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Distance Between Endotracheal Tube Cuff and Vocal Cords Measured by Ultrasound in Chinese Adults: A prospective case control study

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4 **Distance Between Endotracheal Tube Cuff and Vocal Cords Measured by**
5 **Ultrasound in Chinese Adults: A prospective case control study**
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Distance Between Endotracheal Tube Cuff and Vocal Cords Measured by Ultrasound in Chinese Adults: A prospective case control study

Abstract

Background and objective Unrecognized malposition of the endotracheal tube can lead to severe complications in patients under general anesthesia. The purpose of this study was to estimate the occurrence of too shallow or too deep intubation using the traditional 23/21 rule and to verify the feasibility of using ultrasound to measure the distance between the upper edge of saline-inflated cuff and the vocal cords.

Design Prospective case control study.

Setting A tertiary hospital in Beijing, China.

Methods In this prospective study, 105 adult patients who required general anesthesia with an endotracheal tube (ETT) were enrolled. Prior to induction, ultrasound was used to identify the position of the vocal cords. After intubation, the ETT was fixed at a depth of 23 cm at the upper incisors in men and 21 cm in women. The depth of intubation was verified by video-assisted laryngoscopy, and the correct ETT position was defined as vocal cords lying between the two insertion depth marks. The distance between the upper edge of the saline-inflated cuff and the vocal cords was measured by ultrasound; the ideal distance was considered to be 1.9 cm to 4.1 cm. The tip-to-carina distance was measured using a fiberoptic bronchoscope. The primary outcome was determination of the sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography in determining correct ETT insertion depth.

Results Among the 105 cases, two cuffs were too close to the vocal cords and one too far away from the vocal cords. These diagnoses were made by ultrasound and were in agreement with results from direct laryngoscopy. There was no endobronchial intubation, but in 8.6% of the patients the distance between the tip of the ETT and the

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4 carina was less than 2 cm. The overall accuracy of ultrasound in identifying malposition
5 of the cuff was 100.0% (95% CI: 96.6%–100%). The sensitivity, specificity, positive
6 predictive value, and negative predictive value of ultrasound were, respectively, 100%
7 (95% CI: 96.5%–100%), 100% (95% CI: 29.2%–100%), 100% (95% CI: 96.5%–100%)
8 and 100% (95% CI: 29.2%–100%).
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15 **Conclusion** The distance from the cuff to the vocal cords may be too short or too long
16 for some patients when the traditional 23/21 rule is used. Identification of the upper
17 edge of the saline-inflated cuff and the vocal cords by ultrasound to assess the location
18 of the ETT is a reliable method. It can be used to avoid malposition of the ETT cuff and
19 reduce the incidence of vocal cords injury after intubation.
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26 **Article summary**

27 **Strengths and limitations of this study**

- 28 ● Unrecognized malposition of the endotracheal tube can lead to severe
29 complications in patients under general anesthesia.
- 30 ● The distance from the cuff to the vocal cords may be too short or too long for some
31 patients when the traditional 23/21 intubation rule is used.
- 32 ● Identification of the upper edge of the saline-inflated cuff and the vocal cords by
33 ultrasound to assess the location of the ETT is a reliable method.
- 34 ● It can be used to avoid malposition of the ETT cuff and reduce the incidence of
35 vocal cords injury after intubation.
- 36 ● Since the number of incorrect tube positions in our study was small, a larger
37 sample size study may be needed to verify our results.
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49 **Introduction**

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52 Tracheal intubation is a routine procedure of resuscitation and general anesthesia. The
53 appropriate depth of endotracheal intubation should be confirmed after intubation and
54 during surgery because a malposition of endotracheal tube (ETT) can lead to serious
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4 complications. Placing the tube too deeply may stimulate the carina, and unrecognized
5 endobronchial intubation may result in single-lung ventilation, hypoxemia, and
6 atelectasis of the nonventilated lung.¹ On the other hand, if the ETT is placed too
7 shallowly, the tube cuff's impingement on the vocal cords may lead to vocal cords injury,
8 compression of the recurrent laryngeal nerve, and even accidental extubation.²
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15 An optimal ETT placement should ensure sufficient distance (2–5 cm) between the tip
16 of the ETT and the carina³ and sufficient distance (1.5–2.5 cm) between the proximal
17 margin of the cuff to the vocal cords.^{2 4} Most ETTs for the adults have two black
18 insertion guide marks at 2 and 4 cm above the cuff or one mark at 2 to 3 cm above the
19 cuff. ⁵ Alignment of the marks with the vocal cords helps to place the ETT at the correct
20 depth. ⁶ However, this technique relies on visualization of the vocal cords with a
21 laryngoscope (i.e., grade I or II view). A large tongue, prominent teeth, a short neck, or
22 blood and secretions may make visualization of the ETT's position within the glottis
23 difficult. Besides, under some circumstances, such as using blind intubation or a Shikani
24 or Bonfil optical stylet to guide intubation, the depth markers cannot be observed.
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35 Under such circumstances, intubation depth is commonly determined according to
36 experience, usually 23 cm for male and 21 cm for female patients.⁷⁻⁹ After intubation,
37 auscultation of breath sounds is routinely performed to confirm the location of the tube.
38 If endobronchial intubation is suspected, the tube must be withdrawn until bilateral
39 breath sound can be heard. However, auscultation of breath sounds can be unreliable,¹⁰
40 and blind withdrawal of the tube can be hazardous for patients with short tracheas. In
41 some patients the distance from the vocal cords to the carina is identical to or even
42 shorter than the distance from the ETT tip to the insertion guide mark. ⁶ This means
43 that there would not be enough cuff free zone above the vocal cords when breath
44 sounds can be heard from both sides in patients with short tracheas.
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4 Cuff palpation has been suggested as a tactile method to estimate the position of the
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6 EET,^{11 12} but its accuracy is influenced by the thickness of the soft tissue of the anterior
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8 neck and the experience of the operator.¹³ Furthermore, a high-volume low-pressure
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10 cuff may not be palpable despite correct placement. One study has shown that cuff
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12 palpation has only a 26% specificity for indicating incorrect ETT placement.¹⁴ The
13
14 development of ultrasonography has made it possible to identify the ETT cuff more
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16 accurately. In 1987, Raphael et al., for the first time, obtained a clear image of a
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18 saline-inflated cuff by ultrasound.¹⁵ Previous studies used ultrasonic images of
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20 saline-inflated cuffs at or above the suprasternal notch as indicators of appropriate ETT
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22 insertion depth.¹⁶ However, as in the case of auscultation, observing the cuff at or above
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24 the suprasternal notch can rule out too deep intubation but not too shallow intubation.
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27 Since both the vocal cords and the ETT cuff can be visualized using ultrasound, a safe
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29 distance between the vocal cords and the ETT cuff can potentially be guaranteed by
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31 ultrasonography. We hypothesized that ultrasound can be used to estimate the distance
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33 between the upper edge of the ETT cuff and the vocal cords in adults so that the depth
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35 of the ETT can be adjusted accordingly. The purpose of this study was to review
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37 instances of endobronchial intubation and estimate the occurrence of too short a
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39 distance between the cuff and vocal cords in adult Chinese using the 23/21 rule and
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41 also to determine the feasibility of using ultrasound to measure the distance between
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43 the upper edge of saline-inflated cuff and the vocal cords.
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48 **Materials and methods**

