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Intracardiac Thrombosis, Embolism and Anticoagulation Therapy in Patients with Cardiac Amyloidosis – Inspiration from a Case Observation

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1. Introduction

Amyloidosis is uncommon. Data from Olmsted County, Minnesota, report age-adjusted incidences between 6.1 and 10.5 per million person-years.[1] It is estimated that there are 1275 to 3200 new cases annually in the United States.[1, 2] Amyloidosis is classified by the precursor plasma proteins that form the extracellular fibril deposits. The primary systemic type, AL, is due to monoclonal immunoglobulin free light chains, the hereditary ("familial") type is due to mutant transthyretin deposition, the wild type transthyretin type (wild type TTR, or "senile" type) is due to normal wild-type transthyretin deposition, and the secondary type (AA type) is related to amyloid A protein.[2, 3] Amyloidosis, especially the AL type, frequently involves the heart and can cause arrhythmias, heart failure with left ventricular diastolic dysfunction, and sudden cardiac death.[4, 5] In part because of cardiac involvement, AL amyloidosis has the worst prognosis, with a median survival of 6 months when heart failure is present.[2, 5-7] Many patients with cardiac amyloidosis die suddenly, presumably related to either arrhythmia or electromechanical dissociation.[8] However, systematic studies evaluating the causes of death are lacking until recently.

2. Case reports of intracardiac thrombosis in cardiac amyloidosis

We initially saw a 58-year-old woman with primary amyloidosis who presented with biatrial thrombosis while in sinus rhythm. The patient presented with orthopnea, postural hypotension, epigastric pain, anorexia, nausea, vomiting, and lower extremity edema that had progressed for 5 months. Esophageal gastric endoscopy showed negative findings, but a gastric mucosa biopsy specimen was positive for amyloid deposition. Examinations from other institution included a transthoracic echocardiogram and a coronary angiogram 1 month earlier were unremarkable. She was referred to Mayo Clinic for further evaluation. Physical examination findings included a pulse rate of 106 beats per minute, blood pressure of 114/80 mm Hg, and an elevated jugular venous pressure. Her lungs were clear to auscultation. Her heart rate and rhythm were regular and had no appreciable murmur, rub, or gallop. She had mild hepatomegaly and moderate bilateral pitting edema in both lower extremities.

Immunoglobulin G gama monoclonal protein was detected in her serum and urine. The electrocardiogram showed sinus tachycardia and a heart rate of 104 beats per minute, low QRS voltage, and a Q wave in V_1 through V_4. A transthoracic echocardiogram showed a large mobile mass (32×17 mm) protruding from the left atrial appendage (Fig. 1) that was consistent with a thrombus. Concentric left ventricular wall thickening, right ventricular free wall thickening, and the granular "sparkling" appearance of the myocardium was noted. The generalized hypokinetic left ventricle had a mildly reduced ejection fraction of 45 %. Other characteristic findings of cardiac amyloidosis that also were present included thickened cardiac valves and atrial septum, moderately dilated atria, inferior vena cava and hepatic vein dilatation with systolic flow reversal, and small circumferential pericardial effusion. A restrictive left ventricle filling pattern was apparent and suggested considerably elevated left ventricular filling pressure (figure 2). There was minimal atrial reversal in the pulmonary vein. Tissue Doppler echocardiography showed only small mitral A waves but no A′ waves in the mitral annulus (figure 3). These observations suggested atrial electromechanical dissociation, also termed atrial standstill.

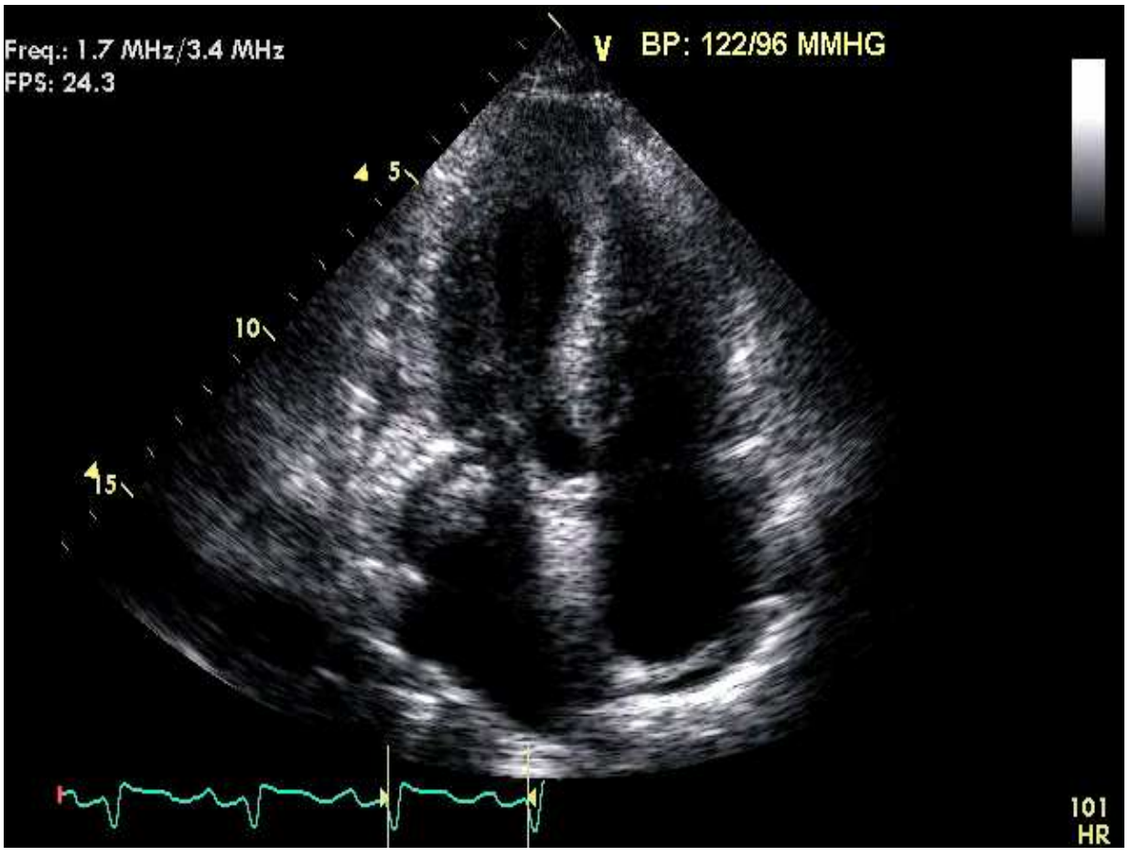


Fig. 1. A transthoracic echocardiogram of 4 chambers view showed a large mobile mass (32×17 mm) protruding from the left atrial appendage that was consistent with a thrombus. Concentric left ventricular wall thickening, right ventricular free wall thickening, and the granular "sparkling" appearance of the myocardium was noted

The patient was immediately hospitalized and received anticoagulation therapy with intravenous heparin. She quickly became confused and hypotensive, had decompensated

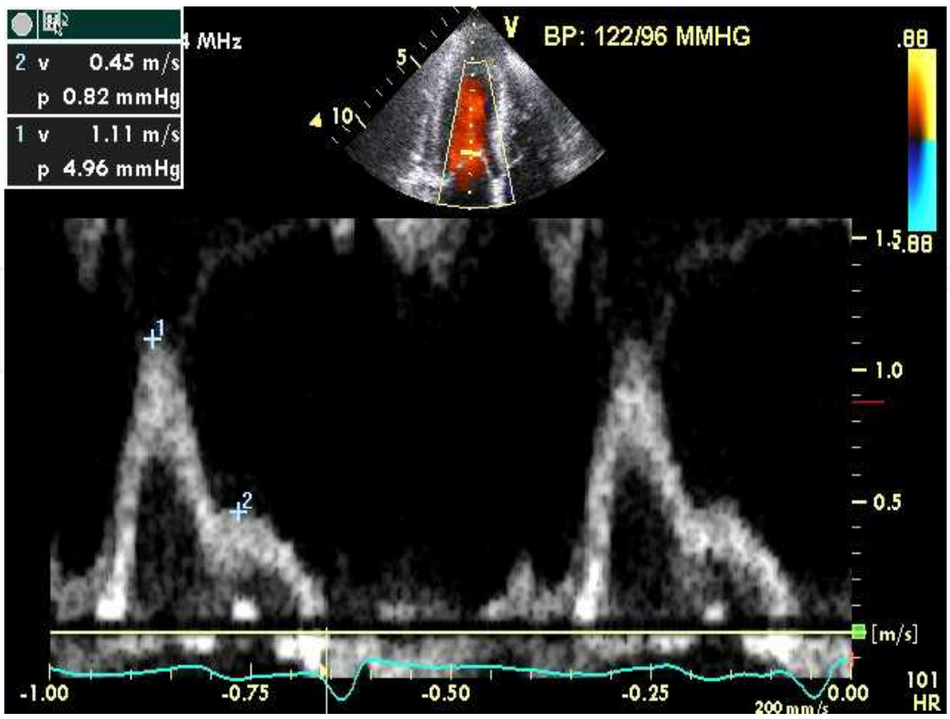


Fig. 2. A restrictive left ventricle filling pattern was apparent and suggested considerably elevated left ventricular filling pressure

