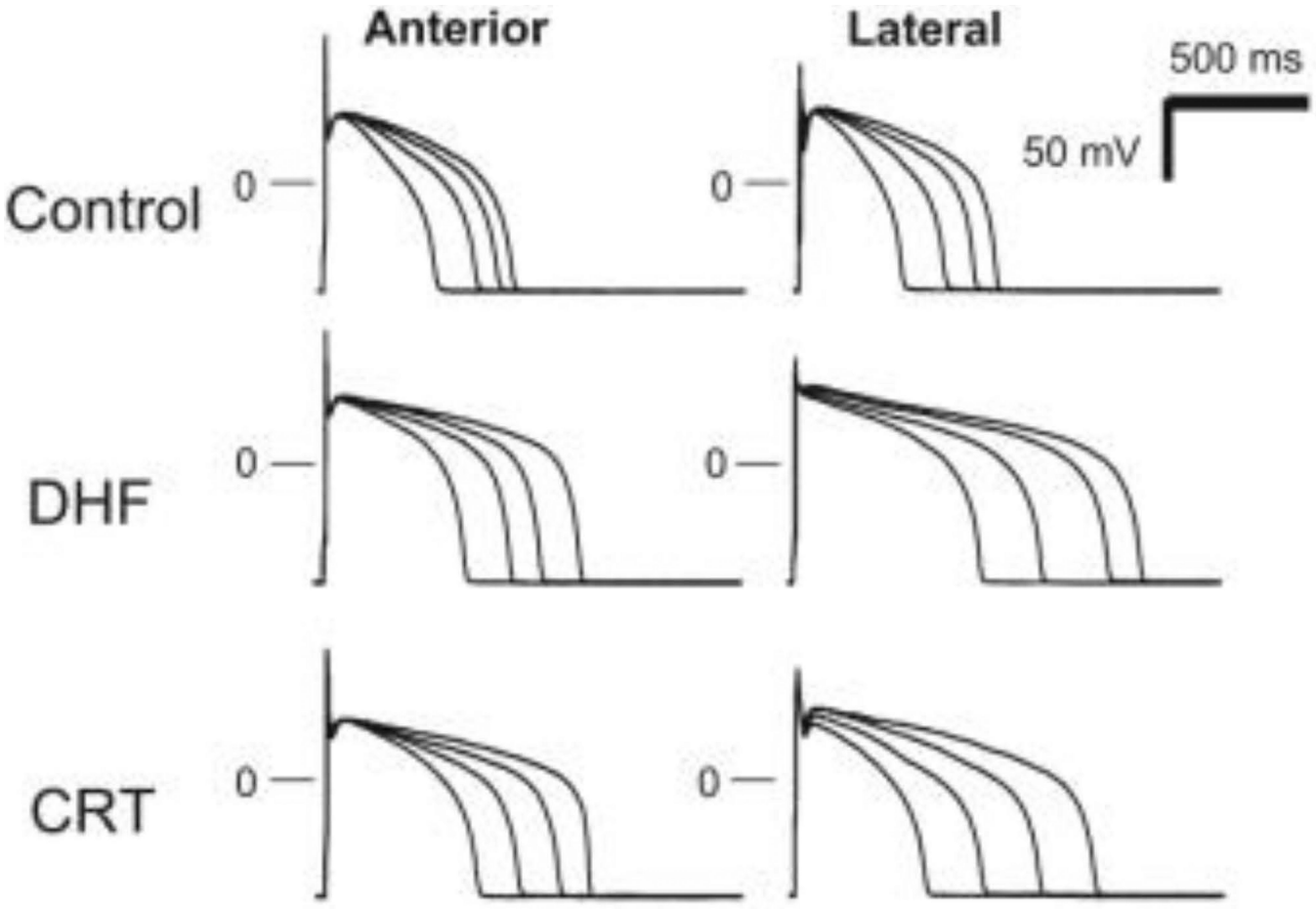

Figure 1.

