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ABSTRACT

Premature ventricular complexes (PVCs) are often observed in patients presenting with heart failure with a reduced ejection fraction (HFrEF). PVCs may in some patients be considered to be the cause of heart failure, while in others it may be the consequence of heart failure. PVCs are important prognostic markers in HFrEF. The uncertainty whether PVCs are the cause or effect in HFrEF impacts clinical decision making. In this review, we discuss the complexity of the cause–effect relationship between PVCs and HFrEF. We demonstrate a workflow with the use of a trial period of amiodarone that may discover whether the reduced LVEF is reversible, the symptoms are due to PVCs and whether biventricular pacing can be increased by the reduction of PVCs. The use of non-invasive and invasive (high-density) mapping techniques may help to improve accuracy and efficacy in the treatment of PVC, which will be demonstrated. With these results in mind, we conclude this review highlighting the future directions for PVC research and treatment.

INTRODUCTION

Patients with heart failure (HF) with reduced ejection fraction (HFrEF) have a higher risk for ventricular arrhythmias like premature ventricular complexes (PVCs), (non-)sustained ventricular arrhythmias, ventricular tachycardia (VT) and ventricular fibrillation (VF).[1] Sustained ventricular arrhythmias are risk markers of mortality due to sudden death and progressive HF.[2] PVCs are considered in HF to be a marker of increased mortality risk.[3] In some cases, PVCs are also considered to be the cause of HF, rather than being the consequence.[4] Furthermore, PVCs may reduce percentages of biventricular pacing and therefore impair efficacy of cardiac resynchronisation therapy (CRT).[5] Clinical decision making is complex without certainty about cause–effect relationship between PVC and HFrEF.[1 4] In the current review, we will provide an overview on PVCs in HFrEF, starting with its prevalence, diagnosis and treatment of PVCs in patients with HFrEF. For an overview of PVCs in the setting of specific cardiomyopathies, for example, hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, which have unique and sustained ventricular arrhythmias, we defer to previous reviews on that specific topic.[6 7] Also recently an excellent general review on PVCs has been published.[8] Furthermore, we will provide a workflow for evaluation of cause–effect relationship of PVC and HFrEF and an outline of the use of (non-)invasive mapping techniques. We conclude this review highlighting future directions for PVC research and treatment.

Prevalence of PVC in HF

The overall prevalence of PVCs in the general population is estimated between 4% and 20%, with higher prevalence in women and advancing age.[9 10] Symptomatic PVCs encountered in the young are more often idiopathic and arise from the (right) ventricular outflow tract (a typical example is shown in figure 1A). It may even be encountered in paediatric population and presents a clinical dilemma due to even fewer datasets. The prevalence of PVCs is however higher in patients with a history of HF, myocardial infarction, coronary artery disease or dilated cardiomyopathy.[3 10 11] In patients with HFrEF, PVCs may even be encountered in up to 97% of patients when ambulatory Holter monitoring is performed indicating that it is a common finding.[11] PVCs in the setting of (ischaemic or non-ischaemic) HFrEF are however often more complex, polymorphic and may arise epicardially (an example of an epicardially originating LV outflow tract PVC is shown in figure 1B).

Clinical presentation of PVC in HF

In general, some patients with PVC may be completely asymptomatic, while others may experience invalidating symptoms. The most prominent symptoms are palpitations and (pre)syncope.[12] If PVCs also occur alongside VT, patients may experience sudden onset and offset palpitations and (pre) syncope. A sudden collapse with loss of consciousness without any precipitating symptoms is only rarely caused by a single PVC.[12] In patients who beforehand are known with HFrEF novel symptoms related to PVCs are more concerning as it may proclaim a high-risk situation. In addition, symptoms of PVCs may also relate to (worsening of) the underlying condition (symptoms like dyspnoea, fatigue or impaired exercise intolerance).[12]

Pathophysiological mechanisms of PVC in HF

From a electrophysiological view, there are three mechanisms underlying PVCs: triggered activity, enhanced automaticity and re-entry.[13] PVCs may be initiated by any of these three mechanisms, and mechanisms can differ over time in the same patient. In (young) patients with structural normal hearts, PVCs are usually due to triggered activity, and the site of origin of the PVC is typically the outflow tract.[12 13] In patients with HFrEF and underlying substrate such as myocardial scarring,

