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Impact of left ventricular longitudinal functional mechanics on the progression of diastolic function in diabetes mellitus

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Abstract

Left ventricular (LV) diastolic dysfunction and longitudinal systolic dysfunction were identified in patients with diabetes mellitus (DM). This study's aim was to investigate the impact of LV longitudinal systolic function on LV diastolic function in DM patients with preserved LV ejection fraction (LVEF). We studied 177 DM patients with preserved LVEF (all $\geq 50\%$), and 82 age-, gender- and LVEF-matched healthy volunteers as control. Global longitudinal strain (GLS) was defined as the average peak strain of 18 segments from standard apical views, $GLS < 18\%$ as subclinical LV systolic dysfunction (LVSD), and LV dispersion as the standard deviation of time-to-peak strain from the same views. For DM patients with LVSD ($n=74$), E/A and E' were lower, and E/E' and isovolumic relaxation time (IVRT) were greater than for DM patients without LVSD ($n=103$) and normal controls ($n=82$). Moreover, these parameters were lower for DM patients without LVSD than for normal controls. Multivariate analysis revealed that GLS was a strong determinative factor for E' and E/E' ($\beta=0.30$, $p<0.001$ and $\beta=-0.25$, $p<0.001$, respectively), as was LV dispersion for E-wave deceleration time and IVRT ($\beta=0.21$, $p=0.002$ and $\beta=0.30$, $p<0.001$, respectively) independently of age. For normal subjects, however, only age was associated with all LV diastolic parameters. In conclusions, in contrast to age-related LV diastolic dysfunction in normal subjects, in DM patients with preserved LVEF, LV diastolic function was associated with LV longitudinal systolic function and LV dispersion independently of age. Our findings have obvious clinical implications for the management of DM patients.

Key Words: diabetes mellitus; diabetic cardiomyopathy; global longitudinal strain; left ventricular dispersion; left ventricular diastolic function; echocardiography

Introduction

According to the World Health Organization, the estimated global prevalence of diabetes mellitus (DM) was an astounding 9% for adults, and DM itself directly caused an equally 1.5 million deaths a year mainly through the increased risk of cardiovascular disease. The steady proliferation of DM is therefore a worldwide problem of vital importance. About 4 decades have passed since the first autopsy cases of diabetic cardiomyopathy by Rubler et al. were reported in 1972[1]. A significant finding mentioned in this report was that DM patients potentially die from congestive heart failure (HF) even without involvement of significant valvular, hypertensive, congenital, alcohol-related and coronary heart disease. Recently, DM has come to be considered an independent predictor of mortality, and also a contributor of the development of HF even in patients with preserved left ventricular (LV) ejection fraction (LVEF)[2, 3]. The detection of subclinical LV dysfunction has thus become increasingly important in the management of asymptomatic DM patients with preserved LVEF.

Diabetic cardiomyopathy is presented as a diastolic dysfunction, which is identified as the earliest functional alteration in the course of diabetic cardiomyopathy, and DM patients with diabetic cardiomyopathy are currently labelled as suffering from HF with preserved LVEF[4-6]. Furthermore, LV longitudinal systolic dysfunction has been also identified in asymptomatic DM patients with preserved LVEF without coronary artery disease. However, the possible associations of LV longitudinal function and LV diastolic function with the development of HF in DM patients

with preserved LVEF remain uncertain. Accordingly, the objective of our study was to test the hypothesis that, unlike age-related LV diastolic dysfunction in normal subjects, LV diastolic function in asymptomatic DM patients with preserved LVEF is affected by LV longitudinal systolic function.

Materials and Methods

Study population

We prospectively enrolled 190 consecutive DM patients who were admitted to Kobe University Hospital between July 2013 and July 2015. Patients were excluded from enrolment study if they met any of the following criteria: (1) history or suspicion of coronary artery disease; (2) LVEF <50%; (3) previous history of open-heart surgery and congenital heart disease; (4) evidence of excessive alcohol intake, toxin exposure, or history of myocarditis; (5) serious renal dysfunction defined as glomerular filtration rate <30 mL/min/1.73m²; (6) uncontrolled hypertension >180/100mmHg; (7) more than moderate valvular heart disease; (8) atrial fibrillation; (9) left bundle branch block. All patients underwent exercise stress or pharmacological testing such as treadmill exercise or stress myocardial perfusion scintigraphy less than 2 weeks after admission, and none of them showed an ischemic response. The diagnosis of DM was based on the World Health Organization criteria[7]. Thirteen of the enrolled patients (7%) were excluded from all subsequent analyses because of suboptimal quality of echocardiographic images. As a result, the

final study population consisted of 177 DM patients. Normal controls with similar age, gender, and EF distribution were randomly taken from our database. The resultant normal control group consisted of 82 subjects with no history of cardiovascular disease and completely normal electrocardiographic findings as well as two-dimensional and Doppler echocardiographic results. This study was approved by the local ethics committee of our institution, and written informed consent was obtained from all patients.

Transthoracic echocardiography

Less than 2 weeks after admission, each patient underwent a resting standard echocardiographic examination by means of a 3.5 MHz transducer on a single commercially available echocardiographic system (Vivid E9; General Electric Medical Systems, Milwaukee, WI). Digital routine grayscale two-dimensional cine loops from three consecutive heartbeats were obtained at end-expiratory apnea from standard parasternal and apical views. Sector width was optimized to allow complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained according to the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[8]. Conventional LV diastolic function was also evaluated based on current guidelines[9]. Early diastolic trans-mitral flow wave velocity (E), late diastolic atrial wave velocity (A) and the E-wave deceleration time (DT) were measured by using the pulsed-wave Doppler recording from the apical views. Isovolumic relaxation time (IVRT) was determined as the time difference from the end of aortic

valve closure until the onset of mitral inflow obtained by placing the cursor of the continuous wave Doppler at the LV outflow tract. Spectral pulsed-wave Doppler-derived early diastolic velocity (E') was obtained from the septal mitral annulus.