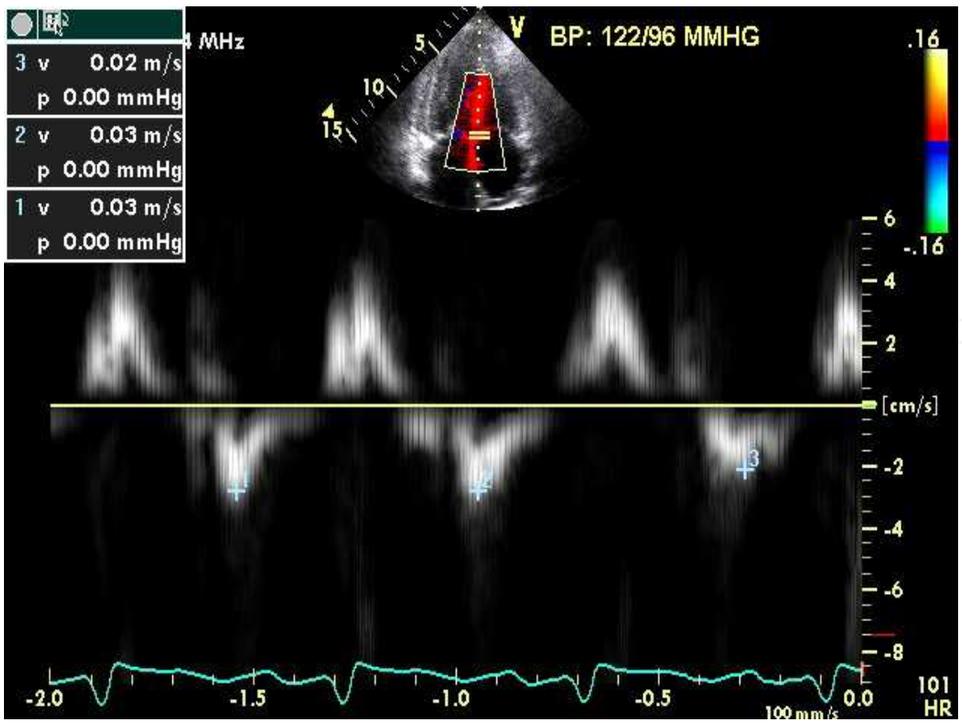


Fig. 3. Tissue Doppler echocardiography showed only small mitral A waves but no A' waves in the mitral annulus

heart failure and then cardiogenic shock, and required inotropic support. On her third hospitalization day, she had a cardiac arrest and could not be resuscitated.

An autopsy confirmed thrombi in the left atrial appendage (Fig. 4) and right atrial appendage, and multiple infarctions were identified in the distal small bowel, ascending colon, bilateral kidneys, and spleen. Histologic studies showed extensive amyloid deposition in the heart, kidney, spleen, gastrointestinal tract, and pancreas (figure 5 a and b). Interestingly, the patient had not reported abdominal pain or other gastrointestinal symptoms, which could suggest that a mesenteric embolism occurred before death.

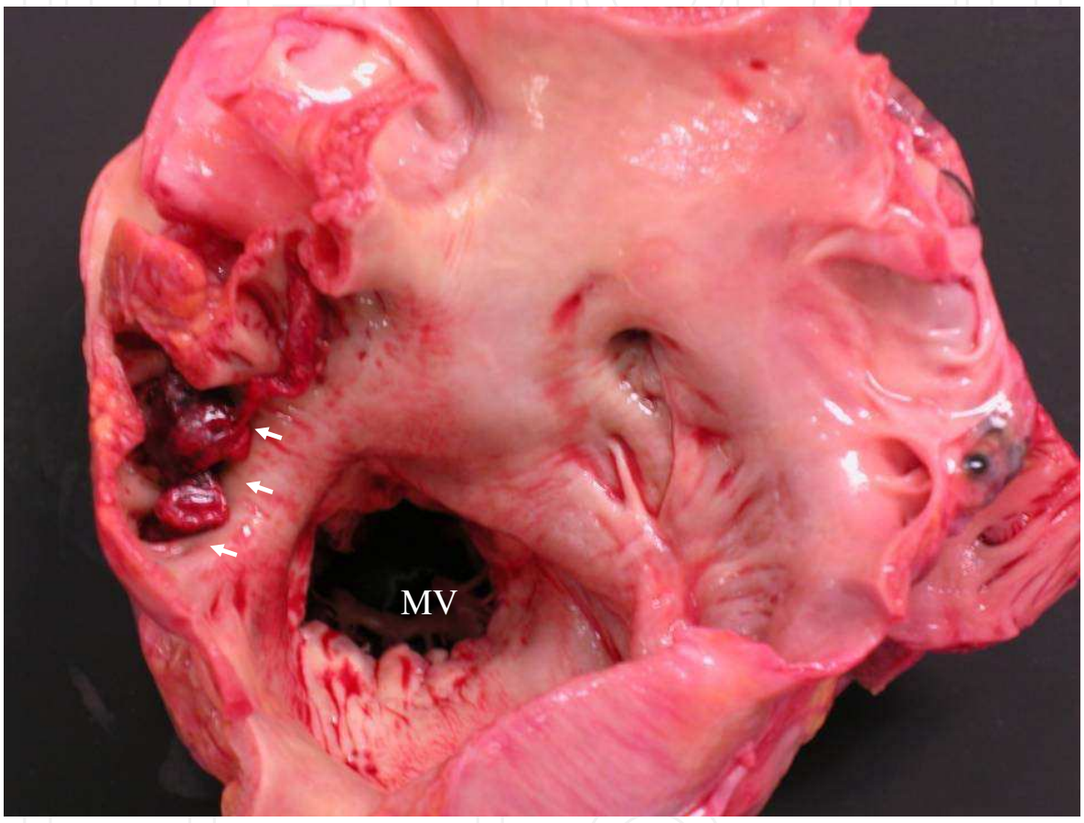
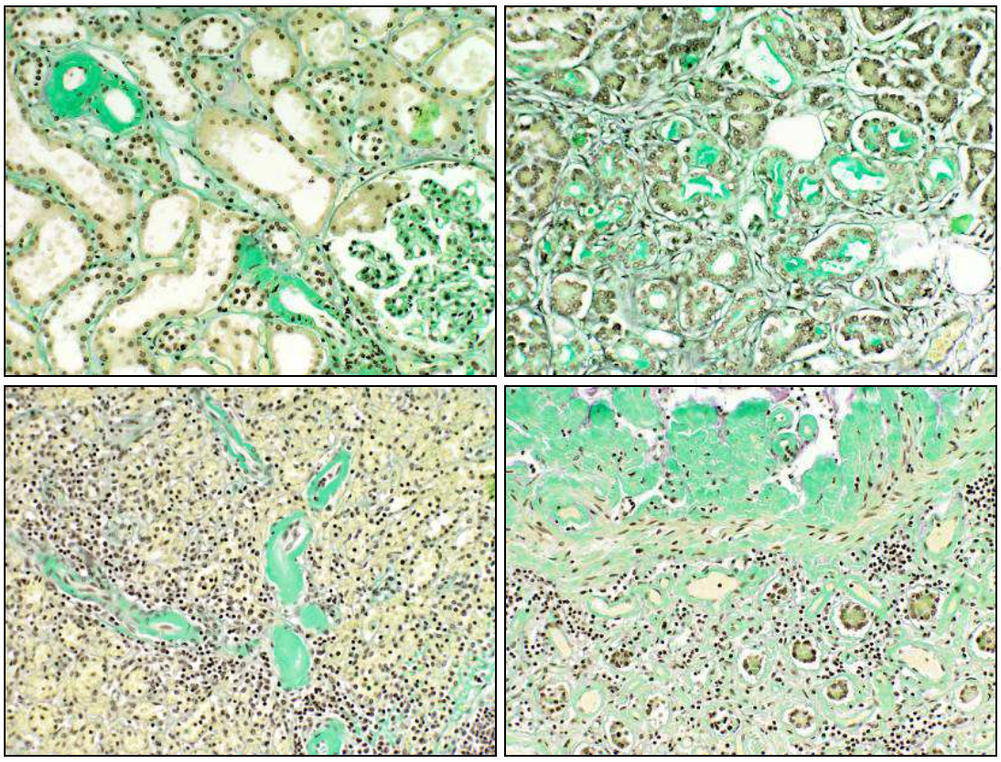


