Estimation of minimal clinically important difference for quadriceps and inspiratory muscle strength in older outpatients with chronic obstructive pulmonary disease: a prospective cohort study

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ABSTRACT. Objective: To estimate the minimal clinically important difference (MCID) of quadriceps and inspiratory muscle strength after a home-based pulmonary rehabilitation program (PRP) in chronic obstructive pulmonary disease (COPD). **Method:** Eighty-five COPD patients were included. Quadriceps maximal voluntary contraction (QMVC) was measured. We measured maximal inspiratory mouth pressure (PImax), the 6-minute walk distance (6MWD), the chronic respiratory questionnaire (CRQ) and the modified Medical Research Council dyspnoea score (mMRC). All measurements were conducted at baseline and at the end of the PRP. The MCID was calculated using anchor-based (using 6MWD, CRQ, and mMRC as possible anchor variables) and distribution-based (half standard deviation and 1.96 standard error of measurement) approaches. Changes in the five variables were compared in patients with and without changes in QMVC or PImax >MCID for each variable. **Results:** Sixty-nine COPD patients (age 75±6 years) were analysed. QMVC improved by 2.4 (95% CI 1.1-3.7) kgf, PImax by 5.8 (2.7-8.8) cmH₂O, 6MWD by 21 (11-32) meters and CRQ by 3.9 (1.6-6.3) points. The MCID of QMVC and PImax was 3.3-7.5 kgf and 17.2-17.6 cmH₂O, respectively. The MCID of QMVC (3.3 kgf) could differentiate individuals with significant improvement in 6MWD and PImax from those without. **Conclusion:** The MCID of QMVC (3.3 kgf) can identify a meaningful change in quadriceps muscle strength after a PRP. The MCID of PImax (17.2 cmH₂O) should be used with careful consideration, because the value is estimated using distributionbased method.

Key words: minimal clinically important difference, muscle strength, chronic obstructive, quadriceps muscle, respiratory muscles

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Weakness of the quadriceps¹⁾ and respiratory muscle²⁾ is an important extrapulmonary manifestation of chronic ob-

structive pulmonary disease (COPD). Quadriceps muscle weakness contributes to exercise intolerance³⁾ and influences survival¹⁾ in COPD, and respiratory muscle weakness leads to dyspnoea and reduced exercise tolerance in COPD⁴⁾. Lower limb muscle strength training alone or in combination with endurance training improves quadriceps muscle strength^{5,6)}, and has inconsistent effects on dyspnoea, exercise capacity and health-related Quality of Life (hQOL) in patients with COPD⁵⁾. Inspiratory muscle training (IMT) alone or combined with a pulmonary rehabilita-

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tion program (PRP) improves inspiratory muscle strength and endurance, dyspnoea and walking distance in patients with COPD^{7,8)}. Therefore, lower limb muscle strength training and IMT are the important parts of PRP in individuals with COPD⁹⁾. In consequences of it, a position statement on pulmonary rehabilitation has stated that quadriceps muscle strength should be measured and, if possible, inspiratory muscle strength also should be measured¹⁰⁾.

When interpreting the effects of PRP, the minimal clinically important difference (MCID) is usually used. The MCID of relevant outcomes of PRP have been established, including dyspnoea¹¹⁾, exercise tolerance¹²⁾ and hQOL¹³⁾ in stable patients with COPD. There is, however, only one report on the MCID of quadriceps muscle strength after PRP in COPD¹⁴⁾, and the MCID of inspiratory muscle strength remains unestablished. Moreover, the MCID of quadriceps muscle strength has been determined using a distribution-based approach¹⁴⁾. Although the MCID can be used to evaluate the effect of PRP, it is desirable to determine MCID using an anchor-based approach¹⁵⁾.

If the MCID of quadriceps and inspiratory muscle strength is established, the MCID could help clinicians not only assess whether improvement in muscle strength is clinically meaningful but also interpret how changes in muscle strength contribute to improvement in relevant outcomes (e.g. dyspnoea, exercise capacity, and hQOL) after PRP in COPD. We aimed to estimate the MCID of quadriceps and inspiratory muscle strength after a 3-month PRP in individuals with COPD using anchor-based and distribution-based approaches.

