European Heart Journal (2006) **27**, 1805–1810
doi:10.1093/eurheartj/ehl106

Sustained improvement in left ventricular diastolic function after alcohol septal ablation for hypertrophic obstructive cardiomyopathy

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Received 23 March 2006; revised 22 May 2006; accepted 26 May 2006; online publish-ahead-of-print 14 June 2006

See page 1769 for the editorial comment on this article (doi:10.1093/eurheartj/ehl127)

KEYWORDS
Echocardiography;
Hypertrophic obstructive cardiomyopathy;
Diastolic dysfunction;
Alcohol septal ablation

Aims Impaired diastolic function is responsible for many of the clinical features of hypertrophic cardiomyopathy. In patients with hypertrophic obstructive cardiomyopathy (HOCM) whose symptoms are refractory to medical therapy, alcohol septal ablation (ASA) reduces left ventricular (LV) outflow tract gradient, with short-term improvement in LV diastolic function. Little is known about the longer term impact of ASA on diastolic function.

Methods and results We evaluated LV diastolic function at baseline and 1- and 2-year follow-up after successful ASA. In 30 patients (58 ± 15 years, 22 men) who underwent successful ASA, New York Heart Association class was lower at 1-year follow-up compared with baseline (3.0 ± 0.5 to 1.5 ± 0.7; $P < 0.0001$). LV outflow tract gradient (76 ± 37 to 19 ± 12; $P < 0.0001$), interventricular septal thickness (19 ± 2 to 14 ± 2; $P < 0.0001$), and left atrial volume (26 ± 5 to 20 ± 4; $P < 0.0001$) were decreased. Significant improvement in E-wave deceleration time, isovolumic relaxation time, early diastolic mitral lateral annular velocity (E'), mitral inflow propagation velocity (V_p), ratio of transmitral early LV filling velocity (E) to early diastolic Doppler tissue imaging of the mitral annulus (E/E'), and E/V_p were observed at 1 year following successful ASA. These changes persisted in the subset cohort ($n = 21$) for whom 2-year data were available.

Conclusion Successful ASA for HOCM leads to significant and sustained improvement in echocardiographic measures of diastolic function, which may contribute to improved functional status after successful ASA.

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is a disorder of the heart characterized by dynamic left ventricular (LV) outflow tract (LVOT) obstruction, mitral regurgitation, and diastolic dysfunction.[1] Many of the clinical and pathophysiological features of HOCM result from diastolic dysfunction.[2,3]

In patients with HOCM whose symptoms are refractory to optimal medical therapy, alcohol septal ablation (ASA) is an alternative to surgical myomectomy.[4] ASA results within 3–6 months in symptomatic improvement through a number of mechanisms, including remodelling of the upper septum with enlargement of the LVOT and reduction in LVOT gradient, reduction in mitral regurgitation severity, and improvement in LV diastolic function.[5–11]

Little is known about the longer term impact of ASA on diastolic function in HOCM.[12,13] The current study was designed to assess both conventional and novel Doppler echocardiographic measurements of diastolic function before and at 1- and 2-year follow-up after ASA.

Methods

Patient population

Between 2001 and 2004, 57 consecutive patients with HOCM underwent ASA at Massachusetts General Hospital, Boston, MA, USA. We excluded 27 patients because of inability to deliver ethanol (six cases) or incomplete diastolic echocardiographic parameters (21 cases). The final cohort included 30 patients in whom diastolic echocardiographic parameters were available at baseline and 1-year follow-up for evaluation. A subset of 21 patients also had 2-year follow-up. Selection criteria for ASA were: (i) symptoms that interfere substantially with quality of life despite optimal medical therapy; (ii) septal thickness $\geq$16 mm; (iii) LVOT gradient $\geq$30 mmHg at rest or $\geq$50 mmHg with provocation; (iv) accessible septal branches, usually of the left anterior descending coronary artery; (v) the absence of significant intrinsic abnormality of the mitral valve and other conditions for which cardiac surgery was indicated. ASA was

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performed as previously described.[14] ASA success was defined as an improvement in New York Heart Association (NYHA) class and a reduction in LVOT gradient by at least 50%.

Echocardiograpy

Parasternal and apical views were obtained using a standard echocardiograph (Philips Sonos 7500, Andover, MA, USA) with a multifrequency transducer and tissue Doppler capability. Standard two-dimensional images, M-mode, spectral and colour Doppler, and Doppler tissue imaging (DTI) were performed. A single observer (D.S.J.), blinded to the clinical data, analysed the echocardiographic images offline.

