Digoxin Use in Cardiac Amyloidosis

Joseph P. Donnelly, MD[a,b], Brett W. Sperry, MD[c], Andrej Gabrovsek, MD[a], Asad Ikram, MD[d], W.H. Wilson Tang, MD[a], Jerry Estep, MD[a], and Mazen Hanna, MD[a,*]

Despite limited options for rate control of atrial fibrillation and for low-output heart failure seen in cardiac amyloidosis (CA), digoxin use is discouraged due to a reported increased risk of sensitivity and toxicity. We present our experience with digoxin use in patients with CA and report the event rate of suspected digoxin-related arrhythmias and toxicity. This is a retrospective study of patients with CA seen at our institution between November 1995 and October 2018. Patients were screened for a history of ≥7 days of continuous digoxin use and stratified based on amyloid precursor protein—transthyretin (ATTR) and immunoglobulin light chain (AL). Medical records were used to identify suspected digoxin-related arrhythmias and toxicity events. Digoxin was used in 69 patients (42 ATTR, 27 AL) for a median duration of 6 months (IQR, 1 to 16). Indication for use was rate control in 64% of patients and symptomatic heart failure management in 36%. Suspected digoxin-related arrhythmias and toxicity events occurred in 12% of patients. No deaths were attributed to digoxin use or toxicity, but 11 patients died while on digoxin—most due to progressive heart failure in the setting of CA. In conclusion, digoxin may be a therapeutic option for rate and symptom control for some patients with AL-CA and ATTR-CA. Rigorous patient selection is recommended, and patients should be closely monitored during digoxin administration. **(Am J Cardiol 2020;133:134−138)**

Introduction

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that, with rare exception, is due to either transthyretin (ATTR) or immunoglobulin light chain (AL) proteins.[1] Atrial fibrillation is difficult to manage in patients with CA, who are already burdened with low cardiac reserve.[2] Beta blockers and calcium channel blockers are problematic in this scenario and current recommendations state that digoxin should generally be avoided.[3] These recommendations are based upon historical case reports[4−5] and a 1981 in vitro study[6] demonstrating that isolated amyloid fibrils bind digoxin. In this manuscript, we sought to describe our institution's experience with digoxin in patients with CA and to determine the event rate of suspected digoxin-related arrhythmias and toxicity.

Methods

Using our institution's Amyloid Heart Disease database, 756 patients with CA seen at the Cleveland Clinic in Cleveland, Ohio between November 1995 and October 2018 were screened for a history of digoxin use. Patients with <7 days of digoxin use were excluded, as well as patients with incomplete medical records. The medical record was examined until the date of last follow up or death. The study population was stratified based on amyloid precursor protein. The diagnosis of ATTR-CA was established through endomyocardial biopsy and/or technetium pyrophosphate scintigraphy with negative monoclonal lab testing.[7] The diagnosis of AL-CA was established by endomyocardial biopsy or extra-cardiac biopsy with advanced cardiac imaging and cardiac biomarkers consistent with the disease.[8] Variables related to patient demographics, amyloidosis history, cardiac history, and digoxin use were compiled. The Modification of Diet in Renal Disease equation was used to determine estimated glomerular filtration rate (eGFR). Comorbidities, New York Heart Association class, heart failure medications, history of atrial fibrillation and/or pacemaker, echocardiography data, and biomarkers were collected at the time of CA diagnosis. Serum creatinine and eGFR were reviewed at the time of digoxin initiation. Suspected digoxin-related arrhythmias and toxicity events were defined as: altered mental status without established cause, use of digoxin immune fab, new-onset junctional rhythm, atrial tachycardia with or without 2:1 block, ventricular tachycardia, ventricular fibrillation, second or third degree AV block, and symptomatic bradycardia. Pulseless electrical activity and asystole were not considered arrhythmias related to digoxin. The Pearson's chi-square test and the Wilcoxon rank-sum test were used to analyze categorical and continuous variables, respectively. Statistical analysis was performed using JMP software version 14.0 (JMP, Cary, North Carolina). A p value of <0.05 was considered statistically significant.

