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Atrial fibrillation-induced tachycardiomyopathy and heart failure: an underappreciated and elusive condition

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Abstract

Many patients with persistent, chronic, or frequently recurring paroxysmal atrial fibrillation (AF) may develop a tachycardiomyopathy (TCM) with left ventricular (LV) dysfunction and heart failure (HF), which is reversible upon restoration and maintenance of sinus rhythm, when feasible, or via better and tighter ventricular rate (VR) control. Mechanisms involved in producing this leading cause of TCM (AF-TCM) include loss of atrial contraction, irregular heart rate, fast VR, neurohumoral activation, and structural myocardial changes. The most important of all mechanisms relates to optimal VR control, which seems to be an elusive target. Uncontrolled AF may also worsen preexisting LV dysfunction and exacerbate HF symptoms. Data, albeit less robust, also point to deleterious effects of slow VRs on LV function. Thus, a J-shaped relationship between VR and clinical outcome has been suggested, with the optimal VR control hovering at ~ 65 bpm, ranging between 60 and 80 bpm; VRs above and below this range may confer higher morbidity and mortality rates. A convergence of recent guidelines is noted towards a stricter rather than a more lenient VR control with target heart rate < 80 bpm at rest and < 110 bpm during moderate exercise which seems to prevent TCM or improve LV function and exercise capacity and relieve TCM-related symptoms and signs. Of course, restoring and maintaining sinus rhythm is always a most desirable target, when feasible, either with drugs or more likely with ablation. All these issues are herein reviewed, current guidelines are discussed and relevant data are tabulated and pictorially illustrated.

Keywords Atrial fibrillation · Tachycardiomyopathy · Heart failure · Left ventricular dysfunction · Ablation

Key Points

- Atrial fibrillation (AF)-induced tachycardiomyopathy (AF-TCM) is the most common type of arrhythmia-induced cardiomyopathy, causing left ventricular (LV) dysfunction and heart failure (HF)
- Mechanisms involved in AF-TCM include principally fast ventricular rates (VR), aided by loss of atrial contraction, irregular heart rate, neurohumoral activation, and structural myocardial changes
- When AF-TCM is suspected in AF patients, VR and rhythm control should be rigorously pursued
- Restoration and maintenance of sinus rhythm, e.g., via ablation, is superior to VR control for prophylaxis and/or recovery of LV function; however, when not feasible or not a choice, VR control is the next best strategy
- Data, albeit less robust, also point to deleterious effects of slow VRs on LV function
- Thus, a J-shaped relationship between VR and clinical outcome has been suggested, with an optimal VR around 65 bpm, ranging between 60 and 80 bpm; VRs above and below this range may confer higher morbidity and mortality rates

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Abbreviations

AF	Atrial fibrillation
AF-TCM	Atrial fibrillation-induced tachycardiomyopathy
AV	Atrioventricular
CAD	Coronary artery disease
CCB	Calcium channel blocker
CM	Cardiomyopathy
CMR	Cardiac magnetic resonance imaging
CRT	Cardiac resynchronization therapy
CRT-D	CRT-defibrillator
CV	Cardiovascular
DCM	Dilated cardiomyopathy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter defibrillator
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PVI	Pulmonary vein isolation

RCT	Randomized controlled trial
SVT	Supraventricular tachycardia
TCM	Tachycardiomyopathy
VR	Ventricular rate

Introduction

Many patients with atrial fibrillation (AF), mostly persistent or chronic AF, but also paroxysmal AF with frequent recurrences, may develop a tachycardiomyopathy (TCM) with left ventricular (LV) dysfunction and heart failure (HF) symptoms, which is a reversible condition upon restoration and maintenance of sinus rhythm, when feasible, or by applying better and tighter ventricular rate (VR) control [1, 2]. This AF-induced tachycardiomyopathy (AF-TCM), which constitutes the most common type of arrhythmia-induced cardiomyopathy (CM), is not readily recognized and can go unnoticed resulting in full-blown HF symptomatology and a status misdiagnosed as primary HF secondarily complicated by AF [3, 4]. Until sinus rhythm is restored or the VR is better controlled either as a management plan or because of suspected TCM, and reversibility of LV function is documented, a correct diagnosis will remain elusive [5]. Restoring and maintaining sinus rhythm, either via cardioversion combined with antiarrhythmic drug therapy, or more effectively via ablation (pulmonary vein isolation-PVI), or at least maintaining stricter VR control are the countermeasures and strategic approaches to prevent and/or reverse AF-TCM [6].

Incidence

Atrial fibrillation and HF share many preceding risk factors, and ≈40% of people with either AF or HF will develop the other condition [7]. Data from the Framingham Study indicated that during the study period of 47 years, 1470 participants developed AF, HF, or both [8]. Among 382 individuals with both conditions, 38% had AF first, 41% had HF first, and 21% had both diagnosed on the same day. The incidence of HF among AF patients was 33 per 1000 person-years, and the incidence of AF among HF patients was 54 per 1000 person-years; development of either condition conferred an increased mortality (hazard ratio (HR) 2.7–3.1 for AF patients developing HF and HR 1.6–2.7 for HF patients developing AF).

In the community, estimates of the incidence of HF in patients with AF ranged from 3.3204 to 5.8239 per 100 person-years of follow-up; the incidence of HF with preserved ejection fraction (HFpEF) may be higher than HF with reduced ejection fraction (HFrEF) (3.3 vs 2.1) [9]. A Dutch study with 8265 participants and mean follow-up of 9.7 years, with 265 participants developing AF, indicated that per 1000 person-years, the incidence rate of HFrEF was 12.75 vs 1.99 for those with vs those without AF, with a multivariable-adjusted HR of AF of 5.79. Corresponding numbers for HFpEF were 4.90 vs 0.85 with and without AF, with a multivariable-adjusted HR of AF of 4.80 [10].

In a recent large cohort study of 25,787 participants free of baseline HF, over a median of 9 years of follow-up, 1109 (4.3%) HF events occurred [11]. In a model adjusted for sociodemographics, cardiovascular (CV) risk factors, and incident coronary artery disease (CAD), AF was associated with increased risk of all HF events (HR 1.67) with no difference between HFrEF versus HFpEF events; these associations were consistent in sex and race subgroups. A meta-analysis of 9 studies reported that individuals with AF have an almost fivefold increased risk of HF (RR, 4.62) [12].

A recent multicenter study reported on 243 patients (age 65 ± 11 years, 73% male) with arrhythmia-induced CM; the most common cause was AF (49%), followed by atrial tachycardia (20%), and premature ventricular contractions (31%) [4]. Rhythm control, effected in 95%, led to improved LV ejection fraction (LVEF) regardless of arrhythmia duration or type.

A prospective observational study identified 9% of all HF admissions ($N = 107$) diagnosed as pure TCM (68 males, age 66.7 ± 14.5 years) ascribed to AF in 78%, atrial flutter in 15% and other arrhythmias in the remainder [13]. Over a median of 22.6 months, 17 recurred, 51 were hospitalized for CV reasons, 2 suffered from thromboembolic events and 1 patient died. The LVEF at discharge (HR 0.96 for each %) and the heart rate at discharge (HR 1.02 for each bpm) were independent predictors of CV-related hospitalization.

