CARDIAC AMYLOIDOSIS: DIAGNOSTIC FEATURES AND CLINICAL IMPLICATIONS

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Seven patients with cardiac amyloidosis were referred to King Khaled University Hospital. All patients in this study developed congestive heart failure. They had a long duration of illness and thickened ventricular wall with marked abnormalities in the left ventricular filling, and normal systolic function. Diastolic function is suggested as a possible mechanism of congestive cardiac failure in the patients presented. The cardiac functional evaluation was made by echocardiography, whereas the diagnosis of amyloidosis was confirmed by rectal biopsy and positive technetium Tc 99m pyrophosphate scintigraphy. The diagnostic characteristic hemodynamic features of the left ventricle and its function are described and discussed with the clinical implications of the presenting features. *Ann Saudi Med 1996;16(4):405-409.*

Amyloidosis is a disease complex resulting from deposition of unique twisted B-plated sheet fibrils formed from various proteins by several different pathogenic mechanisms.[1,2] Extensive infiltration may result in clinically evident disease. Amyloid protein is composed of light chain immunoglobulin formed by a monoclonal population of plasma cells. This is the basis of primary amyloidosis as a consequence of multiple myeloma, whereas, nonimmunological protein is responsible for secondary amyloidosis. Falk demonstrated scattered amyloid deposits localized to the aorta, atria, pulmonary vessels and vessels of other organs as well. He stated that the heart involvement by amyloidosis is the most frequent cause of death associated with immunocyte dyscrasia.[3] In secondary amyloidosis, significant cardiac involvement is uncommon, whereas familial amyloidosis is occasionally associated with overt cardiac involvement. This is manifested late in the course of the disease.[4] In senile amyloidosis, there are small atrial deposits with no functional impairment or extensive ventricular involvement.[5] Patients with cardiac amyloidosis may present with congestive heart failure, dysrhythmias, syncope, and infiltrative-restrictive cardiomyopathy.[6]

This study aims to present the clinical manifestations as well as the echocardiographic diagnostic features of amyloid disease.

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Methods and Materials

Patient Selection

From January 1994 until March 1995, seven patients (five males and two females) were examined at King Khaled University Hospital, cardiology division. Their ages ranged from 31 to 75 years, with a mean of 58.5 years. All cases presented with signs of congestive cardiac failure, class III-IV according to the New York Heart Association classification. All patients were examined clinically, and investigated by chest x-ray, electrocardiography, echocardiography and technetium Tc 99m pyrophosphate cardiac scan. Rectal biopsy was taken from all cases.

Echocardiographic Examination

Two-dimensional echocardiographic studies were performed utilizing the Hewlett Packard Ultrasonoscope and a 2.5 megahertz transducer. This was in accordance with the recommendations of Falk et al.[7] M-Mode measurements of left ventricular internal dimensions and wall thickness were performed according to the American Society of Echocardiography guidelines.[8] Global left ventricular function was estimated by percent change in diameter (% > D) and determined as % > D=[(Dd-Ds)/Dd] x 100 where Dd and Ds are LV end-diastolic and end-systolic dimensions, respectively. Interventricular septum (IVS) and left ventricular posterior wall (LVPW): % < Th was calculated as follows: [(Thd-Ths)/Thd] x 100 where Thd and Ths are the end-diastolic and end-systolic thickness respectively. The rate of systolic thickness was considered reduced if it was less than 30% for the IVS or less than 50% for LVPW. The relative wall thickness (RWT) was estimated from the Gaasch formula:[9] RWT = 2

TABLE 1. *Clinicopathological findings in cardiac amyloidosis.*

Case number	Age (years)	Sex	Presentation	CXR	Tc99m	Diagnosis	Associated disease
1	67	M	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	Diabetic
2	72	F	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	
3	71	M	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	
4	75	M	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	Multiple myeloma
5	31	F	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	Diabetic
6	70	M	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	
7	32	M	CHF	Cardiomegaly +PVC	99Tc +	Rectal biopsy+	Familial Mediterranean fever

Abbr: CHF=congestive heart failure; AF=atrial fibrillation; RBBB=right bundle branch block; CHB=complete heart block; PVC=pulmonary venous congestion.

PWT/2LVID, where the upper normal value is considered to be 49%.

Both cross-sectional area (CSA) and left ventricular mass (LVM) were estimated by Devereux et al.[10] as follows: CSA (cm^2) = II[(DED/2+Th)^2 - (DED/2)^2] where DED = end-diastolic dimension. Th is the end-diastolic wall thickness. LVM (g) = 1.04 [IVS+LVIDd+LVPW)^3-(LVIDd)^3] - 13.6. The normal values in our noninvasive laboratory are CSA 20 cm^2, LVM 220 g for women and 236 g for men, according to Qaraqish and Al-Nozha.[11]

Results

Table 1 represents age, sex, clinical presentation, chest x-ray, histopathology of rectal biopsy and technetium 99m cardiac scan.