Speckle tracking strain analysis

Two-dimensional speckle-tracking strain analyses were performed with dedicated software (EchoPAC version 113; General Electric Medical Systems). Global longitudinal strain (GLS) was determined as the averaged peak longitudinal strain of 18 segments from the three standard apical views, and was expressed as an absolute value (Figure 1)[8]. Furthermore, LV dispersion was defined as the standard deviation of time-to-peak longitudinal strain from the same views (Figure 1)[10]. As previously detailed, the pre-defined cutoff for LV subclinical systolic dysfunction (LVSD) in DM patients with preserved LVEF was set at $GLS < 18\%$ [11-15].

Assessment of clinical data

For the enrolled DM patients, HemoglobinA1c, glycoalbumin, estimated glomerular filtration rate and lipid profile were obtained the day after admission. Albuminuria was quantitated from 24-hour urine collection. Careful medical interviews and detailed physical examinations were methodically and comprehensively performed by experienced diabetologists. Diabetic retinopathy was defined as a condition more serious than simple retinopathy or if previously treated with laser photocoagulation based on the evaluation of retinal photographs by experienced ophthalmologists. Hypertension was defined as > 140 mmHg systolic or > 90 mmHg diastolic blood pressure or

receiving hypertensive medical treatment. Dyslipidemia was defined as fasting low-density lipoprotein ≥ 140 mg/dl, or current use of medication for dyslipidemia. The cardio-ankle vascular index (CAVI) was obtained from all patients for assessment of vascular stiffness with commercially available equipment (VS-1500ATE/ATN; Fukuda-Denshi Company, Ltd., Tokyo, Japan).

Statistical analysis

Continuous variables were expressed as mean values with standard deviation for normally distributed data and medians with interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared by using Student t test or Mann-Whitney U test as appropriate. Proportional differences were evaluated with Fisher's exact test. Comparison of continuous parameters among three subgroups was assessed by one-way analysis of variance, and the Tukey or Steel-Dwass test was then used for post hoc analysis as appropriate. Analysis of covariance was used for comparison of subgroups affected by one covariate which showed linear correlation with them.

Since many parameters were associated with LV diastolic function, baseline data were first divided into the following four categories to clarify independency in DM patients:

- (1) Demographics and comorbidities: age, gender (female), body mass index, DM duration, type 1 DM, retinopathy, hypertension and dyslipidemia
- (2) Blood exam and urinary test results: HbA1c, glycoalbumin, low-density lipoprotein, triglyceride, estimated glomerular filtration rate and log-transformed albuminuria

(3) Cardiovascular measurements: systolic blood pressure, diastolic blood pressure, heart rate, CAVI

(4) Echocardiography (geometric and systolic parameters): end diastolic volume, LVEF, LV mass index, relative wall thickness, GLS, LV dispersion

Second, we chose determinative variables for each of the diastolic parameters such as E/A, DT, IVRT, E' and E/E' by using stepwise multivariate regression analysis for each category, in which a low cut-off p value of 0.15 was used so as not to overlook parameters with a potential influence. We then constructed the final multivariate regression model consisting of variables selected from the four models for each diastolic parameter with a cut-off p value of 0.10 for inclusion into the model. The inter-observer and intra-observer variabilities for GLS and LV dispersion were assessed by means of intra-class correlation coefficient from 20 randomly selected patients. Statistical significance was basically defined as p value < 0.05 for each step. SPSS version 16.0 (SPSS Inc., Chicago, IL) and MedCalc version 14.12.0 (MedCalc Software, Mariakerke, Belgium) were used for all analyses.

Results

Comparison of baseline characteristics

The baseline clinical and echocardiographic characteristics of 177 DM patients and 82 normal controls are presented in Table 1. LVSD, defined as GLS<18%, was detected in 74 DM

patients (42%), and the remaining 103 patients (58%) were classified as DM without LVSD. The mean age of these two groups was similar. Compared with normal controls and DM patients without LVSD, however, DM patients with LVSD were more likely to be obese and hypertensive and have a higher heart rate. Although body mass index of DM patients without LVSD was within normal range, it was significantly larger than that of normal controls. In addition, triglyceride and albuminuria levels in DM patients with LVSD were significantly higher than those in DM patients without LVSD. In addition, QRS duration for DM patients with LVSD was significantly longer than that for normal controls ($p<0.05$), and tended to be longer than that for DM patients without LVSD, but the difference was not statistically significant ($p=0.059$).

Comparison of echocardiographic parameters

E/A and E' for DM patients with LVSD were smaller, and E/E' and IVRT for DM patients with LVSD were larger compared to the other two groups. Moreover, these LV diastolic functional parameters for DM patients without LVSD were significantly more impaired than those for normal controls. According to the current guideline of the classification of LV diastolic functional grade[9], the prevalence of LV diastolic dysfunction in DM patients with LVSD was significantly higher than other 2 groups. GLS for DM patients with LVSD was significantly smaller and LV dispersion for DM patients with LVSD was significantly larger than for the other two groups. However, these two parameters were comparable for DM patients without LVSD and normal controls. In addition, LV mass index had weak correlation with GLS ($r=0.39$, $p<0.001$).

E/A, E' and E/E' significantly correlated with age for all subjects ($r=-0.68$, $p<0.001$; $r=-0.73$, $p<0.001$; $r=0.46$, $p<0.001$, respectively). We next compared E/A, E', and E/E' among subgroups with one covariate, i.e., age, using one way analysis of covariance as shown in Table 2 and Fig. 2. There were significant differences in the associations of each of the parameters of LV diastolic function with age among the three subgroups, suggesting that other factors than age, such as LVSD, were associated with LV diastolic function for DM patients.

