EFFECT OF NONINVASIVE VENTILATION ON RESPIRATORY MUSCLE LOADING AND ENDURANCE IN DUCHENNE PATIENTS

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Abstract

Background: Respiratory muscle weakness in Duchenne (DMD) patients leads to respiratory failure, for which non-invasive positive pressure ventilation (NIPPV) is an effective treatment. This is used at night initially (n-NIPPV), but as the disease progresses, diurnal use (d-NIPPV) is often necessary. The connection between NIPPV and relief of respiratory muscle fatigue remains unclear. **Objectives**: To study the extent to which nocturnal and diurnal NIPPV unload the respiratory muscles and improve respiratory endurance in DMD patients. **Methods**: Fifty patients with DMD assessed at 8pm and 8am. More severely affected patients, with nocturnal hypoventilation, received n-NIPPV; those with daytime dyspnoea also received d-NIPPV via a mouthpiece (2-4 pm). Lung function, modified Borg dyspnoea score, spontaneous breathing pattern, tension-time index (TT0.1=P0.1/MIPxTi/Ttot) and respiratory muscle endurance time (Tlim) against a threshold load of 35% maximum inspiratory pressure were measured. **Results**: More severe respiratory muscle weakness was associated with a higher TT0.1 and lower Tlim. In contrast to non-dyspnoeic patients, dyspnoeic patients (Borg score>2.5/10) showed an increase in Tlim and decrease in TT0.1 after n-NIPPV. At 4pm, immediately after d-NIPPV, dyspnoeic patients had lower TT0.1 and Borg scores with unchanged Tlim. Compared to the control day without d-NIPPV, TT0.1, Borg scores and Tlim were all improved at 8pm. **Conclusions**: In dyspnoeic DMD patients, the load on respiratory muscles increases and endurance capacity decreases with increasing breathlessness during the day, and this is reversed by nocturnal NIPPV. An additional two hours of d-NIPPV unloads respiratory muscles and reverses breathlessness more effectively than n-NIPPV alone.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked disorder which affects skeletal muscles including those of respiration. Vital capacity[1] (VC) and respiratory endurance[2] start to decline in adolescence, and without non-invasive intermittent positive pressure ventilation (NIPPV) death occurs at an average age of 21.5 years[3].
In order to minimize the work[4] and perception[5] of breathing, patients progressively accelerate their respiratory rate. Despite this strategy, at some stage it is no longer possible to maintain adequate alveolar ventilation, and the arterial carbon dioxide pressure (PaCO2) level rises. Nocturnal hypercapnia typically occurs when the VC falls below 40% of the predicted value[6,7], and further progresses to diurnal hypercapnia within 12 months in 70% of the cases[8]. With the use of nocturnal NIPPV (n-NIPPV), daytime hypercapnia is delayed by 4-5 years[9] and survival is prolonged by 5-10 years[10]. Diurnal NIPPV (d-NIPPV) delays further deterioration in VC and prolongs survival above 31 years[9].
In DMD, failure to maintain alveolar ventilation could plausibly be explained by fatigue of the respiratory muscles, although this has never been convincingly demonstrated. Studies of the long-term effects of NIPPV have concluded that improved respiratory drive is the most important factor in restoring alveolar ventilation in neuromuscular patients[11,12], but reducing respiratory drive seems more likely to be a protective mechanism for fatiguing respiratory muscles rather than the primary problem in DMD. We studied non-ambulatory DMD patients at progressive stages of respiratory progression up to the ultimate stage in which permanent assisted ventilation is expected. We used two different but complementary techniques – modified noninvasive tension time index and endurance of a threshold load – to investigate the effects of NIPPV on respiratory muscle loading and endurance capacity in DMD patients. Our hypothesis was that nocturnal NIPPV initiated at the onset of nocturnal hypercapnia does not unload the respiratory muscles, whereas both nocturnal and part-time daytime NIPPV unload respiratory muscles in patients complaining of increasing dyspnoea during daytime unassisted breathing.

METHODS

Fifty consecutive patients with DMD were studied, with a mean (SD) age of 21.6 (5.7) years, weight of 54.3 (18.8) kg and arm span of 164.3 (8.4) cm. They fit into one of the five groups according to the clinical severity of their respiratory muscle involvement. Group 1 (n=10) were able to breathe spontaneously all day and night, and had normal nocturnal gas exchange. Group 2 (n=9) were also able to breathe spontaneously all day and night, but had asymptomatic nocturnal hypoventilation as evidenced by a transcutaneous carbon dioxide tension (TcCO2) which rose above 45 mmHg. Group 3 (n=11) and group 4 (n=11) had been commenced on n-NIPPV to correct symptomatic nocturnal hypoventilation. In a previous study, we found that subjects who were breathless in the evening prior to restarting n-NIPPV were more likely to benefit from d-NIPPV[9]. We therefore subdivided patients using n-NIPPV according to the presence (group 4) or absence (group 3) of a modified Borg dyspnoea score on 10 points in the evening >2.5. Group 5 (n=9) already used NIPPV for symptom relief during the day as well as at night. Symptoms were quoted by a score

on 7 points[9,13], 1 point per symptom present: chronic secretions and cough, perceived dyspnoea, anorexia, moodiness, hand sweating, headache and dysphagia.

