Int J Cardiovasc Sci. 2024; 37:e20240050

VIEWPOINT

Heart Rate Control or Rhythm Control in Patients With Atrial Fibrillation and Cardiac Amyloidosis

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Introduction

Cardiac amyloidosis (CA) manifests as a gradually progressive infiltrative condition characterized by the accumulation of insoluble protein aggregates within the myocardium and cardiac conduction system. The majority of CA cases are associated with precursor proteins, particularly immunoglobulin light chains (AL-CA) and transthyretin (ATTR-CA), which represent over 95% of cases. ATTR precursor substances may originate from a broad spectrum, encompassing both wild-type (ATTRwt) and variant (ATTRv) genes.[1]

Arrhythmias in CA result from a combination of factors. The deposition of amyloid fibrils and infiltration into the myocardium cause thickening of the atrial and ventricular walls, leading to compromised relaxation. Consequently, this cascade results in increased filling pressures and atrial dilation,[2] making individuals more susceptible to atrial fibrillation (AF) and other atrial arrhythmias. While left atrial (LA) enlargement has historically been linked with AF, new-onset AF can occur even without LA enlargement, suggesting a complex pathophysiology of AF in CA, where various processes affect LA structure, function, and mechanics in different ways, thereby heightening the AF risk. The usual manifestation of LA remodeling involves substantial infiltration of the atrial walls, leading to gradual impairment of atrial function and heightened stiffness, often observed without significant LA dilation.[1]

Keywords

Atrial Fibrillation; Amyloidosis; Prealbumin; Heart Failure.

Population prevalence estimates vary depending on the type of amyloidosis; ATTRwt shows the highest association with AF. Sanchis et al. reported an AF prevalence of 44% among patients with CA, notably higher than the estimated 1% prevalence in the general community. Among individuals with ATTRwt, 71% were found to have AF, compared to 26% in those with AL and 19% in those with ATTRv types.[3]

The presence of AF in CA can exert a substantial impact on the clinical stability of patients. In normal ventricles, diastolic filling mainly occurs during early diastole. However, in cases of CA, where ventricles become small and less compliant, there is an increased reliance on late diastolic filling, which is aided by atrial contraction. In CA with AF, where synchronized atrial contraction is lost, there is a significant decrease in stroke volume and an increase in atrial pressure. This condition is commonly associated with worsening symptoms of heart failure, clinical deterioration, and an increased risk of hospitalization, often requiring expedited and personalized treatment.[4]

Pharmacological Management

Due to being frequently underdiagnosed and historically experiencing shorter life expectancies, patients with CA have been overlooked or excluded from numerous clinical trials. Medications aimed at controlling heart rate are often poorly tolerated, and there is a lack of comprehensive data in the literature regarding rhythm control approaches, including anti-arrhythmic therapy and ablation. The scarcity of robust evidence and the complexities involved in managing these arrhythmias further compound the challenges in the clinical monitoring of these patients.

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Editor responsible for the review: Marcus Vinicius Simões

DOI: https://doi.org/10.36660/ijcs.20240050

Manuscript received March 15, 2024; revised manuscript April 8, 2024; accepted April 8, 2024.

There is insufficient solid evidence to definitively establish the superiority of rhythm control over heart rate control in managing cardiac arrhythmias CA.

In a retrospective analysis led by Mints et al., it was concluded that there was no reduced mortality associated with rhythm control under antiarrhythmic drugs, including amiodarone, sotalol, dofetilide, or propafenone, when compared to rate control strategies. Although the evidence remains limited, expert consensus suggests that maintaining patients in sinus rhythm is advisable.[5]

Given the crucial role of atrial contraction in determining left ventricular filling among CA patients, a strategy focused on rhythm control is favored over rate control, especially for symptomatic individuals. Amiodarone stands out as an anti-arrhythmic medication due to its favorable tolerability among the CA population. While flecainide and propafenone are effective in maintaining sinus rhythm in those with paroxysmal AF, their utility in CA patients is restricted. In cases where rhythm control proves ineffective, transitioning to rate control becomes necessary despite its inherent challenges.

