Heart Rate Variability and Hypercapnia in Duchenne Muscular Dystrophy

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Abstract

Objective To investigate the relationship between heart rate variability and hypercapnia.

Patients and Methods We measured the coefficient of variation of R-R interval (CVrr) and arterial blood gas pressures in 73 patients with Duchenne muscular dystrophy.

Results CVrr was negatively correlated with arterial partial pressure of carbon dioxide (PaCO₂). In patients whose CVrr was larger than 5%, 84% of them had no hypercapnia while the other 16% had hypercapnia (PaCO₂ >45 mmHg). In contrast, 27% of those with CVrr smaller than 3% had no hypercapnia, 73% had hypercapnia and 47% had severe hypercapnia (PaCO₂ >50 mmHg).

Conclusion We first showed that CVrr was negatively correlated with PaCO₂, and propose that abnormally low CVrr indicates respiratory insufficiency in patients with Duchenne muscular dystrophy.

Key words: Duchenne muscular dystrophy, hypercapnia, heart rate variability, coefficient of variation of the R-R interval

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Introduction

In patients with Duchenne muscular dystrophy (DMD) a characteristic pattern of respiratory functional changes is observed during childhood and adolescence. Vital capacity (VC) increases until around the age of 10 years similar to the usual development pattern, remains stable for a considerable period, then continuously falls in association with the progression of respiratory muscle weakness. The annual decrease in VC may be as much as 250 mL in the late teenage years (1). Respiratory failure is a major cause of death in DMD patients. Without ventilatory support, the mean life-time is about 19 years, and 73% of DMD patients die of respiratory insufficiency (2). However, mechanical ventilation has extended patient survival time by more than five years (3-5).

Since the tracheostomy positive pressure ventilation

(TPPV) is more difficult to deliver at home than the non-invasive positive pressure ventilation (NPPV), most patients use NPPV first, and when hypercapnia cannot be managed by NPPV, they use TPPV (3). We should monitor the degree of respiratory failure in order to start TPPV at an appropriate time. For monitoring respiratory failure, usually arterial partial pressure of carbon dioxide (PaCO₂) is followed. However, often there is a difficulty in repeated blood gas analyses due to very slender arteries and articular contracture. Another reliable method for respiratory function analysis is VC measurement. In DMD patients, however, this measurement sometimes becomes inaccurate due to orbicularis oris muscle weakness, macroglossia and mental retardation.

On the other hand, the heart rate variability is a well-characterized, noninvasive means of assessing cardiac autonomic nervous system activity (6). The coefficient of the R-R interval variation (CVrr) reflects parasympathetic activity

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Table 1. Clinical Features of Patients with Duchenne Muscular Dystrophy

	All patients (n = 73)		1. No-V (n = 21)		2. NPPV (n = 27)		3. TPPV (n = 25)		ANOVA		Post hoc analyses Scheffe method (p < 0.05)
	mean	SD	mean	SD	mean	SD	mean	SD	f	p	
CVrr	4.06	1.59	4.04	1.58	4.15	1.76	4.00	1.67	0.80	0.454	
age	26	8	18	6	29	6	31	6	29.38	0.000	1 < 2 & 3
HR	94	17	101	15	88	18	81	7	13.00	0.000	2 & 3 < 1
RR	18	3	18	3	19	5	16	3	2.26	0.112	
PaCO ₂	43.3	7.8	43.1	6.3	47.0	7.1	39.5	8.2	6.88	0.002	3 < 2
PaO ₂	101.9	11.9	98.2	12.6	102.1	10.3	104.9	12.4	1.89	0.160	
BNP	54.6	113.5	52.3	160.6	49.7	81.6	61.8	99.1	0.08	0.926	

No-V, no ventilation; NPPV, noninvasive positive pressure ventilation; TPPV, tracheostomy positive pressure ventilation.

CVrr, coefficient of variation of the R-R interval (%); age, years old; HR, heart rate (/min); RR, respiratory rate (/min).

PaCO₂, arterial partial pressure of CO₂; PaO₂, arterial partial pressure of O₂; BNP, brain natriuretic peptide (pg/mL); SD, standard deviation.

Statistical analyses were done with one way ANOVA and *post-hoc* analyses with Scheffe method.

