Intracardiac Thrombosis and Embolism in Patients With Cardiac Amyloidosis

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Background—Patients with primary amyloidosis (AL type) have a poor prognosis, in part due to frequent cardiac involvement. Although intracardiac thrombus has been reported in anecdotal cases, neither its frequency nor its role in causing mortality is known. Furthermore, the clinical and echocardiographic variables that may be associated with thromboembolism in cardiac amyloidosis have not been defined.

Methods and Results—A total of 116 autopsy or explanted cases of cardiac amyloidosis (55 AL and 61 other type) were identified in the Mayo Clinic. Forty-six fatal nonamyloid trauma cases served as controls. Each heart was examined for intracardiac thrombus. The cause of death was determined from autopsy and clinical notes. Intracardiac thrombosis was identified in 38 hearts (33%). Twenty-three had 1 thrombus, whereas 15 had 2 to 5 thrombi. Although subjects in the AL group were younger and had less atrial fibrillation than those with other types of amyloidosis, the AL group had significantly more intracardiac thrombus (51% versus 16%, \( P<0.001 \)) and more fatal embolic events (26% versus 8%, \( P<0.03 \)). Control hearts had no intracardiac thrombus. The presence of both atrial fibrillation and AL was associated with an extremely high risk for thromboembolism (odds ratio 55.0 [95% confidence interval 8.1 to 1131.4]). By multivariate analysis, AL type (odds ratio 8.4 [95% confidence interval 1.8 to 51.2]) and left ventricular diastolic dysfunction (odds ratio 12.2 [95% confidence interval 2.7 to 72.7]) were independently associated with thromboembolism.

Conclusions—A high frequency of intracardiac thrombosis was present in cardiac amyloidosis. Furthermore, thromboembolism caused significant fatality. Several risk factors for thromboembolism were identified. Early screening, especially in high-risk patients, and early anticoagulation might reduce morbidity and mortality.

Key Words: amyloid | thrombus | arrhythmia | echocardiography | diastole

Amyloidosis is uncommon. Data from Olmsted County, Minn, reflect age-adjusted incidences between 6.1 and 10.5 per million person-years.\(^1\) It is estimated that 1275 to 3200 new cases occur annually in the United States.\(^1,2\) Amyloidosis is classified by the precursor plasma proteins that form 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 (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 (LV) 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 from either arrhythmia or electromechanical dissociation.\(^8\) However, systematic studies evaluating the causes of death are lacking.

Clinical Perspective

We recently encountered 2 AL patients with intracardiac thrombosis and pulmonary and systemic emboli that led to death. Both patients were in sinus rhythm with well-preserved LV ejection fraction (LVEF). Only a few similar cases have been reported in the literature.\(^9-12\) The frequency of intracardiac thrombosis and its relationship to thromboembolic complications and mortality are unknown. 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.
Methods

Study Groups
We searched the Mayo Clinic Tissue Registry database for cases of cardiac amyloidosis from 1996 to 2005. 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 nonamyloid fatal trauma cases. The study was approved by the Mayo Clinic Institutional Review Board.

Clinical Data
Clinical information, including demographic data, comorbidities, presence of congestive heart failure (CHF), New York Heart Association (NYHA) functional class, use of anticoagulants, ECGs, echocardiograms, and other laboratory data were abstracted from clinical records. Cardiac rhythm was determined from the patient’s ECG and Holter monitoring data. Other abstracted information included results of bone marrow biopsies, urine and serum protein electrophoreses, immunofixation, serum free light chain assay, genetic testing, and family history.

Transthoracic Echocardiogram
Transthoracic echocardiograms (TTEs) were obtained in 82 of 116 patients. The TTE was reviewed independently without knowledge of the clinical and pathological data. TTE parameters extracted included LVEF, LV end-diastolic diameter, LV end-systolic diameter, 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, and 3=severe), LV diastolic function grade,13 mitral inflow E and A velocity, deceleration time, mitral septal annulus tissue Doppler velocity (early [e'] and late [a'] peak diastolic velocity), and pulmonary venous flow velocity profile (peak systolic velocity [S], peak diastolic velocity [D], D/S, and atrial contractile velocity), E/A, and E/e'.13 Heart rate (HR) and blood pressure (BP) at the time of TTE were documented. Inconsistencies between the reports and the reviews were adjudicated by a third cardiologist.

