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Doppler echocardiographic assessments of left ventricular diastolic filling in patients with amyloid heart disease

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Twenty-eight patients with amyloid heart disease, 9 with primary and 19 with familial amyloidosis, were examined by Doppler echocardiography to characterize transmitral flow velocity patterns and to assess restrictive ventricular hemodynamics. Six of the 28 patients had restrictive ventricular physiology, and the remaining 22 did not. Patients with a restrictive filling process had marked ventricular wall thickening with depressed fractional shortening. The transmitral flow velocity patterns in patients with restriction were characteristically manifested by the increased peak flow velocity and shortening of rapid diastolic filling, which was associated with a reduced flow velocity in atrial systole. In the 22 patients without restriction, the left ventricular filling patterns were subclassified as 1) filling patterns with the prolonged isovolumic relaxation time and reduced early diastolic filling, as well as enhanced atrial contribution to ventricular filling (16 patients with mild echocardiographic abnormalities), 2) normal filling patterns with normal echocardiograms (4 patients), and 3) normal filling patterns, with moderate ventricular wall thickening (2 patients).

These findings suggested that restrictive ventricular hemodynamics can be characterized by the transmitral velocity pattern and that patterns of left ventricular diastolic filling are markedly varied depending on the magnitude of myocardial amyloid deposition in patients with amyloid heart disease.

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Introduction

It is well known that restrictive ventricular hemodynamics are prominent features of some secondary heart muscle disorders, such as amyloid heart disease. However, characterization of the abnormalities in left ventricular (LV) diastolic function has long been controversial in amyloid heart disease[1~5]. Though recently transmitral flow velocity recordings by pulsed wave Doppler echocardiography have been introduced as a noninvasive means to evaluate the LV diastolic properties in a variety of cardiovascular disease states[6~12], reports on Doppler transmitral flow velocity patterns in patients with amyloid heart disease are sparse[13,14].

The present study was undertaken to characterize LV diastolic filling and to assess restrictive ventricular hemodynamics in this disorder, using Doppler echocardiography.

Methods

Study patients: We studied 28 patients with amyloid heart disease, 9 with primary and 19 with familial amyloidosis[15]. All patients underwent cardiac catheterization, M-mode and two-dimensional echocardiography, and Doppler echocardiography. None had any known concomitant heart disease, such as coronary artery disease, valvular heart disease, or congenital heart disease. We examined additional 25 normal volunteers as control subjects, 13 men and 12 women, aged 25 to 70 years (mean 46.5 ± 8.1), with no evidence of cardiovascular disorders. They also underwent echocardiographic studies. Informed consent was obtained from all subjects.

Hemodynamic study: Left and right heart catheterizations were performed in all patients and the following measurements were made: 1) systolic aortic pressure, 2) LV end-diastolic pressure at the R wave on the QRS complex of the electrocardiogram, 3) LV rapid filling wave, and 4) pulmonary capillary wedge pressure. Cardiac output was measured by the thermodilution method.

Diagnostic criteria: Amyloid heart disease was diagnosed because of the results of positive right ventricular endomyocardial biopsy performed in 22 patients and positive technetium-99m-pyrophosphate scanning of the myocardium[16,17] combined with an inverse relationship between LV wall thickness and the electrocardiographic voltage[18] in the remaining 6. Other criteria for restrictive ventricular physiology we used were as follows[9,20]: 1) clinical evidence of congestive heart failure, 2) normal or decreased ventricular chamber size, 3) elevated LV end-diastolic pressure of >12 mmHg and a right ventricular end-diastolic pressure of >7 mmHg, usually with an early diastolic dip followed by an exaggerated and abrupt rise in pressure, and 4) absence of concomitant heart disease.

Echocardiographic study: M-mode echocardiograms derived from two-dimensional images were obtained and the measurements included LV internal end-diastolic and end-systolic dimensions, ventricular septal wall thickness, LV posterior wall thickness and left atrial (LA) dimension. LV fractional shortening was then calculated.