In experiment 1, we studied the effect of n-NIPPV on respiratory muscle loading by comparing evening and morning measurements made at 8 pm and 8am. n-NIPPV (groups 3 and 4) was provided by volume ventilators for an average of 8.9 (SD: 0.9) hours using a nasal mask. The ventilators were set initially with a tidal volume (VT) of 12ml/kg[14] at slightly lower respiratory rate (RR) than the spontaneous rate during sleep. After adjusting the settings to maintain normocapnia with minimal mask leaking, mean (SD) VT and RR were 653 (71) ml and 19.9 (1.7) min^{-1} respectively.

In experiment 2, group 4 (evening dyspnoea) patients received additional d-NIPPV by mouthpiece between 2pm and 4pm. This duration and timing of d-NIPPV reflected use in clinical practice, where a two hour period in the middle of the day relieves symptoms with minimal intrusion on daily activities[15].

Measurements were made at 4pm and 8pm on days with d-NIPPV, and compared with data recorded at 8am, 2pm and 8pm on a separate day after n-NIPPV alone. d-NIPPV used the same ventilator settings as for n-NIPPV, but with a mouthpiece held in place by a rigid plastic retainer placed on the patients' shoulder[9].

We assessed respiratory muscle loading using two different approaches: spontaneous breathing pattern and respiratory muscle endurance. For breathing pattern, subjects were asked to breathe through a mouthpiece for two minutes, from which a 30 second sequence of regular breathing was selected for further analysis. We calculated RR, inspiratory time (Ti), total breath time (Ttot), duty cycle (Ti/Ttot), VT and minute ventilation (VE). Whilst breathing quietly, ten records of 100ms occlusion pressure (P0.1) were electronically triggered in random order over a period of two minutes. The mean value from the three best P0.1 was retained for analysis[16]. Volumes and timing of spontaneous ventilation were obtained by integration of flow signals recorded by a heated Fleisch N°2 pneumotachometer (Metabo, Lausanne, Switzerland).

Spontaneous breathing pattern was compared with the maximum capacity of the respiratory system, as estimated by the best of three VC manoeuvres, three recordings of maximal inspiratory pressures in 1 second (MIP) performed at residual volume[17] and maximal voluntary ventilation (MVV) over 15 seconds. The Tension Time Index (TT0.1) was calculated as (P0.1/MIP) x (Ti/Ttot)[18]. This is a noninvasive variation of the invasive tension-time index of the diaphragm (TTdi)[19] which is used to evaluate fatigue. For TT0.1, a value greater than 0.047 has been shown as the threshold above which the inspiratory muscles are at risk of fatigue[18,20]. For respiratory endurance, the maximal time (Tlim) the patients could hold spontaneous ventilation against a predefined load (35% of MIP) was recorded following the method of Matecki et al.[2]. The spring-loaded treshold valve used by the latter was replaced by a vacuum generator (MEC, Brussels, Belgium) such as described by Chen et al.[21] and used by Hart et al. [22]. The Ethics committee of our institution approved the study. Informed consent from patients and families was obtained prior to the commencement of the study.

Data analysis

One-way analysis of variance (ANOVA) and post-ANOVA Student-Newman-Keuls were used for groups comparisons. Paired t-test was used for paired comparisons.

Data were presented as mean value, standard deviation (standard error of the mean on figures) and the 95% confidence interval. Significance was accepted at $p<0.05$.

RESULTS

Table 1 shows the morning data for each group. From group 1 to 5 there was a progressive increase in age and decline in MIP, MVV and VC. VT fell but VE was maintained by an increase in RR, the ratio of Ti to Ttot remaining stable. Endurance capacity (Tlim) decreased and TT0.1 increased with age and disease progression, suggesting that more severely affected subjects were approaching respiratory muscle fatigue.