Determinative factors of LV diastolic function for normal controls and DM patients

We constructed a two-step multivariate regression analysis for evaluation of independent associations with LV diastolic function for DM patients. Selected variables in the first-step multivariate analysis for each of the LV diastolic parameters are shown in Table 3. Final multivariate analysis was then performed for each LV diastolic function and only significant variables are shown with the corresponding standardized β and p values. A series of multivariate analyses revealed that GLS was a strong determinative factor for E' and E/E' ($\beta=0.30$, $p<0.001$; $\beta=-0.25$, $p<0.001$, respectively), while LV dispersion proved to be a strong determinative factor for DT and IVRT ($\beta=0.21$, $p=0.002$; $\beta=0.30$, $p<0.001$, respectively) independent of age or other clinical factors. On the other hand, GLS and LV dispersion were not associated with LV diastolic functions of normal controls. E/A, E', IVRT and E/E' depended exclusively on age ($\beta=-0.70$, $p<0.001$; $\beta=-0.86$, $p<0.001$; $\beta=0.74$, $p<0.001$; $\beta=0.58$, $p<0.001$, respectively) and DT on age and heart rate ($\beta=0.41$, $p<0.001$; $\beta=-0.27$, $p=0.008$, respectively).

Reproducibility of speckle-tracking parameters

The intra- and inter- observer variability as assessed on the basis of intra-class correlation coefficients were 0.948 (95% CI: 0.855-0.982) and 0.921 (95% CI: 0.775-0.973) for GLS and 0.976 (95% CI: 0.932-0.992) and 0.917 (95% CI: 0.764-0.971) for LV dispersion.

Discussion

This study offers the first evidence that LV longitudinal systolic function and dispersion are closely associated with LV diastolic function independently of age in asymptomatic DM patients with preserved LVEF without coronary artery disease. Such findings were not observed in normal subjects, and their LV diastolic function depended exclusively on age.

Impact of LV longitudinal function on LV relaxation in DM patients

Diabetic cardiomyopathy is currently defined as a diastolic dysfunction identifiable as the earliest functional alteration in the course of diabetic cardiomyopathy[4-6], while DM is known as a significant factor associated with HF with preserved LVEF. However, the exact mechanism of the development of LV diastolic function in DM patients remains uncertain. Although LV longitudinal systolic dysfunction has been identified in asymptomatic DM patients with preserved LVEF without coronary artery disease, LV longitudinal systolic function and LV diastolic function in DM patients are recently thought to be reduced simultaneously even in DM patients with their LVEF preserved[16-18]. Liu et al demonstrated that LV relaxation was significantly impaired even in

normotensive DM patients who were part of a large population-based cohort [19]. The same group also detected stepwise deterioration of both LV systolic and diastolic function in DM patients due to increased albuminuria, and they suggested that progression of uncontrolled DM led to LV diastolic dysfunction as well as LV systolic dysfunction[20]. In addition, some investigators have reported that GLS is associated with LV relaxation such as seen in E and E', and that reduced GLS can coexist with LV diastolic dysfunction in HF patients with normal LVEF[21, 22]. DM often incorporates with hypertension, obesity and microvascular complications, which can affect GLS and LV diastolic function. According to our previously study, obesity, hypertriglyceridemia, nephropathy and neuropathy were associated with GLS in DM patients, but hypertension was not[14].

It was further reported that LV dispersion, which reflects the heterogeneity of timing of regional LV myocardial contraction, plays an important role and serves as a prognostic marker for HF patients independent of LVEF. Zoroufian et al used two-dimensional speckle-tracking strain to demonstrate that asymptomatic DM patients showed significant LV dispersion [23]. However, little is known about LV dispersion in relation to LV diastolic dysfunction. A previously study reported a significant correlation of LV post-systolic wall motion with isovolumic relaxation time for HF patients[24]. Moreover, Santos et al demonstrated that LV dispersion in HF patients with preserved LVEF increased in tandem with the progression of LV diastolic dysfunction and prolonged QRS duration[25]. In our study presented here, QRS duration proved to be a strong determinant factor of

LV dispersion ($\beta=0.20$, $p=0.004$) independent of other associated factors including age, BMI, DM duration and heart rate (data not shown). Furthermore, DM itself and unstable blood sugar control were found to be associated with prolonged QRS and cardiac autonomic neuropathy, and additionally discovered that improvement of metabolic control redounded on shortening of QRS in conjunction with improved LV filling pattern[26]. It can therefore be assumed that prolonged delay in the conducting system of the heart caused by DM is linked to LV diastolic dysfunction via an increase in mechanical LV dispersion.

In this study, GLS was shown to be a strong determinative factor for E' and E/E' , and LV dispersion a strong determinative factor for DT, IVRT independently of age and other clinical factors for DM patients. On the other hand, these LV diastolic functions depended exclusively on age for age-, gender- and LVEF-matched normal controls. In terms of clinical-pathological factors, LV myocardium of DM patients showed patchy myocardial scarring and a greater degree of fibrosis than did hypertensive patients without DM[27]. Our findings suggest that reduced GLS and increased LV dispersion can affect the progression of LV diastolic dysfunction regardless of age, that is to say, LV diastolic dysfunction can be linked to such pathological findings and constitute a plausible explanation for the fact the DM itself is a major risk factor for mortality and development of HF in patients with normal LVEF[3] (Fig. 3).

