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Treatment of ventricular arrhythmias: What's New?

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ABSTRACT

Ventricular arrhythmias can present as asymptomatic premature ventricular complexes (PVCs) or non-sustained ventricular tachycardia (VT), symptomatic presentation of the former arrhythmias, or sustained VT with minimal symptoms to full hemodynamic collapse. The most important and feared consequence of VT is sudden cardiac death (SCD). Independent of SCD risk, frequent ventricular arrhythmias can cause substantial symptoms. Implantable cardioverter defibrillators (ICDs) are the foundation of managing patients at high risk for SCD due to their ability to automatically identify and defibrillate malignant ventricular arrhythmias. Unfortunately, defibrillation is associated with significant physical and emotional adverse effects. Other treatment options include antiarrhythmic drugs, which have substantial toxicities and limited efficacy, and catheter ablation. The techniques and strategies for VT ablation have advanced considerably in recent years leading to a rapid expansion of indications and use. In this review, we discuss current state of the art therapies for ventricular arrhythmias and highlight some of the most promising areas of ongoing development.

Introduction

Ventricular arrhythmias can develop in the setting of myocardial ischemia, fixed structural heart disease due to prior myocardial infarction or non-ischemic disease, cardiac channelopathies, and can also occur in otherwise normal hearts. The spectrum of ventricular arrhythmias includes a range from entirely asymptomatic premature ventricular complexes (PVCs) or non-sustained ventricular tachycardia (VT), symptomatic presentation of the former arrhythmias, sustained VT with minimal symptoms, to sustained VT or VF with hemodynamic collapse.

The most important and feared consequence of VT is sudden cardiac death (SCD). The American Heart Association estimates over 550,000 annual cardiac arrests, which accounts for half of all cardiovascular deaths [1,2]. Independent of SCD risk, frequent ventricular arrhythmias can cause substantial symptoms. Additionally, the causal direction between ventricular arrhythmias and left ventricular dysfunction appears to be circular, as ventricular ectopy directly worsen left ventricular function and frequent VT episodes are indirectly detrimental to left ventricular function through the effect of defibrillator shocks.

Implantable cardioverter defibrillators (ICDs) are the foundation of managing patients at high risk for SCD due to their ability to automatically identify and defibrillate malignant ventricular arrhythmias. Unfortunately, defibrillation is associated with significant physical and emotional adverse effects. Other treatment options include antiarrhythmic drugs, which have substantial toxicities and limited efficacy, and catheter ablation. The techniques and strategies for VT ablation have advanced considerably in recent years leading to a rapid expansion of indications and use.

In this review, we discuss current state of the art therapies for ventricular arrhythmias (Fig. 1), with a focus on monomorphic ventricular arrhythmias, and highlight some of the most promising areas of ongoing development.

Current state of the art therapies

Imaging

Imaging plays a fundamental role in the diagnosis of structural heart disease and in guiding management strategies. Transthoracic echocardiography remains the initial modality of choice, with recommendations for specific arrhythmic etiologies discussed later in this text. Cardiac magnetic resonance imaging (CMR), cardiac computed tomography, and intraprocedural imaging with intracardiac echocardiography (ICE) are also utilized with expanding roles in the management of ventricular arrhythmias.

CMR performed before ablation procedures can identify abnormal and potentially arrhythmogenic substrate by the presence

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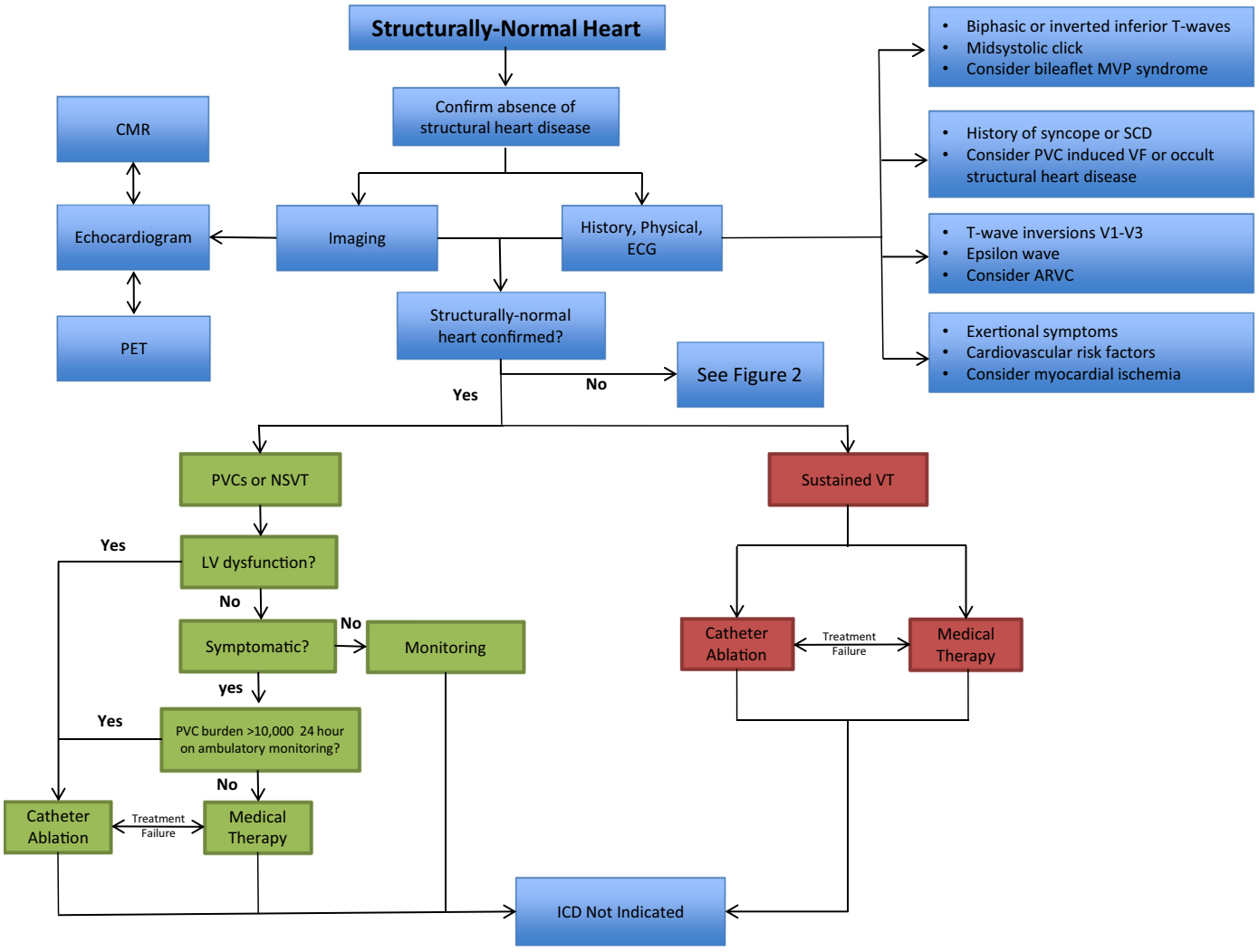

Fig. 1. (a): Ventricular arrhythmias in the setting of a structurally normal heart. ECG: Electrocardiogram; PVC: premature ventricular complex; VT: ventricular tachycardia; NSVT: non-sustained ventricular tachycardia; ICD: implantable cardioverter defibrillator; CMR: cardiac magnetic resonance imaging; PET: positron emission tomography; ARVC: arrhythmogenic right ventricular cardiomyopathy. (b): Sustained VT in the setting of structural heart disease. AAD: antiarrhythmic drugs; ARVC: arrhythmogenic right ventricular cardiomyopathy; ICD: implantable cardioverter defibrillator.

of late gadolinium enhancement, which predicts development of re-entrant VT, and provides targets for catheter ablation, thus improving outcomes (Fig. 2) [3,4]. Cardiac computed tomography has also been shown to identify ablation targets [5,6]. Furthermore, integration of CMR images into electroanatomical mapping has been shown to be feasible for patients with both post-MI and non-ischemic VT and is associated with reduced VT recurrence [7].