Group	1	2	3	4	5
Age (year)	17±2.9	18.6±2.8	21.6±4.6	22.2±3.3	29.1±6.2
***	(14.9-19.1)	(16.4-20.7)	(18.6-24.7)	(19.9-24.4)	(24.5-33.8)
BMI	21.7±6.5	20.7±6.2	20.9±8.8	18.3±6.8	18.8±5.4
(kg/m^2)	(13-28.2)	(16-25.3)	(15-26.8)	(13.7-22.8)	(14.8-22.8)
VC %	44.5 ±16	23.3±5.4	25.9±8.4	14.8±4.2	12.1±2.4
***	(33.1-55.9)	(19.2-27.5)	(20.3-31.6)	(12-17.6)	(10.2-14)
MVV (L/min)	60.8±18.1	34.7±8.2	41.4±11.7	26.4±13.6	18.2±4
***	(47.9-73.7)	(28.4-41)	(33.5-49.2)	(17.2-35.4)	(15.2-21.3)
VT (ml)	425± 188	252±88	305±74	274±84	241±44
**	(291-559)	(184-320)	(256-355)	(218-331)	(208-275)
RR (breath/min)	17.5± 5	22.4±6.4	19.3±4.1	19.6±2.5	24.8±4.8
**	(13.9-21.1)	(17.6-27.3)	(16.6-21.9)	(17.9-21.2)	(21.1-28.5)
VE (L/min)	6.9±2.2	5.3±1.7	5.8±1.4	5.4±1.7	5.9±1.1
	(5.3-8.5)	(4-6.6)	(4.8-6.7)	(4.2-6.6)	(5-6.8)
Ti/Ttot	0.46±0.04	0.44±0.08	0.41±0.08	0.44±0.04	0.43±0.05
	(0.44-0.49)	(0.39-0.5)	(0.36-0.46)	(0.41-0.47)	(0.4-0.47)
MIP (cmH_2O)	46.7±14.8	24.1±8.5	26.9±10.1	14±5.6	11.1±3.2
***	(36.1-57.2)	(17.6-30.6)	(20.1-33.7)	(10.2-17.7)	(8.7-13.5)
P0.1	1.84±0.78	1.61± 0.37	1.42±0.4	1.35± 0.5	1.48±0.71
	(1.28-2.4)	(1.32-1.9)	(1.14-1.69)	(1.02-1.67)	(0.93-2.02)
TT0.1	0.019±0.008	0.034±0.022	0.024±0.01	0.046±0.021	0.059±0.026
*	(0.013-0.025)	(0.017-0.051)	(0.017-0.031)	(0.031-0.06)	(0.039-0.079)
Tlim (sec)	422±186	429±249	256±195	202±197	121±81
**	(288-555)	(237-620)	(125-387)	(70-334)	(59-183)

Table 1: Demographics of the 5 groups of patients with Duchenne Muscular Dystrophy: morning measurements

*Data are presented as mean ± standard deviation (95% confidence interval). ANOVA * p<0.05; **p<0.01; *** p<0.001 ; 1, No assisted ventilation (NIPPV) and 24/24 h normocapnia ; 2, Nocturnal hypercapnia prior to start NIPPV implementation ; 3, Nocturnal NIPPV with no breathlessness ; 4, Nocturnal NIPPV with breathlessness ; 5, Full time NIPPV*

Figure 1 shows the effect of n-NIPPV on TT0.1. More severe respiratory muscle weakness is associated with higher TT0.1, but there is a fall between groups 2 and 3 after n-NIPPV is started. In groups 4 and 5, TT0.1 is considerably lower in the morning when the subjects had just stopped n-NIPPV. Figure 2 shows the same pattern for respiratory muscle endurance. After 2 hours of d-NIPPV, group 4 (dyspnoeic) subjects had a higher VC and Ti but lower TT0.1 (Table 2).

	8 am	8 pm
VC (ml) *	704±195 (573-835)	642±153 (539-745)
RR (breath/min) **	19.6±2.5 (17.9-21.2)	25.8±8.1 (20.4-31.2)
Ti/Ttot	0.44±0.04 (0.41-0.47)	0.44±0.05 (0.4-0.47)
MIP (cmH_2O)	14±5.6 (10.2-17.7)	13.6±6.1 (9.5-17.7)
TT0.1 **	0.046±0.021 (0.031-0.06)	0.081±0.035 (0.58-0.1)
Tlim (sec) *	202±197 (70-334)	149±183 (26-172)
$TcCO_2$ (mmHg)	45.5±.7.8 (40.3-50.8)	46.3±7.9 (40.9-51.6)

Table 2: Comparison of respiratory parameters at 8 am (post NIPPV) and 8 pm (prior to NIPPV) in group 4 patients with evening breathlessness

*Data are presented as mean ± standard deviation (95% confidence interval). Paired t-test comparison (8 am vs 8 pm): * $p<0.05$; ** $p<0.01$*

Figure 3 compares days with n-NIPPV to days with n-NIPPV plus d-NIPPV in this dyspnoeic group. By the evening there had been a deterioration in Borg score, VC, RR, TT0.1 and endurance capacity (Tlim) but they were still better at 8pm following d-NIPPV than the 8pm recordings from the control day when they did not have d-NIPPV. TT0.1 improved immediately after d-NIPPV while changes in Tlim and RR were not significant at 4pm but significant at 8pm. MIP and Ti/Ttot remained stable after n-NIPPV and d-NIPPV. Figure 4 demonstrates the close relationship between changes in breathlessness and TT0.1 during and after NIPPV.

DISCUSSION

We have shown that as patients with DMD become more severely affected by their disease they lose endurance capacity and adopt a breathing pattern which puts them at risk of excessive muscle loading. This is seen in patients who have already had to start n-NIPPV (group 3). In patients with n-NIPPV in whom breathlessness increases during the day (group 4 and 5), the fall in endurance capacity is more pronounced towards the end of the period of the day when they are breathing spontaneously. In these dyspnoeic patients, two hours of d-NIPPV restored morning values of respiratory parameters and alleviated symptoms of dyspnoea for the remainder of the day.