Mechanisms

Mechanisms for the development of HF in AF patients include loss of atrial contraction, irregular heart rate, fast ventricular rate (VR), neurohumoral activation, and structural myocardial changes [14, 15] (Table 1). The most important and common of all mechanisms relates to optimal VR control, which seems to be an elusive target. In general, any persistent or chronic tachycardia (incessant supraventricular or ventricular tachycardia or AF) that occurs more than 10–15% of the day may result in TCM [16]. Persistent tachycardia can impair myocardial contractility, either directly via decreased diastolic filling or through alterations in cellular and neurohormonal mechanisms [3]. Particularly in AF where there is lack of atrial contribution to LV filling, diastolic function is further compromised. A vicious cycle can thus be set in motion, with HF and associated increases in LV filling pressures together with the development of functional mitral regurgitation that can result in mechano-electrical alterations in the left atrium, which can perpetuate AF and TCM [17].

Table 1 Mechanisms leading to atrial fibrillation-induced tachycardiomyopathy

Tachycardia (poor ventricular rate control)
Irregular rhythm
Loss of atrial contraction
Neurohumoral activation
Structural myocardial changes

Importantly, both the atrial tachyarrhythmia caused by AF and the associated rapid VR contribute to atrial remodeling [18]. On one hand, rapid atrial activation abbreviates atrial action potential duration and refractoriness, while increasing atrial vulnerability, further leading to left atrial (LA) structural remodeling, including atrial dilation and fibrosis.

In terms of timing, data from TCM produced by rapid pacing indicate that during the early phase (first 3–7 days) of persistent tachycardia (rapid pacing), some remodeling with LV dilation occurs, with a reduction in LVEF; however, cardiac output and systemic perfusion pressures are not compromised [3]. By the second week, there is further LV dilation, LVEF falls, central venous, and LV filling pressures and systemic vascular resistance are elevated and eventually HF symptoms develop.

In the case of patients already having HF symptoms, the differentiation between compensatory (secondary) tachycardia and primary tachycardia becomes extremely difficult for an a priori diagnosis; it is always an a posteriori diagnosis rendered when the heart rate is brought under control [19]. The diagnosis becomes even more difficult in the setting of an underlying structural heart disease, where the component of worsening HF due to TCM is always missed.

Ventricular rate during AF is usually considered as uncontrolled in patients with mean VR > 80 bpm and maximum VR > 110 bpm [20]. The latest AF guidelines do admit that when TCM is suspected, one should aim for strict target heart rate of < 80 bpm at rest and < 110 bpm during moderate exercise [21]; however, the lenient rate-control strategy (resting heart rate < 110 bpm) has still remained as an option and should be revisited.

Finally, a recent retrospective study reported on endomyocardial biopsy results in patients with TCM ($n = 18$, 81% male, age 60 ± 13 years, 94% HF symptoms NYHA class ≥ II; at baseline 78% had AF/atrial flutter and 12% other forms of tachycardia or frequent extrasystoles) by analyzing samples from a total of 684 consecutive patients with recent-onset HF and reduced LVEF unrelated to valvular or ischemic heart disease and comparing them among patients with TCM, dilated CM (DCM) ($n = 170$) and inflammatory cardiomyopathy (InCM) ($n = 496$) [22]. The VR was higher in patients with TCM compared to DCM and InCM patients (122 ± 25 vs 78 ± 21; $P < 0.001$). Mean LVEF at baseline was lower compared to DCM and InCM (27 ± 12% vs 39 ± 14.6%; $P = 0.001$), but improved to a significantly greater extent during follow-up (20% vs 6%; $P < 0.001$). At follow-up, heart rate and presence of sinus rhythm were similar in all groups; 69% of TCM patients underwent cardioversion or ablation. Compared with DCM patients, TCM patients had stronger myocardial expression of major histocompatibility complex class II and an equal amount of infiltration with T-cells/macrophages. Compared with InCM patients, the presence of T-cells/macrophages was significantly lower in TCM. Caspase 3, a marker of apoptosis, was comparably elevated in TCM/InCM patients. The authors concluded that TCM (mostly AF-TCM) is characterized by immunohistological changes comparable to DCM except for caspase 3 levels, which were similar to those in InCM.

Loss of atrial contraction

Absent atrial contraction during AF with a resultant loss of a 20–25% contribution to total LV stroke volume that such contraction accounts for can by itself lead to the development of HF, especially in patients with diastolic dysfunction [23]. When combined with the deleterious consequences of irregular heart rhythm and particularly a sub-optimally controlled VR, the risk of HF development is greatly enhanced.

The significance of the contribution of atrial contraction to maintaining normal LV function was further corroborated by studies comparing the effect of atrioventricular (AV) nodal ablation and biventricular pacing vs PVI in restoring LV function in patients with AF and HF. In one such study, the pulmonary vein antrum isolation versus AV node ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure (PABA-CHF) study, LVEF improved in 76% of patients who underwent PVI (of whom 88% were free from AF), but only in 25% of patients who underwent AV node ablation with biventricular pacing [24].

Irregular rhythm

Even when the VR is optimal, the irregular rhythm may confer deleterious consequences on systolic and diastolic LV performance; indeed, it has been shown that irregularity of the ventricular rhythm, independent of the VR, may contribute to impairment of cardiac function during AF [25, 26].

A variable duration of diastole due to the beat-to-beat variability adversely affects LV filling and end-diastolic volume. Irregular rhythm adversely influences calcium handling in ventricular myocardium [27]. Furthermore, shorter cycle lengths that compromise LV filling also affect the release of

calcium from the sarcoplasmic reticulum in greater extents than longer cycle lengths [28]. Thus, myocardial contractility and cardiac output are compromised during irregular rhythms compared with regular rhythms with the same average rate; such hemodynamic consequences independent from heart rate include a decreased cardiac output, increased pulmonary capillary wedge pressure, and increased right atrial pressure, all contributing to LV dysfunction [26].

Fast ventricular rate/suboptimal ventricular rate control

Although there is some controversy about the optimal VR control of AF, that is lenient (< 110 bpm) vs strict (< 80 bpm) rate control, lessons need to be learned from TCM that is induced by the incessant forms of supraventricular tachycardias (SVTs), whereby constant rates of 100–140 bpm have been responsible for TCM and HF in such patients, which is reversible either fully when the duration of the SVT is not that long, or partially, albeit to a great extent, when the duration spans several years [29–33]. In general, constant rest heart rates above 100 bpm are deemed to be deleterious as they may lead to TCM [15]. In patients with AF, constant VRs ranging from 120 to 170 bpm have been associated with frank HF, while rates ranging from 100 to 134 have been associated with latent HF [34]. Hence, in this context, a VR control to < 80 bpm at rest and < 100–110 bpm during moderate exercise seems more prudent to avoid the development of TCM. A major caveat relates to the duration of such VR control, which should be throughout a person's (24 h) daily activities (or at least to > 50% of the day) and not limited to periods of rest; thus, such optimal VR control should be confirmed with Holter monitor recordings and not relying on periodic ECGs. This seems to be the major reason why "rapid" AF may escape detection and may not be suspected as a reversible cause of TCM and thus a proper diagnosis may be eluded.

A large study of 1404 patients with HF, fitted with an implantable cardiac resynchronization therapy (CRT) defibrillator (CRT-D), of whom 32% ($n = 443$) had AF over a median of 18 months, showed that VR during AF was uncontrolled in 150 of 443 patients (34%) [20]. Multivariate Cox regression analysis showed that age (hazard ratio (HR) 1.03, $P = 0.028$), and uncontrolled VR (HR 1.69, $P = 0.046$) were the only independent predictors of clinical outcome, assessed by HF hospitalizations and death. The authors concluded that uncontrolled VR occurs in one-third of CRT-D patients, who experience AF, and is associated with HF hospitalizations and death and with sub-optimal CRT.

