Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation

Simon Dubrey, Arthur Pollak, Martha Skinner, Rodney H Falk

Abstract

Thrombus formation in the left atrium is rare in patients in sinus rhythm. In three patients with extensive cardiac amyloidosis transthoracic echocardiography showed large atrial thrombi in or protruding into the body of the left atrium during sinus rhythm. Doppler studies showed no A wave on mitral inflow. Severe atrial and ventricular infiltration by amyloid may have resulted in mechanical atrial standstill with resultant thrombus formation. These findings suggest that patients with severe cardiac amyloidosis may require anticoagulation when atrial function is impaired.

(*Br Heart J* 1995;74:541–544)

Keywords: amyloidosis; thrombus; atrial standstill

Boston University School of Medicine, Section of Cardiology, Boston, Massachusetts, USA
S Dubrey
A Pollak
R H Falk

Boston University School of Medicine, Arthritis Research Centre, Boston, Massachusetts, USA
M Skinner

Correspondence to:
Dr R H Falk, Boston University School of Medicine, Department of Cardiology, The Talbot Building 231 W, 80 East Concord Street, Boston MA 02118, USA.

Accepted for publication 20 April 1995

The formation of thrombus within the cardiac atria is related to factors that result in stasis of blood and most commonly occurs in atrial fibrillation.[1 2] In sinus rhythm thrombi are uncommon and when present (for example, in mitral stenosis) are usually found in the atrial appendages; thrombi in the body of the left atrium during sinus rhythm are exceptional and generally reported in patients with severe mitral stenosis.[3]

In amyloid heart disease the atria and ventricles are infiltrated with extracellular amyloid fibrils. Severe involvement is characterised by a small or absent A wave and a short E wave deceleration time on the Doppler velocity spectrum at the mitral valves.[4] Though this pattern is thought to be caused by restrictive ventricular physiology[5] it may also reflect impaired or absent atrial contractility[6 7] or a combination of both factors.

In support of the concept of atrial failure in amyloidosis we present three cases of cardiac amyloidosis in which atrial standstill, complicated by atrial thrombi, occurred in the presence of confirmed sinus rhythm.

Case 1

A 44 year old white woman presented with a history of rapidly progressive fatigue, shortness of breath, paroxysmal nocturnal dyspnoea, and several near syncopal episodes. Clinical examination showed sinus tachycardia with a blood pressure of 90/60 mm Hg, a considerable increase in jugular venous pressure, oedema to both knees, and a soft pansystolic murmur over the precordium.

The chest radiograph showed cardiomegaly. The electrocardiogram showed sinus rhythm at a rate of 125 beats per minute, low voltage complexes, first degree heart block, and a pseudo-infarction QS pattern in precordial leads V1 to V3. An echocardiogram showed a highly reflective pattern in the myocardium, normal ventricular volumes, decreased left ventricular systolic function, and a calculated ejection fraction of 30%. A small pericardial effusion was noted in addition to enlargement of both atria, with moderate mitral regurgitation and mild tricuspid regurgitation (table). A large thrombus (2·0 × 2·0) cm was present within the body of the left atrium (fig 1A and B). Pulsed wave Doppler examination of left ventricular inflow showed no A wave and a short E wave deceleration time (124 ms normal range 159–199 ms).[8] Cardiac catheterisation showed normal coronary arteries, and a right ventricular endomyocardial biopsy specimen was positive for amyloid by Congo red staining. The bone marrow contained 10–20% plasma cells. Although serum protein and immunoelectrophoresis were normal, examination by immunoelectrophoresis of the urine showed lambda light chains.

The patient was diagnosed as having primary amyloidosis with severe cardiac involvement; treatment with diuretics and intravenous heparin was started. Heparin was replaced by oral warfarin. Because of her continued clinical deterioration she was referred for heart transplantation but she died of fulminant congestive cardiac failure 4 months after cardiac amyloidosis was diagnosed. An echocardiogram performed 2 weeks before she

Summary of the echocardiographic features and location of the atrial thrombi in the three cases

Patient	*LV mean wall thickness (cm)*	*LVEF (%)*	*Atrial septal thickening*	*Left atrial diameter (cm)*	*Biatrial dilatation*	*Location of thrombus*	*Valve dysfunction*
1	1·7	30	Present	4·5	Present	LA, RAa	MR, TR
2	1·4	30	Present	4·9	Present	LA, LAa	MR, TR, PR
3	1·8	55	Present	4·2	Present	LA, LAa, RA	MR, TR, PR

LA, left atrial body; LAa, left atrial appendage; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PR, pulmonary regurgitation; RA, right atrial body; RAa, right atrial appendage; TR, tricuspid regurgitation.

