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Discrepancy between Systolic and Diastolic Dysfunction
of the Left Ventricle
in Patients with Duchenne Muscular Dystrophy

(Duchenne 型進行性筋ジストロフィー症患者における
左室収縮障害と拡張障害の解離)

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Duchenne 型進行性筋ジストロフィー症患者における
左室収縮障害と拡張障害の解離

竹中　晃、横田充弘、岩瀬正嗣、宮口和彦、林博史、斎藤英彦

Akira Takenaka, MD, Mitsuhiro Yokota*, MD, Masatsugu Iwase, MD, Kazuhiko Miyaguchi, MD, Hiroshi Hayashi, MD, and Hidehiko Saito, MD.

From *First Department of Internal Medicine,*
Nagoya University School of Medicine, and
*Department of Clinical Laboratory**,*
Nagoya University Hospital,
Nagoya, Japan.

Reprint requests: Mitsuhiro Yokota, MD,
Department of Clinical Laboratory,
Nagoya University Hospital,
65, Tsurumai-cho, Showa-ku, Nagoya, Japan, 466.
Tel. (052) 741-2111 (Ext 2360)

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Abstract

To assess the systolic and diastolic dysfunction of the left ventricle (LV) in relation to age and the severity of impaired activity in Duchenne muscular dystrophy (DMD), we performed M-mode, two-dimensional and pulsed-wave Doppler echocardiography. Subjects consisted of 45 males with DMD aged 8 to 25 years and age-matched healthy controls. We observed that systolic dysfunction began in the first decade of life, with some patients showing severe systolic dysfunction in their early teens. However, such dysfunction did not always depend on the severity of the skeletal muscle disease. No patients with DMD showed an increase in peak atrial velocity and time-velocity integrals of the atrial contraction velocity curve, findings frequently reported to precede the abnormalities in many cardiac diseases; it was thought they did not have an increase in left atrial compensation. Diastolic dysfunction may not routinely precede or accompany the systolic dysfunction in DMD, in contradistinction to most of studies in patients with ischaemic or hypertensive heart disease. DMD patients may usually show a predominance of systolic dysfunction.

Introduction

Duchenne muscular dystrophy (DMD) is a sex-linked recessive disorder that leads to the degeneration of the systemic skeletal and cardiac muscles. Its onset is in the first decade of life. Most patients die during their second decade from respiratory insufficiency produced by the respiratory muscle impairment or from respiratory infections such as pneumonia[1]. Another cause of death is severe cardiac failure caused by the impairment of cardiac muscles[1]. The cardiac involvement of DMD[1-5] has been well documented. Many reports have described the electrocardiographic abnormalities[6-9,12,13] that predict the cardiac pathology[8-11]. Other reports have emphasized the importance of assessing the left ventricular (LV) function using M-mode and two-dimensional echocardiographic techniques[13-21]. The cardiac failure usually develops shortly before death without prodromal symptoms. Latent congestive heart failure may be present in some patients who do not demonstrate overt cardiac decompensation .

Congestive heart failure is usually associated with ventricular systolic dysfunction and cardiac enlargement. It has recently been recognized that left ventricular diastolic dysfunction produces congestive heart failure in the absence of an overtly abnormal systolic performance in patients with systemic hypertension or ischaemic heart disease[22-26]. There are few reports on the cardiac condition of patients with DMD, especially regarding the diastolic abnormalities. Our objective was to assess the systolic and diastolic dysfunction of the left ventricle in relation to age and the severity of impaired activity in patients with DMD using M-mode, two-dimensional and pulsed-wave Doppler echocardiographic techniques.

Materials and methods

STUDY POPULATION

We studied 45 males with DMD aged 8 to 25 years (mean ± SD, 14.7 ± 4.1 years) who had been admitted to the Suzuka National Sanatorium. Their height ranged from 1.12 to 1.61 m (1.45 ± 0.13 m), the body weight from 17.0 to 50.4 kg (32.3 ± 9.4 kg), and the body surface area (BSA) from 0.77 to 1.50 m^2 (1.15 ± 0.19 m^2). DMD was diagnosed on the basis of established criteria[1], including the history of the patient and his family, physical examination, serum creatine phosphokinase activity, and the results of electromyography and muscle biopsy. They were classified into disease stages ranging from stage 1, least severe, to stage 8, most severe, according to the criteria of Swinyard and Deaver[27]. This classification is based on the pattern, ability and method of ambulation, and adequacy of activities of daily living (Table 1). Six patients showed signs of respiratory insufficiency ($PaCO_2 > 50$ torr); 2 of whom required a body respirator[28]. Except for 4 patients taking digitalis, none was receiving cardiac medications at the time of study. All had a normal blood pressure. None had overt signs of dehydration, left-sided heart failure (pulmonary venous congestion on the chest roentgenogram , pulmonary rales, effusion), or right-sided heart failure (peripheral edema, hepatomegaly, ascites). Only one patient had experienced a previous episode of congestive heart failure.

The control group consisted of 40 normal males aged 7 to 25 years (16.4 ± 5.2 years) who were selected at random to undergo echocardiographic examinations to evaluate the normal spectrum of LV ejection fraction (EF) and pulsed-wave Doppler measurements of LV diastolic function. Informed consent was obtained from each participant before the study.