In post-MI patients, a computational model has been developed that utilizes CMR data to predict reentrant circuits in or near abnormal myocardial tissue caused by electrical stimuli from various locations. This is then used to predict the propensity for developing VT and appears to outperform current clinical methods of risk stratification including LVEF and electrophysiology studies [8].

Patients with VT frequently have ICDs, which has traditionally limited their availability and utility due concerns about safety and artifact [9]. Recently, the safety of thoracic magnetic resonance imaging, including CMR, has been demonstrated when a standardized protocol for programming and monitoring is employed [10]. Artifact associated with ICDs can also been managed with modified techniques including the use of a modified wideband pulse sequence for late gadolinium enhancement imaging [11–13] . The presence of an ICD should not be considered a contraindication to obtaining valuable information from pre-procedural CMR. The possibility of electromagnetic interference with ICDs is minimal with CT, compared to CMR. Additionally, while lead related artifacts are larger on CT, artifacts related to the generator, which can be quite large on CMR, are minimal with CT. On CT imaging, both wall thickness and attenuation have been successfully utilized to localize arrhythmic substrates [14,15].

Intra-procedural imaging with ICE is a unique imaging modality that can provide high-resolution real-time visualization of cardiac structures and catheters. This can increase the safety of common techniques including trans-septal puncture [16]. During electrophysiology studies, ICE images can be integrated with electroanatomic systems to provide accurate 3-dimentional anatomic maps. Continuous ICE monitoring during the procedure also allows for catheter guidance to anatomically challenging regions, assurance of adequate contact force, and early recognition of complications including pericardial effusion or thrombus formation [17,18].

Idiopathic ventricular arrhythmias

A subset of patients with ventricular arrhythmias and no identifiable genetic arrhythmia syndrome has structurally normal hearts

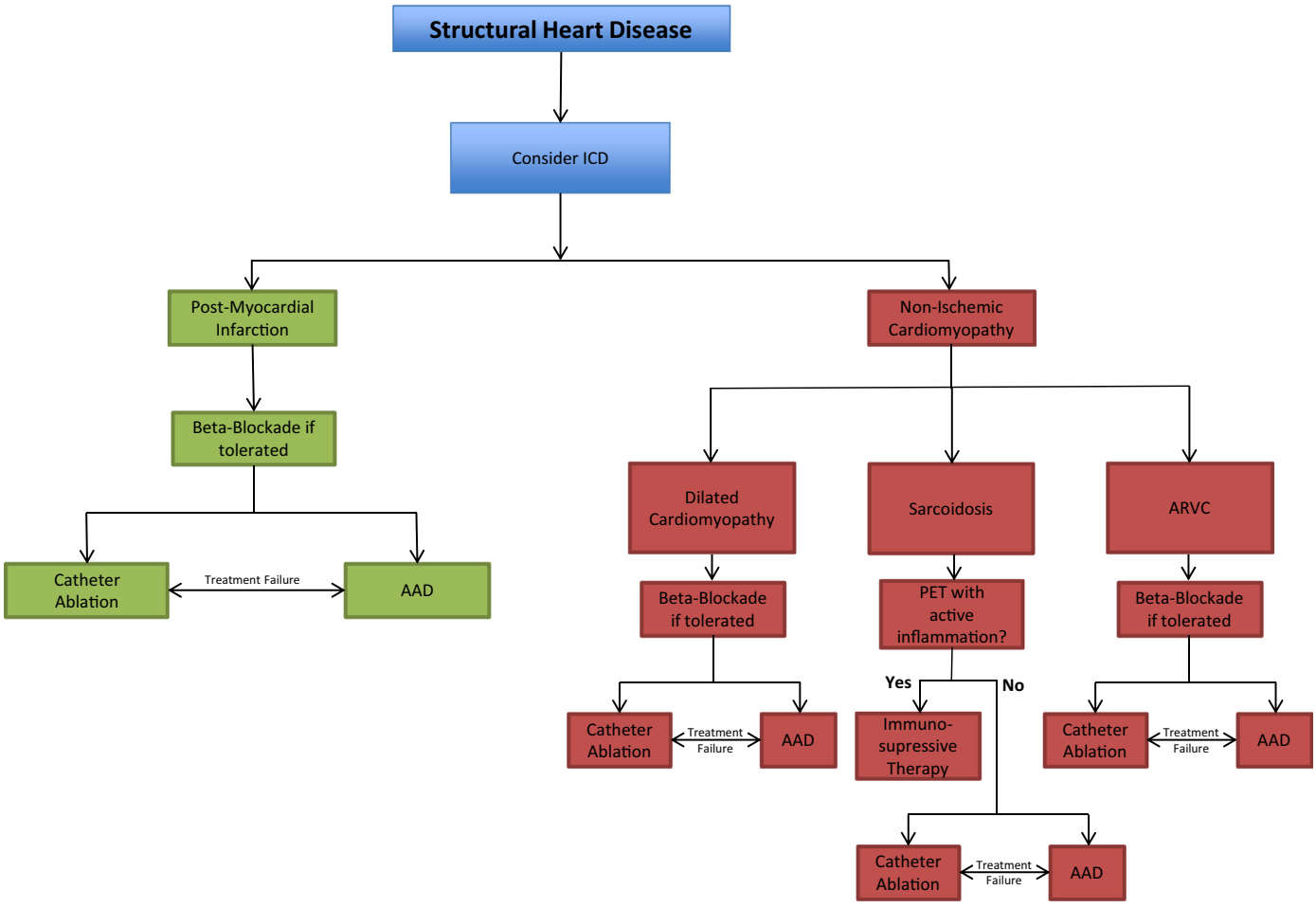

Fig. 1. Continued

with preserved cardiac function and no myocardial scar. These patients are considered to have idiopathic ventricular arrhythmias, which includes PVCs and VT. Though hemodynamic compromise or severe symptoms are uncommon, patients can experience palpitations or left ventricular dysfunction. Idiopathic PVCs and VT are characterized by whether or not they arise from the outflow tracts.

Premature ventricular complexes

Idiopathic PVCs are the most common ventricular arrhythmias in patients with structurally normal hearts. Approximately 40% of adults experience PVCs on 24 h Holter monitoring [19]. While PVCs are generally considered benign, recent population studies have suggested that PVC burden is associated with increased morality and risk of congestive heart failure [20]. The risk of developing PVC-induced cardiomyopathy can be predicted by significant PVC burden (> 10%), PVC QRS complex width (> 150 ms), and circadian variability [21–23].