Muscle fatigue involves loss of capacity for developing force and/or velocity of contraction, which is reversible by rest[23]. Previous studies have focused on measures of strength, such as MIP, and failed to show any significant effect of NIPPV. In our study MIP did not change, and so it could be argued that we have not demonstrated respiratory muscle fatigue. We suggest that TT0.1 and Tlim appear to be more sensitive to changes in the function of the respiratory muscles, and are more physiological than measures of strength. Our study could also be criticised for not documenting that NIPPV rested the respiratory muscles, but this is a consistent finding of previous studies which fits with our clinical observation of the subjects[24,25,26].

Reduction in the work of breathing (ie the load on the muscles) as a consequence of inflation of the chest by mechanical ventilation could also explain our results. We did not measure lung or chest wall compliance, but the small increase in VC with no change in MIP seen after n-NIPPV and d-NIPPV would be consistent with increased compliance of the respiratory system, except in group 3 patients where VC was paradoxically reduced after n-NIPPV. In kyphoscoliosis, periods of daytime intermittent positive pressure breathing (IPPB) from 5-10[27,28] to 120 minutes[15] improved VC, but in another study 20 minutes had no effect[29]. No change in VC following short periods of IPPB has been observed in patients with respiratory muscle weakness[29,30]. An exception is amyotrophic lateral sclerosis (ALS) patients in whom 5 minutes of IPPB via mouthpiece improved static lung compliance[31]. ALS patients however may not be comparable to patients with a less severe disease progression such as DMD patients[31].

In the natural progression of DMD, nocturnal hypercapnia precedes daytime symptoms[32], suggesting a strategy which allows PaCO2 to rise rather than subject the respiratory muscles to a load which they are unable to sustain. The sensation of breathlessness results from increasing effort as weaker muscles strive to maintain normocapnia[9]. At this stage patients adopt a breathing pattern which puts them at high risk of respiratory muscle fatigue, and their endurance is reduced as evidenced by their capacity to tolerate an external load. NIPPV reverses these changes. Recovery of respiratory drive has been demonstrated in neuromuscular patients as a longer term effect of n-NIPPV; we suggest that this could reflect an increase in the capacity of the respiratory muscles, allowing the respiratory centres to increase ventilation without putting the respiratory muscles at risk of fatigue.

This study also showed that 2 hours of d-NIPPV provided similar physiologic effects on spontaneous breathing and dyspnoea than a full night with NIPPV. There were some differences between d-NIPPV and n-NIPPV, since a nasal mask is commonly used in lying position, but is less easy to use during the daytime in the sitting position. Patients therefore chose mouthpiece for daytime use. The main difference between mouthpiece and nasal NIPPV is that nasal mask is used by a sleeping patient at night while mouthpiece is used by a conscious patient during the day. During daytime ventilation, patients actively purse the lips around the mouthpiece to be fully inflated only two or three times per minute[9]. Compared to the nasal mask at night, the better control on leaking and synchronism provided by the mouthpiece should explain why a short period of daytime ventilation is so effective in improving the markers for respiratory fatigue. However, the disparity between changes in TT0.1 and Tlim immediately after d-NIPPV was unexpected in group 4 dyspnoeic patients (fig.3). This disparity refers to the high intra-individual variability in this group, probably reflecting the difficulty found in some patients to undergo an endurance test immediately after relaxing their respiratory muscles with d-NIPPV. Four hours after d-NIPPV, the disparity between TT0.1 and Tlim was significantly reduced. The correlation between changes in TT0.1 and Borg score suggest that the Borg score is a reliable marker of the load on respiratory muscles in patients in whom daytime ventilation is expected in a next future. The current results suggest that additional d-NIPPV is beneficial in reducing the load on the respiratory muscles as soon as dyspnoea is present in the evening. Further research however is required to confirm these benefits.

In conclusion, our results suggest that in patients with DMD the load on respiratory muscles and associated risk for respiratory fatigue increases with respiratory muscle weakness. Several years after nocturnal NIPPV implementation, breathless and other physiological markers of respiratory muscle loading rise from morning to evening. This study shows that these markers of loading and possible peripheral fatigue are closely related to dyspnoea. Both are reduced and endurance capacity enhanced following nocturnal NIPPV. Our data suggest that, in patients who are dyspnoeic when they are breathing unassisted from morning towards evening, two hours of d-NIPPV is able to reverse breathlessness and associated signs of respiratory muscle loading more effectively than n-NIPPV alone.

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Figure legends

Figure 1: The noninvasive tension-time index (TT0.1) in the 5 groups of Duchenne patients.
*Columns represent mean values; errors bars represent 1 standard error of the mean (SEM). White columns: evening TT0.1; black columns: morning TT0.1; Paired t-test (evening vs morning) ** p<0.01*

Figure 2: Endurance capacity (Tlim) in the 5 groups of Duchenne patients

*Columns represent mean values; errors bars represent 1 standard error of the mean (SEM). White columns: evening Tlim; black columns: morning Tlim; Paired t-test (evening vs morning) * p<0.05*

Figure 3: The impact of nocturnal (□) and diurnal (▲) ventilation on daytime noninvasive tension-time index (TT0.1, panel A) and endurance capacity (Tlim, panel B) in group 4 dyspnoeic patients
*The grey area represent the period of diurnal (D) mechanical ventilation. Dots represent mean values, errors bars represent SEM. Paired t-test: ** p<0.01; *** p<0.001*

Figure 4: Changes over 24 hours in tension time index (TT0.1) and breathlessness (Modified Borg score on 10 points) in group 4 dyspnoeic patients.
Data are presented as % of baseline values measured at 8pm prior to nocturnal NIPPV. See legends on figure 3.