ECHOCARDIOGRAPHIC EXAMINATION

Each patient underwent a M-mode, two-dimensional and pulsed-wave Doppler echocardiographic examination. Images were obtained on a Hewlett-Packard 77020AC phased-array sector scanner with a 2.5 MHz transducer and were recorded on VHS videotape. Recordings were done with the subject breathing freely. The patients were studied in either the supine or left lateral decubitus, with the transducer in the fourth or fifth left intercostal space close to the sternum. If pectus excavatum or straight thoracic spine was present, an additional approach was included in the examination. Simultaneous echoes from the interventricular septum and the LV posterior wall were obtained at the level of the tips of the mitral leaflets. Only high quality tracings showing clear continuous echoes throughout the cardiac cycle were used for analysis according to the recommendations of the American Society of Echocardiography[29]. We obtained interventricular septal thickness (IVST), LV posterior wall thickness (LVPWT), LV diastolic dimension (LVDd) and LV systolic dimension (LVDs). We adopted normal ranges of echocardiographic measurements by Henry et al.[30]. The apical four-chamber view was used to estimate LV volume. A detailed outline of this method and its validation has been previously reported[31]. We concentrated on the left ventricle, with the septum placed vertically in the center of the imaging field and the lateral walls well visualized. Because of loss of visual integration in the stop frame mode, each image was traced manually and then the video recording played in real time under the tracing to ensure visually accurate endocardial definition. The LV volume formula used is based on the area-length method of Sandler and Dodge[32], where $V = 8X2/3\pi Y$ (V=LV volume, X=LV area, Y=LV length). LV end-diastolic volume and LV end-systolic volume were obtained, and LV ejection fraction (EF) was calculated. After the two-dimensional examination, mitral and aortic flow were obtained from the cardiac apex using pulsed-wave Doppler echocardiography. For mitral flow, the sample volume was placed in the left ventricular inflow tract at the level of the mitral leaflet tips. For aortic flow, the sample volume was placed in the left ventricular outflow tract just below the level of the aortic valve. Doppler measurements were taken by replaying the videotaped velocity tracing. Variables of diastolic function included: 1) peak early (E) and peak atrial filling velocity (A); 2) ratio of A to E (A/E); 3) time-velocity integrals of the atrial (IA) and total filling velocity curve (IF); and 4) ratio of IA to IF (IA/IF). Cardiac output (CO) was the product of the time-velocity integral of left ventricular outflow, aortic annulus diameter at mid-systole using the parasternal long axis view, and the heart rate. Cardiac index (CI) was calculated from the quotient of CO divided by the BSA. We used the EF and CI as indices of systolic function.

DATA ANALYSIS

The M-mode, two-dimensional and Doppler measurements analyzed represent the average of three cardiac cycles. Linear regression analysis was used to compare the systolic indices obtained by echocardiography with age or disease stage, and to compare EF with A/E or IA/IF. Nonpaired t-tests were used for comparisons between DMD patients and the controls. A probability (p) value less than 0.05 was considered statistically significant. All data are expressed as mean ± 1 standard deviation (SD).

Results

RELATION BETWEEN PATIENT AGE AND DISEASE STAGE

Figure 1 shows that the functional disability of the DMD patients worsened

with age.

TWO-DIMENSIONAL AND PULSED-WAVE DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT OF SYSTOLIC FUNCTION

Because of the severe deformity of the thorax, clear images on two-dimensional and Doppler echocardiography could be obtained in only a limited number of patients. We were able to measure EF in 37/45 (82.2 %) patients and CI in 41/45 (91.1 %) patients. Two patients who showed moderate or severe mitral regurgitation on pulsed-wave Doppler echocardiography were excluded from the following analysis.

The EF in the healthy controls ranged from 53.9 to 83.0 % (69.4 ± 6.2 %). Figure 2 shows the relationships between EF and age, and CI and age, in the DMD patients. EF ranged from 16.8 to 63.7 % (46.7 ± 12.5 %), and CI ranged from 1.31 to 6.88 L/min/m^2 (2.68 ± 1.06 L/min/m^2). The EF and age ($r = 0.57$, $p < 0.01$) and the CI and age ($r = 0.43$, $p < 0.01$) were negatively correlated. The youngest subject with an EF below 50 % was 11 years old and the youngest with a CI below 2.2 was 8 years old.

We observed no correlations between the EF or CI and disease stage (Figure 3). Values for EF and CI were widely distributed over disease stages, although a low EF or CI value was more prevalent in the advanced stages.

PULSED-WAVE DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT OF DIASTOLIC FUNCTION

While early transmitral flow and atrial contraction began to merge in some patients when their heart rate increased[33,34], we were able to record diastolic parameters in 39/45 (86.7 %) patients. Similarly, two patients who showed mitral regurgitation on pulsed-wave Doppler echocardiography were excluded from the following analysis.

Comparisons of E, A, and A/E between the patients and the controls are shown in Figure 4. Significant differences between groups were observed for E and A/E ($p < 0.01$). However, there were no significant differences between groups for A values.

Comparisons of IA, IF, and IA/IF between the patients and the controls are shown in Figure 5. IA was significantly lower in the DMD patients than in controls ($p < 0.05$).

RELATION BETWEEN EF AND A/E AND IA/IF

We found no significant correlation between age and A/E or between age and IA/IF in controls. We defined an abnormal A/E (> 0.81) and an abnormal IA/IF (> 0.38) as being above the mean value + 2SD in controls. In the patients, we found no correlations between EF and A/E, or EF and IA/IF (Figure 6). EF in 3 patients who had an A/E greater than 0.81 was 38.5 %, 49.7 %, and 54.0 %, respectively. Normal A/E were found in 13/33 (39.4 %) patients with an EF below 50 %. The EF in 4 patients who had an IA/IF above 0.38 was 25.6 %, 49.7 %, 50.3 %, and 54.0 %, respectively. Normal IA/IF accompanied by EF below 50 % was found in 13/33 (39.4 %) patients.

RELATION BETWEEN CARDIAC ANATOMICAL MEASUREMENTS (LVDd, LVDs, IVST, LVPWT) AND EF, A/E AND IA/IF

Summary of cardiac anatomical measurements using M-mode echocardiographic technique in DMD patients are showed in Table 2. We observed no correlations except that LVDd and/or LVDs over normal ranges were more prevalent in low EF values.

