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STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

Electrical management of heart failure: from pathophysiology to treatment

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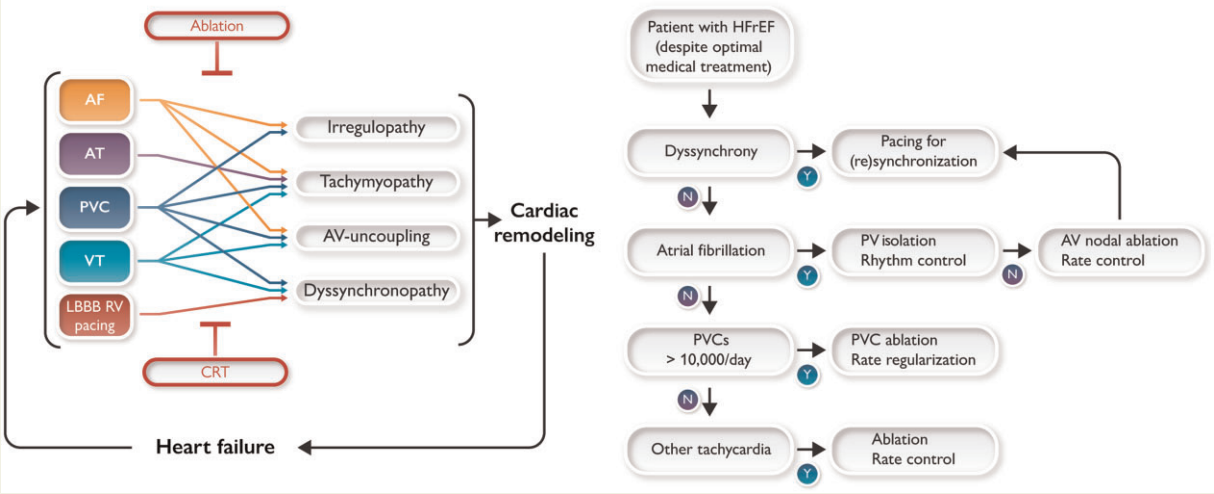

Graphical Abstract Upper panel: Schematic representation of the interaction between the various arrhythmia and conduction abnormalities with four electrical abnormalities and their consequences for remodelling and developing heart failure. Red text in boxes indicates the therapeutic approaches that treat the electrical abnormalities and thereby also heart failure. CRT, cardiac resynchronization therapy. Lower panel: Flow chart of recommended checks for the eligibility of heart failure with reduced ejection fraction patients for the various electrical therapies based on the evidence presented in the upper panel and guidelines.

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Abstract

Electrical disturbances, such as atrial fibrillation (AF), dyssynchrony, tachycardia, and premature ventricular contractions (PVCs), are present in most patients with heart failure (HF). While these disturbances may be the consequence of HF, increasing evidence suggests that they may also cause or aggravate HF. Animal studies show that longer-lasting left bundle branch block, tachycardia, AF, and PVCs lead to functional derangements at the organ, cellular, and molecular level. Conversely, electrical treatment may reverse or mitigate HF. Clinical studies have shown the superiority of atrial and pulmonary vein ablation for rhythm control and AV nodal ablation for rate control in AF patients when compared with medical treatment. Ablation of PVCs can also improve left ventricular function. Cardiac resynchronization therapy (CRT) is an established adjunct therapy currently undergoing several interesting innovations. The current guideline recommendations reflect the safety and efficacy of these ablation therapies and CRT, but currently, these therapies are heavily underutilized. This review focuses on the electrical treatment of HF with reduced ejection fraction (HFrEF). We believe that the team of specialists treating an HF patient should incorporate an electrophysiologist in order to achieve a more widespread use of electrical therapies in the management of HFrEF and should also include individual conditions of the patient, such as body size and gender in therapy fine-tuning.

Keywords heart failure • tachycardia • atrial fibrillation • premature ventricular contractions • ventricular dyssynchrony • resynchronization therapy • ablation

Introduction

Heart failure (HF) has many causes, the most commonly considered being volume overload, inflammation, ischaemia, valvular dysfunction, or genetic derangements. Treatment is largely based on restoring coronary blood flow, treatment of valvular abnormalities, and use of HF medications.

Electrical disorders are frequent in patients with HF. Approximately one-third of HF patients has ventricular conduction abnormalities,[1,2] one-third to half has atrial fibrillation (AF),[3] and almost a half may suffer from premature ventricular contractions (PVCs).[4] These electrical disturbances may contribute to, or are the primary cause of, the HF syndrome. This also implies that treatment of them could be either first line or adjunct therapy for HF.

In this review, we consider four different kinds of electrical cardiomyopathy:

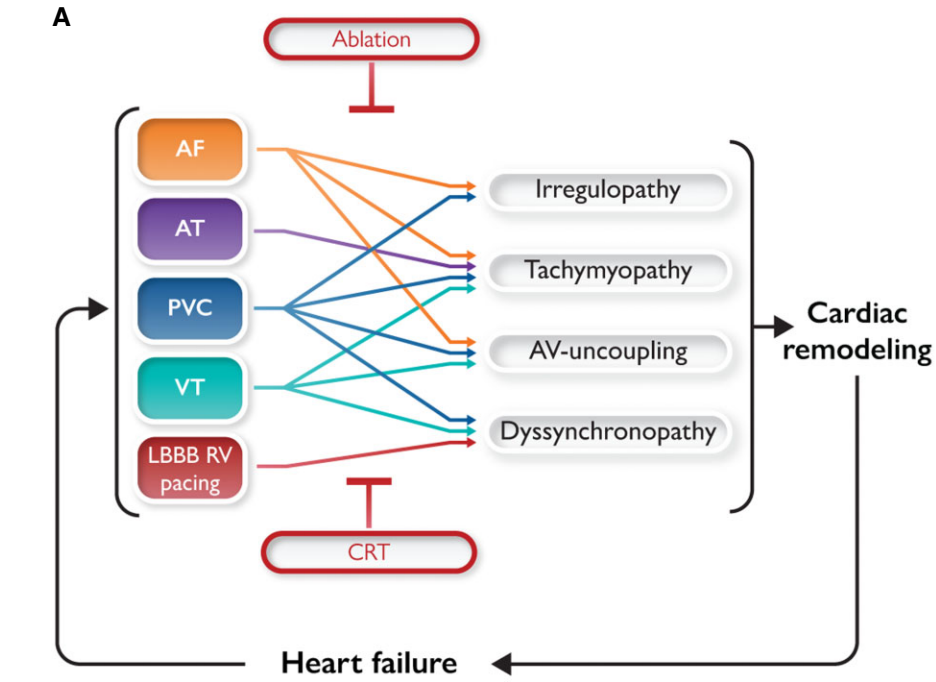
- Tachymyopathy: reversible cardiac dysfunction solely due to an increase in ventricular rates occurring during frequent atrial tachycardia (AT) (more commonly) and ventricular tachycardia (VT).
- Irregulopathy: cardiac dysfunction caused by irregular heart rhythm occurring in AF, frequent PVCs and premature atrial contractions (PAC's).
- Atrioventricular (AV) dissociation (lack or low contribution of atrial contraction to filling): clinically occurring in significantly prolonged PR interval, ventricular paced beats retrogradely conducted to the atria and during VT, PVC, and AF.
- Cardiac dysfunction caused by non-synchronous ventricular activation and contraction: clinically, this is most prominent in left bundle branch block (LBBB), but also right bundle branch block (RBBB), and intraventricular conduction delay (IVCD), chronic right ventricular (RV) pacing, and during VT and PVC.

