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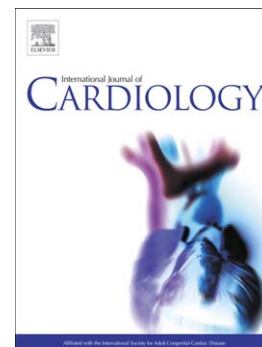
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Prognostic Impact of Venous Thromboembolism in Patients with Duchenne Muscular

Dystrophy: Prospective Multicenter 5-Year Cohort Study

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Key words Duchenne;

Muscular dystrophy;

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Risk factor;

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Duchenne muscular dystrophy (DMD) is a rare X-linked genetic myopathy characterized by progressive systemic muscle weakness, severe cardiomyopathy, and premature death.[1, 2] Although patients with DMD have multiple underlying predispositions to venous thromboembolism (VTE), little is known about its prevalence and prognostic impact.[3, 4]

From July 2007 to December 2008, a total of 102 male patients with DMD in long-term (more than a year) hospitalization were enrolled and prospectively followed-up until the end of October 2014. The institutional review boards from the participating centers approved the study and written consent was obtained from the patients and/or their relatives. The primary outcome of the study was all-cause death. Secondary outcomes were bleeding events under anticoagulation therapy and new-onset acute pulmonary thromboembolism (PTE).

At the study entry, 24 of 102 patients had subclinical deep vein thrombosis (DVT, Figure 1). Two patients had past history of VTE and 1 patient had received warfarinization therapy. After the study entry, 1 patient underwent IVC filter device implantation, 3 patients started anticoagulation therapy, and 1 patient started low-dose aspirin therapy. Baseline age, height, blood pressure, heart rate, laboratory values other than D-dimer testing, and medications administered showed no significant differences (Table 1). Patients with DVT had significantly lower body weight ($p=0.010$). A trend toward an increased risk for DVT was observed in the status of higher rates of ventilator use ($p=0.170$) and higher rates of immobility ($p=0.079$). D-dimer testing showed a high negative predictive value of 0.90 (95%CI:

0.84-0.95) with a limited positive predictive value of 0.45 (95%CI: 0.35-0.52) for the diagnosis of DVT.

Survival prognosis was successfully followed-up in 100 of 102 patients (98%) until either the end of the study or the primary endpoint was reached (median follow-up: 5.1 years; interquartile range: 3.7-5.4 years). During 5-year follow-up, 31 patients died. However, no significant difference in survival prognosis was observed (Log-rank $p=0.77$) between patients with (8/24 died) and without (23/78 died) DVT (Figure 2). Multivariate Cox analysis revealed the only 2 independent prognostic factors were age (relative hazard 1.10 [95% CI: 1.02-1.19], $p=0.011$) and heart rate (relative hazard 1.05 [95% CI: 1.02-1.09], $p=0.001$). However, DVT had no significant impact (relative hazard 1.22 [95% CI: 0.37-4.07], $p=0.749$) on survival prognosis. No bleeding event under anticoagulation therapy was observed. Acute PTE events occurred in 4 patients. Due to the limited number of events, no prognostic differences were found between the patients with baseline DVT (2 events in 24 patients) and patients without baseline DVT (2 events in 78 patients, Log-rank $p=0.202$).

This study revealed a high prevalence (24%) of silent DVT in long-hospitalized patients with DMD. The decrease in body muscle mass, probably through muscle pump disorder, seems to be the most important risk factor for DVT. Ventilator use and prolonged immobility may be other risk factors for DVT although their differences did not reach statistical significance. Physiological thoracic breathing causes the vacuum aspiration mechanism that contributes to venous return.

However, ventilator use, mostly noninvasive positive-pressure ventilation, may have caused the reduction of venous return and DVT. Prolonged immobility also showed a possible association with DVT. On the other hand, dehydration and/or hypovolemia seem to have a negligible impact on DVT. Taken together, these results suggest that particularly in low-weight and ventilated patients, the use of elastic compression stockings to augment muscle pumping and daily active wheelchair use should be encouraged.

Although a high prevalence of DVT was observed, limited PTE events occurred only to a limited degree at 1.6 per 100 patient-years, which was lower than the incidence rate of 3.9 per 100 patient-years from The Japan VTE Treatment Registry cohort study.[5] The common clinical symptoms of acute PTE are dyspnea and chest pain.[6] On the other hand, patients with DMD frequently experience chest discomfort with a sudden drop in SpO₂ resulting from progressive heart failure and respiratory failure, maladaptation to ventilator settings, and sputum clogging.

These similarities of clinical presentations may have caused the underestimation of PTE events.

In the long-term prognosis, the presence of DVT was not associated with survival prognosis. However, obvious acute PTE events were associated with a high mortality since 75% of the patients died within 2 years. The reported mortality rate of acute PTE in Japan is 14% while the mortality rate ranges from 2% to 30% in Europe and the United States.[6] Although the number of subjects may be too limited to discuss mortality, the reason for the high mortality rate might be that most patients with

DMD had baseline respiratory failure and heart failure. These underlying conditions most likely made the patients vulnerable in the face of additional PTE events.

