PULMONARY HYPERTENSION IN PROGRESSIVE MUSCULAR DYSTROPHY OF THE DUCHENNE TYPE

MASAYUKI YOTSUKURA, M.D., MASAHITO MIYAGAWA, M.D., TSUNEO TSUYA, M.D.
TADAYUKI ISHIHARA, M.D.*, AND KYOZO ISHIKAWA, M.D., F.A.C.C.

Right heart catheterization was performed in 8 patients with progressive muscular dystrophy of the Duchenne type (DMD) at the advanced stage. A mean pulmonary arterial pressure in excess of 20 mmHg was observed in all cases. Five of them showed severe pulmonary hypertension with a mean pressure above 40 mmHg. Since pulmonary hypertension was relieved by correction of hypoxemia, this represented a precapillary pulmonary hypertension caused by constriction of the pulmonary artery. Furthermore, elevation of the mean right atrial pressure above 5 mmHg was observed in 6 of the 8 cases, indicating the possible presence of right ventricular failure. Despite the presence of left ventricular dysfunction as assessed by echocardiogram, no manifestations of left ventricular failure, such as dyspnea and pulmonary rales, were noted in any of the patients. In conclusion, it can be said that even in the terminal stage of DMD, the left ventricular function may, in fact, still remain not markedly involved, and that respiratory failure, as well as right ventricular failure caused by precapillary pulmonary hypertension, will tend to occur frequently and may play a determinant role in prognosis of the advanced DMD patient.

PROGRESSIVE muscular dystrophy of the Duchenne type (DMD) is a recessive sex-linked familial disorder causing degeneration of the systemic skeletal and cardiac muscles. The disease occurs in early childhood, and most patients die at around 20 years of age from respiratory failure due to impairment of the respiratory muscles, heart failure due to myocardial impairment, asphyxia due to inadequate swallowing, or infections such as pneumonia.¹

Non-invasive examinations including electrocardiography, echocardiography and mechanocardiography show a gradual reduction in cardiac function, particularly the left ventricular func-

tion, with progression of impairment of the skeletal muscles.²⁻¹³ Although reduced cardiac function and respiratory failure coexist in the terminal stage of the disease, knowledge about the state of the cardiopulmonary system at this stage remains incomplete.

Since no definite causative treatment has been established for the disease, all currently available treatments are necessarily conservative, and appropriate management of respiratory failure and heart failure is still the primary means of prolonging the patients' life. An accurate evaluation of the hemodynamics in the terminal stage is thus indispensable. In the current study, we performed right heart catheterization in patients with DMD in the terminal stage, in the hope that an understanding of its pathophysiology might provide useful additional information concerning

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Second Department of Internal Medicine, Kyorin University, School of Medicine; *National Higashisaitama Hospital

Mailing address: Kyozo Ishikawa, M.D., Second Department of Internal Medicine Kyorin University School of Medicine, 6-20 Shinkawa, Mitaka-City, Tokyo 181, Japan

TABLE I CLINICAL DATA

Patient	Age (years)	Sex	Swinyard- Deavers' stage	Body weight (kg)	Vital capacity (ml)	Hemoglobin (g/dl)	Two-dimensional echocardiogram		
							LVDd (mm)	LVDs (mm)	WMI
Case 1	20	Male	8	25.5	220	12.8	40	29	+12
Case 2	22	Male	8	22.0	310	14.4	42	30	+8
Case 3	23	Male	8	30.7	350	15.7	32	18	+10
Case 4	23	Male	8	41.0	440	14.0	40	26	+12
Case 5	16	Male	8	19.4	116	15.2	40	30	+8
Case 6	20	Male	8	19.5	380	13.9	38	28	+6
Case 7	19	Male	8	34.0	500	15.8	42	32	+6
Case 8	22	Male	8	22.0	510	13.1	50	42	+9
Mean	20.6		8	26.8	353.3	14.4	40.5	29.4	+8.9

Abbreviations: LVDd = left ventricular dimension, diastole; LVDs = left ventricular dimension, systole; WMI = wall motion index

an effective treatment.

