

Effects of transcutaneous electrical diaphragmatic stimulation on respiratory function in patients with prolonged mechanical ventilation

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Abstract:

PURPOSE: Muscle atrophy and diaphragm dysfunction are common with prolonged mechanical ventilation (PMV). Electrical stimulation on peripheral muscles has been shown to be beneficial in the improvement of muscle function. This study examined the effects of transcutaneous electrical diaphragmatic stimulation (TEDS) on respiratory muscle strength and weaning outcomes in patients with PMV.

METHODS: Participants on ventilation for ≥ 21 days were randomly assigned to TEDS ($n = 29$) and control ($n = 30$) groups. The TEDS group received muscle electrical stimulation for 30 min/session/day throughout the intervention. Pulmonary function parameters (tidal volume, respiratory rate, and rapid shallow breathing index), and respiratory muscle strength (Pimax, Pemax) were assessed. The hospitalization outcome, including weaning rate and length of stay, was followed up until discharge.

RESULTS: After TEDS, there was a significant increase in Pemax (10 [8–20] vs. 20 [10–22] cmH₂O, $P = 0.034$) in the intervention group. At the end of the study, the improvement of minute volume in the TEDS group (0.64 [–0.67]) was significantly higher than the control group (–0.64 [–2.5–0.78]) ($P = 0.008$). In the control group, there was no significant difference between pre- and post-measurement of weaning parameters. There was a significant difference between groups in the weaning rate, with a higher rate in the TEDS group (90%) when compared with that in the control group (66.7%) ($P = 0.021$).

CONCLUSION: TEDS was significantly associated with increased respiratory muscle strength in patients with PMV. TEDS may be useful to facilitate weaning in this population.

Keywords:

Diaphragmatic, electrical stimulation, respiratory muscle, weaning

Mechanical ventilation is considered an essential modality of saving lives for patients with critical illness. In December 2019, a novel viral disease which has been known as coronavirus (COVID-19) widespread worldwide and becomes a global pandemic disease.^[1,2] According to the WHO, the COVID-19 can induce acute hypoxemia respiratory failure that may lead

to acute respiratory distress syndrome.^[3] The onset of COVID-19 disease leads to death because of substantial damage to lung alveoli and failure of the respiratory system. COVID-19 patients are suffering from quickly developed pneumonia and require admission to the intensive care unit (ICU) for advanced medical care.^[1,2] Mechanical ventilation provides benefits in the improvement of oxygenation and survival rate for patients in the ICU. However, as patients recover from acute

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illness, more and more patients suffered from chronic critical illness, and become prolonged mechanical ventilation (PMV). It has been reported that patients with COVID-19 pneumonia have spent 38 days in the ICU, whereas 15 days in the ICU for non-COVID patients.^[4]

Patients who have been on mechanical ventilation for more than 21 days are defined as PMV.^[5] PMV could lead to cardiopulmonary and systemic complications that resulted to prolonged hospitalization and increased mortality rate. Both pulmonary complications and diaphragm weakness could have occurred under the assistance mode of mechanical ventilation.^[6-8] In addition, sepsis, prolong bedridden, and steroids contribute to critical illness-related neuropathy/myopathy, and lead to both extremity and respiratory muscle weakness.^[9]

There is compelling evidence showing that pulmonary rehabilitation can improve respiratory muscle strength and pulmonary function in patients with chronic pulmonary dysfunction.^[10,11] Respiratory muscle training exercise, a component of pulmonary rehabilitation programs, can help patients translate gains in muscle strength into pulmonary function.^[1] However, patients receiving PMV may be too fragile to undergo respiratory muscle training, given their severely impaired respiratory muscle function and consciousness status. Consequently, there is growing interest in the use of nonvolitional assistive technologies that facilitate muscle training, such as electrical muscle stimulation.

Electrical muscle stimulation induces muscle contraction by applying a series of electrical stimuli to the muscle.^[12] It has been used to increase peripheral muscle mass and muscle strength after prolonged immobilization.^[13] The application of electrical stimulation on the prevention of muscle weakness in ICU patients.^[14] However, the present study focused on the prevention of peripheral muscle dysfunction. Respiratory muscles play an important role during the weaning process in patients with MV. Transcutaneous electrical diaphragmatic stimulation (TEDS) has been used to improve respiratory muscle strength in patients with respiratory muscle weakness.^[15] A previous study reported that patients with chronic obstructive pulmonary disease (COPD) showed increased lung volume and oxygen saturation after a single session of TEDS.^[16] However, the effects of TEDS on the PMV population remain unclear. The purpose of this study was to examine the effects of TEDS on respiratory muscle function and weaning outcomes in patients with PMV.