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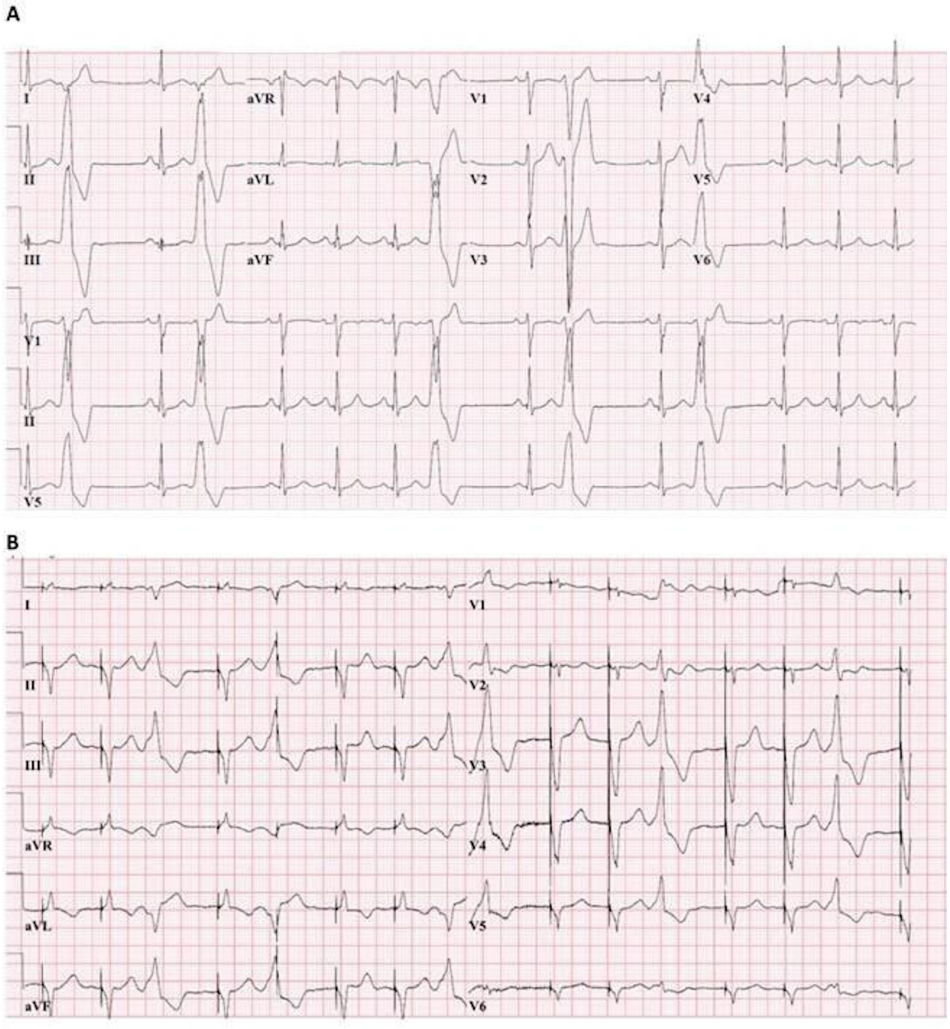

Figure 1 (A) Idiopathic right ventricular outflow tract PVC in a young patient. (B) Epicardial LVOT PVC in a patient with CRT. CRT, cardiac resynchronisation therapy; PVC, premature ventricular complex.

next to triggered activity, re-entrant mechanisms may also play a role. Myocardial scar may harbour surviving muscle bundles with heterogenous conduction pattern and high degree of refractory periods dispersion setting the stage for triggered activity and re-entry.[12] The site of origin of postinfarction PVC's usually correspond to the exit site of VT. Ablation of these PVC often renders the VT non-inducible.[14] There is a complex interplay between HFrEF and PVCs. On one hand, PVCs occur as a consequence of underlying substrate; on the other hand, the PVCs contribute to worsening of ventricular function. Pathophysiological mechanisms underlying development and reversal of PVC-induced ventricular dysfunction is still incompletely understood.[12]Figure 2 shows the hypothetical relationship between these two conditions PVC-induced HFrEF and HFrEF-induced PVCs. In this figure, it is hypothesised that PVC-induced HFrEF and HFrEF-induced PVCs have different substrate, but many triggers and modulators may be similar. Also hypothetically one condition can lead to the other under the right substrate, triggers and modulators (Coumel's triangle).

Clinical diagnosis of PVC in HF

In clinical practice, it is often difficult to distinguish between primary HFrEF with PVCs as a symptom or primary PVCs leading to HFrEF. Even when it seems that there is primary HFrEF due to a structural cause, presence of PVCs may worsen HFrEF and further impair prognosis. Also there may be common risk factors that increase the risk to develop either PVCs or HF. A higher burden is associated with a greater chance on PVC-induced HFrEF, but it may be induced by any PVC burden.[2 15 16] Clinical risk factors have been sought to identify patients who are susceptible to develop worsening of left ventricular ejection fraction (LVEF) due to PVCs. Factors like wider PVC QRS duration (>150 ms), an epicardial origin, presence of polymorphic PVCs, retrograde atrial activation of PVC and interpolation of PVCs are all associated with this outcome.[15 17–19] However, the lack of palpitations (OR 3.95), PVC burden (OR 6.61 for the highest quartile) and epicardial origin (OR 7.95) appear to be the most predominant factors to identify whom may develop lower LVEF due to PVCs.[15] In a small study of 174 patients with frequent idiopathic PVC who were referred for ablation, it was shown that patients who had a decreased LVEF had a mean PVC burden of 33%±13% as compared with those with normal LVEF 13%±12%.[16] Baman *et al*[16] demonstrated that a higher PVC burden was independently associated with PVC-induced cardiomyopathy. In their analysis, a PVC burden of >24% best separated the patient population with HFrEF. Of note, PVC burden may vary daily, and a single measurement with low PVC burden should not rule out PVC cardiomyopathy.