Doppler echocardiography was performed using a real-time two-dimensional Doppler imaging system (Toshiba SSH-40A/SDS-21A with a 2.4 or 3.5 MHz transducer) or a real-time two-dimensional color flow imaging system (Hewlett-Packard 77020A with a 2.5 or 3.5 MHz transducer, Aloka SSD-870 with a 2.5 or 3.5 MHz transducer, or Toshiba SSH-160A with a 2.5 or 3.5 MHz transducer). Doppler recordings of transmitral flow velocity were obtained through an apical 4-chamber view with a Doppler cursor oriented parallel to the long-

axis plane of the LV, and the sample volume carefully placed at the tip of the mitral leaflets. In the pulsed wave Doppler examination, the following variables were obtained: 1) peak flow velocity during rapid diastolic filling (peak E) and at atrial contraction (peak A), 2) the ratio of peak E to peak A (E/A ratio), 3) LV isovolumic relaxation time (IRT), i.e., the time interval from the aortic closing component of the second heart sound on the phonocardiogram to the onset of diastolic flow velocity, and 4) deceleration time (DT) of early diastolic filling, i.e., the time from peak E to an extrapolation of the line along the decrease in velocity to the baseline. Mitral regurgitation (MR) was identified by continuous wave Doppler ultrasonography or by color flow imaging in multiple views and was classified as mild, moderate, or severe[21~23].

Statistical methods: Data are presented as means±one standard deviation. Each of the values obtained from the study patients was compared with that of the upper or lower limits of the normal subjects. Student's unpaired t test and chi-square statistics were used when comparing the data of the clinical characteristics and cardiac catheterization. Differences in the Doppler results among the 3 groups were analyzed by one way analysis of variance. Statistical significance was assumed when p value was less than 0.05.

Results

Patient characteristics: Six of the 9 patients with primary amyloidosis and 3 of the 19 with familial amyloidosis had grade III or IV (New York Heart Association (NYHA) classification) congestive heart failure on entry into this study. According to the hemodynamic criteria, 6 of the 28 patients were clinically judged to have restrictive ventricular physiology, and the remaining 22 were judged otherwise. Patients with restrictions were significantly older and had higher heart rates than patients without restriction. The cardiac index and stroke volume were significantly lower in patients with restrictive physiology than in patients without (**Table 1**).

As shown in **Table 2**, no significant difference was observed in blood pressure between patients with and without restrictive filling process. Ventricular wall thickness and the LA dimension were significantly greater and fractional shortening was lower in patients with restrictive physiology than in patients without restriction (**Figs. 1, 2**). Mild-to-moderate MR was detected in 18 (64%) of the 28 patients. All patients with restriction had MR, as compared with 12 (55%) of the 19 without it ($p<0.05$). MR was found to be moderate in all restrictive patients (**Fig. 1**) and moderate in 3 and mild in 9 in patients without restriction

Table 1. Hemodynamic findings

	Restrictive	Nonrestrictive	p value
Number of patients	6	22	
Age (yrs)	57.0 ± 5.2	44.6 ± 9.7	<0.01
HR (beats/min)	74.8 ±10.6	65.5 ± 8.9	<0.05
AoP (mean) (mmHg)	89.3 ±12.2	95.3 ±13.4	NS
LVEDP (mmHg)	22.8 ± 3.3	10.4 ± 2.5	<0.001
LVRFW (mmHg)	8.2 ± 3.0	2.0 ± 1.1	<0.001
PCWP (mean) (mmHg)	22.0 ± 7.6	8.7 ± 3.9	<0.001
CI (l/min/m^2)	1.75± 0.23	2.88± 0.45	<0.001
SV (ml/beat)	45.2 ± 1.5	65.9 ± 1.2	<0.001

HR=heart rate; AoP=aortic pressure; LVEDP=left ventricular end-diastolic pressure; LVRFW=left ventricular rapid filling wave; PCWP=pulmonary capillary wedge pressure; CI=cardiac index; SV=stroke volume.