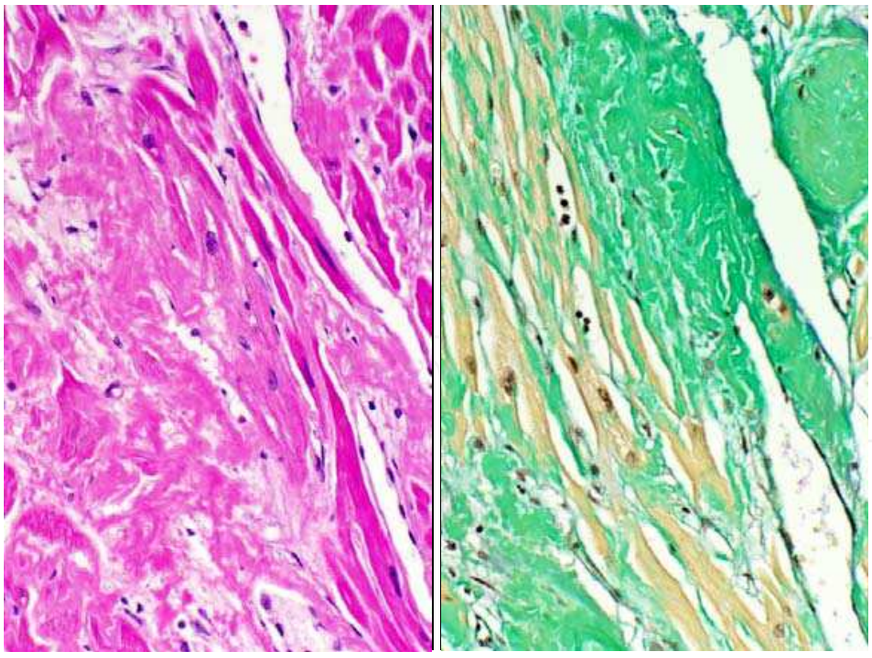
Fig. 4. An intracardiac thrombus in the left atrial appendage (LAA); MV: mitral valve

The mechanism underlying intracardiac thrombosis in sinus rhythm for a patient with cardiac amyloidosis was not clear. We postulated that severely reduced atrial contractility attributable to amyloid infiltrate, increased left atrial afterload, and left atrial enlargement with depressed left ventricle systolic and diastolic function may partially explain why the patient developed left atrial thrombosis in sinus rhythm.

There have been only a few similar case reports in the literature.[9-12] These cases shared some common salient clinical features. First, all the patients were in normal sinus rhythm, which is very rare for intracardiac thrombosis while in sinus rhythm. Second, their LVEF were normal or only mild depressed. Third, intracardiac thrombosis was often undiagnosed until the index catastrophic pulmonary or systemic embolism. Forth, very poor outcome with most patients died with in a few days and few months after the diagnosis. The characteristics of these subjects were summarized in the Table 1.



(a)



(b)

Fig. 5. Extensive interstitial amyloid deposition in the heart (figure a), kidney, spleen, gastrointestinal tract, and pancreas (figure b). The amyloid was stained as light pink on the Congo red stain and as green on sulfated Alcian blue stain

Authors	No	Presentation	Location	Rhythm	Method	Out come
Botker[9]	1	46 W, AL, recurrent stroke,	LA	SR	Autopsy	Died 1 m later of cardiac/renal failure
Plehn[24]	1	58 W; AL, CHF, LVEF 50%.	LAA	SR	TTE	Stroke/Heart Tx 4mons/died 14 mons
Browne[10]	2	66 M, MM, CHF, LVEF 46%, RLE embolism	Atria/LV	SR/PVC	Autopsy	Deceased in 3 days due to CHf/shock SCD 6
		54 M, AL, nephrotic syndrome, CHF, LVEF 57%, RLE embolism.	Unclear	SR/PAC	Autopsy	mons later
Willens[15]	1	74 W, CHF, LLE embolism. Mild LV systolic dysfunction.	L/RAA	SR	TEE	Deceased "several mons" later
Dubrey[17]	3	44/W; AL, CHF, EF 30%	L/RAA	SR	Autopsy	Died of CHF 4 m later
		52 W; AL, CHF,	LAA	SR	TTE	Died of CHF 1 m later
		58 W; AL, CHF, LVEF 50%	LAA	SR	TTE	Stroke/Heart Tx 4 m later /Died 14 m later
Cools[12]	1	64 M, MM, sever edema, and CHF no nephrotic syndrome ?LVEF	IVC	SR	CT/US	Deceased 4 mons later intestine infarction
Santarone[11, 16]	3	60 W, AL, CHF, nl LVEF	Atria	SR	TTE/TEE	SCD/PE 15 d later
		62 W, AL, CHF, nl LVEF	LAA	SR	TEE	Died of CHF 9 m later
		65 M, AL, SOB, nl LVEF	LAA	SR/PVC	TTE	SCD 4 m later

Table 1. Summary of the case report on intracardaic thrombosis and their clinical features in cardiac amyloidosis

3. Intracardiac thrombosis and embolism from autopsy data at the Mayo Clinic

The frequency of intracardiac thrombosis and its relationship to thromboembolic complications and mortality had been not well established. To clarify this issue, we reviewed autopsy and explanted hearts with various types of amyloidosis to determine how frequently intracardiac thrombi are present and how frequently they cause embolic events or death. We then elucidated the clinical and echocardiographic characteristics that predict intracardiac thrombosis and embolism. We searched the Mayo Clinic Tissue Registry database for cases of cardiac amyloidosis from1996 to 2005.[13] Of 142 cases, 26 were excluded because of inadequate tissue or incomplete clinical information. The remaining 116 cases included 112 autopsy cases and 4 surgically explanted hearts. A control group included 46 non-amyloid fatal trauma cases.

3.1 Transthoracic echocardiogram

Transthoracic echocardiograms (TTE) were obtained in 82/116 patients. The TTE was reviewed independently without knowledge of the clinical and pathological data. TTE parameters extracted included left ventricular (LV) ejection fraction (LVEF), LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), stroke volume, ventricular septum thickness, LV posterior wall thickness, right ventricular (RV) free wall thickness, RV systolic pressure, left atrium (LA) volume index, right atrium (RA) enlargement (0=normal, 1=mild, 2=moderate, 3=severe), LV diastolic function grade,[14] mitral inflow E and A velocity, deceleration time, mitral septal annulus tissue Doppler velocity (early peak diastolic velocity: e', late peak diastolic velocity: a') and pulmonary venous flow profile

[peak systolic velocity (S), peak diastolic velocity (D), D/S, and atrial contractile velocity], E/A, and E/e′.[14] HR and BP at the time of TTE were documented.

3.2 Pathology data

All cardiac chambers were examined for thrombi. Thrombi were characterized as to their exact anatomic location and size. The presence of cardiac amyloid was confirmed with Congo red or sulfated Alcian blue stain. Amyloid subtype was determined immunohistochemically with antibodies against serum amyloid P component, lambda and kappa free immunoglobulin light chains, transthyretin, amyloid A component, and beta-2 microglobulin.

3.3 Cause of death

The autopsy reports were evaluated by a pathologist and a cardiologist without knowledge of the patient's clinical diagnosis (i.e., trauma, amyloidosis, amyloidosis type, or cardiac rhythm). Death was due to a thromboembolic cause if: major acute pulmonary emboli were present, irrespective of pulmonary infarction; mesenteric artery embolism with bowel infarction was present; major embolic stroke with associated intracranial hemorrhage was present or if emboli were the cause of complications such as aspiration pneumonia and death; renal infarcts were present with renal failure; or death occurred during or shortly after surgical intervention for emboli.

3.4 Results

Age ranged from 31-101 years (mean of 72±16). Sixty-one percent were men. In the control group, mean age was 55±27 years; 69% were men. The demographic data for the amyloid patients are shown in Table 2. There were 55 AL cases, 55 wild type TTR cases, 4 AA types, and 2 familial types. Because AA and familial types are rare (n = 6), they were combined into one group with the TTR cases (called other, n=61). Results were similar with and without these. Compared with the other amyloid group, the AL was younger; had less AF; a shorter survival time from the onset of symptoms and less commonly had CAD (Table 2). They had thicker ventricular architecture. There were no significant difference in CHF history in two groups but the AL type had greater value for NYHA class. There were no differences in gender, ethnicity, creatine, and LVEF.

3.4.1 Intracardiac thrombus

Intracardiac thrombi were identified in 38/116 (33%) hearts. Twenty-three had 1 thrombus while 15 had 2-5 thrombi for a total of 63. Thirty-six were in the RA, 19 in the LA (Figure 1), 4 on the coronary sinus valve, 3 in the RV, and 1 in the LV. No intracardiac thrombus was identified in the 46 fatal trauma subjects. There were significant differences in the frequency of intracardiac thrombosis between the cardiac amyloid group and the control group (33% versus 0%, $p<0.0001$). The AL group had more intracardiac thrombi than the other amyloid group (51% versus 16%, $p<0.0001$). Of the 4 AA cases, 2 had intracardiac thrombus. There were none in the familial cases.