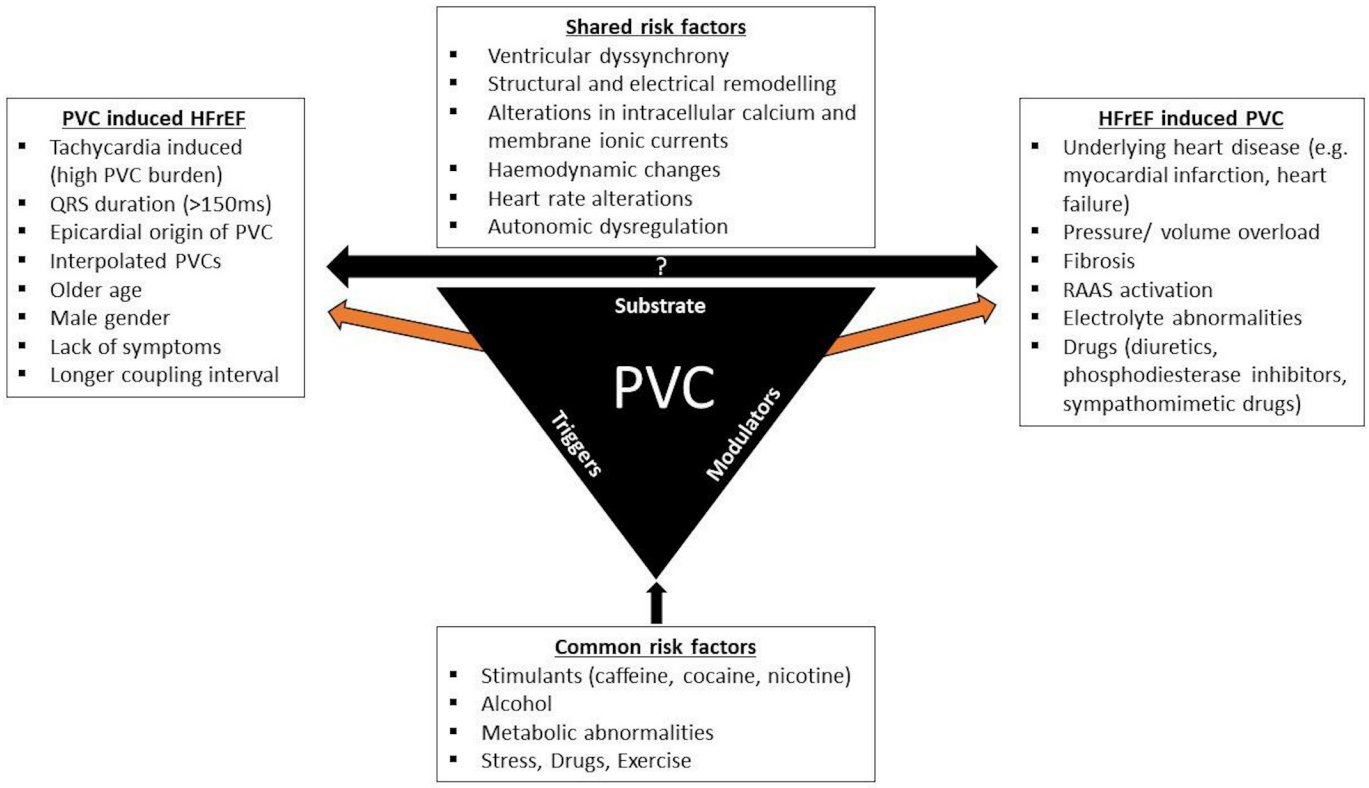

Figure 2 Hypothetical figure of the interplay (using Coumel's triangle) of HFrEF-induced PVC, PVC-induced HFrEF and the possible link between the two. HFrEF, heart failure with reduced ejection fraction; PVC, premature ventricular complex; RAAS, renin–angiotensin–aldosterone system.

PVCs and prognosis

In postmyocardial infarction HF patients, the amount and repetitiveness of PVC on 24-hour Holter monitoring was associated with LVEF and mortality.[20] In addition, >10 PVCs per hour on a 24-hour Holter monitoring was associated with mortality, irrespective of LVEF in patients with postmyocardial infarction.[21] Multiform PVCs increase the risk for adverse events as compared with monomorphic, especially in those with congestive heart failure and previous myocardial infarction.[22] Based on studies with both ischaemic and non-ischaemic aetiology of HF, a relation between New York Heart Association (NYHA) functional class and presence of PVCs and non-sustained ventricular arrhythmias seems present.[23] There is abundant evidence that sustained ventricular arrhythmias are associated with sudden death and progression of HF.[24–28] Some studies have reported a strong association between ventricular arrhythmias and mortality in ischaemic/non-ischaemic HF patients,[24–26] whereas others found a weaker correlation.[27 28] Despite LVEF, no other predictors of sudden cardiac death have been identified; this is the reason that LV dysfunction is still the most important component of the guidelines implantable cardioverter defibrillator (ICD) recommendations.[29] Presence of PVCs may be considered as markers (and thus progression) of disease and, along this line, should chaperon treatment of HFrEF and/or underlying structural disease. This in combination with follow-up and monitoring of arrhythmias to avoid a too early (or too late) arrhythmogenic intervention. Another way of interpreting available literature regarding PVCs is to consider PVCs as a prestage of sustained ventricular arrhythmias, and sustained ventricular arrhythmias are clearly associated with poor outcome in HF.[24–28] Treatment of PVCs may help to prevent sustained ventricular arrhythmias in HF. It is however unknown whether long-term suppression of PVC might be associated with a mortality benefit. Thus far, absence of positive effects of PVC treatment in HF may be caused by side effects/complications of this treatment. Potentially, novel therapies with greater beneficial effects of PVCs or less side effects/complications may shift the balance towards a better benefit/risk ratio of treating PVCs in HF. Additional research in the area of prognosis by PVC suppression is clearly needed.