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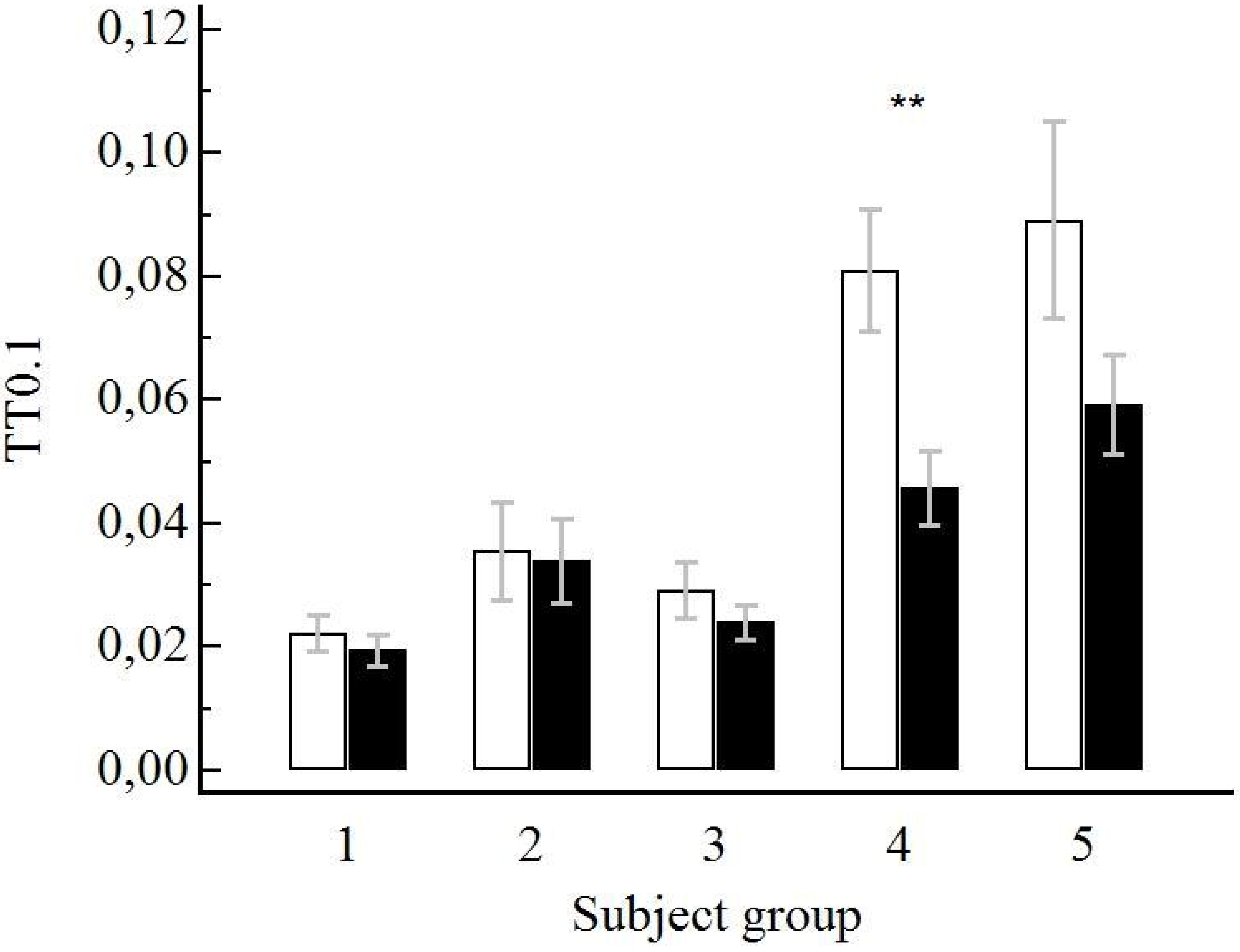