49 Patient and public involvement

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51 Patients were not involved in the development of the design, recruitment or conduct of
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53 the study. The results will not be disseminated to study participants.
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56 Following approval from the institutional review board (Peking University Third
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4 Hospital Ethics Committee, IRB00006761-2016163), patients aged 18 to 70 who were
5 scheduled for elective cervical surgery under general anesthesia were recruited in this
6 prospective case control study. Written informed consent was obtained from all
7 patients. The exclusion criteria included difficult airway (Mallampati classification 3
8 and 4, mouth opening <3 cm), abnormal airway or chest anatomy, and a history of
9 cervical trauma or cervical surgery.
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16 17 Equipment and researchers

18 A reinforced ETT with a 7.0- or 8.0-mm inner diameter (ID) (Covidien Mallinckrodt,
19 USA), with two insertion guide marks was used in the present study, which involved
20 four investigators: an anesthesiologist experienced in airway ultrasonography using a
21 38-mm 6-13 MHz linear ultrasound probe (Turbo SonoSite HFL, Bothell, WA), an
22 anesthesiologist experienced in fiberoptic bronchoscopy (FOB), a senior resident, and
23 an anesthetic assistant. The two anesthesiologists who performed the ultrasound and
24 FOB examinations were blind to the results of laryngoscopy.
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33 34 Ultrasound assessment of vocal cords

35 When the patient reached the operation room, routine monitors (pulse oximeter,
36 noninvasive blood pressure cuff, and electrocardiogram) were placed. The patient was
37 in a neutral position. The ultrasound probe was placed transversely on the neck
38 perpendicular to the skin. The probe was moved cranially or caudally until the true
39 vocal cords could be identified (Figure 1). Along the midpoints of the short axis of the
40 probe, line A was drawn on the patient's skin (Figure 2) to mark the position of true
41 vocal cords. If the vocal cords could not be clearly identified, the patient was excluded.
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50 51 Intubation

52 Following the induction of anesthesia, an ETT (7.0-mm ID for females, 8.0-mm ID for
53 males) was inserted by the resident and the insertion depth was determined using the
54 23/21 cm rule (23 cm at the upper incisor teeth in men and 21 cm in women) using a
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4 video-assisted laryngoscope (Zhejiang UE Medical Corporation, Tai Zhou, China). The
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6 ETT was held in place by the assistant, then the position of the vocal cords relative to
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8 the depth markers was verified under video laryngoscopy. If the vocal cords could not
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10 be seen, the patient would be excluded. Once the vocal cords were seen, the ETT was
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12 connected to the ventilator for mechanical ventilation and anesthesia was maintained
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14 with propofol 6 to 8 mg/kg per hour.
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16 17 Ultrasound assessment of ETT cuff