PVCs and CRT

A specific situation in which PVCs can impact prognosis is in the setting of CRT. In HFrEF patients with dyssynchrony biventricular pacing can improve symptoms, LVEF and prognosis.[30] To achieve this, near continuous biventricular pacing is needed, so the presence of PVCs can cause lower percentages of biventricular pacing (figure 1B shows how PVCs may reduce the percentage of biventricular pacing).[31] When observing patients with <98% biventricular pacing, in one in five patients, PVCs are the explanation.[32] Another report showed that even a relatively low frequency of PVCs (≥0.1%) resulted in a higher probability of low biventricular pacing (<97%).[30] In the same study, PVC-induced low biventricular pacing resulted in less reverse remodelling and a higher risk of hospitalisation of HF, ventricular tachyarrhythmias and death.[30] The mechanism by which this is induced could be due to the interplay of device-induced blanking periods in response to sensed PVCs resulting in loss of synchrony in subsequent heartbeats.[30] This is furthermore highlighted in a subanalysis of Multicenter Automatic Defibrillator Implantation Trial-CRT where non-outflow tract PVCs yield a similar prognosis as true outflow tract PVCs, implying that the origin of the PVCs does not seem to influence outcome and PVCs in general may lead to HF or death.[5] In such cases, antiarrhythmic drugs or catheter ablation to suppress PVCs may be