Patients with CA habitually exhibit significant diastolic dysfunction with restrictive features. This condition necessitates compensatory tachycardia to maintain sufficient cardiac output. Consequently, the utilization of beta-blockers, calcium-channel blockers, and digoxin warrants careful consideration in CA patients due to their potential to depress compensatory heart rate response. This depression can significantly impact cardiac output, contributing to the poor tolerance observed with these medications in CA. Beta-blockers and non-dihydropyridine calcium channel blockers (CCBs) are typically the first-line choices for rate control in AF. Nevertheless, researchers caution against the use of non-dihydropyridine CCBs due to their negative impact on cardiac contractility and rhythm, as well as their association with increased hypotension risk. While beta-blockers may not be well tolerated by some patients, employing lower doses could still serve as an effective means of achieving rate control in AF cases with a swift ventricular response. The utilization of digoxin in amyloidosis remains a contentious topic due to its heightened potential for toxicity.[5,6]

Tafamidis works by binding to ATTR, which prevents the dissociation of tetramers and the formation of amyloids. This medication has been associated with reductions in overall mortality and hospitalizations due to cardiovascular issues. Additionally, it helps slow down the decline in both functional capacity and quality of life compared to a placebo. A retrospective study involving 473 patients with CA concluded that, in univariate analysis, the use of tafamidis was linked to a lower incidence of AF, with a hazard ratio of 0.43 ($p = 0.003$).[7]

CA has been linked to a heightened risk of intracardiac thrombus, stroke, and systemic embolism when compared to the general population. Myocardial amyloid infiltration affecting both the right and left atria has been suggested as a pathophysiological mechanism leading to decreased atrial contractility, blood stagnation, endothelial dysfunction, and a relatively hypercoagulable state, which predisposes individuals to thrombus formation. Recent studies indicate that the presence of AF in CA patients may further increase the risk of intracardiac thrombus and stroke, suggesting that anticoagulation may be necessary for all patients regardless of their CHA2DS2-VASc score. While data from randomized controlled trials regarding the potential advantages of new oral anticoagulants versus vitamin K antagonists in CA patients with AF are lacking, recent evidence suggests that direct oral anticoagulants (DOACs) can be safely and effectively used in this patientpopulation.[8]

Non-Pharmacological Management of AF in CA

The utilization of direct current cardioversion in individuals with AF and CA has been documented, albeit with questionable outcomes regarding success and recurrence rates. Sanchis et al. noted a relatively elevated incidence of AF recurrence within three months (55%) and one year (70%) post-direct current cardioversion. Nonetheless, it should be noted that complications such as ventricular arrhythmia, bradyarrhythmia, hypoxemia, and stroke may pose greater risks in patients with CA.[9]

Data are scarce regarding the safety and effectiveness of catheter ablation for atrial arrhythmias in patients with CA. In a study by Donnellan et al., outcomes of 72 patients with ATTR-CA and AF were reported. Among them, 24 patients underwent catheter ablation, while a matched control group received medical management. Over a mean follow-up period of 39 +/- 26 months after ablation, the recurrence rate of AF was found to be 58%. However, compared to the medically managed group, those who underwent ablation exhibited lower rates of death, as well as hospitalization due to heart failure or arrhythmia. Ullah et al. utilized global health data from 148,133 patients diagnosed with AF and heart failure who underwent AF ablation. Within this dataset, a subgroup comprising 616 patients was identified,

with 293 having concomitant AF-CA and 323 without CA. At index admission, AF ablation in patients with CA was associated with significantly higher adjusted odds of net adverse clinical events (MACE) [adjusted odds ratio (aOR) 4.21, 95% CI 1.7-5.20], in-hospital mortality (aOR 9.03, 95% CI 1.12-72.70) compared with non-CA-AF. Additionally, AF ablation in patients with CA, as opposed to those without CA, demonstrated comparatively increased rates of all-cause in-hospital mortality and net adverse events at the 30-day follow-up mark. These findings underscore the importance of conducting additional studies to ascertain whether AF ablation in the context of CA represents an effective strategy for rhythm control.[10-12]

Conclusion

AF is a common arrhythmia in CA patients, and the mechanisms related to its development are multifactorial. The occurrence of AF in CA can have a major impact on patients' clinical stability, and rhythm control is usually the first strategy of choice in comparison to frequency control. However, clinical management remains a major challenge, and more studies are necessary in this scenario.

Author Contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual content: Trevizan LLB, Mangini S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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