

# Factors associated with decreased lung compliance in subjects with permanent ventilation dependence:A follow-up study

著者	Onozawa Shinichi, Someya Fujiko, Nuriya Eiji
著者別表示	小ノ澤 真一, 染矢 富士子, 塗谷 栄治
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# Factors associated with decreased lung compliance in subjects with permanent ventilation dependence: A follow-up study

Shinichi Onozawa\* , Fujiko Someya<sup>1)</sup>, Eiji Nuriya<sup>2)</sup>

## Abstract

**Background:** Lung compliance is a parameter of lung expansion. In patients on ventilator management, it affects ventilatory status and mortality. There are few studies on permanent ventilator dependence (PVD), a condition defined as when a patient has been on ventilator management for more than three months. We aimed to clarify the longitudinal factors affecting lung compliance during the chronic period in PVD subjects.

**Methods:** A follow-up study was performed on 24 PVD subjects who had been on ventilator management for approximately 6 years. Static (Cst) and dynamic (Cdyn) lung compliance and alveolar-arterial PO<sub>2</sub> difference (P(A-a)O<sub>2</sub>) were assessed twice between 2019 and 2020, and the before and after results were compared for each assessment. We examined the correlation of changes in Cst and Cdyn over time with BMI, age, duration of ventilation dependence, and the incidence of pneumonia. The subjects were divided into two groups according to the presence of atelectasis, and changes in Cst, Cdyn, and P(A-a)O<sub>2</sub> were compared between the two groups.

**Results:** There were no significant changes in lung compliance between the two measurements in the follow-up. However, at the individual level, a decrease in BMI inhibited the decrease in Cst. There was no relationship between differences in Cst or Cdyn and P(A-a)O<sub>2</sub>, age, ventilator management days, or the incidence of pneumonia. Differences in P(A-a)O<sub>2</sub> were not observed between the two groups divided according to the presence of atelectasis.

**Conclusions:** Increased BMI affected lung compliance in PVD subjects during the chronic period. Regarding atelectasis, its relationship with differences in Cst and Cdyn was not clear, and impaired lung compliance was considered to resolve after several years of PVD.

## KEY WORDS

Permanent ventilation dependence, Mechanical ventilation, Lung compliance, Body mass index, Atelectasis

## Introduction

Long-term ventilatory management is defined as prolonged acute mechanical ventilation: more than 4 days of ventilatory management, or prolonged mechanical ventilation (PMV): more than 21 days of continuous ventilatory support for at least 6 hours per day<sup>1)</sup>. Permanent ventilation dependence (PVD)

is defined as the failure to wean the patient from the ventilator for more than 3 months<sup>2)</sup>. Long-term ventilator management was reported to be associated with an increased risk of pneumonia, respiratory muscle atrophy, decreased lung capacity, decreased lung compliance, and atelectasis<sup>3-5)</sup>. Lung compliance is an index of lung and thorax distensibility, and its decrease

Division of Health Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa City, Japan  
Asanogawa General Hospital Rehabilitation Center, Kanazawa City, Japan

1) School of Health Sciences, Kanazawa University, Kanazawa City, Japan

2) Department of Anesthesia, Asanogawa General Hospital, Kanazawa City, Japan

\* Corresponding author

causes an increase in respiratory workload, a decrease in ventilation rate, and an increase in respiratory rate<sup>6</sup>). There are two main types of lung compliance: static lung compliance (Cst), which indicates the expansibility of the lung and thorax, and dynamic lung compliance (Cdyn), which is the value of Cst plus the airway resistance component<sup>7</sup>). In PMV, Cst is an important index that affects mortality and weaning from ventilation<sup>8</sup>). In patients with neuromuscular diseases with reduced respiratory function, such as amyotrophic lateral sclerosis, it is important to maintain and improve lung compliance to prevent respiratory complications<sup>9</sup>). On the other hand, there are few previous studies on PVD. In an animal study conducted on adult dogs, Miki et al.<sup>10</sup> revealed that chronic atelectasis for 3 months affected lung compliance even after re-inflation. Sato et al.<sup>11</sup> reported a high incidence of atelectasis in PVD subjects, but it was not clear whether atelectasis was a factor of decreased lung compliance. In a previous cross-sectional study, we evaluated Cst and Cdyn in subjects with PVD, and found that a larger body mass index (BMI), ventilatory management days, alveolar-aerobic oxygen difference ( $P(A-a)O_2$ ), and rapid shallow breathing index are factors related to a smaller Cst and Cdyn<sup>12</sup>). Furthermore, Cst may be influenced by the presence of atelectasis, age, and incidence of pneumonia. Thus, lung compliance is known to decrease in patients undergoing long-term ventilation management, but the time course has not been clarified. Based on the report that prolonged duration of ventilation dependence affects lung compliance, we hypothesized that lung compliance decreases with the passage of about 1 year. Therefore, we re-evaluated the lung compliance in PVD subjects approximately 1 year after the last evaluation to confirm the progressive impairment in lung compliance and the affecting factors after long-term treatment for PVD.