3.4.2 Embolic events and cause of death

There were 23 embolic events in patients with amyloid. There were 19 fatal and 4 non-fatal emboli. AL patients had more fatal thromboembolism (14/53; 26%) than the other amyloid

patients (5/59; 8 %) and than the control group (1/46; 2%; p<0.001). Embolic fatalities for the AL group included 7 pulmonary emboli (PE), 1 mesentery artery embolus with bowel infarction, 1 iliac artery embolus and the patient died during attempted embolectomy, and 5 cases with multiple emboli. In addition, there were 4 non-fatal embolic events in the AL group including 3 found at autopsy and 1 with PE and brachial artery embolism who survived after cardiac transplant. Among the other amyloid group, there were 5 embolic fatalities, including 3 PEs, 1 mesenteric artery embolus with bowel infarction, and 1 case with multiple systemic emboli.

	AL (n=55)	Other Amyloid (n=61)	P value
Age, years	60 ± 11	83 ± 11	<0.0001
Gender, % male	61	62	=0.80
Ethnic, % Caucasian	100	100	=0.53
Atrial fibrillation, %	22	45	=0.008
Anticoagulation , %	26	37	=0.21
Survival time (months)	23 ± 25	63 ± 12	=0.01
CAD by autopsy, % *	10	90	<0.0001
CAD severity score (0 to 4) *	1.5 (1.2-1.5)	3.3 (2.9-3.5)	<0.0001
Cardiac mass, g	532±150	474±132	=0.017
LV septal thickness, mm	16.5±4.2	16.0±4.2	=0.26
LV posterior wall, mm	16.0±3.5	14.7±3.8	=0.029
RV free wall, mm	6.0±2.4	4.9±1.7	=0.006
CHF (%)	77	63	=0.10
NYHA class (1-4)	2.8±1.2	2.1±1.2	=0.01
LVEF (%)	50 ± 18	52 ± 16	=0.66
Creatine mg/dL	2.3 ± 1.5	1.8 ± 1.1	=0.07

CAD = coronary artery disease; CAD severity score at autopsy: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe.

Table 2. Patient characteristics in AL and the other amyloid groups

3.4.3 Clinical characteristics, TTE and thromboembolism

Forty-five subjects (40%) had intracardiac thrombosis, embolism or both. Compared to the group without thromboembolism, they were younger, less often hypertensive, had more AL type, and lower systolic BP (Table 3). The thromboembolic group had less CAD and when present, less extensive involvement. Other demographic and clinical variables were similar.
TTE features are in Table 3. Times from TTE to death were similar. The thromboembolic group had a higher HR at TTE, a smaller LVEDD, thicker LV posterior and RV walls, a smaller SV, a lower RV systolic pressure, a lower LVEF, worse LV diastolic function, a shorter deceleration time, poorer LA mechanical activity (a lower A and a' velocity), and a higher E/A and E/e' than the non thromboembolic group. Furthermore, PV peak systolic velocity and A velocity were significantly lower and D/S was higher. LA volume index and RA size were not different (Table 4). RV wall was thicker in subjects who had RA thrombosis compared with those who did not have RA thrombosis (7.9±2.7 mm vs. 6.6±3.1 mm, p=0.02).

3.4.4 Multivariate analysis and ROC

By multivariate analysis, AL type [OR=15.6 (2.8-117.6), p=0.001] and AF [OR=6.0 (1.7-26.7), p=0.004] were independently associated with thromboembolism in a model with clinical variables (Table 5) with high odds ratios for both [OR=55.0 (8.1-1131.5), p<0.0001]. For TTE

variables, RV wall thickness [OR=1.3 (1.0-1.7), p=0.03] with 1 mm increase in the wall, LV diastolic function [OR 8.8 (1.6-64.1), p=0.01] with restrictive pattern (grade 3 or 4) compared with grade 2 or less, and HR at echo [OR=1.7 (1.1-2.9), p=0.02] with 10 beats/minute of increase were independently associated with thromboembolism. There were no differences in thromboembolic risk between LV diastolic function grade 2 versus grade 1 or normal diastolic function. When both clinical and TTE variables were included in the analyses, AL type [OR 8.4 (1.8-51.2), p=0.006], LV diastolic function [OR=12.2 (2.7-72.7), p=0.0008] and a higher HR [OR=1.1 (1.0-1.2), p=0.048] were independently associated with thromboembolism (Table 5). Other variables were not associated with thromboembolism including atrial sizes.
The receiver operating characteristic curve (ROC) for using LV diastolic function grade to predict thromboembolism is shown in Figure 2. Grade 3 LV diastolic dysfunction had a sensitivity of 78% and a specificity of 79%. The area under curve was 0.81. Using amyloid type, LV diastolic function, and HR, the area under the curve was 0.87. Presence of both LV diastolic grade 3 or 4 and AL type increased specificity to 94 % but decreased sensitivity to 56 % as one would expect.

	With (n=45)	Without (n=71)	P value
Age, years	65 ± 2.2	77 ± 1.8	<0.0001
Gender, % male	58	62	0.67
Body mass index, kg/m^2	26.0±0.9	26.7±0.8	0.54
Hypertension, %	17	41	0.008
Diabetes, %	7	19	0.08
CHF, %	65	71	0.55
NYHA class (1-4)	2.4±1.3	2.3±1.2	0.65
Atrial fibrillation, %	37	33	0.64
Anticoagulation , %	36	28	0.42
Cancer, %	15	22	0.41
Syncope, %	34	17	0.08
AL amyloidosis, %	73	31	<0.0001
Stem cell transplant, %	23	10	0.09
Recent operation, %	10	17	0.31
History of thrombosis, %	27	24	0.76
Systolic BP, mm Hg	111±18	128±24	0.0005
Diastolic BP, mm Hg	67±12	69±15	0.54
Creatinine, mg/dL	2.2±1.7	1.9±1.1	0.17
CAD by autopsy, %	29.3	55.4	0.008
CAD severity score (0 to 4) *	2.0±1.2	2.7±1.3	0.02

* CAD severity score: 0 = no, 1 = minimal, 2 = mild, 3 = moderate and 4 = severe.

Table 3. Characteristics in patients with and without Thromboembolism

3.5 Discussion

The Mayo autopsy study of patients with cardiac amyloidosis identifies a high frequency of intracardiac thrombosis, especially in AL patients, despite normal sinus rhythm and relatively preserved LVEF. Most thrombi arose in the atria. Thrombosis and embolism caused significant fatality. AL type, AF, poor LV diastolic function, RV wall thickness by TTE, and higher HR were independent predictors for thromboembolism. Many risk factors

	With (n=35)	Without (n=47)	P Value
Time (from TTE to death), day	15 (1-55)	43 (2-209)	0.12
HR at echo, beats/min	86±17	79±14	0.02
LV end diastolic diameter, mm	44.3±7.8	48.1±8.1	0.04
LV end systolic diameter, mm	32.4±9.3	33.1±9.8	0.76
LV septal thickness, mm	14.2±3.9	12.9±3.3	0.12
LV posterior wall thickness, mm	13.8±3.6	12.2±3.1	0.03
RV free wall thickness, mm	8.3±3.6	5.9±2.1	0.0007
LA volume index (cc/m^2)	40.1±14.9	48.2±35.2	0.21
RA enlargement (0-3)	1.8±1.2	1.4±1.1	0.08
Stroke volume, mL	51.1±20.9	67.6±23.4	0.002
RV systolic pressure, mm Hg	44.3±9.4	51.1±15.9	0.045
LVEF (%)	46±19	54±15	0.03
LV diastolic function grade (0-4)	3.1±1.1	1.9±0.8	0.0001
Mitral deceleration time (ms)	160±37	193±60	0.006
Mitral E velocity (m/s)	0.87±0.21	0.90±0.26	0.65
Mitral A velocity (m/s)	0.27±0.29	0.52±0.33	0.0008
E/A	3.4±2.6	2.0±1.9	0.03
Mitral annulus e' velocity (cm/s)	4.4±2.3	5.9±2.7	0.06
Mitral annulus a' velocity (cm/s)	2.3±3.3	6.6±4.7	0.003
E/e'	23±12	16±8	0.02
PV systolic velocity, m/s	0.32±0.18	0.48±0.20	0.002
PV diastolic velocity, m/s	0.65±0.20	0.60±0.18	0.37
PV A velocity, m/s	0.14±0.13	0.24±0.13	0.008
PV diastolic/systolic ratio	3.0±2.3	1.5±0.8	0.001

Table 4. TTE characteristics in subjects with and without Thromboembolism

Dependent Variate	Models *	Predictors	OR	95 % CI	P value
Thromboembolism	Model 1	AL type	15.6	2.8-117.6	0.001
		AF	6.0	1.7-26.7	0.004
		AL and AF	55.0	8.1-1131.5	0.0001
Thromboembolism	Model 2	RV free wall	1.3	1.0-1.7	0.03
		LV diastolic function	8.8	1.6-64.1	0.01
		Heart rate	1.7	1.1-2.9	0.02
Thromboembolism	Model 3	AL type	8.4	1.8-51.2	0.006
		LV diastolic function	12.2	2.7-72.7	0.0008
		Heart rate	1.1	1.0-1.2	0.048

CI = confidence interval.
* Model 1: Clinical variates included are age, amyloid type, AF, hypertension, and CAD.
Model 2: Echo variates included are RV wall thickness, LV diastolic function, LVEF, SV, mitral A velocity, and HR at TTE.
Model 3: Combined model with variates included amyloid type, AF, RV free wall, LV diastolic function, SV, and HR.