Figure 1 depicts the putative mechanism to the depression of cardiac pump function by LBBB, frequent PVC, AT, VT, and AF, thus resulting in one of these cardiomyopathies. However, in a given patient, a different combination of these mechanisms could be the causative condition of HF. The clearest example of an electrical therapy that improves patient outcomes is cardiac resynchronization therapy (CRT). CRT is an effective therapy for patients with HF with reduced ejection fraction (HFrEF) and electrical dyssynchrony and results in considerable improvement of quality of life, reverse myocardial remodelling, as well as lower morbidity and mortality. Correction of the other electrical disturbances provides similar although less well-proven benefits. Catheter ablation is a well-established option for AF and other supraventricular tachycardias (SVTs). Similarly, ablation of myocardial substrate (areas that give rise to the origin of PVCs, VT, and SVTs) may contribute to the treatment of HF.

This review paper aims to explain from a pathophysiological perspective how electrical disorders and HFrEF intertwine to better understand the potential value of 'electrical therapies' for HFrEF. Selection of the best therapy/ies for electrical abnormalities in HFrEF patients must occur in the context of other HF interventions and comorbidities (*Graphical Abstract*). As recently suggested by the position paper jointly developed by the Heart Failure Association of the European Society of Cardiology (ESC), the growing HF treatment armamentarium requires the setting of a multidisciplinary HF team at each centre and the early referral/evaluation.[9] Continued and better coordination of the complex care of such patients in daily clinical practice is a challenge yet essential to deliver effective and timely management. We hope to contribute to better coordination between the various subspecialities within cardiology by emphasizing the considerable potential for electrical therapies in the treatment of HFrEF.

Pathobiology

The pathophysiology of cardiomyopathies associated with arrhythmias or electrical disturbances frequently has overlapping intrinsic cardiac triggers, primarily including irregular rhythm associated with post-extrasystolic potentiation (PESP), abnormal ventricular mechanics due to ventricular dyssynchrony, tachycardia, and AV uncoupling (*Figure 1A*).[4] Experimental models to understand the consequences of these triggers have shown common cardiac remodelling at the organ, tissue, and cellular level (especially oxidative and



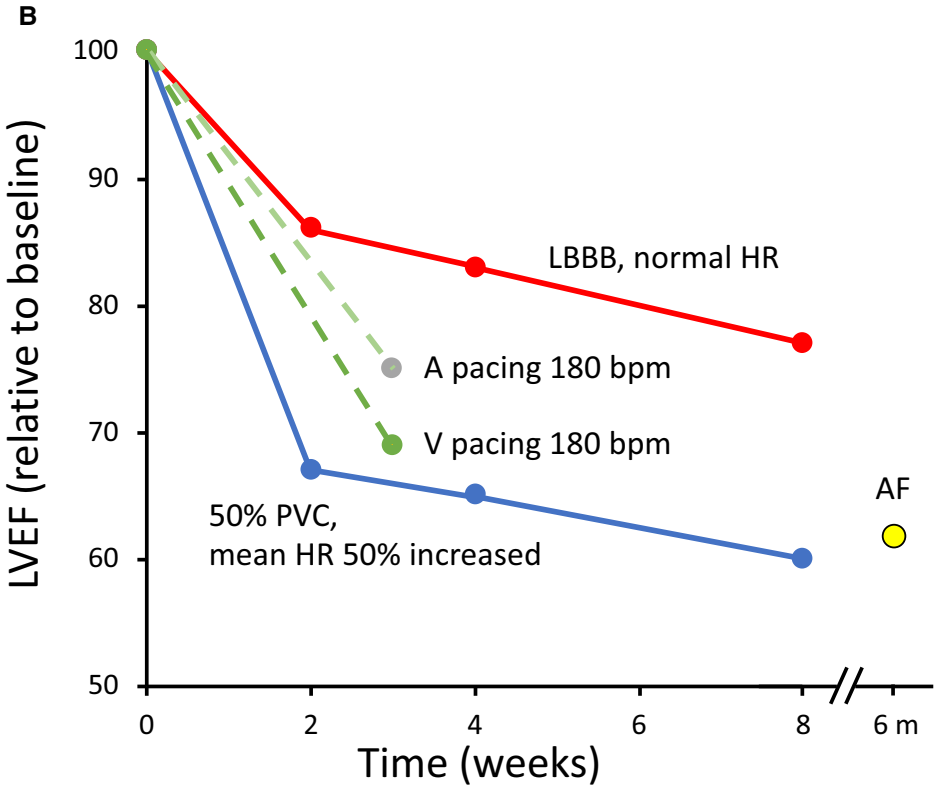


Figure 1 Upper panel (A): Schematic representation of the interaction between the various arrhythmia and conduction abnormalities with the four pathophysiological mechanisms / triggers and their consequences for remodelling and developing heart failure. Red text in boxes indicate the therapeutic approaches that primarily treat the electrical abnormalities, but thereby also of failure. CRT, cardiac resynchronization therapy. Lower panel (B): Relative reduction in left ventricular ejection fraction after five electrophysiological interventions in experimental studies in dogs: left bundle branch block by radiofrequency ablation and maintained normal heart rate,[5] atrial (A) and ventricular (V) pacing at 180 b.p.m. for 3 weeks,[6] a pacing protocol simulating premature ventricular contractions with an average premature ventricular contraction burden of ~50%[7] and chronic atrial fibrillation for 6 months.[8]

Table 1 Pathophysiological mechanisms of cardiomyopathies associated with arrhythmias or electrical disturbances