## Methods

### 1. Subjects

The subjects were PVD subjects admitted to the ventilator center of Asanogawa General Hospital who underwent ventilator management for more than 3 months. First, Cst and Cdyn were measured in 2019, and complications of atelectasis and pneumonia, age, sex, height, weight, BMI, and ventilatory

management days were collected from the records as basic information.  $PaO_2$ ,  $PaCO_2$ , and  $FiO_2$  were measured as blood biochemical findings, gas exchange capacity was assessed, and  $P(A-a)O_2$  was calculated. Similar measurements were taken during 2020, with a minimum of 435 days, a maximum of 557 days, and a median of 505 days after the initial measurement. This study was conducted based on approval by the ethical review committee of Asanogawa General Hospital (approval number 174). The selection criteria were as follows: the purpose, significance, and methods of the study, protection of personal information, and possible risks were explained to the subjects or their families, and written consent was received. In 2019, 32 subjects were admitted to our hospital, and 29 provided consent. Exclusion criteria at the second evaluation were new abnormalities in the neurological, respiratory, cardiovascular, renal, or urological organs, or worsening of physician-diagnosed symptoms. A flowchart of subjects from baseline to follow-up is shown in Fig. 1. Of the 29 PVD subjects who completed the baseline assessment, 24 (89.6%) were able to complete the follow-up assessment; however, 5 subjects discontinued assessment due to worsening symptoms; 3 subjects died and 2 subjects had measurement difficulties.

### 2. Study Design

#### Follow-up study

### 3. Endpoints and measurement methods

Cst and Cdyn were measured using the end-inspiratory pause method<sup>6</sup>) with a Servo-s ventilator (MAQUET Critical care AB, Sweden). Before the measurement, we performed sputum suctioning and measured the cuff pressure of the tracheal tube to prevent any effects on measurement values, and we confirmed that there was no air leakage from the mouth or tracheostomy during ventilation. The original ventilator settings were changed by the physician for the measurement to volume control continuous mandatory ventilation or volume control intermittent mandatory ventilation, the inspiratory flow waveform was changed to a square wave, and the end-expiratory pause time was set to 0.3-0.5 seconds. Tidal volume ( $V_t$ ) and positive end-expiratory pressure (PEEP) were set to similar values when measured at baseline and



Table 1. Baseline and follow-up characteristics of the subjects

Parameters		Baseline	Follow up	p-value
Age		75.4 ± 9.7	76.7 ± 9.7	
Sex (n)	male		10	
	female		14	
Height (cm)			157.9 ± 8.7	
Weight (kg)		53.0 ± 10.6	51.8 ± 9.4	
Body mass index		21.2 ± 3.5	20.7 ± 3.0	
duration of ventilation dependence		2341 ± 1547	2855 ± 1529	
Number of pneumonia incidences per patient		2 (1-3)	2 (1-3)	
Static lung compliance (ml/H <sub>2</sub> O)		35.88 ± 10.16	35.32 ± 9.34	0.66
Dynamic lung compliance (ml/H <sub>2</sub> O)		23.14 ± 5.96	22.00 ± 6.01	0.23
Alveolar-arterial oxygen difference		21.73 ± 20.13	19.33 ± 21.16	0.58
Diagnosis (n)	Spinal cord injury		6	
	Hyoxic encephalopathy		3	
	Head trauma		1	
	Subarachnoid hemorrhage		4	
	Acute subdural hematoma		2	
	Brainstem infarction		2	
	Spinal cord infarction		1	
	Amyotrophic lateral sclerosis		4	
	Parkinson's disease		1	

Table 2. Cst, Cdyn, and A-aDO<sub>2</sub> t-test by the presence of atelectasis  
Data are calculated values of baseline minus follow-up  
\*p<.05