Method

Study design and patients

This study was a prospective cohort study conducted in an acute care hospital. Eighty-five participants of the current study were outpatients with COPD who were referred for a PRP and enrolled in a 3-month PRP from March to September in 2015 to 2017 in our hospital. The inclusion criteria were as follows: age ≥ 65 years, diagnosis of COPD according to international guidelines¹⁶⁾, no exacerbations of COPD in the previous 3 months and the ability to provide written informed consent. The exclusion criteria were as follows: diagnosis of dementia or other mental disorders, inability to communicate and neurological or musculoskeletal conditions that limit mobility. All measurements were performed at initiation and the end of PRP. This study was performed in conformity with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of Akita City Hospital, 2015 (accepted No.14).

Quadriceps muscle strength

Quadriceps maximal voluntary contraction (QMVC) was measured using the Hydromusculator GT-160 (OG

Giken Co., Okayama, Tokyo, Japan) in accordance with the technique described by Seymour *et al.*¹⁷⁾. Outpatients were positioned in a standard fashion (seated with knees and hips flexed at 90 degrees) and their hip joints and thighs were fixed with belts to ensure that they remained seated. QMVC was defined as the highest mean force that could be sustained for longer than 1 s. Measurements were repeated at least thrice. A rest period of 30 to 60 s was provided between each contraction to allow outpatients to recover from each effort. The highest force was recorded as the patient's QMVC.

Inspiratory muscle strength

Maximal inspiratory mouth pressure (P_Imax) was measured as respiratory muscle strength using a respiratory dynamometer (VITALOPOWER KH-101, Chest MI, Inc., Tokyo, Japan) following the method recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS)¹⁸⁾. The inspiratory pressure was maintained for at least 1.5 s, and the maximum pressure sustained for 1 s was recorded as P_Imax. After careful instructions and practice, measurements were repeated at least thrice, and the highest measurement was used for analysis.

Anchor variables

The modified Medical Research Council dyspnoea score (mMRC)¹⁹⁾, 6-minute walk distance (6MWD) and chronic respiratory questionnaire total score (CRQ)^{20,21)} were selected as anchor variables for determining MCID for quadriceps and inspiratory muscle strength, because these outcomes are relevant to individuals with COPD and MCID of the three outcomes is established.

The 6MWD test was performed in accordance with the European Respiratory Society (ERS)/American Thoracic Society (ATS) technical standards²²⁾. The examiners encouraged outpatients every minute of the test using two phrases: "You are doing well" or "Keep up the good work". Outpatients were allowed to stop and rest during the test, but were instructed to resume walking as soon as they could. Outpatients did not practice the 6MWT and underwent a single test.

Pulmonary rehabilitation program

The 3-month PRP was a multidisciplinary home-based program including supervised breathing and exercise training ones every two weeks, education ones a month at our hospital, and unsupervised home-based training every day except days with supervised sessions at their home²³⁾. Exercise training included upper and lower limb exercises including COPD sitting exercise²⁴⁾, respiratory muscle stretching, level walking, and inspiratory muscle training (IMT). COPD sitting exercise was performed 1 to 2 sets according to their tolerance. Intensity of level walking was set at 3 to 4 on modified Borg dyspnoea scale. Outpatients were in-

structed to walk at least 15 min and increase the duration of walking up to 60 min. IMT was performed using an inspiratory muscle trainer set at a training intensity of 30%-40% of the PImax. Outpatients were instructed to perform 30-breath twice. The intensity of exercise was reset based on the patient's condition at supervised sessions. The outpatients also underwent a monthly 45-min education program including lectures about equipment use, nutrition, stress management, relaxation techniques, home exercises and the benefits of PRP. Outpatients were asked to practice the same program at their home. Outpatients were instructed to record in an exercise diary each time they completed home-based training. The diary included a checkbox to indicate which of the 4 prescribed exercises were completed. We checked their records at supervised session. Completion of PRP was defined when the completion rate of PRP was more than 60%.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, NY, USA). The assumption of normality was assessed graphically and using the Shapiro-Wilk test. P-values <0.05 were considered statistically significant. To check attrition bias, we compared baseline characteristics of outpatients with COPD who completed RPR (completer) to those not (non-completer).