METHODS

Patients

Out of 156 male patients with DMD hospitalized in the Neuromuscular Center at National Higashisaitama Hospital from October, 1983 to September, 1986, 8 patients in the terminal stage, who showed severe respiratory failure, were selected for right heart catheterization. Respiratory failure was suspected from the clinical manifestation of cyanosis and shallow breathing, and was finally confirmed by hypoxemia and hypercapnia. The patients ranged in age from 16 to 23 years with a mean of 20.6 years. The diagnosis of DMD was based on the history, clinical findings and rate of progression and was confirmed in all cases by electromyography, serial serum enzyme determinations and muscle biopsy.

DMD patients are usually classified into 8 stages from the mild, stage 1, to the most severe, stage 8, according to Swinyard-Deaver's classification.¹⁴ This classification is based on the pattern, ability and the method of ambulation, and on the degree of adequacy in activities of daily life. All of the eight cases belonged to stage 8, being bedridden or wheelchairbound and unable to perform any activity of daily life without maximum assistance.

Measurements of the right atrial pressure (RAP), pulmonary arterial pressure (PAP), and

pulmonary capillary wedge pressure (PCWP) were made, using a Swan-Ganz balloon-tipped catheter. Thermodilution cardiac output (average of three recordings with less than 10% variation) was also measured.

The patients experienced some difficulty when lying flat on the bed, because they had marked chest and spinal deformities. Thus, when recording the pressures, special care was taken to lay them on the bed as flat as possible. Two of the eight patients were catheterized not only during spontaneous respiration but also under assisted respiration with a Bird Mark II respirator. Chest X-ray studies, blood gas analysis, and two-dimensional echocardiography were also performed on the same day as the right heart catheterization. Vital capacity was measured within a week after the right heart catheterization.

Echocardiography was carried out with a commercially available phased-array sector scanner (Toshiba Incorporated, Model SSH-11A) using a 2.4 MHz transducer. Real-time images of cross-sectional echocardiography (CSE) were recorded on one-half-inch videotape cassettes using a Victor video recorder. For the purposes of analysis, following the method of Heger et al,¹⁵ the ventricle was divided into nine segments identified by their locations on the cross-sectional echocardiographic image. Each segment was evaluated for the degree of asynergy. To grade the severity of segmental asynergy, each segment was assigned a numerical score based on the type

TABLE II HEMODYNAMIC DATA

Patient	Blood pressure (mmHg)	Heart rate (beats/min)	Right heart catheterization							Arterial blood gas analysis				
			RAP (mmHg)	PAP (mean) (mmHg)	PCWP (mmHg)	CO (L/min)	CI (L/min/m ²)	SV (ml)	SI (ml/m ²)	PVR (dyn/sec/cm ⁵)	pH	PO ₂ (mmHg)	PCO ₂ (mmHg)	BE
Case 1	124/84	122	2	67/42 (52)	5	4.1	3.9	40	33	963	7.31	39.8	93.4	+15.8
Case 2	118/86	112	12	65/31 (48)	24	4.9	4.5	44	40	426	7.26	31.2	83.8	+7.0
Case 3	110/72	135	8	63/41 (53)	11						7.36	31.7	91.7	+18.0
Case 4	120/88	116	5	60/36 (47)	9	6.1	4.5	53	39	676	7.27	32.6	84.4	+12.8
Case 5	104/80	102	13	56/28 (40)	27						7.31	35.8	69.4	+6.4
Case 6	140/74	123	9	49/32 (38)	10	4.4	4.5	36	37	498	7.24	39.4	71.4	+2.8
Case 7	132/70	120	1	40/17 (27)	5	4.6	3.7	43	34	476	7.31	39.0	80.9	+13.4
Case 8	100/68	109	7	31/22 (27)	7	4.2	4.5	38	41	356	7.34	50.4	88.9	+7.6