Another study performed an observational analysis using data from the Get With The Guidelines-HF Program linked with Medicare data on 13,981 patients with AF and HF, of whom 9100 (65%) had strict rate control (< 80 bpm), 4617 (33%) had lenient rate control (< 110 bpm), and 264 (1.9%) had poor rate control by resting heart rate on the day of discharge [35]. After multivariable adjustment, compared with strict rate control, lenient rate control conferred higher adjusted risks of death (HR 1.21, $P < 0.001$), all-cause readmission (HR 1.09, $P < 0.002$), death or all-cause readmission (HR 1.11, $P < 0.001$), but not CV readmission (HR 1.08, $P = 0.051$) at 90 days. The authors concluded that in patients with HF and AF, heart rates > 80 bpm were associated with adverse outcomes irrespective of LVEF.

Suboptimal VR control

According to a study comprising 5299 patients (1902 patients with implantable cardioverter defibrillator-ICD and 3397 patients with CRT-D), uncontrolled VR, defined as VR > 90 bpm for ICD and > 100 bpm for CRT-D patients, the prevalence of poor VR control was 24.8% among ICD patients and 28.6% among CRT-D patients [36]. Importantly, more patients were identified as having poor VR control with continuous monitoring compared to intermittent monitoring (sensitivity range = 8–31%). Furthermore, 11.6% of ICD patients and 17.9% of CRT-D patients experienced ≥ 7 days with poor VR control, to which the sensitivities of annual 7- and 21-day recordings were < 7% and < 20%, respectively. The authors concluded that a significant proportion of permanent AF patients experience poor VR control that would be missed with random intermittent monitoring.

Another study of 519 patients with AF indicated that 1 day of high burden (≥ 6 h) of paroxysmal AF with good rate control (VR during AF ≤ 90 bpm) in the last 30 days increases risk for HF hospitalization in the next 30 days (HR 3.4, $P < 0.001$) [37]. The risk increases further (HR 5.9, $P < 0.001$) with 1 day of poor rate control (VR during AF > 90 bpm), during persistent AF or high burden (≥ 6 h) paroxysmal AF in the last 30 days. These observations attest to the notion of a deleterious effect on LV function of both irregular heart rhythm and poor VR control.

A study exploring the effect of controlling VR on heart function in 82 patients with HF and AF, divided into a control group (conventional therapy, $n = 41$) and a study group (use of metoprolol to decrease resting heart rates to 55–60 beats/min, $n = 41$), showed that after 3 months of treatment, LVEF and the cardiac output levels in the two groups were increased, albeit the levels in the study group were higher than the levels in the control group; there were opposite trends in the LV end-systolic diameter levels, the LV end-diastolic dimension levels, and the N-terminal pro b-type natriuretic peptide (NT-proBNP), serum C-reactive protein (CRP), tumor necrosis factor (TNF)-α, and interleukin (IL)-6 levels (all $P < 0.05$) [38]. After 6 months, the readmission

and HF rates and the incidence of adverse events in the study group were lower than they were in the control group (all $P < 0.05$).

Although there are studies indicating that lenient VR control (resting heart rate target < 110 bpm) is an acceptable strategy in AF patients with HF having similar results with a strict VR control strategy (resting heart rate target < 80 bpm and a heart rate target during moderate exercise < 110 bpm) [39, 40], post hoc analyses of these same studies have indicated that patients with lower mean heart rates during AF (≤ 80 in one study and < 100 in another study) had a better outcome than patients with higher heart rates ≥ 100 (HRs 0.69 and 0.58, respectively, for ≤ 80 and < 100 compared with ≥ 100 bpm) [41]. This continued controversy has compelled investigators to plan for further randomized controlled trials (RCTs) on this unsettled issue [42].

On the other hand, there are mathematical model studies suggesting that lower VRs (50 vs 130 bpm) during permanent AF led to improved hemodynamic parameters, cardiac efficiency, and lower oxygen consumption [43]. Importantly, clinical studies indicate an optimal range for VR of 60–80 bpm (see discussion below).

Of course, the ideal situation is rendered when the arrhythmia is abolished, e.g., by ablation, and then one witnesses the reversibility of TCM post-procedurally; when ablation is not contemplated (e.g., chronic AF, patient's preference) or has failed, then one should target optimal VR control. In this context, a significant benefit of AF ablation has been shown even in AF patients with good rate control, identifying AF as an underappreciated reversible cause of LV systolic dysfunction [44].

Genetics

It is not well understood why some patients with AF develop HF and others do not. Some findings may suggest a genetic component in AF-TCM by showing a significantly increased rate of developing HF in situations where such AF patients have a family member with HF/CM [45], or have pathogenic/potentially pathogenic variants in genes associated with CM [46].

A Danish nationwide cohort study ($N = 10{,}605$) examining the long-term rate of developing HF in patients < 73 years of age with newly diagnosed AF based on their family history of HF or dilated CM (DCM) showed that having a family member with HF or DCM conferred a > 50% increase in the rate of incident HF during the following 5 years after AF (8.4% vs 4.5%; adjusted HR, 1.49), cumulative incidence of the composite of HF/death: 9.2% vs 5.6%, adjusted HR 1.36 [45]. However, after 5 years, only 5% of the cohort developed HF. Importantly, ~ 17% of patients with AF in the study had a family member with pre-existing HF or DCM, but having such a family history of HF/DCM was associated with an 87% increase in 5-year incidence of HF compared with those without.

Other studies with longer follow-up and older patients than the previous study have shown that about two thirds of people living with AF from any cause will develop HF during the course of their disease, whereas AF develops in only one third of people with pre-existing HF [8, 47].

Importantly, early-onset AF can be the initial manifestation of a more serious underlying inherited CM or arrhythmia syndrome. According to a prospective study enrolling patients with AF diagnosed before 66 years of age and undergoing whole genome sequencing, rare variants were identified in a panel of 145 genes that are included on CM and arrhythmia panels [46]. Disease-associated variants were defined as pathogenic/likely pathogenic variants in genes associated with autosomal dominant or X-linked dominant disorders. Among 1293 participants (72% male; median age at enrollment, 56 years; median age at AF diagnosis, 50 years), genetic testing identified 131 participants (10.1%) with a disease-associated variant. The likelihood of a disease-associated variant was the highest in participants with AF diagnosed before the age of 30 years (16.8%) and the lowest after the age of 60 years (7.1%). Disease-associated variants were more often associated with inherited CM syndromes compared with inherited arrhythmias. The most common genes were TTN (titin) ($n = 38$) associated with DCM and early-onset AF; MYH7 (myosin, heavy chain 7) ($n = 18$) and MYH6 ($n = 10$) associated with hypertrophic CM; LMNA ($n = 9$) encoding lamin A and C and responsible for an arrhythmogenic form of DCM with early-onset conduction disease, ventricular tachycardia, and AF; and KCNQ1 ($n = 8$) causing long QT syndrome type 1. The authors concluded that the use of genetic testing is supported in early-onset AF (< 30 years of age) as it identified a disease-associated variant in 10% of such patients. Most pathogenic/likely pathogenic variants were in genes associated with CM.