Regarding the global prognosis, age and heart rate, but not DVT, were the significant prognostic factors. Age can reasonably be considered a factor in such a genetic disease with early mortality. A rapid heart rate may also be reasonable considering that heart failure is the major cause of premature death in patients with DMD. Previous studies have shown that a rapid heart rate is an independent prognostic factor in various types of heart failure.[7, 8] Indeed, baseline heart rates of 85-87 bpm were relatively high despite the fact 35% of the patients were treated with beta blockers. The early mortality due to heart failure might be associated with a rapid heart rate in patients with DMD. A weak association between a poor prognosis and BNP values was also shown (relative hazard 1.22 [95% CI: 0.37-4.07], $p=0.749$). Further studies are warranted to clarify the associations between heart rate, beta-blocker treatments, progressive cardiomyopathy, and prognosis in patients with DMD.

A high prevalence of silent DVT was observed in long-hospitalized patients with DMD. Low body weight was a risk factor for DVT. Ventilator use and immobility also were possible risk factors. Although the global prognostic impact of VTE was limited, patients with acute PTE showed a high mortality. Neurologists and cardiologists should pay more attention to the prevention and diagnosis of VTE, particularly in high-risk patients with DMD.

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Figure Legends

Figure 1. Representative images of compression ultrasonography.

[A]: With compression, the femoral vein is deformed but does not show complete compression due to venous thrombosis in a 24-year-old patient with DMD. [B]: Femoral venous thrombosis in a 20-year-old patient with DMD. [C]: Chronic soleal venous thrombosis in a 29-year-old patient with DMD.

Figure 2. Impact of VTE on long-term prognosis

Kaplan-Meier analysis for all-cause mortality revealed no significant differences were observed in the prognosis between patients with and without DVT.