Paired t-tests were used to determine changes in QMVC, PImax, 6MWD and CRQ before and after PRP. Wilcoxon's signed rank test was used for mMRC. Pearson's or Spearman's rank correlations were performed to assess correlations between changes in anchors and muscle strength.

For estimating MCID of muscle strength, we used anchor-based⁽¹⁴⁾ and distribution-based^(25,26) methods in accordance with previous studies. In the current study, a change of 1 point in mMRC⁽¹¹⁾, 30 metres on the 6MWD test⁽¹²⁾ and 10 points on the CRQ⁽¹³⁾ were considered as clinically significant changes. The anchor was used to calculate MCID for QMVC and PImax if the anchors fulfilled the following criteria: anchors changed significantly after PRP, and the correlation between changes in QMVC and PImax and changes in anchors was more than 0.3. The MCID of the QMVC and PImax was estimated by calculating the mean change in QMVC and PImax in those achieving the MCID for the mMRC (> 1 point improvement), 6MWD (> 30 meters improvement), or CRQ (> 10 points improvement). For distribution-based methods, we calculated half the standard deviation (SD) (0.5 SD)⁽¹⁴⁾ and 1.96 standard error of measurement (SEM)^(25,26).

After estimating MCID, we divided the outpatients into two groups according to whether their QMVC or PImax had improved more than the lower limit of MCID of QMVC or PImax. We then compared changes in mMRC, 6

Figure 1. Study flow chart

COPD, chronic obstructive pulmonary disease; PRP, pulmonary rehabilitation program; mMRC, modified Medical Research Council dyspnoea score; CRQ, chronic respiratory questionnaire.

MWD, CRQ, QMVC and PImax. An independent samples t-test was used for continuous variables and the Mann-Whitney U-test for nonparametric.

Sample size was estimated with the program G*Power 3.1 for paired t-test with an α of 0.05, power of 0.80, two tails and expected effect size of 0.34 which was derived from the lower limit of effect size of PRP on QOL and exercise capacity in patients with COPD⁽²⁷⁾. The calculated sample size was 70, and considering a possible 15% drop-out and missing data rate, the final sample size was determined to be 81.

Results

The study flow chart is shown in Figure 1. Eighty-three out of 85 outpatients with COPD underwent baseline assessment and enrolled in the PRP. Finally, 69 outpatients were included in analysis. There were 18 missing data for mMRC and 13 for CRQ, respectively. Baseline characteristics of the completer and non-completer are displayed in Table 1.

Changes in anchors and muscle strength after PRP are shown in Table 2. The 6MWD improved more than 30 metres in 26 out of 69 outpatients, and the CRQ total increased by more than 10 points in ten out of 56 outpatients.

Figure 2 shows the results of the correlation analyses. There was a correlation ($r, >0.3$) between changes in quadriceps muscle strength and 6MWD. Therefore, 6MWD was used as an anchor to calculate the MCID of QMVC. Table 3 shows the MCID of QMVC and PImax.

Table 4, 5 show the differences in changes in mMRC, 6MWD, CRQ, QMVC and PImax between the outpatients with minimal clinically important changes in QMVC (>3.3