Bradycardiomyopathy

Although the association of persistent bradycardia and HF is not well studied, there are a few data that support this link. Sinus bradycardia has been reported to worsen the outcome of patients with HF [48]. A case report suggested a causative relation between sinus bradycardia and a dilating "cardiomyopathy" (bradycardiomyopathy) causing HF; symptoms subsided, LV function recovered, and LV enlargement regressed after restoring normal heart rate with atrial pacemaker implantation [49]. A study of 117 patients with symptomatic sick sinus syndrome with a mean resting heart rate of ~ 45 bpm showed that an increase in heart rate induced

by oral theophylline or dual-chamber pacing reduced the incidence of overt HF indicating that persistent sinus bradycardia seems to play a role in the genesis of HF [50].

In a similar context, a persistent slow VR during AF together with the adverse effects of irregular rhythm and loss of atrial contribution might account for a bradycardiomyopathy or contribute to worsening HF symptoms. An indirect clue to this entity has been provided by studies indicating that cardiac resynchronization therapy (CRT) yielded comparable beneficial effects for patients with AF and slow VR (< 60 bpm) as compared with those in sinus rhythm, by not only correcting electrical dyssynchrony but also optimizing heart rate via increased biventricular pacing rate [51]. As also mentioned, a registry study of 2812 patients with permanent AF indicated that slow VR (< 60 bpm) was associated with higher mortality rate, as was a faster VR (> 80 bpm) [52]. However, this issue needs further studies.

Chronotropic incompetence

Chronotropic incompetence has been defined as a peak exercise heart rate < 75–80% of the maximal predicted heart rate for age (220-age bpm) [53, 54]. However, such standards relate to sinus rhythm, while VRs may vary widely in an individual patient with AF, with fluctuating slow and fast extremes depending on the net fleeting effect of several factors influencing AV node conduction (e.g., AV node structural integrity, concealed conduction, autonomic tone, and drug effects) [55]. Thus, the range of heart rates observed in normal individuals in sinus rhythm cannot be extrapolated to patients with AF; hence, one needs to recognize the "normal" extent and distribution of slow VRs and prolonged ventricular pauses in patients with AF. Patients with AF respond differently to exercise; chronotropic incompetence can occur during the early, late, or both stages during exercise in AF patients when compared to gradual acceleration in normal individuals [56]. Thus, chronotropic response is inherently inappropriate in AF with bradycardic and tachycardic fluctuations which can adversely affect LV function. Indeed, clinical data have shown that chronotropic incompetence is associated with more severe HF and worse prognosis [57, 58].

A prospective study evaluating the incidence and significance of chronotropic incompetence in 211 patients indicated that the incidence was higher in patients with AF (67%, $P < 0.0005$) and sick sinus syndrome (49%, $P < 0.012$) than in those with AV block (30%) [59]. With pacemaker implantation, the bradycardic component is remedied; however, attention should also be paid to the tachycardic response which should be optimized with sensor-driven modulation combined with either AV nodal slowing drugs or AV node ablation; in the latter case, ideally, a CRT device will provide an optimal rate response and also correct electrical dyssynchrony [60, 61].

Heart failure-induced atrial fibrillation

As mentioned, persistent AF can lead to arrhythmia-induced CM and HFrEF. Of course, there is always the possibility that HF can induce AF by various mechanisms including atrial stretch that may increase dispersion of refractoriness and alter anisotropic and conduction properties facilitating AF; neurohumoral activation that may lead to atrial fibrosis which can change atrial conduction and promote AF; remodeling of atrial ion channels that affects the occurrence and persistence of AF [17].

Data from the Framingham Heart Study indicate that AF occurs in > 50% of individuals with HF, and HF occurs in > 30% of individuals with AF [47]. Both HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) are associated with a higher incidence of AF; an almost two-fold higher incidence of AF has been reported in patients of HF of either type compared with controls [11].

On the other hand, in patients with HF and AF, fast VR can affect atrial systolic function, reduce cardiac output, and aggravate HF, hence the need for effective rhythm control in such patients, preferably and more effectively achieved via catheter ablation conferring a lower rate of death from any cause or hospitalization for worsening HF compared with medical therapy [62].

Concurring AF in patients with CM confers worsened prognosis [63]. It seems that patients in whom HF precedes AF (prevalent HF) have higher mortality and higher risk of re-hospitalization for HF [64]. Catheter ablation significantly lowers odds of all-cause mortality at 1 year [63].

AF an underappreciated reversible cause of LV systolic dysfunction and/or heart failure

Heart failure and AF often coexist, and each adversely affects the other, so that the chicken or the egg dilemma is often contemplated [6]. In this context, the bidirectional reciprocal and deleterious influence of these two conditions poses great problems to afflicted patients. It is only after restoration and maintenance of sinus rhythm that the proper answer to this question is rendered.

Both the irregular rhythm and the fast VR contribute to the emergence or worsening of TCM and HF, with the preponderance of data indicating the rapid VR may be a more significant contributory factor rather than the irregularity; indeed, data from comparative studies show that

pulmonary-vein isolation (PVI) with restoration of sinus rhythm is superior to atrioventricular (AV) node ablation with biventricular pacing applied in patients with HF who have drug-refractory AF [24]; the difference being that the former strategy remedies both irregular rhythm and fast VR by restoring sinus rhythm, while the latter approach regularizes rhythm but lacks the recovery of atrial contribution.

The CAMERA-MRI (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) study, a cardiac magnetic resonance (CMR) imaging-guided RCT, where 66 patients with persistent AF and CM (LVEF ≤ 45%) were randomized to catheter ablation ($n=33$) or medical rate control ($n=33$), showed that the ablation group had a significant improvement in LVEF compared with the medical care group (18 ± 13% vs 4.4 ± 13%; $P<0.0001$) with normalization of LVEF to ≥ 50% noted in 58% versus 9% ($P=0.0002$) [44]. To reiterate, this significant benefit conferred by AF ablation in patients with good rate control identifies AF as an underappreciated reversible cause of LV systolic dysfunction.

Sudden death

Whether there is an increased risk of sudden death in AF-TCM or any arrhythmia-induced CM remains a moot point [65]. However, patients with HF, whatever the etiology, and an LVEF that remains below 35% need to be considered for sudden cardiac death protection following guideline recommendations for implantation of an ICD. Whether patients with recovered TCM and normalized LV function continue to have increased risk of lethal arrhythmia due to pathological remodeling also remains controversial. A case series of 24 patients (17 men; age 46 ± 16 years) with TCM and HF (mean LVEF 26 ± 9%) caused by AF in over half (54%) of the patients ($n=13$), and other arrhythmias in the remainder, reported that there were 3 cases of sudden death in patients with AF-TCM, months to years later, with normal LVEF and no symptoms of HF or recurrent tachycardia [66].

Management

Optimal ventricular rate control

Although a more individualized approach may be a better way to address the issue of AF-TCM, optimal VR control at rest but also during exertion is most important to avoid TCM and also probably to reverse it. Among patients with permanent AF, there appears to be a J-shaped relationship between heart rate and mortality, according to the results of the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) [52]. According with this registry study, among 2812 outpatients with permanent AF, analyses of continuous heart rates indicated that optimal VR control seems to hover around 65 bpm within a range between 60 and 80 bpm, while rates above and below this range may confer higher mortality rates (Fig. 1).