Single ventricular cell action potential recordings from different areas of failing hearts in Control conditions, from a failing heart with left ventricular dyssynchrony (DHF), and from a heart after cardiac resynchronization therapy (CRT). Note changes in rate induced action potential duration (APD) shortening. From Aiba and Tomaselli, J Cardiovasc Transl Res. 2012. Permission granted.

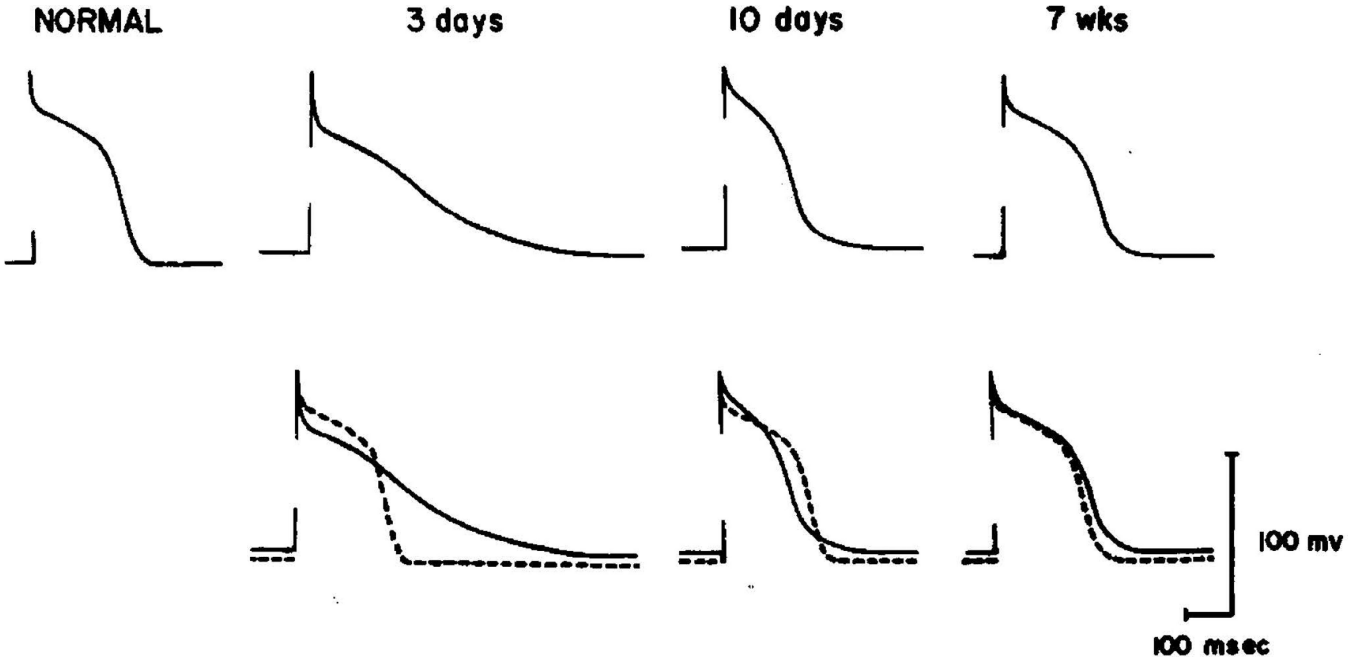

Figure 2.

Action potentials (AP) of subendocardial Purkinje fibers (PF) surviving in the post-myocardial infarction (MI) canine endocardium. Normal means a PF recording from noninfarcted area. Within 3 days post coronary artery occlusion, the PF AP prolongs, by 10days it shortens, and by 7 weeks post occlusion, the AP appears like normal. Below is the normal AP (dashed line) that is superimposed on APs post-MI. From Wit and Friedman, Arch Intern Med. 1975. Permission granted.