Clinical implications

The pathogenesis of diabetic cardiomyopathy is considered to be multifactorial, but both

LV longitudinal systolic function and LV diastolic function could be key factors for the development of HF in asymptomatic DM patients with preserved LVEF. However, the association of these functions with the development of HF remains uncertain. Moreover, Doppler-derived conventional echocardiographic parameters of LV diastolic function are greatly affected by age and are characterized by strong load dependency[28, 29]. Even if DM patients with preserved LVEF are in clinically stable condition, findings for the assessment of GLS and LV dispersion may predict future development of LV diastolic dysfunction. It is therefore advisable for diabetologists and cardiologists to jointly strategize for better management of DM patients to them from developing and suffering from HF.

Study limitations

This was a cross-sectional study which covered a relatively small number of patients in a single center, so that future studies of larger patient populations with longitudinal cohort design are necessary to validate our findings. Finally, this population included DM patients with hypertension, so that another study using normotensive DM patients may be performed to confirm a direct effect of DM on LV longitudinal systolic function and LV diastolic function.

Conclusions

In contrast to age-related LV diastolic dysfunction in normal subjects, in asymptomatic DM patients with preserved LVEF without coronary artery disease, some important parameters for LV diastolic function was associated with LV longitudinal systolic function and LV dispersion

independently of age. Our findings thus have obvious clinical implications for the management of DM patients.

Compliance with Ethical Standards

Conflict of interest: Yasuhide Mochizuki declares that he has no conflict of interest. Hidekazu Tanaka declares that he has no conflict of interest. Kensuke Matsumoto declares that he has no conflict of interest. Hiroyuki Sano declares that he has no conflict of interest. Hiroyuki Shimoura declares that he has no conflict of interest. Hiroyuki Shimoura declares that he has no conflict of interest. Junichi Ooka declares that he has no conflict of interest. Takuma Sawa declares that he has no conflict of interest. Yoshiki Motoji declares that he has no conflict of interest. Keiko Ryo-Koriyama declares that he has no conflict of interest. Yushi Hirota declares that he has no conflict of interest. Wataru Ogawa declares that he has no conflict of interest. Ken-ichi Hirata declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Informed consent was obtained from the patient.

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Figure Legends

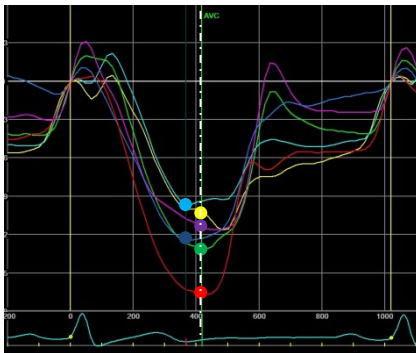
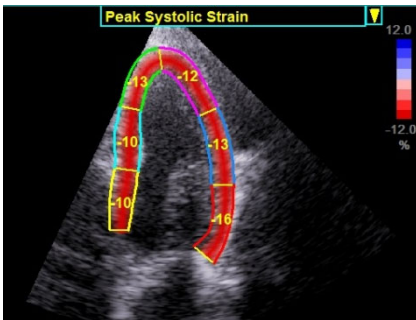
Figure 1: Example of two-dimensional speckle-tracking imaging obtained from the three standard apical views and corresponding longitudinal time-strain curves from 18 left ventricular (LV) segments. Global longitudinal strain was determined as the averaged peak longitudinal strain of 18 segments, and was expressed as an absolute value. LV dispersion was defined as the standard deviation of time-to-peak longitudinal strain from 18 segments.

Figure 2: Dot plots of left ventricular (LV) diastolic function including E/A, E' and E/E' versus age in normal controls, diabetes mellitus (DM) patients with LV subclinical systolic dysfunction (LVSD), and DM patients without LVSD.

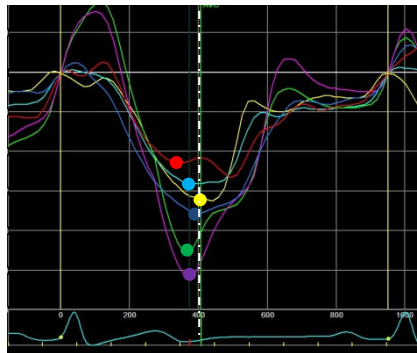
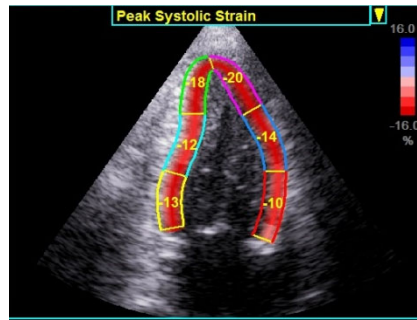
Figure 3: Schema of the impact of global longitudinal strain (GLS) and left ventricular (LV) dispersion on LV diastolic function in normal subject and diabetes mellitus. In contrast to age-related LV diastolic dysfunction in normal subject, in diabetes mellitus, LV diastolic function was associated with LV longitudinal functional mechanics such as GLS and LV dispersion independently of age.

Global Longitudinal Strain

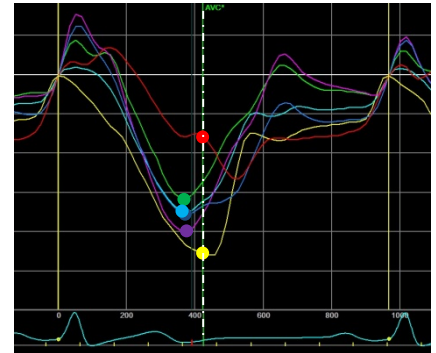
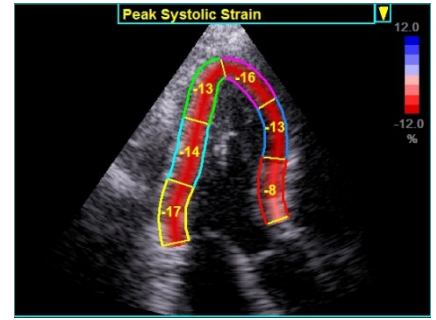
Apical 4-chamber view