A stringent VR control helps not only to relieve symptoms but also to prevent the development of TCM and HF [67]. This is in keeping with data from several studies indicating that in patients with AF-TCM and uncontrolled VR (≥ 110 bpm) responsible for severe LV dysfunction and HF, TCM was reversible upon VR control to mean rates ~ 60 bpm [19]. Such data clearly indicate the critical importance of a lower VR in patients with AF. Studies utilizing 24-h Holter recordings have provided the pattern of ventricular responses on a continuous basis on various rate-lowering agents [19, 68]. From such recordings, the so-called heart rate burden can be computed to differentiate the period of time during the 24 h when the VR in AF exceeds the normal range of heart rates in an individual patient in sinus rhythm. Based on this approach, the ideal range of VRs in AF may be determined and maintained by VR-lowering agents. However, currently, there is no consensus regarding the optimal VR in a patient with AF; nevertheless, as mentioned, hitherto the data point to an optimal resting VR around 65 bpm (range 60–80 bpm), rendering it possible that continuous and sustained control of VR over 24 h might lead to sustained improvement in LV function and exercise capacity together with relief of symptoms.

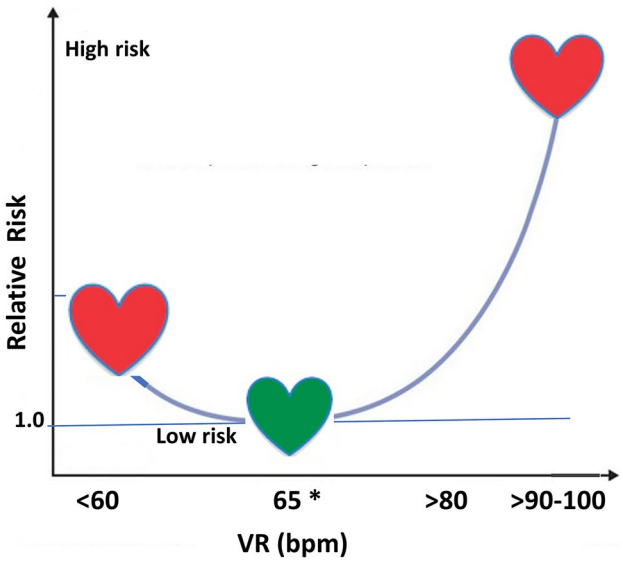

Fig. 1 A J-curve association between ventricular rate (VR) and left ventricular function and clinical outcome has been suggested in patients with atrial fibrillation (AF), with optimal VR at rest around 65 bpm (*) and a range between 60 and 80 bpm (see text for discussion)

Optimal VR control can usually be achieved with the use of combined drug therapy rather than monotherapy that includes beta-blockers and calcium-channel blockers (CCBs), achieving the lowest mean exercise-induced VR in patients with chronic AF [68]. In more difficult cases, the use of amiodarone may be needed to achieve this goal, as a VR control agent of last resort [69]. Difficulty is encountered in VR control in patients with compromised LV function (LVEF < 40%) and/or HF where the use of CCBs, particularly of verapamil, is considered to be contra-indicated due to their negative inotropic action, although the use of diltiazem has been shown to be safe for the acute management of AF with rapid VR in patients with HFrEF [70]. This is probably because diltiazem appears to have a less pronounced negative inotropic effect than verapamil [71]; on the other hand, the effect of rapid ventricular response with its attendant significantly compromised LV filling appears to matter more than the mild/moderate adverse inotropic effect of the drug. In keeping with the above, a study in patients with chronic AF has indicated that digoxin or diltiazem, as monotherapy, was least effective for controlling VR in AF during daily activity, while combined treatment with digoxin and atenolol produced the most effective VR control reflecting a synergistic effect on the AV node trailed by the combination of digoxin and diltiazem [68]. However, in clinical practice, beta-blockers with or without digoxin lack behind in efficacy compared with the effectiveness of a CCB, again with or without digoxin; as the use of digoxin has been rather outdated for various reasons [72], the use of diltiazem seems to be a more practical and efficient approach to rate control [73–76]. When a beta-blocker is combined with a CCB, a lower dosage of each individual drug should be used to avoid side-effects, such as AV block.

As mentioned, in patients with HF and AF, resting heart rates > 80 bpm were associated with adverse outcomes irrespective of LVEF [35]. Thus, poor rate control, defined as resting VR > 80–100 bpm, is quite common (25–30%) and increases risk for HF symptoms [37]. Furthermore, many more patients may be identified as having poor VR control with continuous monitoring compared to intermittent monitoring [36]. In the end, as mentioned, a stringent VR control not only alleviates symptoms but also prevents the development of TCM and HF [67].

Rhythm control

Rhythm control in patients with AF and HF can be attained with use of antiarrhythmic drugs, e.g., amiodarone, but more effectively via ablation. According to recent US registry data, amiodarone was the most commonly (38%) prescribed antiarrhythmic drug for AF (51% paroxysmal AF), regardless of age or history of coronary artery disease or HF, and despite its high long-term risk of drug toxicity [77].

Catheter ablation

Several prospective and retrospective studies and randomized controlled trials (RCTs) have evaluated the effect of AF ablation in patients with AF and HF on the improvement or reversibility of LV function and patient symptomatology and/or clinical course (Table 2) [24, 44, 62, 78–85]. Many studies showed significant improvement in LV function and/or clinical symptoms of HF after ablation [24, 62, 78–80, 83]; some have even reported normalization of LVEF [44, 85].

A prospective study evaluated the effect of catheter ablation of AF on LV function in 58 patients with HF and an LVEF < 45% compared to a matched control group of 58 patients without HF who were undergoing ablation for AF. After 12 ± 7 months, 78% of patients with HF and 84% of the controls remained in sinus rhythm (P = NS) with or without antiarrhythmic drugs [84]. Patients with HF had significant improvement in LV function (increases in LVEF of 21 ± 13%; $P < 0.001$), LV dimensions, exercise capacity, symptoms, and quality of life. The LVEF improved significantly in patients with and without concurrent structural heart disease and those with adequate or inadequate rate control ($P < 0.001$). The authors concluded that restoration and maintenance of sinus rhythm by catheter ablation without the use of drugs in patients with HF and AF significantly improve cardiac function, symptoms, exercise capacity, and quality of life.

A study compared the results of ablation in 659 AF patients categorized in 3 groups, TCM group ($n = 61$), controls with normal LVEF (control group, $n = 562$) and patients with HF due to structural CM (HF group, $n = 36$) [2]. Compared to controls, patients with TCM were younger, had a shorter AF course and more often had persistent AF, with lower LVEF (40% vs. 62%, $P < 0.05$), larger left atrial diameter (LAD: 46 vs. 41 mm, $P < 0.05$) and LV end-diastolic diameter (LVEDD: 55 vs. 51 mm, $P < 0.05$). TCM patients had significant improvement at 6-month follow-up, including those patients with AF recurrence. The probability of being arrhythmia-free did not differ between the TCM group and the other groups after a first or last procedure. The only independent predictor of AF recurrence was LAD. The authors concluded that patients with AF-TCM benefit from ablation, with a significant improvement in LVEF, LVEDD, and LAD. The outcome after ablation of this group did not differ from patients with no structural CM.