Pathology Data
All cardiac chambers were examined for thrombi. Tumor emboli 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, a and k free immunoglobulin light chains, transthyretin (prealbumin), amyloid A component, and B-2 microglobulin.

Cause of Death
Autopsy reports were evaluated by a pathologist and a cardiologist without knowledge of the patient’s clinical diagnosis (ie, trauma, amyloidosis, amyloidosis type, or cardiac rhythm). Death was considered due to a thromboembolic cause if (1) major acute pulmonary emboli were present, irrespective of pulmonary infarction; (2) mesenteric artery embolism with bowel infarction was present; (3) major embolic stroke with associated intracranial hemorrhage was present, or if emboli were the cause of complications such as aspiration pneumonia and death; (4) renal infarcts were present with renal failure; or (5) death occurred during or shortly after surgical intervention for emboli.

Statistical Analysis
Data are expressed as mean±SD for continuous and ordinal variables and as percentages for categorical data. χ2 Tests were used to compare categorical data. Unpaired Student t tests were used to compare continuous variables. Wilcoxon rank-sum test was used to compare ordinal variables.

Univariate and multivariate analyses were performed to identify factors associated with thromboembolism. Multivariate analysis was performed with nominal logistic regression. Variables significant with a probability value ≤0.05 in univariate analysis were included in multivariate analyses. Nonsignificant variables were removed. Results are reported with odds ratio (OR), 95% confidence interval (CI), and probability value.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 1. Patient Characteristics in AL and Other Amyloid Groups

<table>
<thead>
<tr>
<th></th>
<th>AL (n=55)</th>
<th>Other Amyloid (n=61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±11</td>
<td>83±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>61</td>
<td>62</td>
<td>0.80</td>
</tr>
<tr>
<td>Ethnic, % white</td>
<td>100</td>
<td>100</td>
<td>0.53</td>
</tr>
<tr>
<td>AF, %</td>
<td>22</td>
<td>45</td>
<td>0.008</td>
</tr>
<tr>
<td>Anticoagulation, %</td>
<td>26</td>
<td>37</td>
<td>0.21</td>
</tr>
<tr>
<td>Survival time, mo</td>
<td>23±25</td>
<td>63±12</td>
<td>0.01</td>
</tr>
<tr>
<td>CAD by autopsy, %</td>
<td>10</td>
<td>90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD severity score*</td>
<td>1.5 (1.2–1.5)</td>
<td>3.3 (2.9–3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac mass, g</td>
<td>532±150</td>
<td>474±132</td>
<td>0.017</td>
</tr>
<tr>
<td>LV septal thickness, mm</td>
<td>16.5±4.2</td>
<td>16.0±4.2</td>
<td>0.26</td>
</tr>
<tr>
<td>LV posterior wall, mm</td>
<td>16.0±3.5</td>
<td>14.7±3.8</td>
<td>0.029</td>
</tr>
<tr>
<td>RV free wall, mm</td>
<td>6.0±2.4</td>
<td>4.9±1.7</td>
<td>0.006</td>
</tr>
<tr>
<td>CHF, %</td>
<td>77</td>
<td>63</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean NYHA class (1–4)</td>
<td>2.8±1.2</td>
<td>2.1±1.2</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>50±18</td>
<td>52±16</td>
<td>0.66</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>2.3±1.5</td>
<td>1.8±1.1</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Results

Demographic Data
Ages ranged from 31 to 101 years (mean 72±16 years). Sixty-one percent of case subjects were men. In the control group, mean age was 55±27 years; 69% were men. Demographic data for the amyloidosis patients are shown in Table 1. Because limited data were available for the control trauma group, the demographic data in Table 1 are only for the amyloidosis cases.

Amyloid Subtypes
Fifty-five AL cases, 55 wild-type transthyretin cases, 4 AA types, and 2 familial types were included in the study. Because AA and familial types are rare (n=6), they were combined into 1 group with the transthyretin cases (called “other,” n=61). Results were similar with and without these 6 cases. Compared with the other amyloidosis group, AL subjects were younger, had less atrial fibrillation (AF), had a shorter survival time from the onset of symptoms, and less commonly had coronary artery disease (CAD; Table 1). AL subjects had thicker ventricular architecture than other subjects. No significant differences in CHF history were evident between the 2 groups, but those with the AL type of amyloidosis had higher values for NYHA class. No differences were evident in gender, ethnicity, creatinine, or LVEF (all P>0.05).