	Atelectasis		p-value
	presence	absence	
Cst	-2.69 ± 5.43	2.51 ± 5.75	.01*
Cdyn	-1.63 ± 3.52	2.81 ± 4.28	.03*
P(A-a)O <sub>2</sub>	2.57 ± 26.28	2.31 ± 18.95	.98

subjects had been diagnosed with pneumonia at least once during 1 year, with a median of two pneumonia cases per subject (Table 1). There was no difference in the number of pneumonia incidence depending on the atelectasis. No significant differences were found in the difference in P(A-a)O<sub>2</sub> between groups in terms of atelectasis. A decrease in Cst was related to an increased BMI (r=-0.41, p=0.047), but P(A-a)O<sub>2</sub>, age, ventilatory management days, and pneumonia incidence were not associated with the differences in Cst or Cdyn (Table 3).

### Discussion

In the present study, there was no correlation between the difference between Cst and Cdyn and the duration of ventilation dependence, rejecting the hypothesis that lung compliance decreases over time by a period of approximately 1 year. In cross-sectional observations, decreased lung compliance was

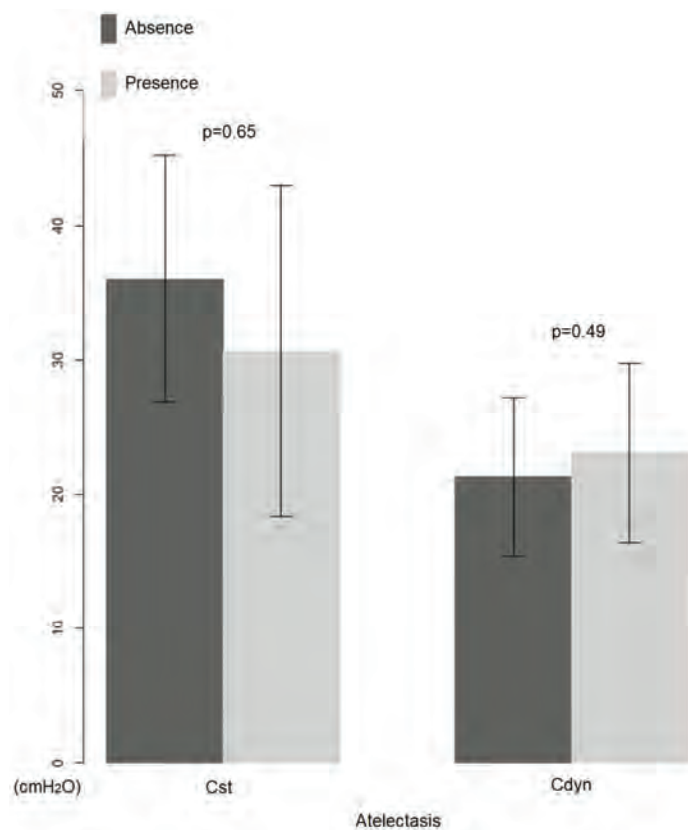


Fig 2. Comparison of Cst and Cdyn between groups by the presence of atelectasis.  
The values of Cst and Cdyn were measured in 2020 and compared by grouping the patients according to the presence of atelectasis.

reported in the studies performed at several months to approximately 1 year after the introduction of long-term ventilatory management<sup>8,12,14,15</sup>. To the extent

Table 3. Correlation coefficients for each item with differences in Cst and Cdyn

	Static lung compliance			Dynamic lung compliance		
	Correlation coefficient	95%CI	p-value	Correlation coefficient	95%CI	p-value
Body mass index	-0.41	(-0.69 to -0.01)	.047*	-0.38	(-0.68 to 0.03)	.07
Alveolar-arterial oxygen difference	0.32	(-0.09 to 0.64)	.12	0.34	(-0.08 to 0.65)	.10
Age	0.17	(-0.25 to 0.53)	.43	0.26	(-0.16 to 0.60)	.20
duration of ventilation dependence	-0.14	(-0.52 to 0.28)	.51	-0.33	(-0.65 to 0.09)	.12
Number of pneumonia incidences per patient	0.09	(-0.32 to 0.48)	.66	0.23	(-0.19 to 0.58)	.27

\*p<.05

of approximately 1 year, the duration of ventilation dependence was negatively correlated with both Cst and Cdyn<sup>12)</sup>. This suggested that 6-year management, as in this study, is sufficient to demonstrate stable lung compliance, but we were unable to conclude that an additional year after long-term ventilatory management of PVD is associated with poorer lung compliance. In the acute phase after the introduction of a ventilator, lung compliance was reported to decrease due to lung injury, such as acute respiratory distress syndrome, and this decrease was sustained to some extent by progressive lung fibrosis<sup>16)</sup>. In patients with spinal cord injury without ventilator management and parenchymal lung abnormalities, lung compliance decreased at 1 month after injury, but the decrease did not last for 12 months<sup>17)</sup>. This supports the present study and significant changes in lung compliance may occur in the early stages of ventilator introduction, exhibiting minor fluctuations in response to personal changes, such as BMI, and other factors thereafter.