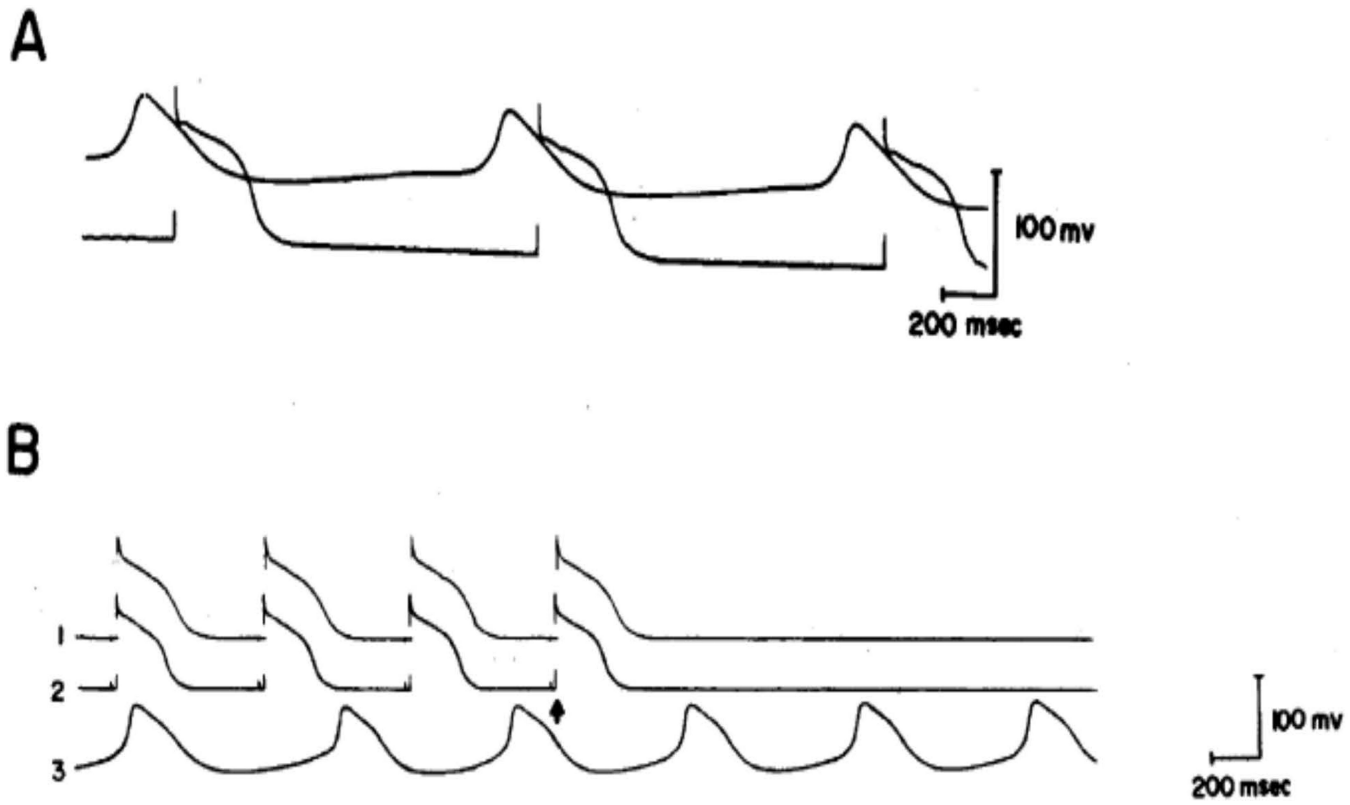

Figure 3.

Two examples of Purkinje fiber (PF) activity recorded from subendocardium of the post-myocardial infarction (MI) heart. Panel A upper shows a PF action potential (AP) that is spontaneously active with a slow phase 4 of depolarization. It is not stimulated. Lower is AP from a PF in an adjacent region which is activated by the spontaneous PF above. Panel B shows APs from 3 sites in another infarcted preparation. In 1 and 2, stimulus activates healthy looking APs. In 3, a PF AP that is spontaneously active appears not to be affected by the stimulation. When stimulus is turned off, PF of 3 continues to depolarize but does not activate the other regions (exit block). From Janse and Wit, Physiol Rev. 1989. Permission granted.