Table 1. Baseline characteristics of the completer and non-completer

Variables	Completer	Non-completer	P value	95%CI (lower~upper)
n	69	14	N.A.	N.A.
Age, years	75 (6)	73 (6)	0.200	-1~6
Sex(m:f), n	65:4	14:0	N.A.	N.A.
Height, cm	162.2 (6.7)	167.6 (4.5)	0.006	-9.1~-1.6
Weight, kg	54.6 (10.3)	59.6 (7.6)	0.094	-10.7~0.9
BMI, kg/m ²	20.7 (3.4)	21.2 (2.4)	0.620	-2.4~1.4
FFM, kg	42.1 (7.7)	49.9 (5.6)	0.001	-12.1~-3.5
FFMI, kg/m ²	15.9 (2.3)	17.8 (1.6)	0.005	-3.1~-0.6
FEV ₁ , L	1.34 (0.63)	1.35 (0.67)	0.992	-0.37~0.37
FEV ₁ , %pred	57 (26)	56 (27)	0.432	-17~7
GOLD stage, I/II/III/IV	12/27/21/9	1/7/4/2	0.684	N.A.
mMRC	2 (1, 3)	2 (1, 3)	0.025	0~1
6MWD, m	401 (156)	443 (198)	0.378	-138~53
CRQ, point	104.8 (22.7)	104.1 (17.7)	0.918	-12.3~13.7
QMVC, kg	31.5 (10.6)	42.8 (11.5)	0.001	-17.5~-5.0
QMVC-BW	0.58 (0.17)	0.70 (0.17)	0.011	-0.23~-0.03
PImax, cmH ₂ O	69.0 (34.4)	112.5 (35.7)	< 0.001	-63.6~-23.3

SD, standard deviation; N.A., not applicable; m, male; f, female; BMI, body mass index; FFM, fat free mass; FFMI, fat free mass index; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease classification of severity of airflow obstruction; mMRC, modified medical research council dyspnea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; QMVC, quadriceps isometric maximum voluntary contraction. Data are presented as mean (SD) or median (25th, 75th percentile).

Table 2. Changes in outcome measures before and after 3 months pulmonary rehabilitation program

Variables	Baseline	at 3 months	Mean difference	P value	95%CI (lower~upper)
mMRC (n = 51)	2 (1, 3)	2 (1.5, 3)	N.A.	0.881	N.A.
6MWD, m (n = 69)	401 (156)	422 (156)	21 (43)	< 0.001	11~32
CRQ, point (n = 56)	104.8 (22.7)	108.7 (22.2)	4.0 (8.7)	< 0.001	1.6~6.3
QMVC, kg (n = 69)	31.5 (10.6)	33.9 (11.2)	2.4 (5.4)	< 0.001	1.1~3.7
QMVC-BW (n = 69)	0.58 (0.17)	0.61 (0.16)	0.04 (0.10)	0.008	0.01~0.06
PImax, cmH ₂ O (n = 69)	69.0 (34.4)	74.8 (33.2)	5.8 (12.7)	< 0.001	2.7~8.8

N.A., not applicable; mMRC, modified medical research council dyspnea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; QMVC, quadriceps isometric maximum voluntary contraction. Data are presented as mean (SD) or median (25th, 75th percentile).

kgf) or PImax (>17.2 cmH₂O) (responder-QMVC and responder-PImax, respectively) and those without (non-responder-QMVC and non-responder-PImax, respectively). Changes in 6MWD and PImax were significantly greater in responder-QMVC outpatients compared to non-responder-QMVC outpatients. In contrast, only changes in PImax were significantly different between responder-PImax and non-responder-PImax outpatients.

Discussion

To the best of our knowledge, this is the first study to report the MCIDs of QMVC and PImax using anchor-based and distribution-based methods in outpatients with COPD

who underwent a PRP. These MCID values can be used to evaluate whether the changes in quadriceps and inspiratory muscle strength are clinically important after PRP in outpatients with COPD.

MCID of quadriceps muscle strength

To date, there have been no reports on the MCID of QMVC calculated using the anchor-based method, so the values may enable clinicians to evaluate whether the changes in quadriceps muscle strength is clinically meaningful. MCID of 3.3 kgf is 10.5% of the mean of baseline QMVC (3.3 to 31.5 kgf). The value is reported to be within and near the lower limit of the mean changes in isometric quadriceps muscle strength (10 - 21%) in patients with

Figure 2. Correlation between changes in QMVC and PImax and changes in 6MWD and CRQ

Δ, changes in each outcome; QMVC, quadriceps isometric maximum voluntary contraction; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; r_s , Spearman's rank correlation coefficients; r , Pearson's correlation coefficients.