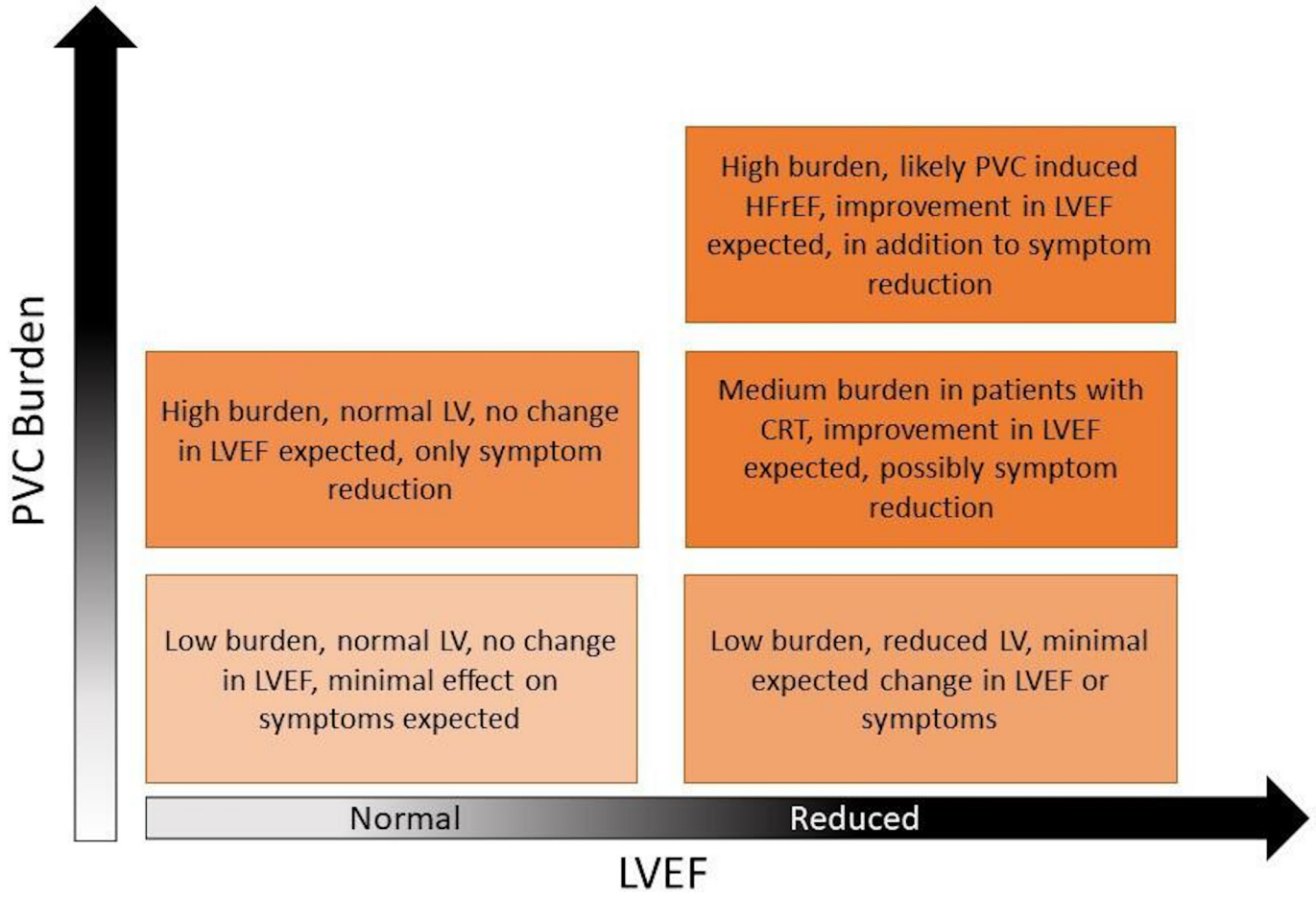

Figure 3 Relation of PVC burden and the occurrence of PVC-induced cardiomyopathy and the improvement expected from catheter ablation. A higher PVC burden is associated with PVC-induced cardiomyopathy.[16] Improvement in LVEF in patients with CRT in relation to PVC burden and catheter ablation is expected from a higher PVC burden.[34] CRT, cardiac resynchronisation therapy; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex.

needed, next to adequate treatment of HF and/or underlying structural disease.[1 33 34] In a small study of 65 CRT patients who were all non-responsive to CRT had >10.000 PVCs on 24-hour Holter. These patients under PVC ablation (76 foci) with acute and long-term success rate of 91% and 88% after 12±4 months of follow-up.[34] The elimination of PVCs by radiofrequency catheter ablation improved LVEF (26.2%±5.5% to 32.7%±6.7%, p<0.001), NYHA functional class (3.0 to 2.0, p<0.001) and enhanced reverse remodelling of the left ventricle.[34] A higher PVC burden was associated with an improvement in LVEF after catheter ablation; in these patients, mean percentage biventricular pacing increased from 76%±12% to 98%±2% (figure 3).[34]

Diagnostic workflow

In case uncertainty exists about the PVC relation with LVEF, percentage of biventricular pacing, or symptoms, a temporary treatment with antiarrhythmic drugs is also a possibility to observe whether the LVEF, percentage of biventricular pacing or symptoms improves while diminishing PVC burden. Our personal workflow is not supported by clinical evidence (or guidelines) but particularly helpful in clinical practice may be a temporary treatment with amiodarone. In general, a 2-week loading dose (200 mg three times a day) and thereafter 200 mg once a day for a period of 3 months with re-evaluation with Holter monitoring and echocardiogram. This will provide valuable information to help the shared decision-making process regarding catheter ablation and help to balance advantages of ablation over procedural complications. In patients with a clear relation between PVCs and LVEF, percentage of biventricular pacing, or symptoms this step can be skipped. Our workflow is shown in figure 4.

Pharmacological treatment or catheter ablation for PVCs in the setting of HF

Indications for treatment of PVC in the setting of HF include: (1) symptomatic PVC burden, (2) presumed PVC-induced LV dysfunction or (3) PVCs initiating life-threatening arrhythmia such as VT/VF. At present, there is no indication for treatment of frequent PVCs in the absence of symptoms or LV dysfunction. If there is a high PVC burden (>10%), follow-up echocardiography may identify patients who develop ectopy-mediated cardiomyopathy. In general, patients with HF and frequent PVCs should be treated with HF guideline-directed medical therapy. Following unloading of the heart, the number of PVCs may already decrease, which may demonstrate that the PVCs are the result rather than the cause of HF in a specific patient. If PVCs persist, the diagnosis of PVC-induced cardiomyopathy can be confirmed following improvement in LV function after PVC suppression. Most evidence for treatment of PVCs, either with drug therapy or catheter ablation, is acquired from studies performed in patients with non-structural heart disease