Data are shown as mean±SD or mean (95% CI), unless otherwise indicated.

*CAD severity score at autopsy (range of 0 to 4): 0=none, 1=minimal, 2=mild, 3=moderate, and 4=severe.
Intracardiac Thrombus

Intracardiac thrombi were identified in 38 (33%) of 116 hearts. Twenty-three had 1 thrombus, whereas 15 had 2 to 5 thrombi, for a total of 63 thrombi. Thirty-six of these thrombi 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 thrombi were identified in the 46 subjects with fatal trauma. Significant differences existed in the frequency of intracardiac thrombosis between the cardiac amyloidosis group and the control group (33% versus 0%, \( P < 0.0001 \)). The AL group had more intracardiac thrombi than the other amyloidosis group (51% versus 16%, \( P < 0.0001 \)). Of the 4 AA cases, 2 had intracardiac thrombus. No thrombi occurred in the familial cases.

Embolic Events and Cause of Death

Twenty-three embolic events occurred in patients with amyloidosis. Nineteen emboli were fatal and 4 were nonfatal. AL patients had more fatal thromboemboli (14 or 53, 26%) than the other amyloidosis patients (5 of 59; 8%) and the control group (1 of 46, 2%; \( P < 0.0001 \)). Embolic fatalities for the AL group included 7 pulmonary emboli, 1 mesentery artery embolus with bowel infarction, 1 iliac artery embolus (the patient died during attempted embolectomy), and 5 with multiple emboli. In addition, 4 nonfatal embolic events occurred in the AL group, including 3 found at autopsy and 1 patient with pulmonary emboli and brachial artery embolism who survived after cardiac transplantation. In the other amyloidosis group, 5 embolic fatalities occurred, including 3 pulmonary emboli, 1 mesenteric artery embolus with bowel infarction, and 1 case with multiple systemic emboli.

Clinical Characteristics, TTE, and Thromboembolism

Forty-five subjects (40%) had intracardiac thrombus, embolism, or both. Compared with the group without thromboembolism, they were younger, were less often hypertensive, had more AL type, and had a lower systolic BP (Table 2). The thromboembolic group had less CAD, and when CAD was present, less extensive involvement. Other demographic and clinical variables were similar.

### Table 2. Characteristics in Patients With and Without Thromboembolism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With (n=45)</th>
<th>Without (n=71)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±2.2</td>
<td>77±1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>58</td>
<td>62</td>
<td>0.67</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.0±0.9</td>
<td>26.7±0.8</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>17</td>
<td>41</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7</td>
<td>19</td>
<td>0.08</td>
</tr>
<tr>
<td>CHF, %</td>
<td>65</td>
<td>71</td>
<td>0.55</td>
</tr>
<tr>
<td>NYHA class (1–4)</td>
<td>2.4±1.3</td>
<td>2.3±1.2</td>
<td>0.65</td>
</tr>
<tr>
<td>AF, %</td>
<td>37</td>
<td>33</td>
<td>0.64</td>
</tr>
<tr>
<td>Anticoagulation, %</td>
<td>36</td>
<td>28</td>
<td>0.42</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>15</td>
<td>22</td>
<td>0.41</td>
</tr>
<tr>
<td>Syncope, %</td>
<td>34</td>
<td>17</td>
<td>0.08</td>
</tr>
<tr>
<td>AL amyloidosis, %</td>
<td>73</td>
<td>31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stem cell transplant, %</td>
<td>23</td>
<td>10</td>
<td>0.09</td>
</tr>
<tr>
<td>Recent operation, %</td>
<td>10</td>
<td>17</td>
<td>0.31</td>
</tr>
<tr>
<td>History of thrombosis, %</td>
<td>27</td>
<td>24</td>
<td>0.76</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>111±18</td>
<td>128±24</td>
<td>0.0005</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>67±12</td>
<td>69±15</td>
<td>0.54</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>2.2±1.7</td>
<td>1.9±1.1</td>
<td>0.17</td>
</tr>
<tr>
<td>CAD by autopsy, %</td>
<td>29.3</td>
<td>55.4</td>
<td>0.008</td>
</tr>
<tr>
<td>CAD severity score (0–4)</td>
<td>2.0±1.2</td>
<td>2.7±1.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD unless otherwise indicated.