Table 3. Minimal clinically important differences of muscle strength

	Anchor-based	Distribution-based	
	Anchor: 6MWD	0.5 SD	1.96 SEM
QMVC, kg	3.3	5.3	7.5
PImax, cmH ₂ O	N.A.	17.2	17.6

6MWD, six-minute walk distance; SD, standard deviation; SEM, standard error of measurement; QMVC, quadriceps isometric maximum voluntary contraction; PImax, maximum inspiratory pressure; N.A., not applicable.

The SEM of QMVC and PImax is 3.8 kgf and 9.0 cmH₂O, respectively.

COPD who completed a muscle strength training program⁶). Therefore, the MCID value of 3.3 kgf is acceptable. Although the MCID of QMVC estimated using a distribution-based approach was higher than the MCID estimated using an anchor-based approach, we recommend using 3.3 kgf as the MCID of QMVC. The first reason for this is that the MCID derived from a distribution-based approach may be clinically significant, but not minimal¹⁵). Another reason is because a distribution-based approach is anchor-free, and

an MCID estimated using a distribution-based approach could be meaning-free¹⁵). Moreover, changes in 6MWD and PImax were significantly higher in responder-QMVC outpatients compared to non-responder-QMVC outpatients. Therefore, the MCID of QMVC (3.3 kgf) derived from the anchor-based approach should be used. When using this value, measurement error of QMVC should be considered, because the SEM²⁵) of QMVC (3.8 kgf) was slightly higher than 3.3 kgf. For example, if the change in QMVC falls within 3.3 to 3.8 kgf, it is unclear whether the change is training-related or due to a measurement error. In contrast, if the change in QMVC exceeds 3.8 kgf, clinicians could be confident that the improvement in QMVC is not due to measurement error and may contribute to at least improvement in exercise capacity and respiratory muscle strength.

MCID of inspiratory muscle strength

This is the first study to investigate the MCID of PImax (17.2 - 17.6 cmH₂O) in outpatients with COPD using a distribution-based approach. The value was similar to overall changes in PImax (13.0 cmH₂O) that was calculated by meta-analysis after IMT in patients with COPD⁷). Previous clinical trial experience, including a systematic review and meta-analysis of clinical trial literature, could be used to de-

Table 4. Changes in outcomes in patients with clinically minimal changes in QMVC

Variables	Δ QMVC, kgf		P value	95%CI
	>3.3 (n=27)	$3.3 \leq$ (n=42)		
Δ MRC	0 (0, 0)	0 (0, 0)	0.980	0 ~ 0
Δ 6MWD, m	31.0 (16.0, 60.0)*	6.5 (-9.0, 40.0)	0.002	10.0 ~ 48.0
Δ CRQ, point	2.0 (0, 7.5)	2.0 (-2.0, 7.0)	0.703	-3.0 ~ 4.0
Δ QMVC, kg	5.1 (3.9, 11.2)*	0.35 (-2.50, 1.90)	< 0.001	4.9 ~ 10.2
Δ PImax, cmH ₂ O	9.6 (13.8)*	3.3 (11.5)	0.044	0.2 ~ 12.4

Δ , changes in each outcome; QMVC, quadriceps isometric maximum voluntary contraction; mMRC, modified Medical Research Council dyspnoea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; PImax, maximum inspiratory pressure.

* $p < 0.05$.

Data are presented as mean (SD) or median (25th, 75th percentile).

Table 5. Changes in outcomes in patients with clinically minimal changes in PImax

Variables	Δ PImax, cmH ₂ O		P value	95%CI
	>17.2 (n=16)	$17.2 \leq$ (n=53)		
Δ MRC	0 (0, 0)	0 (0, 0)	0.788	0 ~ 0
Δ 6MWD, m	20.6 (53.7)	21.3 (40.4)	0.956	-25.6 ~ 24.2
Δ CRQ, point	2.0 (0, 8)	2.0 (-1.0, 7.0)	0.640	-4.0 ~ 6.0
Δ QMVC, kg	3.6 (-2.4, 5.3)	2.0 (-0.3, 3.9)	0.486	-2.9 ~ 3.6
Δ QMVC-BW	0.05 (-0.06, 0.10)	0.03 (0.00, 0.06)	0.594	-0.05 ~ 0.06
Δ PImax, cmH ₂ O	21.4 (19.1, 24.7)*	1.3 (-4.0, 5.8)	< 0.001	17.5 ~ 24.8

Δ , changes in each outcome; PImax, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnoea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; QMVC, quadriceps isometric maximum voluntary contraction.