Table 2. Correlations between Each Clinical Feature

		age	HR	RR	PaCO ₂	PaO ₂	BNP
CVrr	r	0.039	-0.308	-0.075	-0.573	0.260	0.013
	p value	0.743	0.008 #	0.530	0.000 ##	0.026	0.916
age	r		-0.368	-0.119	0.004	0.205	0.243
	p value		0.001 ##	0.315	0.976	0.082	0.038
HR	r			0.044	0.164	-0.329	-0.225
	p value			0.710	0.166	0.004 #	0.056
RR	r				0.174	-0.250	0.226
	p value				0.142	0.033	0.054
PaCO ₂	r					-0.473	-0.116
	p value					0.000 ##	0.328
PaO ₂	r						0.005
	p value						0.966

CVrr, coefficient of variation of the R-R interval (%); age, years; HR, heart rate (/min); RR, respiratory rate (/min).

PaCO₂, arterial partial pressure of CO₂; PaO₂, arterial partial pressure of O₂; BNP, brain natriuretic peptide (pg/mL).

Statistical analyses were done with Spearman rank correlation test.

#, p < 0.01; ##, p < 0.001

and has some correlation with respiratory function (7, 8). The above situation in DMD facilitates estimation of hypercapnia using CVrr. In this study, we investigated the relationship between CVrr and hypercapnia and propose that CVrr measurement is one of the useful methods of predicting the hypercapnia in DMD patients.

Patients and Methods

We studied 73 patients with DMD (age, 6-44 years; clinical features are shown in Table 1). All subjects were admitted to our hospital for evaluation of their cardiopulmonary or neurological conditions. In all patients, the diagnosis was confirmed by a genetic study (abnormality of dystrophin gene) or muscular biopsy (absence of dystrophin protein). All patients became wheelchair-bound by the age of 12. At the time of our study, 52 patients were supported by mechanical ventilation (27 by NPPV and 25 by TPPV) and 21 patients were not (No-V); none of the patients had any signs of lung diseases (e.g. pneumonia, atelectasis, lung edema and so on) on chest X-ray and/or lung computed tomography. Thirty-six patients took medications for chronic heart failure (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and β -blocker, 14 patients; ACEI/ARB only, 20 patients; β -blocker only, 2 patients).

CVrr, heart rate (HR), respiratory rate (RR), brain natriuretic peptide (BNP), PaCO₂ and arterial partial pressure of oxygen (PaO₂) were measured. Before these measurements, physical conditions in all patients had been checked. If a patient had an unusual condition (high body temperature, HR or RR abnormalities), he was excluded from the present study.

After resting in a supine position for 30 minutes or longer, a standard 12-lead electrocardiography was recorded with an ECG machine (FCP-4101; Fukuda Denshi, Tokyo, Japan), and the R-R intervals were measured for three minutes. From the recorded R-R intervals, the CVrr was obtained by dividing their standard deviation (SD) by the mean (M). Thus, CVrr (%) = (SD/M) * 100. Arterial blood gas analysis was also performed just after the ECG recording.

For comparisons of each clinical feature between ventilation types, we used one-factor analysis of variation (ANOVA) and *post-hoc* analyses by the Scheffe method (Table 1), and Spearman rank correlation test for analysis of the relations between clinical features (Table 2).

Results

Clinical features of all the patients are shown in Table 1. No-V patients were younger and had a higher HR than the

Figure 1. Correlations between the coefficient of variation in the R-R interval (CVrr) and arterial partial pressure of carbon dioxide (PaCO₂) in DMD patients. A: All DMD patients (n=73). B: DMD patients without any ventilator (n=21). C: DMD patients with NPPV (n=27). D: DMD patients with TPPV (n=25). CVrr was negatively correlated with PaCO₂ significantly in all DMD patients and in all groups.

other two patient groups. The PaCO₂ of TPPV patients was lower than that of NPPV patients.

In analyses of correlations between clinical features (Table 2), there was a significant negative correlation between CVrr and PaCO₂ in all patients ($r = -0.573$, $p < 0.001$; Fig. 1A) and in any groups of patients (Fig. 1B, C and D). HR was negatively correlated with age and CVrr. As expected, PaCO₂ was negatively correlated with PaO₂. Between patients with and without medications for heart failure, there were no significant differences in CVrr (ACEI/ARB, $F = 1.415$, $p = 0.238$; β -blocker, $F = 2.837$, $p = 0.097$).