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19 The ultrasound probe was placed sagittal on the neck, perpendicular to the skin, and
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21 above the suprasternal notch. The ETT cuff was then inflated with 8 mL of saline. A
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23 pressure gauge was used to measure the cuff pressure; if the pressure exceeded 30
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25 cmH₂O, the patient would be excluded. After the injection of saline, two parallel
26
27 hyperechogenic lines would appear on ultrasound screen, as shown in Figure 3. The
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29 upper line represented the anterior wall of cuff, and the lower line represented the
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31 anterior wall of ETT. The junction of these two lines or the proximal starting point of
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33 the upper line represented the proximal margin of the cuff. Then the probe was moved
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35 along the midline of the neck until an image of the proximal margin of the cuff appeared
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37 at the center of the screen. Line B (Figure 2) was then drawn on the skin along the
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39 midpoints of the long axis of the probe. The distance between lines A and B (AB),
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41 representing the distance between the vocal cords and the proximal edge of the cuff
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43 (VCD), was measured. Then a towel was placed to cover the neck. With the ventilator
44
45 disconnected, the tip-carina distance and the incisors-carina distances were measured
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47 ¹⁷ by the anesthesiologist, who was blind to the marks on patient's neck, using a
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49 2.8-mm FOB (TIC-SD-I, Zhejiang UE Medical Corporation, Tai Zhou China). For patients
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51 with suitable VCDs (1.9–4.1 cm), the saline was drawn out of the cuff and the cuff filled
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53 with the proper amount of air. Finally, the tube was secured with tape. For patients with
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55 unsuitable VCDs (<1.9 cm or >4.1 cm), the saline was drawn out of the cuff and the tube
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57 moved cephalad or caudally based on the calculated distance to get the desired VCD.
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59 Then the video-assisted laryngoscope was again used to confirm the relative position of
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4 the glottis and the two insertion guide marks.
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7 **Statistical analysis**

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10 The primary outcome was the accuracy of the ultrasound image confirming the proper
11 depth of the ETT. The distance between the proximal margin of the cuff and the first
12 and second insertion guide marks of the ETT was 2 ± 0.1 cm and 4 ± 0.1 cm respectively.
13
14 The depth by ultrasound was defined as correct (AB distance between 1.9 and 4.1 cm),
15 too shallow (AB distance <1.9 cm), or too deep (AB distance >4.1 cm). The depth was
16 also defined by video-assisted laryngoscopy as correct (vocal cords lying between the
17 two insertion guide marks), too shallow (both marks above vocal cords), or too deep
18 (both marks below vocal cords). Both shallow and deep placements were considered to
19 be incorrect.
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28 According to the results of preliminary tests, an accuracy of 90% was considered
29 acceptable; to obtain an α error of 0.05 and a statistical power of 0.8, the calculated
30 sample size was 102 patients using PASS11.0 (NCSS LLC, Utah) software. A total of 120
31 patients were recruited to provide for potential dropouts. SPSS version 20.0 (SPSS, Inc.,
32 Chicago, IL) was used for data management. The normality of data was assessed using
33 the Shapiro-Wilk test. Normally distributed variables were expressed as the mean \pm SD
34 and compared between genders using Student's *t*-test. Non-normally distributed
35 variables were expressed as the median (range) and analyzed using the Mann-Whitney
36 U test. Ultrasound was compared with the gold standard of HC video-assisted
37 laryngoscopy as a diagnostic test; accuracy, sensitivity, specificity, positive predictive
38 value (PPV), and negative predictive value (NPV) were calculated. The corresponding
39 95% confidence intervals (CIs) were calculated based on the Clopper-Pearson method
40 in SAS 9.4 (SAS Inc., NC). Agreement between ultrasound and video-assisted
41 laryngoscopy was evaluated by the kappa consistency test. $P < .05$ was considered to be
42 statistically significant.
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Results

A total of 120 patients were initially enrolled in the study and 105 were included in the final analysis. Figure 4 presents the allocation process. The demographic data of the 105 patients who completed the trial are presented in Table 1. The differences in height, weight, and thyromental distance between males and females were statistically significant ($P < .05$). There was no significant difference in VCD detected by ultrasound and the tip-carina distance detected by FOB between males and females (Table 1).

Table 1 Patient Demographics

	Total (n=105)	Female (n=62)	Male (n=43)	P (Male vs Female)
Age (yr)	53 (20, 69)	53 (20, 69)	54 (20, 65)	0.757
Weight (kg)	64.0 ± 9.8	60.6 ± 8.9	68.9 ± 8.7	<0.001
Height (cm)	164.8 ± 8.5	160.0 ± 6.6	171.7 ± 5.9	<0.001
BMI	23.0 (17.0, 33.7)	22.8 (18.8, 33.7)	23.1 (17.0, 30.9)	0.669
VCD (cm)	2.9±0.6	2.9±0.6	3.0±0.6	0.607
TCD (cm)	3.6 (1.3, 6.4)	3.4 (1.3, 6.4)	3.6 (1.9, 6.4)	0.124

Variables are presented as mean ± SD (range) or median (range), CVD: vocal cords -cuff -distance, TCD: tip- carina distance, P- comparison between male and female

The diagnoses of too shallow an intubation for one female and one male and too deep an intubation for one female made by ultrasound was in agreement with the diagnoses made by direct laryngoscopy. After inserting the tube forward for about 1.5 cm, the glottis in each of the two shallow intubation patients lay between the two depth makers as confirmed by video-assisted laryngoscopy. After pulling the tube up about 1cm, the glottis position of the deep intubation patient was also corrected. The distances from the ETT tip to the carina measured by FOB were between 1.4 to 6.4 cm with no statistical difference between males and females; this distance was less than 2 cm for 1

male and 8 female patients. The data on these patients are shown in Table 2.