		Tachy-cardiomyopathy	PVC-mediated cardiomyopathy	AF-mediated cardiomyopathy	LBBB-mediated cardiomyopathy
Triggers	Rhythm	Fast but regular	Irregular	Irregular	Regular
	Post-extrasystolic potentiation	Absent	Present[a]	Variable	Absent
	AV coupling	Preserved[b]	Dissociated[c,d]	Non-existent	Preserved[e]
	LV dyssynchrony	Only present in VT	Intermittent[c,f]	None	Continuous
	Myocardial blood flow	Reduced[f]	??	Likely reduced	reduced (septum)
	Haemodynamic compromise	Present, low EF	(?) Likely present	(?) Likely present	Present, low EF
	Intrinsic autonomic nerve activity	(?) Unchanged	Significantly increased[f]	[g]	[g]
Cardiac intrinsic effects					
Tissue	Inflammation	Present[a]	Absent	[g]	[g]
	Fibrosis	Increased[a]	Mild[f]	[g]	Variable
	Oxidative, metabolic stress	Present	(?) Likely present	(?) Likely present	Present
Cellular	Ventricular electrical remodelling	Present	Present[f]	[g]	**Present**
	Ca^{2+} transient	Reduced[f]	Reduced[f]	[g]	Reduced[f]
	Action potential duration	Increased[f]	Prolonged[f] (heterogeneous)	[g]	Heterogeneous[f]
	β-adrenergic signalling	Decreased[f]	[g]	[g]	Decreased
Organ	Hypertrophy	Eccentric[a]	Eccentric[f]	[g]	Asymmetric, eccentric
	Ejection fraction	Reduced[a]	Reduced[a]	Reduced[d]	Reduced[a]
Extrinsic (non-cardiac) effects					
	Neurohumoral	+; BNP; Symp; RAAS	+; BNP; Symp; RAAS	+; BNP; Symp; RAAS	+; BNP; Symp; RAAS
Recovery	LV ejection fraction	Normalized[a]	Normalized[a]	Normalized[d]	Normalized[a]
	Dimensions	Partially dilated[a]	Normalized[a]	[g]	Normalized[d]
	Diastolic dysfunction	Persistent[d]	[g]	[g]	[g]
	Electrical remodelling	[g]	[g]	[g]	Partial reversal
	Hypertrophy	Reactive[a]	[g]	[g]	Partial reversal
	Fibrosis	Reactive/persistent[a]	(?) Persistent[f]	[g]	[g]

AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; EF, ejection fraction; LBBB, left bundle branch bock; LV, left ventricular; PVC, premature ventricular contraction; Symp, sympathetic tone; RAAS, renin–angiotensin–aldosterone system; VT, ventricular tachycardia.
[a]Patient and animal data.
[b]Ustained VT will frequently have AV dissociation.
[c]During PVCs only.
[d]Patient data.
[e]AV delay is frequently prolonged.
[f]Animal data.
[g]Unknown.

metabolic stress, eccentric hypertrophy, calcium mishandling) (*Table 1*) that leads to contractile dysfunction and autonomic remodelling.[10–15] *Figure 1B* shows data from several experimental studies in dogs. Data from these studies indicate that ventricular dyssynchrony (LBBB) without an essential change in heart rate causes a ~20% relative decrease in left ventricular ejection fraction (LVEF), while also rapid atrial and ventricular pacing and a 50% burden of PVCs cause 25–33% decreases in LVEF.

Irregular rhythm

Irregular rhythm is the result of PVCs, premature atrial contractions (PACs), and AF.[4,16–18] An important aspect of irregular rhythm is PESP, a phenomenon that refers to an increase in contractility that is associated with Ca^{2+} overload.[16,19,20] The role of PESP as a trigger for the development of HF is supported by a study in isolated myocytes and intact myocardium showing that irregular cycles of excitation and contraction induce an altered profile of gene and protein expression including down-regulation of sarcoplasmic reticulum ATPase 2a pump (SERCA) and an abnormal ratio of phosphorylated to total phospholamban (PLB).[21] Using a combination of echocardiographic imaging and computer simulations, Lyon *et al.*[22] showed that during AF, left ventricular (LV) peak strain is larger with larger RR interval in the preceding heartbeat. Importantly, this relationship is more variable at fast than at slow heart rates, because of insufficient reserve capacity of LV diastolic filling time. Therefore, the effect of cardiac loading may vary depending on both acute beat-to-beat changes in RR interval and mean preceding heart rate.[23]

Ventricular dyssynchrony

Ventricular dyssynchrony refers to an uncoordinated contraction within and between the two ventricles and is present when ventricular activation occurs outside the normal conduction system such as in LBBB, VT, chronic RV pacing, pre-excitation syndrome, and PVCs. Dyssynchrony causes disruption and progression of dyssynergic wall motion, resulting in contractile dysfunction and HF, most extensively studied in LBBB. Studies in animal models of dyssynchronous HF have reported changes in Ca^{2+} dynamics (SERCA and PLB) and gap junction remodelling, particularly in the late-activated, high-stress LV free wall[24–26] that could partly explain the deterioration of LV function and propensity to arrhythmias.[10]

Tachycardia

Animal and clinical studies have shown that the mechanism of tachymyopathy is multifactorial, including subclinical ischaemia due to underperfusion caused by short diastolic periods and reduced blood pressure combined with increased demands, abnormalities in cellular energetics, redox stress, and calcium overload.[6,27] These stressors lead to a cascade of mechanisms that ultimately trigger a wide range of maladaptive reprogramming, leading to prolongation of the action potential, abnormal excitation–contraction coupling, and depression of contractile function.[10–13] Tachycardia plays a role in HFrEF in patients with sustained AT or VT and AF without adequate rate control. Rapid rates may be accompanied by rate-dependent bundle branch block (dyssynchrony) that further reduces pump efficiency and worsens haemodynamics.

Atrioventricular dissociation

The optimal coupling between atria and ventricles implies the completion of atrial contraction and subsequent atrial filling of the ventricles before the onset of systole. Atrioventricular dissociation can be complete (random intervals between the atrial and ventricular contraction) or a constantly prolonged interval between the two (in the case of prolonged PR interval on the ECG). Atrioventricular dissociation can result in increased atrial pressure,[28] inadequate ventricular filling, and/or diastolic mitral regurgitation,[29] all factors that decrease ventricular stroke volume and, therefore, may contribute to the development of HF. Ventricularly paced beats with retrograde conduction to the atrium, a cause of pacemaker syndrome, may have similar effects. Finally, a prolonged PR interval causes a long pause between the end of atrial contraction and onset of ventricular contraction, causing diastolic mitral regurgitation and suboptimal ventricular filling.[30,31]

Understanding the role of other potential triggers of these cardiomyopathies, including haemodynamic compromise, decreased myocardial flow, and intrinsic autonomic nerve activity, is challenging due to the overlap with the primary triggers described above.

Tachycardia-mediated cardiomyopathy

The time to develop and the severity of tachycardia-mediated cardiomyopathy (T-CM) are dependent on the type, rate, and duration of tachycardia.[32] Although likely underestimated, the prevalence of T-CM has been reported in close to 3% of all patients referred for catheter ablation.[33] Although less common, AT and permanent junctional reciprocating tachycardia are also frequently associated with T-CM with a prevalence as high as 59 and 23%, respectively.[34,35] Nevertheless, AF and atrial flutter are some of the most frequent causes of T-CM due to their high prevalence in the adult population.[36] Tachycardia-mediated cardiomyopathy typically presents with palpitations, HF symptoms, and severe LV systolic dysfunction. Tachycardia-mediated cardiomyopathy should be strongly considered in patients with poor LV systolic function and persistent or frequent paroxysmal tachycardia without other obvious aetiology. Importantly, T-CM diagnosis can only be confirmed if LV recovery is documented within few weeks or months after treatment.