The CAMTAF (Catheter Ablation Versus Medical Treatment of AF in Heart Failure) trial randomized patients with persistent AF, symptomatic HF, and LVEF < 50% to catheter ablation ($n = 26$, LVEF 32 ± 8%) or medical rate control ($n = 24$, LVEF 34 ± 12%) [80]. At 6 months, freedom from AF was achieved in 21/26 (81%) off antiarrhythmic drugs; LVEF at 6 months in the ablation group was

Table 2 Randomized controlled studies of AF ablation in patients with heart failure/possible AF-TCM

Author/year	Study/type of AF	Patients/controls (intervention)	LVEF/NYHA class	FU	Results	Comments
Khan et al./2008 [24]	PABA-CHF/PAF, PersAF	41 (PVI)/40 (AVN ablation + CRT)	< 40% (27 ± 8% vs 29 ± 7%)/ II-III	6 mos	PVI: ● Improved QOL ($P < 0.001$), ● Longer 6-min-walk distance (340 m vs. 297 m, $P < 0.001$) ● ***higher LVEF (35% vs 28%, P < 0.001)***	–PVI: ● 88% with AAD and 71% with no AAD were free of AF at 6 mos ● PV stenosis in 2 pts, PE in 1, PEd in 1 pt –AVN ablation /CRT: ● Lead dislodgment in 1 pt & pneumothorax in 1 pt
MacDonald et al./2011 [78]	Pers AF	22 (PVI)/19 (VRC)	< 35%/II–IV	6 mos	● Increase in CMR LVEF (RFA vs medical group): 4.5 ± 11.1% vs 2.8 ± 6.7% ($P = 0.6$) ● Increase in radionuclide LVEF (RFA vs medical group): + 8.2 ± 12% vs + 1.4 ± 5.9%; $P = 0.032$)	● SR at end of study in RFA vs medical group: 50% vs 0% ● RFA did not improve NT-proBNP, 6-min walk distance or QOL ● Serious complications of RFA: 15%
Jones et al./2013 [79]	ARC-HF/PersAF	26 (PVI)/26 (VRC)	≤ 35% (21.5 ± 8.3% vs 24.9 ± 7.2%)/II–IV	1 y	● Peak VO_2, increased significantly after ablation (difference + 3.07 ml/kg/min, $P = 0.018$) ● Ablation improved QOL ($P = 0.019$) & BNP ($P = 0.045$)	● The change in peak VO2 was not evident at 3 mos ● Ablation showed non-significant trends toward improved 6-min walk distance ($P = 0.095$) and LVEF ($P = 0.055$)
Hunter et al./2014 [80]	CAMTAF/PersAF	26 (PVI)/24 (VRC)	< 50% (32 ± 8% vs 34 ± 12%)/ II–IV	6 mos	● PVI: 81% freedom from AF off AAD ● LVEF 40 ± 12% at 6 months in the ablation group vs 31 ± 13% in the VRC group ($P = 0.015$)	Ablation improved peak VO2 (22 ± 6 vs 18 ± 6 mL/kg/min; $P = 0.014$) and QOL ($P = 0.001$)
Di Biase et al./2016 [81]	AATAC/PersAF	102 (PVI)/101 (Amio)	< 40% (29 ± 5% vs 30 ± 8%/ II–III	≥ 2 y	● AF recurrence free: 70% vs 34% (log-rank $P < 0.001$) ● Unplanned hospitalization: 31% vs 57% ($P < 0.001$) (RR, 0.55) ● Mortality: 8% vs 18% ($P = 0.037$)	The success rate of RFA in different centers after a single procedure ranged from 29 to 61%

Table 2 (continued)

Author/year	Study/type of AF	Patients/controls (intervention)	LVEF/NYHA class	FU	Results	Comments
Prabhu et al./2017 [44]	CAMERA-MRI/PersAF	33 (RFA)/33 (VRC)	≤45% (32 ± 9.4% vs 34 ± 7.8)/ II–IV	6 mos	Intention-to-treat analysis: ● LVEF improved by 18 ± 13% vs 4.4 ± 13% ($P < 0.0001$) ● LVEF normalized (≥50%) in 58% vs 9% ($P = 0.0002$)	● Mean AF burden post-RFA: 1.6 ± 5.0% at 6 mos ● In RFA group, absence of LGE predicted greater improvements in LVEF (10.7%; $P = 0.0069$) & normalization at 6 mos (73% vs 29%; $P = 0.0093$)
Marrouche et al./2018 [62]	CASTLE-AF/PAF, PersAF	179 (RFA)/184 (rhythm/rate control)	≤35% / II–IV (median LVEF 32.5%)	37.5 mos (median)	● Primary end point (death from any cause or hospitalization for worsening HF): 28.5% vs 44.6% (HR, 0.62; $P = 0.007$)	● Death from any cause: 13.4% vs 25% (HR, 0.53; $P = 0.01$) ● HF hospitalization: 20.7% vs 35.9% (HR, 0.56; $P = 0.004$) ● CV death: 11.2% vs 22.3% (HR, 0.49; $P = 0.009$)
Kuck et al./2019 [82]	AMICA/PersAF	68 (PVI)/72 (rhythm/rate control)	≤35% / II–III (median LVEF 27.6%)	1 y	LVEF increased in ablation pts by 8.8% and in medical pts by 7.3% ($P = 0.36$)	● SR at 1 year: 73.5% vs 50% ● No difference in secondary end point outcome (6-min walk test, QOL, NT-proBNP)
Packer et al./2021 [83]	CABANA substudy/PAF, PersAF	378 (PVI)/400 (rhythm/rate control)	778 pts: II–IV/LVEF available in 571 pts (73%): 79% had an LVEF ≥ 50%, 11.7% LVEF 40–49%, 9.3% LVEF < 40%	5 y	Ablation vs drug therapy: ● 36% relative reduction in primary composite end point of death, stroke, serious bleeding, or cardiac arrest (HR, 0.64) ● 43% relative reduction in all-cause mortality (HR, 0.57)	● AF recurrence was decreased with ablation (HR, 0.56) ● QOL and symptom scores favored the ablation arm

AAD, antiarrhythmic drug(s); *AF*, atrial fibrillation; *AF-TCM*, atrial fibrillation-related tachycardiomyopathy; *Amio*, amiodarone; *AVN*, atrioventricular node; *BNP*, brain natriuretic peptide; *CM*, cardiomyopathy; *CRT*, cardiac resynchronization therapy; *FU*, follow-up; *HR*, hazard ratio; *LGE*, late gadolinium enhancement; *LVEF*, left ventricular ejection fraction; *mos*, months; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *NYHA*, New York Heart Association; *PE*, pericardial effusion; *PEd*, pulmonary edema; *PV*, pulmonary vein; *PVI*, pulmonary vein isolation; *QOL*, quality of life; *RFA*, radiofrequency ablation; *RR*, relative risk; *SR*, sinus rhythm; *VRC*, ventricular rate control

40 ± 12% compared with 31 ± 13% in the rate control group ($P = 0.015$). Ablation was associated with better peak oxygen consumption ($P = 0.014$) and quality of life ($P = 0.001$) compared with rate control.

As mentioned, the CAMERA-MRI study compared 33 patients with persistent AF and idiopathic CM (LVEF ≤ 45%) who were randomized to catheter ablation with 33 patients assigned to medical rate control [44]. After optimization of rate control and before randomization, patients underwent cardiac magnetic resonance (CMR) imaging to assess LVEF and late gadolinium enhancement (LGE) to assess for myocardial fibrosis. In the intention-to-treat analysis, absolute LVEF improved by 18 ± 13% in the ablation group compared with 4.4 ± 13% in the medical rate control group ($P < 0.0001$) and normalized (LVEF ≥ 50%) in 58% versus 9% ($P = 0.0002$). In the ablation group, the absence of LGE predicted greater improvements in absolute LVEF (10.7%; $P = 0.0069$) and normalization at 6 months (73% vs 29%; $P = 0.0093$).