Table 2. Data of the three patients with incorrect insertion depth

Patient	CVD (cm)	Sex	Age (y)	Height (cm)	Weight (kg)	BMI (kg/m ²)	TCD (cm)
1	1.1	M	20	188	80	22.6	6.4
2	1.4	F	61	162	60	22.8	3.3
3	4.4	F	61	152	52	22.5	1.3

CVD: Cuff – vocal cords distance, TCD: Tip- carina distance,

Using video-assisted laryngoscopy as the standard criterion (Table 3), the overall accuracy of ultrasound was 100.0% (95% confidence interval [CI]:96.6–100%), with a sensitivity of 100% (95% CI: 96.5%–100%), a specificity of 100% (95% CI: 29.2%–100%), PPV 100% (95% CI: 96.5%–100%), and NPV 100% (95% CI: 29.2%–100%), and 100.0% (95% confidence interval [CI]:96.6–100%) in detecting the correct position of the ETT. Overall, the correct identification of tracheal versus bronchial intubation was 100.0% (95% confidence interval [CI]:96.6–100%). The kappa value was 1.

Table 3. Results of Ultrasound vs. Video assisted laryngoscope

Ultrasound	Video assisted laryngoscope	
	Positive	Negative
Correct	102	0
Incorrect	0	3

Video assisted laryngoscope: identifying the relationship of vocal cords and depth markers.

Positive: vocal cords lied between two depth markers; otherwise it is negative. Ultrasound: identifying the distance between upper edge of cuff and the glottis. Proper: the distance between upper edge of cuff and glottis was in the range of 1.9 to 4.1cm; otherwise it is improper.

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Discussion

Among the 105 cases using the 23/21 rule, two cuffs were too close to the vocal cords and one too far away from the vocal cords. The diagnoses of too deep intubation and too shallow intubation made by ultrasound were in agreement with direct laryngoscopy. The distances measured by ultrasound had high accuracy, sensitivity, specificity, PPV, and NPV for identifying the position of ETT at the level of the glottis. It was also found that malposition of the ETT could be corrected based on the results of ultrasound.

Unlike previous studies, which were mainly focused on the avoidance of too deep an intubation, our study was concerned with the safety of the vocal cords as a priority. We believe that for most adults, instances of ETT cuff impingement on the vocal cords or compression of the recurrent laryngeal nerve are more harmful—and more readily ignored—than endobronchial intubation.

In an early study, Cavo et al.² pointed out that the rigid thyroid lamina was lateral to the anterior branch of the recurrent laryngeal nerve; they suspected that the vulnerable point of the recurrent laryngeal nerve lay between 6 and 10 mm below the posterior end of the free edge of the vocal cord. Several studies have shown that extension of the neck and concomitant movement of the ETT was a risk factor for vocal cord injury owing to neck extension during withdrawal of the ETT from the trachea (1.9 cm in Conrardy's study,³ 1.7 ± 0.8 cm in Kim's study,¹⁸ and 0.9 ± 0.9 cm in Hartrey's study⁵). Under external force, the withdrawal distance of the ETT is increased.¹⁹ Since the cuff-free area of 2 to 4 cm above the vocal cords can be guaranteed by observing the insertion guide marks, this criterion was adopted as the standard for correct ETT positioning in the present study.

Our study showed that in using 23/21 rule, the rate of correct ETT positioning was as high as 97.1%. In only one male patient, by measuring the distance of VCD and

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4 observing the intubation guide marks, the tube insertion was considered to be too deep.
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6 The endotracheal tube's tip-to-carina distance in this case was 1.3 cm, which was the
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8 shortest found in any patient. Apart from this patient, there were 8 patients who had an
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10 ETT-to-carina distance of less than 2 cm.

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13 The VCD of one male and one female patient was less than 1.9 cm (1.1 cm and 1.4 cm,
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15 respectively). An anesthesiologist has suggested that it would be safer to use a 22/20
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17 rule for Asian people to avoid endobronchial intubation.^{9 20} However, if the 22/20 rule
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19 had been used in our study, the number of patients with a VCD less than 1.9 cm would
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21 have increased to 12, with a greater risk of harmful impingement of the cuff on the
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23 vocal cords.

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26 In our study, the VCD was measured with ultrasound. Although some studies have used
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28 FOB to make sure that the ETT cuff was 2 to 3 cm below the vocal cords,^{21 22} we found it
29
30 difficult to identify the cuff and the vocal cords via FOB when the ETT was already in
31
32 place. We used direct video-assisted laryngoscopy to verify the position of the vocal
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34 cords with respect to the ETT cuff. Although a quantitative measurement could not be
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36 achieved with laryngoscopy, agreement on correct position of ETT using two these two
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38 methods can still be justified.

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41 With the increasing popularity of ultrasound use in the field of anesthesia, several
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43 studies have used ultrasound to help confirm the depth of intubation. McKay et al.²³
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45 observed an ultrasound image of tracheal ring undulation caused as the ETT was
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47 advanced and considered it as an indication of proper ETT depth. Actually, such an
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49 image can only be regarded as a sign of endotracheal intubation. Uya et al.²⁴ defined
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51 adequate ETT placement as complete visualization of the saline-injected ETT cuff at the
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53 suprasternal notch. Similarly, Tessaroa et al.¹⁶ considered that ultrasonography of the
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55 saline-inflated cuff at the suprasternal notch represented correct ETT insertion depth.
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57 Some concern has been raised about how far above the suprasternal notch the cuff