The main treatment of T-CM is the elimination of tachycardia with either antiarrhythmics and/or catheter ablation. In the ESC guidelines, catheter ablation has a IB indication to reverse LV dysfunction in AF patients when T-CM is probable.[37] However, standard HF medical therapy should not be ignored to maximize LV recovery. While eliminating tachycardia will resolve LV systolic dysfunction and HF symptoms, persistent myocardial fibrosis will remain and in part contribute to an 8–12% risk of sudden cardiac death (SCD) in patients with VT despite resolution of T-CM.[4,32,38] Surveillance of recurrent tachycardia after treatment is key, since its recurrence can result in a more rapid and severe clinical presentation.[4,38] Therefore, catheter ablation should be strongly considered in patients with arrhythmias known to have a high success rate (e.g. atrial flutter, AT, AV reciprocating tachycardia).

Premature ventricular contraction-mediated cardiomyopathy

Premature ventricular contractions are the most frequent ventricular arrhythmia and commonly associated with HF, ventricular arrhythmias, and SCD.[4,39,40] Frequent PVCs are recognized as a reversible cause of LV systolic dysfunction referred to as 'PVC-mediated cardiomyopathy' (PVC-CM), where PVC suppression will improve and even normalize LV function. The prevalence of PVC-CM is estimated between 10 and 29% in patients with frequent PVCs (>5–10%).[4,40,41] While PVC burden is the most consistent predictor of PVC-M, various factors, including genetics, comorbidities, cardiac phenotype, or PVC features and length of

Table 2 Clinical and premature ventricular contraction features to identify premature ventricular contraction-mediated cardiomyopathy

	CM resulting in PVCs	PVCs causing CM
Patient characteristics	Older with known heart disease	Healthy otherwise
Comorbidities	CAD, myocarditis, RV dysplasia[a]	No prior cardiac hx
Echocardiogram	Segmental hypokinesis, LVEF <25%	Global hypokinesis, LVEF 35 ± 10%[b]
Cardiac MRI (late gadolinium enhancement)	Significant scar	Absence or minimal scar burden (≤9 g)
PVC frequency	<5000/24 h (<5%)	≥10 000/24 h (≥10%)
PVC pattern	Multifocal	Monomorphic
QRS morphology	Non-specific	RVOT/LVOT/ epicardial
Response to PVC suppression	No change in LV function	Improvement of LV function

CAD, coronary artery disease; CM, cardiomyopathy; LVEF, left ventricular ejection fraction; RV, right ventricular; RVOT, right ventricular outflow tract; LV, left ventricular; LVOT, left ventricular outflow tract; MRI, magnetic resonance imaging.
[a]PVCs can cause a superimposed PVC-mediated cardiomyopathy even patients with other comorbidities.
[b]While PVC-mediated cardiomyopathy does not typically present with severe left ventricular systolic dysfunction (LVEF <25%), LVEF alone should not exclude the diagnosis of PVC-mediated cardiomyopathy. Reproduced with permission from Huizar *et al.*[17]

exposure, play a role in the susceptibility or resilience to develop PVC-CM.[42,43] In addition, PVCs with a longer QRS duration and epicardial location are more frequently associated with PVC-CM,[4,41,44] supporting the role of LV dyssynchrony in PVC-CM (*Table 2* and *Figure 1*).

Premature ventricular contraction-mediated cardiomyopathy can present with or without fatigue, HF symptoms, syncope, and SCD.[4,17,39,45] Frequently, patients are referred for bradycardia due to bigeminy where heart rate is underestimated (i.e. pseudo-bradycardia) due to the lack of pulse pressure generated by PVC. The time to develop PVC-CM is unknown, but probably months or years of exposure to frequent PVCs are needed.[17,44]

Premature ventricular contraction-mediated cardiomyopathy diagnosis should be suspected if PVC burden is >5–10% and other causes of HF are excluded, and confirmed only if PVC suppression improves and even normalizes LV function. A major diagnosis challenge is when PVCs cannot be successfully eliminated. A frequent dilemma is to determine whether the PVCs are a bystander or the cause of CM. Some PVCs and clinical features (e.g. absence of scar) can assist to differentiate these two scenarios (*Table 2*).[4,17]

Treatment

Successful treatment of PVC-CM requires at least an 80% reduction in PVCs due to a significant day-to-day PVC variability.[4,46] While PVC ablation or antiarrhythmic drugs offer overall a good long-term suppression, standard HF guideline-directed medical therapy is essential and should be optimized, but beta-blockers and antiarrhythmic drugs are often unsuccessful in suppressing PVCs or not tolerated.[4,17,41,44,47] Premature ventricular contraction ablation is, therefore, preferred due to higher PVC reduction rate and low recurrence.[47,48] Premature ventricular contraction ablation is a low-risk procedure (1.5–2.8%) with estimated acute and long-term suppression between 80–90% and 60–90%, respectively.[4,41,44] However, PVC ablation can be challenging due to the inability to reach PVC origin [e.g. intramural location, LV summit (most basal part of the septum and LV wall)] or catheter instability. Specific technologies, such as cryoablation and contact force sensor catheters, can assist in improving success and overcome some limitations.[49] Moreover, intracardiac echocardiography frequently assist PVC ablation within papillary muscle origin.[50]

Premature ventricular contraction ablation has been reported to reverse remodelling with the improvement of LV and mitral valve function, B-type natriuretic peptide levels, and renal function.[4,41,47] Factors that predict the PVC-CM diagnosis also forsee response to PVC ablation.[4] Importantly, a scar mass <9 g (cardiac magnetic resonance) predicts LV recovery.[51] Besides improving LV function, PVC ablation may also improve survival or long-term outcomes as suggested by the Congestive heart failure: Survival trial of antiarrhythmic therapy (CHF-STAT) study and the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial.[40,52] Future clinical studies are clearly needed to better understand the clinical impact of PVC-CM and its treatment.

Atrial fibrillation

Atrial fibrillation and HF often coexist, and are accompanied by worse adverse outcomes. Several options are available to treat AF divided into rate and rhythm control. Both strategies have invasive (ablation) and non-invasive (pharmacological) approaches.