To investigate whether the CVrr is useful for estimating hypercapnia in DMD patients, we classified the patients according to the CVrr and hypercapnia (Table 3). Here, we defined “hypercapnia” as PaCO₂ greater than 45 mmHg (1, 9), and “severe hypercapnia” as PaCO₂ greater than 50 mmHg. We usually use the latter value as a critical respiratory failure, and if a patient shows this value, we should consider further respiratory support (1, 10). In 26 DMD patients with a CVrr $> 5\%$, 4 (15%) patients were classified as having “hypercapnia”. In 15 patients with a CVrr $< 3\%$, 11 (73%) had “hypercapnia” and 7 (47%) had severe hypercapnia. This tendency was observed irrespective of respirator support or not.

Discussion

The conspicuous finding of this study is that the CVrr clearly correlated with the respiratory function of the pa-

tient. The low CVrr indicates that respiratory dysfunction is mainly due to hypo-ventilation.

CVrr and PaCO₂

In DMD patients, CVrr was negatively correlated with PaCO₂ and HR. Various factors have been reported to affect the CVrr (11-13). In the present patients, the hypercapnia is the most probable factor to explain decreased CVrr. The direct relationship between CVrr and hypercapnia has not been studied in humans. Hypercapnia is well known to increase respiratory neuron firings in the brainstem (15, 16) and then increase the respiratory rate and volume (14, 15) as well as a reduction of parasympathetic activity (17). Based on these studies (14-17), hypercapnia would decrease the parasympathetic nervous system activity and CVrr. In fact, in an animal study, hypercapnia decreased “high frequency” heart rate variability (8) [i.e. respiratory sinus arrhythmia as measured by spectral power (18)]. The present findings confirm that the same series of events occur in humans.

Positive pressure ventilation effects on CVrr

In an animal study, acute introduction of positive pressure ventilation sometimes increased the sympathetic activity with a small reduction of parasympathetic activity (19). Regardless of with or without positive pressure ventilation, negative correlations between CVrr and PaCO₂ were present in any groups of DMD patients (Table 3 & Fig. 1). The ventilator effect on CVrr would be small, and would not have affected the negative correlation between CVrr and

Table 3. CVrr and Hypercapnia

All patients (n = 73)	CVrr					
	smaller than 3% (n = 15)		3 - 5% (n = 33)		larger than 5% (n = 25)	
	Ratio (%)	n	Ratio (%)	n	Ratio (%)	n
No hypercapnia (PaCO ₂ < or = 45 mmHg)	27	4	61	20	84	21
Hypercapnia (PaCO ₂ > 45 mmHg)	73	11	39	13	16	4
Severe hypercapnia (PaCO ₂ > 50 mmHg)	47	7	15	5	0	0
Patients without ventilator (n = 21)	(n = 4)		(n = 12)		(n = 5)	
No hypercapnia	25	1	58	7	100	5
Hypercapnia	75	3	42	5	0	0
Severe hypercapnia	50	2	17	2	0	0
Patients with NPPV (n = 27)	(n = 7)		(n = 12)		(n = 8)	
No hypercapnia	14	1	50	6	50	4
Hypercapnia	86	6	50	6	50	4
Severe hypercapnia	57	4	25	3	0	0
Patients with TPPV (n = 25)	(n = 4)		(n = 9)		(n = 12)	
No hypercapnia	50	2	78	7	100	12
Hypercapnia	50	2	22	2	0	0
Severe hypercapnia	25	1	0	0	0	0

PaCO₂, arterial partial pressure of CO₂.

PaCO₂ in this study.

Can hypercapnia be estimated by CVrr?

When CVrr was larger than 5%, 84% of patients had no "hypercapnia". This indicates that most of these patients did not have respiratory problems. In contrast, when CVrr was less than 3%, most of them had respiratory problems. About half of these patients had severe hypercapnia. This indicates that we should carefully examine the respiratory condition in patients with CVrr <3%.