Table 5. Predictors for thromboembolism by multivariate analyses

in patients without amyloidosis such as age, CHF, hypertension and diabetes were not significantly associated with thromboembolism from the Mayo Autopsy study. Surprisingly, atrial size was not associated with thromboembolism despite the fact that most thrombi were found in the atria. Measures of atrial mechanical activity such as A velocity and a' velocity were different only in univariate analyses but not multivariate analyses.

3.5.1 Intracardiac thrombosis in cardiac amyloidosis

The high incidence of intracardiac thrombosis from Mayo autopsy study confirms the observations of Roberts.[4] AL type was associated with a 51% incidence compared to only 16% in the other amyloid groups despite the fact that these groups were older and more frequently had AF. Other than case reports and a small autopsy study,[10,12,15-17] the Mayo's investigation was the only systemic study to report the high frequency of intracardiac thrombosis and clinical thromboembolic complications resulting in mortality. Roberts et al retrospectively studied 49 AL and 5 familial type hearts and identified intracardiac thrombi in 26%. The clinical implications of these thrombi are unknown. Halligan et al. found 2% of biopsy-proven AL patients had clinically documented thromboembolism[18] and thrombosis was associated increased mortality. Common features of previous reports include middle-age years of patients, relatively preserved LVEF despite clinical CHF and multiple thrombi. A majority of the patients had a poor prognosis. Most patients were in sinus rhythm.

3.5.2 Intracardiac thrombosis and embolism

Twenty-six percent of our patients died from embolic complications in the AL group. Not all patients with documented embolism had intracardiac thrombosis at autopsy (30%) perhaps because some thrombi had been dislodged prior to death. Alternatively, some patients could have had other sources for thrombi.

3.5.3 Clinical variables and thromboembolism

Several studies show that advanced age, AF, CHF, diabetes, and hypertension are risk factors for thromboembolism in non amyloid patients.[19,20] In the Mayo autopsy investigation, the mean age was younger in patients with thromboembolism. This is because primary amyloid patients were much younger than the non primary patients and they were 8.4 times more likely to develop thromboembolism. Thromboembolic patients also had a fewer comorbidities because of their younger age. By multivariate analyses, only two clinical variables, AF and AL cardiac amyloidosis, were independently associated with thromboembolism. After TTE variables and clinical variables were introduced into the analysis, AF was no longer an independent risk factor. This is likely because AF was associated with poor atrial mechanical activity and LV diastolic dysfunction. Nonetheless, we suggest that when present, AF should be considered a marker of possible intracardiac thrombosis, especially in AL patients. On the other hand, higher heart rate at TTE is independently associated with increased risk for thromboembolism. Increased heart rate reflects the underline severity of disease and therefore indicates decompensation.

Of interest, the presence of CAD and the severity of CAD at autopsy were negatively associated with intracardiac thrombosis and embolic events. This is likely because CAD is associated with older age and the mean age in our study was significantly older in the other amyloid groups. After adjusting for age, amyloid type, and other variables, CAD was not associated with intracardiac thrombosis or embolism.

Clinical CHF and NYHA class were not significantly different in patients with or without thromboembolism. Multivariate analyses only confirmed an association between poor LV diastolic function, i.e., restrictive diastology (class 3 or 4) by TTE and intracardiac thrombosis and embolism. Because many patients were elderly with multiple comorbidities, the clinical diagnosis of CHF or NYHA class is subjective indicator of over all well being and may not be always accurate. TTE with structure and function evaluation (including diastolic measures) provides more comprehensive information and is more helpful for risk stratification.

3.5.4 TTE characters and thromboembolism

Multivariate analyses showed only LV diastolic function and higher HR at TTE, and to a lesser extent, RV wall thickness were significantly associated with thromboembolism. Poor atrial mechanical activity (mitral A and a' velocity) was significant only in univariate analyses. The observation was not surprising because LV diastolic function was graded based on several echo features including mitral inflow profile and mitral tissue Doppler.

RV wall thickness is associated with abnormal RV diastolic function.[21] Advanced RV infiltrate by amyloid (≥7mm) was associated with a restrictive tricuspid inflow filling pattern; lesser thickness was associated with abnormal RV relaxation.[21] In the current study, the mean RV wall thickness was 8.3 mm in the thromboembolic group. A thickened RV wall therefore reflected more advanced amyloid deposition with a poor RV diastolic function and with consequent stasis and thrombosis.

The LA volume index and RA size were not significantly different in the patients with and without thromboembolism although the indexes were large in both (>40cc/m^2). One would speculate that atrial size should be bigger in the thromboembolic group because of poor LV diastolic function, higher LV/LA filling pressure as estimated by E/e' and a thicker RV wall. In the study, 73% of thromboembolic patients had AL amyloid and thus a worse prognosis. It may be that patients with AL amyloidosis do not have time to develop atrial enlargement because of short survival times. In addition advanced age and comorbidities contribute to increased LA size[22] and thromboembolic patients were younger and had a fewer comorbidities. Finally, it is possible that amyloid infiltrate in the atria prevented them from being distended as suggested by Modesto et al with strain imaging.[23]

3.5.5 Mechanism for thromboembolism

Our TTE data support the concept stasis could lead to intracardiac thrombosis. Even though the mean LVEF was relatively-preserved, those with intracardiac thrombosis had lower LVEF. Furthermore, the LV diastolic function and atrial mechanical activity were more impaired. Reduced atrial contractility secondary to amyloid infiltration has been reported[17,24] and LV diastolic function is typically impaired before systolic function.[25] The combination of systolic and diastolic ventricular dysfunction, chronic amyloid infiltrate in the atria, and direct toxic effect on myocardium[26] could lead to atrial mechanical dysfunction, atrial enlargement, and blood stasis.[23,27] Such atrial electrical-mechanical dissociation may partially explain why many cardiac amyloidosis patients developed atrial thrombosis while in sinus rhythm.[17,24,28] It is possible that endomyocardial damage and endothelial dysfunction from amyloid depositions may be responsible.[29,30] Hypercoagulability may also contribute.[7,31]

3.5.6 Summary of the Mayo autopsy study

There was a high frequency of intracardiac thrombosis in patients with cardiac amyloidosis, especially the AL type, despite sinus rhythm and preserved LVEF. Intracardiac thrombosis

leads to embolic events and mortality. The presence of AL type, AF, poor LV diastolic function, greater RV wall thickness, and higher heart rare were associated with thromboembolism. Poor LV diastolic function and atrial mechanical activity are likely contributory to the complication. Transesophageal echocardiography (TEE) may be indicated for earlier detection[11] in the high risk patients since TTE is well known for its insensitivity in detecting intracardiac thrombosis especially in the atria. If intracardiac thrombosis is detected, anticoagulation therapy may be indicated. However, anticoagulation may exacerbate the hemorrhagic tendency well known in amyloidosis because of fragile blood vessel walls secondary to amyloid deposition and the coexisting coagulopathy.[2,31] Three AL amyloid patients in this study died from massive gastrointestinal bleeding.

4. TEE, intracardiac thrombosis, embolism and anticoagulation therapy in patients with cardiac amyloidosis

The autopsy study have identified a high prevalence of intracardiac thrombosis in these patients at autopsy, especially in AL cardiac amyloidosis.[4,13] Furthermore, in our autopsy series, systemic embolism was a significant cause of mortality.[13] However, it is possible that autopsy series may over emphasize the frequency of intracardiac thrombosis and there only have been a few anecdotal reports in the literature on intracardiac thrombosis detected by TEE or TTE in live patients.[9-12,15-17] The prevalence of intracardiac thrombus and the effects of anticoagulation in living cardiac amyloid patients has not been reported. Accordingly, we evaluated both TTE and TEE studies from patients with various types of cardiac amyloidosis to determine how frequently detectable intracardiac thrombi are present; the clinical and echocardiographic characteristics associated with their presence; and the effects of therapeutic anticoagulation.