Apical 2-chamber view

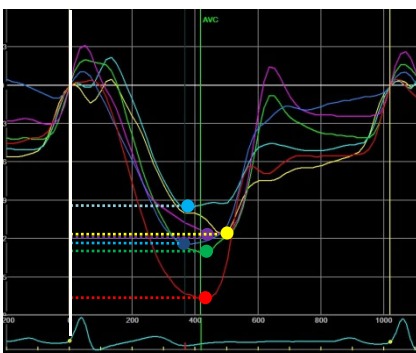
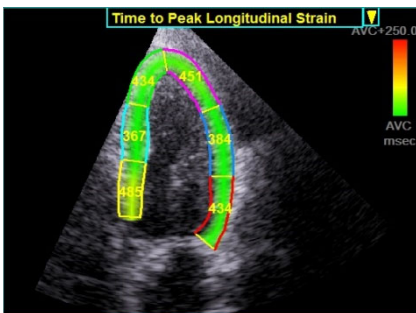


Apical long-axis view

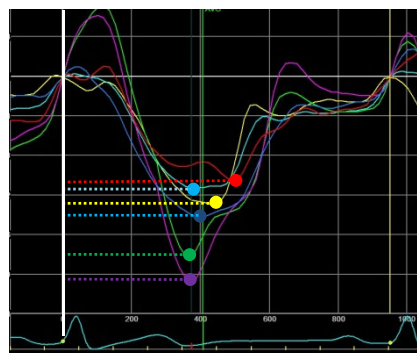
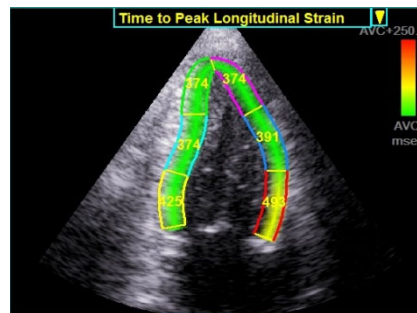