Table 2. Clinical characteristics

	Restrictive	Nonrestrictive	p value
Number of patients	6	22	
Systolic BP (mmHg)	106 ±13	112 ±13	NS
Diastolic BP (mmHg)	64 ± 9	69 ±10	NS
VST (mm)	18.0± 1.1	12.3± 2.6	<0.001
PWT (mm)	17.8± 1.3	12.0± 2.4	<0.001
EDD (mm)	40.1± 5.4	44.5± 4.3	<0.05
ESD (mm)	29.3± 5.6	29.7± 5.0	NS
FS (%)	28.0± 4.2	36.5± 3.7	<0.001
LAD (mm)	38.7± 3.7	32.3± 4.9	<0.01
Incidence: CHF (%)	6(100)	3(14)	<0.001
MR (%)	6(100)	12(55)	<0.05

BP=blood pressure; VST=ventricular septal wall thickness; PWT=posterior wall thickness; EDD=end-diastolic dimension; ESD=end-systolic dimension; FS=fractional shortening; LAD=left atrial dimension; CHF=congestive heart failure; MR=mitral regurgitation.

(**Fig. 2**).

Doppler echocardiographic findings: At least one abnormality in the index of transmitral flow velocity was present in all of the 6 patients with restrictive physiology (**Fig. 3**) and in 16 (73%) of the 22 without restriction (**Fig. 4**). The remaining 6 patients exhibited normal values for each index, 4 of whom had normal echocardiographic features; whereas, 2 showed moderate wall thickening. In patients with a restrictive filling process, increased peak E was observed in 4 of the 6 patients, decreased peak A in 3, an increase in E/A ratio in all, shortening of the IRT in 2 and shortening of DT in 5. The mean peak E and E/A ratio in the group with restrictive physiology (86.5±19.5 cm/s and 3.01±0.61) were significantly greater than those in patients without restriction (50.0±12.7 cm/s, $p<0.001$ and 1.00±0.31, $p<0.001$), and in normal subjects (56.7±9.8 cm/s, $p<0.05$ and 1.52±0.26, $p<0.01$). Peak A was significantly lower in patients with restriction (29.5±8.6 cm/s) than in patients without restriction (52.0±14.3 cm/s, $p<0.001$) and in normal subjects (37.8±6.0 cm/s, $p<0.05$) (**Fig. 5**). The IRT was significantly shorter in patients with a restrictive filling process (64.6±4.0 ms) than that in patients without restriction (107.2±28.2 ms, $p<0.001$) and in normal subjects (71.2±8.6 ms, $p<0.05$). The DT was also significantly shorter in patients with restriction (82.3±9.0 ms), compared with that in patients without restriction (162.9±50.8 ms, $p<0.001$) and in normal subjects (128.9±20.6, $p<0.001$) (**Fig. 6**). In 22 patients with nonrestrictive ventricular physiology, there were a decrease in peak E in 3, an increase in peak A in 10, a decrease in E/A ratio in 8, prolongation of IRT in 14 and prolongation of DT in 10. The group with a nonrestrictive filling process, as a whole, showed a slightly lower peak E and significantly greater peak A ($p<0.001$) with a depressed E/A ratio ($p<0.001$) than did the normal subjects (**Fig. 5**). The IRT and DT were significantly prolonged in patients with nonrestrictive physiology compared with normal subjects ($p<0.001$ and $p<0.05$, respectively) (**Fig. 6**).