4.1 Study groups

We searched the Mayo Clinic Hematology Data base for all cases of amyloidosis from 1999 to 2007. There were 156 patients had cardiac amyloid who also had TEE. The detail of exclusion and inclusion criteria was reported elsewhere.[32]

Clinical information, including demographic data, comorbidities, presence of heart failure (HF), New York Heart Association (NYHA) functional class, the use of anticoagulants prior and at the time of TEE, ECG, TTE, TEE, MRI and other laboratory data were abstracted from clinical records. Cardiac rhythm was determined from the patient's ECG, Holter monitoring data, and medical records. INR and APTT around the time of TEE were charted. Therapeutic anticoagulation was defined as INR ≥ 2 at the time of TEE or documented two or more consecutive therapeutic INR 2-3 prior to TEE for those with long term anticoagulation, or at least 48 hours of intravenous heparin therapy or 48 hours of subcutaneous low molecular weight heparin therapy prior to TEE. Other abstracted information included results of tissue biopsies, urine and serum protein electrophoresis, immunofixation, serum free light chain assay, genetic testing, and family history.[13]

4.2 Echocardiograms

TTE and TEE studies were reviewed independently without knowledge of the clinical and pathological data and was reported previously[13] The TEE studies were reviewed for presence or absence of intracardiac thrombus and their location and size.[14] Left atrial appendage (LAA) and LA spontaneous contrast and their severity were semi-quantified as

none, mild, moderate or severe (0, 1, 2, or 3 respectively).[33] Left atrial appendage emptying velocity was measured by pulse Doppler echocardiography as previously reported.[33] The degree of atherosclerosis in aorta was semi-quantified as none, mild, moderate or severe.[34 35] HR and BP at the time of TEE were documented.

4.3 Demographic data and amyloid subtypes

Amyloidosis was AL type in 80, 56 wild TTR type, 17 mutant TTR type, and 3 AA type (Table 6). Because AA are rare, they were combined into one group with the wild and mutant TTR cases (called other amyloidosis, n=76). Compared with other amyloid group, the AL group was younger; had fewer males, less AF, was less often receiving anticoagulation therapy and less often had a history of hypertension, and were more likely to be treated with stem cell transplantation, all $p \leq 0.05$ (Table 6). There was no significant difference in a history of HF, NYHA class or other variables between the two groups listed in Table 1 (all $p>0.05$).

	All Patients (n=156)	AL (n=80)	Other Amyloid (n=76)	P value
Age, years	67 ± 11	61 ± 10	74 ± 9	<0.0001
Gender, % male	77	65	89	0.0003
Body mass index, kg/m²	26.1 ± 4.4	26.4±4.2	25.6±4.7	0.35
Heart Rate, bpm	81 ± 18	81 ± 19	80 ± 16	0.51
Systolic BP, mm Hg	118 ± 22	117±21	120±22	0.29
Diastolic BP, mm Hg	70 ± 14	71±13	69±14	0.34
Atrial fibrillation, %	64	56	72	0.03
Anticoagulation, %	43	33	54	0.007
Hypertension, %	39	30	49	0.02
Diabetes, %	5	4	7	0.43
NYHA class 1, %	21	20	22	0.95
NYHA class 2, %	35	34	36	
NYHA class 3, %	37	39	34	
NYHA class 4, %	8	9	8	
Median NYHA class	2 (1-3)	2 (1-3)	2 (1-3)	0.64
Syncope, %	24	21	26	0.46
Stem cell transplant, %	11	21	0	<0.0001
History of thromboembolism,%	22	24	21	0.69

Table 6. Patient characteristics in AL and the other amyloid groups in TEE study

4.4 Indications for TEE

TEE was performed in 57 patients (37%) for AF and/or prior to direct current cardioversion, in 33 patients (21%) searching for source for embolism, in 14 patients (9%) for evaluation of valvular heart disease, in 12 patients (8%) for rule out endocarditis, and in 6 patients (4%) for other reasons. TEE was performed prospectively in 34 cardiac amyloid patients (22%)

after our initial autopsy observations at the discretion of referral hematologists or cardiologists. All TEE studies were performed without major complications or mortality. All patients with TEE also had TTE studies with exception in one.

4.5 Intracardiac thrombus

There were 58 intracardiac thrombi identified in 42 (27%) of 156 patients by TEE. Most patients with thrombi (30 patients, 71%) had 1 thrombus while 8 patients (19%) had 2 thrombi, and 4 patients (10%) had 3. Most clots occurred in the left atrium/appendage (n=32) or in the right atrium/appendage (n=19). Of all of these thrombi detected by TEE, only 3 were detected by TTE. There was a significant difference in the frequency of intracardiac thrombosis between patients with AL amyloidosis and the other types (35% vs. 18%, p=0.02). The frequencies for intracardiac thrombosis were 18% for wild TTR type, 17% for mutant TTR type, and 33% for AA type.

The frequency of intracardiac thrombi in those receiving therapeutic anticoagulants was only 13%, much lower than in those not on therapeutic anticoagulant therapy at the time of TEE studies (37%, p=0.001). We further analyzed these patients on chronic anticoagulation with therapeutic INR at the time of TEE with stratifying findings according to persistent or permanent AF versus non AF. Chronic anticoagulation was associated with a significantly lower risk for intracardiac thrombosis [prevalence 18 % (6/33) versus 50 % (13/26) in those who were not on anticoagulation, p=0.01]. Similar trend was observed for patients who had no AF with respective intracardiac thrombosis prevalence 0 % (0/12) in chronic anticoagulation group versus 20 % (8/40) in the no anticoagulation group, p=0.09.

4.6 Clinical characteristics and thrombosis

Compared to the group without thrombosis, the intracardiac thrombosis group was younger, had more AF but was less apt to be receiving therapeutic anticoagulation (table 7). They were also more likely to have AL amyloidosis, had a lower systolic BP and faster heart rate, all $p \leq 0.05$. Similar results were obtained after the exclusion of patients who had AF. The prevalences of intracardiac thrombosis were 0% (0/21) in other types of cardiac amyloid patients who had no AF; 23% (8/35) in those with AL amyloidosis who had no AF, 25% (14/55) in other types with AF; and 44% (20/45) in AL patients with AF, p=0.0002. Other demographic and clinical variables were similar. Interestingly, the group with thrombosis did not have more frequent documented history of embolism. Furthermore, there was no significant difference in prevalence of intracardiac thrombosis between those patients studied retrospectively and those studied prospectively (31% vs. 25%, p=0.25).

4.7 TTE and thrombosis (table 8)

The group with thrombi had a smaller LV end diastolic dimension, a thicker LV posterior wall, a larger RA size, a smaller SV and CI, a lower LVEF, worse LV diastolic function, a shorter deceleration time, poorer LA mechanical activity (a lower A and a' velocity), and a higher E/A and E/e' than the non thrombotic group. Furthermore, PV peak systolic velocity and A velocity were significantly lower and D/S was higher (all $p \leq 0.05$). LA volume index was not statistically different. After exclusion of AF patients, the differences of several TTE parameters between the thrombosis group and the non thrombosis group were no longer statistically different although the trends were similar (table 8).

	All Patients				Patients without AF		
Thrombus status	All (n=156)	With (n=42)	Without (n=114)	P value	With (n=8)	Without (n=48)	P value
Age, years	67 ± 11	64 ± 12	69 ± 11	0.02	56 ± 9	65±12	0.04
Gender, % male	77	64	82	0.06	50	63	0.23
Body mass index, kg/m^2	26.1 ± 4.4	25.2±4.7	26.4±4.3	0.18	24.5±2.9	25.6±3.9	0.55
Hypertension, %	39	26	43	0.06	13	41	0.12
Diabetes, %	5	2	6	0.35	0	7	0.53
CHF, %	79	88	75	0.36	88	62	0.46
NYHA class 1, %	21	12	25	0.36	12	38	0.46
NYHA class 2, %	35	36	34		25	27	
NYHA class 3, %	37	43	34		50	29	
NYHA class 4, %	8	9	7		13	6	
Median NYHA class	2 (1-3)	3 (1-4)	2 (1-3)	0.10	3 (1-4)	2 (1-3)	0.11
Atrial fibrillation, %	64	81	58	0.008	0	0	--
Anticoagulation, %	43	21	51	0.001	0	29	0.05
Syncope, %	24	29	22	0.39	27	14	0.18
AL amyloidosis, %	51	67	46	0.02	100	56	0.01
Stem cell transplant, %	11	12	11	0.93	14	20	0.62
History of thromboembolism, %	22	24	22	0.92	32	30	1.00
Nephrotic Syndrome, %	17	24	15	0.23	25	27	0.90
Systolic BP, mm Hg	118 ± 22	110 ± 20	122 ± 22	0.002	91 ± 7	122 ± 21	0.0001
Diastolic BP, mm Hg	70 ± 14	68±13	71±14	0.18	57±10	71±15	0.02
Heart Rate, bpm	81 ± 18	86 ± 16	79 ± 18	0.01	87±14	78±14	0.13

Table 7. Characteristics in patients with and without Intracardiac Thrombosis in TEE study

4.8 TEE and thrombosis (table 9)

Those with intracardiac thrombi more frequently had spontaneous echo contrast in the LA, and also more severe spontaneous echo contrast in both the LA and LAA and, lower LAA emptying velocity compared to the non thrombotic group. There is no difference in the degree of atherosclerosis in aorta. Similar results were obtained after the exclusion of patients who had AF.