Results

There were 69 patients (42 ATTR, 27 AL) treated with digoxin for ≥7 days identified from an original screening population of 756 patients (356 ATTR, 366 AL, 34 other/untyped). The median duration of digoxin therapy in the

[a]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic Foundation, Cleveland, Ohio; [b]Department of Chemistry, The Scripps Research Institute, La Jolla, California; [c]Saint Luke's Mid America Heart Institute, Kansas City, Missouri; and [d]Department of Neurology, The University of New Mexico Health Sciences Center, Albuquerque, New Mexico. Manuscript received April 12, 2020; revised manuscript received and accepted July 13, 2020.

*Corresponding author: Tel: (216) 444-3490.

E-mail address: hannam@ccf.org (M. Hanna).

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Table 1
Baseline demographics and digoxin dosing

Variable	Total n = 69	ATTR n = 42	AL n = 27	p-value
Median Age at CA Diagnosis (years), median (IQR)	72 (65-79)	75 (69-83)	66 (62-73)	0.008
Men	53 (77%)	37 (88%)	16 (59%)	0.006
Black	24 (35%)	19 (45%)	5 (19%)	0.023
Hypertension	53 (77%)	35 (83%)	18 (67%)	0.109
Dyslipidemia	45 (65%)	31 (74%)	14 (52%)	0.062
Diabetes mellitus	16 (23%)	12 (29%)	4 (15%)	0.186
Coronary Artery Disease	30 (43%)	20 (48%)	10 (37%)	0.387
Atrial Flutter/Fibrillation				
Paroxysmal	22 (32%)	9 (21%)	13 (48%)	0.020
Chronic	26 (38%)	22 (52%)	4 (15%)	0.002
Pacemaker	23 (33%)	20 (48%)	3 (11%)	0.002
Serum Creatinine (mg/dL), median (IQR)	1.30 (1.08-1.63)	1.33 (1.08-1.63)	1.26 (0.98-1.54)	0.563
eGFR (ml/min/1.73m^2), median (IQR)	60.3 (47.7-76.4)	62.1 (48.9-76.4)	57.6 (44.6-76.4)	0.810
Daily Digoxin Dose (mg)				
0.031	4 (6%)	2 (5%)	2 (7%)	0.646
0.063	22 (32%)	18 (43%)	4 (15%)	0.015
0.125	36 (52%)	18 (43%)	17 (63%)	0.150
0.250	7 (10%)	3 (7%)	4 (15%)	0.303
Digoxin Use Prior to CA Diagnosis	29 (42%)	19 (45%)	10 (37%)	0.501
Diuretic	57 (83%)	37 (88%)	20 (74%)	0.134
β-Blocker	44 (64%)	29 (69%)	15 (56%)	0.255
ACEi/ARB	32 (46%)	20 (48%)	12 (44%)	0.796
Amiodarone	19 (28%)	10 (24%)	9 (33%)	0.387
Calcium Channel Blocker				
Diltiazem or verapamil	3 (4%)	3 (7%)	0 (0%)	0.156
Nifedipine or amlodipine	2 (3%)	1 (3%)	1 (2%)	0.749

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker; CA = cardiac amyloidosis; eGFR = the modification of diet in renal disease (MDRD) estimated glomerular filtration rate; IQR = interquartile range.

total cohort of digoxin-treated patients was 6 months (IQR 1 to 16 months), with a median of 10 months (IQR 3 to 38 months) for the patients with ATTR and 2 months (IQR 1 to 7 months) for the patients with AL. Digoxin was used for rate control of atrial fibrillation in 64% (64% of ATTR, 63% of AL) and management of symptomatic heart failure without atrial fibrillation in 36% (36% of ATTR, 37% of AL). As shown in Table 1, 29 patients were using digoxin prior to establishing the diagnosis of CA (45% of ATTR, 37% of AL); it was discontinued in 12 of those patients due to the physician concern of increased potential for toxicity. The most common dose of digoxin was 0.125 mg daily, accounting for 52% of the total cohort of digoxin-treated patients. Only 10% were treated with the higher 0.250 mg per day dose (7% of ATTR, 15% of AL). Digoxin was initiated at our center in 57 patients with a median serum creatinine of 1.3mg/dL (IQR, 1.1 to 1.6 mg/dL) and eGFR of 60.3 ml/min/1.73 m^2 (IQR, 47.7 to 76.4 ml/min/1.73 m^2).