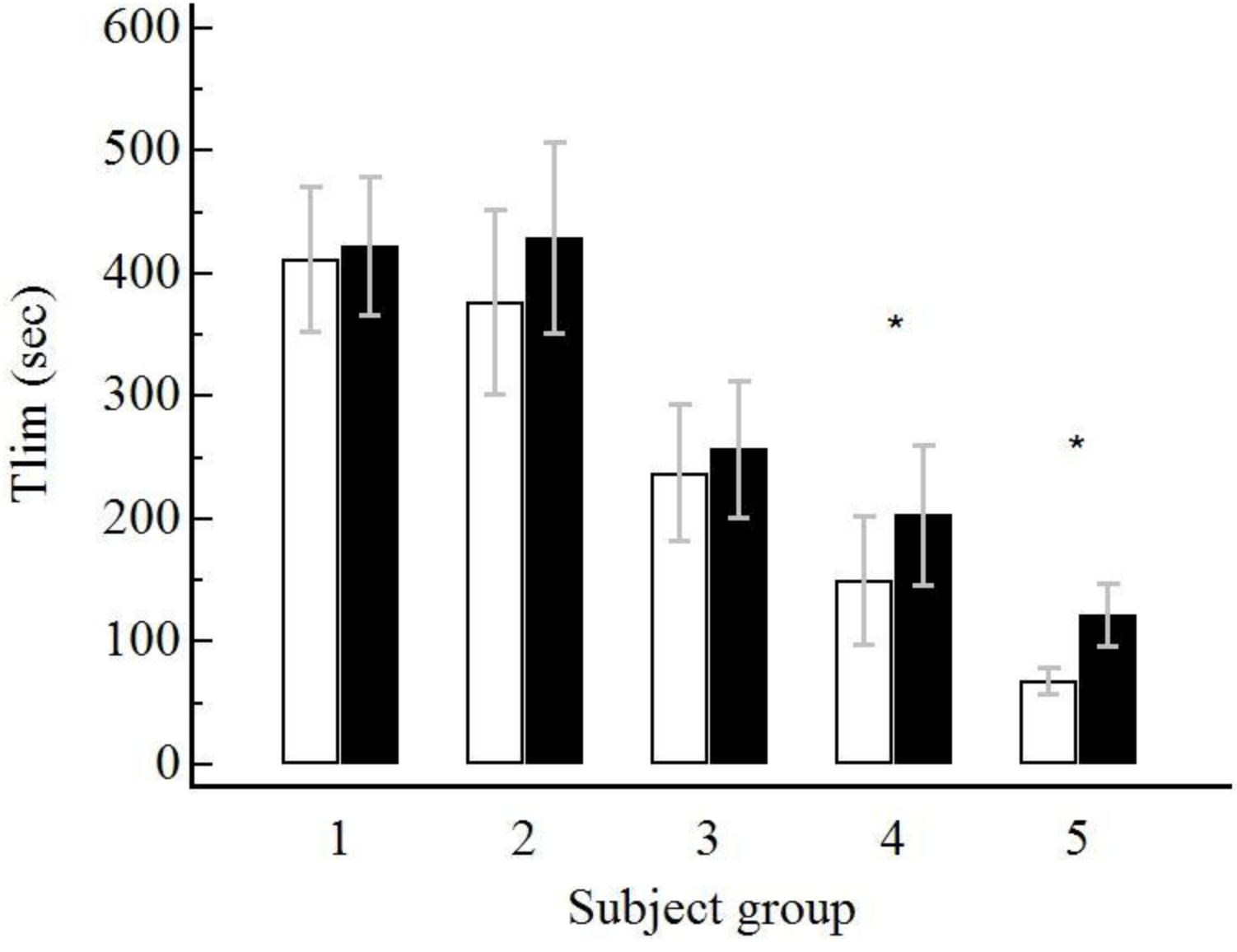

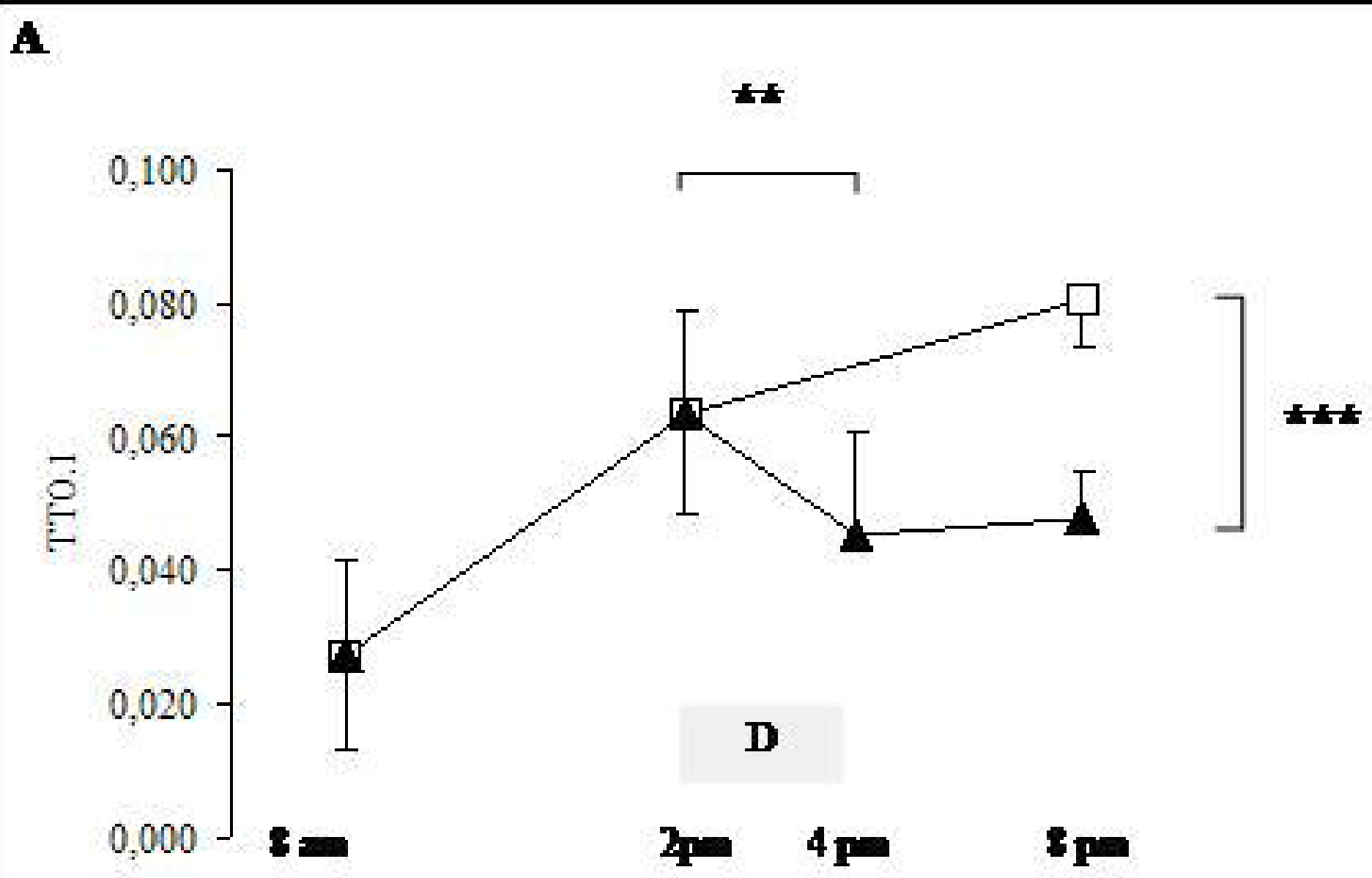
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