In conclusion, we found that CVrr was negatively correlated with PaCO₂, and we propose that low CVrr is one of the signs of respiratory insufficiency in patients with Duchenne muscular dystrophy.

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References

- Baydur A, Gilgoff I, Prentice W, Carlson M, Fischer DA. Decline in respiratory function and experience with long term assisted ventilation in advanced Duchenne's muscular dystrophy. *Chest* **97**: 884-889, 1990.
- Rideau Y, Gatin G, Bach J, Gines G. Prolongation of life in Duchenne's muscular dystrophy. *Acta Neurol* **5**: 118-124, 1983.
- Simonds AK, Muntoni F, Hearther S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* **53**: 949-952, 1998.
- Jeppesen J, Green A, Steffensen BF, Rahbek J. The Duchenne muscular dystrophy population in Denmark, 1977-2001: prevalence, incidence and survival in relation to the introduction of ventilator use. *Neuromuscul Disord* **13**: 804-812, 2003.
- Mochizuki H, Miyatake S, Suzuki M, et al. Mental retardation and lifetime events of Duchenne muscular dystrophy in Japan. *Intern Med* **47**: 1207-1210, 2008.
- Pagani M, Lombardi F, Guzzetti S, et al. A power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* **59**: 178-193, 1986.
- Lanza GA, DelloRusso A, Giglio V, et al. Impairment of cardiac autonomic function in patients with Duchenne muscular dystrophy: relationship to myocardial and respiratory function. *Am Heart J* **141**: 808-812, 2001.
- Campen MJ, Tagaito Y, Jenkins TP, Balbir A, O'Donnell CP. Heart rate variability responses to hypoxic and hypercapnic exposures in different mouse strains. *J Appl Physiol* **99**: 807-813, 2005.
- Misuri G, Lanini B, Gigliotti F, et al. Mechanism of CO₂ retention in patients with neuromuscular disease. *Chest* **117**: 447-453, 2000.
- Nomori H, Ishihara T. Pressure-controlled ventilation via a mini tracheostomy tube for patients with neuromuscular disease. *Neurology* **55**: 698-702, 2000.
- Hayano J, Sakakibara Y, Yamada M, et al. Diurnal variations in vagal and sympathetic cardiac control. *Am J Physiol Heart Circ Physiol* **258**: H642-H646, 1990.
- Huikuri HV, Niemela MJ, Ojala S, Rantala A, Ikaheimo MJ, Airaksinen KE. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease: Effects of arousal and upright posture. *Circulation* **90**: 121-126, 1994.
- Lioy F, Hanna BD, Polosa C. Cardiovascular control by medullary surface chemoreceptors. *J Auton Nerv Syst* **3**: 1-7, 1981.
- Tankersley CG, Fitzgerald RS, Kleiberger SR. Differential control of ventilation among inbred strains of mice. *Am J Physiol Regul Integr Comp Physiol* **267**: R1371-R1377, 1994.
- Putnam RW, Conrad SC, Gdovin MJ, Erlichman JS, Leiter JC. Neonatal maturation of the hypercapnic ventilatory response and central neural

- CO₂ chemosensitivity. *Respir Physiol Neurobiol* **149**: 165-179, 2005.
- 16.** Dean JB, Bayliss DA, Erickson JT, Lawing WL, Millhorn DE. Depolarization and stimulation of neurons in nucleus tractus solitarii by carbon dioxide does not require chemical synaptic input. *Neuroscience* **36**: 207-216, 1990.
- 17.** Gilbey MP, Jordan D, Richter DW, Spyer KM. Synaptic mechanisms involved in the inspiratory modulation of vagal cardio-inhibitory neurons in the cat. *J Physiol* **356**: 65-78, 1984.
- 18.** Laude D, Weise F, Girard A, Elghozi JL. Spectral analysis of systolic blood pressure and heart rate oscillations related to respiration. *Clin Exp Pharmacol Physiol* **22**: 352-357, 1995.
- 19.** Frazier SK, Moser DK, Stone KS. Heart rate variability and hemodynamic alterations in canines with normal cardiac function during exposure to pressure support, continuous positive airway pressure, and a combination of pressure support and continuous positive airway pressure. *Biol Res Nurs* **2**: 167-174, 2001.

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