Discussion

This study demonstrates the markedly heterogeneous pattern of transmitral flow velocity in patients with amyloid heart disease. The results also show that restrictive ventricular hemodynamics are characterized by the increased peak flow velocity as well as a shortened rapid diastolic filling associated with reduced flow velo-

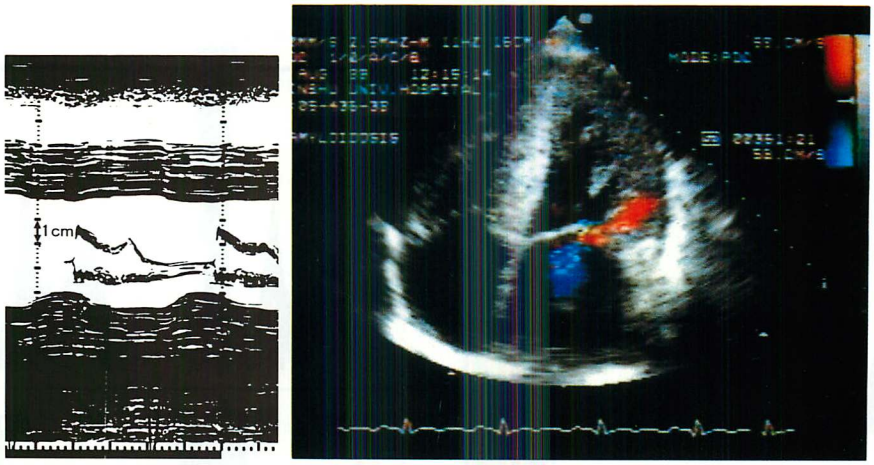

Fig. 1. M-mode and two-dimensional color Doppler echocardiograms of a 61-year-old woman with biopsy-proved amyloid heart disease and restrictive ventricular physiology.
Note marked ventricular wall thickening with depressed fractional shortening and moderate mitral regurgitation.

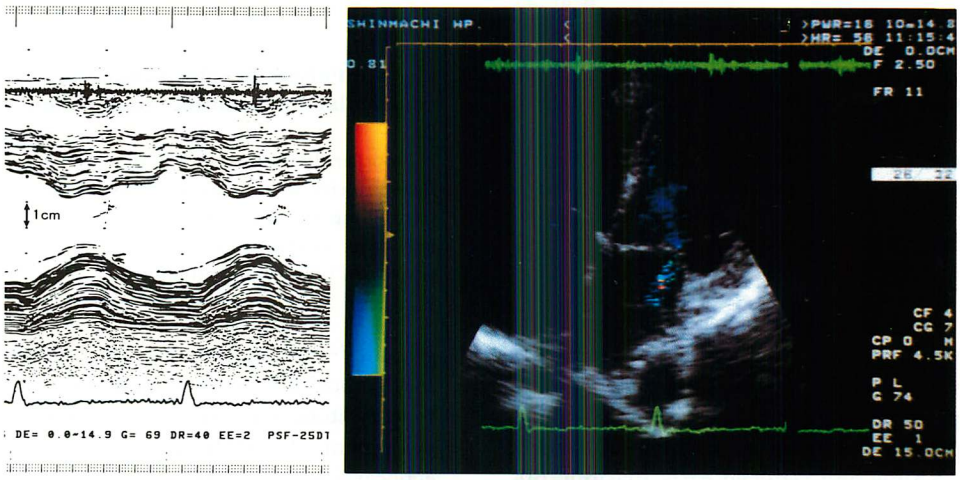

Fig. 2. M-mode and two-dimensional color Doppler echocardiograms of a 44-year-old woman with biopsy-proved cardiac amyloidosis and nonrestrictive ventricular physiology.
Ventricular septal wall thickness and posterior wall thickness are increased, but fractional shortening is normal. A mild mitral regurgitation is observed..

city of atrial systole on the Doppler mitral flow velocity curve.