Discussion

In 1954, Walton and Nattrass reported that DMD usually begins in the first three years of life but occasionally later, and usually progresses rapidly without periods of apparent arrest, leading to total disability and often death in adolescence, although patients sometimes survive into adulthood[35]. We therefore regarded the age of the patient as an indicator of disease duration. In this study group, the severity of skeletal muscle dysfunction progressed with age. There was a wide range in disease stages, from stage 2 to stage 8, according to the Swinyard and Deaver classification, and a wide range in patient age, from 8 to 25 years.

Although myocardial involvement is common in DMD, the clinical stage at which it appears and the manner of cardiac deterioration (i.e., of the systolic and diastolic dysfunction) are not well known. We attempted to assess cardiac function by using pulsed-wave Doppler in addition to performing M-mode and two-dimensional echocardiographic techniques in patients with DMD.

The echocardiographic assessment of LV systolic function in patients with DMD has been described. Ahmad et al. found that EF measured by M-mode echocardiography was within the normal range in 13 children with DMD aged 5 to 12 years[15]. Heymsfield et al. found no significant differences in EF measured by M-mode between patients with early-stage DMD who ranged from 4 to 10 years of age and the age-matched controls. The EF was reduced in patients with late-stage DMD aged 9 to 17 years[16]. However, there are problems associated with the M-mode derived EF calculation. Because patients with DMD have a severe deformity of the thorax, the motions of the interventricular septum and the LV posterior wall cannot be accurately evaluated by the perpendicular M-mode beam. Thus, the evaluation of EF by M-mode echocardiography can be done only in the mild stages of DMD and may therefore introduce some error. Another problem with M-mode evaluations is that degeneration of the cardiac muscle does not occur diffusely in DMD, so that this procedure produces an over- or underestimation. We measured EF using two-dimensional echocardiography with the assumption that the LV chamber could be represented by an ellipsoid of revolution reference figure[32]. Two-dimensional echocardiography provides a more accurate measurement of EF than M-mode echocardiography. EF measured by the area-length method and CI measured by the pulsed-wave Doppler method were found to decrease with advancing age. We found that the systolic dysfunction appeared in the first decade of life, with some patients showing severe systolic dysfunction in their early teens. Thus, the dysfunction did not always depend on the severity of the skeletal muscle disease.

A few studies have assed the LV diastolic function in DMD by digitized M-mode echocardiography[14-17]. Kovick et al. suggested that the maximal diastolic endocardial velocity (DEVM) decreased in DMD patients, reflecting the impaired myocardial relaxation caused by dystrophic heart disease[14]. DEVM corresponds closely to the velocity of early diastolic flow. We found that this flow velocity was significantly lower in DMD patients than in controls. Although our results agreed with those of Kovick et al., diastolic dysfunction would also be assessed in combination with early and late diastolic flow velocity. When patients with systemic hypertension or ischaemic heart disease show cardiac deterioration, there is often an increase in late diastolic flow velocity suggestive of an increase in left atrial compensation[36]. We did not find such an increase in late diastolic flow velocity or the time-velocity integral of the atrial filling velocity curve in the DMD patients. Previous necropsy studies have demonstrated that the most severe changes in patients with DMD involve the posterobasal region of the left ventricle, with only minimal changes seen in the atrial musculature[11]. Also, it has been reported that fibrosis first occurs in the LV posterobasal segment, with only rare involvement of the atria[10]. Our observations did not explain why there is no increase in left atrial compensation in these patients. A possible explanation is that the severe deformity of the thorax may restrict the motion of the left atrial wall.

When we investigated the relation between the systolic and the diastolic dysfunction in DMD, the results suggested that systolic dysfunction might predominate. Few patients might have diastolic dysfunction either preceding or accompanying the systolic dysfunction. It has been observed that, in patients with DMD, the lumina of the main trunk of the coronary arteries and the visualized branches are very smooth, and that the arteriopathy of the small intramural coronary artery is not located in the areas of myocardial fibrosis[2,3,9-11]. The cardiac deterioration of DMD thus does not depend on the deterioration of the coronary arteries; mechanisms other than those involved in systemic hypertension or ischaemic heart disease may be involved.

We adopted normal ranges of echocardiographic measurements by Henry et al. based on both the age and the BSA. Because it has been reported that healthy boys matched with respect to age had a greater BSA than their DMD counterparts and healthy subjects matched on the basis of BSA were younger than their DMD opposite members[16]. LV dimensions and septal wall plus posterior wall thickness were compared among subjects with (with complete and incomplete relaxation) and without coronary artery disease[37]. Although we also attempted the similar comparisons, we observed no correlations except that LVDd and/or LVDs over normal ranges were more prevalent in low EF values. As above mentioned, we thought that it was difficult to obtain accurate cardiac anatomical measurements using M-mode echocardiographic technique in DMD patients.

There are many problems or limitations to identifying the mechanism of cardiac deterioration in DMD patients in the present study. LV diastolic filling is the result of the interactions of several factors, including LV relaxation, passive compliance, LV loading conditions and heart rate[34,38-41]. Therefore, it is not surprising that the pattern of LV diastolic filling as assessed by Doppler echocardiography would also be influenced by these variables. Nevertheless, the Doppler transmitral velocity profile has been widely used as a means of assessing diastolic function. Right ventricular impairment not examined in this study may produce LV impairment[42-44]. The evaluation of right ventricular function is needed in further study. The heart rate ranged from 69 to 128/min (91 ± 14 /min) in patients with DMD and from 65 to 92 /min (78 ± 8 /min) in controls. Thus the heart rate of DMD patients was significantly more rapid than that of controls. Ten patients showed sinus tachycardia, which was unpredictable in onset and duration, often appearing during even a minimal stimulus, such as raising the patient in bed. In view of this lability of the tachycardia, one cannot rely upon a single determination of pulse rate, or the rate obtained from electrocardiograms, for determining the overall incidence of tachycardia[1]. Tachycardia was reported to be a feature of both early and late stages, confirming earlier observations on DMD patients of unspecified age[1,3,6,9]. Transmitral flows depend on the heart rate[34,40,41]. Respiration has been shown to alter early and late velocities, particularly in children[45]. These problems are difficult to resolve because respiratory failure is one of its cause. We did not make an assessment of isovolumic relaxation[46] because of difficulty of clear phonocardiogram recordings caused by the severe deformity of the thorax and respiratory insufficiency. Even if we obtain the LV isovolumic relaxation time, it may be shorter in children because of a more rapid rate of LV relaxation and has been reported[47] to be affected by several factors in addition to left atrial pressure at the time of mitral valve opening and the rate of LV relaxation. Serial