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

TTE features are given in Table 3. Times from TTE to death were similar. The thromboembolic group had a higher HR at TTE, a smaller LV end-diastolic diameter, thicker LV posterior and RV walls, smaller stroke volume, lower RV systolic pressure, lower LV EF, worse LV diastolic function, a shorter deceleration time, poorer LA mechanical activity (lower A and a’ velocity), and higher E/A and E/e’ than the nonthromboembolic group (all \( P \leq 0.05 \)). Furthermore, pulmonary venous flow peak systolic velocity and A velocity were significantly lower, and D/S was higher. LA volume index and RA size were not different (Table 3). The RV wall was thicker in subjects who had RA thrombosis than in those who did not (7.9±2.7 versus 6.6±3.1 mm, \( P = 0.02 \)).

Multivariate Analysis and Receiver Operating Characteristic Curve

By multivariate analysis, AL type (OR 15.6, 95% CI 2.8 to 117.6, \( P = 0.001 \)) and AF (OR 6.0, 95% CI 1.7 to 26.7, \( P = 0.004 \)) were independently associated with thromboembolism in a model with clinical variables (Table 4), with high OR for both (OR 55.0, 95% CI 8.1 to 1131.5, \( P < 0.0001 \)). For TTE variables, RV wall thickness (OR 1.3, 95% CI 1.0 to 1.7, \( P = 0.03 \)) with 1-mm increase in the wall, LV diastolic function (OR 8.8, 95% CI 1.6 to 64.1, \( P = 0.01 \)) with restrictive pattern (grade 3 or 4) compared with grade 2 or less, and HR at echocardiography (OR 1.7, 95% CI 1.1 to 2.9, \( P = 0.02 \)) with a 10-bpm increase were independently associated with thromboembolism. No differences existed in thromboembolic risk between LV diastolic function grade 2 and
Table 3. TTE Characteristics in Subjects With and Without Thromboembolism

<table>
<thead>
<tr>
<th></th>
<th>With (n=35)</th>
<th>Without (n=47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from TTE to death, d</td>
<td>15 (1-55)</td>
<td>43 (2-209)</td>
<td>0.12</td>
</tr>
<tr>
<td>HR at echocardiography, bpm</td>
<td>86±17</td>
<td>79±14</td>
<td>0.02</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>44.3±7.8</td>
<td>48.1±8.1</td>
<td>0.04</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>32.4±9.3</td>
<td>33.1±9.8</td>
<td>0.76</td>
</tr>
<tr>
<td>LV septal thickness, mm</td>
<td>14.2±3.9</td>
<td>12.9±3.3</td>
<td>0.12</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>13.8±3.6</td>
<td>12.2±3.1</td>
<td>0.03</td>
</tr>
<tr>
<td>RV free wall thickness, mm</td>
<td>8.3±3.6</td>
<td>5.9±2.1</td>
<td>0.0007</td>
</tr>
<tr>
<td>LA volume index, mL/m²</td>
<td>40.1±14.9</td>
<td>48.2±35.2</td>
<td>0.21</td>
</tr>
<tr>
<td>RA enlargement (0–3)</td>
<td>1.8±1.2</td>
<td>1.4±1.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>51.1±20.9</td>
<td>67.6±23.4</td>
<td>0.002</td>
</tr>
<tr>
<td>RV systolic pressure, mm Hg</td>
<td>44.3±9.4</td>
<td>51.1±15.9</td>
<td>0.045</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>46±19</td>
<td>54±15</td>
<td>0.03</td>
</tr>
<tr>
<td>LV diastolic function grade (0–4)</td>
<td>3.1±1.1</td>
<td>1.9±0.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mitral deceleration time, ms</td>
<td>160±37</td>
<td>193±60</td>
<td>0.006</td>
</tr>
<tr>
<td>Mitral E velocity, m/s</td>
<td>0.87±0.21</td>
<td>0.90±0.26</td>
<td>0.65</td>
</tr>
<tr>
<td>Mitral A velocity, m/s</td>
<td>0.27±0.29</td>
<td>0.52±0.33</td>
<td>0.0008</td>
</tr>
<tr>
<td>E/A</td>
<td>3.4±2.6</td>
<td>2.0±1.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral annulus e′, velocity, cm/s</td>
<td>4.4±2.3</td>
<td>5.9±2.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Mitral annulus a′, velocity, cm/s</td>
<td>2.3±3.3</td>
<td>6.6±4.7</td>
<td>0.003</td>
</tr>
<tr>
<td>E/e′</td>
<td>23±12</td>
<td>16±8</td>
<td>0.02</td>
</tr>
<tr>
<td>PV systolic velocity, m/s</td>
<td>0.32±0.18</td>
<td>0.48±0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>PV diastolic velocity, m/s</td>
<td>0.65±0.20</td>
<td>0.60±0.18</td>
<td>0.37</td>
</tr>
<tr>
<td>PV A velocity, m/s</td>
<td>0.14±0.13</td>
<td>0.24±0.13</td>
<td>0.008</td>
</tr>
<tr>
<td>PV diastolic/systolic ratio</td>
<td>3.0±2.3</td>
<td>1.5±0.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD. PV indicates pulmonary venous flow.