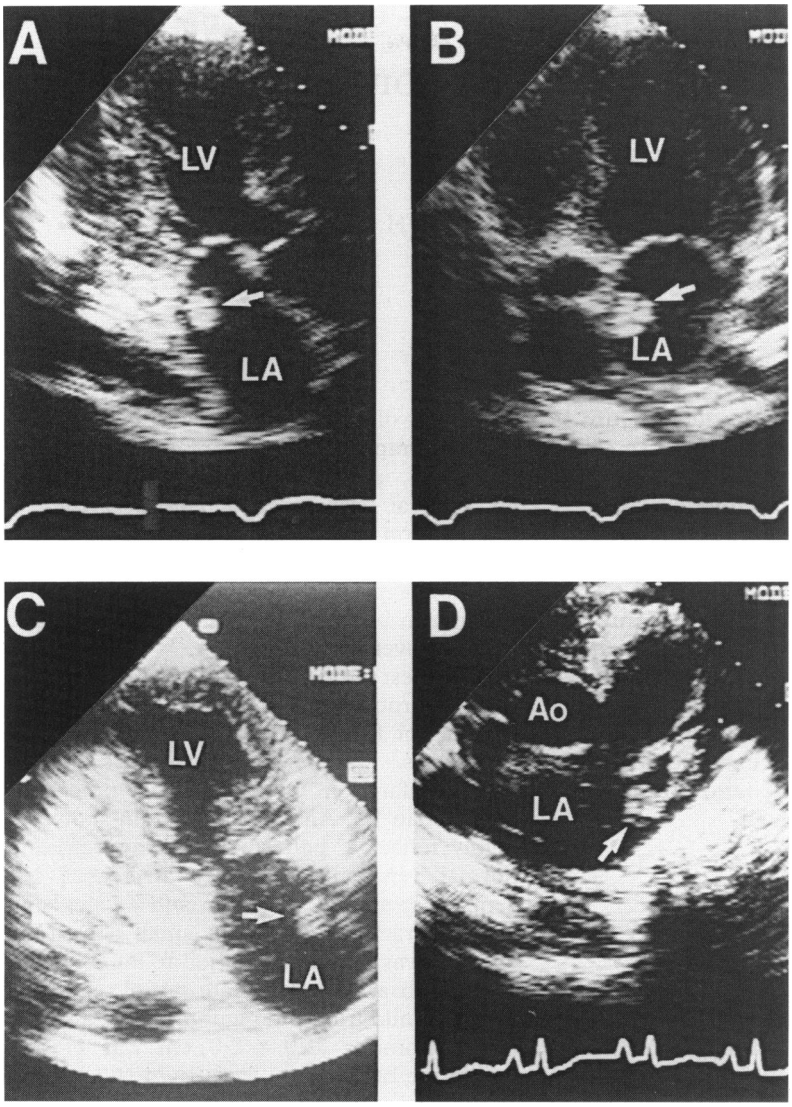

Figure 1 (A and B) Apical three chamber and four chamber views from case 1 showing thrombus (arrowed) within the left atrium. (C) Apical two chamber view from case 2 showing thrombus (arrowed) protruding into the body of the left atrium. (D) Parasternal short axis view from case 3 at the level of the aorta showing an elongated thrombus (arrowed) protruding from the left atrial appendage.

died showed severe biventricular global systolic dysfunction with a calculated left ventricular ejection fraction of less than 25%. Thrombus was plainly visible in the left atrium.

At necropsy there was biventricular wall thickening and extensive infiltration of about 70% of the myocardium with amyloid. The remaining cardiac muscle showed degeneration and compensatory hypertrophy. Thrombus was found in the left atrium and also in the right atrial appendage.