A significant negative correlation between BMI and Cst was found in the present study, and body size indexed by BMI also affected Cst longitudinally in subjects with PVD. A previous cross-sectional study<sup>11,12)</sup> with a comparable BMI distribution range to that of the subjects in the present study also showed that the BMI of PVD subjects was significantly lower, which supports the present study. The general effects of obesity (BMI > 30) on Cst during ventilator management have been reported<sup>18-20)</sup>. The cause of the decreased Cst in obesity was considered to be the result of atelectasis due to the decrease in functional residual capacity caused by the increased abdominal mass and intra-abdominal pressure<sup>20)</sup>. Although the mean BMI in the PVD subjects in this study was within the normal range, a relationship between BMI and Cst was observed. This suggested that skeletal muscle loss

and fat gain occurred due to the older age and less physical activity of the subjects in this study. Therefore, it is necessary to clarify the relationship between Cst and BMI in PVD subjects considering not only BMI but also body composition, such as fat and skeletal muscle mass ratio, in the future. In addition, the BMI influences airway resistance in obesity and Cdyn is a value obtained by adding the airway resistance component to Cst<sup>21)</sup>. Therefore, BMI affected airway resistance in obese subjects<sup>22)</sup>. However, no significant correlation was observed between Cdyn and BMI in this study. In general, airway resistance is determined by the cross-sectional area, length, and a number of airways, and airway compression by fat is thought to affect airway resistance. The BMI of the subjects in this study was not considered sufficiently high to cause airway resistance.

In a cross-sectional study<sup>12)</sup>, Cst was significantly lower in subjects with atelectasis. However, in the present study, there was no difference in lung compliance between subjects with and without atelectasis, and we were unable to confirm if atelectasis affected the decrease in lung compliance. Longitudinally, both Cst and Cdyn increased in the group with atelectasis, and atelectasis did not exacerbate lung compliance, although no improvement was noted in radiographic findings. One possible explanation is that atelectasis inhibits the expansion of lung tissue, which may result in compensatory lung growth<sup>23)</sup>. This compensation refers to lung hyperinflation that occurs mainly after lung resection, such as in lung cancer, and is a response to mechanical stimulation or alveolar hypoxia that causes regeneration and expansion of alveoli<sup>23)</sup>. Compensatory lung growth was also reported to occur in collapsed alveoli such as atelectasis<sup>24)</sup>. In an animal study<sup>25)</sup>, compensatory lung growth was noted when positive pressure ventilation was applied

as a mechanical stimulus and after pneumonectomy. In the group without atelectasis in this study, both Cst and Cdyn decreased, and lung compliance fluctuated without marked lung volume limitation by atelectasis. The present study was conducted for an approximately 1-year period, but it may be necessary to observe longer-term changes to assess the relationship between Cst and Cdyn and atelectasis. Of note, 4 of the 5 subjects who dropped out from the study had atelectasis, suggesting that atelectasis increases the risk of death.

There was no significant difference in the difference in  $P(A-a)O_2$  between groups with and without atelectasis in the present study. In a cross-sectional study of PVD subjects<sup>12)</sup>, Cst was significantly lower and the incidence of pneumonia was higher in subjects with atelectasis, suggesting that the presence of atelectasis and alveolar fibrosis after pneumonia impaired gas exchange capacity and reduced  $P(A-a)O_2$ . Our study suggests that atelectasis does not cause further  $P(A-a)O_2$  reduction in 1 year of the long-term course of the disease. In a study of shorter ventilatory management<sup>8)</sup>, the ventilator weaning rate and survival rate of PMV were not affected by the ventilatory management days. In addition, fibrosis of lung tissue associated with inflammatory changes affects lung compliance in acute respiratory distress syndrome and often develops in relatively severe pneumonia<sup>8, 26)</sup>. In the present study, the subjects had no abnormality in the lung parenchyma necessitating ventilator management, and no severe pneumonia, such as acute respiratory distress syndrome, was found after ventilator management. Pneumonia that developed was relatively mild and was not at the level of fibrosis in the lung tissue. Moreover, hypoxic pulmonary vasoconstriction<sup>27)</sup> and compensatory lung growth<sup>23)</sup> may be effective to maintain gas exchange.