In the present study, patients with restrictive hemodynamics showed marked myocardial amyloid infiltration associated with slightly depressed LV systolic function and a high incidence of MR[24] as assessed by echocardiography. Abnormal Doppler flow velocity patterns seemed characteristic of restrictive hemodynamics, with an early and abrupt completion of

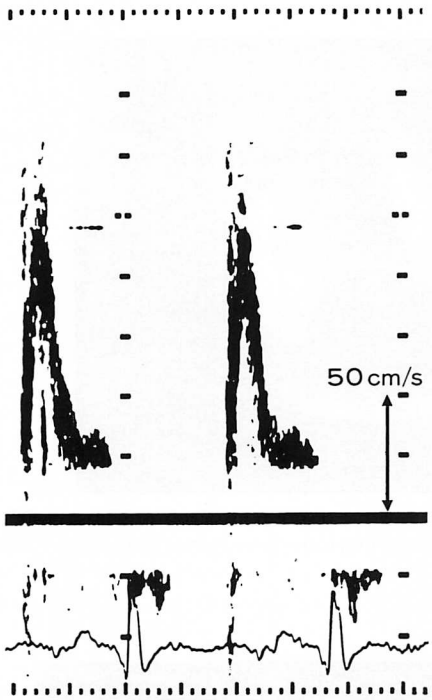

Fig. 3. Pulsed Doppler echocardiogram of left ventricular inflow of the same patient as in Fig. 1.

Transmitral flow velocity pattern shows an increased peak flow velocity and a shortening of the deceleration time of early diastolic filling with a reduced peak flow velocity at atrial contraction.

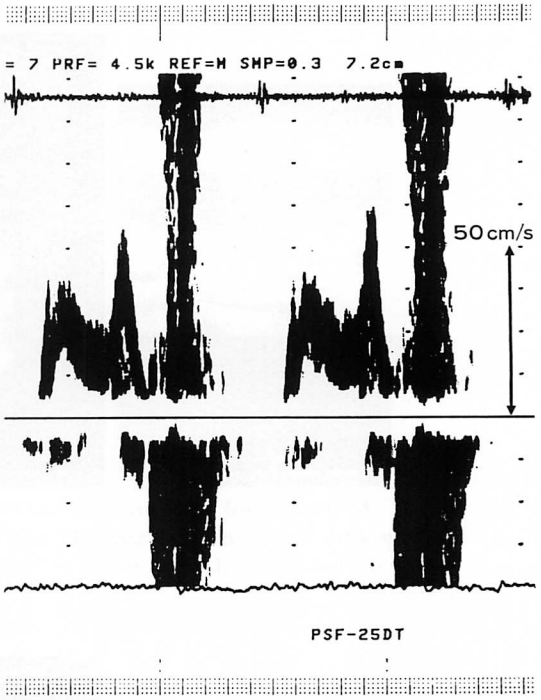

Fig. 4. Pulsed Doppler echocardiogram of left ventricular inflow of the same patient as in Fig. 2.

Doppler flow velocity pattern shows a reduced peak flow velocity as well as a prolongation of early diastolic filling and an increased peak flow velocity during atrial contraction. Left ventricular isovolumic relaxation time is also prolonged.

early diastolic filling. The patterns were quite different from those of patients with nonrestrictive physiology. In the latter group, the LV filling patterns were classified as either: 1) a filling pattern with the prolonged isovolumic relaxation time and reduced early diastolic filling as well as enhanced atrial contribution to ventricular filling or 2) a normal filling pattern. Some patients with normal patterns had normal echocardiograms while others exhibited moderate ventricular wall thickening. These findings indicated that there may be a wide spectrum of LV diastolic filling patterns depending on the magnitude of myocardial amyloid deposition in patients with amyloid heart disease. The results also confirmed the findings of prior echocardiographic[17,25~27], radionuclide angiographic[28], and mechanocardiographic[29] studies which indicated that diastolic impairment may precede the development of systolic dysfunction and definite echocardiographic abnormalities in this disorder.