Associated Medical Diseases

Two patients were diabetics, one patient was diagnosed to have multiple myeloma and another patient had familial Mediterranean fever (FMF).

Chest X-rays

All cases showed gross cardiomegaly and pulmonary venous congestion.

Electrocardiogram

The electrocardiogram showed low voltage in all leads in five patients (Table 2). A left ventricular hypertrophy pattern was noted in one patient. Dysrhythmias and A/V blocks were detected in four cases in the form of atrial fibrillation, 3rd degree A-V block and right bundle branch block.

TABLE 2. *The electrocardiographic findings in patients with amyloidosis.*

Patient no.	Rhythm	Blocks	Voltage
1	AF	–	Low
2	NSR	–	Low
3	NSR	RBBB	Low
4	NSR	–	Low
5	–	CHB	Normal
6	AF	–	Low
7	NSR	–	Normal

Abbr: AF=atrial fibrillation; NSR=normal sinus rhythm; RBBB=right bundle branch block; CHB=complete heart block.

Technetium Tc 99m Pyrophosphate Scintigraphy

This scan was performed in all patients where cardiac amyloidosis was suspected. The scan demonstrated significantly reduced left ventricular ejection fraction with definite evidence of diastolic dysfunction.

Histopathology

Rectal biopsy was taken from all cases and renal biopsy from one patient. All specimens were positive for amyloid deposits.

Echocardiography Results

Table 3 summarizes echocardiographic data in seven cases with cardiac amyloidosis. The LV end-diastolic dimension was normal in all studied patients (LVIDd 35-56). The interventricular septum and LV posterior wall were thickened in all patients, whereas right ventricular anterior wall thickness and left atrial dilatation were detected in five cases (71%) respectively.

TABLE 3. *Echocardiographic findings in cardiac amyloidosis.*

Case	LVIDd (mm)	LVIDs (mm)	LVPW (mm)	IVS (mm)	IVS/LVPW	RVAW (mm)	LAD (mm)	Valves thickened
1	37	27	13	14	1.08	7	25	++
2	45	36	18	17	0.94	11	42	++
3	52	34	13	13	1.0	6	46	++
4	53	42	12	12	1.0	8	49	++
5	45	38	15	16	1.07	8	45	++
6	48	29	16	16	1.0	8	38	++
7	48	30	18	18	1.0	8	48	++
Mean	46.8+5	33.4+5	15+2.2	15+2	1.01+0.04	8+1.4	42+7.7	

Abbr: LVIDd=left ventricular end-diastolic dimension; LVPW=left ventricular posterior wall thickness; RVAW=right ventricular anterior wall thickness; LAD=left atrial dimension; LVIDs=left ventricular end-diastolic dimension; IVS=interventricular septal thickness.

TABLE 4. *LV functions in cardiac amyloidosis.*

		Rate of systolic thickening					
Case	% of fractional shortening	VCF	IVS	LVPW	RWT	CSA	LVM 9g)
1	27%	0.90	14%	15%	7%	21.4	238
2	20%	1.0	11%	5%	80%	35.6	424
3	34%	1.2	23%	38%	50%	26.6	325
4	21%	0.7	17%	25%	45%	24.5	306
5	15%	0.48	12%	26%	66%	28.3	348
6	39%	0.99	12%	19%	66%	32.2	346
7	20%	0.74	24%	18%	75%	37.3	488
Mean	25+8	0.85+0.2	16+5%	21+9.5%	65+12%	29.4+5.4	354+75

Abbr: VCF=velocity of circumferential fiber shortening; IVS=interventricular septal thickness; CSA=cross-sectional area; LVM=left ventricular mass; RWT=relative wall thickness.

Table 4 summarizes the left ventricular functions and mass in the studied cases with cardiac amyloidosis. Systolic thickening for IV septum (% > Th < 30%) and LV posterior wall (% > Th < 50%) was reduced in all patients. Global LV function was estimated by the fractional shortening percentage (% > D), which was reduced (< 30%) in five cases (71%).

The relative wall thickness was increased in six cases (86%) with a mean value of 65 ± 12%. Cross-sectional area (CSA) was increased in all studied patients with a mean value of 29 ± 5 cm^2. The LV mass (LVM) was increased in all cases with a mean value of 354 ± 75 g.

Table 5 summarizes the two-dimensional echocardiographic findings. All studies showed normal LV cavity dimensions or smaller than normal, whereas the LVPW and IVS showed increased thickness in all patients. The most impressive finding in this respect was the uniform hyperrefractive "granular sparkling" appearance of the thickened myocardium. Five patients showed thick right ventricular anterior wall, while the right ventricular cavity was dilated in three patients. Left and right atrial dilatations were detected in five cases respectively. The cardiac valves were thickened in all presented cases. Mild to moderate pericardial effusion was observed in five cases (71%).