Case 2

A 52 year old white woman presented with increasing shortness of breath on exertion. Her pulse was regular (90 beats per minute) and blood pressure was 100/50 mm Hg; the jugular venous pressure was elevated by 11 cm and there was pitting oedema to both knees.

The electrocardiogram showed sinus rhythm, low voltage complexes, and a pseudoinfarction QS pattern in leads V1–V3, I, and aVL in addition to T wave flattening in the inferior and lateral leads (fig 2). A chest radiograph showed cardiomegaly with mild vascular congestion and bilateral pleural effusions. An echocardiogram showed biventricular wall thickening and left ventricular systolic dysfunction with an ejection fraction of 30%. The atrioventricular, aortic, and pulmonary valves appeared thickened with moderate mitral and tricuspid regurgitation on colour flow Doppler (table 1). The inter-atrial septum was thickened and both atria were considerably dilated; a mobile 2·0 × 2·0 cm thrombus protruded from the left atrial appendage into the body of the left atrium (fig 1C). Doppler flow analysis showed no A wave flow at the mitral valve position though a small A wave was visualised at the tricuspid annulus. The mitral E wave deceleration time was short (142 ms).

Free monoclonal lambda light chains were found in the serum and urine. A fat aspirate was positive for the diagnosis of amyloidosis. A skeletal survey was negative for multiple myeloma and primary amyloidosis was diagnosed. Treatment for cardiac failure was initiated with frusemide and spironolactone and the patient was anticoagulated orally with warfarin. Two weeks later a repeat echocardiogram showed that the thrombus was smaller. However, 2 weeks after this echocardiogram and a total of 4 weeks from the diagnosis of cardiac amyloidosis she died of rapidly progressive heart failure. Necropsy was not performed.

Case 3

A 58 year old white, previously healthy, woman presented with a 7 month history of cough, increasing shortness of breath on exertion, and ankle swelling. Examination showed a regular pulse and the blood pressure of 120/80 mm Hg. Scant basal rales were present, the jugular venous pressure was elevated and there was bilateral peripheral oedema.

The chest radiograph showed mild cardiomegaly and interstitial oedema. The electrocardiogram confirmed sinus rhythm at 94 beats per minute, with decreased voltage amplitude, right axis deviation, and loss of R wave progression. An echocardiogram showed concentric biventricular wall thickening with increased myocardial echogenicity, typical of cardiac amyloidosis. There was considerable biatrial dilatation with moderate mitral regurgitation and a left ventricular ejection fraction at the lower limit of normal. Cardiac catheterisation showed normal coronary arteries, and an endomyocardial biopsy confirmed a diagnosis of amyloidosis: the haemodynamic data have been reported elsewhere.[6] Bone marrow aspiration showed 5% plasma cells and serum electrophoresis supported a diagnosis of primary amyloidosis with the finding of free monoclonal lambda light chains.

The patient was treated with diuretics and a low dose of angiotensin converting enzyme inhibitor in addition to colchicine, melphalan, and prednisolone. A month after the diagnosis of cardiac amyloidosis a repeat echocardio-