Discussion

The present data from a large autopsy study of patients with cardiac amyloidosis identify 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 mortality. We identified AL type, AF, poor LV diastolic function, RV wall thickness by TTE, and higher HR as independent predictors for thromboembolism. Many risk factors in patients without amyloidosis, such as age, CHF, hypertension, and diabetes mellitus, were not significantly associated with thromboembolism. 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 and not in multivariate analyses.

Intracardiac Thrombosis in Cardiac Amyloidosis

The high incidence of intracardiac thrombosis in the present study confirms the observations by Roberts and Waller. AL type was associated with a 51% incidence compared with only 16% in the other amyloidosis groups despite the fact that those groups were older and more frequently had AF. Apart from case reports and a small autopsy study, the present investigation is the only study to report the high frequency of intracardiac thrombosis and clinical thromboembolic complications that resulted in mortality. Roberts and Waller retrospectively studied 49 AL and 5 familial amyloidosis-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, and thrombosis was associated with increased mortality. Common features of previous reports include middle-aged 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, as in the present study.

Intracardiac Thrombosis and Embolism

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

Clinical Variables and Thromboembolism

Several studies show that advanced age, AF, CHF, diabetes mellitus, and hypertension are risk factors for thromboembolism in nonamyloidosis patients. In the present study, the mean age was younger in patients with thromboembolism. This is because patients with primary amyloidosis were much younger than patients with nonprimary amyloidosis, and they were 8.4 times more likely to develop thromboembolism. Thromboembolic patients also had fewer comorbidities because of their younger age. By multivariate analyses, only 2 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 underlying severity of disease and therefore indicates decompensation.

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 of patients in the present study was significantly greater in the groups with nonprimary amyloidosis. After adjustment 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 by TTE and intracardiac thrombosis and embolism. Because many patients were elderly and had multiple comorbidities, the clinical diagnosis of CHF or NYHA class is a subjective indicator of overall well-being and may not always be accurate. TTE with structure and function evaluation (including diastolic measures) provides more comprehensive information and is more helpful for risk stratification.

TTE Characteristics and Thromboembolism

Multivariate analyses showed that only LV diastolic function, 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. This observation was not surprising, because LV diastolic function was graded on the basis of several echocardiographic features, including mitral inflow profile and mitral tissue Doppler imaging.

RV wall thickness is associated with abnormal RV diastolic function. Advanced RV infiltrate by amyloid (>7 mm) was associated with a restrictive tricuspid inflow filling pattern; lesser thickness was associated with abnormal RV relaxation. In the present 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 poor RV diastolic function and consequent stasis and thrombosis.

LA volume index and RA size were not significantly different in patients with and without thromboembolism, although the indexes were large in both (>40 mL/m²). One would speculate that atrial size should be greater 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. We do not have a data-driven explanation for these findings. In the present 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, and thromboembolic patients were younger and had fewer comorbidities. Finally, it is possible that amyloid infiltrate in the atria prevented the atria from being distended, as suggested by Modesto et al with strain imaging.

Mechanism for Thromboembolism
The mechanisms for intracardiac thrombosis in cardiac amyloid patients are unclear. It is possible that endomyocardial damage and endothelial dysfunction from amyloid deposition may be responsible. Hypercoagulability may also contribute.