Abbreviations: RAP = right atrial pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; CI = cardiac index; SV = stroke volume; SI = stroke index; PVR = pulmonary vascular resistance; BE = base excess

of wall motion noted. The following scores were given: hyperkinesis, -1; normal, 0; hypokinesis, +1; akinesis, +2; and dyskinesis, +3. The wall motion index (WMI), which provides an overall evaluation of the left ventricular (LV) asynergy, was then obtained by summing the scores for each of the nine segments.

RESULTS

Clinical:

During the 3-year period of observation, 29 out of the 156 patients with DMD died. Twenty-five of these 29 (86%) died of respiratory failure, 2 (7%) of congestive heart failure, and the other 2 (7%) of unknown causes.

Table I summarizes the pertinent clinical data on the 8 patients studied in this investigation. None of the 8 patients complained of dyspnea either at rest or even when moving in wheelchairs. In all patients, the heart size was found to be within normal limits on physical examination and by teleroentgenography. The cardiac sounds were of poor quality, and neither accentuation of the second pulmonic sound nor diastolic gallop were observed in any of them. The body weight ranged from 19.4 to 41.0 kg and all patients showed marked emaciation. Rales were not heard in the lung field and chest X-rays revealed no pulmonary congestion in any of them. All patients showed tachycardia of more than 100 beats per minute with a mean value of 117 per minute. The vital capacity was markedly reduced with a mean value of 353.3 ml. The hemoglobin level was within the normal range in all patients and the mean value was 14.4 g/dl. Blood gas analysis revealed a mean pH of 7.30 (7.24-7.36), mean PO₂ of 37.5 (31.2-50.4) mmHg, and mean PCO₂ of 82.9 (71.4-93.4) mmHg, suggesting hypoxemia and hypercapnia, which are features of respiratory acidosis.

Echocardiograms:

Both the LV diastolic dimension and LV systolic dimension remained within normal limits, ranging from 32 to 50 mm (mean, 40.5 mm) and from 18 to 42 mm (mean 29.4 mm), respectively. The wall motion index ranged from +6 to +12 (mean, +8.9), suggesting severe abnormality of LV wall motion in all patients. In seven of the eight patients, the posterobasal wall of the left ventricle showed akinesis or dyskinesis.

TABLE III HEMODYNAMIC DATA BEFORE AND AFTER ASSISTED RESPIRATION

Patient		Right heart catheterization			Arterial blood gas analysis			
		RAP (mmHg)	PAP (mean) (mmHg)	PCWP (mmHg)	pH	PO ₂ (mmHg)	PCO ₂ (mmHg)	BE
Case 1	Spontaneous respiration	2	67/42 (52)	5	7.31	39.8	93.4	+15.8
	Assisted respiration	4	23/12 (16)	10	7.63	169.4	24.0	+4.2
Case 5	Spontaneous respiration	13	56/28 (40)	27	7.31	35.8	69.4	+6.4
	Assisted respiration	—	24/14 (18)	21	7.44	210.4	36.8	+3.0

Abbreviations: RAP = right atrial pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; BE = base excess

Hemodynamics:

Table II summarizes the results of right heart catheterization. An RAP exceeding 5 mmHg was noted in six patients. In all patients, the mean PAP was elevated, ranging from 27 to 53 mmHg (mean, 41.5 mmHg). PCWP was extremely high in 2 cases (case 2, 24 mmHg; case 5, 27 mmHg), but was within normal limits in the remaining 6 cases. The cardiac output and cardiac index, in 6 patients, were all within normal limits, while the stroke resistance was elevated in all the patients.

