Cardiac amyloidosis

Subjects: Allergy

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Cardiac amyloidosis (CA) is considered to be associated with an increased risk of sudden cardiac death (SCD) due to ventricular tachyarrhythmias and electromechanical dissociation.

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1. Introduction

Amyloidosis is a rare systemic disease characterized by the extracellular deposition of pathological insoluble fibrillar protein, known as amyloid, within various organs (mainly the heart and kidneys). The most common types of cardiac amyloidosis (CA) are caused by immunoglobulin-derived light chains (AL) and the precursor protein transthyretin (ATTR). Cardiac involvement occurs up to 60% patients, more commonly in AL amyloidosis and results in worse prognosis [1]. Therefore, increased clinician awareness and early CA diagnosis is crucial to improve outcomes. CA should be suspected particularly in patients with heart failure with preserved left ventricular ejection fraction (HFpEF) presenting “red flag” signs such as (1) either symmetrical or asymmetrical unexplained left and right ventricular hypertrophy with concomitant diastolic dysfunction and reduced global longitudinal left ventricular strain (LV GLS) with an “apical sparing” pattern in echocardiography, (2) discrepancy between the LV wall thickness and QRS voltage and the presence of pseudo-infarct pattern in electrocardiography, especially if associated with increased levels of N-terminal pro B-type natriuretic peptide (NT-proBNP [2]. Cardiac magnetic resonance imaging, endomyocardial biopsy and nuclear imaging play an important role in CA diagnosis. [2]. The treatment depends on the type of amyloidosis.

Chemotherapy and hematopoietic stem cell transplantation is primarily aimed at managing a clonal plasma cell dyscrasia in AL amyloidosis. On the contrary, chemotherapy plays no role in the treatment of ATTR CA. Clinical studies on various therapeutic agents that modify/inhibit amyloid fibril formation or stabilize mutant transthyretin (TTR) fibers are in progress [3][4]. Tafamidis, a TTR tetramer stabilizer, is the most extensively studied medication that showed the reduction in all-cause mortality and hospitalization rates in ATTR CA, especially if applied in early stages of the disease [5]. Apart from tetramer stabilizers, gene silencing drugs that interfere with the production of an abnormal form of TTR have been investigated. Among them, patisiran have led to the reversal of structural changes in the myocardium. Doxycycline, a tetracycline antibiotic, can potentially interfere with amyloid fibril formation through an unknown mechanism enhancing LV mechanical function [5].

Although novel treatment vastly improved survival in AL and ATTR cardiac amyloidosis, cardiovascular events account for more than two-thirds of fatal casualties in both groups [6]. Moreover, sudden cardiac death (SCD) accounts for up to 50% of all cardiac deaths [7]. Electromechanical dissociation is thought to be the most common cause of SCD in patients with cardiac amyloidosis; however, ventricular arrhythmias and conduction abnormalities are also common [8]. To date, a number of factors have been described, indicating an increased risk of overall mortality. However, little is known about risk factors for ventricular tachyarrhythmia’s as a cause of SCD in patients with amyloidosis and cardiac involvement. Therefore, identification of patients with CA who may be eligible for implantable cardioverter-defibrillator (ICD) is challenging. It remains unclear whether ICD prevents SCD in these patients.

2. Prognostic Factors and Electrophysiological Abnormalities in Patients with Cardiac Amyloidosis

Cardiac involvement is the determinant of prognosis in CA. Risk of death in patients with AL amyloidosis can be stratified using the revised Mayo staging models, including cardiac biomarkers: serum troponins (cTnT ≥ 0.025 ng/mL), NT-proBNP (≥1.800 pg/mL) and serum immunoglobulin free light chain difference (FLC-diff) ≥ 18 mg/dL) [9]. Kumar et al. assigned one point for each of these abnormalities [9]. Their median overall survival from diagnosis was 94.1, 40.3, 14, and 5.8 months, respectively. A European collaborative study additionally reported that very high NT-proBNP levels (>8500 pg/mL) indicate patients at very high risk with a median overall survival of only 3 months [10]. Lilleness at al. demonstrated that easier and

more accessible prognostic scoring system, the Boston University staging system, including BNP (>81 pg/mL) and cTnI (>0.1 ng/mL), also accurately identified cardiac involvement and stratified overall survival [11]. Similar to AL amyloidosis, a staging system including markers of increased myocardial stress, such as NT-proBNP and high sensitivity cTnT, has been proposed for ATTR amyloidosis. Patients with both: cTnT > 0.05 ng/mL and NT-proBNP > 3.000 pg/mL had the worst prognosis with a median survival of only 20 months [12]. Additional to elevation in cardiac biomarkers, renal dysfunction was also identified as a significant risk factor of worse prognosis. In the recently proposed prognostic system for staging ATTR amyloidosis, patients with decreased estimated glomerular filtation rate (eGFR < 45 mL/min/1.73 m^2) and NT-proBNP > 3.000 pg/mL had significantly worse survival compared to those not meeting these cut-off values [13].

However, the mentioned staging models only predict overall mortality. Moreover, there is no significant correlation between cardiac biomarkers levels and the risk of ventricular arrhythmias [14].