Ablation has also been used successfully as an emergency procedure in patients with atrial tachyarrhythmias (mainly AF and atrial flutter) presenting with cardiogenic shock secondary to severe form of TCM, whereby dramatic improvement of clinical status and LVEF was reported [86].

A word of caution regarding ablation in patients with AF and HF relates to patient selection process for such interventional therapy, as a recent study comprising 656 patients showed that patients with HFrEF and AF had an approximate threefold higher risk for a composite of all-cause death, HF hospitalization, and stroke or systemic embolism following AF ablation compared with patients with preserved LVEF [87]. Importantly, the prevalence of coronary artery disease (CAD) and CMs was higher among patients with reduced as compared with preserved LVEF. Thus, the best candidate for ablation seems to be the AF patient where AF has preceded the development of HF and AF-TCM is strongly suspected, while CAD and other types of CM have been ruled out (Fig. 2). Other factors to be considered unfavorable for a good outcome of ablation may include a more advanced HF class, ischemic or other structural etiology of HF, significant left atrial and LV fibrosis (as detected by LGE enhancement), high (> 50%) AF burden, and late timing of ablation [88].

In the context of proper patient selection for ablation, the Catheter Ablation versus Standard Conventional Therapy in Patients with LV Dysfunction and AF (CASTLE-AF) trial showed that catheter ablation for AF ($n = 179$) in patients with HF, all in New York Heart Association (NYHA) class II–IV, having LVEF ≤ 35% and an implanted cardioverter-defibrillator (ICD), conferred a significantly lower rate of a composite end-point of death from any cause or hospitalization for worsening HF than was medical therapy focusing on rate or rhythm control ($n = 184$) [62]. After a median follow-up of 37.8 months, the primary composite end point occurred in fewer patients in the ablation group than in the medical-therapy group (28.5% vs 44.6%; HR, 0.62; $P = 0.007$).

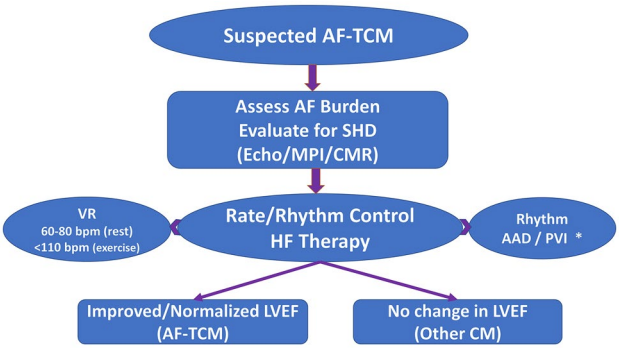

Fig. 2 An algorithm is proposed to evaluate and manage atrial fibrillation-related tachycardiomyopathy (AF-TCM). *AAD*, antiarrhythmic drug(s); *AF*, atrial fibrillation; *CM*, cardiomyopathy; *CMR*. cardiac magnetic resonance (imaging); *Echo*, echocardiography; *HF*, heart failure; *LVEF*, left ventricular ejection fraction; *MPI*, myocardial perfusion imaging; *PVI*, pulmonary vein isolation; *SHD*, structural heart disease; *VR*, ventricular rate

Similarly, a retrospective analysis compared outcomes of catheter ablation for persistent AF in a cohort of patients with previously diagnosed TCM and LVEF < 50% ($n = 45$; age 58 ± 8 years; 91% male) with those with normal LVEF (non-TCM; $n = 440$; age 55 ± 9 years; 95% male) [85]. In the TCM group, LVEF improved from 35.8% ± 8.1% to 57.5% ± 8.3% after ablation. During 3.3 ± 1.5 years follow-up, arrhythmia-free survival after ablation was significantly higher in the TCM group as compared with the medical group (69% vs 42%; $P = 0.001$).

According to a meta-analysis of 7 studies, including 856 patients with AF and systolic HF, catheter ablation of AF was associated with a significant increase in LVEF (mean difference 6.8%; $P < 0.001$) and 6-min walk test (mean difference 29.3 m; $P = 0.001$), and improvement in quality of life ($P = 0.007$) [89]. The risk of all-cause mortality was significantly lower in the AF ablation arm (OR 0.49; $P = 0.002$).

Importantly, intervention has to occur relatively early and for less advanced disease to have patients avail themselves of the benefits conferred by ablation or rhythm control, in general. In the context of early intervention, the Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST-AFNET 4) trial randomly assigned 2789 patients who had AF diagnosed early (≤ 1 year before enrollment, median time since diagnosis, 36 d) and CV conditions to receive either early rhythm control with antiarrhythmic drugs (AADs) or ablation ($n = 1395$) or usual care ($n = 1394$) [90]. Over a median of 5.1 years, a first-primary-outcome event (CV death, stroke, or HF hospitalization or acute coronary syndrome) occurred in 249 of the patients assigned to early rhythm

control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5 per 100 person-years) (HR, 0.79; $P=0.005$). The percentage of patients with a primary safety outcome event (death, stroke, or serious adverse event) did not differ significantly between the groups; serious adverse events related to rhythm-control therapy occurred in 4.9% vs 1.4%, respectively. Symptoms and LV function at 2 years did not differ significantly between the groups. The authors concluded that early rhythm-control therapy was associated with a lower risk of adverse CV outcomes than usual care among patients with early AF and CV conditions. However, no data are available from this trial on the specific subgroup of TCM.

In the context of advanced HF, a rather limited ablation benefit has been suggested in patients with seriously advanced HF, as shown by the results of the AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) trial [82]. In this trial, among 140 patients (aged 65 ± 8 years, 90% men) with persistent/longstanding persistent AF and LVEF ≤ 35% assigned to ablation ($n=68$) or best medical therapy ($n=72$), at 1 year, LVEF had increased in ablation patients only by 8.8% vs 7.3% in the medical group ($P=0.36$). Sinus rhythm at 1 year was recorded in 73.5% vs 50%, respectively. Ablation patients in AMICA had a lower median LVEF (27.6% vs 32.5% in CASTLE-AF), a higher prevalence of persistent AF (100% vs 70%), more advanced symptoms (NYHA III/IV 60% vs 31%), and more CRT-Ds (43% vs 27%).

AV node ablation and pacing

In patients with refractory AF and difficult-to-control VRs, atrioventricular (AV) node ablation followed by permanent pacemaker implantation, preferably a cardiac resynchronization therapy (CRT) device, have an important role [91]. It is crucial to avoid right ventricular apical pacing in this circumstance, as there is a plethora of studies emphasizing the deleterious effects of long-term right ventricular apical pacing [92, 93]. However, AF decreases the efficacy of CRT compared to AV paced patients, even when AV node ablation can ensure optimal biventricular pacing; the potential benefits must be weighed against the risks associated with creating pacemaker dependency [94, 95]. Importantly, PVI, when feasible, is always better that AV node ablation [24].

Impact of atrial fibrillation on cardiac resynchronization therapy

Atrial fibrillation may attenuate the response to CRT both due to a reduction in biventricular pacing and the loss of AV synchrony [96]. In patients with persistent or permanent AF and HF who have an implanted CRT device, a high percentage (≥ 98%) of biventricular pacing is required to achieve effective CRT [97].