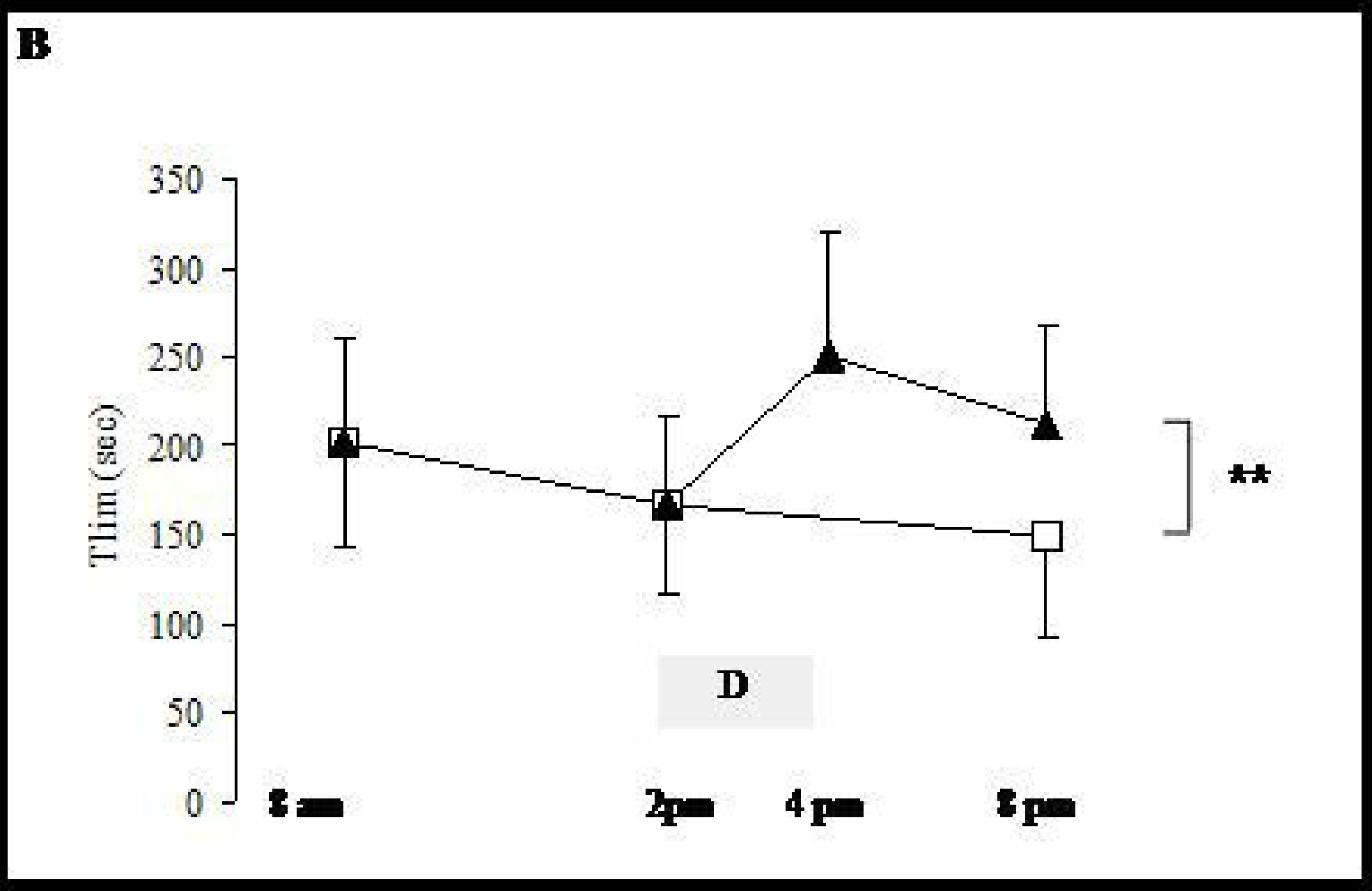
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