studies may be helpful to assess LV diastolic properties or progression disease.

Cardiac deterioration can be assessed by pulsed-wave Doppler in addition to M-mode and two-dimensional echocardiography in those patients without overt cardiac failure. However, because of the thoracic deformity, it is often difficult to obtain a good image in DMD patients. Kyphoscoliosis frequently reduces the width of the intercostal spaces, preventing good imaging. We used careful positioning to preserve image quality. The indices of LV systolic and diastolic function could be obtained more easily and clearly with pulsed-wave Doppler echocardiography than with two-dimensional echocardiography. Therefore, the pulsed-wave Doppler is more suitable for evaluating the LV function of DMD patients. Future studies on cardiac function may help to define the abnormality leading to LV dysfunction.

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Table 2 Cardiac anatomical measurements in DMD patients

	LVDd(mm)	LVDs(mm)	IVST(mm)	LVPWT(mm)
Mean	45	33	8	7
SD	8	10	2	1
Max	68	66	13	10
Min	32	18	5	4
>normal	20/42 (48%)	24/42 (57%)	9/41 (22%)	13/41 (31%)
normal	22/42 (52%)	18/42 (43%)	23/41 (56%)	20/41 (49%)
<normal	0/42	0/42	9/41 (22%)	8/41 (20%)

Summary of cardiac anatomical measurements using M-mode echocardiographic technique in DMD patients. We used normal ranges of echocardiographic measurements by Henry et al. based on two factors, the age and the body surface area. LVDd = LV diastolic dimension; LVDs = LV systolic dimension; IVST = interventricular septal thickness; LVPWT = LV posterior wall thickness

Table 1 Disease stage, number and age in 45 DMD patients

Stage	No.	Age(years) Mean ± SD (range)
1	0	
2	1	8
3	1	8
4	6	9.8 ± 0.9 (9-11)
5	3	13.3 ± 2.1 (11-16)
6	16	15.3 ± 3.1 (11-20)
7	9	17.0 ± 4.8 (11-25)
8	9	16.6 ± 2.3 (14-21)

No. = number of patients;

Figure legends

Figure 1 Relation between age and disease stage in DMD, according to the criteria of Swinyard and Deaver in DMD. The functional disability was aggravated with age.

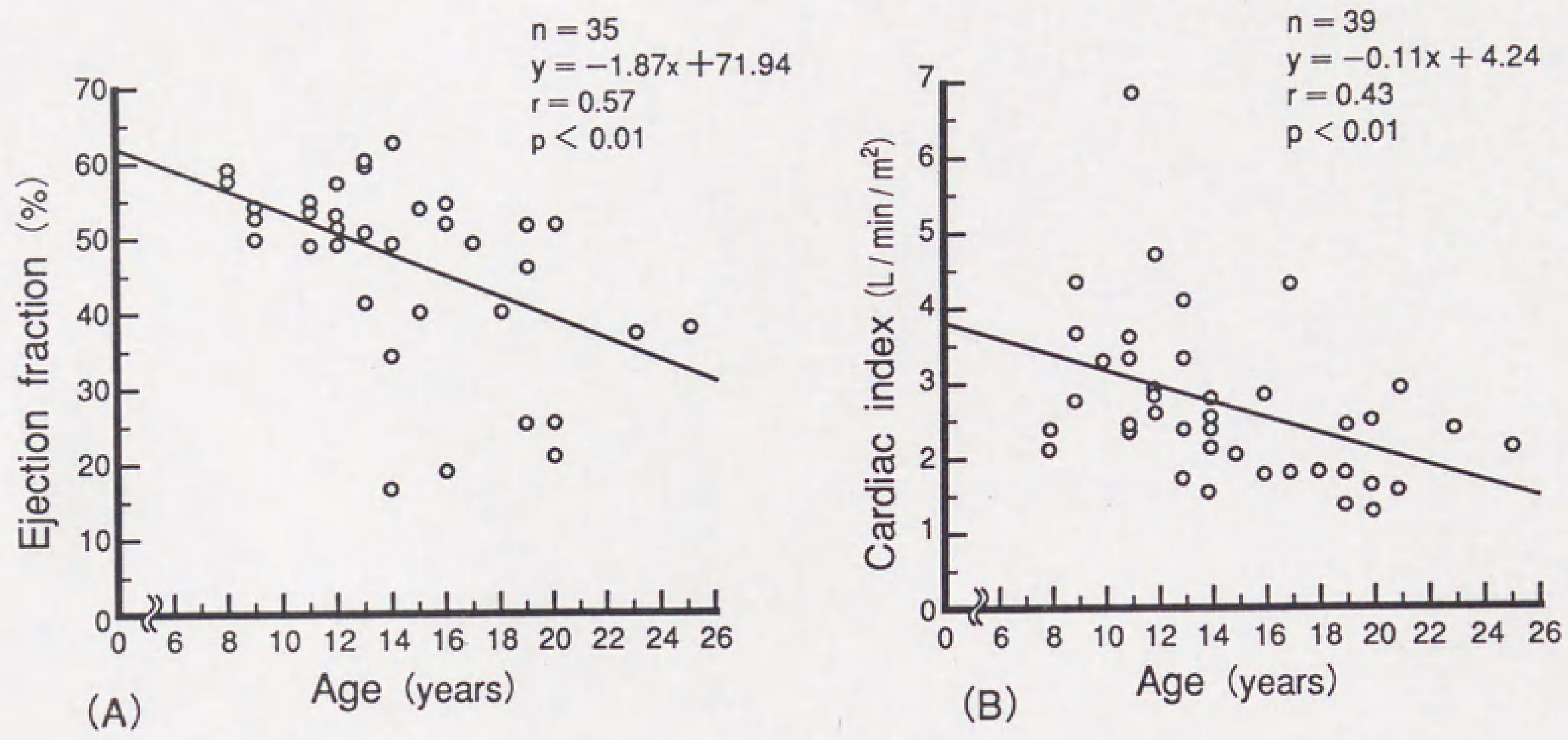
Figure 2 A) Relation between age and ejection fraction, measured by the area-length method, in DMD ($r = 0.57$, $p < 0.01$). (B) Relation between age and cardiac index, assessed by pulsed-wave Doppler method, in DMD ($r = 0.43$, $p < 0.01$).