Table III shows the results of blood gas analysis and right heart catheterization before and after the use of the respirator in 2 patients. The hypoxemia and hypercapnia observed during spontaneous respiration were relieved following the use of the respirator, and the respiratory acidosis also disappeared. The mean PAP values during spontaneous respiration and after the use of the respirator were 52 and 16 mmHg in one patient, and 40 and 18 mmHg in the other, respectively.

DISCUSSION

In the terminal stage, a majority of patients with DMD show a severe degree of respiratory failure due to impairment of the respiratory muscles. Respiratory failure, not congestive heart failure, can thus be reasonably considered as the main cause of death in this disease. In other words, it can be postulated that, in a majority of cases, impairment of the respiratory muscles may advance more rapidly and more extensively than that of the myocardium.

Several hemodynamic studies were performed on patients with DMD.¹⁶⁻²² However, none of the patients showed evidence of respiratory

failure. It is possible therefore, that all of these patients were in the stages where respiratory failure had not yet emerged.

In the present study, we performed right heart catheterization in 8 DMD patients in the advanced stage showing severe respiratory failure, not complicated by infection. It was no surprise to find that they had pulmonary hypertension. In general, pulmonary hypertension can be either postcapillary or precapillary. Von Euler et al²³ suggested that severe hypoxemia induced constriction of the pulmonary artery, which caused precapillary hypertension, and was promoted by hypercapnia and acidosis.

In the two patients who underwent assisted respiration, pulmonary hypertension, which was observed under spontaneous respiration, disappeared after the use of the respirator. This observation seems to substantiate the hypothesis that constriction of the pulmonary arterioles due to hypoxemia might be mainly responsible for the genesis of pulmonary hypertension in the advanced stage of DMD. The normal PCWP in 6 of our 8 patients indicated precapillary pulmonary hypertension due to hypoxemia rather than postcapillary pulmonary hypertension. In the remaining 2 patients (case 2 and case 5), however, PCWP was elevated despite the absence of symptoms of left heart failure, indicating coexistence of postcapillary as well as precapillary hypertension. Of the 8 patients, 5 showed an elevated RAP of above 5 mmHg. These findings suggest the possibility that right heart failure due to precapillary pulmonary hypertension may be present or will occur sooner or later in most patients in an advanced stage of DMD.

Cardiac output was reduced in all 5 patients examined, but the cardiac index remained within

the normal range because of the small body surface area. Although the stroke volume was also reduced, the reduction in cardiac output appears to have been partially compensated by the notable tachycardia observed in all patients. It seemed reasonable to expect from the current echocardiographic findings that advanced DMD patients like our cases would have obvious manifestations of LV failure such as dyspnea or pulmonary rales. However, contrary to our expectation, all of our 8 cases showed no apparent clinical manifestations of LV failure. The reasons for this discrepancy are unlikely to be entirely related to an error in the clinical assessment of physical findings. We cannot, however, exclude the possibility that the administration of oxygen, routinely used in the terminal stage of DMD, could have altered the hemodynamic basis for the physical findings. It also seems possible that strict restriction of physical activity allows the heart to pump an adequate supply of blood to meet the metabolic needs of the body. Another possibility requiring consideration is that the LV dysfunction may be overestimated by the echocardiogram and may not actually be severe enough for the development of overt LV failure.

Neal et al²⁴ suggested muscular dystrophy as a disease causing chronic cor pulmonale due to hypoventilation, but pulmonary hypertension has never been reported in patients with DMD. To our knowledge, this is the first report to demonstrate the presence of pulmonary hypertension caused by hypoxemia in DMD patients in the advanced stage. It can thus be concluded that even in the terminal stage of DMD, the LV function may still remain not markedly involved and that respiratory failure as well as right ventricular dysfunction caused by precapillary pulmonary hypertension may play a determinant role in the prognosis of the advanced DMD patients.

It is hoped that the results of this study will be useful in gaining a better understanding of the pathophysiology of DMD and, furthermore, will provide a stimulus for the development of a better remedy for this disease.

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