Several investigators have recently reported similar observations on the Doppler transmitral flow velocity pattern in various disease states, including hypertrophic cardiomyopathy[30,31], dilated cardiomyopathy[32~34], coronary artery disease[33,35~37], and valvular aortic stenosis[38,39]. It has generally been accepted that Doppler mitral flow velocities accurately reflect the pressure difference between the LV and LA during

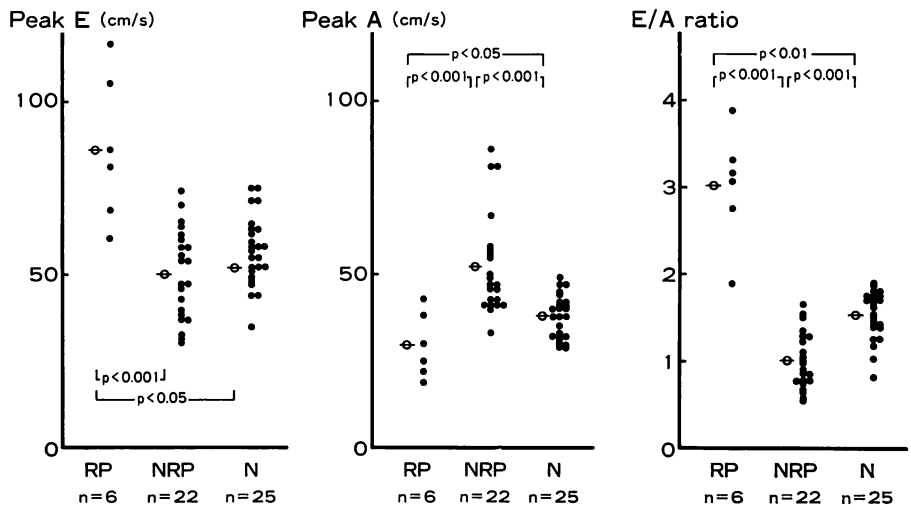

Fig. 5. Comparison of Doppler-derived indexes of left ventricular diastolic function (I).
Peak E=peak flow velocity of early diastolic filling; Peak A=peak flow velocity at atrial contraction; E/A=the ratio of peak E to peak A.

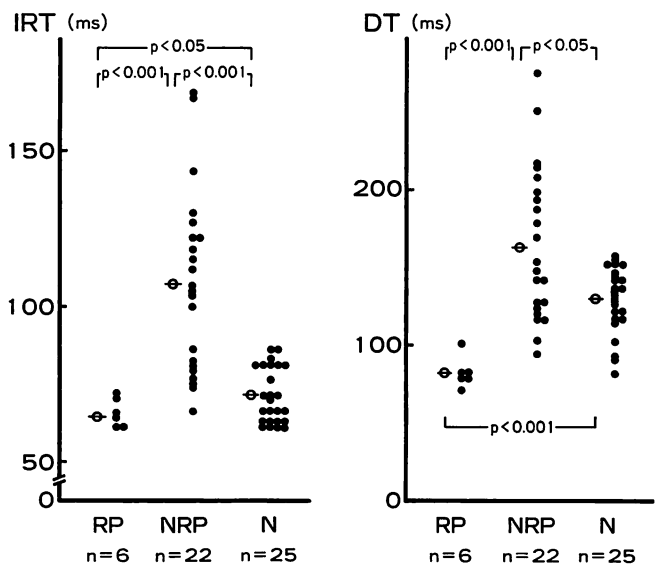

Fig. 6. Comparison of Doppler-derived indexes of left ventricular diastolic function (II).
IRT=isovolumic relaxation time; DT=deceleration time of peak flow velocity of early diastolic filling.