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4 should be located.²⁵⁻²⁷
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8 Our study was the first to use ultrasound to measure VCD. In awake patients, in the
9 ultrasound transverse view, the hyperechoic vocal ligaments can easily be visualized.
10 During phonation, the true cords move toward the midline. Surface projection of the
11 vocal cords can then be marked on the skin after obtaining the optimal image of the
12 true vocal cords. Surface projection of the proximal edge of the cuff can also be marked
13 on the skin, as in the present study. Our results show that this is a reliable method for
14 identifying incorrect intubation depth. Also, adjustment of insertion depth can be made
15 based on the VCD obtained with this method. One can argue that it is needless to
16 measure VCD in every patient intubated with the 23/21 rule. However, for patients
17 whose necks are in extension during surgery, pre-surgery evaluation of the relative
18 position of the vocal cords and cuff may be necessary. In the present study, although
19 patients with Mallampati classification 3 and 4 and mouth opening less than 3 fingers
20 were excluded, vocal cords could not be completely exposed using video-assisted
21 laryngoscope on 11 of 120 patients. Measuring the VCD as shown in the present study
22 may serve as an alternative under such circumstances.
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36 37 Limitations of the study

38 There are several limitations to our study. Firstly, the number of incorrect tube
39 positions in our study was small. A larger sample size study may be needed to verify
40 our results. Secondly, for some male patients with prominent Adam's apples, the probe
41 could not be fully attached to the skin and the vocal cords could not be completely seen.
42 Three male patients were excluded from the study due to unsatisfactory ultrasound
43 images of the glottis. Putting a water-filled pad between the probe and the skin may
44 increase the contact area and enhance ultrasound imaging. Thirdly, although too
45 shallow an intubation can be avoided using the present method, too deep intubation
46 cannot. Using lung ultrasound technique, endobronchial intubation can be determined,
47 and bronchial intubation avoided.²¹ For patients with extremely short airways, the
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proper choice is to select an ETT with a short distance from the catheter tip to the upper edge of the cuff. Lastly, the ultrasound examination was done by experienced anesthesiologists. More training is needed for inexperienced anesthesiologists, although a study has shown that this technique can be easily learned.²⁴

Conclusion

Ultrasonography of the upper edge of a saline-inflated ETT cuff appears to be a simple and reliable method for identifying the distance between the vocal cords and the proximal edge of the ETT cuff, and malposition of the ETT can be corrected according to the results of the ultrasound. Confirmation of a safe distance from the upper margin of the cuff to the vocal cords may prevent injury to the vocal cords and recurrent laryngeal nerve.

Uncategorized References

1. Owen R, Cheney F. Endobronchial intubation: a preventable complication. *Anesthesiology* 1987;67(2):255-7.
2. Cavo J, John W. True vocal cord paralysis following intubation. *Laryngoscope* 1985;95(11):1352-9.
3. Conrardy P, Goodman L, Lainge F, et al. Alteration of endotracheal tube position. Flexion and extension of the neck. *Crit Care Med* 1976;4(1):8-12.
4. Mehta S. Intubation guide marks for correct tube placement A clinical study. *Anaesthesia* 1991;46(4):306-8.
5. Hartrey R, Kestin I. Movement of oral and nasal tracheal tubes as a result of changes in head and neck position. *Anaesthesia* 1995;50(8):682-7.
6. Chong D, Greenland K, Tan S, et al. The clinical implication of the vocal cords–carina distance in anaesthetized Chinese adults during orotracheal intubation. *British journal of anaesthesia* 2006;97(4):489-95. doi: 10.1093/bja/ael186
7. Stone D, Gal T. Airway management: in Miller's Anesthesia. Airway Management: In Miller's Anesthesia. 6th ed, Philadelphia. Elsevier Churchill Livingstone 2005:P1431-2. doi: 10.1097/EJA.0b013e328333a0f0
8. Dorsch J, Dorsch S. Tracheal tubes: Understanding Anesthesia Equipment. 4th Ed, Baltimore: Williams and Wilki 1999:589. doi: 10.1097/CCM.0b013e31824e68ae
9. Mitsuda S, Moriyama K, Yorozu T. Optimal insertion depth of endotracheal tube among Japanese. *J Anesth* 2014;28(3):477. doi: 10.1007/s00540-013-1739-9
10. Vezzani A, Manca T, Brusasco C, et al. Diagnostic value of chest ultrasound after cardiac