Discussion

The cross-sectional echocardiographic features of cardiac amyloidosis were first described as early as 1981.[12] Echocardiography in patients with either familial or primary cardiac amyloidosis reveals appearances that are unusual in other myocardial disease. Thickened left ventricular wall, increased myocardial echogenicity, increased atrial septal thickness and increased right ventricular wall thickness have been described in the presented cases of this study. Plehn et al. stated that atrial thickening and failure are important characteristic components of the diastolic failure observed in cardiac amyloidosis.[13] Our study demonstrated the inverse relationship between echo-derived LV mass and voltagely derived ECG, where these patients tend to have a low voltage ECG while paradoxically they have LV hypertrophy by echocardiography. In 1982, Carrol et al. considered such inverse relationships a diagnostic test for cardiac amyloidosis.[14] The most interesting and characteristic feature noted was the diffuse uniform

TABLE 5. *Two-dimensional echocardiographic findings in patients with cardiac amyloidosis.*

	Thickness					Size					
Case	IVS	PW	RVAW	IAS	Valves	LV	RV	LA	RA	Sparkling intensity	PE
1	+	+	N	N	+	N	1	N	1	++	++
2	++	++	+	+	+	N		+		+++	+
3	+	+	N	N	+	N		+		++	-
4	+	+	+	=	+	N		+		++	-
5	++	++	+	+	+	N		+		+++	++
6	++	++	+	+	+	N		N		+++	++
7	++	++	+	+	+	N		+		+++	++

Abbr:IVS=interventricular septum; PW=posterior left ventricular wall; RVAW=right ventricular anterior wall; LV=left ventricle; RV=right ventricle; LA=left atrium; RA=right atrium; PE=pericardial effusion.

hyperrefractile appearance, which was termed "granular sparkling" by Siquiera-Filho et al.[12] This is presumably secondary to the amyloid deposits and resultant pathologic changes.

Falk et al. suggested that this appearance in association with LV thickening in a patient with unexplained heart failure was virtually diagnostic of amyloid heart disease.[7] Cueto-Garcia et al. concluded that echocardiographic examination is an important tool for establishing the presence of cardiac amyloid involvement and may be useful in estimating prognosis in such patients.[15] Mild to moderate pericardial effusion was detected in five cases of the presented study, and was attributed to amyloid deposits in the pericardial sac and, in addition, to be due to the development of congestive heart failure. Although cardiac amyloidosis is considered to be a specific heart muscle disease, it shares the hemodynamic and clinical features of restrictive cardiomyopathy,[16] resulting in impairment of LV diastolic function. The LV walls were thickened in all patients with significantly increased LV mass, CSA and voltage/mass mismatch.[14] The relative wall thickness (RWT) was increased in six patients in the presented study, which can reflect not only appropriate hypertrophy but can also explain the stiffness of the nonfunctioning amyloid deposits. Scintigraphy with technetium Tc 99m pyrophosphate is often strongly positive with prominent cardiac involvement, as positive scans tend to correlate with extensive cardiac involvement.

The availability of technetium-labeled myocardial perfusion agents makes the assessment of left ventricular diastolic function of utmost importance, with the clinical recognition of the entity of congestive heart failure that is associated with normal systolic and abnormal diastolic function. Hongo et al., by the use of radionuclide material, attributed the mechanism that contributed to an abnormal diastolic filling to the increased ventricular wall thickness, which might be attributed to intramyocardial amyloid infiltration with resultant loss of myocardial fibers.[17] Another possible mechanism of diastolic function impairment is myocardial ischemia resulting from amyloid deposition in the intramural coronary arteries, as shown by autopsy studies.[18] Cardiac valve involvement was not reported in the presented cases, despite this possibility being well known. The possibility of the onset of clinical and hemodynamic signs of valvular dysfunction has not been clearly documented. Richard et al. reported a case of mitral regurgitation secondary to mitral valve involvement in cardiac amyloidosis. They stated that although cardiac manifestation reflected predominantly diffuse myocardial amyloidosis, the endocardium, the valves and the pericardium may be involved as well.[19]

Clinical Implications and Prognostic Signs

Amyloidosis is a disease complex that results from deposition of unique twisted B-plated sheet fibrils formed from various proteins by several different pathogenic mechanisms. Clinically evident disease does not appear unless there is extensive organ infiltration. Cardiac involvement is a common finding and is the most frequent cause of death in amyloidosis associated with an immunocyte dyscrasia. Amyloid deposits result in functional impairment to extensive ventricular involvement with resultant cardiac failure. All patients in this study developed congestive cardiac failure with a long period of illness, and marked abnormalities in LV diastolic filling are the suggested mechanism for the failing heart.

The treatment of cardiac amyloid disease is generally ineffective and unsatisfactory,[4] but careful use of low doses of diuretics and vasodilators may afford some symptomatic benefit. Some medications have selective binding to amyloid fibrils as digitalis glycosides, as well as calcium antagonists, which may lead to serious arrhythmias and exacerbation of congestive heart failure manifestations.

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