The median age at diagnosis of CA was 72 years old (IQR, 65 to 79) with 77% male and 35% Black. Hereditary variant ATTR (ATTRv) was confirmed by genetic testing in 13 patients (31% of ATTR), consisting of 12 patients with a Val-122-Ile mutation and 1 patient with a Ser-77-Tyr mutation. There were 24 patients (57% of ATTR) with confirmed wild type ATTR (ATTRwt). Genetic testing was not performed in 5 patients (12%) with ATTR. Of the patients with AL, 74% were typed as lambda light chain and 26% as kappa light chain.

Atrial fibrillation, either permanent or paroxysmal, was present in 74% of ATTR patients and 63% of AL patients at the time of CA diagnosis (Table 1). Most patients were New York Heart Association Class III at the time of CA diagnosis, accounting for 55% of the patients with ATTR and 67% of patients with AL (Supplemental Table 1). There were 64% of patients on concomitant beta blocker therapy.

Eleven patients (16%) died while on digoxin, but no deaths were attributed to a clinical suspicion of digoxin use or toxicity; 8 deaths were from progressive heart failure while in hospice care, one from traumatic subarachnoid hemorrhage, one due to asystole during a hospitalization for severe esophagitis, and one from myocardial infarction.

Suspected digoxin toxicity and arrhythmias are summarized in Table 2 and occurred in 8 out of 69 patients (12%) of the study population. Ventricular tachycardia (VT) was seen in 2 patients. Patient #1 with ATTRwt-CA had a left ventricular assist device and was on a chronic milrinone infusion for right ventricular heart failure. He developed an episode of VT storm requiring 20 implantable cardioverter-defibrillator (ICD) shocks in the context of also being quinidine and metronizadole with a digoxin level of 0.6 ng/ml. The patient recovered and digoxin was discontinued. Patient #2 had ATTRv-CA due to the Val-122I-Ile mutation and was admitted with cardiogenic shock and pneumonia. In that context, he developed VT requiring 6 ICD firings leading to discontinuation of digoxin (no level was obtained at time of the event however 2 weeks prior to the event it

Table 2
Potential digoxin-related arrhythmias & toxicity events

Patient #	Gender, Age (years), Amyloid Type	Event Description	Digoxin Duration at Time of Event (Months)	Digoxin Level (ng/ml)	Creatinine at Event/Baseline (mg/dL)	Δ Treatment	Outcome, Months from Event
1	M, 73, ATTRwt	VT with ICD shock	141	N/A	2.53/1.40	Stopped digoxin	Death, 22
2	M, 68, ATTRv V122I	VT storm and cardiogenic shock	41	N/A	1.28/0.85	Stopped digoxin	Death, 0.5
3	F, 81, ATTRv V122I	Junctional tachycardia	2	0.4	2.30/2.00	Stopped digoxin	Death, 4
4	F,76, AL-λ	Accelerated junctional rhythm	9	0.6	1.01/0.80	Stopped Digoxin	Death, 0.6
5	F, 58, AL-λ	Junctional bradycardia	1	1.8	1.16/1.10	Stopped digoxin	Death, 11
6	F, 66, AL-κ	Symptomatic bradycardia	8	3.8*	1.41/1.03	Stopped digoxin*	Death, 0.6
7	M, 83, ATTRv V122I	Symptomatic bradycardia	1	0.9	1.64/1.40	Stopped digoxin	Alive, 60
8	M, 63, ATTRwt	Bradycardia	2	2.8	1.74/1.46	Stopped digoxin	Death, 0.2

* Received digoxin immune fab.