4.9 Multivariate analysis and ROC (table 10)

By multivariate analysis, AF, therapeutic anticoagulation, and lower systolic BP were independently associated with intracardiac thrombosis while there was a borderline trend for AL type in the model when only clinical variables were used. For TTE variables, LV diastolic function was the only variable independently associated with intracardiac thrombosis. Comparing restrictive filling with non restrictive filling LV diastolic function, the OR is 10.6 with 95% CI 1.5-220.3, p=0.04. For TEE variables, the only independent variable associated with intracardiac thrombosis was LAA emptying velocity. When clinical, TTE and TEE variables which were statistically significant by the above 3 models were included in the final model, AF, anticoagulation therapy, LV diastolic function, and LAA emptying velocity were independently associated with intracardiac thrombosis.

The receiver operating characteristic analysis for LAA emptying velocity to predict intracardiac thrombosis is performed. Using 15 cm/s as the cut off, LAA emptying velocity had a sensitivity of 70% and a specificity of 73%. By using 23 cm/s as the cut off, which is

		All Patients			Patients without AF		
Thrombus Status		With (n=42)	Without (n=114)	P value	With (n=8)	Without (n=48)	P value
LV end diastolic diameter, mm	45±8	43±8	46±7	0.02	44±9	45±8	0.77
LV end systolic diameter, mm	32±8	33±10	32±8	0.55	37±10	30±9	0.09
LV septal thickness, mm	15.7±3.9	16.3±3.6	15.3±3.9	0.20	15±3.7	14.9±3.6	0.95
LV posterior wall thickness, mm	14.8±3.3	15.8±3.2	14.4±3.2	0.02	14.4±3.1	13.9±3.1	0.67
RV free wall thickness, mm	8.8±2.5	9.5±2.9	8.5±2.3	0.08	9.8±2.3	8.6±2.5	0.33
LA volume index, ml/m^2)	48±22	51±17	47±23	0.38	43±7	41±29	0.90
RA enlargement (0-3)	2 (0-3)	3 (1-3)	2 (0-3)	0.008	2 (1-3)	1 (0-3)	0.10
Normal RA, %	15	5	19	0.04	0	40	0.20
Mild RAE, %	14	7	16		29	18	
Moderate RAE, %	26	29	25		29	12	
Severe RAE, %	45	59	40		42	30	
Stroke volume, mL	65±23	51±18	71±23	0.0009	40±11	73±26	0.001
CI, L/m^2/min	2.6±0.8	2.3±0.6	2.8±0.9	0.0002	1.9±0.5	2.9±1.0	0.008
LVEF, %	50.9±14.9	43.2±13.7	53.8±14.4	0.0001	37.8±15	56±15	0.002
Median LV diastolic function	3 (1-4)	3 (3-4)	2 (1-3)	0.0001	4 (3-4)	2(1-3)	0.0002
Normal LV diastolic function, %	1	0	1	0.0001	0	2	0.0001
LV diastolic function 1, %	14	0	18		0	35	
LV diastolic function 2, %	31	8	39		0	35	
LV diastolic function 3, %	43	59	38		43	26	
LV diastolic function 4, %	11	33	4		57	2	
Mitral deceleration time, ms	181±54	159±39	188±56	0.004	144±24	195±65	0.09
Mitral E velocity, m/s	0.94±0.29	0.93±0.26	0.94±0.31	0.85	0.90±0.24	0.96±0.33	0.70
Mitral A velocity, m/s	0.44±0.33	0.21±0.18	0.52±0.33	0.0001	0.28±0.10	0.64±0.35	0.0003
E/A	2.7±1.9	3.9±2.2	2.3±1.6	0.001	5.0±3.0	2.1±1.9	0.004
Mitral annulus s' velocity, cm/s	4.6±1.8	3.7±1.8	4.9±1.7	0.008	3.0±1.0	5.3±1.6	0.01
Mitral annulus e' velocity, cm/s	4.5±1.8	3.6±1.4	4.8±1.9	0.002	3.5±1.0	5.0±2.0	0.09
Mitral annulus a' velocity, cm/s	3.0±2.6	1.8±2.1	3.6±2.9	0.01	2.0±1.0	4.6±3.1	0.11
E/e'	23±12	29±15	21±10	0.002	27±13	21±11	0.21
PV systolic velocity, m/s	0.35±0.18	0.28±0.18	0.38±0.18	0.009	0.22±0.11	0.46±0.18	0.007
PV diastolic velocity, m/s	0.62±0.20	0.64±0.18	0.61±0.20	0.45	0.67±0.23	0.55±0.22	0.23
PV A velocity, m/s	0.21±0.14	0.13±0.11	0.23±0.14	0.004	0.10±0.12	0.27±0.16	0.03
PV diastolic/systolic ratio	2.4±1.8	3.0±1.7	2.2±1.8	0.05	3.1±0.7	1.5±1.2	0.008
RV systolic pressure, mm Hg	42.7±12.3	44.4±11.6	42.1±12.6	0.33	40±9	41±14	0.89

Table 8. TTE characteristics in patients with and without intracardiac thrombosis

comparable as reported previously,[33] the sensitivity increased to 100% but specificity decreased to 53%. The area under curve was 0.81. Using grade 3 as a cut off value for LV diastolic function, it had a sensitivity of 92% and a specificity of 59%. The area under curve was 0.82.

No significant differences existed in intracardiac thrombosis between LV diastolic function grade 2 and grade 1 [0% (0/21) vs. 7% (3/46), p=0.49]. The prevalence of intracardiac thrombosis was 44% for grade 3 or 4. Comparing restrictive filling pattern (grade 3 or 4 diastolic function) with non restrictive filling pattern (grade 1 or 2), the OR for intracardiac thrombosis is 17.1 with 95% CI 5.9-73.8, p<0.0001, by univariate analysis.

	All Patients				Patients without AF		
Thrombus Status	All (n=156)	With (n=42)	Without (n=114)	P value	With (n=8)	Without (n=48)	P value
LAA emptying velocity, cm/s	23 ± 14	13 ± 5	27 ± 15	0.0001	11±2	35±17	0.03
LAA spontaneous contrast (%)	61	92	50	0.0001	100	30	0.004
No LAA spontaneous contrast (%)	39	8	50	0.0001	0	71	0.0001
LAA spontaneous contrast 1 (%)	8	0	11		0	11	
LAA spontaneous contrast 2 (%)	17	14	18		0	9	
LAA spontaneous contrast 3 (%)	36	78	22		100	9	
Medium LAA spontaneous contrast	2 (0-3)	3 (1-3)	1 (0-3)	0.0001	3 (3-3)	0 (0-2)	0.0001
No LA spontaneous contrast (%)	39	8	50	0.0001	0	73	0.001
LA spontaneous contrast 1 (%)	9	0	13		0	9	
LA spontaneous contrast 2 (%)	29	46	23		40	11	
LA spontaneous contrast 3 (%)	23	46	14		60	7	
Medium LA spontaneous contrast	2 (0-3)	2 (2-3)	0 (0-2)	0.0001	2 (2-3)	0 (0-2)	0.0001
Atherosclerosis (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	0.63	1 (0-1)	1 (0-2)	0.96

Table 9. TEE characteristics in subjects with and without intracardiac thrombosis

Dependent Variate	Models *	Predictors	OR	95 % CI	P value
Thrombosis	Model 1	AL type	2.3	0.96-5.6	0.06
		AF	6.8	2.5-20.7	0.0001
		Anticoagulation	0.2	0.07-0.47	0.0003
		SBP	0.7	0.55-0.87	0.0008
	Model 2	LV diastolic function@	10.6	1.5-220.3	0.04
	Model 3	LAA emptying velocity$	0.2	0.05-0.57	0.002
	Model 4	AF	11.8	1.0-395.2	0.05
		Anticoagulation	0.09	0.01-0.51	0.006
		LV diastolic function@	15.2	7.5->999.9	0.008
		LAA emptying velocity$	0.1	0.01-0.32	0.0001

* Model 1: Clinical variates included are amyloid type, AF, anticoagulation, HR and SBP (with 10 mmHg increase).