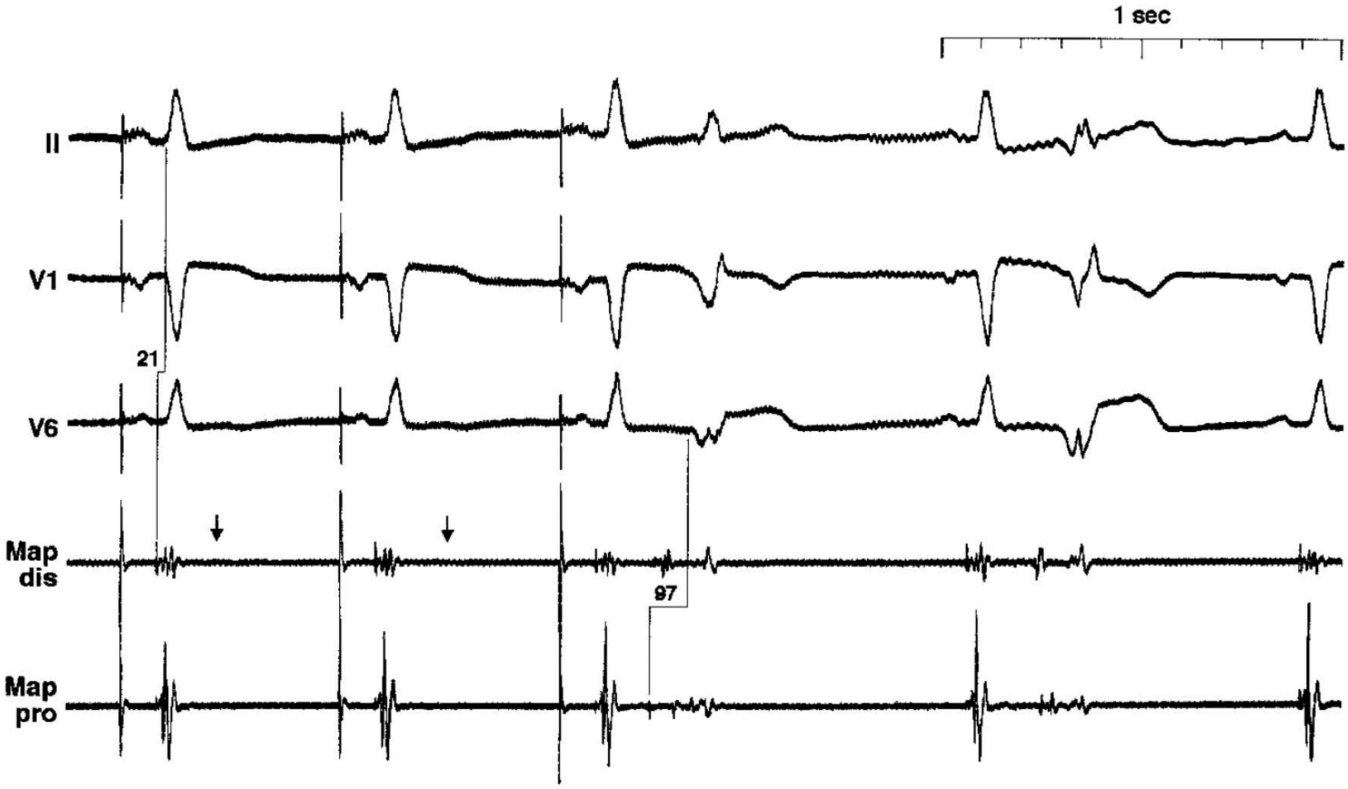

Figure 4.

Intracardiac electrogram during triggering PVC. Mapping catheter is at the successful ablation site. No diastolic potential detected after first 2 atrial paced beats (arrow). Note Purkinje potential preceding PVC after third atrial paced beat by 97 ms. From Bansch et al, Circulation 2003. Permission granted.