LV interventricular septal thickness (IVS), posterior wall thickness, cavity dimensions and volumes, and left atrial size indexed to body surface area were determined from two-dimensional images according to established criteria including the modified Simpson's method.[15] Continuous-wave Doppler was used to measure the peak velocity across the LVOT in the apical five-chamber or long-axis view, and the peak pressure gradient was estimated using the simplified Bernouilli equation. The ratio of the mitral regurgitant jet to the left atrial cavity was measured with two-dimensional colour flow Doppler imaging as a qualitative index of the severity of mitral regurgitation (mild = 1, moderate = 2, moderate to severe = 3, and severe = 4).[16]

LV diastolic function was assessed using both conventional and novel diastolic parameters. Transmitral LV filling velocity at the tips of the mitral valve leaflets was obtained from the apical four-chamber view using pulsed-wave Doppler echocardiography. The transmitral LV filling signal was traced manually and the following variables were obtained: peak early (*E*) and late (*A*) transmitral velocities, *E*/*A* ratio, and E-wave deceleration time. Isovolumic relaxation time was determined by the time interval between the end of aortic outflow during systole and the onset of mitral inflow during diastole.

Doppler tissue imaging indices were measured in early diastole (*E*′) and with atrial contraction (*A*′) at the lateral region of the mitral annulus. Colour M-mode Doppler image of LV filling flow in early diastole was obtained from the apical four-chamber view. Flow propagation velocity (V_p) was determined as the slope of peak velocity of early diastolic filling flow on the colour M-mode image.[17] Finally, the dimensionless indices E/E' and E/V_p were calculated.[18,19] The estimated left atrial pressure was subsequently calculated as $E/E' \times 1.25 + 1.9$.[20]

Statistics

The data are summarized as mean ± SD or number (percentage). χ^2 and Fischer exact tests were applied to compare categorical variables. Paired *t*-test was used to compare echocardiographic parameters at baseline and 1-year follow-up. Repeated measures of ANOVA with *post hoc* comparisons were applied to evaluate mean changes at different time points for patients with 2-year follow-up. Significance levels were adjusted for multiple comparisons using the Bonferroni correction and, therefore, *P*-value of <0.002 was considered significant. The change in IVS following ASA was compared with changes in both conventional and novel LV diastolic parameters by simple linear-regression analysis. A *P*-value of <0.05 was considered significant. The Statistical Analysis System 8.01 (SAS Institute, Cary, NC, USA) was used to perform the analysis.

Results

Baseline characteristics

The age of the study patients in the entire group ($n = 30$) was 58 ± 15 (range 32–82 years, 22 men) and in the subset with 2-year follow-up ($n = 21$), it was 58 ± 16 (range 32 to 82 years, 17 men) (*Tables 1* and *2*). The mean NYHA class was 3.0 ± 0.5 prior to ASA despite optimal medical therapy that consisted of beta-blockers in 25 (83%) patients, calcium-channel blockers in 15 (50%), and/or disopyramide in three (10%). All patients had baseline resting LVOT gradients >30 mmHg (76 ± 37, range 31–200 mmHg).

Effect of ASA on NYHA functional class

NYHA class decreased from 3.0 ± 0.5 to 1.5 ± 0.7 at 1-year ($P < 0.0001$) (*Figure 1*) and continued to improve in the subset cohort at 2-year follow-up (*Tables 1* and *2*). During follow-up, medications were not significantly different from those at baseline (*Tables 1* and *2*). In the short-term follow-up of these HOCM patients following ASA, the medications (particularly beta-blockers) are held constant, whenever possible, so as to isolate the effect of the ablation itself.