Similarly, we found no significant correlation between age and differences in Cst and Cdyn in the PVD subjects in this study. The relationship between age and lung compliance has been described in many previous studies in patients not receiving ventilator management, and lung compliance was reported to decrease with age due to the decrease in lung rib cage distensibility<sup>10, 27-30)</sup>. Although no previous studies were found on this point in subjects with PVD, the age of

PMV subjects did not affect the lung compliance<sup>32)</sup> and was unlikely to have an important effect<sup>8)</sup>. Therefore, age may have no effect on lung function or other factors in long-term ventilator management for reasons other than the short observation period.

The limitations of this study are that we were unable to ethically adopt this study method for subjects whose condition deteriorated; therefore, we limited our study to subjects with stable symptoms. Multivariate analysis was considered desirable for examining multiple factors, and its methodology was discussed. However, since this was a study at a single institution with long-term hospitalization and a small number of subjects, we used correlation coefficients in this study. It is necessary to increase the number of cases and conduct follow-up studies at multiple institutions in the future. Furthermore, the follow-up period was only 1 year and long-term changes were not sufficiently confirmed. All subjects in the study had a neurological diagnosis. As neurological respiratory impairment requires prolonged ventilation by a different mechanism than primary lung disease, changes in compliance levels over time may be different in subjects with chronic respiratory failure without primary lung disease. In addition, in this study, the effects of comorbidities could not be examined because of the small number of subjects. For example, it has been reported that diabetes mellitus may cause a decrease in lung elasticity<sup>33)</sup>. It is also necessary to examine the difference in lung compliance over time in patients with comorbidities.

## Conclusion

Ventilator management is considered to reduce lung compliance, but no progressive influence was observed after long-term management of approximately 6 years in subjects with PVD. The individual fluctuation in lung compliance was affected by BMI at re-evaluation after an additional 1 year. The relationship between atelectasis and the difference in lung compliance was unable to be clarified. A longer observation of atelectasis, and the severity of pneumonia and other lesions must be considered to identify factors related to the changes in lung compliance.

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## 人工呼吸依存患者における肺コンプライアンス低下の要因について：追跡研究

小ノ澤 真一<sup>\*</sup>, 染矢 富士子<sup>1)</sup>, 塗谷 栄治<sup>2)</sup>

### 要 旨

肺のコンプライアンスとは肺の拡張性を測るパラメーターである。人工呼吸器管理患者の肺コンプライアンスは、人工呼吸管理の状態や死亡率に影響する。しかし、人工呼吸器依存 (Permanent ventilator dependence:以下,PVD)患者に関する研究は少ない。PVDとは、患者が3カ月以上人工呼吸器の管理を受けている場合に定義される状態である。本研究では、PVD患者の経時的な肺コンプライアンスの変化と、要因を明らかにすることを目的とした。方法は追跡研究で、約6年間人工呼吸器を装着していたPVD患者24名を対象に、静的(以下,Cst)と動的(以下,Cdyn)肺コンプライアンスと肺泡気動脈血酸素分圧較差(以下, P(A-a)O<sub>2</sub>)について2019年から2020年にかけて2回評価を行い、それぞれ前後を比較した。CstとCdynの経時変化とBMI、年齢、人工呼吸器管理日数、肺炎発生率との相関を調べた。患者を無気肺の有無で2群に分け、Cst、Cdyn、P(A-a)O<sub>2</sub>の経時変化を2群間で比較した。結果として、2回測定した経時変化では、Cst、Cdynに大きな変化はなかった。個別の変化としては、BMIの低下がCstの低下を抑制した。P(A-a)O<sub>2</sub>、年齢、人工呼吸器管理日数、肺炎の発生率とCst、Cdynの経時変化に関連はなかった。P(A-a)O<sub>2</sub>の差は、無気肺で分けた2群間では差がなかった。結論としてBMIはPVD患者の肺コンプライアンスに影響を与えた。無気肺についてはCstやCdynの差との関係は明らかではなく、肺コンプライアンス低下はPVDの状態となった数年後には軽微な変動のみになるものと考えられた。