LV Dispersion

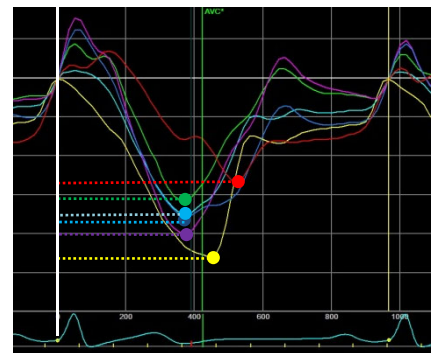
Apical 4-chamber view

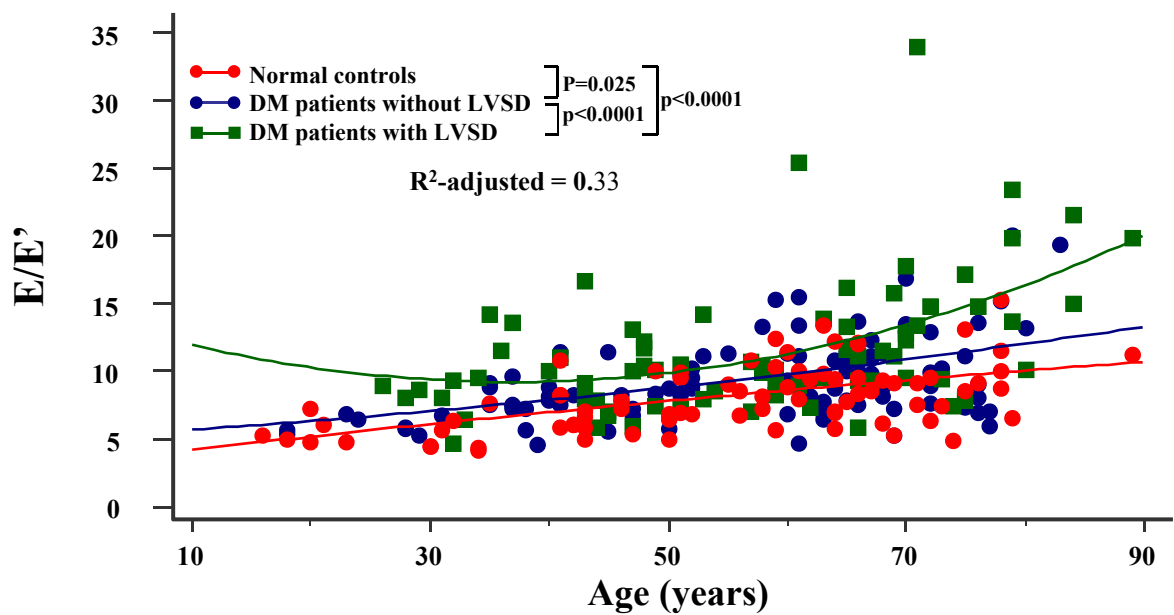
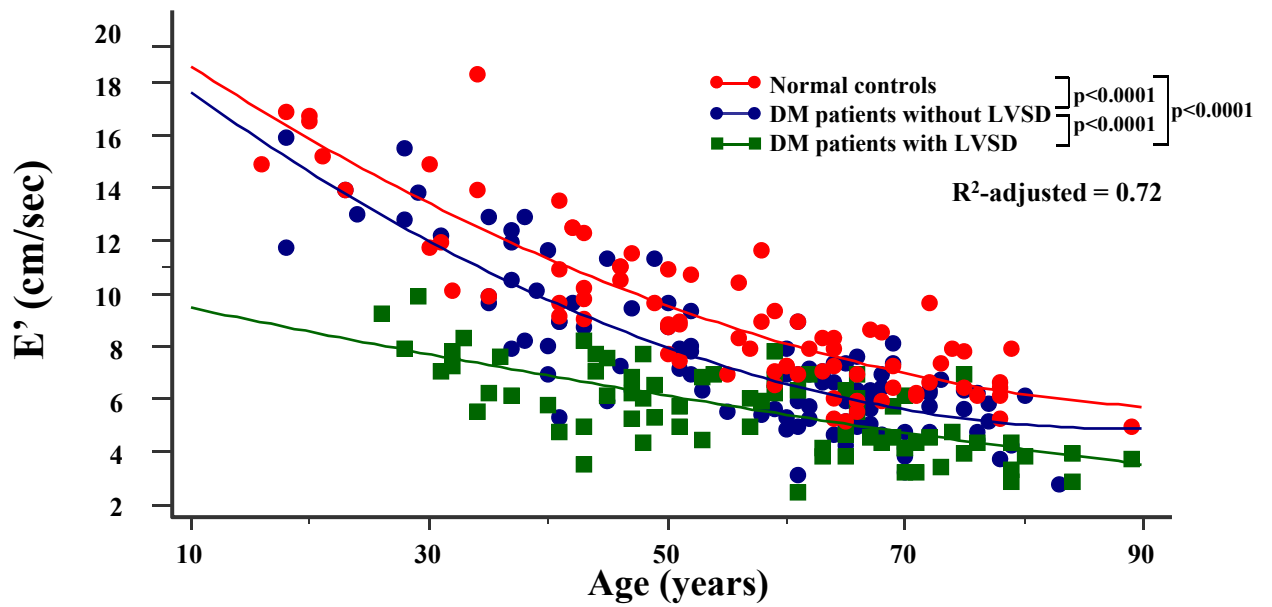
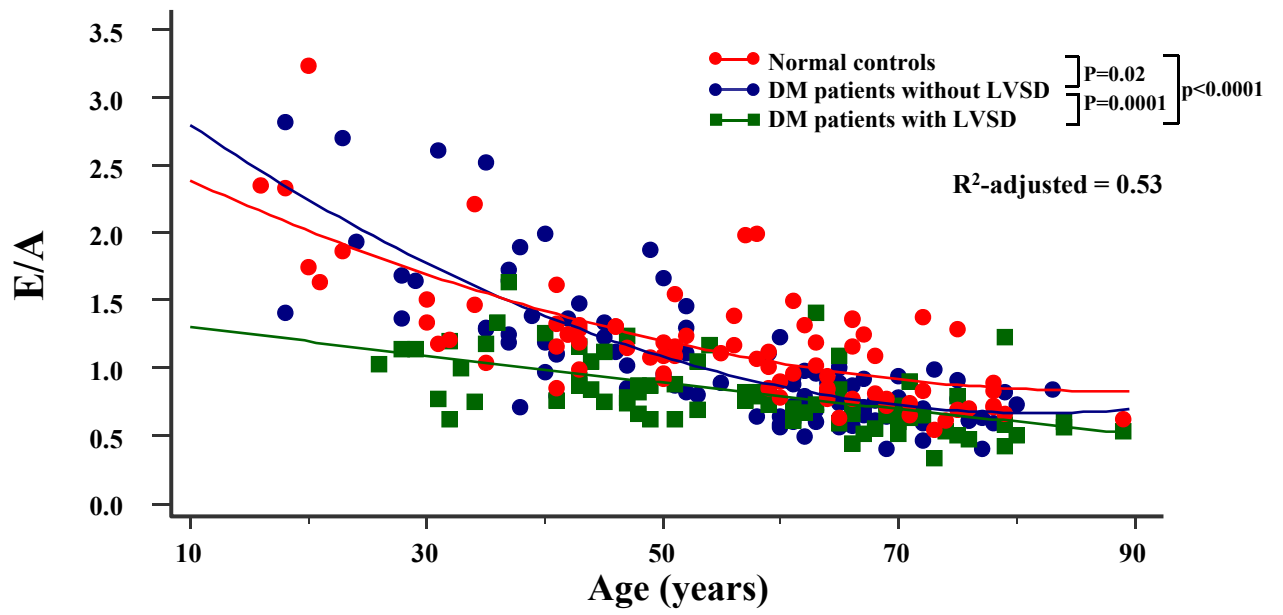