Outflow tract sources

The most common site of PVCs in patients with structurally normal hearts is the right ventricular outflow tract (RVOT) although left ventricular outflow tract (LVOT) origin is not uncommon. The mechanism of outflow tract PVCs is usually delayed after depolarizations and triggered activity due to intracellular calcium overload. The PVCs can frequently be induced with exercise, high catecholamine states, or isoproterenol and suppressed with vagal maneuvers or sedation.

Outflow tract PVCs are commonly noted on electrocardiogram (ECG) or stress testing and evaluation with routine blood work including electrolyte measurements and thyroid function tests should be considered along with assessment of left ventricular function with transthoracic echocardiography. Additional evaluation and management depends on the presence and severity of symptoms and evidence of underlying heart disease. If symptomatic, patients commonly report palpitations and less frequently light-headedness or chest pain. If frequent or symptomatic PVCs occur, ambulatory cardiac monitoring should be considered to assess the true PVC burden, presence of multiple PVC morphologies, and correlation with symptoms.

Treatment is recommended in patients with symptoms associated with PVCs or evidence of PVC-induced cardiomyopathy and can be considered in asymptomatic patients with > 10% PVC burden. While their efficacy is limited, beta-blockers are first line therapy given a favorable safety profile [24]. If beta-blockade is unsuccessful or not tolerated, non-dihydropyridine calcium-channel blockers can be used although additional antiarrhythmic agents, including amiodarone, sotalol, or flecainide, are generally reserved for patients who cannot undergo or have failed catheter ablation. There is increasing evidence that flecainide may be safe and effective in these patients [25]. In the absence of symptoms and with < 10% burden of PVCs, often no further treatment is required.

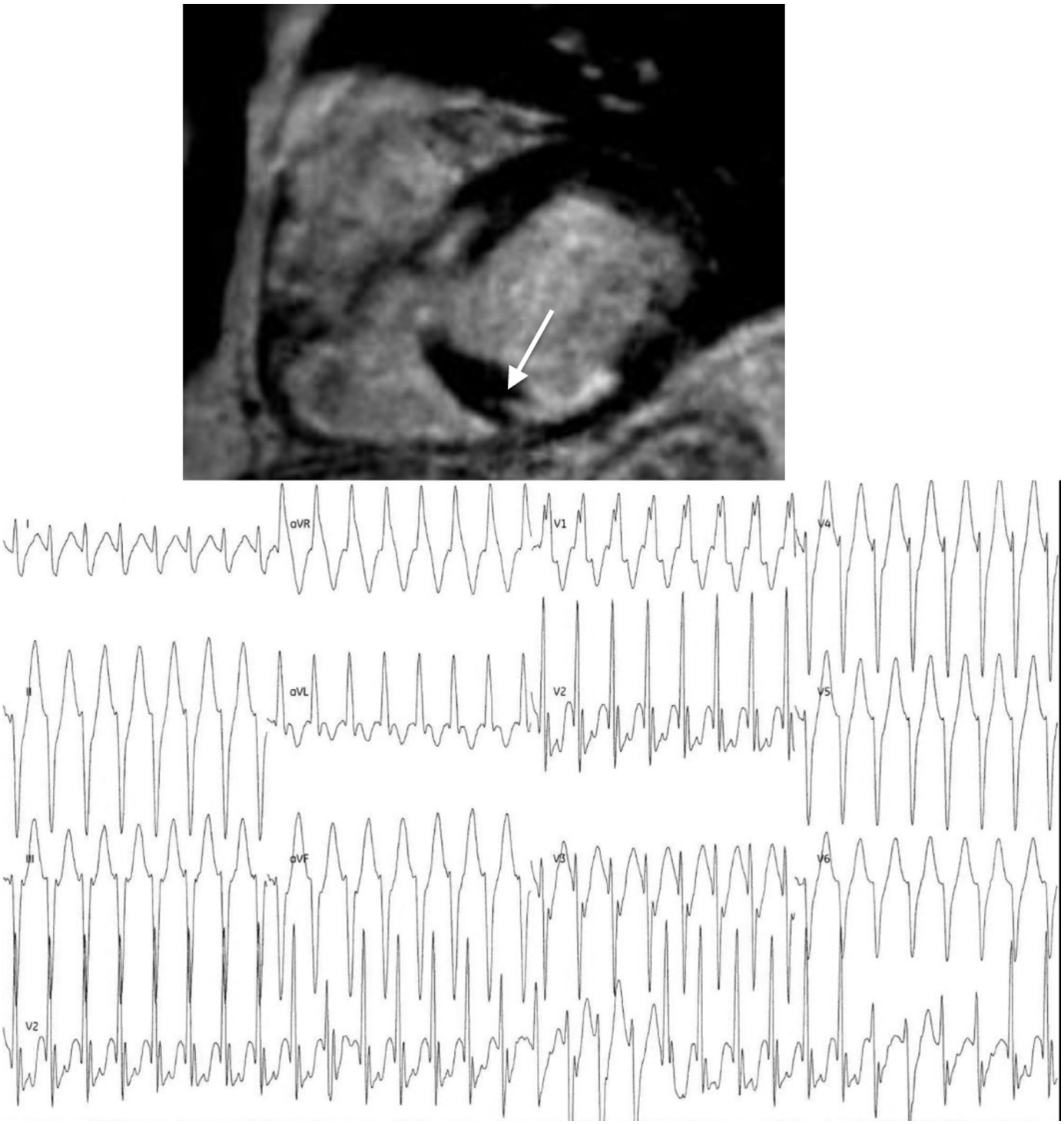

Fig. 2. Cardiac magnetic resonance imaging showing late gadolinium enhancement (arrow) in the inferoseptum consistent with the right bundle superior axis VT suggestive of an inferospetal exit site on electrocardiogram.

Circadian variability of PVCs can also be helpful to predict the risk of developing cardiomyopathy and to guide therapeutic decisions. In addition to overall daily PVC burden, consistent frequency throughout the day is an independent predictor of developing PVC-induced left ventricular dysfunction [23]. Ambulatory monitoring of circadian variability of PVC burden and the association with baseline heart rate can guide management decisions as well. Patients with PVCs that occur during fast baseline heart rates are more likely to be response to induction with isoproterenol during ablation and patients with PVCs that are heart rate independent are less likely to have successful catheter ablation [23,26]. We have found the administration of IV calcium or even esmolol to be helpful for PVC induction in such cases.

Catheter ablation can target outflow tract arrhythmias that arise from the RVOT, LVOT, aortic cusps, or aorto-mitral continuity. ECG is useful to localize PVCs prior to catheter ablation. PVCs that orig-

inate from the outflow tracts are characterized on ECG by a positive QRS complex in the inferior leads and a left bundle branch block morphology in lead V1 (rS). ECG can be used to distinguish RVOT and LVOT sources based on the precordial R-wave transition from a predominate S wave to a predominate R wave (rS to Rs). Transitions before V3 suggest an LVOT source and after V3 suggest an RVOT source [27]. If the transition occurs at V3, comparison to the patient's sinus rhythm pre-cordial transition can be helpful: a V2 transition ratio $[R/(R+S)_{VT} \div R/(R+S)_{sinus}] \geq 0.60$ suggests LVOT origin and pre-cordial transition of the ventricular arrhythmia that is later than in the patient's sinus rhythm excludes LVOT origin [28].

