Cardiac amyloidosis and its electrophysiologic manifestations

Jose R. Martinez-Parachini, MD, and Ansel P. Amaral, MD, PhD

1 Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
2 Saint Francis Hospital and Heart Center, Roslyn, NY, USA

Address for Correspondence
1211 21st Avenue, Nashville, Tennessee 37232-8802.
Corresponding Author: Jose R. Martinez-Parachini, MD
Department of Medicine, Division of Cardiovascular Disease
Vanderbilt Heart and Vascular Institute, Medical Center East, South Tower
E-mail: jose.martinez-parachini@vumc.org

Amyloidosis is caused by deposition of abnormal amyloid fibrils with the feared consequence of end stage organ failure. Cardiac amyloidosis (CA) is an increasingly recognized antecedent of cardiomyopathy. CA is classified into transthyretin variants (ATTRwt – wild type and ATTRv – genetic variant) and a light chain variant (AL); each of these variants can be associated with unique electrophysiologic abnormalities. Pacing indications in current societal guidelines do not specify treatment options in infiltrative cardiac diseases, such as CA, and new disease modifying treatments are altering the landscape for intervention. Given the paucity of data, national and international groups have differing treatment options and recommendations. In this review, we aim to update and highlight the differing electrophysiologic changes seen in CA, their respective treatment course and suggest areas for future intervention.

Keywords: cardiac amyloidosis, conduction disease, arrhythmia

Introduction

Cardiac amyloidosis (CA) is defined by the European Society of Cardiology (ESC) as an extracellular deposition of misfolded proteins, which are most commonly fibrils, composed of monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR) accounting for 90% of CA. The other 10% includes much rarer proteins such as apolipoproteins, fibrinogen, lysozyme, and insulin among others (1). Amyloid is further classified as AL, ATTRwt (wild type) and ATTRv (genetic variant). There has been a steady increase in reported CA, most likely due to the improvement of non-invasive diagnostic studies. A recent study in Hungary described a cohort of ATTRv which included patients with restrictive cardiomyopathy (2). The ESC provided a position statement for the diagnosis and treatment of CA in 2021, with a focus on imaging (echocardiograms, cardiac magnetic resonance imaging), genetic testing and endomyocardial biopsy (3). CA is typically diagnosed in the presence of heart failure, however, electrophysiologic changes can commonly manifest prior to the presentation of heart failure symptoms. Atrial fibrillation is well known to accompany the disease. Conduction system disease and ventricular arrhythmias are also present. We present a brief overview of CA with an emphasis on the current ESC guidelines and provide an approach to treatments for the electrophysiologic manifestations of CA (3).
Pathogenesis

Amyloid fibril deposition causes disruption to the myocardial architecture which is likely to effect the transmission of electrical impulses. In AL CA, this occurs secondarily to antibody light chain deposition and in ATTR CA this occurs secondarily to deposition of misfolded transthyretin monomers (4). Furthermore, animal models (5) by Liao and Sousa and in vitro studies (6) have demonstrated a direct cytotoxic effect with induction of apoptosis and oxidative stress by the deposited proteins which occur in a concentration dependent manner. AL amyloid is thought to have a more acute presentation given its increased direct cytotoxic effect in contrast to a more insidious ATTR amyloid presentation; ATTR however, is known to be neurotoxic and possibly have a direct effect on the conductive tissue. The cardiac conduction system lies in the intersection between myocardium and neuronal tissue (7, 8). ATTR can directly prolong action potentials through calcium dysregulation producing several electrophysiologic changes (3). A loss of sympathetic fibers driven by the direct deposition of amyloid fibrils and remodeling of gap junctions (9) is a leading hypothesis with ongoing research. The sentinel position of the conduction system at the interaction between myocardial and neuronal tissue have previously been reviewed (10) by Hartnett.

Electrocardiography

There are several electrocardiographic (EKG) findings that are related to CA. Low voltage (diminished QRS amplitude) has classically been linked to CA however, CA may be present in its absence. Patients, who meet LVH criteria by EKG, tend to be better evaluated with progressive EKGs, where a decrease in voltage from prior studies can be appropriately assessed. Unfortunately, traditional criteria for low voltage (RS amplitude <5 mm in all limb leads and <10 mm in all precordial leads) appears to have a reduced sensitivity and specificity as an individual diagnostic measure (11). Other suggestive EKG findings include: pseudo-infarct patterns (QS waves on 2 consecutive leads of at least ¼ the R wave amplitude) present in the absence of ischemic disease, atrial dysrhythmias, and conduction disease (atrial fibrillation, flutter, sinus node disease, AV nodal disease) which is further discussed below (12). It is rare to find an EKG with no abnormalities in the presence of CA.