Effect of ASA on left heart dimensions and haemodynamics

LV outflow tract gradients decreased from 76 ± 37 to 19 ± 12 mmHg ($P < 0.0001$) at 1-year follow-up and from

Table 1 Clinical and echocardiographic findings in all patients ($n = 30$)

Characteristics	Baseline	1 year follow-up	*P*-value
Age (years)	58 ± 15		
Male gender (%)	22 (73)		
NYHA	3.0 ± 0.5	1.5 ± 0.7	<0.0001
HR (bpm)	76 ± 12	74 ± 10	0.6527
SBP (mmHg)	126 ± 13	132 ± 22	0.4531
Cardiac medications			
Beta-blockers (%)	25 (83)	23 (77)	0.6525
Calcium antagonists (%)	15 (50)	13 (43)	0.5448
Disopyramide (%)	3 (10)	4 (13)	0.6845
Left heart dimensions			
IVS (mm)	19 ± 2	14 ± 2	<0.0001
PWT (mm)	13 ± 1	12 ± 2	0.5343
LAVI (mL/m^2)	26 ± 5	20 ± 4	0.0002
LVEDVI (mL/m^2)	57 ± 10	72 ± 11	<0.0001
EF (%)	68 ± 5	66 ± 7	0.6232
Doppler-derived pressure measurements			
LAP (mmHg)	21 ± 5	14 ± 3	<0.0001
LVOT (mmHg)	76 ± 37	19 ± 12	<0.0001
Doppler echocardiography			
MR grade	2.6 ± 0.5	1.4 ± 0.5	<0.0001
Mitral E velocity (cm/s)	91 ± 18	90 ± 21	0.8073
Mitral A velocity (cm/s)	96 ± 36	92 ± 36	0.7980
E/A ratio	1.04 ± 0.4	1.01 ± 0.4	0.5324
E deceleration time (ms)	238 ± 17	168 ± 18	<0.0001
IVRT (ms)	122 ± 20	89 ± 6	<0.0001
Doppler tissue imaging			
Lateral *E*′ (cm/s)	6.5 ± 1.8	8.7 ± 2.3	<0.0001
V_p (cm/s)	34 ± 6	63 ± 12	<0.0001
E/E' (lateral)	15 ± 4	10 ± 2	<0.0001
E/V_p	2.7 ± 0.7	1.5 ± 0.5	<0.0001

Values are mean ± SD. HR, heart rate; SBP, systolic blood pressure; IVRT, isovolumic relaxation time; LAVI, left atrial volume indexed to body surface area; LAP, estimated left atrial pressure; LVEDVI, left end-diastolic volume indexed to body surface area; LVOT, LV outflow tract gradient; MR, mitral regurgitation.

Table 2 Clinical and echocardiographic findings at 2-year follow-up ($n = 21$)

Characteristics	Baseline	1 year follow-up	2 year follow-up
Age (years)	58 ± 16		
Male gender (%)	17 (81)		
NYHA	3.0 ± 0.5	1.6 ± 0.7*	1.1 ± 0.4*
HR (bpm)	75 ± 10	70 ± 12	76 ± 15
SBP (mmHg)	125 ± 12	130 ± 21	134 ± 11
Cardiac medications			
Beta-blockers (%)	16 (76)	15 (71)	13 (62)
Calcium antagonists (%)	10 (48)	9 (43)	9 (43)
Disopyramide (%)	2 (10)	3 (14)	2 (10)
Left heart dimensions			
IVS (mm)	19 ± 2	14 ± 1*	14 ± 1*
PWT (mm)	13 ± 1	12 ± 2	12 ± 3
LAVI (mL/m^2)	23 ± 5	20 ± 5*	20 ± 5*
LVEDVI (mL/m^2)	60 ± 10	74 ± 12*	78 ± 13*
EF (%)	67 ± 5	65 ± 8	66 ± 7
Doppler-derived pressure measurements			
LAP (mmHg)	20 ± 6	15 ± 3*	15 ± 3*
LVOT (mmHg)	75 ± 34	19 ± 12*	18 ± 13*
Doppler echocardiography			
MR grade	2.4 ± 0.5	1.3 ± 0.5*	1.3 ± 0.5*
Mitral E velocity (cm/s)	89 ± 19	98 ± 22*	91 ± 24
Mitral A velocity (cm/s)	101 ± 44	104 ± 45	99 ± 41
E/*A* ratio	1.04 ± 0.5	1.06 ± 0.5	1.01 ± 0.6
E deceleration time (ms)	238 ± 18	165 ± 20*	154 ± 32*
IVRT (ms)	118 ± 21	89 ± 6*	91 ± 5*
DTI			
Lateral *E*′ (cm/s)	6.8 ± 1.8	8.4 ± 2.4*	8.2 ± 2.7*
V_p (cm/s)	36 ± 7	63 ± 11*	68 ± 14*
E/*E*′ (lateral)	15 ± 4	10 ± 2*	10 ± 2*
E/V_p	2.6 ± 0.7	1.5 ± 0.6*	1.1 ± 0.4*

Values are mean ± SD. *P*-values were calculated by ANOVA.
*$P < 0.0001$ vs. baseline.