Methods

This prospective study was performed in the Respiratory Care Center (RCC) of Chang Gung Memorial Hospital,

Keelung, Taiwan. The inclusion criteria for this study were as follows: (1) Age ≥ 20 years; (2) have been mechanical ventilated for >6 h/day and for >21 days; and (3) medical stability (PaO₂ ≥ 60 mmHg at 40% FiO₂, the absence of signs and symptoms of infection, and hemodynamic stability). The exclusion criteria included acute lung or systemic infection, hemodynamic instability, patients with pacemakers, abdominal distention, and pregnancy. The study was approved by the hospital's institutional review board (IRB No: 201700096A3) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants or their relatives before inclusion. The study has been registered in Clinical Trial Registry (NCT04741724).

Study procedure

This study followed a prospective and randomized design. Before participant recruitment, sequential sealed envelopes were prepared by an independent investigator, with one envelope chosen randomly by another investigator for each participant. Demographic data such as age, sex, body weight, height, and diagnosis at RCC admission were recorded for each participant. Participants were then assigned into a TEDS group or control group according to the label in the envelope. Participants assigned to the TEDS group received daily TEDS until the end of the weaning trial. Participants in the control group received similar medical treatment except for the TEDS program.

Transcutaneous electrical diaphragmatic stimulation intervention

The TEDS intervention involved a 30 min/day, 5 days/week routine. During each session, rectangular electrodes were placed on the parasternal region beside the xiphoid process; the sixth and seventh intercostal spaces in line with the mid-axillary line. TEDS was performed using a commercial stimulator (Omnistim 500, ZMI, Taiwan) applying biphasic waves at a stimulation frequency of 30 Hz, pulse width of 400 μ s, and rise time of 0.7s.^[15,16] TEDS intensity was gradually increased until visible muscle contraction was observed. Participants in the control group received similar electrode placement and intervention duration, except that the stimulator power was off. During the study, the vital signs of the patients were recorded from bedside monitors, and ventilatory parameters (lung compliance, airway resistance) were recorded from the ventilator.

Outcomes measures

The primary outcome was pulmonary function and respiratory muscle strength and was measured at baseline and at the end of the program. The secondary outcome was the hospitalization outcomes of the participants during their RCC stay.

Pulmonary function and respiratory muscle strength measurements

Participants were required to maintain the semi-Fowler's position during the measurement of weaning profiles. During the measurement, the participant's endotracheal or tracheostomy tubes were temporarily disconnected from the ventilator and connected to a spirometer (Respiradyne II, Sherwood, USA). Once the participants were stable, the investigator activated the spirometer and measured the minute volume and respiratory rate. To measure the maximum inspiratory mouth pressure (Pimax) and maximal expiratory pressure (Pemax), the investigator connected the endotracheal or tracheostomy tube to a T-tube and placed a manometer (Boehringer Laboratories, Norristown, PA, USA) at one end of the T-tube using a one-way valve. After the inspiratory/expiratory port was manually occluded, the investigator instructed the participant to inhale/exhale actively against the occluded airway during breathing cycles for 20–25 s; the most value was recorded as Pimax/Pemax.^[17]

Weaning outcomes

Weaning outcomes were monitored until the participants were discharged from the RCC. Survival status, mechanical ventilation weaning status, days of mechanical ventilation use in the RCC, and RCC length of stay were recorded from the participant's medical records. Weaning from the mechanical ventilator was considered successful if the participant was continuously free from MV for >5 consecutive days.^[18]

Statistical analysis

The main outcome was Pimax observed in participants after completion of the TEDS trial. The sample size was calculated according to data from a previous study that used Pimax.^[19] Based on the study's results, the mean difference between admission and discharge statuses was 8.3 cmH₂O, so that a sample size of >19 participants for each group would be needed for 80% power and an alpha level of .05. When allowing for 30%–50% dropouts, the sample size was increased to 30 participants.