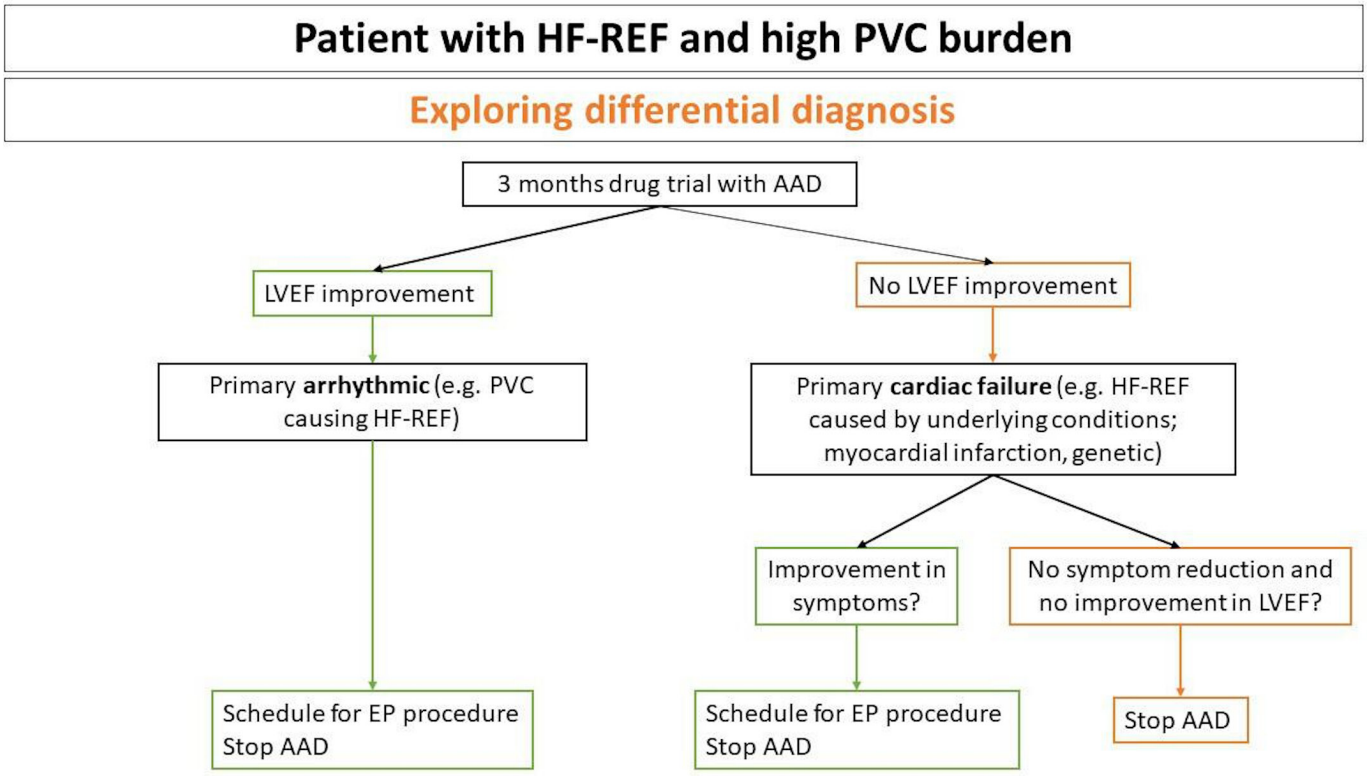

Figure 4 Our diagnostic workflow for the evaluation of PVCs in patients presenting with heart failure and a reduced ejection fraction. AAD, antiarrhtyhmic drugs; HFrEF, heart failure with reduced ejection fraction; PVC, premature ventricular complex.

and idiopathic PVCs. These data cannot be easily extrapolated to the patient population with marked reduced LVEF. It is common practice to initiate beta-blocker or a calcium-channel antagonist for symptomatic PVCs. However, calcium-channel blockers are generally contraindicated in patients with (severe) LV dysfunction. In addition, class Ic agents are very effective in suppressing PVCs but, as demonstrated in the Cardiac Arrhythmia Suppression Trial, may lead to ventricular proarrhythmia in patients with previous myocardial infarction.[35] Amiodarone appears to be the safest option particularly in severely reduced LV function. In a small series in patients with a PVC burden >20 000/day, it was demonstrated

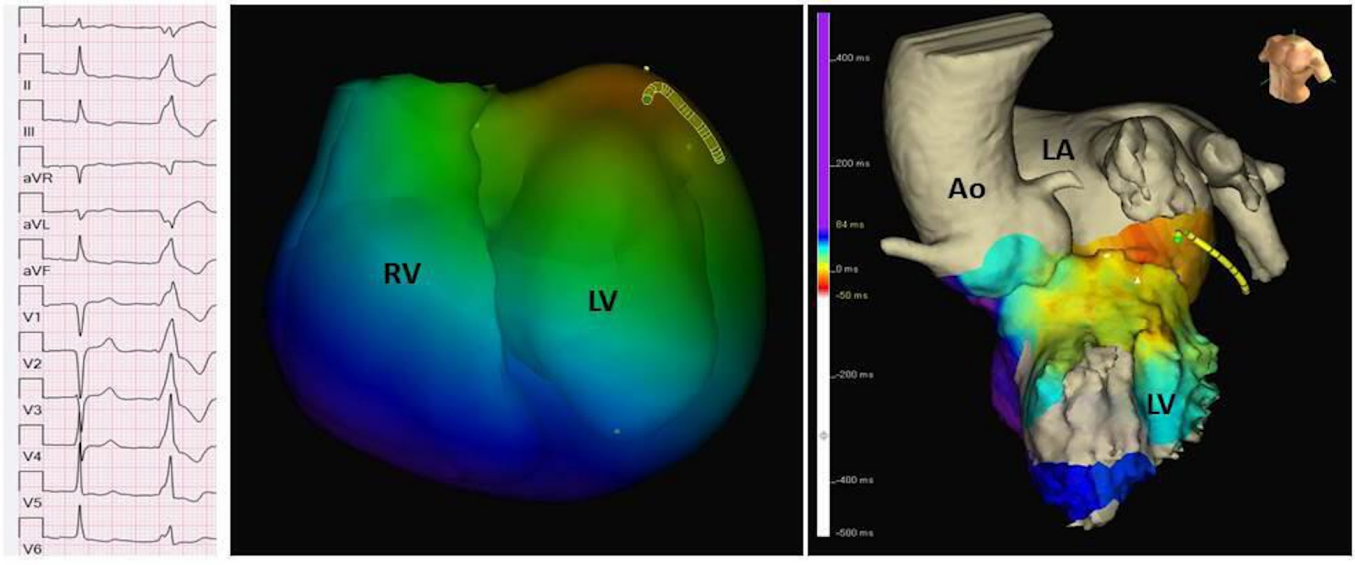

Figure 5 Integration of non-invasive mapping and invasive mapping of an LV anterobasal originated PVC. Left panel shows the PVC with right bundle branch block, positively in the inferior leads and positive concordance. Middle panel shows non-invasive mapping (VIVO, Catheter Precision Inc) of the PVC; red colour indicated the area of earliest activation. Right panel shows the activation of the PVC projected on the three-dimensional anatomy; again, red colour indicates the area of earliest activation. Ao, aortic root; LA, left atrium; LV, left ventricle; PVC, premature ventricular complex; RV, right ventricle.