Although rate control is a management strategy in AF,[53] the optimal heart rate target in AF patients is unclear yet. Rate control is the background treatment for all AF patients, including those receiving treatment with a rhythm control strategy. Randomized trials did not show a difference in the composite endpoint of clinical events, New York Heart Association class, or hospitalizations between the strict (target heart rate <80 b.p.m. at rest and <110 b.p.m. during moderate exercise) and lenient (heart rate target <110 b.p.m.) arm irrespective of activity level.[54,55] Notably, only a small portion of patients included in these studies had HFrEF. Still, the ESC HF guidelines recommend 'lenient rate control' (meaning <110 b.p.m. at rest) as the initial approach, regardless of HF status (with the exception of tachycardia-induced cardiomyopathy).[56]

Pharmacological approaches for rhythm and rate control appear equivalent strategies with respect to outcome.[57–59] Available studies showed a low success in maintenance of sinus rhythm, but the presence of sinus rhythm was associated with better LV function[57,59,60] and survival.[61] The slight increase in LVEF and beneficial

consequences of maintaining sinus rhythm may not translate into long-term effect on mortality and morbidity due to the adverse effects associated with antiarrhythmics.

Electrophysiological approaches for rate and rhythm control provide more specific and definitive solutions. The rhythm control option of catheter ablation has been tested in several prospective randomized controlled trials (RCTs).[62–64] All these relatively small studies consistently showed greater improvement of LV function, and quality of life in the catheter ablation arm compared with medical therapy. Moreover, in HF in patients with AF and LVEF ≤35%, catheter ablation provided a significantly lower composite endpoint of mortality and hospitalization than pharmacological therapy. Notably, the recent long-term results of the Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Heart Failure-An MRI-Guided Multicenter Randomized Controlled Trial (CAMERA-MRI) study showed an absolute increase in LVEF with catheter ablation of 16.4 ± 13.3% compared with 8.6 ± 7.6% in medical therapy ($P = 0.001$).[65] At 4.0 ± 0.9 years of follow-up in the catheter ablation group, the absence of ventricular late gadolinium enhancement was associated with a greater improvement in absolute LVEF (19 ± 13 vs. 10 ± 11%; $P = 0.04$) and LVEF normalization in 19 patients (58%) vs. 4 patients (18%; $P = 0.008$) compared with the late gadolinium enhancement-positive group. Therefore, recent clinical practice guidelines recommend catheter ablation as an alternative to pharmacological therapy at Level of evidence I for patients with paroxysmal or persistent AF and HF.[37]

When medication for rate control fails, ablation of the AV node and pacemaker implantation can be considered. The procedure is relatively simple and has a low complication rate and low long-term mortality risk, especially when the pacemaker is implanted a few weeks before AV node ablation and the initial pacing rate after ablation is set at >70 b.p.m. While this will not restore sinus rhythm and AV coupling, the procedure does not worsen LV function and may even improve LVEF in selected patients.[66] Most studies have included older patients with limited life expectancy. For younger patients, ablation of the AV node should only be considered if there is urgent need for rate control and all other pharmacological and non-pharmacological treatment options have been carefully considered. The choice of pacing therapy (RV or biventricular pacing) depends on patient characteristics. The results of the APAF-CRT study, which was performed in severely symptomatic patients with permanent AF and within 1 year of HF hospitalization irrespective of LVEF, showed that AV node ablation combined with CRT is preferred.[67,68] In this study, patients with narrow QRS complex had a 62% lower risk for the combined endpoint of mortality, HF hospitalization or worsening of HF, and a 72% lower risk of all-cause mortality and HF hospitalization in the ablate and pace group when compared with the pharmacological rate control group. Forty per cent of the study patients had LVEF ≤35%. The combination of biventricular pacing and AV node ablation also shows superior outcomes in patients with a conventional CRT indication who obtain the suboptimal level of biventricular stimulation due to AF with intrinsic conduction.[69] More physiological pacing, such as His bundle pacing (HBP) and left bundle branch pacing (LBBP) (see below), may evolve as an attractive alternative pacing mode, as currently tested in ongoing clinical trials.

Dyssynchrony and resynchronization therapy

Disease prevalence

In a Swedish registry, LBBB and IVCD were found in ∼25 and ∼15% of patients with HFrEF, respectively.[2] The presence of both LBBB and IVCD increased the risk of all-cause mortality by ∼30%. In transcutaneous aortic valve implantation procedure, new-onset LBBB may even increase the risk of mortality by ∼50%.[70] The pathophysiology paragraph describes the serious consequences of ventricular dyssynchrony. Therefore, ventricular dyssynchrony is an important therapeutic target in patients with HFrEF. It has been estimated that at least 400 patients per million of the population would be eligible for CRT, but in practice, only Germany and Italy at least approach such implantation numbers in Europe.[71]

Cardiac resynchronization therapy

According to current guidelines,[71] good candidates for CRT are those with HFrEF and an abnormal QRS complex (LBBB morphology and/or QRS duration >130 ms). Likewise, because activation sequence in RV pacing mimicks that of LBBB, CRT is indicated for patients who are RV paced for a significant portion and have LVEF <35% and patients with LVEF <40% with high-degree AV block who have an indication for ventricular pacing.[71]

As reviewed in the guideline documents, randomized trials have clearly and consistently shown the benefit of CRT with regard to HF symptoms, HF hospitalization, and survival.[71] Many studies report that approximately one-third of patients receiving CRT are non-responders in terms of LV reverse remodelling, clinical improvement, or both. Lately, however, the response definitions have been challenged since recent evidence indicates that patients who are stable during CRT also benefit from this therapy.[72] Therefore, perception of lack of response such as in patients with ischaemic heart disease who more commonly present with IVCD should not preclude patients from this potentially life-saving treatment.

Patient selection

The most important factor that determines the CRT effect is the presence of an 'electrical substrate' in the patient, i.e. the amount of viable tissue that can be resynchronized. The largest benefit is commonly observed in patients with a 'true' LBBB and no evidence of ischaemic heart disease, and commonly women (see below). However, currently used ECG criteria (QRS duration and LBBB) have weaknesses. QRS duration poorly expresses the amount of resynchronizable tissue and its critical value is body size-dependent.[73] The definition of LBBB based on ECG criteria is complicated by its subjective assessment and multiple ECG criteria of LBBB that lead to widely different percentages of LBBB patients in cohorts of CRT patients.[74,75] Recent studies indicate that the electrical substrate may be better identified when using the area under the QRS complex (*Figure 2*).[76,80,81] These promising results may be explained by the fact that QRS area reflects late LV activation, independent of QRS morphology.[82] QRS area is also inversely related to the presence of ischaemic heart disease and scar size,[83,84] factors that reduce CRT response. A randomized study is required to provide final proof of this approach, while standard addition of the calculation of QRS