Patients with CA can present with a prolonged QT interval. The diffuse nature of CA allows for less dispersion of the QT seen in a lead electrocardiogram when compared to hypertrophic cardiomyopathy patients (13). Orini et al. suggest part of the QT prolongation is caused by an increase to the QRS complex and agree AL has more pronounced repolarization abnormalities than ATTR possibly secondary to AL’s cytotoxic effects (14).

Atrial fibrillation

Atrial fibrillation (AF) is the most common abnormal electrophysiologic presentation of CA. The direct deposition of fibrils in the atrial myocardium, with elevated left atrial pressures secondary to diastolic dysfunction in CA, are precipitating factors. Its prevalence in prospective and retrospective trials have varied widely from 10-75% (primarily due to cohorts ranging from 15-382 patients) (15–17). The technological advancements in ambulatory cardiac telemetry monitoring have allowed for an increased incidence in identifying patients at risk for CA, and subsequent imaging modalities have led to appropriate diagnoses. AF is found most frequently in ATTRwt, followed by ATTRv and lastly AL CA. It is hypothesized that ATTRwt’s increased rate of AF may be related to these variants increased age of diagnosis (12, 15).

One of the primary management strategies in AF is a focus on stroke risk and anticoagulation. Age-adjusted rates of cardiac thrombi leading to stroke and end organ thrombosis are more common in CA than the general population. Nicol et al. report a 5-10% risk of thrombi in patients with cardiac involvement in a review of thromboembolism in systemic amyloidosis for ESC Heart Failure (17). Additionally, the authors noted that AL CA confers a higher thromboembolism risk, given its propensity for hypercoagulability, which can be further exacerbated when patients have renal dysfunction. Feng et al. demonstrated that thrombotic risk is highest with AL CA, low systolic pressure, low atrial emptying velocity and diastolic dysfunction (18, 19). Left atrial appendage (LAA) thrombus must be excluded prior to attempted electrical cardioversion (CV) in CA (2). The initiation of systemic anticoagulation in CA, in the absence of atrial fibrillation, continues to be a subject of debate. The ESC, American Heart Association (AHA) and Japanese Cardiology Society (JSC) support anticoagulation in patients with elevated risk factors for thrombi, even in the presence of sinus rhythm (20). These risk factors include echocardiographic changes with a decreased A-wave amplitude and decreased LAA velocities (21).

Management

Treatment of AF in CA varies due to poor tolerance of rate control and an increased stroke risk (10). CA is typically accompanied by findings of a small left ventricle, diastolic dysfunction and a restrictive physiology pattern. A decrease in the heart rate with beta blockade (BB) or calcium channel blockade (CCB) causes the overall cardiac output to decrease, resulting in signifi-
cant symptoms and intolerance to medications (22, 23). Case reports have demonstrated that amyloid fibrils bind pharmacotherapies and enhance effective drug concentrations available to receptors at the cellular level, causing further depression of left ventricular function (23). Similarly, AV nodal dysfunction limits therapies. Digoxin may be used, albeit cautiously, as many CA patients have concurrent renal dysfunction. A rhythm control strategy is usually impeded by antecedent heart failure or concurrent renal disease, which limits the use of Class Ic (flecainide, propafenone) as well as Class III (dofetilide, dronedarone, sotalol) agents. The ESC recommends amiodarone as a first line therapy along with the AHA, German Cardiac Society (Deutsche Gesellschaft für Kardiologie –DGK), and Canadian Cardiac Society and Canadian Heart Failure Society (CCS/CHFS) (16, 20, 21, 24, 25). Unfortunately, given the long-term toxicities associated with amiodarone, other approaches are generally favored, as addressed below.