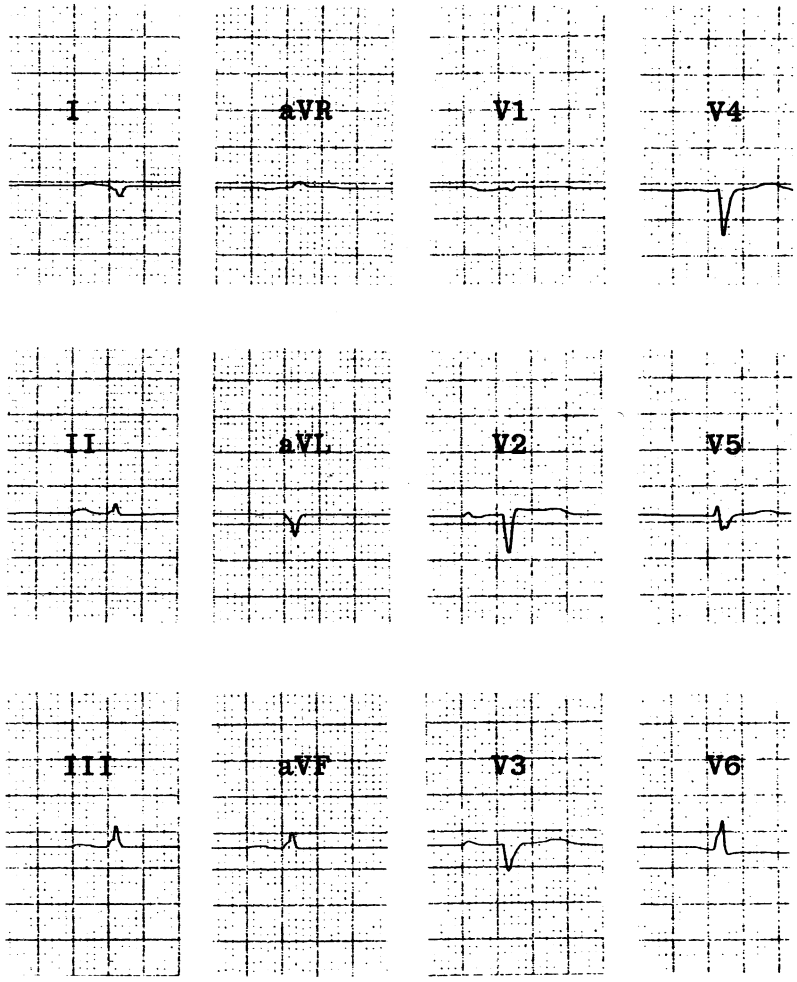

Figure 2 Electrocardiogram from patient 2 showing low voltage complexes and a pseudo-infarction QS pattern in leads V1-V3, I, and aVL in addition to T wave flattening in the inferior and lateral leads.

gram was performed; this now showed an elongated mobile dumb-bell shaped thrombus measuring 1·6 × 4·4 cm which filled the left atrial appendage and protruded into the body of the left atrium (fig 1D, table 1). Though the patient was in sinus rhythm at the time of the study, pulsed wave Doppler interrogation of flow through the mitral valve failed to show an atrial contribution to left ventricular filling (fig 3). The deceleration time of the left ventricular inflow E wave was considerably shortened (93 ms), indicating a restrictive inflow pattern. Before anticoagulation could be started, the patient had sudden onset of left homonymous hemianopia, scintillating scotoma, with occipital and bitemporal headaches. A computed tomogram showed a right occipital infarction. On repeat echocardiography the thrombus was no longer visible, indicating recent embolisation. Because of the earlier evidence of thrombus and a thromboembolic event oral treatment with warfarin was started.

Four months later and 5 months after diagnosis the patient's cardiac state rapidly deteriorated. She was referred for orthotopic heart transplantation. At operation the explanted heart was found to have thrombus in the right atrium in addition to residual thrombus in the left atrial body and appendage. She lived for 14 months after the cardiac transplant and died in pulmonary failure caused by amyloid infiltration in the lung.

Discussion

There is controversy about whether the apparent decline in an atrial contribution to ventricular filling in amyloidosis with significant cardiac involvement is caused by a restrictive ventricular physiology, atrial failure, or a combination of both factors. The patients we describe, three women with New York Heart Association class IV heart failure caused by primary (amyloid light chain) cardiac amyloidosis, had extensive infiltration of both the ventricular and atrial myocardium. All three showed either a reduced or an absent A wave on the Doppler mitral valve velocity spectrum. An increase in ventricular end diastolic pressures resulting in a restrictive filling pattern has been proposed as the cause of the reduced atrial contribution, as a result of an increase in atrial afterload.[9] The E wave deceleration times in our three cases are significantly shorter than those reported for normal subjects of the same age;[8] supporting the argument that a restrictive physiology contributes to the absence of an atrial contribution. An alternative theory to explain the reduced A wave is that atrial contraction is severely impaired or absent because of amyloid infiltration of the atrial walls.[7] This proposed mechanism is supported by the haemodynamic data obtained from case 3 at catheterisation and reported by Plehn *et al.*[6]