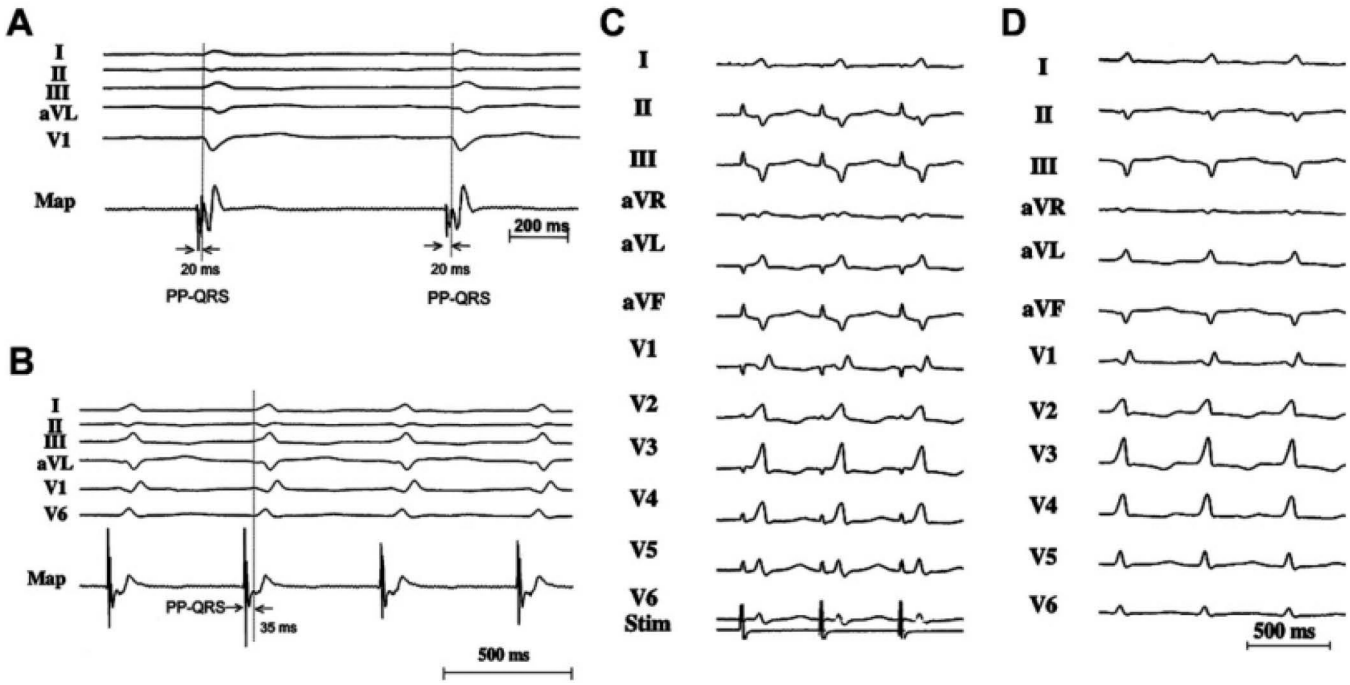

Figure 5.

Intracardiac electrogram demonstrating that the Purkinje system is part of the VT circuit. Mapping catheter (Map) is located in the posteroseptal left ventricle where Purkinje potential is seen 20ms pre-QRS during sinus rhythm (A) and even earlier at 35ms pre-QRS during VT (B). Pace map (C) matched the VT configuration (D) from the site showing a Purkinje potential in sinus rhythm. From Bogun et al, JACC. 2006. Permission granted.