Activation mapping is the preferred technique for PVC source identification and targeting with ablation. Activation mapping relies on frequent PVCs or induction, for example with isoproterenol. When PVCs occur, activation mapping identifies the site of the earliest local ventricular activation as the target for ablation. When PVCs cannot be induced during the procedure, pace mapping can be used at various sites to compare the paced QRS morphology to the known PVC morphology.

Optimal PVC ablation utilizes activation mapping. The inability to induce PVCs is the most common reason for ablation failure as pace mapping alone has lower specificity and spatial resolution [29,30]. Outflow tract PVC ablation has favorable outcomes with acute success rates of 80–100% and RVOT origin is the factor most predictive of ablation success [31]. Procedural risks include vascular injury (hematoma, pseudoaneurysm, AV fistula), which occurs in approximately 2% of patients, and cardiac tamponade, coronary artery injury, or AV block ($< 1\%$) [30,31].

The overall prognosis for outflow tract PVCs is excellent with recurrence rates post ablation of 0–23%. Among patients with PVC-induced left ventricular dysfunction, degree of PVC burden reduction predicts success with over 80% of patients experiencing an improvement in ventricular function [32].

Non-Outflow tract sources

Non-outflow tract PVCs most commonly arise from the papillary muscles or fascicles. Triggered activity is felt to be the mechanism for papillary muscle sources – either the anterolateral and posteromedial papillary muscles, which originate from the mid anterolateral and mid inferior left ventricle respectively. These sources make up approximately 5–10% of idiopathic ventricular arrhythmias and appear on ECG with a right bundle branch like morphology with either superior or inferior axis depending on the papillary muscle source [31]. Fascicular ventricular arrhythmias, in contrast, typically do not present as isolated PVCs and will be discussed in the VT section of this text.

Non-outflow tract PVCs are managed similarly to outflow tract PVCs. Symptoms beyond palpitations are infrequent from PVCs alone and therapy depends on the presence of symptoms and PVC burden with the same criteria. While minimally effective, beta-blockers are first line therapy for symptomatic papillary muscle PVCs and additional antiarrhythmic drugs are only recommended if catheter ablation fails or is contraindicated.

Catheter ablation for papillary muscle PVCs requires localizing the origin to a papillary muscle with pre-procedural imaging, activation mapping, or less-ideally pace mapping, with the location confirmed with intracardiac echocardiography (Fig. 3). While generally effective, the success rate of ~60% is lower than for other idiopathic PVC ablations owing to the deep intramural locations of the thick papillary muscles and the challenges of maintaining stable catheter contact with the actively contracting papillary muscle [31]. Given these challenges, papillary muscle ablation is often prolonged compared to ablation of other idiopathic ventricular arrhythmias but is associated with similar complication rates [33].

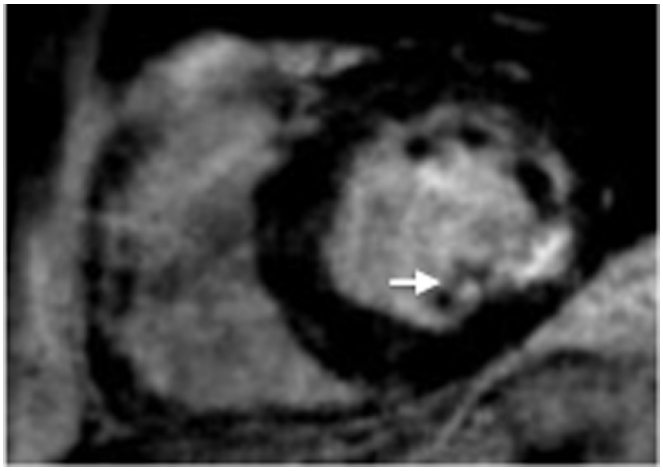

Fig. 3. Involvement of the lateral wall as well as posteromedial papillary muscle (arrow) with late gadolinium enhancement on cardiac magnetic resonance imaging, suggestive of scar infiltration into the papillary muscles.

Recurrence after ablation often occurs with a slightly altered morphology due to modification of the original exit site [31].

Risk stratification

While PVCs in structurally normal hearts are generally benign as discussed above, there is need for additional risk stratification in special situations.

When papillary or fascicular PVCs alternate with outflow tract PVCs in patients with bileaflet mitral valve prolapse, the risk of SCD appears to be elevated [34]. The risk appears to be highest in young women with biphasic or inverted T-waves in the inferior leads on baseline ECG and should be considered in patients with audible midsystolic click although the overall risk in this population is not well characterized [35]. The mechanism is felt to involve fibrosis of the papillary muscles and the inferobasal left ventricular wall due to myocardial stretch by the prolapsing leaflet [36,37]. CMR can be used to identify this often-concealed arrhythmic substrate [36].

Isolated PVCs can rarely initiate polymorphic VT or ventricular fibrillation (VF) and this possibility should be considered in patients who present with syncope or resuscitated SCD and exhibit PVCs on monitoring. In these cases, PVCs have been described to predominantly arise from the Purkinje system or the RVOT but can be observed from other foci [38]. While the majority of PVCs occur at relative fixed coupling interval from the preceding QRS complex, increased variability in this interval along with multifocal PVCs or non-sustained VT may be associated with increased risk of malignant arrhythmias and SCD [39,40]. This may reflect different patterns of activation distal to PVC origin, or variable simultaneous arrhythmogenic mechanisms. Furthermore, focal structural abnormalities may exist that are not identified with standard imaging techniques. Given the causal implication of PVCs in polymorphic VT and VF, catheter ablation of PVC triggers has the potential to cure these conditions [31]. Nevertheless, an ICD is indicated for prophylaxis of sudden death given the possibility of PVC source recovery or activation of other PVC sources.

Ventricular tachycardia

While less common than PVCs in structurally normal hearts, VT is more likely to result in symptoms, especially palpitations. Severe symptoms or hemodynamic compromise is still rare and the risk of SCD is low even with sustained idiopathic VT at rapid rates. For this reason, placement of an ICD is generally not indicated. Similar

to idiopathic PVCs, idiopathic VT is predominately classified based on whether it arises from the outflow tracts. Identification of outflow or non-outflow tract VT should result in further evaluation including laboratory tests and transthoracic echocardiogram to ensure there are no reversible causes or underlying structural heart disease.

Outflow tract sources

Outflow tract VT originates from the same locations as do outflow tract PVCs. The mechanism is most frequently delayed after depolarizations and triggered activity in structurally normal hearts. The acute management of sustained outflow tract VT, which is recognized based on the same ECG characteristics of outflow tract PVCs, exploits the mechanistic dependence on cyclic AMP, which is effectively inhibited by vagal maneuvers or adenosine.