Abbreviations: AL-κ = kappa light chain amyloidosis; AL-λ = lambda light chain amyloidosis; ATTRv V122I = hereditary variant transthyretin amyloidosis, Val-122-Ile mutation; ATTRwt = wild-type transthyretin amyloidosis; ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.

was 1.4 ng/ml). He was stabilized and died 15 days later of heart failure while in hospice care.

New-onset junctional rhythms were seen in 3 patients. Patient #3 developed junctional tachycardia in the setting of acute decompensated heart failure with a digoxin level in the normal range (0.4 ng/ml); the patient died of heart failure 4 months later while on hospice. Patient #4 was on digoxin therapy prior to the diagnosis of AL-CA and was found to be in an accelerated junctional rhythm leading to discontinuation of digoxin and resolution of the rhythm. She received a dose of bortezimib and died 1 week later of a cardiac arrest due to pulseless electrical activity while in a nursing home. Patient #5 developed junctional bradycardia with a digoxin level of 1.8 ng/ml; digoxin was stopped, and the patient died of heart failure and toxic megacolon 11 months later.

Symptomatic bradycardia developed in 3 patients. Patient #6 with kappa AL-CA was on digoxin 0.250 mg daily as an outpatient prior to knowledge of the diagnosis and had a body mass index of 21 kg/m^2. During an admission for low output heart failure and acute kidney injury she developed symptomatic bradycardia with a digoxin level of 3.8 ng/ml; digoxin was stopped, Digoxin immune fab was given, and the bradycardia improved. The patient died 19 days after digoxin discontinuation due to anuric renal failure and progressive heart failure. Patient #7 experienced symptomatic bradycardia (digoxin level 0.9 ng/ml) which resolved upon cessation of digoxin; the patient remains alive at the time of this writing almost 60 months following the event. Patient #8 was admitted for enterococcal sepsis and was transferred to the intensive care unit with altered mental status, where intermittent bradycardia was found on telemetry. Digoxin level was found to be 2.8 ng/ml and digoxin was stopped. The patient died of sepsis 7 days following digoxin cessation.

Discussion

In this study, we describe a mixed cohort of patients with both AL-CA and ATTR-CA who received digoxin for ≥7 days. To our knowledge, this is the only such study to assess digoxin use in patients with ATTR-CA. We found that 8 out of 69 patients, 12% of this cohort, developed an adverse event that may have been associated with digoxin use over a median duration of 6 months. There was 1 serious adverse event that required use of digoxin immune fab. While 16% of the patient cohort died while on digoxin, no deaths were felt to be directly related to digoxin-related arrhythmia or toxicity events.

The scientific theory behind increased digoxin sensitivity in CA relies almost exclusively on a 1981 in vitro study which demonstrated avid digoxin binding to isolated AL and AA (serum amyloid A) amyloid fibrils.[6] When lyophilized AL and AA fibrils were separately incubated with digoxin in Tris-buffered saline at room temperate for 90 minutes, more than 20% of the digoxin remained bound to the amyloid fibrils, independent of pH (range 5.0 to 9.0) and calcium concentration.[6] An in vitro homogenate of cardiac muscle and amyloid fibrils demonstrated significantly more digoxin binding affinity compared with a nonamyloid heart homogenate but less than that of isolated fibrils.[6] The study's authors suggest that such avid binding to extracellular amyloid fibrils could lead to localized increases of digoxin concentration and activation of the digoxin receptors on the surface of cardiomyocytes, even in cases where plasma digoxin levels are low. However, the hypothesis that fibril bound digoxin can stimulate cardiomyocytes is untested. Additionally, digoxin binding to ATTR fibrils was not addressed. Historical case reports from the 1960s are often cited as in vivo support,[4,5] but no robust clinical evidence exists that suggests patients with CA are more at risk for digoxin sensitivity compared with the general heart failure population.