- surgery: a comparison with chest X-ray and auscultation. *Journal of cardiothoracic and vascular anaesthesia* 2014;28(6):1527-32. doi: 10.1053/j.jvca.2014.04.012 [published Online First: 2014/09/30]
11. Pattnaik S, Bodra R. Ballotability of cuff to confirm the correct intratracheal position of the endotracheal tube in the intensive care unit. *Eur J Anaesthesiol* 2000;17(9):587-90. doi: 10.1007/s12630-009-9077-y
 12. Pollard R, Lobato E. Endotracheal tube location verified reliably by cuff palpation *Anest Analg* 1995;81(1):135-8.
 13. McKay W, Klonarakis J, Pelivanov V, et al. Tracheal palpation to assess endotracheal tube depth:an exploratory study. *Can J Anesth* 2014;61(3):229-34.
 14. Ledrick D, Plewa M, Casey K, et al. Evaluation of manual cuff palpation to confirm proper endotracheal tube depth. *Prehosp Disaster Med* 2008;23(3):270-4.
 15. Rapheal D, Conard F. Ultrasound confirmation of endotracheal tube placement. *J Clin Ultrasound* 1987;15(7):459-62.
 16. Tessaro M, Salant E, Arroyo A, et al. Tracheal rapid ultrasound saline test (T.R.U.S.T.) for confirming correct endotracheal tube depth in children. *Resuscitation* 2015;89(10):8-12. doi: 10.1016/j.resuscitation.2014.08.033
 17. Cherg C, Wong C, Hsu C, et al. Airway length in adult :estimation of the optimal endotracheal tube kength for orotracheal intubation. *J Clin Anesth* 2002;14(4):271-4.
 18. Kim J, Kim H, Ahn W, et al. Head rotation, flexion, and extension alter endotracheal tube position in adults and children. *Can J Anaesth* 2009;56(10):751-6. doi: 10.1007/s12630-009-9158-y
 19. Buckley J, Brown A, Shin J, et al. A comparison of the haider tube-guard endotracheal tube holder versus adhesive tape to determine if this novel device can reduce endotracheal tube movement and prevent unplanned extubation. *Anesthesia and analgesia* 2016;122(5):1439-43. doi: 10.1213/ANE.0000000000001222
 20. Falzone E, Hoffmann C, Pasquier P, et al. Proper depth placement of oral endotracheal tubes in adults: 21/23 cm or 20/22 cm? *J Clin Anesth* 2012;24(2):165-6; author reply 66. doi: 10.1016/j.jclinane.2011.08.004
 21. Ramsingh D, Frank E, Haughton R, et al. Auscultation versus point-of-care ultrasound to determine endotracheal versus bronchial intubation: A diagnostic accuracy study. *Anesthesiology* 2016;124(5):1012-20. doi: 10.1097/ALN.0000000000001073
 22. Salem MR. Verification of endotracheal tube position. *Anesthesiol Clin North America* 2001;19(4):813-39.
 23. Mckay W, Wang A, Yip K, et al. Tracheal ultrasound to assess endotracheal tube depth: an exploratory study. *Can J Anaesth* 2015;62(6):667-68. doi: 10.1007/s12630-015-0313-3
 24. Uya A, Apear D, Patel K, et al. Can novice sonographers accurately locate an endotracheal tube with a saline-filled cuff in a cadaver model? A pilot study. *Acad Emerg Med* 2012;19(3):361-64. doi: 10.1111/j.1553-2712.2012.01306.x
 25. Li Y, Wang J, Wei X. Confirmation of endotracheal tube depth using ultrasound in adults. *Can J Anaesth* 2015;62(7):832.
 26. Mckay W, Wang A, Yip K, et al. In reply: Confirmation of endotracheal tube depth using ultrasound in adults. *Can J Anaesth* 2015;62(7):833-34. doi:

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4 10.1007/s12630-015-0360-9

5 27. Li Y, Wang J, Wei X. Confirmation of the depth of the endotracheal tube: where should
6 the cuff be? *Resuscitation* 2015;88:e7. doi: 10.1016/j.resuscitation.2014.11.032
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10 **Footnotes**

11
12 **Contributors** ML designed the study and revised the final manuscript as submitted. XC
13 and WZ contributed equally to this paper, and they were both the first authors. XC, WZ,
14 ZY and JG carried out all data collection. XC and WZ carried out data analyses and
15 drafted the initial manuscript. All authors approved the final manuscript as submitted.
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28

29 **Competing interests:** None.
30

31 **Patient consent:** Patient consent obtained.
32

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34 **Ethics approval:** The study was approved by Peking University Third Hospital Ethics
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36

37 **Provenance and peer review:** Not commissioned; externally peer reviewed.
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40 **Data sharing statement:** A full anonymized dataset is available from the
41 corresponding author on request.
42

43 **Figure legend**

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45 Figure 1. Transverse scan over the glottis. asterisks, thyroid cartilage; V: vocal cords.
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47
48 Figure 2. Demonstration of probe placement. Line A: probe placed at the level of vocal
49 cord, Line B: probe placed at the level of proximal edge of tube cuff
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52 Figure 3. Longitudinal view of the intubated trachea, with the cuff of the endotracheal
53 tube inflated with saline. Arrows pointing downwards - anterior wall of the cuff. Arrows
54 pointing upwards - anterior wall of the ETT.
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57 Figure 4. Allocation process
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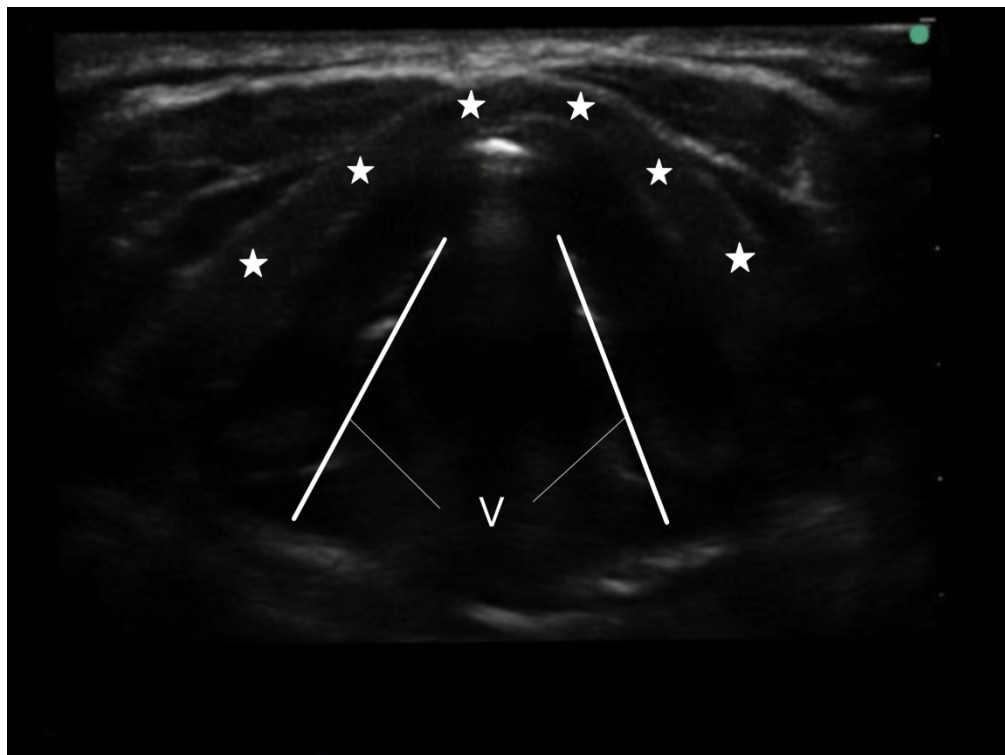


Figure 1. Transverse scan over the glottis. asterisks, thyroid cartilage; V: vocal cords.