Outflow tract VT that is confirmed to be idiopathic can be medically managed comparably to PVCs with AV-nodal blocking agents, although catheter ablation is generally considered first line for symptomatic VT. Alternative antiarrhythmic drugs such as amiodarone, sotalol, or flecainide can be considered in patients who cannot undergo or have failed ablation. Catheter ablation of outflow tract VT is technically identical to that described for outflow tract PVCs. Excellent outcomes with low procedural risk can be achieved especially with RVOT sources and when induction of VT permits activation mapping to be utilized [31].

Non-Outflow tract sources

The papillary muscles or fascicles are the most common origins of non-outflow tract VT. Triggered activity occurring in the papillary muscles can cause PVCs as discussed previously or sustained or non-sustained VT. These arrhythmias are triggered by increased adrenergic tone and are therefore often brought out by exercise. First line management targets this mechanism with beta-blockers to limit adrenergic input. Unfortunately, they are often minimally effective.

Catheter ablation is considered in patients who fail or do not tolerate beta-blockade and for the rare patients with papillary VT who present with syncope. The procedure is the same as for papillary muscle PVCs with success largely dependent on the ability to induce VT during the procedure. Due to the challenge of maintaining stable catheter contact with the contracting papillary muscle, cryoablation can be considered for improved catheter stability and is associated with higher success rates [33].

Unlike papillary muscle sources, fascicular ventricular arrhythmias are commonly VT as opposed to isolated PVCs. The ECG appearance is consistent with a right bundle branch block with a superior or right axis depending on whether the PVC originates from the left posterior or left anterior fascicle. Compared with papillary muscle PVCs, fascicular PVCs have a narrower QRS (127 ± 11 ms vs 150 ± 15 ms) and have an rsR/ pattern in lead V1 [41].

In structurally normal hearts, fascicular VT is generally caused by re-entry involving presumably abnormal Purkinje tissue with slow anterograde conduction that creates a circuit with one of the fascicles (most commonly the posterior fascicle) acting as the rapidly conducting retrograde limb. The ECG appearance varies depending on the exit site of the circuit from the retrograde-conducting fascicle. Over 90% of fascicular VT exits from the left posterior fascicle, which results in a right bundle branch block appearance with a superior axis. Most of the remaining fascicular VTs exit from the left anterior fascicle and are distinguished by a right bundle branch block with a right axis. Rarely ($< 1\%$), simultaneous anterograde activation of the left anterior and posterior fascicles with slow retrograde conduction through a separate septal fascicle can result in upper septal fascicular VT, characterized by a relatively narrow (QRS < 110 ms) and normal axis [42]. Automatic or triggered activity of the Purkinje fibers can also cause fascicular VT although this is more common in patients with ischemic heart disease [43].

Management of fascicular VT depends on the underlying mechanism. *Re*-entrant fascicular VT is uniquely sensitive to calcium channel blockers, especially verapamil, which can be given intravenously to acutely terminate sustained fascicular VT. Oral long-term verapamil can also be used, although over 20% of patients experience recurrent VT [44]. While beta-blockers can be effective for triggered activity mediated focal Purkinje VT, they are generally ineffective for re-entrant fascicular VT [30]. Catheter ablation is frequently preferred given a favorable safety profile and high success rate in a population that is young (generally ages 15–40 years) and could avoid the need for daily life-long medication [45]. Medical therapy can be considered in patients with infrequent or mild symptoms and those who decline catheter ablation [31].

There are several strategies for ablation of fascicular VT in the absence of structural heart disease depending on the underlying mechanism and whether the VT can be induced during the procedure [30]. When triggered activity results in focal Purkinje ventricular arrhythmias, ablation targets the earliest Purkinje potentials along the left ventricular septum. For re-entrant, verapamil-sensitive fascicular sources, either the anterograde Purkinje potentials can be targeted or, in the case where no VT can be induced, a linear lesion perpendicular to the ventricular long access can be created in the mid-inferior septum [30,31]. Induction is often challenging and the physical presence of the mapping catheter can suppress the arrhythmia. Several alternative approaches have been utilized for ablation [31]. Overall, the long-term success rate of fascicular VT ablation is $\sim$70% with acute efficacy of 85–100% [46]. Complications are rare with rates $< 5\%$ and similar to ablation of other idiopathic ventricular arrhythmias [30].

Risk stratification

While VT in structurally normal hearts is generally benign as discussed above, further evaluation is necessary in special situations to clarify the absence of underlying structural heart disease.

Although transthoracic echocardiography is recommended for any patient with frequent PVCs or VT, suspicion of underlying structural heart disease must be particularly high in certain cases. Arrhythmogenic right ventricular cardiomyopathy (ARVC) and cardiac sarcoidosis can result in scarring in the outflow tract and cause apparent idiopathic outflow tract PVCs or VT. Clues to an underlying cardiomyopathy include the presence of high-risk symptoms, including syncope, multiple PVC morphologies, or other ECG abnormalities such as T-wave inversions in V1-V3 or the presence of an epsilon wave suggestive of ARVC.

When the degree of suspicion for underlying cardiomyopathy is high despite a normal transthoracic echocardiogram, CMR or positron emission tomography (PET) should be considered (Fig. 4). Furthermore, the presence of any exertional symptoms or significant traditional risk factors for ischemic heart disease should prompt coronary evaluation before categorization as idiopathic VT.

Summary

In structurally normal hearts with PVCs or VT, catheter ablation offers a favorable safety profile and should be considered as a first line strategy in patients with sustained idiopathic VT or PVCs that are symptomatic, frequent, or result in left ventricular dysfunction. Medical therapy remains an option for patients who fail catheter ablation and for those who are unwilling or unable to undergo this procedure. It is important to recognize that the risk of SCD in these patients is low and ICDs should not be utilized except in rare high-risk situations.

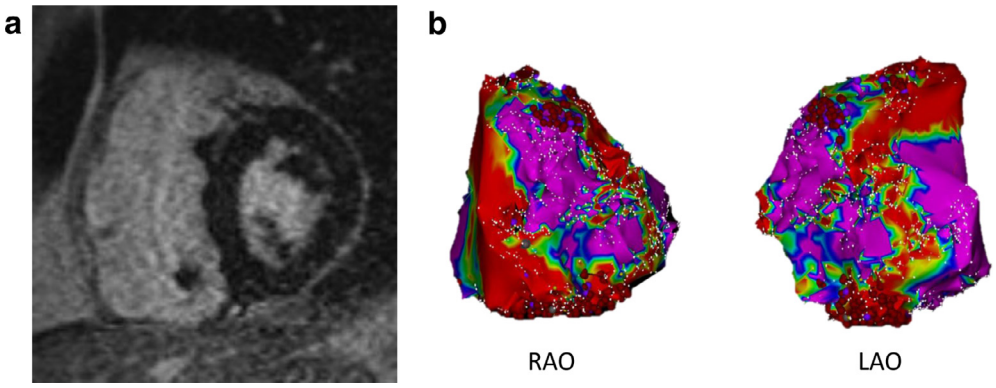

Fig. 4. (a) Short axis cardiac magnetic resonance image showing extensive right ventricular dilation and aneurysmal changes with (b) corresponding right ventricular voltage map in right-anterior-oblique and left-anterior-oblique projections confirming large regions of scar with low voltage (red < 0.5 mV) in a patient with arrhythmogenic right ventricular cardiomyopathy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Ventricular arrhythmias in patients with structural heart disease

The majority of patients with sustained ventricular arrhythmias have underlying structural heart disease, which can include prior myocardial infarction (MI), dilated non-ischemic cardiomyopathy (NICM), cardiac sarcoidosis, and ARVC. Unlike idiopathic ventricular arrhythmias, VT in patients with structural heart disease frequently has hemodynamic consequences and is associated with an increased risk of SCD. The management strategies and their success vary depending on the underlying structural abnormality.