Apical 2-chamber view



Apical long-axis view





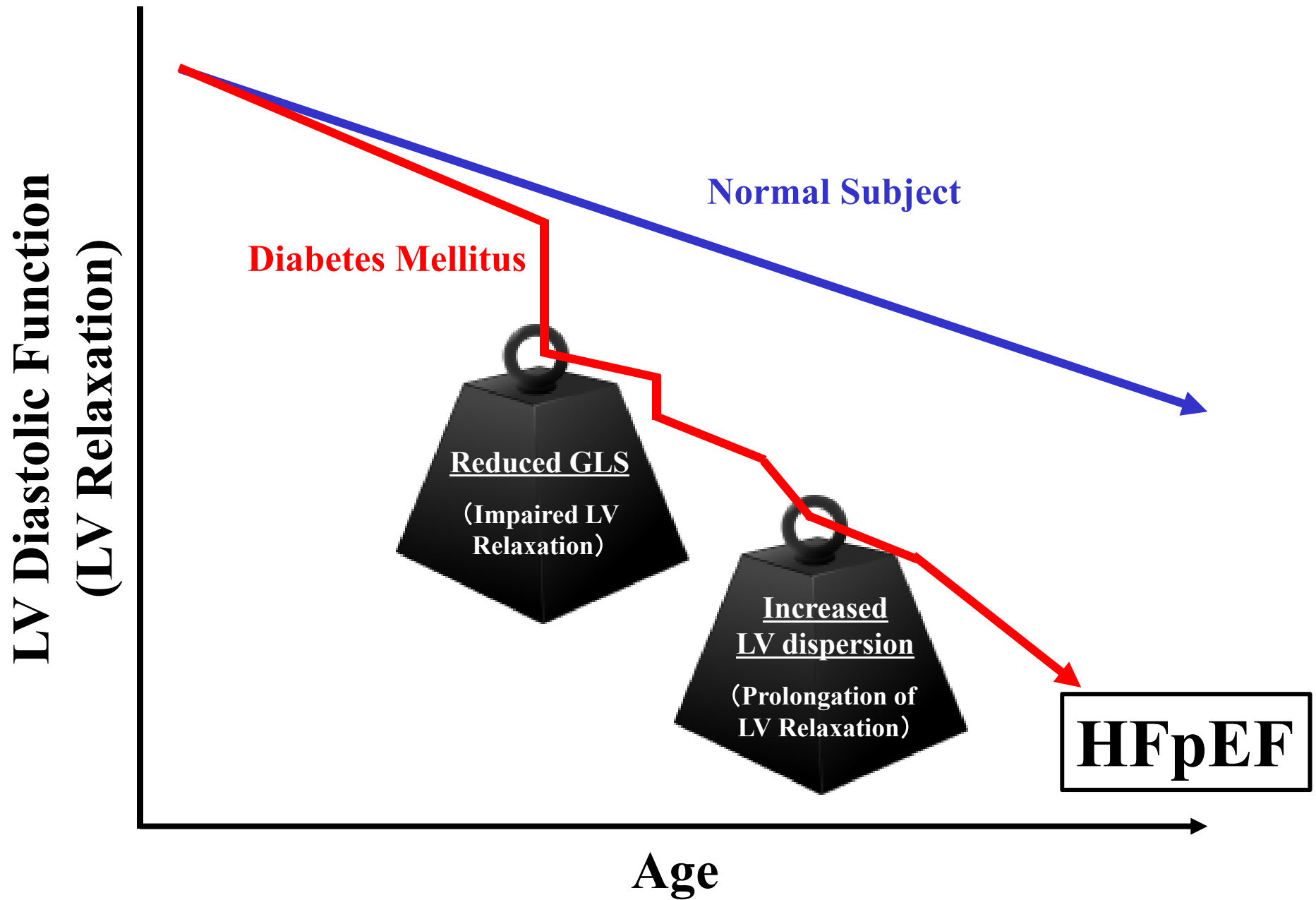


Table 1
Baseline Characteristics of Subjects

	Normal Controls (n=82)	DM patients <u>without</u> LVSD (n=103)	DM patients <u>with</u> LVSD (n=74)
<u>Clinical Data</u>			
Age, years	55±17	56±16	57±17
Female, n (%)	49(60)	65(63)	33(45)*
Height, m	1.62±0.97	1.60±0.09	1.62±0.10
Weight, kg	57±13	60±12†	70±17*
Body Mass Index, kg/m ²	22±3	23±4†	27±5*
Systolic blood pressure, mmHg	117±19	121±17	132±21*
Heart rate, bpm	66±11	67±11	73±11*
QRS duration, msec	88±10	90±13	93±15†
DM duration, years	-	11±8	13±10
CAVI	-	7.4±2.6	6.8±3.3
DM type 2, n (%)	-	60(58)	65(88)‡
Hypertension, n (%)	-	43(42)	36(48)
Dyslipidemia, n (%)	-	56(54)	42(57)
Retinopathy, n (%)	-	29(28)	30(41)
<u>Blood Exam and Urinary Test</u>			
HbA1c, %	-	8.6±2.3	8.7±1.9
Glycoalbumin, %	-	24.8±9.4	23.1±9.0
Low-density lipoprotein, mg/dl	-	101±34	109±34

Triglyceride, mg/dl	-	111±67	166±75‡
eGFR, ml/min/1.73m ²	-	77±22	72±29
Albuminuria, mg/day	-	8(3.5-18)	39(9.5-200)‡
<u>Medical treatment</u>			
CCB, n (%)	-	24(23)	28(38)
ACEI/ARB, n (%)	-	32(31)	41(55)‡
β-Blocker, n (%)	-	6(6)	8(11)
Statin, n (%)	-	36(35)	41(55)‡
Insulin, n (%)	-	65(63)	45(61)
DPP-4I, n (%)	-	32(31)	36(49)‡
GLP-1RA, n (%)	-	6(6)	9(12)
Sulfonylurea, n (%)	-	16(16)	14(19)
α-GI, n (%)	-	17(16)	15(20)
Thiazolidine, n (%)	-	5(5)	8(11)
Metformin, n (%)	-	35(34)	36(49)
<u>Echocardiography</u>			
Left atrial volume index, ml/m ²	26±9	28±7	31±10*
Relative wall thickness	0.39±0.07	0.41±0.10	0.51±0.11*
LV mass index, g/m ²	71±19	69±18	85±19*
LV end systolic volume, ml	27±9	24±8	29±11‡
LV end diastolic volume, ml	76±23	72±21	79±22
LV ejection fraction, %	66±5	67±4	65±5‡
Stroke volume, ml	68±15	64±13	63±13

E/A	1.19±0.45	1.03±0.49†	0.82±0.26*
DT	181±40	195±50	196±57
IVRT	68±17	81±21†	89±21*
E'	9.3±3.1	7.5±2.8†	5.7±1.6*
E/E'	8.1±2.4	9.5±3.0†	11.7±5*
Global longitudinal strain, %	20.5±2.0	20.5±1.7	16.0±1.8*
LV Dispersion, msec	34±10	37±15	46±13*
<u>LV diastolic function</u>			
Normal, n (%)	69 (84)	86 (83)	42 (57) *
Intermediate, n (%)	13 (16)	14 (14)	21 (28) *
Diastolic dysfunction, n (%)	0 (0)	3 (3)	11 (15) *

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

DM=diabetes mellitus; CAVI= Cardio-Ankle Vascular Index; GFR=estimated glomerular filtration rate; CCB=calcium channel blocker;

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; DPP-4I=dipeptidyl peptidase-4 inhibitor; GLP-1RA=glucagon like peptide-1receptor agonist; α-GI=α-glucosidase inhibitor; LV=left ventricular; E=peak early diastolic mitral flow velocity; A=peak late diastolic mitral flow velocity; DT=E wave deceleration time; IVRT= isovolumic relaxation time; E'= Spectral pulsed-wave Doppler–derived early diastolic velocity from the septal mitral annulus.