The finding of large atrial thrombi within the body of the atrium or protruding into it in patients with sinus rhythm is unusual and suggestive of profound atrial stasis. Formation of thrombus within the cardiac atria most commonly occurs in atrial fibrillation;[1,2] though patients with a predisposition to marked stasis, such as those with mitral stenosis, have been described as developing atrial thrombi while in sinus rhythm.[3] In significant mitral stenosis when blood stasis is most severe, thrombi may occur not only in the left atrial appendage but also in the body of the left atrium,[1,10] although this usually occurs in atrial fibrillation. Rarely, electromechanical dissociation of the atrium in mitral stenosis has also been associated with thrombus in the body of the left atrium during sinus rhythm.[3] Mitral regurgitation is considered by some to reduce the risk of thrombus formation even in the presence of massive dilatation of the left atrium[11] or atrial fibrillation.[12,13] There was considerable mitral regurgitation in all three of our patients but it did not prevent the formation of large atrial thrombi, which suggests that an additional thrombogenic factor may have been present in these patients.

Despite the atrial dilatation and immobility caused by amyloid infiltration, reports of large atrial thrombi within the body of the atria are surprisingly sparse.[14] In a large series of 54 patients with extensive cardiac amyloidosis who came to necropsy, thrombi were observed in one or more cardiac chambers in 26% of the patients.[15] However, though there were

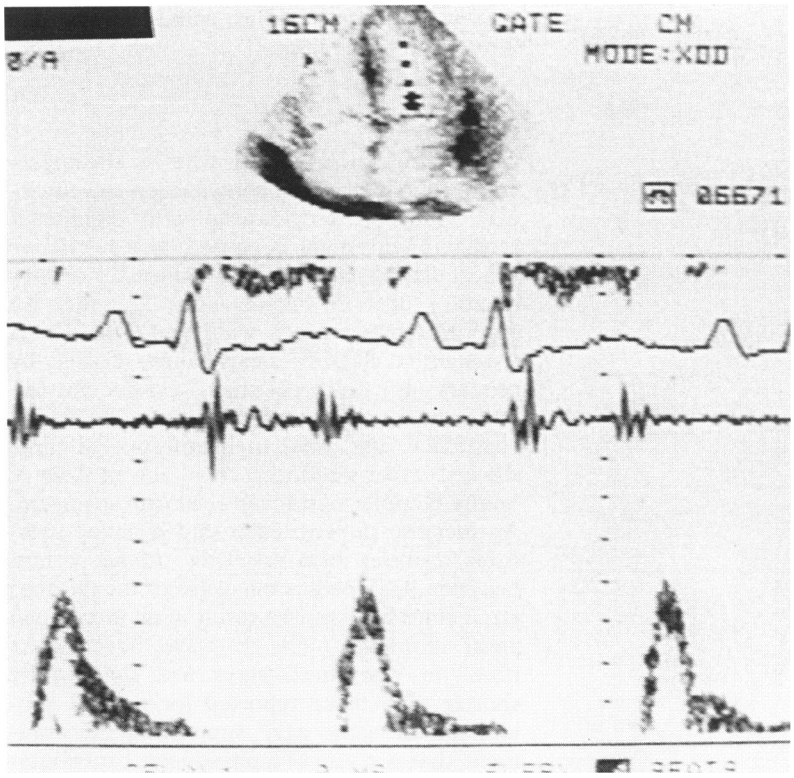

Figure 3 Doppler echocardiogram from case 3 showing mitral flow from an apical four chamber view at the level of the leaflet tips. The simultaneous electrocardiogram shows sinus rhythm; no A wave is seen in late diastole on the Doppler flow pattern.

thrombi in the right atrial appendage in 19% of patient and in the left atrial appendage in 13%, no thrombi were found within the body of the atria. Brown *et al* described two cases of primary amyloidosis, in whom one was found to have multiple mural thrombi in both atria at necropsy.[16] In common with our patient (case 3), both patients they describe had acute systemic thromboembolic events while in sinus rhythm. Histology showed disruption of the endocardial layer by amyloid with overlying mural thrombosis.[16] Macroscopically the atrial endocardium may appear "gritty" because of amyloid infiltration: this was found in one or both atria of all 54 patients described by Roberts *et al*.[15] Localised infiltration of the endocardium with amyloid may be the necessary additional factor that results in thrombus formation and subsequent thromboembolic events.