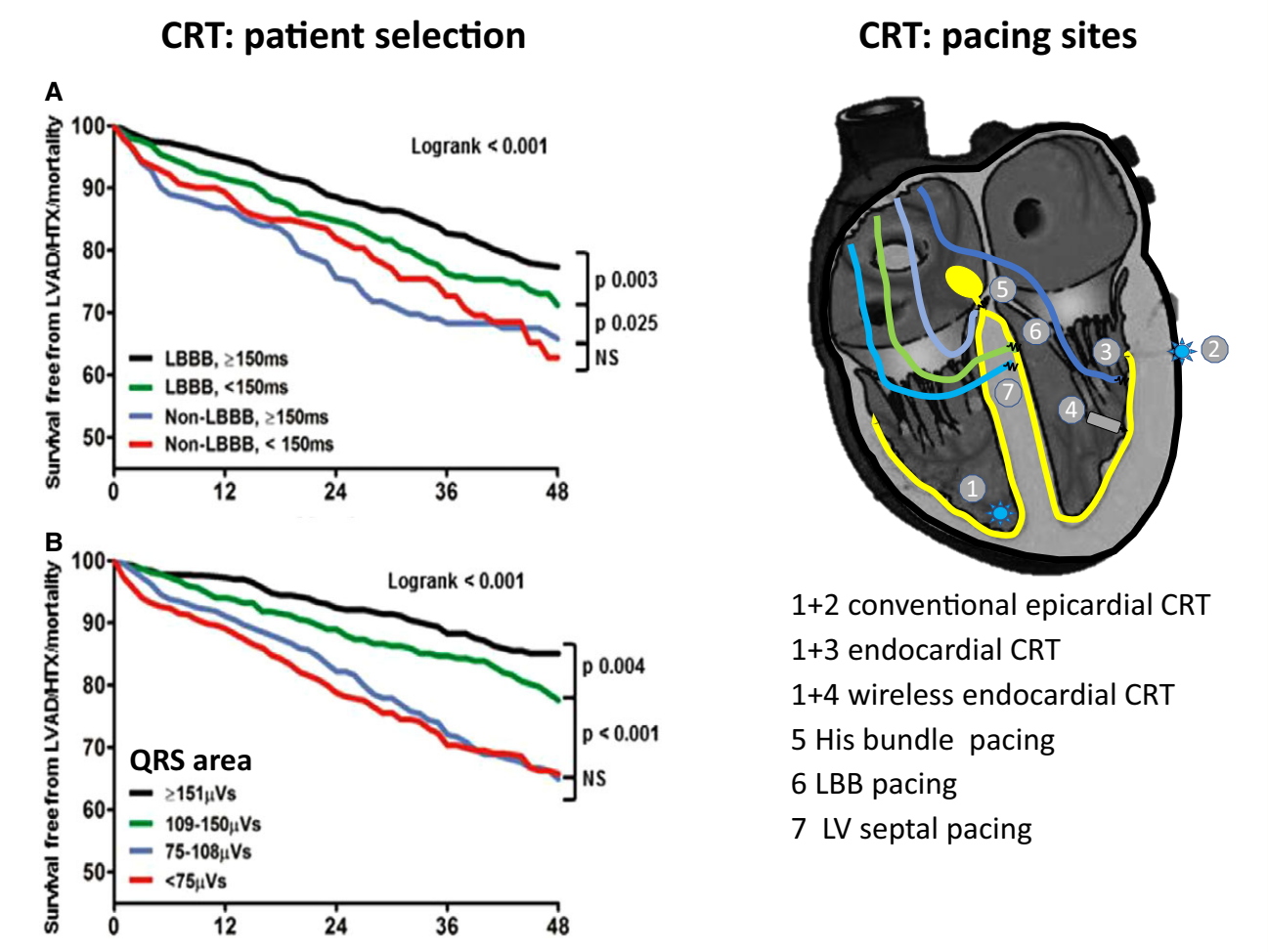


Figure 2 Upper panels: Electrocardiographic selection criteria for cardiac resynchronization therapy and their relation to outcome (combined endpoint of survival free from left ventricular assist device implant, heart transplant, or death) in a study on ~1500 patients. (*A*) Conventional criteria (left bundle branch block and QRS duration >150 ms), (*B*) area under the QRS complex (QRSarea). The presence of left bundle branch block is a determinant of cardiac resynchronization therapy outcome, in particular if QRS duration is >150 ms, but QRSarea >109 μV s is a stronger determinant of cardiac resynchronization therapy outcome than left bundle branch block.[76] Lower panels: Schematic overview of the current options for cardiac resynchronization therapy. Positions 1 and 2 indicate the conventional right ventricular and left ventricular pacing locations. Endocardial cardiac resynchronization therapy can be achieved by introducing a conventional pacing lead through the foramen ovale and the mitral valve into the left ventricle (3) or using a wireless pacing electrode (4) that is stimulated using an ultrasound transducer.[77] His bundle (5), left bundle branch (6), and deep left ventricular septal pacing (7) is performed using a 4 Fr lead introduced transvenously and screwed in the septum. Small studies also investigated the combination of His bundle pacing (HOT-CRT)[78] or left bundle branch pacing with left ventricular pacing (LOT-CRT).[79]

area to ECG equipment would greatly enhance the use of this parameter.

A previously proposed approach for improving patient selection was the use of markers of mechanical dyssynchrony in addition to ECG criteria, in particular using speckle tracking echocardiography. After initial promising results, large randomized trials have not been able to show a consistent benefit when using time-to-peak shortening as a measure of dyssynchrony.[85,86] Simpler markers, such as apical rocking and septal flash, are improving the prediction of CRT response in single-centre evaluation,[87] but suffer from relatively low intercentre agreement.[88] Interesting new developments are the use of deformation patterns in addition to electrical dyssynchrony criteria[89] and myocardial work,[88] but these need to be confirmed in randomized studies.

Atrial fibrillation patients do not derive the same benefit from CRT, which may be due to several factors such as insufficient amount of biventricular stimulation (as discussed above), fusion or pseudofusion beats without proper biventricular stimulation, and lack of atrial contribution to ventricular filling.

Right ventricular pacing even in a percentage as low as 20% may induce RV dyssynchrony and by time HF.[71] Therefore, patients with LVEF ≤40% in need of RV pacing such as those with high-degree AV block should be given CRT pacing (Recommendation IA in pacing guidelines). This recommendation includes patients in AF.[71]

Therapy delivery

Apart from delivery of at least 95% biventricular stimulation, a second factor determining the outcome of CRT is the position of

the LV lead. The optimal LV position appears to differ between patients, therefore requiring a personalized approach. There is general agreement that the best (epicardial) LV lead position is the viable region with the latest intrinsic activation. However, two studies attempting to validate this tailored approach were small and results were not clearly better than the default use of the (postero) lateral vein, because the choice of veins to implant the lead is limited (usually two veins, not all of them being suitable for most leads).[90] A larger study, comparing strategies of LV lead positioning using electrical determination of the latest activated region with that of mechanically latest activated region outside a scar, found no significant difference between these strategies.[91] Multipoint pacing (MPP) has been studied in an RCT setting, but its use was not superior to conventional CRT for reverse remodelling, despite earlier promising findings in smaller studies. However, because most LV leads implanted are quadripolar, reprogramming the device to MPP may be an option in case of poor response. The SMART-MSP study showed that of the patients that did not respond to CRT after 6 months, half could be converted to responders by activating MPP. These patients had a significantly lower risk of HF decompensation at the subsequent 6-month follow-up.[92]

Several approaches have been employed to deliver LV pacing at the endocardium in order to create more physiological activation in CRT. However, implantation of a lead, using a trans-atrial septal approach, resulted in transient ischaemic attacks and non-disabling strokes in 6.8 and 3.8% of cases.[93] The conceptually novel approach of implanting encapsuled piezo-electric (receiver) crystals to the LV endocardium that is activated using ultrasound seems more promising in the prevention of coagulation problems. The WiSE-CRT[94] and SELECT-LV studies[77] showed the feasibility and efficacy of this approach, although peri-procedural/device-related events occurred in ~8% of patients, and additional 10% events in the post-procedural phase. Currently, this novel technology is tested in a large prospective study.[95]

Recently evolving and physiologically superior approaches to resynchronization are endocardial CRT,[96] HBP,[97] LBBP,[97] and deep LV septal pacing (LVSP)[98,99] (*Figure 2*).