Post-Myocardial infarction

Following MI, infarcted tissue forms a scar made-up of electrically inert fibrotic tissue that can contain interconnected electrically active myocardial fibrils. This provides the heterogeneous myocardial tissue necessary for functional unidirectional block, slow conduction, and the perpetuation of reentrant ventricular arrhythmias [47]. Numerous pathways often exist in individual patients, creating multiple simultaneous circuits and variable VT morphologies on ECG, which reflects the site of exit of the re-entrant circuit.

Additional mechanisms of post-MI VT include automatic or triggered activity in the Purkinje fibers that can present as fascicular VT. When focal Purkinje PVCs occur adjacent to the scar boarder, polymorphic VT or VF can be triggered [48]. In the setting of acute ischemia, VT is generally attributed to delayed after depolarizations and triggered activity [49,50].

The foundation of management for all patients following MI is guideline directed therapy for coronary artery disease and cardiomyopathy. This includes neurohormonal modulation, which has been shown to prevent the harmful remodeling that occurs in the setting of increased neurohormonal activation [51]. Pharmacologic modulation of the neurohormonal system may impact the frequency of ventricular arrhythmias [52,53]. Similarly, sympathetic denervation plays an important role in mitigating the arrhythmia burden in these patients. Locally denervated myocardium, which can be assessed by imaging, is association with ventricular arrhythmias and risk of SCD [54–56]. Areas of viable myocardium without local innervation may be prone to arrhythmias due to significantly longer refractory periods [55,57]. Catheter ablation may modify this abnormal innervation, decreasing the risk of arrhythmias [58].

ICDs are the mainstay for primary and secondary prevention of VT in patients with ischemic heart disease given the high risk of SCD and their ability to terminate VT and improve morality [2]. Beta-blockers are also recommended as they have been shown to improve morality in this population, although they are insufficient to prevent recurrence of VT [59]. Amiodarone, sotalol, or mexiletine can be added to suppress VT. While the most benefit is from amiodarone, it is associated with significant adverse effects including pulmonary, hepatic, and thyroid toxicity. An antiarrhythmic drug strategy decreases the rate of VT as defined by need for an appropriate ICD therapy by ~1/3 but does not significantly improve mortality [60].

Catheter ablation can be performed using the same techniques described for idiopathic VT to map and ablate the source. Substrate modification is also generally performed during catheter ablation with destruction of arrhythmogenic substrate that is indirectly identified by the presence of abnormal electrograms, (e.g. fractionated, low voltage potentials, or late signals after the QRS), or evidence of scar on imaging [50,61].

Mechanical assist devices can be useful to allow mapping of hemodynamically unstable VT and for patients who may not tolerate the prolonged invasive procedure. The PAAINESD risk score (Pulmonary disease, Age > 60 years, general Anesthesia, Ischemic cardiomyopathy, New York Heart Association functional class III or IV, Ejection fraction $< 25\%$, VT Storm, Diabetes mellitus) may be useful to predict the need for hemodynamic support [62].

Catheter ablation for patients with ischemic cardiomyopathy has been evaluated in five randomized trials. The first, the substrate mapping and ablation in sinus rhythm to halt ventricular tachycardia (SMASH-VT), which randomized relatively low risk patients who had a prior VT episode but had not received antiarrhythmic drugs (class I or III), demonstrated a 65% reduction in appropriate ICD therapy with ablation [63]. The ventricular tachycardia ablation in coronary heart disease (VTACH) study, randomized patients with reduced left ventricular function and stable VT to ICD alone versus catheter ablation and ICD, and showed improved freedom from VT with ablation over 2 years of follow-up [64]. The Substrate modification study (SMS) and the catheter ablation for ventricular tachycardia in patients with Implantable cardioverter defibrillator (CALYPSO) trial failed to decrease their primary endpoints with CALYPSO being terminated early due to difficulty with enrollment [65,66]. Recently, the ventricular tachycardia ablation versus escalated antiarrhythmic drug therapy in ischemic heart disease (VANISH) trial specifically compared catheter ablation to escalated antiarrhythmic drug therapy and found a 28% reduction in a composite endpoint of death, VT storm, or appropriate ICD shock with ablation. The result was primarily driven by reduction in ICD shocks in patients who had already failed amiodarone at lower doses [67].

Overall, recurrence of VT in this population happens in ¼ to ½ of patients within the first year and many patients require addi-

tional procedures and continued antiarrhythmic drugs [50]. Procedural complications include vascular injury in 2% of patients as well as potentially life threatening complications of cardiac perforation (1.5%), uncontrollable VT (2.5%), stroke or TIA (0.5%), heart block (1%), coronary artery injury (~0.2%), and acute hemodynamic decompensation requiring procedural termination or mechanical support (11%) [62]. Although these procedural risks are significant, this population has a life-threatening condition with a very high mortality rate when inadequately treated and regardless of whether procedural complications occur, the early morality rate is high after catheter ablation owing both to recurrent VT and advanced heart failure.

Based on the available data, catheter ablation is recommended in post-MI patients with recurrent VT despite antiarrhythmic drug therapy or in those who cannot tolerate antiarrhythmic drugs. Furthermore, it should be considered for post-MI patients with recurrent VT as an alterative to antiarrhythmic therapy. Catheter ablation offers a trade-off between the procedural risks and the side effects of antiarrhythmic drugs.

Non-ischemic cardiomyopathy

Patients with dilated cardiomyopathy without a prior history of MI are a diverse group with multiple etiologies of left ventricular dysfunction. Varying patterns of myocardial scar, including no fibrosis in up to 30%, to extensive mid-wall fibrosis, as well as patchy interstitial fibrosis can be observed [68]. While multiple mechanisms of VT have been demonstrated, re-entry is the most common [50,69]. In approximately 40% of these patients, CMR identifies evidence of late gadolinium enhancement, which may be more commonly mid-myocardial or epicardial compared to the predominately subendocardial scar in post-MI patients. Late gadolinium enhancement is an important predictor of sudden cardiac death [70].

Bundle branch re-entrant VT can also occur, typically in patient with dilated cardiomyopathy and conduction disease, in which a macro re-entrant circuit is established most commonly with the right bundle conducting antegrade and the left bundle conducting retrograde resulting in a left bundle branch morphology pattern on ECG. This classically results in very rapid rate with significant hemodynamic effects [71].