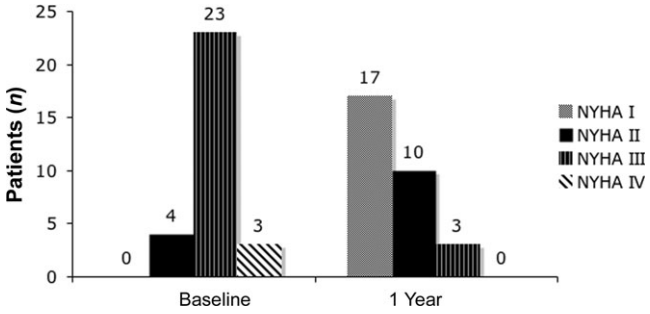

Figure 1 Change in NYHA class at 1 year after ASA.

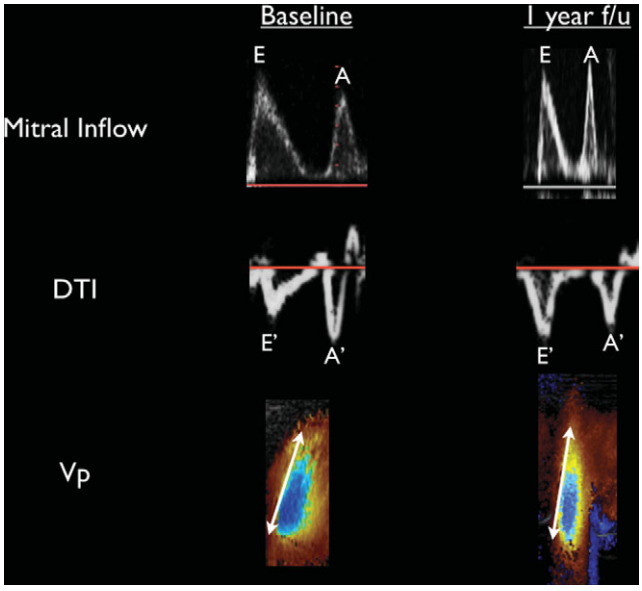

Figure 2 Representative examples of mitral inflow, DTI, and propagation velocity (V_p) at baseline and 1 year following ASA in the same patient. Heart rate and sweep speeds are similar at both time points. *E*, mitral E velocity; *A*, mitral A velocity; *E*′, early diastolic velocity of the lateral annulus; *A*′, late diastolic velocity of the lateral annulus; V_p, propagation velocity.

75 ± 34 to 18 ± 13 mmHg ($P < 0.0001$) at 2-year follow-up. In addition, the degree of mitral regurgitation decreased (2.6 ± 0.5 to 1.4 ± 0.5, $P < 0.001$, at 1-year follow-up and 2.4 ± 0.5 to 1.3 ± 0.5, $P < 0.001$, at 2-year follow-up).

Changes in left heart dimensions in patients with HOCM at 1- and 2-year follow-up are shown in *Tables 1* and *2*, respectively. Although there was no significant difference in posterior wall thickness over time, basal IVS significantly decreased following ASA (19 ± 2 to 14 ± 2 mm, $P < 0.0001$). Both left atrial volume indexed to body surface area (26 ± 5 to 20 ± 4 mL/m^2, $P = 0.0002$) and Doppler-derived left atrial pressure (21 ± 5 to 14 ± 3 mmHg, $P < 0.0001$) were significantly reduced following ASA at 1 year, and this change was sustained in the subset population with 2-year follow-up. Additionally, there was a significant increase in LV end-diastolic volume indexed to body surface area (57 ± 10 to 72 ± 11 mL/m^2, $P < 0.0001$).

Effect of ASA on diastolic dysfunction parameters

Figure 2 illustrates examples of mitral inflow, DTI, and propagation velocity (V_p) parameters at baseline and 1-year follow-up in the same patient. All 30 patients had abnormal diastolic function at baseline, either having a pseudonormal pattern ($n = 21$) or a delayed relaxation pattern ($n = 9$). There was no significant change in mean transmitral E-wave, transmitral A-wave, or *E*/*A* ratio after ASA. E deceleration time and isovolumic relaxation time were, however, significantly shorter and normalized 1 year after ASA (*Table 1*). This improvement was sustained at 2 years (*Table 2*).