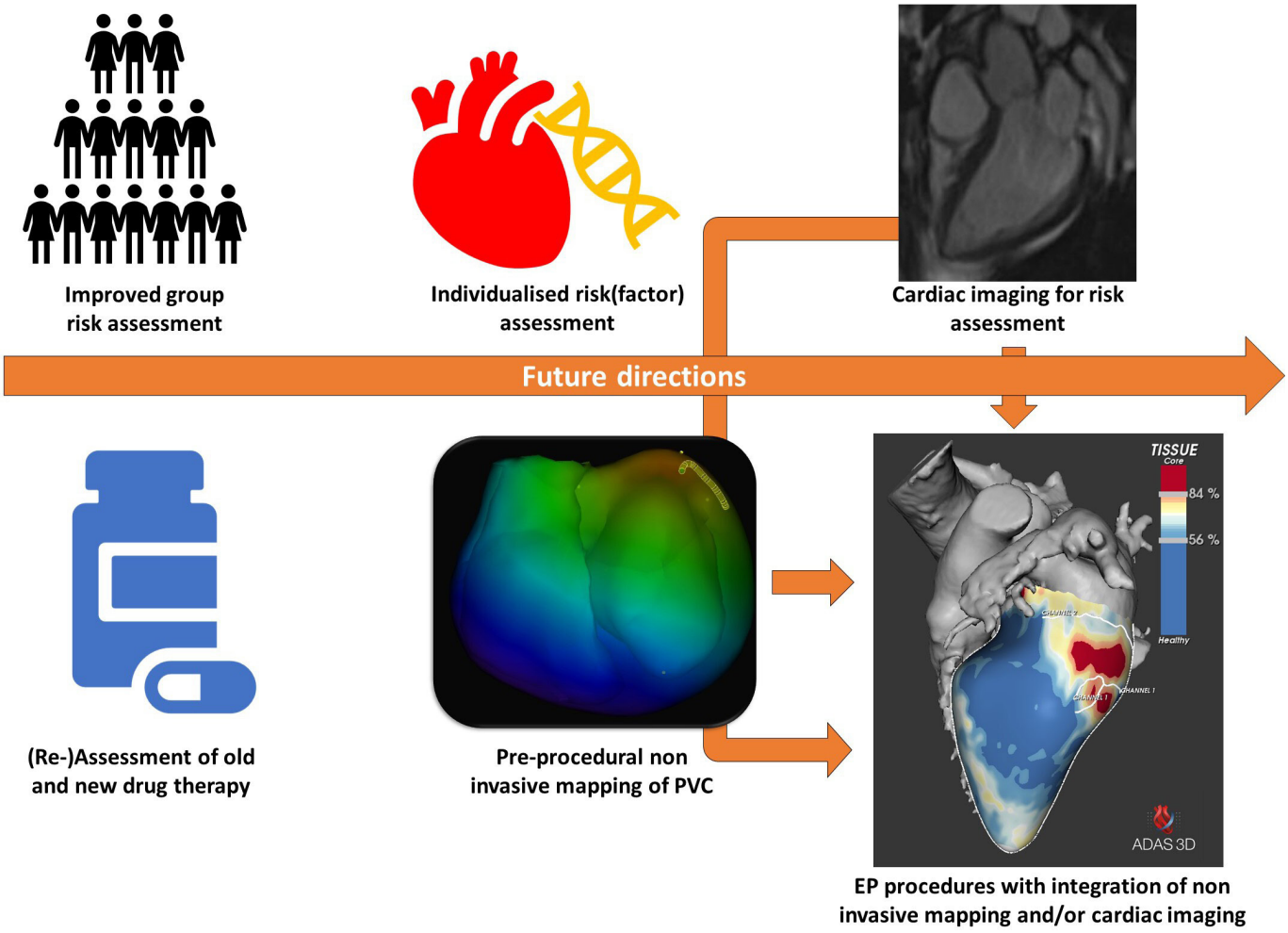

Figure 6 Future directions in PVC research and treatment. Essential aspects will be to identify the groups and patients at risk, (re-)assessment of drug therapy and optimisation of electrophysiological (pre-)procedural data by using cardiac imaging (CT or CMR) and non-invasive mapping. Right lower panel shows current use of cardiac imaging in electrophysiology, red indicates there is scar tissue and blue indicates healthy tissue (ADAS 3D, Galgo Medical). By integrating these data preprocedurally, a work plan for the electrophysiological procedure can be developed before starting the procedure itself.