889x666mm (72 x 72 DPI)

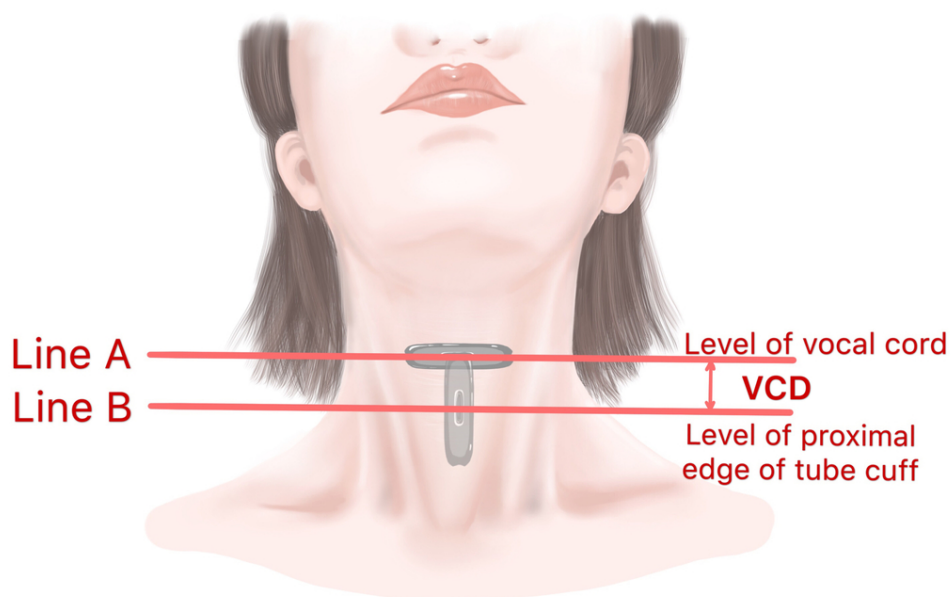


Figure 2. Demonstration of probe placement. Line A: probe placed at the level of vocal cord, Line B: probe placed at the level of proximal edge of tube cuff

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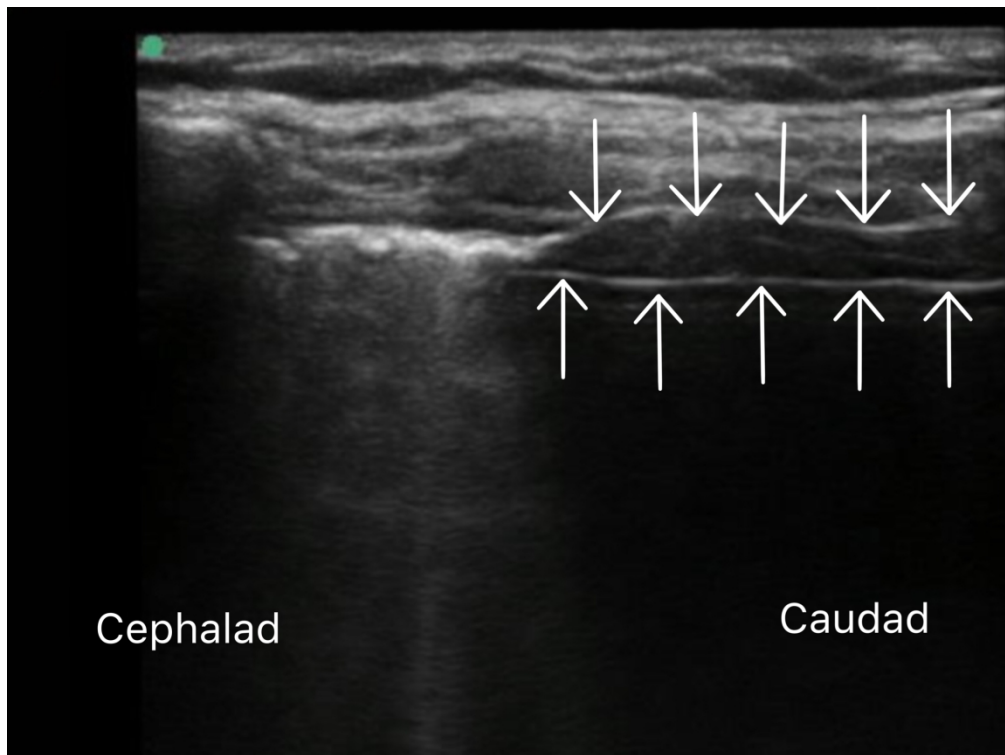


Figure 3. Longitudinal view of the intubated trachea, with the cuff of the endotracheal tube inflated with saline. Arrows pointing downwards - anterior wall of the cuff. Arrows pointing upwards - anterior wall of the ETT.