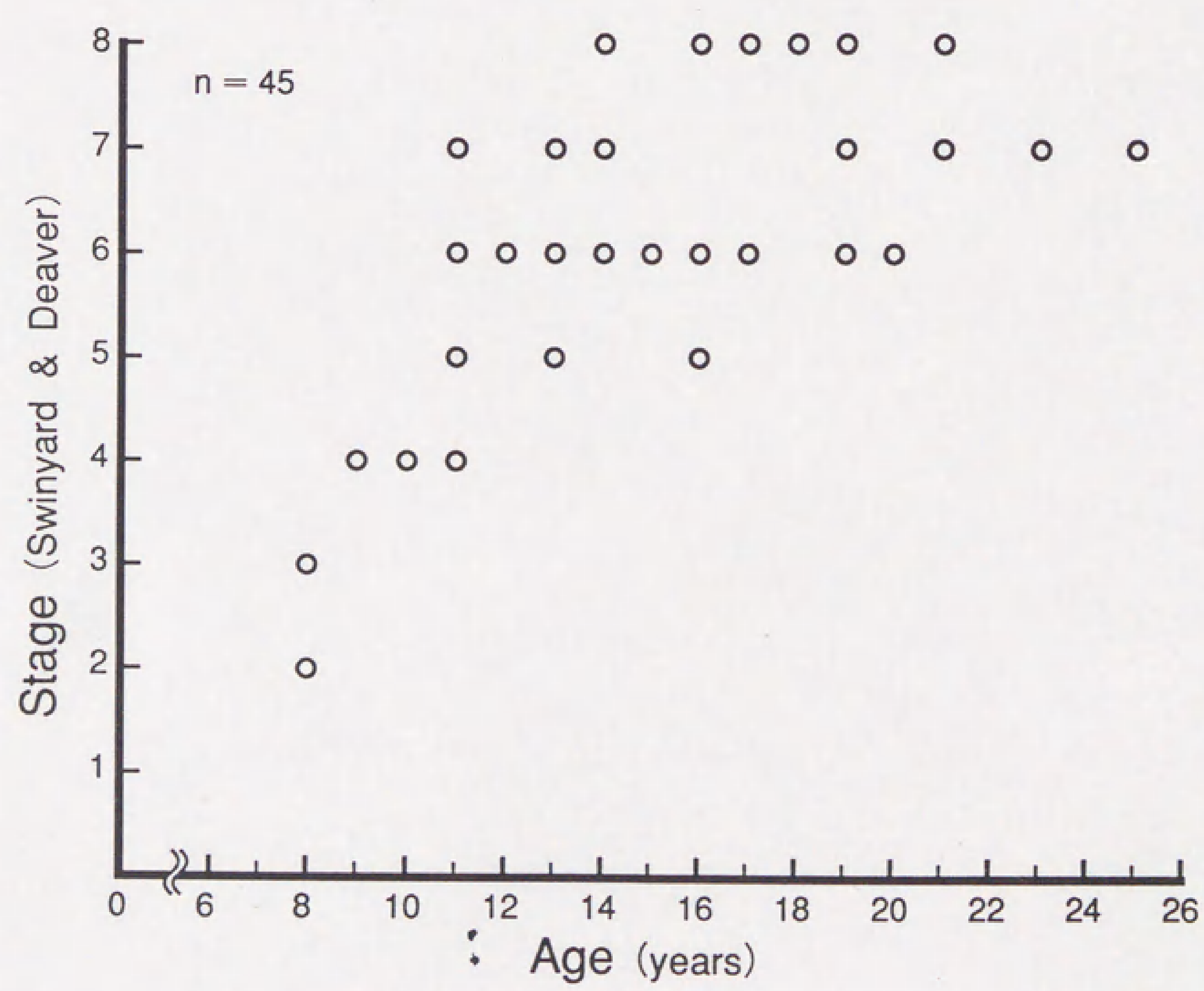
Figure 3 (A) Relation between stage and ejection fraction, measured by the area-length method, in DMD. (B) Relation between stage and cardiac index, assessed by pulsed-wave Doppler method, in DMD patients. No correlations were found.