The present TTE data support the concept that stasis could lead to intracardiac thrombosis. Even though the mean LVEF was relatively preserved, those with intracardiac thrombosis had lower LVEF. Furthermore, LV diastolic function and atrial mechanical activity were more impaired in patients with intracardiac thrombosis. Reduced atrial contractility secondary to amyloid infiltration has been reported previously, and LV diastolic function is typically impaired before systolic function. The combination of systolic and diastolic ventricular dysfunction, chronic amyloid infiltrate in the atria, and a direct toxic effect on myocardium could lead to atrial mechanical dysfunction, atrial enlargement, and blood stasis. Such atrial electrical-mechanical dissociation may explain in part why patients in the present study developed atrial thrombosis while in sinus rhythm.

Future Directions
TTE is known for its insensitivity in detecting intracardiac thrombosis, especially in the atria. Therefore, transesophageal echocardiography may be indicated for earlier detection in high-risk patients. If intracardiac thrombosis is detected, anticoagulation therapy may be indicated; however, anticoagulation may exacerbate the hemorrhagic tendency that is known to occur in amyloidosis because of fragile blood vessel walls secondary to amyloid deposition and the coexisting coagulopathy. Three AL amyloid patients in the present study died of massive gastrointestinal bleeding.

A recent study suggests that chemotherapy in AL patients with cardiac involvement results in clinical improvement despite an unchanged TTE appearance. Improvement may be due to abolition of the production of fresh light chains, which are toxic to myocardium because they increase oxidant stress and cause diastolic dysfunction. 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 with chemotherapy, stem cell transplantation, and possibly cardiac transplantation might improve the prognosis. Prospective data are needed.

Study Limitations
The high frequency of intracardiac thrombosis could be related in part to referral bias in our tertiary practice. On the other hand, the frequency of embolism could be underestimated, because small emboli may have been overlooked. In addition, 26 cases were excluded from our initial sample because of incomplete clinical data or missing tissue, and TTEs were not obtained in all patients. Thus, selection bias could be introduced. For example, those who did have TTE were younger (69±15 versus 79±16 years, P<0.001), were more likely to have the AL type of amyloid (56% versus 32%, P=0.04), and had larger cardiac mass (518±146 versus 459±127 g, P=0.04) than those who did not have TTE. No significant differences existed in gender, AF, history of CHF, NYHA class, anticoagulation, frequency of intracardiac thrombosis, RV and LV wall thickness, or CAD (all P>0.05; data not shown). Because few patients had transesophageal echocardiography, we could not evaluate spontaneous echocardiographic contrast and LA appendage peak velocity, which are better surrogates for blood stasis and LA mechanical function. Because of the retrospective study design and limited number of patients undergoing anticoagulation, we could not evaluate whether anticoagulation would prevent thromboembolism. Further prospective study is needed to specifically answer this question. Finally, even though the present study is the largest autopsy study thus far to address thromboembolism in amyloidosis patients, it consisted of only 45 events and therefore may have lacked the power to detect factors that only have mild to moderate effects on thromboembolism. Moreover, CIs for the ORs were wide, particularly for the group with AF and AL amyloid, because of the relatively small sample size.

Summary
A high frequency of intracardiac thrombosis was present in patients with cardiac amyloidosis, especially those with the AL type, despite the presence of 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 rate were associated with thromboembolism. Poor LV diastolic function and atrial mechanical activity likely contribute to the complication of intracardiac thrombosis. Early screening for intracardiac thrombosis by transesophageal echocardiography, especially in patients at high risk, may be indicated, and early anticoagulation should be considered.

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Disclosures
None.

References


CLINICAL PERSPECTIVE

The present study was designed to evaluate the frequency of intracardiac thrombosis and embolism in patients with cardiac amyloidosis after we observed an index case in which it occurred. We explored 116 autopsy or explanted hearts pathologically, echocardiographically, and clinically to investigate pathology, intracardiac thrombosis, and cause of death. A high frequency of intracardiac thrombosis was present in patients with cardiac amyloidosis (33%), especially among those with the AL type (51%), despite sinus rhythm and preserved left ventricular ejection fraction in the majority of the cases. Intracardiac thrombosis frequently was associated with embolic events and mortality. Often, embolic events were unnoticed clinically, and patients were thought to have died suddenly of arrhythmia. The presence of the AL type of amyloidosis, atrial fibrillation, poor left ventricular diastolic function, increased right ventricular wall thickness, and faster heart rates were associated with an increased risk for thromboembolism. Early screening for intracardiac thrombosis by transesophageal echocardiography, especially in patients who display clinical characteristics, would identify these cases as high risk. The role of early anticoagulation needs to be defined, but given the high frequency of embolism, it should be considered carefully.
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