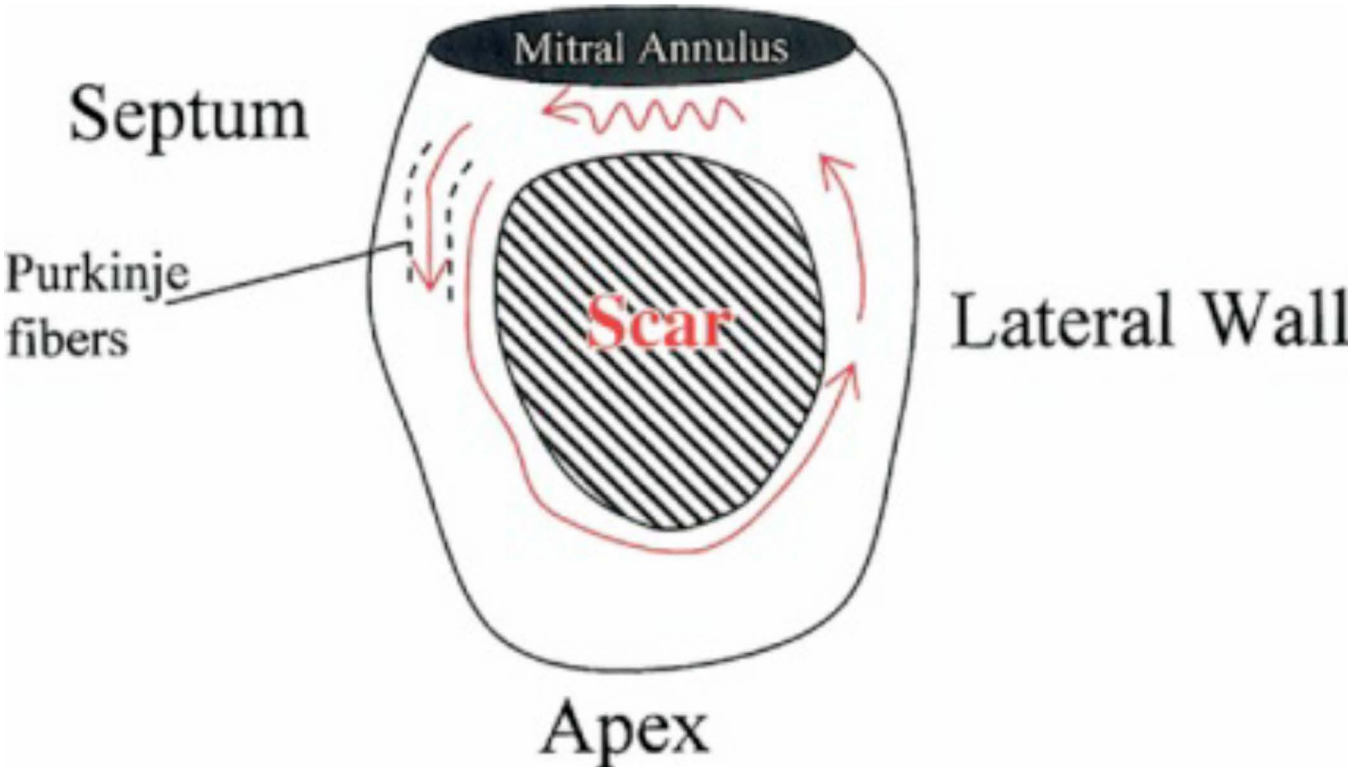

Figure 6.
Illustration of a macroreentry circuit including Purkinje fibers around a central area of scar. From Bogun et al, JACC. 2006. Permission granted.