DTI parameters of diastolic function were abnormal in all patients at baseline and were improved up to 2 years following ASA (*Table 2*). Similar trends in diastolic parameters were observed in the same patient. The lateral mitral annular velocity (*E*′) improved after ASA (6.5 ± 1.8 to 8.7 ± 2.3 cm/s, $P < 0.0001$, at 1 year; 6.8 ± 1.8 to 8.2 ± 2.7 cm/s, $P < 0.05$, at 2 years). Flow propagation (V_p) velocity, which was abnormally delayed prior to treatment, increased to the normal range at follow-up (34 ± 6 to 63 ± 12 cm/s, $P < 0.0001$, at 1 year; 35 ± 7 to 68 ± 14 cm/s, $P < 0.0001$, at 2 years). There was a weak but significant correlation between the reduction in IVS following ASA and the improvement in V_p at 1 year ($r = 0.45$, $P = 0.02$, *Figure 3*). Both *E*/*E*′ and *E*/V_p showed improvement at 1 and 2 years after ASA.

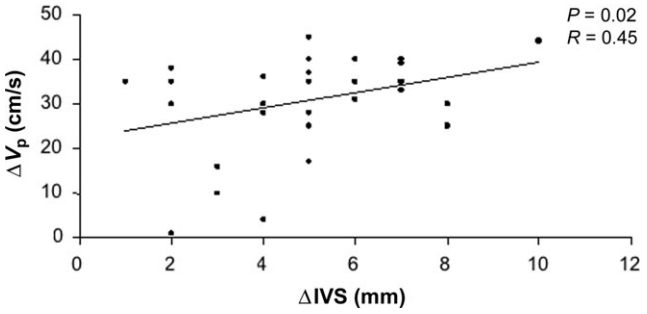

Figure 3 Correlation of change in IVS with change in propagation velocity (V_p) at 1 year after ASA.

Discussion

Although many patients with HOCM are asymptomatic throughout life, some present with limiting symptoms of exertional dyspnoea, which likely results in large part from diastolic dysfunction.[2,3] A spectrum of diastolic abnormalities, including an increase in mean left atrial and LV end-diastolic pressures, a prolonged time constant of relaxation, and increased myocardial stiffness, have been described in HOCM patients.[21] Although Nagueh *et al.*[12] demonstrated improvement in diastolic function up to 6 months after ASA, our study extends this to demonstrate the longer term effect of ASA, with persistence of the improvement in echocardiographic indices of diastolic function up to 2 years after a successful procedure.

Conventional diastolic dysfunction parameters

Many non-invasive approaches have been used to detect diastolic dysfunction in patients with HOCM, and analysis of the transmitral flow velocity pattern has been most often used.[22,23] The transmitral Doppler flow (E-wave, A-wave, E/A ratio) is strongly influenced by factors such as age and loading conditions and thus may be unreliable for estimating LV filling pressures in HOCM patients.[21] There is an inconsistent relationship between conventional diastolic indices and the severity of LV hypertrophy, LV end-diastolic pressure, and exercise tolerance in HOCM patients.[24–26] These limitations of conventional Doppler indices in HOCM patients are also reflected in our study. With the exception of deceleration time and isovolumic relaxation time, no other conventional parameter improved following ASA despite an improvement in NYHA functional class.

Both deceleration time and isovolumic relaxation time were prolonged at baseline in our HOCM patients and normalized following ASA at 1- and 2-year follow-up. These diastolic parameters are primarily affected by both left atrial pressure and myocardial relaxation. Either an increase in left atrial pressure or a faster rate of ventricular relaxation can result in shortening of the isovolumic relaxation time and a steeper E-wave deceleration rate.[27] Our study demonstrated that estimated left atrial pressure (E/E' and E/V_p) significantly decreased following ASA. This finding suggests that the normalization of deceleration time and isovolumic relaxation time was due not to higher filling pressures but rather to an improvement in myocardial relaxation. Importantly, the improvement in V_p in our patient cohort further supports the normalization of ventricular relaxation following ASA.