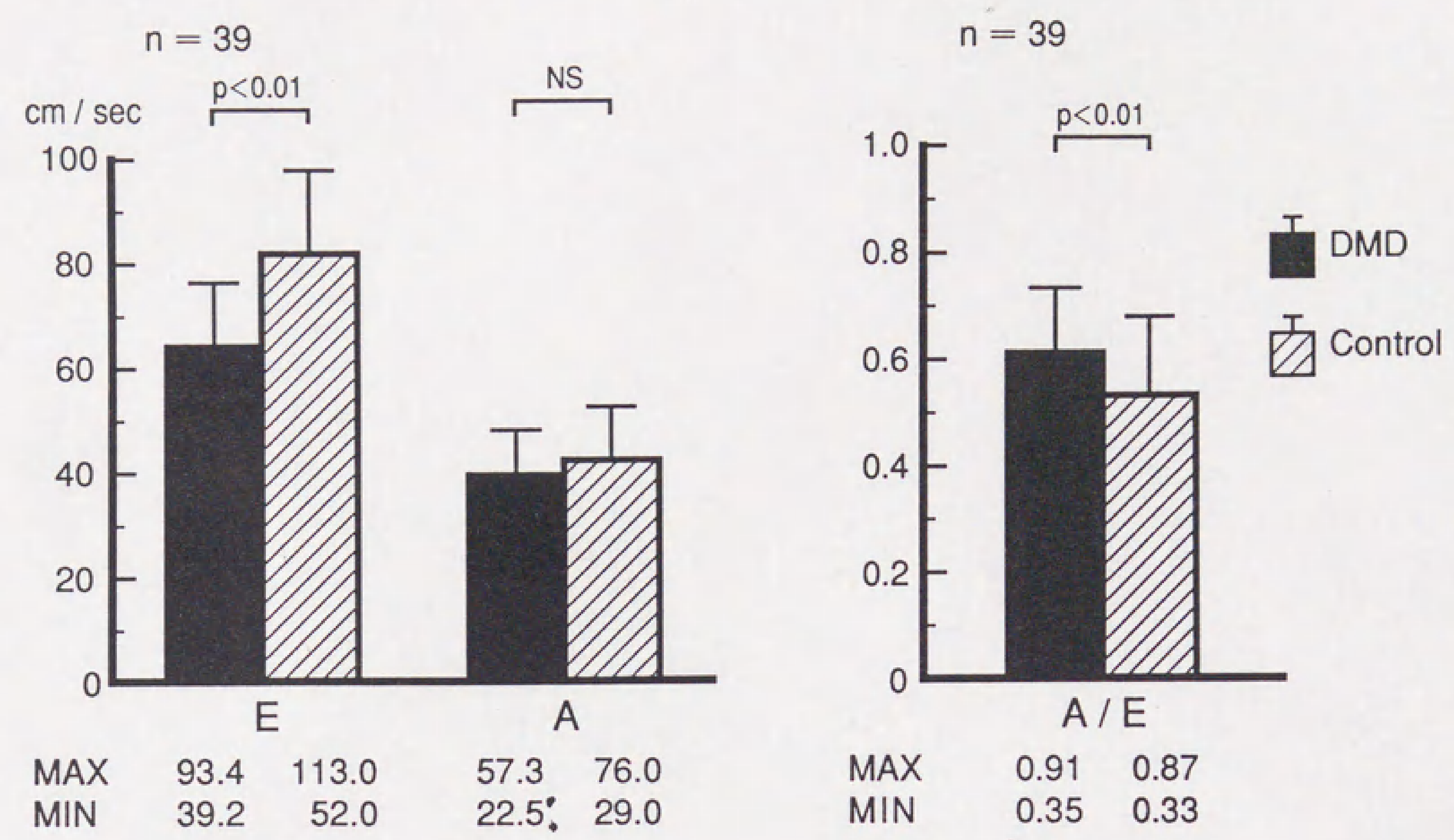
Figure 4 Mean LV inflow measurements in DMD patients and controls. Solid columns represent the mean measurement in DMD patients, while hatched columns represent the mean measurement in controls. Vertical bars represent 1 standard deviation (SD) in each column. Maximum and minimum values are shown below the x-axis. E = peak velocity of the LV inflow in early diastole; A = peak velocity of the LV inflow in atrial systole; A/E = ratio of A to E; NS = not statistically significant.