Analysis was conducted using the SPSS v. 17 (IBM, Armonk, NY, USA). The normality of distribution was examined using the Shapiro-Wilk test. The results are expressed as the mean ± standard deviation for normal distributions, and as median (25th–75th percentiles) for nonnormal distributions. Baseline characteristics, pre- and post-intervention, and noncategorical hospitalization outcomes of the TEDS and control groups were compared using an unpaired Student's *t*-test or Mann-Whitney U test. A paired *t*-test (or Wilcoxon signed-rank test) was used to examine the intervention effects on the pulmonary function within groups. A Chi-square test was used to analyze differences in the

MV weaning rate between the groups. $P < 0.05$ indicated statistical significance.

Results

From August 2017 to July 2018, 105 patients were screened for eligibility for the study [Figure 1]. Forty-five patients in the RCC were excluded for not meeting the inclusion criteria ($n = 32$) or for declining to participate in the study ($n = 12$). Thus, 59 participants were randomized into the TEDS ($n = 29$) and control groups ($n = 30$), and all the participants completed the study.

Table 1 presents a summary of the demographic and clinical characteristics of the participants. Patients were admitted to the RCC due to difficult weaning. Reasons for admission to the hospital were mostly diseases involving the respiratory system. No significant differences existed between the TEDS and control groups in terms of age (73.3 ± 12.6 vs. 77.1 ± 8.2 years, $P = 0.171$), body mass index (22.1 ± 5.0 vs. 23.4 ± 4.2 kg/m², $P = 0.300$), or disease severity (APACHE II score 18.6 ± 3.9 vs. 18.2 ± 4.1 , $P = 0.713$). The mean number of TEDS sessions was

Table 1: Baseline characteristics of study participants

	TEDS (n=29)	Control (n=30)	P
Age (years)	73.3±12.3	77.1±8.2	0.171
Sex (male/female)	21/8	22/8	0.584
APACHE score	18.6±3.9	18.2±4.1	0.713
BMI	22.1±5.0	23.4±4.2	0.300
Body height (cm)	162.0±8.5	161.7±8.4	0.892
Body weight (kg)	57.7±11.3	61.1±10.9	0.242
Reasons for admitting to hospital (n)			
Respiratory system	11	9	
Cardiovascular system	2	7	
Gastrointestine system	2	2	
Neurological system	11	4	
Sepsis	1	4	
Cancer	2	2	
Others		2	

TEDS=Transcutaneous electrical diaphragmatic stimulation, APACHE=Acute physiologic assessment and chronic health evaluation, BMI=Body mass index

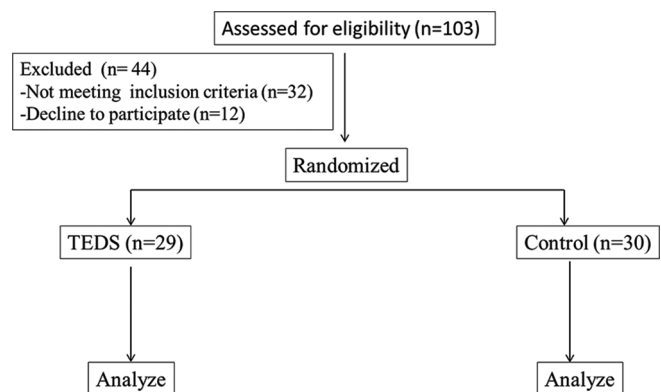


Figure 1: Flow chart of subject participation and analysis

9.9 ± 5.9 in the TEDS group. There were five participants in the TEDS group, and six patients in the control group that were tracheostomized.