that amiodarone reduced PVC burden by >75% and LVEF increased from 27%±10% at baseline to 49%±17% after 6 months of treatment.[36] Long-term amiodarone therapy is limited by considerable side effect profile but is effective for suppressing ventricular arrhythmias and improving LVEF.[37 38] Sotalol can also suppress PVCs, but careful monitoring of the QT-interval is critical.[39] Class Ic agents are contraindicated in postmyocardial infarction setting. However, in a small recent series with presumed PVC-induced cardiomyopathy, mean PVC burden decreased from 36.2%±3.5% to 10.0%±2.4% and mean LVEF increased from 37.4%±2.0% to 49.0%±1.9%.[40] In some patients, myocardial delayed enhancement was observed on Cardiovascular magnetic resonance imaging (CMR) (all <5% of total myocardium); also, these patients experienced an improvement in LVEF.[40] Over an average 3.8±0.9 treatment-years, no sustained ventricular arrhythmias or sudden cardiac deaths occurred. Although this treatment should not be routinely recommended, it may be an alternative in a selective patient population, for example, patients who have side effects or a contraindication on amiodarone and those who have failed catheter ablations or difficult to reach regions in addition to a contraindication for amiodarone. In absence of long-term data, or replication by other groups, precaution should be taken, and flecainide should probably only be administered in those who have also an ICD. At present, there are no randomised trials comparing efficacy and safety of catheter ablation versus pharmacological therapy in patients with HF. In non-structural heart disease, ablation of right ventricular outflow tract PVCs (figure 1A) was superior to drug treatment with metoprolol or propafenone in a randomised trial.[41] Ablation was performed with high success rates (80%–95%) and low complication rates.[41] Particularly reverse remodelling after successful ablation is observed in patients younger of age.[42] Ablation of PVCs from the LV summit, papillary muscle or parahisian is more complex and has lower efficacy and may require multiple procedures or epicardial access. It is reasonable to consider ablation as first-line treatment for frequent idiopathic monomorphic PVCs that have favourable site of origin such as right ventricular outflow tract. In a retrospective series of 121 patients with PVC cardiomyopathy, catheter ablation led to larger reductions in PVC burden than antiarrhythmic drug therapy and in 47% of ablation patients, LVEF normalised as compared with 21% of patients on antiarrhythmic drugs.[43] A prospective multicentre study with patients who had a mean LVEF 32%±8% and 21%±12% PVC burden showed that LVEF increased to

39%±12% and PVC burden decreased to 3.8%±6% at long-term follow-up with catheter ablation.[44] High-risk ablation procedures are indicated in highly symptomatic patients and can be a shared decision after discussing alternative pharmacological treatments. Pre-electrophysiological work-up before the procedure should include 12-lead ECG recording for site of origin analysis. Several algorithms are available that accurately predict site of origin of PVCs from the 12-lead ECG.[45] A (12-lead) Holter recording can be performed for quantification of the number and morphologies of the PVCs. Multiple PVCs morphologies may reduce success rate of catheter ablation.[46] Cardiac MRI may be helpful to identify scar formation in the ventricles.[47] Often, PVCs arise from the scar border zone.[47] Dedicated imaging software can create a detailed 3D heart model including scar areas from cardiac MRIs that subsequently can be imported in electrophysiological mapping system and serve as a roadmap for the procedure.[48]Preprocedural body surface mapping may also help in identifying the site of origin of PVCs. Integrating information from multiple surface ECG leads with ventricular anatomy for CT or MRI scan show epicardial site of onset (figure 5). PVC ablation techniques are based on identification and ablation of the site with earliest endocardial or epicardial activation during clinical PVC. Current mapping systems allow quick high-density mapping of the PVCs with automatic detection algorithms in combination with high-density mapping catheters. Another strategy is to pace at various sites and match the QRS morphology of the paced and PVC complex using automated pace mapping algorithms. Ablation is performed at the site with the best QRS morphology match.[49] Both strategies are complimentary and can be used in the same procedure. Complication of catheter ablation of PVCs occur in approximately 0%–5% of cases.[46] Usually complications are minor and related to vascular access (pseudoaneurysm, haematoma and arteriovenous fistula), but severe complications such as cardiac tamponade, AV block, stroke/TIA and coronary artery or aortic dissection can occur.[46] Evolving techniques include stereotactic radiation therapy for drug refractory ventricular arrhythmias, and preliminary data suggest that PVCs can also be ablated with this technique.[50] Currently, this is considered a 'bail out' procedure for patients without vascular access, inaccessible ablation sites or multiple failed catheter ablations. Studies in this field are ongoing and will assess long-term efficacy and complication rates of these procedures.

CONCLUSIONS

PVCs are often encountered in clinical practice in patients presenting with a reduced LVEF. In this overview paper, we showed our approach to this often clinically challenging diagnosis. A trial period of amiodarone may discover whether reduced LVEF is reversible, symptoms are due to PVCs and whether biventricular pacing can be increased by reduction of PVCs. Non-invasive and invasive (high-density) mapping techniques may help to improve accuracy and efficacy in the treatment of PVC. Future studies (figure 6) will seek to explore which patients are truly at risk for increased morbidity and mortality, and reassessment should take place of old and new drugs for PVC suppression. Integration of non-invasive cardiac imaging and electrophysiological mapping will potentially aid to increase safety and efficacy of invasive radiofrequency ablation.

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