diastole, meanwhile, the flow velocity patterns are known to depend on multiple factors[40], including LA pressure at the opening of the mitral valve, ventricular relaxation, myocardial and chamber compliance of the LV and LA, passive viscoelastic properties of the myocardium,

heart rate, age, ventricular loading conditions, and valvular regurgitation. Therefore, in some studies in which Doppler echocardiographic measurements were compared with hemodynamic parameters, only weak, though significant correlations were found between the DT of early diastolic filling and the mean pulmonary capillary wedge pressure or LV rapid filling wave[33], and between late diastolic flow velocity and maximal negative dP/dt[35], LV end-diastolic pressure[34,39,39], or LV ejection fraction[38,39]. More recently, Stoddard et al.[37] reported that reduced early diastolic filling with compensatorily-augmented contribution of atrial systole to LV filling may reflect impaired relaxation instead of increased ventricular chamber stiffness, and that diminished atrial systolic filling may be related to increased chamber stiffness. Abnormalities in LV relaxation combined with chamber stiffness may influence the Doppler transmitral flow velocity pattern and complicate the evaluation of LV diastolic function in a clinical setting.

In our study, several mechanisms were considered as the possible causes of variable LV filling patterns in patients with amyloid heart disease. First, at a very early stage of myocardial amyloid deposition, LA pressure, LV pressure, and LV relaxation are all normal, which results in a normal filling pattern. Second, with progression of amyloid infiltration and prolonged LV relaxation, opening of the mitral valve will occur later on and the early diastolic transmitral pressure gradient will be reduced, assuming that LA pressure at the mitral valve opening remains constant. This leads to a prolongation of the IRT, a reduction in velocity as well as the prolongation of early diastolic filling, and an exaggerated atrial systolic filling as a compensatory mechanism[13]. In our study, most of the patients with this filling pattern showed normal pulmonary capillary wedge pressures as well as normal LV end-diastolic pressures. Third, in the far advanced stage, in which the patient's heart is very stiff as a result of profound amyloid infiltration, the disease is more symptomatic with high filling pressures. Elevated LA pressure, partly due to MR, at the time of mitral valve opening can be responsible for a greater peak mitral flow velocity in early diastole. In addition, an abrupt decrease in the transmitral pressure gradient as a result of rapid elevation of the LV diastolic pressure may account for shortening of the DT of the peak flow velocity of early diastolic filling. Moreover, an increased LV end-diastolic pressure can reduce the end-diastolic pressure difference between the LA and LV, reflecting a relatively reduced late diastolic peak flow velocity. This finding is consistent with the previous results obtained by Greenberg et al[41]; that the increasing LV filling pressure was associated with a decrease in atrial contribution to ventricular filling.

Fourth, some patients with nonrestrictive physiology and moderate amyloid deposition showed a normal LV diastolic filling pattern in the present study. This pattern may occur as the early diastolic pressure difference between the LA and gradually increased LV due to the elevated LA pressure[33]. To confirm these findings, further longitudinal investigations on precise hemodynamic correlates of Doppler-derived indexes of LV diastolic function are necessary.

要　約

心アミロイドーシスにおける左室拡張期流入動態：ドップラー心エコー図法による評価

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拘束型心筋症の血行動態を評価する目的で，心アミロイドーシスにおける左室流入血流パターンの特徴を検討した．本症患者28例（原発性9例，家族性19例）を対象とし，パルス・ドップラー法を施行した．8例が拘束型を呈し，非拘束型22例に比して心室壁の著明な肥厚および fractional shortening の低下を示した．左室流入血流パターンは，拘束型では拡張早期最大流入速度増加，減

速時間短縮，心房収縮期最大流入速度減少という特徴所見を呈した．一方，非拘束型では以下の3つの流入パターンのいずれかを示した．1) 左室等容拡張時間延長，拡張早期最大流入速度減少，減速時間延長，心房収縮期最大流入速度増加（軽度の心エコー図異常を伴った16例），2) 正常パターン（正常心エコー図を示した4例），3) 正常パターン（中等度の心室壁肥厚を認めた2例）．

以上より，心アミロイドーシスでは心筋へのアミロイド沈着の程度と関連して，左室流入血流パターンは多様であり，拘束型では非拘束型とは異なった特徴所見を示すと考えられる．

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