The excellent electrocardiographic and functional benefit of resynchronization using a single ventricular lead (HBP,[100,101] LBBP,[102] and LVSP)[99] is explained by the increasing evidence that in about two-thirds of CRT candidates, the 'LBBB' is actually located very proximal in the left bundle branch or even His bundle[103] in combination with a more physiological sequence of activation (septum > LV free wall and endocardium > epicardium).[104] These single-lead resynchronization approaches may expand the acceptance and application of CRT, using a simple dual-chamber pacemaker. Of these three approaches, HBP is practically more difficult and long-term reliability has come into question.[105] In that regard, LBBP and LVSP appear more promising, because of lower dislodgement rate and lower and more stable lead performance, but long-term data are even less than for HBP.

Device optimization

Device optimization implies programming of the interval between atrial and ventricular stimulation (AV delay) and, for biventricular pacing, between RV and LV stimulation (VV delay) and multi-site LV stimulation (LV1–LV2) in quadripolar leads. Conventionally, such optimization is performed a single time using echocardiography (if any). However, studies showed limited to no benefit of such one-time optimization compared with using the default setting.[106] More promising results have been obtained in studies where device-based algorithms were used that perform optimization in an automated and ambulatory fashion. Adaptive CRT adjusts AV delay and withholds RV pacing to create a fusion of LV stimulation with intrinsic conduction. This approach was shown to increase device longevity and to reduce the risk of developing AF.[107] Also the SyncAV algorithm dynamically adjusts AV delays to the intrinsic conduction, but also has the option of a programmable offset, aiming at creating a triple wavefront of activation. This algorithm improved electrical resynchronization,[108] but until now reports on clinical benefits have been published. The SONR algorithm employs an accelerometer integrated into the RV or RA pacing lead. Using the amplitude of the SonR1 signal (equivalent to the first heart sound), the SONR algorithm automatically determines the optimal combination of AV and VV delay in an ambulatory fashion. The RESPOND-CRT trial randomized almost a thousand patients to SONR or echocardiography optimization. While SONR marginally increased CRT response (NYHA class) by 5% points ($P = 0.13$), and lowered combined risk of death and hospitalization ($P = 0.12$), hospitalization alone had a 35% risk reduction ($P = 0.01$).[109]

Other electrical therapies

Cardiac contractility modulation (CCM) consists of the delivery of non-excitatory electrical signals in the absolute ventricular refractory period to the RV septum.[110] The FIX trials were performed in patients with New York Heart Association (NYHA) Class III–IV HF, with an LVEF ≥25 to ≤45% and QRS duration <130 ms. In these studies, CCM was associated with a small improvement in exercise tolerance and quality of life.[111]

The poor cardiac function creates imbalances in the autonomic nervous system. During recent years, several approaches for modulations of the autonomic nervous system have been investigated in patients not eligible for CRT, in particular vagal nerve stimulation, renal (sympathetic) nerve ablation, and baroreceptor stimulation. Despite promising results in preclinical models, clinical trials showed only limited or no benefits. A randomized clinical trial failed to show significant reverse remodelling by vagal nerve stimulation over a 6-month follow-up.[112] There is no randomized clinical trial showing a significant benefit of renal denervation in HF patients. Baroreceptor stimulation, performed with a novel electrical stimulation device with electrodes in the vicinity of the carotid baroreceptors, was shown to significantly improve the quality of life and exercise capacity and to reduce N-terminal pro-B-type natriuretic peptide in HF patients,[113] but studies indicating significant improvements in hard clinical endpoints are yet lacking.

Recommendation and implementation of electrical therapies for heart failure

Current ESC/European Heart Rhythm Association (EHRA) guidelines recommend catheter ablation of AF to reverse LV dysfunction, independent of their symptom status (Class I) and in selected AF patients with HF to improve survival and reduce HF hospitalization (Class IIa).[37] Catheter ablation for SVTs is recommended (Class IB) in patients with