Comparisons of pulmonary function within the TEDS and control groups are presented in Table 2. There was no difference between the TEDS and control group in the baseline measurement. After TEDS, participants in the TEDS group showed a tendency for reduced RSBI (pre vs. post: 115 [59–150] vs. 105 [67–100], compared to baseline measurements; however, this increase was not statistically significant ($P = 0.08$). Following TEDS, participants demonstrated a significantly higher Pemax (20.0 [10.0–22.0] cmH₂O) compared with their baseline (10 [8–20] cmH₂O; $P = 0.034$) [Table 2]. There was a tendency for the decrease of Pimax in the control group (from 29 [20–36.5] to 26.5 [19.5–30.5] cmH₂O), whereas no changes in the TEDS group (20 [15–30] to 20 [16–40] cmH₂O). However, the difference did not reach statistically significant. In the control group, there was no statistical difference in the pulmonary function between baseline and postmeasurements. The changes (Δ) after study in each group were defined as: the difference between baseline and the completion of the study. At the end of the study, the improvement of minute volume in the TEDS group (0.64 [-0.67–2.3] L) was significantly higher than the control group (-0.64 [-2.5–0.78] L ($P = 0.008$) [Table 3].

The physiologic responses during the first session of TEDS are presented in Table 4. After 30 min of TEDS, no significant difference was noted in heart rate, respiratory rate, blood pressure, and oxygen saturation. Similar tendency was also found in the second and the last session. The hospitalization outcomes of the participants are presented in Table 5. The rate of successful MV weaning in the TEDS group (90.0%) was higher than that in the control group (66.7%) ($P = 0.021$). The length of RCC stay was 20.8 ± 10.0 days in the TEDS group and 22.7 ± 8.6 days in the control group ($P = 0.761$). The weaning days was 8.3 ± 6.1 days in the TEDS group and

9.4 ± 5.3 days in the control group ($P = 0.495$)/There was no difference in the length of RCC stay and weaning days between the TEDS and control group.

Discussion

The aim of this study was to investigate the effectiveness of TEDS on respiratory muscles and hospitalization outcomes. We also evaluate the feasibilities of TEDS employing an TEDS program in patients with PMV. In the present study, patients with PMV showed an increase in expiratory muscle strength after TEDS.

In the present study, patients with PMV showed an increase in expiratory muscle strength after the intervention. In a study, examining the effects of TEDS on hospitalized patients with the chronic cardiorespiratory disease, Azambuja *et al.* reported that the intervention group had a significant increase in Pemax.^[20] It has been reported that the placement of electrodes in the parasternal region beside the xiphoid process releases electrical current to the phrenic nerve, which may penetrate the diaphragm and cause a contraction.^[21] In addition, the electrical current may also induce contraction of the abdominal muscles, which are the main components of the expiratory muscles. Pemax is an indicator of expiratory muscle strength. During TEDS, the abdominal muscle may be also involved, due to the overlap of the stimulation region, since the high density of the current may have generated a wide electric field to simulate both diaphragm and abdominal muscles.^[16] This may contribute to the significant improvement of Pemax in our study.

Expiratory muscles play an essential role in airway clearance, the prevention of atelectasis, and the improvement of minute ventilation in conditions of high workload of breathing and/or low respiratory capacity.^[16,22] For patients with mechanical ventilation, the presence of weak expiratory muscles is often associated with poor weaning outcomes due to

Table 2: Pulmonary function and respiratory muscle strength in pre- and post- measurements

	TEDS			Control		
	Pre	Post	P	Pre	Post	P
C _L (ml/cmH ₂ O)	43 (34-53)	36 (30-54)	0.427	45.5 (30.8-57)	44.9 (30-55.3)	0.380
Raw (cmH ₂ O/ml/s)	14 (11.6-16)	12 (11-15)	0.101	13 (12-15.3)	12.5 (10.4-14)	0.381
RR (bpm)	18 (15-20)	17 (13-24)	0.493	19 (15.8-24)	17.5 (15.8-22)	0.434
Vt (ml)	421 (343-485)	424 (358-487)	0.967	429 (336.5-479.5)	376 (333.5-445)	0.313
MV (L)	6.9 (5.9-8.3)	7.3 (6.3-9)	0.342	8.0 (6.5-9.3)	6.8 (5.8-8.3)	0.181
SpO ₂ (%)	98 (97-100)	98 (97-100)	0.384	98 (96-100)	99 (99-100)	0.213
RSBI	115 (59-150)	105 (67-100)	0.081	99.5 (60.8-123.8)	101.5 (69.3-137.8)	0.516
Pimax (cmH ₂ O)	20 (15-30)	20 (16-40)	0.148	29 (20-36.5)	26.5 (19.5-30.5)	0.307
Pemax (cmH ₂ O)	10 (8-20)	20 (10-22)	0.034	18 (10-40)	17 (20-25.5)	0.777