Doppler tissue imaging

Recently, newer echocardiographic modalities such as Doppler tissue imaging have demonstrated clinical relevance among patients with a variety of myocardial disorders. In HOCM patients, Doppler tissue imaging has been demonstrated to predict gene mutations, to be an accurate noninvasive means of assessing left atrial filling pressure due to less load dependence, and to correlate with response to specific therapeutic interventions for the disease.[28,29]

Early diastolic mitral annular velocity (E') has been proposed to be a useful index for the evaluation of LV relaxation in patients with HOCM.[23] Matsumura reported that HOCM patients have lower early diastolic Doppler tissue imaging velocities (E') than age- and gender-matched controls,[26] a finding confirmed in our HOCM patients at baseline. Nagueh *et al.*[12] previously demonstrated a modest improvement in lateral E' at 6 months following ASA; our study confirmed sustained improvement of E' up to 2 years following after the procedure.

LV early diastolic flow propagation velocity (V_p) measured by colour M-mode Doppler echocardiography is a useful index of LV diastolic function and correlates with the time constant of myocardial relaxation, τ, in patients with HOCM.[17] Nishihara *et al.*[17] compared HOCM patients with age- and gender-matched controls and demonstrated that V_p was abnormally low in HOCM patients compared with the normal value of >55 cm/s, reflecting the abnormal myocardial relaxation properties of the small LV cavities. Our study is the first to demonstrate sustained improvement in V_p following ASA, again reflecting improved diastolic function after the procedure. The normalization of V_p likely results from ventricular remodelling observed following ASA, with both regression of hypertrophy and an increase in LV end-diastolic volume. This finding is supported by the correlation noted between reduction in IVS following ASA and improvement in V_p in our patient population.

Left atrial volumes

Left atrial enlargement is a marker of disease severity in patients with HOCM.[12,30] Woo *et al.*[30] recently demonstrated that a left atrial diameter >46 mm is a predictor of overall mortality in patients undergoing myomectomy for HOCM. Enlargement of the left atrial chamber in HOCM patients reflects the extent of mitral regurgitation, elevation in left atrial and LV pressures, and abnormal diastolic filling.[30,31] Recently, van Dockum *et al.*[32] demonstrated, using cardiac magnetic resonance imaging, a significant decrease in left atrial dimension 6 months after ASA.

All 30 patients in our study had increased left atrial volumes indexed to body surface area at baseline, reflecting advanced diastolic dysfunction and chronically high filling pressures.[29] Following successful ASA, both left atrial volume and the degree of mitral regurgitation were reduced and there was a concomitant significant reduction in estimated left atrial pressure (E/E' and E/V_p). Our study thus is the first to demonstrate sustained reduction in left atrial dimensions in patients with 2-year follow-up.

Limitations

The primary limitation of this study is the small sample size. Larger studies are thus needed in order to make more substantive conclusions regarding the relationship of diastolic parameters and functional improvement in HOCM patients following ASA.

Conclusion

In patients with HCM and basal obstruction, echocardiographic indices of diastolic function improve after ASA. These favourable changes are sustained for up to 2 years after the procedure. The improvement in LV relaxation and decrease in left atrial and LV filling pressures may contribute to the improvement in symptoms and exercise tolerance of patients with HOCM managed with ASA.

Conflict of interest: none declared.

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Clinical vignette

doi:10.1093/eurheartj/ehi745
Online publish-ahead-of-print 2 February 2006

Obstructive intramural coronary amyloidosis: a distinct phenotype of cardiac amyloidosis that can cause acute heart failure