Medical therapy is similar to that discussed for post-MI patients with VT. ICDs are the mainstay of management given their mortality benefit for both primary and secondary prevention [2]. Recently, the defibrillator implantation in patients with nonischemic systolic heart failure (DANISH) study demonstrated a lack of significant improvement in all-cause morality among those who received an ICD, although sudden cardiac death was decreased [72]. These results have led to debate about the utility of primary prevention ICD implantation in NICM patients, especially when elderly or at increased risk of non-arrhythmic death. It is important to interpret these results with the caveat that a majority of patients in both groups of the study (58%), received cardiac resynchronization therapy, which likely significant improved all-cause mortality in both groups, making it more challenging to identify the benefit of the defibrillator during the follow-up period.

Beta-blockers are nearly universally recommended and provide a strong mortality benefit in patients with reduced left ventricular function [59]. Antiarrhythmic drugs can be used in the same fashion, with amiodarone providing the most benefit and additional agents including sotalol, mexiletine, and dofetilide being used with limited effectiveness. Each of these agents is associated with significant toxicities and risks include QTc prolongation leading to torsade de pointes and severe lung, liver, and thyroid dysfunction with amiodarone [2].

Catheter ablation efficacy in patients with patients with dilated cardiomyopathy tends to be lower than in post-MI patients [73]. This is due to faster and more commonly unmappable VT morphologies, varying architecture of the underlying myocardial fibrosis that makes successful substrate modification challenging, as well as the deep mid-myocardial and epicardial regions of scar that are more challenging to reach with endovascular ablation techniques. There is a unique propensity for abnormal endocardial voltage and VT origin of the peri-valvular region, which influences ablation targets [69].

While mapping techniques are generally similar to those used in post-MI patients, unipolar mapping has been shown to help identify deeper mid-myocardial and epicardial arrhythmogenic substrate [74]. Epicardial ablation, which involves accessing the epicardial space generally with a percutaneous subxiphoid puncture, can be used to target epicardial scar with improved outcomes. Percutaneous epicardial access is unfortunately often not feasible in patients with adhesions from prior surgery, but a modified approach with a surgical subxiphoid or lateral thoracotomy can be utilized. For patients with indications for simultaneous cardiac surgery, ablation can be performed with open sternotomy [75]. However, utilization of mapping systems can be challenging in this scenario. This epicardial ablation technique can also be valuable for post-MI patients who fail endocardial ablation or have evidence of epicardial or transmural scar on CMR [50,75–77].

Cardiac sarcoidosis

Characterized on histopathology by non-caseating granulomas, sarcoidosis is a systemic inflammatory process that can affect the myocardium with or without involvement of other organs. While heart failure can occur, patients frequently present with heart block or ventricular arrhythmias [78]. The inflammation and scarring results in a highly complex myocardial substrate with VT occurring secondary to increased automaticity, triggered activity, and scar-mediated re-entry [79].

PET and CMR can be used to aid in diagnosis of cardiac sarcoidosis and to characterize the arrhythmogenic substrate in the setting of VT. T2 weighted CMR and PET identify active myocardial inflammation that can be managed with a combination of antiarrhythmic drugs and immunosuppressive therapy, especially corticosteroids [79]. Patients without active inflammation on PET but with VT associated with scar in a later phase of the disease are more likely to benefit from ablation than immunosuppressive agents targeting inflammation [80]. A recent study suggests that a significant percentage of patients with unexplained cardiomyopathy and ventricular arrhythmias have evidence of focal myocardial inflammation on PET, which may be targeted with immunosuppressive therapy [81].

Late gadolinium enhancement on CMR typically identifies scar that may reflect re-entry and can be amenable to catheter ablation using the techniques described for patients with dilated cardiomyopathy [82]. While data are limited in this population, the outcomes for catheter ablation in cardiac sarcoidosis are poor with approximately 50% recurrence rate within 2 years, and ablation should only be considered when medical management fails [50,82].

Arrhythmogenic right ventricular cardiomyopathy

Ventricular arrhythmias are common in patients with ARVC and are frequently the primary manifestation of this inherited cardiomyopathy. Fibrofatty tissue replaces normal right ventricular, and occasionally left ventricular myocardium and typically involves the basal inferior and anterior RV and lateral basal LV although

other regions can be affected. The mechanism of sustained VT in this population is scar-related re-entry [83,84].

PVCs and VT associated with ARVC can be confused with idiopathic outflow tract VT with a left bundle branch block morphology and inferior axis. As discussed previously, a high degree of suspicion in the presence of associated ECG features is often necessary to make this diagnosis.

Medical therapy for VT in ARVC is limited and ICDs are the mainstay of therapy for patients with high risk features or history of sustained VT. Pharmacotherapy generally consists of beta-blockers and amiodarone or sotalol can be added to decreases the frequency of recurrent VT [2]. Although recommended, the efficacy of these antiarrhythmic drugs is limited with some evidence suggesting only amiodarone successfully prevents VT [85].

In patients with recurrent symptomatic VT despite beta-blockade, catheter ablation can be considered. Early mapping studies demonstrated the peri-valvular area as a common source of VT and target for catheter ablation although success remains limited with endocardial ablation [86]. More recently, extensive abnormal epicardial substrate has been identified and addition of epicardial mapping and ablation has improved outcomes [87]. Combined endocardial and epicardial ablation is associated with 71% VT-free survival over nearly 5 years of follow-up [88].

Summary

It is important to remember that antiarrhythmic drugs or catheter ablation are not substitutes for ICDs in this population at high risk for sudden cardiac death. Typical medical therapy for recurrent VT in patients with structural heart disease includes a combination of beta-blockers and amiodarone, although sotalol and mexiletine can be considered. Especially in post-MI patients with recurrent VT despite AAD therapy, catheter ablation is a valuable strategy that avoids some of the adverse events associated with antiarrhythmic drug therapy.

Channelopathies

Life threatening ventricular arrhythmias can result from genetic abnormalities in the myocardial cellular membrane function, which is regulated by ion channels for sodium potassium, and calcium. Genetic abnormalities result in several unique syndromes with classic triggers, ECG findings, and management strategies. Several of the more common and well-characterized syndromes are discussed here.

Long QT syndrome

Though first described in the 1950′s, long QT syndrome (LQTS) is the best known and understood channelopathy because of the extensive genotype-phenotype correlations made in the 1990s [89]. LQTS classically presents as syncope triggered by severe emotional or physical stress or auditory stimuli. Several clinical diagnostic features are useful including prolonged QTc intervals (especially $\geq$ 480 ms) without an identifiable cause, history of syncope, family history, documented Torsade de pointes, or T wave alternans. When clinical suspicion is high, genetic testing should be performed to identify any of the common genes mutations and to classify patients by LQTS subtypes.

Avoidance of QT prolonging medications is mandatory. Beta-blockade with propranolol or nadolol is the therapeutic cornerstone and is recommended for most patients [90]. Left cardiac sympathetic denervation has also been shown to be effective and should only be considered in patients who fail or are unable to tolerate beta-blockade [91]. ICD use is associated with significant risk including inappropriate shocks and should only be considered for a subset of high-risk patients following appropriate beta-blockade. Specific genetic mutations and LQTS subtypes have important individualized therapeutic goals, which are beyond the scope of this review.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT), often due to mutations in the RYR2-encoded ryanodine receptor, typically causes exercise induced VT and manifests clinically as syncope, seizures, or SCD associated with exercise. The VT is classically bidirectional and occurs in the absence of identifiable structural heart disease. Resting ECG is often normal so a high degree of suspicion is necessary in patients presenting with a history consistent with cardiac syncope with exertion. Holter-monitoring or stress testing can identify bidirectional VT or, more commonly, PVCs that progress to bigeminy and further in frequency as heart rates increase. Ectopy typically resolves at or before peak workload is achieved and sustained VT during testing is uncommon.