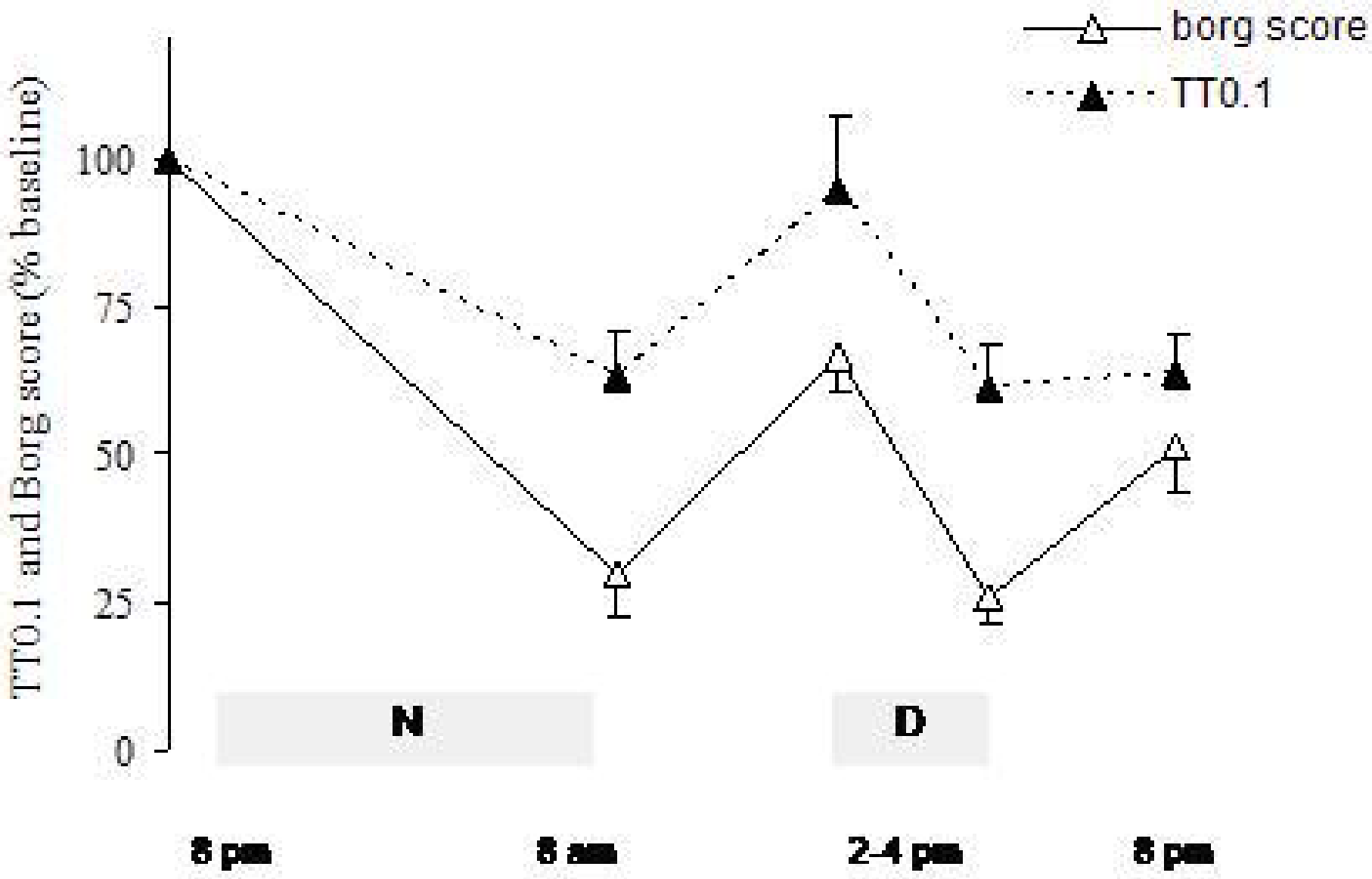
borg score
TT0.1
TT0.1 and Borg score (% baseline)
100
75
50
25
0
N
D
8 pm
8 am
2-4 pm
8 pm