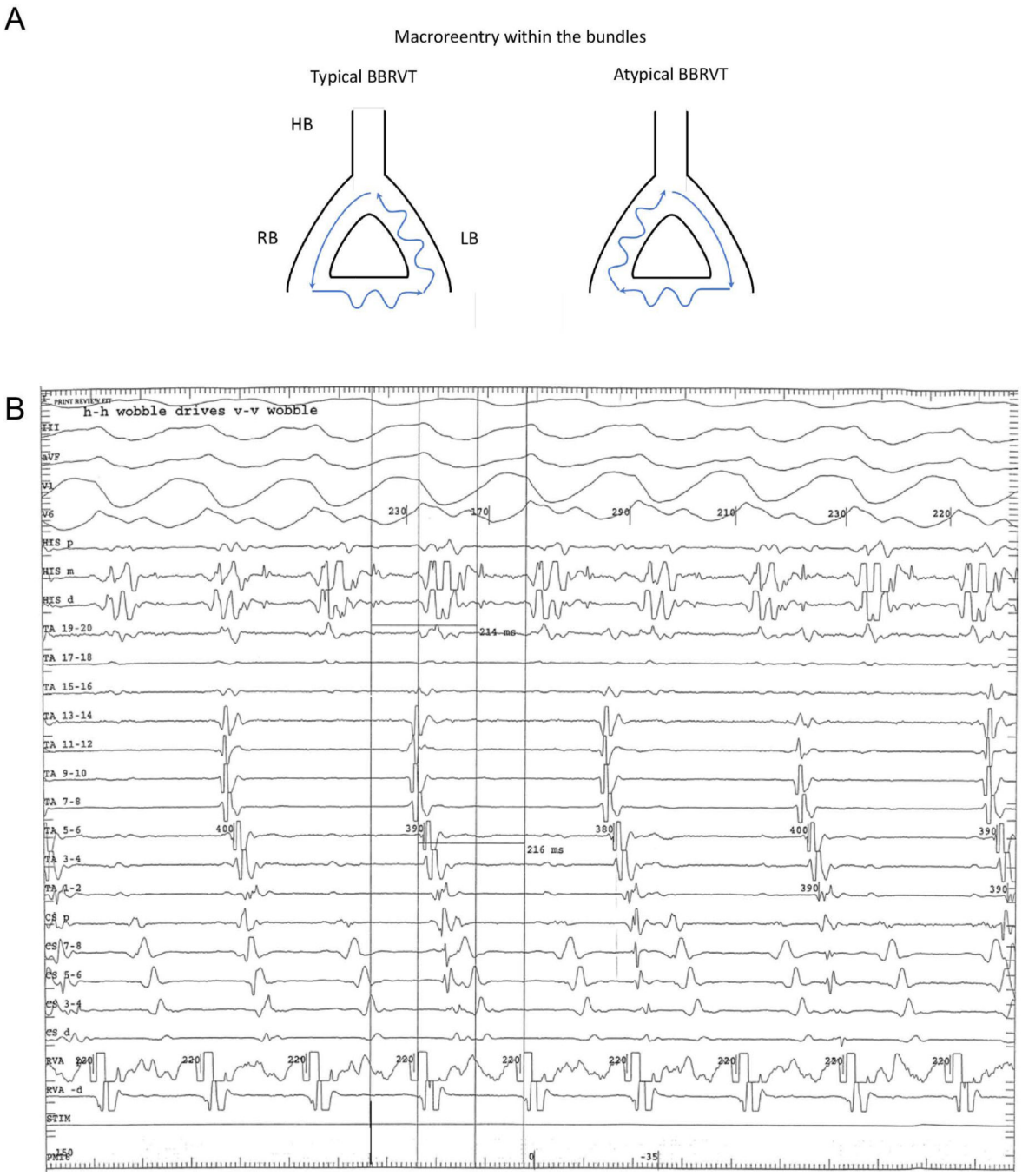

Figure 7.

A) Bundle branch reentry tachycardia utilizes a macroreentry circuit. Typical bundle branch reentry uses the right bundle branch as the antegrade limb and the left bundle branch/ fascicles as the retrograde limb. Atypical bundle branch reentry employs the right bundle branch as the retrograde limb. BBRVT=Bundle branch reentry VT. HB=Bundle of His. RB=Right bundle. LB=Left bundle. B) Typical bundle branch reentry results in tachycardia with a LBBB morphology and conventional intracardiac findings of His recording preceding the QRS and HH wobble driving VV wobble.