* $p < 0.05$.

Data are presented as mean (SD) or median (25th, 75th percentile).

termine clinically significant changes in an outcome¹⁵⁾. Therefore, the MCID of PImax in the current study was acceptable. The value enables clinicians to evaluate the changes in PImax is clinically significant in terms of inspiratory muscle strength. We note that the MCID of PImax is anchor-free, so it is unclear whether improvement in PImax by more than MCID contributes to improvement in other relevant outcomes. Indeed, no significant difference in changes in the anchors was found in responder-PImax compared to non-responder-PImax outpatients in the current study. These results suggest that PImax may not always be a relevant outcome in stable outpatients with COPD undergoing PRP. In other words, PImax should be chosen as an outcome in stable COPD outpatients with reduced inspiratory muscle strength and persistent activity-related dyspnoea²⁸⁾.

Relationships between muscle strength and anchor variables

In the current study, we chose the mMRC, 6MWD and

CRQ as possible anchors due to their known MCID and relevance in individuals with COPD undergoing PRP. mMRC failed to improve after PRP and could not be used as an anchor. A possible explanation of it is that mMRC is a 5 grades scale and was not responsive to assess the effect of PRP. This is in line with previous study²⁹⁾. Correlations between changes in PImax and 6MWD were very weak, so 6MWD could not be used as an anchor for PImax. A possible explanation for the weak relationships is that many other variables, including pulmonary function, body composition and psychological factors, contribute to 6MWD in patients with COPD^{30,31)}. Therefore, correlations between changes in PImax and 6MWD were very weak. Correlations between changes in muscle strength and hQOL were very weak, so CRQ could not be used as an anchor for QMVC and PImax. A possible explanation for the weak relationships is that variability in the correlation between physical performance and hQOL has previously been shown³²⁾, which is consistent with our nonsignificant and very weak correlations between changes in muscle strength

and CRQ. Therefore, correlations between changes in QMVC and PImax and changes in CRQ were very weak in this study.

Limitations

There were several limitations to this study. First, this study was a single-centre study, so the possibility of selection bias cannot be ignored. Second, attrition bias should be carefully considered, because quadriceps muscle strength at baseline was significantly lower in completer than non-completer. Copay et al. reported that the change in patient-reported outcomes depends on the baseline status of the patient³³. Therefore, patient characteristics should be carefully considered when using the MCID values estimated in the current study. Third, our PRP was a multidisciplinary home-based program. Thus, it was unclear whether the MCID of QMVC and PImax in this study could be used in individuals with COPD undergoing supervised PRP. Fourth, effects of PRP were relatively smaller in our study comparing with a previous systematic review²⁷. This could affect the MCID of QMVC estimated by anchor-based method in the current study, as the number of outpatients used to calculate MCID is relatively small ($n = 26$). Fifth, only 6 MWD was used as an anchor to calculate MCID of QMVC due to the weak correlations of changes in QMVC and PImax to changes in anchor variables. It is recommended that multiple anchors be used to estimate MCID of an outcome when using anchor-based method¹⁵. Finally, the MCID of the QMVC was estimated only by calculating the mean change in QMVC in those achieving the MCID for the 6 MWD (> 30 meters improvement). This method had potential risk for overestimation of MCID of QMVC, because outpatients with large improvement in 6MWD were included to calculate MCID of QMVC. These two limitations could also affect the value of MCID of QMVC.

Conclusions

The MCID of QMVC and PImax was estimated in outpatients with COPD who underwent a PRP. A gain of at least 3.3 kgf and 17.2 cmH₂O represented a clinically meaningful improvement in quadriceps and inspiratory muscle strength after the PRP, and these values can be used to evaluate the outcomes of PRP.

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Conflict of Interest: The authors have no competing interests to declare.

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