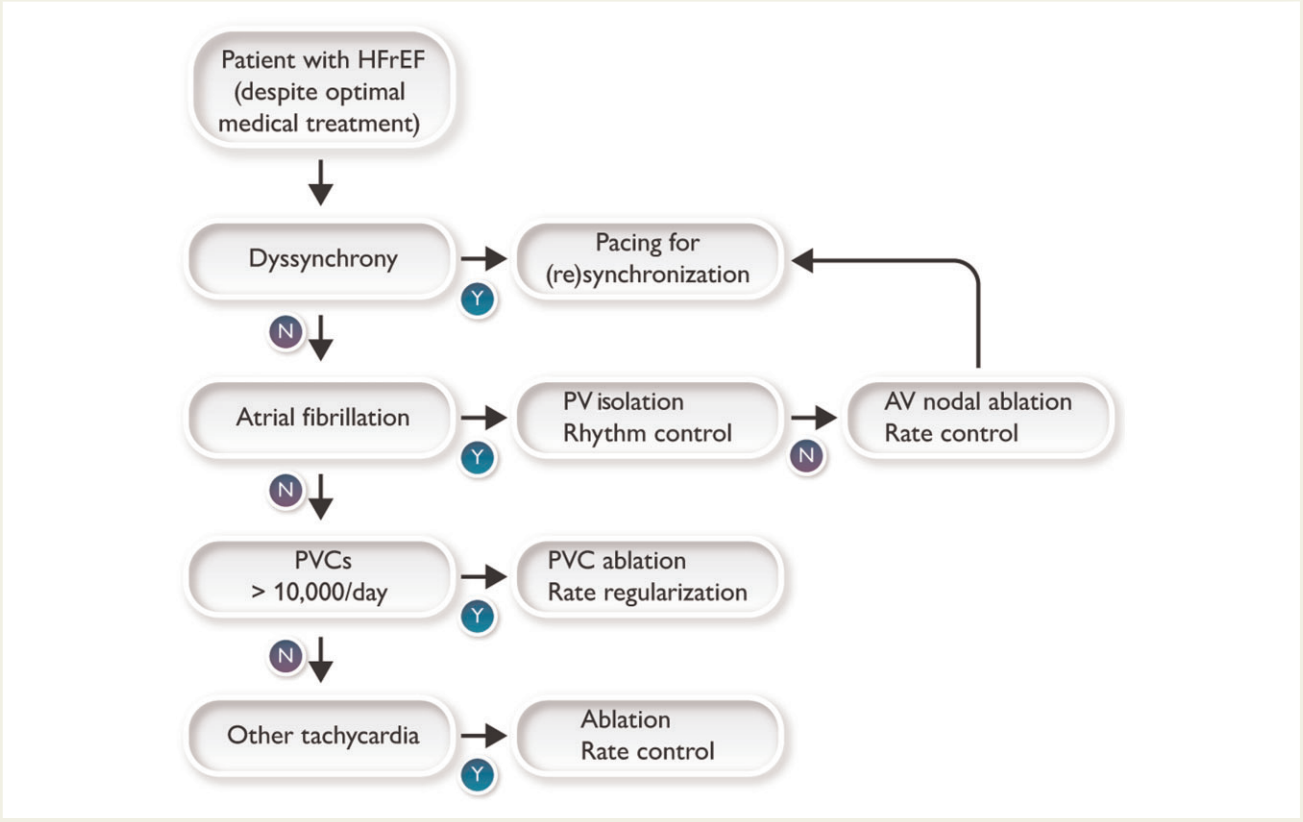


Figure 3 Schematic representation of judgement that is recommended for optimal treatment of heart failure patients, based on the evidence presented in this article.

reduced LV function and frequent or persistent elevated heart rate above 100 b.p.m. consistent with T-CM.[114]

Catheter ablation for PVCs is recommended in symptomatic or asymptomatic patients with frequent monomorphic PVCs and suspected PVC-CM (Class I), as well as non-responders of CRT due to suboptimal biventricular pacing (Class IIa).[115]

Similarly, CRT is recommended (on the top of optimal medical therapy) in symptomatic HFrEF patients in sinus rhythm and QRS duration ≥130 ms (Class I–II depending on QRS width and morphology).[71] Other groups that may be considered for CRT include NYHA Class III–IV HFrEF patients in AF and a QRS duration ≥130 ms, provided a strategy to ensure biventricular capture is in place, and occasionally as an upgrade to a conventional pacemaker or an implantable cardioverter defibrillator in patients who develop worsening systolic function with >20% RV pacing.[71]

Based on the abovementioned evidence and guideline recommendation, we propose the decision schedule presented in *Figure 3*. Each HFrEF patient should be checked for treatment of dyssynchrony, persistent tachycardia, AF, and PVCs.

However, clinical practice is far from optimal.

In the case of CRT, the optimal combination of medical therapy and CRT is performed in a minority of patients who qualify for CRT. European data suggest that only one in three eligible patients actually receives a CRT device.[116] Moreover, only 20–30% of patients implanted with CRT are on maximal guideline recommended doses before CRT.[116] But a delay in CRT implementation may be suboptimal since HF medication is less effective in achieving reverse remodelling in patients with LBBB, when compared with HFrEF patients with narrow QRS.[117]

A recent joint position statement from several cardiac societies of the ESC described in-depth theoretical and practical strategies to achieve more comprehensive CRT referral and post-procedural care by focusing on four actionable domains: (i) overcoming CRT under-utilization, (ii) better understanding of pre-implant characteristics, (iii) abandoning the term 'non-response' and replacing this by the concept of disease modification, and (iv) implementing a dedicated post-implant CRT care pathway.[118]

Similarly, in old frail patients with HFrEF and AF, the utilization of medical therapy to preserve sinus rhythm has shown to be detrimental compared with AF ablation or AV node ablation plus CRT.[118] Therefore, it seems wise to more frequently consider device therapy and/or ablation as adjunctive therapies with a synergistic effect rather than consecutive therapies to be used only if medical therapy fails.

Unfortunately, the diagnosis of T-CM and PVC-CM is frequently missed due to the lack of using long-term ambulatory monitors to identify subclinical and intermittent arrhythmias. Appropriate treatment of T-CM and PVC-CM does not only improve LV systolic function but likely to impact morbidity and mortality.[32,40] Therefore, implementing care pathways, comparable to that for CRT, for the aforementioned ablation treatments seem advisable. Finally, the implementation of electrical therapies can be further improved by

better integration of cardiological and non-specialist care, leading to better post-implant management.[119,120]

Gender differences in electrical heart failure and its treatment

Personalized electrical management of HF should include gender consideration. Currently, device therapy and ablation are especially underused in women with HF. Striking is that while women are less likely to receive CRT, they derive more benefit from this therapy than men.[1] This difference can partly be explained by differences in risk factors (more non-ischaemic cardiomyopathy, lower scar burden, less LV dilatation, more LBBB). A meta-analysis of three randomized studies by the Food and Drug Administration showed CRT benefit in women with QRS duration >130 ms while the benefit for men only started at QRS duration >150 ms.[121] This difference may be explained by the fact that women are generally smaller, including their heart and body size.[122,123]

The lower referral for CRT in women may be related to sex/gender bias in referral patterns and women more often having HF with preserved ejection fraction than HFrEF.[1] In addition, the shorter QRS duration in women make them (unjustified) fall into the weaker recommendations of the CRT guidelines.[71,73] Alternatively, there is a fear that women derive more complications from CRT therapy than men. In the CRT Survey II comprising 11.088 new CRT implantations, women did have had a higher procedural complication rate, in particular related to vascular access as evidenced by pneumothorax (1.4%), coronary sinus dissection (2.1%), and pericardial tamponade (0.3%).[1] The probable cause is the smaller dimensions of vessels in women compared with men. Nonetheless, women should not be withheld CRT, and an individual approach in assessing CRT eligibility based on body size is probably helpful in increasing access to CRT across gender and ethnicity.

Female patients are also under-referred for AF ablation[124] and receive significantly less ICD therapy than men.[124] While only a single study suggests that PVC-CM is more prevalent in males,[125] it is not clear that there are gender differences in the treatment of PVC-CM or T-CM.

Conclusions

A review of the literature provides evidence that 'electrical' diseases like AF, AT, PVCs, LBBB, and AV uncoupling may seriously impact cardiac pump function and may cause or contribute to worsening HF.

Likewise, electrical therapies, like ablation and resynchronization pacing, have been shown and are guideline recommended to contribute to the treatment of HF patients with any of these electrical diseases.

Despite all this, there is a considerable underutilitzation of these therapies in the treatment of HF patients. Therefore, we recommend that an electrocardiologist becomes part of the treatment team of the HF patient. Besides the promotion of the electrical therapies, such a treatment should also pay attention to personal aspects of the patient such as sex and body size.

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