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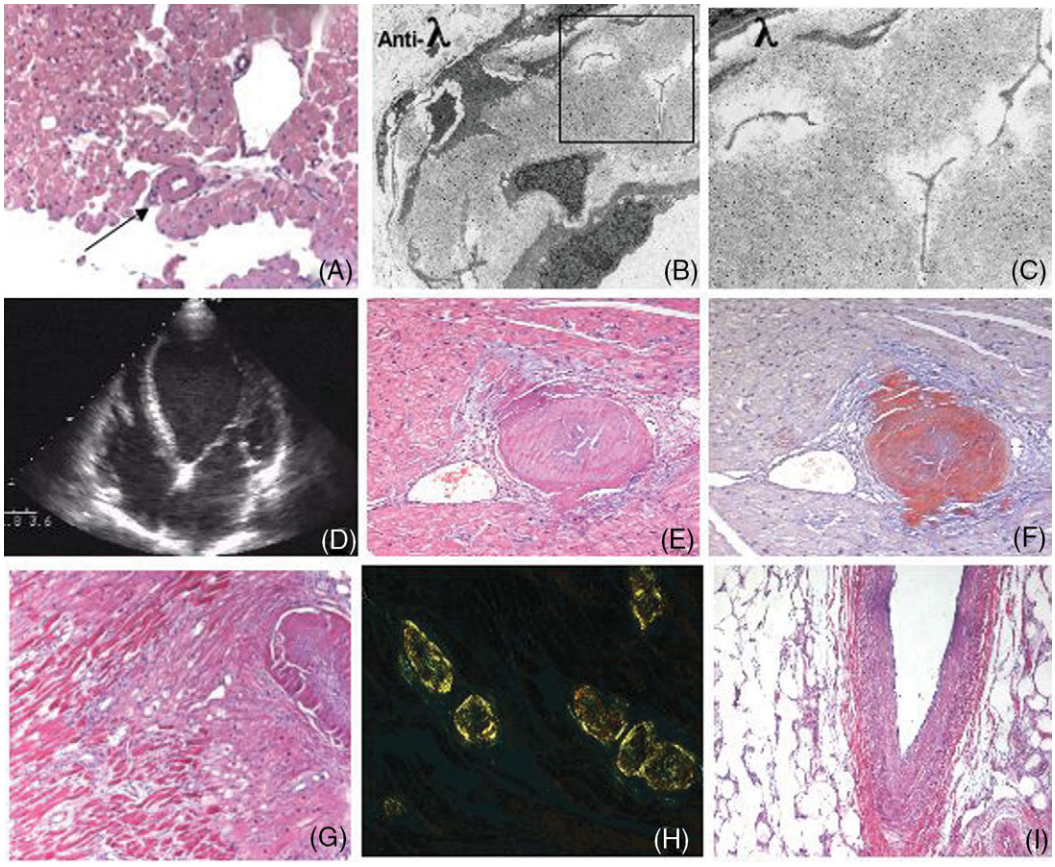

A 66-year-old man was admitted to a cardiology unit with diagnosis of congestive heart failure, having complained of worsening asthenia and myalgia for several months before referral. Family history was aspecific. Echocardiography showed a moderately dilated and uniformly hypokinetic left ventricle (end-diastolic diameter 68 mm; ejection fraction 35%); wall thickness was normal. Coronary angiography showed normal epicardial arteries. After temporary improvement during treatment with beta-blockers and ACE-inhibitors, heart failure became severe and left ventricular ejection fraction fell to 20%. Suspected myocarditis prompted a right ventricular endomyocardial biopsy (Panel A), which excluded inflammation but identified amyloid infiltration of small intramural vessels without interstitial involvement. A left ventricular assist device was urgently implanted: histopathological examination of the excised left ventricular apex confirmed obstructive intramural coronary amyloidosis without interstitial deposits and with foci of coagulative necrosis. The patient died a few days later because of gastroenteric haemorrhage (autopsy was not performed) (Panels B–D).

This case documents the existence of isolated intramural coronary obstruction as a peculiar phenotype of cardiac amyloidosis (distinct from the more common amyloidotic cardiomyopathy) (Panels E–I). This rare type of amyloidotic cardiac involvement—which in this patient led to a mistaken clinical diagnosis of myocarditis—must be recognized as one of the possible causes of acute or rapidly progressive heart failure.

Panel A. Endomyocardial biopsy sample showing the small arteriolar vessel (arrow) that led to the diagnosis (H&E staining).

Panels B and C. Electron micrograph of the sample showing specific immunostaining of amyloid fibrils with anti-λ light chain monoclonal antibodies.

Panel D. Echocardiography, 1 day before the implantation of the left ventricular assist device, shows left ventricular dilation. The left ventricular apex removed at implantation displays amyloid exclusively infiltrating small intramural vessels.

Panels E and F. Small intramural arteriolar vessels heavily infiltrated by amyloid deposits [(E) H&E stain and (F) Congo Red stain].

Panel G. Left portion shows hypereosinophilic coagulative necrosis (non-necrotic myocardium is seen on the right); left margin: small vessel infiltrated by amyloid with thrombosis (H&E staining).

Panel H. Polarized light view of Congo Red-stained small intramural arteriolae: there are no amyloid deposits in the myocardial interstitium.

Panel I. Portion of the epicardial apical left anterior descending coronary artery showing the absence of amyloid infiltration.

This study was supported by research grant 'Ricerche Finalizzate e Correnti' I.R.C.C.S. Policlinico San Matteo, Pavia, Italy.