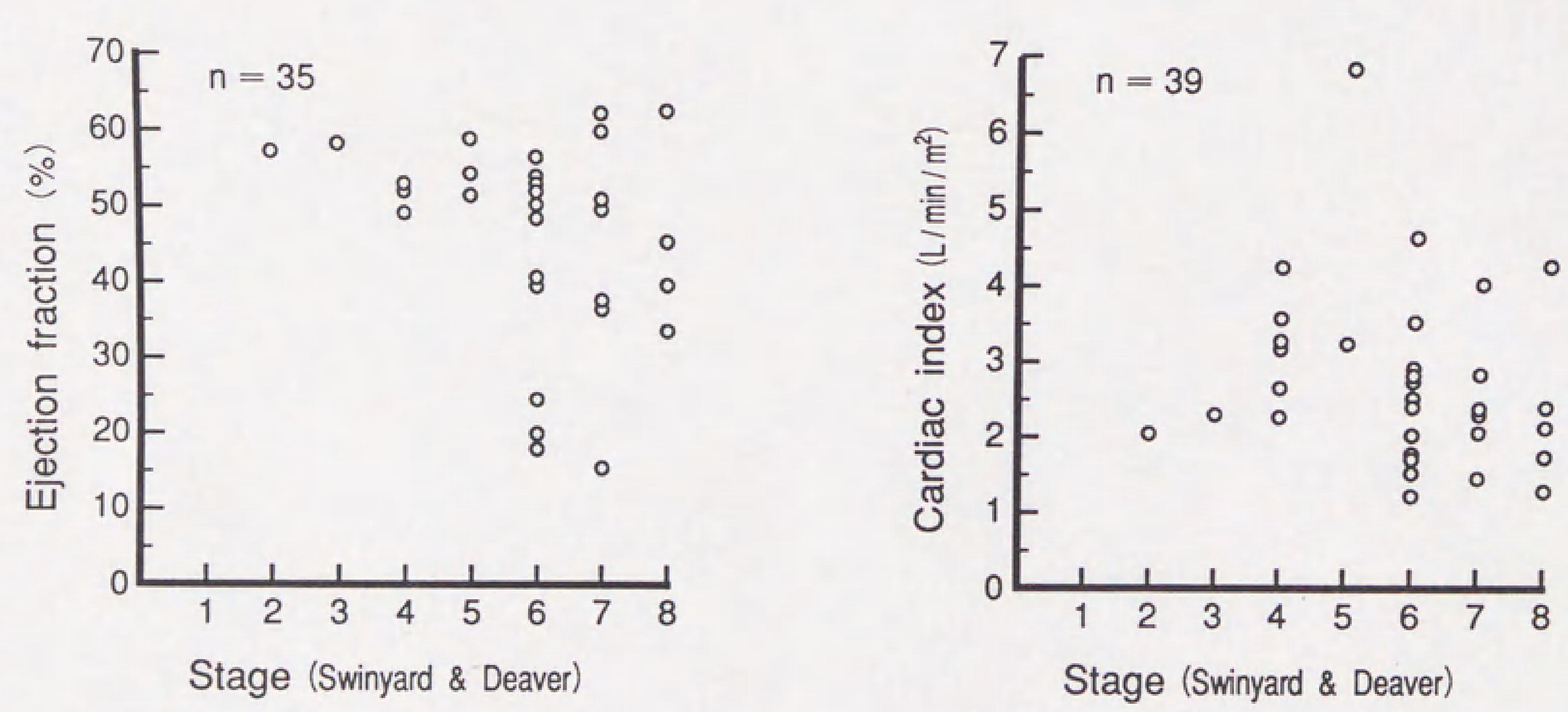
Figure 5 Mean LV inflow measurements in DMD patients and controls. Solid columns represent the mean measurement in DMD, while hatched columns represent the mean measurement in controls. Vertical bars represent 1 standard deviation (SD) in each column. Maximum and minimum values are shown below the x-axis. Significant differences between groups were observed for IA ($p < 0.05$), IF ($p < 0.01$), and IA/IF ($p < 0.01$). IA = area under the atrial velocity curve of the LV inflow; IF = total flow velocity area of the LV inflow; IA/IF = ratio of IA to IF

Figure 6 Scatterplot showing relation between EF and A/E (A) and EF and IA/IF (B) in DMD patients. No correlations were observed. Dashed line represents the upper limit of normal for A/E or IA/IF (mean ± 2SD in controls).


n = 35
y = −1.87x +71.94
r = 0.57
p < 0.01
Ejection fraction (%)
Age (years)
(A)
n = 39
y = −0.11x + 4.24
r = 0.43
p < 0.01
Cardiac index (L / min / m2)
Age (years)
(B)

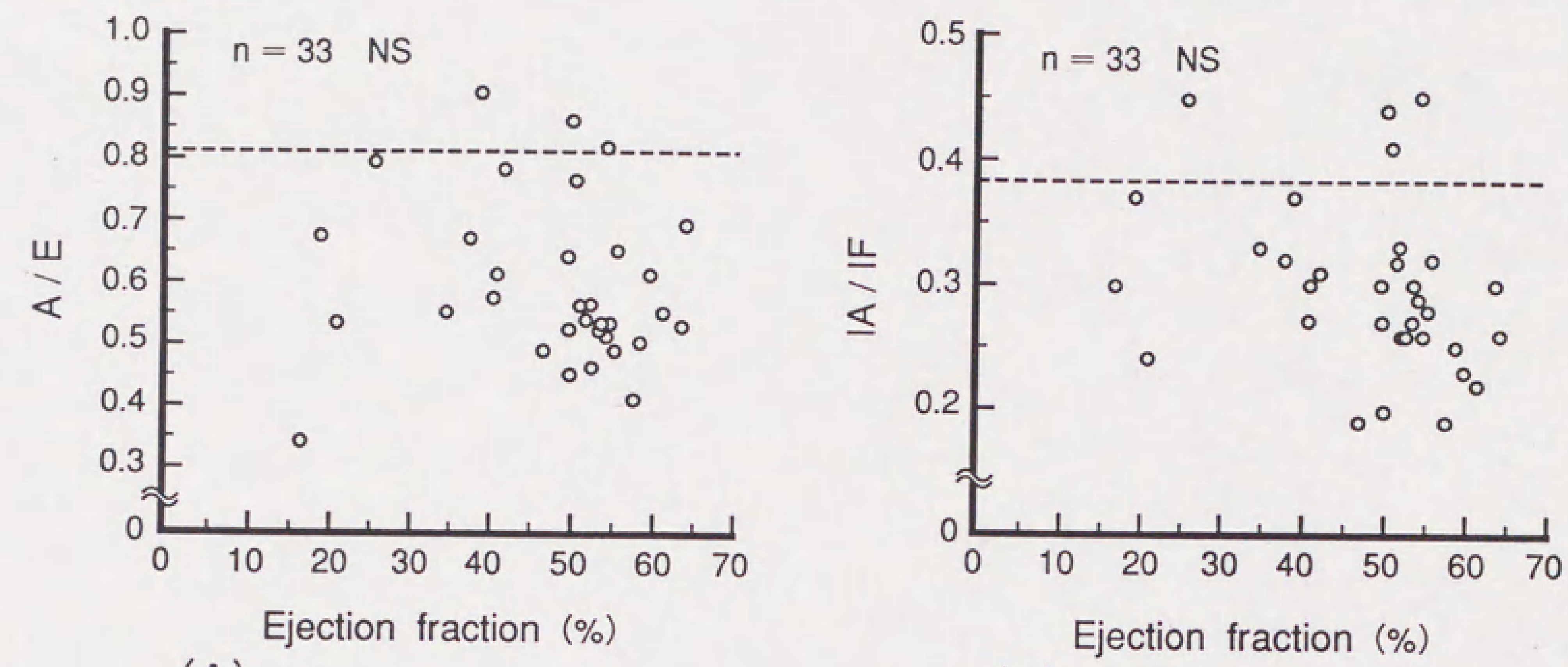

n = 45
Stage (Swinyard & Deaver)
Age (years)