Established pro-thrombotic factors in CA include heart failure, AF, and atrial myopathy. The choice of anticoagulation for AF reveals no significant difference in prevention of thromboembolic events between warfarin or novel oral anticoagulants (26) LAA occlusion is considered favorable, as it would be for the general population, without major contraindications. However, there is a paucity of data to suggest LAA occlusion as a primary treatment modality. Occlusion devices have been suspected to be a nidus in CA for thrombus and thus, further investigation is warranted (3). CV is effective, if applied early in the disease course of AF. Advanced disease confers poor effectiveness of CV alone. El-am et al. showed that CA in Stage 1 (defined as: both biomarkers negative; troponin and N-terminal pro-brain natriuretic peptide [NT-pro-BNP]) maintains sinus rhythm for 30 days in 90% of patients as opposed to 33% in Stage 3 (both biomarkers positive) patients after electrical cardioversion (27). Catheter ablation is safe and confers few perioperative complications. Despite this treatment modality, there is a high recurrence rate, especially with (heart failure and myopathy) disease progression. Donnellan et al. and El-am et al. showed that recurrence in Stage 1 is less (36%) as opposed to Stage 3 (90%) disease. They also demonstrated lower hospitalization rates (18% vs. 72%) and lower mortality (19% vs. 75%) with an early rhythm control strategy (28). Electroanatomic mapping has been employed to reveal disease severity, with extensive low voltage scar being demonstrated as the disease stages progress. Although treatment and management opinions from the major Cardiovascular Societies differ, there is consensus that early treatment of AF with a rhythm control strategy confers better morbidity and mortality outcomes in patients with CA (29).

Sinus node dysfunction

Sinus node dysfunction is defined as the inability of the sinus node to produce a physiologic increase in heart rate. It can be divided into sinus bradycardia, sinus

![FIGURE 1. Treatment for electrophysiologic manifestations of cardiac amyloidosis](image-url)
pauses, and sinus arrest. Although CA has a high prevalence of conduction disease, sinus node dysfunction is overall rare. Its prevalence in a single center retrospective study was 7% with higher incidence in ATTRv patient’s vs. ATTRwt (8% vs. 6%) (30) based on parameters of age, which appear to be equivalent to the general population.

Atrioventricular nodal disease (AVND)

AVND is a common finding in CA. Large cohort studies have demonstrated that first degree heart block is present in 49% of patients with ATTRwt and 43% of patient with ATTRv, but only 15% of AL CA (30). Notably, the stage of CA does not correlate with AVND progression, although QRS duration of greater than 120 milliseconds confers an increased risk for AVND progression (30). High degree AV block has an incidence of between 9.5% to 13% as reported in single center studies and multicenter retrospective studies by Donnellan et al. and Rapezzi et al. respectively. AVND and pacemaker placement is most commonly seen in ATTRwt followed by ATTRv with rates of 10% and 7% respectively (30, 31). CA patients that require pacemaker implantation have a high likelihood of worsening AVND and pacemaker dependence. Donnellan et al. revealed in a small observational study that progression of AVND and RV pacing dependence from 35.5% at 6 months to 96.2% at 5 years (32), which appears to have a significantly higher burden than the typical population. A high burden of RV pacing of more than 40% is associated with worsening NYHA functional class, worsening ejection fraction and increased mitral regurgitation that at times can be improved with cardiac resynchronization therapy (CRT) (33). The high likelihood of a need for more than 40% pacing and the clinical improvement with CRT should prompt clinicians to evaluate for bi-ventricular pacing whenever a pacing indication occurs with CA. The ESC 2021 guidelines for cardiac pacing and resynchronization fail to provide clear recommendations for pacing in infiltrative diseases, including CA. The guidelines mention physiologic pacing as second line to standard CRT and recognize the need for further studies and data in the CA population. Few case reports with successful physiologic pacing in CA (34) are available in the literature at the time of this review, which makes physiologic pacing far from becoming part of traditional practice (35).