Our findings support the suggestion that thromboembolic events in amyloidosis may arise from the heart.[16] We have described three patients in whom electromechanical dissociation within the cardiac atria seemed to result in thrombus formation. Whether an apparent lack of atrial contribution to ventricular filling is due primarily to atrial dysfunction or to a restrictive ventricular physiology is unclear, but a combination of both factors seems most likely. Thrombosis occurs when there is an abnormality of blood flow, of the endothelium, or of factors involved with coagulation itself—the classic Virchow's triad. In cardiac amyloidosis it seems likely that at least the first two of these criteria may be satisfied. Clinically, the decision whether to anticoagulate patients with cardiac amyloidosis and mechanical atrial standstill is still not resolved. However, there seems little doubt that once thrombus is detected, anticoagulation should be started even though the severity of the underlying disease is associated with a poor prognosis.

This study was supported by grants from the US National Institutes of Health (AR 40414, AR 20613 and RR 533).

1 Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. *Stroke* 1985;**16**:182–8.
2 Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;**17**:622–6.
3 Rittoo D, Sutherland GR, Currie P, Starkey IR, Shaw TRD. A prospective study of left atrial spontaneous echo contrast and thrombus in 100 consecutive patients referred for balloon dilation of the mitral valve. *J Am Soc Echocardiogr* 1994;**7**:516–27.
4 Klein AL, Hatle LK, Taliercio CP, Oh JK, Kyle RA, Gertz MA, *et al*. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a doppler echocardiography study. *Circulation* 1991;**83**:808–16.
5 Klein AL, Hatle LK, Burstow DJ, Seward JB, Kyle RA, Bailey KR, *et al*. Doppler characterisation of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol* 1989;**13**:1017–26.
6 Plehn JF, Southworth J, Cornwell GG. Brief report: Atrial systolic failure in primary amyloidosis. *N Engl J Med* 1992;**327**:1570–3.
7 Hayashi T, Yamanaka T, Fujinuma S, Kobayashi S, Yamaguchi H, Hatanu H, *et al*. Left ventricular filling disturbances in cardiac amyloidosis. *Am J Noninvas Cardiol* 1994;**8**:156–61.
8 Klein AL, Cohen GI. Doppler echocardiographic assessment of constrictive pericarditis, cardiac amyloidosis, and cardiac tamponade. *Cleve Clin J Med* 1992;**59**:278–90.
9 Greenberg B, Chatterjee K, Parmley WW, Werner JA, Holly AN. The influence of left ventricular filling pressure on atrial contribution to cardiac output. *Am Heart J* 1979;**98**:742–51.
10 Come PC, Riley MF, Bivas NK. Roles of echocardiography and arrhythmia monitoring in the evaluation of patients with suspected systemic embolism. *Ann Neurol* 1983; 527–31.
11 Daley R, Franks R. Massive dilation of the left auricle. *Q J Med* 1949;**18**:81–92.
12 Blackshear JL, Pearce LA, Asinger RW, Dittrich HC, Goldman ME, Zabalgoitia M, *et al*. Mitral regurgitation associated with reduced thromboembolic events in high-risk patients with nonrheumatic atrial fibrillation. *Am J Cardiol* 1993;**72**:840–3.
13 Movsowitz C, Meyerowitz CB, Jacobs LE, Meyerwitz CB, Podolsky L, Ioli A, *et al*. Significant mitral regurgitation is protective against left atrial spontaneous echo contrast and thrombus as assessed by transesophageal echocardiography. *J Am Soc Echocardiogr* 1993;**6**:107–14.
14 Nakano T, Futagami Y, Konishi T, Takezawa H. An autopsy case of primary amyloidosis with huge thrombi in both the right and left atrium. *Nippon Naika Gakkai Zasshi (J Jap Soc Intern Med)* 1986;**75**:1297–302.
15 Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: analysis of 54 necroscopsy patients. *Am J Cardiol* 1983;**52**:137–46.
16 Browne RS, Schneiderman H, Kayani N, Radford MJ, Hager WD. Amyloid heart disease manifested by systemic arterial emboli. *Chest* 1992;**102**:304–7.