Model 2: TTE variables included are LV diastolic function (@: grade 3 or 4 versus grade 2 or less), LVEF, SV, and mitral A velocity.

Model 3: TEE variables included are LAA emptying velocity ($: increase in 10cm/s in velocity), spontaneous echo contrast in LA and LAA (semi-quantification as 0-3).

Model 4: Combined model included amyloid type, AF, anticoagulation, SBP, LV diastolic function, and LAA emptying velocity.

Table 10. Predictors for thromboembolism by multivariate analyses

Multivariate analysis with AF, LAA emptying velocity, and LV diastolic function as dependent variables increased area under curve to 0.85. When further stratifying thrombosis risk based on LAA emptying velocity and LV diastolic function, we found 0% intracardiac thrombosis in patients with LAA emptying velocity > 15 cm/s and LV diastolic function grade ≤ 2, 26 % in patients with either LAA emptying velocity ≤ 15 cm/s or LV diastolic grade 3 or 4, and 67% in patients who had both ($p<0.0001$). Similar results were obtained after further stratification by AF. The respective prevalence of intracardiac thrombosis was 0%, 15%, and 50% for non AF patients ($p=0.02$), and 0%, 32%, and 72% for AF patients ($p=0.002$).

4.10 Clinical implications of TEE study

Our data from a large TEE study of patients with different types of cardiac amyloidosis confirms our previous autopsy study describing a high frequency of intracardiac thrombosis. We were able to identify that AF, poor LV diastolic function, and LA mechanical dysfunction as indicated by a low LAA emptying velocity were independent predictors of intracardiac thrombosis. Furthermore, it appears from our data that therapeutic anticoagulation therapy protects against intracardiac thrombosis. Low systolic blood pressure also was independently associated with increased risk for intracardiac thrombosis while AL type cardiac amyloidosis had a borderline trend when only clinical variables were considered for multivariates analyses.

4.11 Intracardiac thrombosis in cardiac amyloidosis

Our TEE study confirms the observations of Roberts and our prior autopsy study which showed a high prevalence of intracardiac thrombosis in cardiac amyloidosis.[4] AL type was associated with a 35% prevalence of intracardiac thrombosis compared to 18% in the other amyloid groups despite the fact that the other amyloid groups were older and more frequently had AF. The prevalence of intracardiac thrombosis in TTR related amyloid (either wild or mutant TTR) is comparable to that reported in the AF population without anticoagulation.[36-38] In comparison, AL patients have a higher prevalence of intracardiac thrombosis than that reported in the general non amyloid AF population.[36-38] In fact, the prevalence of intracardiac thrombosis is comparable to that reported in patients with severe mitral valve stenosis with AF, which had the highest prevalence of intracardiac thrombosis (33%).[39]

4.12 Clinical variables and intracardiac thrombosis

In our current study, AF and low systolic BP were independently associated with thrombosis. A low SBP may reflect a low cardiac out put status and severe amyloid heart disease with cardiac decompensation. Most importantly, we identified that therapeutic anticoagulation was significantly associated with a decreased risk for intracardiac thrombosis by both univariate and multivariate analyses.

Clinical HF and NYHA class were not significantly different in patients with or without thrombosis as observed in the Mayo autopsy study.[13] Because many patients were elderly with multiple comorbidities, the clinical diagnosis of HF or NYHA class is a subjective indicator of over all well being and may not be always accurate for grading the severity of heart failure. Moreover, other traditional risk factors for thromboembolism such as age, diabetes and hypertension were not significantly associated with intracardiac thrombosis.

We speculated that risk factors with only modest effect could not be detected in this special study population, in which overwhelming effects from AL type, AF, and anticoagulation therapy are likely to have masked their modest effects.

4.13 TTE, TEE characters and intracardiac thrombosis

Univariate analysis showed that the group with thrombi had evidence of more advanced cardiac amyloid deposition as indicated by a smaller LV end diastolic dimension, a thicker LV wall, and also poorer LV systolic and diastolic function, a higher LV filling pressure estimated by E/e' as well as less LA mechanical activity than the group without thrombi. Furthermore, LA and LAA spontaneous contrast were more often present and more pronounced in those with intracardiac thrombi. Similar TTE and TEE results were obtained after exclusion of AF patients. Therefore, AF only plays a partial role for intracardiac thrombosis. Multivariate analyses showed that the only two echo variable: i.e. LV diastolic dysfunction and low LAA emptying velocity, in addition to AF, were independently associated with intracardiac thrombosis. The Mayo autopsy and TEE studies and prior study support the hypothesis that the combination of systolic and diastolic ventricular dysfunction and chronic amyloid infiltrate in the atria lead to atrial mechanical dysfunction,[17,24] atrial enlargement, and blood stasis.[23,27] Such atrial electrical-mechanical dissociation at least partially explains why some cardiac amyloid patients developed atrial thrombosis while in sinus rhythm.[17, 24, 28]

4.14 Anticoagulation and intracardiac thrombosis

We identified that therapeutic anticoagulation therapy at the time of TEE was associated with a significant lower risk for intracardiac thrombosis. Thus, effective anticoagulation might reduce thromboembolism, which is a significant contributor for mortality in cardiac amyloid patients.[13] However, anticoagulation may exacerbate the hemorrhagic tendency, which is a well known complication of amyloidosis because of fragile blood vessel walls secondary to amyloid deposition and the coexisting coagulopathy in such patients.[2,31] In our prior autopsy series, three cardiac amyloid patients died from massive gastrointestinal bleeding.[13] Therefore, the potential benefits of anticoagulation must be carefully weighed against possible hemorrhagic complications before anticoagulation is initiated.

5. Further directions

A recent study suggests that chemotherapy in AL patients with cardiac involvement results in a clinical improvement despite an unchanged TTE appearance.[40] Improvement may be due to the abolition of the production of new light chains, which are toxic to myocardium by increasing oxidant stress and causing diastolic dysfunction.[26,41] Furthermore, there has been report of echocardiographic improvement and decreased amyloid accumulation by 99m Tc-PYP scintigram after chemotherapy and stem cell transplant.[42] Therefore, it is possible that early detection of amyloidosis, vigilant screening for intracardiac thrombosis with early anticoagulation, and more aggressive treatment of the underlying plasma dyscrasia might improve the prognosis. [3,23,43,44] Because of retrospective study design and limited number of patients on anticoagulation, we could not evaluate whether anticoagulation will prevent thromboembolism. Further prospective study is needed to specifically answer this question.

6. Summary

We demonstrated a high frequency of intracardiac thrombosis in patients with cardiac amyloidosis from both autopsy study and from TEE study. The risk for intracardiac thrombosis and thromboembolism is especially high in patients who had the AL type, presented with AF, had poor LV diastolic function, and poor atrial mechanical function were independently associated with increased risk. Importantly, therapeutic anticoagulation therapy appeared protective against intracardiac thrombosis. Early screening for intracardiac thrombosis by TEE, especially in the high risk patient as identified in our studies, may be indicated. If intracardiac thrombosis or severe LAA mechanical dysfunction (especially with coexisting restrictive LV filling) is detected, anticoagulation should be carefully considered.

7. References

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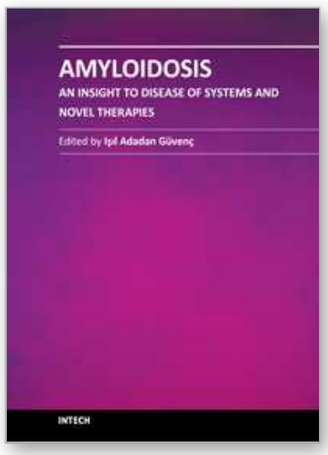

Amyloidosis - An Insight to Disease of Systems and Novel Therapies

Edited by Dr. Işıl Adadan Güvenç

ISBN 978-953-307-795-6
Hard cover, 194 pages
Publisher InTech
Published online 16, November, 2011
Published in print edition November, 2011

Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of interest for many researchers and there have been a growing number of case reports in the literature for the last decade. The aim of this book is to help the reader become familiar with the presentation, diagnosis and treatment modalities of systemic and localized amyloidosis of specific organs or systems and also cover the latest advancements in therapy.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Dali Feng, Kyle Klarich and Jae K. Oh (2011). Intracardiac Thrombosis, Embolism and Anticoagulation Therapy in Patients with Cardiac Amyloidosis – Inspiration from a Case Observation, Amyloidosis - An Insight to Disease of Systems and Novel Therapies, Dr. Işıl Adadan Güvenç (Ed.), ISBN: 978-953-307-795-6, InTech, Available from: http://www.intechopen.com/books/amyloidosis-an-insight-to-disease-of-systems-and-novel-therapies/intracardiac-thrombosis-embolism-and-anticoagulation-therapy-in-patients-with-cardiac-amyloidosis-in

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