Genetic testing is recommended in patients with suspected CPVT. Structural heart abnormalities must be ruled out with echocardiogram and or CMR. Digoxin toxicity must also be considered in any patient presenting with biventricular VT along with CPVT. Once a diagnosis of CPVT is made, disqualification from competitive sports is generally advised [92]. Beta-blockade, preferably with nadolol, are highly effective and the addition of flecainide can be considered in patients who fail nadolol [92]. Left cardiac sympathetic denervation can also be considered.

ICDs should be used with extreme caution in these patients. There is a well-documented risk of electrical storm with an initial appropriate or inappropriate shock increasing the risk of further catecholamine driven arrhythmias in a potentially fatal cycle. When ICDs are implanted, patients should always have simultaneous pharmacologic therapy to decrease the likelihood of electrical storm [93].

Brugada syndrome

The genetic basis for Brugada syndrome appears to be highly complex, involving over 20 genes [93]. The classic syndrome involves a patient with SCD due to ventricular fibrillation in the setting of a typical ECG pattern with ST elevations in the right precordial leads. The true clinical phenotypes, however, are more complex with a majority of patients with the ECG pattern never having documented syncope or arrhythmia. This challenge is multiplied by the fact that the ECG pattern may change in different clinical and environmental states. The diagnostic criteria have changed multiple times since this syndrome was first described and the majority of attention is focused on patients with Type 1 Brugada ECGs, that is $\geq$ 2 mm J point elevation in a right precordial lead with a coved ST segment followed by a negative T wave [94].

Unlike LQTS and CPVT, ICDs are recommended for all symptomatic patients with Brugada Syndrome. Avoidance of certain drugs that block the cardiac sodium channel are recommended as well as avoidance of fever and large quantities of alcohol. Prophylactic quinidine is often used and if electrical storm occurs, isoproterenol can effectively suppress arrhythmia [94,95]. Recently, ablation of the epicardial surface of the right ventricular outflow tract has been shown to eliminate the Brugada pattern on ECG and to reduce the risk of arrhythmias [96]. There are no universally accepted therapies for asymptomatic patients with Brugada pattern on ECG.

What' new

In recent years there have been many advances in the management of VT. Here we discuss some of the groundbreaking work

in pre-procedural imaging and risk stratification as well as novel mapping and ablation techniques.

New mapping techniques

Novel methods are under development to identify intramural arrhythmogenic substrate that is poorly localized by traditional mapping techniques. The use of an intramural needle has been shown to effectively map deep intramural sources of arrhythmia not well localized by surface catheters [97]. A multipolar 2.5F catheter advanced into a venous septal perforator branch has also been used to identify intramural septal sources and guide ablation [98].

Several novel mapping systems have also been released in recent years. *RHYTHMIA HDx*™ is produced by Boston Scientific and utilizes a multielectrode basket catheter with small, closely spaced electrodes. It is designed to rapidly generate high-resolution activation maps and uses a novel algorithm to annotate high density acquired intracardiac electrograms, thus suggesting critical ablation targets [99]. However, the volume of acquired electrograms limits the ability of users to check individual annotations and thus validation of the output can be difficult. Similarly, the *EnSite Precision*™ (St. Jude Medical) [100], and *CONFIDENSE*™ algorithms (*CARTO*®, Biosense Webster) provide high speed multi-electrode mapping and may improve the accuracy of target identification, provided accurate window settings and electrogram annotation [101].

New ablation techniques

A variety of novel ablation techniques are being developed to reach intramural sources that are difficult to access with current endo- and epicardial techniques. These techniques have focused on improving the biophysics of radiofrequency ablation and the anatomic access to abnormal substrate.

Novel biophysical approaches

While unipolar radiofrequency ablation is the standard for VT ablations, bipolar ablation utilizing two ablation catheters on opposing ventricular walls has been shown to be effective in cases of refractory arrhythmia given its ability to produce larger lesions and to reach deep intramural sources [102]. The value of bipolar ablation is being examined in an ongoing non-randomized study (Bipolar ventricular tachycardia (VT) Study, NCT 02,374,476).

Irrigation of ablation catheters with half-normal saline (0.45% or 4.5 gs per liter of sodium chloride) or 5% dextrose in water (D5) as opposed to traditional normal saline (0.9%) irrigation solutions has been shown to create larger and deeper ablation lesions in ex vivo and in vivo animal models [103]. This is felt to work by decreasing the dispersion of the radiofrequency energy into the higher charge density of normal saline solution, allowing more current to be delivered to the target tissue. In endocardial regions with rapid blood flow, however, the fluid mixes with blood quickly and any charge modification may become insignificant. The clinical benefits of this techniques as well as possible risks have not been thoroughly demonstrated and warrant further study.

A major paradigm shift for arrhythmia suppression that is currently under investigation involves cardiac stereotactic radiation to induce tissue death through apoptosis and microvascular injury. Low-dose ionizing radiation is delivered to targeted tissue based on pre-procedural imaging and noninvasive electrocardiographic imaging during VT. Current data is very limited but suggest the potential to drastically reduce VT burden in patients with high-risk refractory VT without the need for a prolonged interventional procedure [104]. Damage to adjacent tissue remains a concern, especially without the ability to gate radiation delivery to the cardiac cycle. The potential long-term consequences of cardiac radiation are substantial but may be less clinically important in this population. ENCORE (EP-guided Noninvasive Cardiac radioablation for the treatment of ventricular tachycardia) is a non-randomized trial currently evaluating the safety and efficacy of this treatment strategy.

Novel anatomic approaches

An intramural needle technique has also been proposed to reach intramural sources for ablation [97]. Two non-randomized studies are currently enrolling to evaluate the safety and effectiveness of intramural needle ablation. Although these novel techniques for targeting intramural sources of VT are promising, their long-term effectiveness and the safety of creating larger lesions remain to be established.

Case reports have suggested that cannulation of select coronary arteries and veins may allow targeted infusion of ethanol to ablate VT originating from intramural locations that failed traditional radiofrequency ablation [105]. This technique requires that a coronary artery or vein be accessible in a distribution that matches the identified VT source.

Surgical ablation techniques have also matured in recent years with a hybrid electrophysiology and cardiac surgery approach. The substrate is characterized and critical components of the VT circuit identified in the electrophysiology lab prior to performing surgical cryoablation requiring a sternotomy and cardiopulmonary bypass. While invasive, this technique can result in transmural ablation lesions [106]. Surgical and non-surgical techniques have also been developed to modulate the autonomic nervous system with cardiac and renal sympathetic denervation [107,108]. These techniques have demonstrated promising results in decreasing sustained VT and ICD shocks. In patients with refractory VT or VT storm, sympathetic denervation has been shown to achieve a 58% 1-year freedom from VT [108,109]. There is limited data on long-term outcomes and on alternative methods of sympathetic denervation.

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