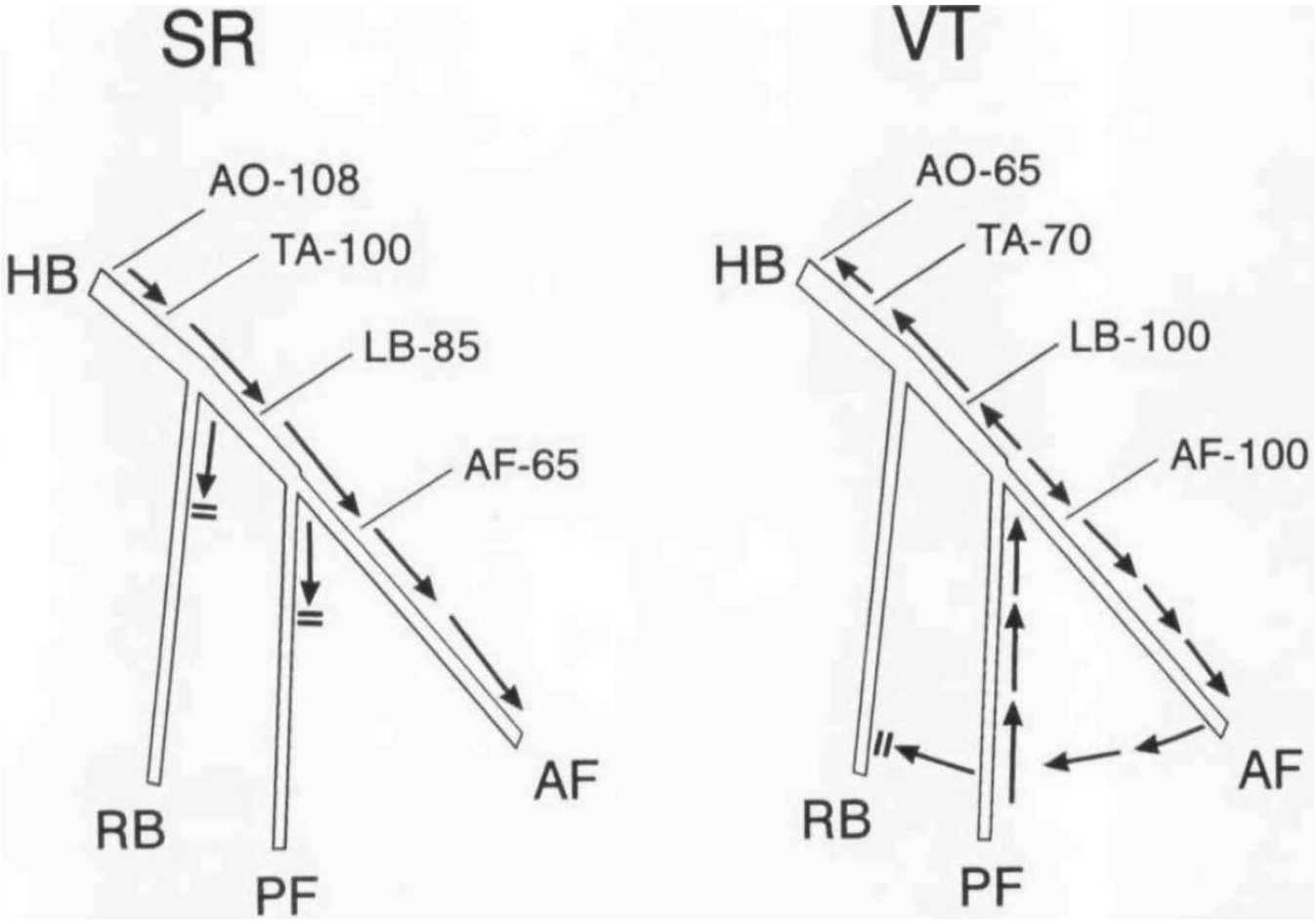

Figure 8.

Schema for interfascicular reentry tachycardia. Listed conduction times (ms) are to ventricular activation during sinus rhythm (SR) and ventricular tachycardia (VT). Note that the AF-V conduction time during VT is the same as the LB-V conduction time, ruling out antegrade conduction over the common bundle. Electrophysiology study demonstrated that the antegrade limb was the anterior fascicle and the retrograde limb the posterior fascicle. Note that this schema is a simplification that does not reflect the complex interweaving within the fascicles. From Crijns, et al. JCE 1995. Permission granted.