CA presents several management challenges related to congestion, low-output heart failure, and burden of arrhythmias. Studies have shown that atrial fibrillation is common in patients with CA and affects up to 70% of patients with ATTRwt[9] and 34% of patients with AL amyloidosis.[10] Atrial fibrillation with rapid ventricular response is typically poorly tolerated in these patients, with associated hypotension and low cardiac output. Digoxin's lack of negative inotropic effects coupled with its neutral effect on blood pressure would seemingly make it one of the few medical options available to treat atrial fibrillation in the setting of CA.[11] Furthermore, using digoxin for rate control in these situations can allow a reduction in the dose of beta blocker to achieve that goal. However, the 2016 AHA scientific statement addressing digoxin use in CA states that digoxin should be avoided in CA with designated Level of

Evidence C.[12] The statement warns of potential toxicity in the setting of normal serum digoxin levels, only citing Rubinow et al.[6]

Muchtar et al reported findings from a group of 107 patients with AL-CA and showed a similar 11.2% rate of suspected digoxin toxicity after a median duration of 5 months of therapy.[13] The most predominant initial digoxin dose was similar (0.125mg daily) and there was a similar rate of physician discontinuation, predominantly due to preference (16% compared with 17% in our study). The authors concluded that digoxin may be cautiously utilized in AL amyloidosis patients with lower initial doses and frequent monitoring of drug levels, creatinine, and electrolytes.

Despite the controversy surrounding digoxin use in CA, a clinical trial is unlikely and would be difficult to design. Arrhythmias seen in digoxin toxicity, including bradycardia and heart block, are also associated with advanced CA.[14,15] Digoxin is often not initiated until the advanced stages of CA, rendering the separation between toxicity event and natural history difficult to distinguish. We reported every arrhythmia event experienced by our study population while on digoxin to account for this resemblance. Potential for avid binding to amyloid fibrils should heighten the treating physician's suspicion for digoxin toxicity in patients with CA, even at normal plasma digoxin levels, but this should not translate into an absolute contraindication for use. It is notable that 88% of this cohort treated with digoxin did not have a digoxin related adverse event. If the decision is to use digoxin, it should be dosed according to renal function and estimated muscle mass. Also, it would be appropriate to check a digoxin level after steady state is achieved as well as intermittently thereafter in order to avoid increased levels. With limited treatment options available for patients with CA who have atrial fibrillation needing rate control or with low output heart failure, treating physicians may have to balance the risks and benefits of using digoxin in certain scenarios where there are no other good options.

The findings of this study need to be viewed in the context of several limitations. First, this is a retrospective analysis of a small cohort of patients without standardized patient selection, dosing, follow-up, or reasons for discontinuation. Data were collected from electronic medical records and relied on historical documentation by multiple providers. Patients on digoxin prior to coming to our institution could have had unaccounted events despite thorough review of outside medical records. Digoxin levels were not systematically checked. In addition, we do not compare the rate of arrhythmias seen in our patients on digoxin with a control cohort of patients with amyloidosis. Finally, we do not comment on efficacy of digoxin for each individual patient with regards to rate control for atrial fibrillation or for low output heart failure.

We conclude that digoxin may be cautiously used in selected patients with AL-CA or ATTR-CA at lower doses with close monitoring of drug levels, renal function, and electrolytes. Physicians, using both clinical judgment and an assessment of risk versus benefit, may decide to use this medication in atrial fibrillation with uncontrolled ventricular rate or low output heart failure when no other reasonable options exist.

Authors' contribution

Joseph P. Donnelly, MD: Writing-Original Draft, Methodology, Formal analysis; ***Brett W Sperry, MD:*** Conceptualization, Methodology, Writing-Reviewing & Editing; ***Andrej Gabrovsek, MD:*** Writing-Reviewing & Editing; ***Asad Ikram, MD:*** Data Curation; ***W.H. Wilson Tang, MD:*** Writing-Reviewing & Editing; ***Jerry Estep, MD:*** Writing-Reviewing & Editing; ***Mazen Hanna, MD:*** Conceptualization, Methodology, Formal analysis, Writing-Original Draft, Writing-Reviewing & Editing, Supervision, Funding acquisition.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.034.

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