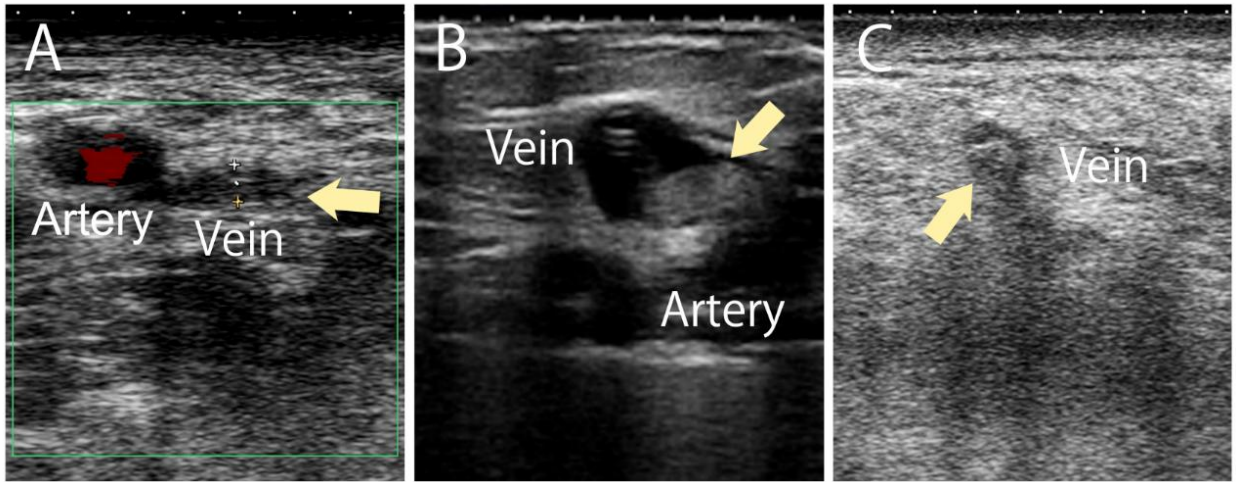


Figure 1

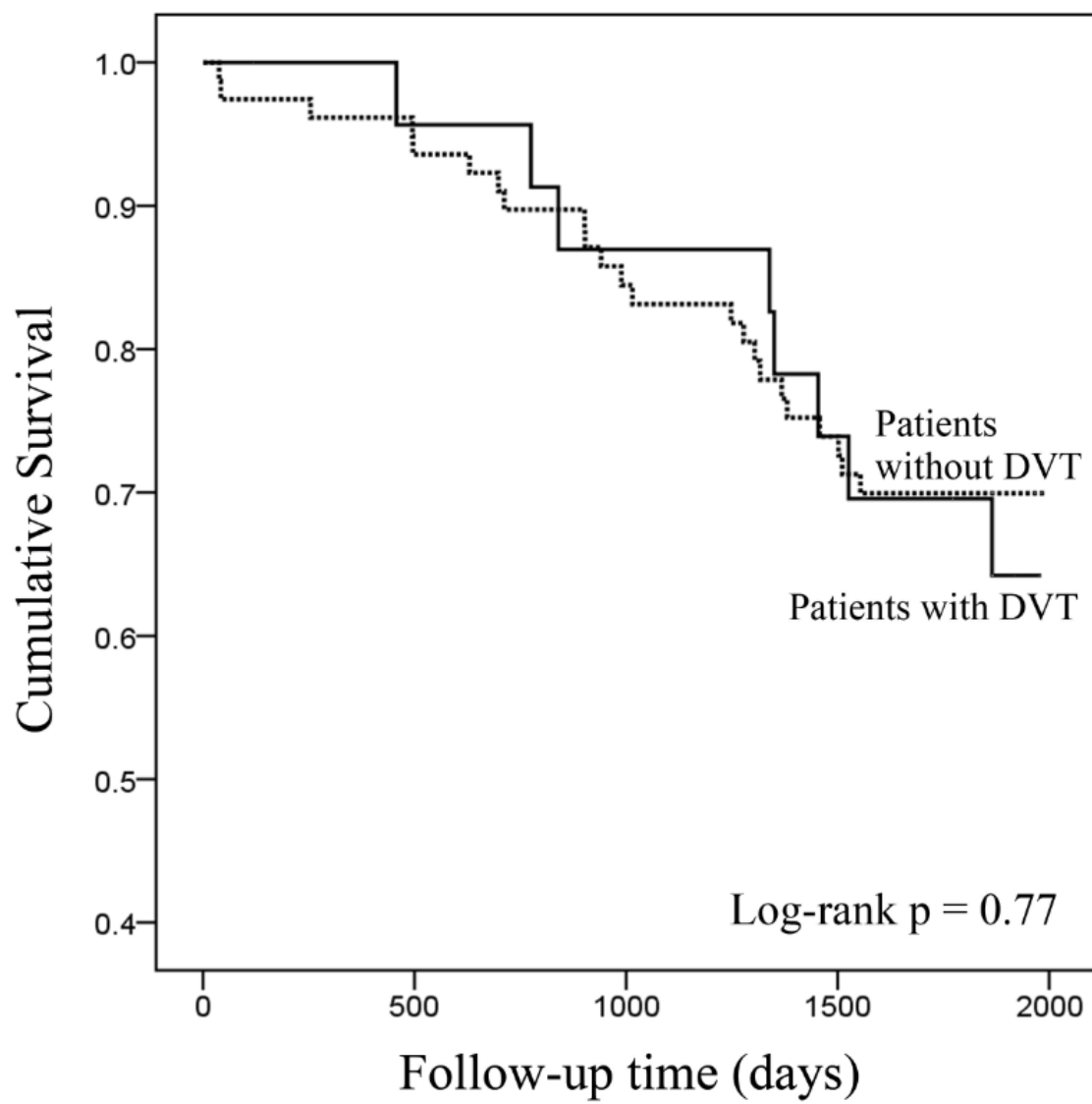


Figure 2

Table 1. Baseline characteristics

	Patients without DVT (n = 78)	Patients with DVT (n = 24)	p Value
Age (year)	25.8 ± 7.9	26.9 ± 7.3	0.436
Height (cm)	156.8 ± 9.7	155.0 ± 11.4	0.465
Weight (kg)	37.4 ± 14.2	31.5 ± 9.7	0.010*
Systolic BP (mmHg)	105.2 ± 13.7	104.4 ± 17.2	0.802
Diastolic BP (mmHg)	65.0 ± 10.9	67.4 ± 10.6	0.342
Heart rate (bpm)	84.9 ± 16.3	87.2 ± 16.7	0.541
Serum CK (IU/l)	698 ± 753	510 ± 465	0.435
Hematocrit (%)	40.6 ± 4.2	41.1 ± 4.9	0.620
Serum Sodium (mEq/l)	138.6 ± 3.7	137.5 ± 3.8	0.208
Plasma BNP (pg/ml)	69.6 ± 246.1	44.0 ± 78.7	0.625
IVC Diameter (mm)	10.9 ± 4.1	10.8 ± 4.1	0.999
Ventilator use, n (%)	50 (64)	19 (79)	0.170
ACEi / ARB use, n (%)	42 (54)	13 (54)	0.978
Beta Blocker use, n (%)	29 (37)	7 (29)	0.630
Diuretics use, n (%)	28 (36)	6 (25)	0.230
Warfarin use, n (%)	0 (0)	1 (4)	0.240
Immobility, n (%)	36 (46)	16 (67)	0.079
D-dimer Positive, n (%)	22 (28)	18 (75)	0.001*

Values are mean \pm SD or percentages. D-dimer positive was defined as a value over the cut-off of 500 ng/ml. Immobility was defined by long-term bed-bound rest with transfer to a wheelchair less than twice per week. ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = brain natriuretic peptide, BP = blood pressure, CK = creatine kinase, and IVC = inferior vena cava. * $p < 0.050$.