Data are expressed as median (25th–75th percentiles). Vt=Tidal volume, RR=Respiratory rate, MV=Minute volume, RSBI=Rapid shallow breathing index, C_L=Lung compliance, Raw=Airway resistance, Pemax=Maximal expiratory pressure, Pimax=Maximum inspiratory mouth pressure, TEDS=Transcutaneous electrical diaphragmatic stimulation

Table 3: Comparisons of changes between transcutaneous electrical diaphragmatic stimulation and control groups

	TEDS	Control	P
ΔC_L (ml/cmH ₂ O)	-0.2 (-6.6-6)	0.75 (-3-6)	0.540
ΔR_{aw} (cmH ₂ O/ml/s)	0 (-3-2)	-0.10 (-2-1.0)	0.937
ΔRR (bpm)	1 (-3-6)	0 (-6-3.3)	0.142
ΔV_t (ml)	5 (-31-88)	-10 (-104-49.8)	0.182
ΔMV (L)	0.64 (-0.67-2.3)	-0.64 (-2.5-0.78)	0.008
ΔSpO_2 (%)	0 (-1-2)	0 (-1-2.5)	0.780
$\Delta RSBI$	-14 (-33-13.3)	0 (-10-10)	0.554
ΔP_{imax} (cmH ₂ O)	1.0 (-2--6)	0 (-1--1)	0.233
ΔP_{emax} (cmH ₂ O)	2 (-2--10)	1 (-15--8)	0.224

Data are expressed as median (25th-75th percentiles). V_t=Tidal volume, RR=Respiratory rate, MV=Minute volume, RSBI=Rapid shallow breathing index, C_L=Lung compliance, R_{aw}=Airway resistance, P_{emax}=Maximal expiratory pressure, P_{imax}=Maximum inspiratory mouth pressure, TEDS=Transcutaneous electrical diaphragmatic stimulation

Table 4: Vital sign response during the 1st, 2nd and the last transcutaneous electrical diaphragmatic stimulation session

	Pre	Post	P
1 st TEDS session			
HR (bpm)	83.9±16.2	82.7±16.2	0.394
RR (bpm)	17.1±3.9	18.5±5.8	0.052
SBP (mmHg)	123.8±24.2	130.0±24.0	0.207
DBP (mmHg)	63.9±8.1	65.9±11.2	0.895
SpO ₂ (%)	97.7±1.9	97.7±1.7	0.209
2 nd TEDS session			
HR (bpm)	86.6±16.3	87.3±15.8	0.515
RR (bpm)	17.9±5.9	18.8±6.3	0.186
SBP (mmHg)	128.3±17.1	126.3±19.0	0.254
DBP (mmHg)	67.1±12.2	67.4±9.8	0.905
SpO ₂ (%)	98.1±1.9	98.3±1.9	0.325
Last session			
HR (bpm)	88.6±13.3	87.8±12.3	0.555
RR (bpm)	18.6±6.7	19.9±6.7	0.125
SBP (mmHg)	120.8±16.9	119.7±12.0	0.581
DBP (mmHg)	64.3±14.8	64.1±13.0	0.908
SpO ₂ (%)	98.4±1.5	98.6±1.6	0.485

RR=Respiratory rate, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate, TEDS=Transcutaneous electrical diaphragmatic stimulation

Table 5: Hospitalization outcomes in transcutaneous electrical diaphragmatic stimulation and control groups

	TEDS	Control	P
Weaning successful rate, n (%)	27 (90)	20 (66.7)	0.021
Mortality (n)	1	0	0.353
Length of stay in RCC (days)	20.8±10.0	22.7±8.6	0.761
Ventilator days in RCC (days)	14.5±10.9	19.5±14.2	0.239
Weaning days in RCC (days)	8.3±6.1	9.4±5.3	0.495

RCC=Respiratory care center, TEDS=Transcutaneous electrical diaphragmatic stimulation

respiratory complications.^[22] It has been suggested that some mechanical ventilation modes may (partly) silence respiratory centers in the brainstem, resulting in disuse

of both inspiratory and expiratory muscles.^[23] Vorona *et al.* reported that respiratory muscle training, even only inspiratory muscle training, was also associated with improvement in maximal expiratory strength. The abdominal muscles play an essential role in the cough reflex and in enhancing neuromuscular coupling of the diaphragm by optimizing the length-tension relationship of the diaphragm before inspiration, effectively improving the load-capacity balance of the muscle.^[24] In our study, we also found that the weaning rate TED group was higher than that in the control group. The enhancement of expiratory muscles may thus provide beneficial effects in the weaning outcomes for patients with PMV.