Risk assessment of arrhythmic SCD in cardiac amyloidosis is still not well-defined. Understanding the pathophysiology of ventricular arrhythmias (VA) in CA is crucial to predict the risk of death. Amyloid in the extracellular spaces distorts the myocardial cells and can also infiltrate cardiac conduction system and coronary arteries. Besides infiltration, amyloidogenic light chains in AL amyloidosis may directly impair cardiomyocyte function through an increase in cellular oxidant stress. It appears that myocardial scarring and fibrosis that are typical of chronic ischemic or non-ischemic cardiomyopathies are less common in CA. Among imaging studies, cardiac magnetic resonance (CMR) plays an important role not only in the diagnosis of CA but also provides important prognostic information. In amyloidosis, CMR enables myocardial tissue characterization by means of T_1- and T_2-weighted imaging sequences, T_1 mapping (pre- and post-contrast), late gadolinium enhancement (LGE) and extracellular volume (ECV) imaging. Global subendocardial or transmural pattern of LGE, and to a lesser degree, a focal patchy LGE, are all features of CA. LGE has been recognized as a marker of amyloidogenesis and fibrosis. The extent of LGE may also serve as a surrogate of arrhythmogenic substrate for the occurrence of ventricular arrhythmias [2][15]. The two-year survival in CA patients without LGE was 92%, whereas it was significantly lower in those who showed subendocardial or transmural LGE (81% and 45%, respectively) [16]. Both in AL and ATTR cardiac amyloidosis, the presence of transmural LGE has been shown to be an independent predictor of worse survival [16]. However, the limitation of LGE is that it is difficult to quantify, making it difficult to track changes in CA, e.g., due to treatment. This has been overcome with the use of the technique of T_1 mapping, which showed that native T_1 values (pre-gadolinium contrast) are markedly higher in regions of amyloid deposition (or diffuse fibrosis). Post-contrast T_1 mapping following gadolinium administration enables estimation of ECV. The ECV values are significantly elevated in CA and ECV is a robust marker of prognosis in CA. Moreover, the assessment of ECV as well as native T_1 values enables tracking the disease over time and response to therapy. Additionally, T_2 mapping provides data on T_2 relaxation times which represent a myocardial edema and active inflammation and is potentially linked with arrhythmogenic potential. However, data on T_2 mapping in CA are scarce so far. In a recent study [17], the presence of myocardial edema was shown in CA, as indicated by increased T_2 relaxation times in patients with amyloidosis compared to control subjects and in untreated AL amyloidosis compared with treated AL and ATTR amyloidosis. In this study, T_2 was a predictor of prognosis in AL amyloidosis, which may suggest mechanisms additional to amyloid infiltration contributing to mortality in this disease. The cause and mechanisms of ventricular arrhythmias in CA, however, are poorly understood and are likely to be multifactorial [18][19].

To better understand the underlying pathophysiology, Orini et al. combined the assessment of the electrophysiological and structural ventricular substrate from 21 CA patients (11 AL and 10 ATTR) [20]. The authors used a special electrocardiographic system with 256 electrodes for non-invasive epicardial mapping of ventricular potentials and cardiac magnetic resonance (CMR) imaging. When compared with healthy volunteers, patients with CA had significantly lower epicardial signal amplitude, slower and heterogeneous intraventricular conduction and prolonged and more spatially dispersed repolarization. Moreover, epicardial signal fractionation and average repolarization time increased with extracellular volume calculated in CMR. A strong inverse correlation was found between epicardial signal amplitude and native T1 in CMR. Both epicardial conduction and repolarization abnormalities were more notable in patients with AL amyloidosis compared with ATTR. Spatial conduction-repolarization heterogeneity is thought to be a marker of increased propensity to VA and sudden arrhythmic death in patients with heart failure and may contribute to higher mortality in AL amyloidosis [21]. This study also suggests a link between conduction-repolarization delay and increased extracellular deposition.

Invasive electrophysiological study (EPS) is infrequently performed in CA patients, and we found only two studies determining the spectrum of electrophysiological abnormalities among CA patients in EPS. Reisinger at al. demonstrated a prolongation of the His-ventricular (HV) interval >55 ms in the majority of the examined population (23 of 25 patients with AL amyloidosis confirmed in biopsy), which indicated disease of the distal His-Purkinje system [7]. Markedly prolonged HV interval (≥80 ms) was the only independent predictor for SCD in the multivariate analysis. The authors concluded that

prolongation of the HV interval does not only indicate a risk of complete atrio-ventricular block due to the conduction system infiltration with amyloid fibrils and bradyarrhythmia as a potential cause of death, it may also indicate severe myocardial infiltration and serve as a marker of the propensity for lethal VA or acute electromechanical dissociation. Interestingly, in this study, monomorphic ventricular tachycardia (VT) was induced only in four patients during programmed ventricular stimulation, and similarly to other non-ischemic cardiomyopathies, VT non-inducibility showed little prognostic value.

In a study of 18 CA patients, Barbhaiya at al. demonstrated a prolonged HV interval >55 ms in all patients, which was more significant in those with ATTR amyloidosis (14 patients) [22]. Additionally, CA patients with concomitant atrial fibrillation (AF) or atrial tachycardia had larger areas of low voltage, as revealed by detailed left atrium mapping compared to age-matched controls of patients with persistent AF. Of the six patients who underwent programmed ventricular stimulation, two patients had induced monomorphic VT and received an ICD. However, the authors did not evaluate the effect of their findings on mortality.

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