A large US retrospective observational analysis of 54,019 patients fitted with a CRT-D device (mean age 70 ± 11 years; 73% male; follow-up, 2.3 ± 1.2 years) showed that a high proportion of patients with permanent (69%) and persistent (62%) AF did not achieve high percentage (> 98%) of biventricular pacing [98]. Relative to no/little AF, patients with AF had increased mortality (permanent AF: HR 1.28, $P<0.001$; persistent AF: HR 1.51; $P<0.001$). Relative to patients with biventricular pacing > 98%, patients with reduced biventricular had increased mortality (biventricular pacing 90–98%: HR 1.20, $P<0.001$; biventricular pacing < 90%: HR 1.32, $P<0.001$). The authors suggested that a shift toward more aggressive rate control and more pacing may be necessary in patients with AF to maximize the benefits of CRT. Indeed, AV node ablation plus CRT has been shown to be superior to pharmacological therapy in reducing HF hospitalization and mortality in HF patients with permanent AF and narrow QRS, irrespective of their baseline LVEF [61, 99]. In the same context, data from a large US registry comprising 8951 patients with HF and AF showed that CRT-D vs ICD alone conferred lower risks of mortality (HR 0.83), all-cause readmission (HR 0.86), and HF readmission (HR 0.68), with a similar risk of complications (HR 0.88) compared with ICD alone [100].

Finally, a meta-analysis of 19 studies comparing the effects of CRT ($N=5324$) in HF patients with AF ($n=1399$) and in sinus rhythm (SR) ($n=3925$) showed that all-cause mortality was higher in patients with AF (odds ratio (OR) 1.69; $P=0.002$) with no significant difference in CV mortality [101]. AF was associated with an increased likelihood of lack of response to CRT (OR 1.41; $P=0.001$). Among patients with AF, ablation of the AV node conferred a reduction in all-cause mortality (OR 0.42; $P=0.008$), CV death (OR 0.39; $P=0.005$), and the number of non-responders to CRT (OR 0.30; $P=0.03$). Thus, despite a higher all-cause death and non-response to CRT, compared to patients in SR, many patients with AF benefit from CRT. Atrioventricular nodal ablation appears to increase the benefits of CRT in patients with AF.

Guidelines

Current guidelines of the European Society of Cardiology (ESC) for AF management recommend that lenient VR control with heart-rate target < 110 bpm is an acceptable approach, while strict VR control with target heart rate < 80 bpm at rest and < 110 bpm during moderate exercise is recommended when dictated by symptoms or for TCM [21]. Similarly, the 2021 ESC guidelines for HF indicate that a lenient rate control (VR < 110 bpm at rest) is an

acceptable initial approach with, however, treatment targeting a lower heart rate (VR < 80 bpm at rest and < 110 bpm during moderate exercise) in case of persistent symptoms or cardiac dysfunction likely related to tachycardia (e.g., TCM) [102]. A 2019 consensus statement of the Heart Failure Association of the ESC indicates that the optimal resting VR for patients with HF and AF may be 70–90 bpm [103].

The American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines endorse the strict target with a resting VR target of < 80 bpm (Class IIa recommendation) in preference to the lenient target of < 110 bpm (Class IIb recommendation) [104, 105]. The Canadian Cardiovascular Society (CCS)/Canadian Heart Rhythm Society (CHRS) uses a target of < 100 bpm (Strong Recommendation), based on the observation that resting VRs > 100 bpm were associated with adverse outcomes in AFFIRM [106] and RACE [39, 107] studies and that very few patients in the lenient rate-control arm of RACE-II had resting HRs > 100 bpm [39, 69].

A J-curve association

As mentioned, in patients with permanent AF, a J-shaped relationship between heart rate and mortality has been suggested (ORBIT-AF Registry), whereby optimal VR control lies around 65 bpm with a range between 60 and 80 bpm; VRs above and below this range may confer higher mortality rates (Fig. 1) [52].

For patients with HF and AF, data indicate that patients with AF who did not achieve strict VR control were at elevated risk of adverse outcomes (death and readmission) irrespective of the presence or absence of reduced LVEF [35]. Specifically, an observational analysis using data on 13,981 patients with AF and HF, of whom 9100 (65%) had strict rate control, 4617 (33%) had lenient rate control, and 264 (1.9%) had poor rate control by resting heart rate on the day of discharge, showed that after multivariable adjustment, compared with strict rate control, lenient rate control was associated with higher adjusted risks of death (HR 1.21, $P < 0.001$), all-cause readmission (HR 1.09, $P < 0.002$), death or all-cause readmission (HR 1.11, $P < 0.001$), but not CV readmission (HR 1.08, $P = 0.051$) at 3 months [35]. The authors concluded that VRs > 80 bpm were associated with adverse outcomes irrespective of LVEF.

In keeping with data supporting an optimal VR < 80 bpm, a recent prospective multicenter cohort study from Japan comprising 144 AF patients with HFrEF (mean age 75 years, 34% female), indicated that over a median follow-up of 1.5 years, the primary endpoint of all-cause death occurred in 41 (28.5%) patients with high VR (> 81 bpm) associated with a progressively increased risk of mortality (log-rank test, $P = 0.034$; HR adjusted for several covariates, 1.979; $P = 0.048$) [108].

Finally, based on a validated computational model, a study investigating if the cerebral hemodynamic consequences and alterations induced by AF are modulated by mean VR, suggested that a rate control strategy aiming to ~ 60 bpm could be beneficial in terms of cognitive outcomes in patients with permanent AF [109]. As mentioned, such models indicate that lower VRs during permanent AF improve hemodynamic parameters and cardiac efficiency and lower oxygen consumption [43].

Conclusion

AF-induced TCM constitutes the most prevalent type of a reversible arrhythmia-induced TCM, is not readily recognized and can elude diagnosis resulting in full-blown HF symptomatology and a condition misdiagnosed as primary HF secondarily complicated by AF [13, 65]. In patients with AF having signs of CM and/or HF, VR and rhythm control should be rigorously and swiftly pursued as AF-TCM may be a highly suspect cause for these signs and symptoms, until proven otherwise. Restoration and maintenance of sinus rhythm is always superior to VR control for prophylaxis against AF-TCM or for recovery of systolic LV function in case of already established TCM. However, when this is not feasible or not a choice, VR control is the next best strategy [110]. Data reviewed herein point to a J-curve pattern between VR and clinical outcomes in AF patients (Fig. 1) indicating that one should aim for a strict rather than lenient VR control with an optimal resting VR ~ 65 bpm (range 60–80 bpm), which seems to avert TCM or confer a sustained improvement in LV function and exercise capacity together with relief of symptoms related to TCM. Of course, restoring and maintaining sinus rhythm is always a most desirable target, when feasible, either with drugs or more likely with ablation (Fig. 2).

Author contribution All authors contributed to the preparation of this manuscript and approved the final version. ASM conceived and designed the project, curated/analyzed the data, wrote the initial draft, and edited/approved the final product; TAM conducted literature search, designed the figures, and edited/revised the manuscript; AAM conducted literature search, constructed the tables, and edited/revised the manuscript; HM supervised the project, analyzed the data, reviewed, revised, edited, and approved the manuscript.

Data availability No new data were generated or analyzed in support of this research.

Declarations

Conflict of interest The authors declare no competing interests.

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