Ventricular Arrhythmias

Ventricular arrhythmias in CA and their impact on morbidity and mortality continue to be poorly understood. Proposed mechanisms for CA-induced ventricular arrhythmias include patchy infiltration, microvascular ischemia and direct cytotoxicity to cardiomyocytes (with AL CA as the primary culprit) (30). Premature ventricular contractions and non-sustained ventricular tachycardia are the most common ventricular arrhythmias (74%); this is followed by re-entrant ventricular tachycardia circuits in 19% of CA (36). Mortality due to cardiac arrest in CA seems to be driven by pulseless electrical activity (PEA) arrests rather than fatal ventricular arrhythmias. PEA is often preceded by bradycardia and AV block as demonstrated by Sayed et
al., who revealed this finding in 64% of 272 patients with implanted loop recorders (37). The role of ICDs in patients with CA continues to be disputed. A recent review of major guidelines shows agreement for secondary prevention in CA, however primary prevention for CA remains controversial. The ESC does not recommend a primary prevention ICD while the DGK, CCS/CHFS, JCS and AHA label it as “considered” if the patient has a life expectancy greater than 1 year (29). There are multiple tools available to determine the likelihood of patient survival as greater than 1 year after ICD implant, but the authors of this review continue to advocate for shared decision making as the primary strategy in determining ICD implantation.

Defibrillation thresholds caused by amyloid deposition within the myocardial wall may cause unsuccessful ICD therapies to be delivered, which argues for the role of defibrillation threshold testing (36, 38). The largest studies to date assessing survival after ICD implantation in CA come from the US national cardiovascular data registry (N=472). A 1:5 comparison of CA to non-ischemic cardiomyopathy (NICM) revealed a mortality of 11.3% in NICM versus 26.9% in CA (38). AL CA has a higher rate of appropriate therapy delivered, suggesting certain populations within CA may benefit from ICD placement. Kim et al. reported that patients with CA receive therapy as early as 2.7 months after implantation vs. 23.4 months in a non-amyloid NICM population (39). These findings suggest that certain patient populations within CA may benefit from ICD implantation and subsequent therapies. There are no current biomarkers or clinical findings that help identify patients at risk for CA, although many have been proposed. These include: syncope, cerebrovascular disease, diabetes, renal disease, and reduced ejection fraction (LVEF <50%). Inversely related troponin and NT-pro-BNP in advanced stages of CA usually are confounders from advanced heart failure (29, 38). As new disease modifying therapies become available, specifics on treatment for infiltrative diseases continues to be flexible, and needs to be personalized through shared decision making as the fundamental approach in determining ICD therapy options.

**Disease modifying therapies**

ATTR-CA has seen recent major advances in disease modifying therapies. Tafamidis is a transthyretin tetramer stabilizer that prevents dissolution into monomers and subsequent amyloid fibril formation; it is labeled as a molecule stabilizing treatment (40). Patisiran is a oligonucleotide agent that slows production of transthyretin through RNA inhibition (41). Tafamidis has a mortality benefit and morbidity benefit in preventing cardiovascular hospitalizations for both ATTRv and ATTRwt (40). Patisiran has demonstrated beneficial physiologic improvements in cardiac output and stabilization of ventricular wall thickness (41, 42). Solomon et al. showed that patients treated with patisiran for ATTRv had a decrease in arrhythmia burden, when compared to placebo (18.9% vs. 28.6%). This cohort included supraventricular arrhythmias (10.1% vs. 16.9%), high grade conduction disease (6.8%, vs. 9.1%) and ventricular arrhythmias/cardiac arrest (2.7% vs. 6.8%) (42). These disease modifying therapies suggest a direct effect on the electrophysiologic abnormalities associated with CA and will be an area of aggressive research in the near future. It is important to note, that disease modifying therapies, to date, exclude AL CA. Inotersan lowers hepatic production of both ATTRv and ATTRwt and is associated with improved neuropathy and quality of life (43). A subgroup with cardiomyopathy was present in 63% of patients in a study by Benson et al. that was not powered to measure the effects of inotersan on cardiac disease. To answer this there are ongoing trials powered for its cardiac effect (44).

**Conclusions**

The deposition of amyloid fibrils within myocardial tissue has a wide range of electrophysiological consequences most commonly atrial fibrillation. AV nodal disease continues to have similar indications to the general population however, as more data becomes available, specifics on treatment for infiltrative disease and CA are likely to appear. ICD therapy for patients continues to be flexible, and needs to be personalized through shared decision making with the patient. As disease modifying therapies continue to be implemented, further research is needed to understand how this will affect electrophysiologic interventions.

**Conflicts of interest**

Drs. Martinez-Parachini and Amaral report no conflicts.

**Funding:** None

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