*: significant difference vs. normal controls and DM without LVSD (p<0.05)

†: significant difference vs. normal controls (p<0.05)

‡: significant difference vs. DM without LVSD (p<0.05)

Table 2
Analysis of Covariance for LV Diastolic Parameters among Subgroups

	Pairwise comparisons	p value*	95% CI*
E/A (R ² -adjusted = 0.53)	DM patients without LVSD vs. DM patients with LVSD	0.0001	0.085 – 0.310
	DM patients without LVSD vs. Normal controls	0.02	0.015 – 0.233
	DM patients with LVSD vs. Normal controls	<0.0001	0.203 – 0.440
E' (R ² -adjusted = 0.72)	DM patients without LVSD vs. DM patients with LVSD	<0.0001	1.194 – 2.359
	DM patients without LVSD vs. Normal controls	<0.0001	0.968 – 2.100
	DM patients with LVSD vs. Normal controls	<0.0001	2.697 – 3.924
E/E' (R ² -adjusted = 0.33)	DM patients without LVSD vs. DM patients with LVSD	<0.0001	0.993 – 3.253
	DM patients without LVSD vs. Normal controls	0.025	0.116 – 2.314
	DM patients with LVSD vs. Normal controls	<0.0001	2.147 – 4.529

*Bonferoni corrected p value and 95% Confidence Interval for differences of 2 subgroups

Covariate for analysis of covariance; age

CI=confidence interval; LVSD=left ventricular systolic dysfunction; NC=normal control; E=peak early diastolic mitral flow velocity; A=peak late diastolic mitral flow velocity; E'= Spectral pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus

Table 3
Multivariate Analysis for LV Diastolic Function in DM Patients

Dependent Variable	Selected variables at first step analysis	Final multivariate analysis
E/A	(1) Age, type 1DM, Retinopathy, Dyslipidemia (2) eGFR, Triglyceride (3) sBP, HR, CAVI (4) EDV, GLS, Dispersion	Age: $\beta=-0.58$, $p<0.001$ HR: $\beta=-0.29$, $p<0.001$ type 1DM: $\beta=0.17$, $p=0.003$ LV dispersion:$\beta=-0.14$, $p=0.013$
DT	(1) Age, type 1DM, Retinopathy, Dyslipidemia (2) GA, eGFR (3) HR, CAVI (4) EDV, GLS, Dispersion	HR: $\beta=-0.32$, $p<0.001$ Age: $\beta=0.31$, $p<0.001$ LV dispersion:$\beta=0.21$, $p=0.002$ type 1DM: $\beta=0.15$, $p=0.024$
IVRT	(1) Age, Gender(Female), Dyslipidemia (2) HbA1c, eGFR (3) CAVI (4) EDV, GLS, Dispersion	Age: $\beta=0.30$, $p<0.001$ LV dispersion:$\beta=0.30$, $p<0.001$ Gender(Female): $\beta=-0.18$, $p=0.007$ HbA1c: $\beta=0.17$, $p=0.011$
E'	(1) Age, type 1DM, Retinopathy, Hypertension (2) Triglyceride, eGFR (3) sBP, CAVI (4) EDV, LVMI, RWT, GLS, Dispersion	Age: $\beta=-0.48$, $p<0.001$ GLS:$\beta=0.30$, $p<0.001$ LV dispersion:$\beta=-0.25$, $p<0.001$ EDV: $\beta=0.17$, $p=0.001$

		type 1DM: $\beta=0.10$, $p=0.028$ LVMI: $\beta=0.11$, $p=0.033$
E/E'	(1) Age, Gender(Female), Retinopathy, Hypertension (2) eGFR, Albuminuria (Log) (3) sBP (4) LVEF, LVMI, GLS, Dispersion	Age: $\beta=0.32$, $p<0.001$ Gender(Female): $\beta=0.29$, $p<0.001$ GLS: $\beta=-0.25$, $p<0.001$ LVMI: $\beta=0.25$, $p<0.001$ eGFR: $\beta=-0.20$, $p<0.003$

E=peak early diastolic mitral flow velocity; A=peak late diastolic mitral flow velocity; DT=E wave deceleration time; IVRT= isovolumic relaxation time; E'= Spectral pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus; GLS=global longitudinal strain; BMI=body mass index; GA= glycoalbumin; eGFR= estimated glomerular filtration rate; sBP= systolic blood pressure; LVMI= LV mass index; RWT= relative wall thickness

Category of variables;

- (1) **Demographics and comorbidities**: age, gender(female), body mass index, DM duration, type 1 DM, retinopathy, hypertension and dyslipidemia
- (2) **Blood exam and urinary test**: HbA1c, glycoalbumin, low-density lipoprotein, triglyceride, estimated glomerular filtration rate and log-transformed albuminuria
- (3) **Cardiovascular measurements**: systolic blood pressure, diastolic blood pressure, heart rate, CAVI
- (4) **Echocardiography** (geometric and systolic parameters): end diastolic volume, LVEF, LV mass index, relative wall thickness, GLS, LV dispersion