n = 39
p<0.01
NS
cm / sec
100
80
60
40
20
0
E
A
MAX 93.4 113.0 57.3 76.0
MIN 39.2 52.0 22.5 29.0
n = 39
p<0.01
1.0
0.8
0.6
0.4
0.2
0
A / E
MAX 0.91 0.87
MIN 0.35 0.33
DMD
Control

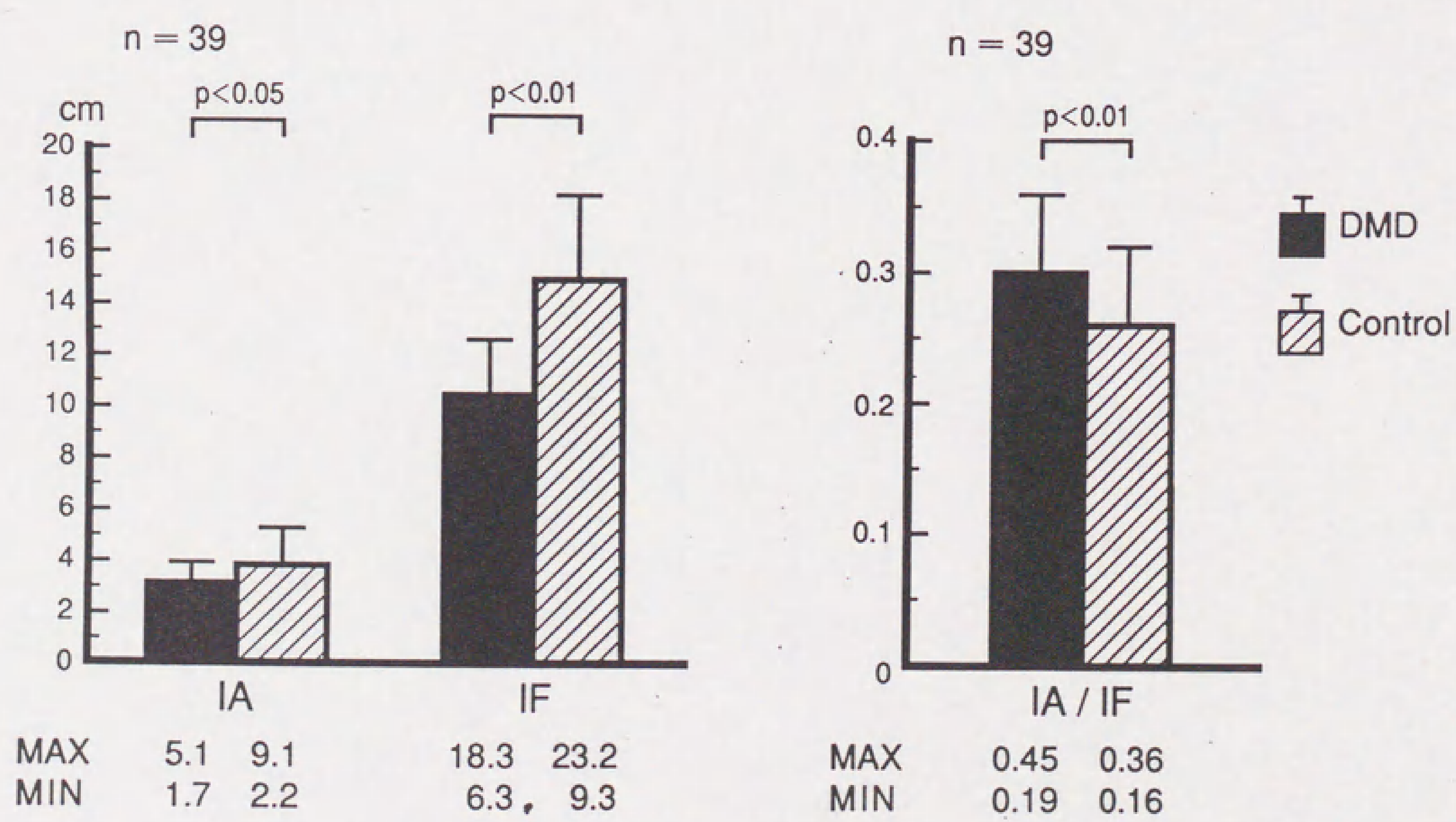

Ejection fraction (%)
n = 35
70
60
50
40
30
20
10
0
1 2 3 4 5 6 7 8
Stage (Swinyard & Deaver)
Cardiac index (L / min / m²)
n = 39
7
6
5
4
3
2
1
0
1 2 3 4 5 6 7 8
Stage (Swinyard & Deaver)

(A)

(B)


A / E
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
n = 33 NS
0 10 20 30 40 50 60 70
Ejection fraction (%)
IA / IF
0.5
0.4
0.3
0.2
0
n = 33 NS
0 10 20 30 40 50 60 70
Ejection fraction (%)

(A) (B)


n = 39
cm
20
18
16
14
12
10
8
6
4
2
0
p<0.05
p<0.01
IA
IF
MAX 5.1 9.1 18.3 23.2
MIN 1.7 2.2 6.3 9.3
n = 39
0.4
0.3
0.2
0.1
0
p<0.01
IA / IF
MAX 0.45 0.36
MIN 0.19 0.16
DMD
Control

竹中晃