Studies have reported that the prolonged use of mechanical ventilation induces diaphragmatic dysfunction, reducing the patients' force generation capacity and lead patients to have difficulty in weaning from the mechanical ventilator.^[6-8] Inspiratory muscle training can produce an improvement in both inspiratory and expiratory muscle strength which may enhance the chances of successfully weaning from ventilation.^[24] In our study, we observed that there was a tendency for the decrease of P_{imax} in the control group (from 29 to 26.5 cm H₂O), whereas no changes in the TEDS group. However, the difference did not reach statistically significant.

To our knowledge, this may be the first study to discuss the effects of TEDS on patients with PMV. Martinelli *et al.* examined the effects of TEDS on COPD patients. They reported that COPD patients presented significant improvements in the minute volume and symptoms after the TEDS intervention.^[25] Recently, in a retrospective case series study with small sample size, Duarte *et al.* compared participants with cervical spinal cord injury submitted to the TEDS or control group. They reported that the TEDS group has a shorter mechanical ventilation duration and length of the ICU stay. However, no statistical significance was reported in their study.^[26] In our study, we also found that the improvement of minute volume in the TEDS group was significantly higher than in the control group. The TEDS group has shorter days of ventilator than the control group. However, the difference did not reach statistically significant, probably due to the small sample size. In addition, the process of weaning from mechanical ventilation could be affected by multiple factors such as cardiovascular integrity, respiratory function, neuromuscular competence, nutrition status, and patients' psychological condition.^[27] Further studies were required to clarify the possible effects of TEDS on the weaning outcome in patients with a similar diagnosis.

Electrical stimulation was well tolerated and presented no side effects during the sessions. The feasibility and

safety of electrical stimulation have been reported.^[28] Segers *et al.* examined the acute effects of peripheral muscle electrical stimulation on critically ill patients and reported no significant changes in vital signs after a 20-min electrical stimulation.^[28] In our study, the vital signs of the participants after 30 min of TEDS showed no difference compared to baseline measurements. None of the participants in the TEDS group complained or showed any side effects during the intervention. The TEDS can be performed in patients who are too fragile to exercise and easily applied after patients' admission to the RCC.

In addition to the issues considered above, this study has some limitations. The first limitation of this study is its small sample size, as the study was not powered to detect a difference in hospitalization outcomes between groups. However, the trends in both pulmonary function and weaning rates were all positive and thus promising. Second, in this study, the effect of TEDS on the diaphragm was indicated by Pimax. However, other methods might evaluate diaphragm function better. Gruther *et al.* used ultrasound to examine the effects of muscle electrical stimulation in critically ill patients and found increased muscle thickness after intervention.^[29] Both critical illness and PMV increase the risks of diaphragm dysfunction such as diaphragm atrophy. Ultrasound can be used to assess the structures of muscles and may be more sensitive in detecting changes in diaphragm function. Third, it is recommended that the occlusion duration should be 30s to detect a full contraction of the respiratory muscle.^[30] The occlusion duration during respiratory muscle strength measurement was about 20–25 s in our study which may be underestimated the respiratory muscle strength and may not be able to predict weaning outcomes correctly. However, both pre- and post-measurements of Pimax/Pemax were performed according to the same protocol. The comparisons between pre- and post-measurements provide information about the changes in respiratory muscle strength.

Conclusion

This study is the first to demonstrate the value of TEDS for patients with PMV. Respiratory muscle weakness is common following PMV. In our study, participants showed increased expiratory muscle strength after the intervention of TEDS, while having no significant changes in the inspiratory muscle strength. The TEDS group also has a higher weaning rate than that in the control group. Future powered study into this effect may be required, with a positive outcome likely to lead to the clinical translation of this technique.

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Conflicts of interest

There are no conflicts of interest.

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