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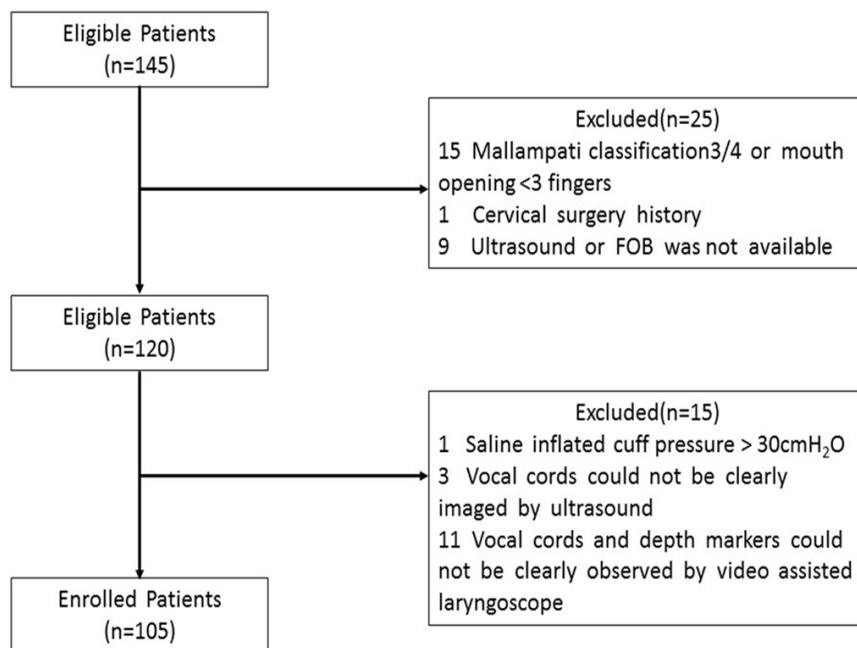


Figure 4. Allocation process

99x99mm (300 x 300 DPI)

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Determining correct tracheal tube insertion depth by measuring Distance Between Endotracheal Tube Cuff and Vocal Cords by Ultrasound in Chinese Adults: A prospective case control study

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1 **Determining correct tracheal tube insertion depth by measuring Distance**
2 **Between Endotracheal Tube Cuff and Vocal Cords by Ultrasound in Chinese Adult**
3 **s: A prospective case control study**

4
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14 **Key words:** Adult anaesthesia < ANAESTHETICS, Intratracheal Intubation,
15 Ultrasonography, Vocal Cord

16 **Words counts:** 3927

17 **Trial registration number:** ChiCTR (Chinese Clinical Trial Registry)-DDD-17011048

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6 2 **Between Endotracheal Tube Cuff and Vocal Cords by Ultrasound in Chinese Adult**
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8 3 **s: A prospective case control study**
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10 4
11 5 **Abstract**
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14 6 **Objectives** Unrecognized malposition of the endotracheal tube can lead to severe
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16 7 complications in patients under general anaesthesia. The purpose of this study was to
17
18 8 verify the feasibility of using ultrasound to measure the distance between the upper
19
20 9 edge of saline-inflated cuff and the vocal cords.
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22
23 10 **Design** Prospective case control study.
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25
26 11 **Setting** A tertiary hospital in Beijing, China.
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29 12 **Methods** In this prospective study, 105 adult patients who required general
30
31 13 anaesthesia were enrolled. Prior to induction, ultrasound was used to identify the
32
33 14 position of the vocal cords. After intubation, the endotracheal tube (ETT) was fixed at a
34
35 15 depth of 23 cm at the upper incisors in men and 21 cm in women. The depth of
36
37 16 intubation was verified by video-assisted laryngoscopy. The distance between the
38
39 17 upper edge of the saline-inflated cuff and the vocal cords was measured by ultrasound;
40
41 18 the ideal distance was considered to be 1.9 cm to 4.1 cm.
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43
44 19 **Results** Among the 105 cases, two cuffs were too close to the vocal cords and one too
45
46 20 far away from the vocal cords. These diagnoses were made by ultrasound and were in
47
48 21 agreement with results from direct laryngoscopy. The overall accuracy of ultrasound in
49
50 22 identifying malposition of the cuff was 100.0% (95% CI: 96.6%–100%). The sensitivity,
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52 23 specificity, positive predictive value, and negative predictive value of ultrasound were,
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54 24 respectively, 100% (95% CI: 96.5%–100%), 100% (95% CI: 29.2%-100%), 100% (95%
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56 25 CI: 96.5%–100%) and 100% (95% CI: 29.2%-100%).
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4 1 **Conclusion** Identification of the upper edge of the saline-inflated cuff and the vocal
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6 2 cords by ultrasound to assess the location of the ETT is a reliable method. It can be
7
8 3 used to avoid malposition of the ETT cuff and reduce the incidence of vocal cords injury
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10 4 after intubation.

11 5 12 13 6 **Article summary**

14 15 7 **Strengths and limitations of this study**

- 16 8 ● Previous studies on intubation depth were mainly focused on how to avoid too
17
18 9 deep intubation. The hazard of too shallow intubation was often neglected.
- 19
20 10 ● We found that the distance between the vocal cord and the upper edge of ETT cuff
21
22 11 can be measured with the aid of ultrasonography. This method might be useful to
23
24 12 avoid malposition of the ETT cuff and reduce the incidence of vocal cords injury
25
26 13 after intubation.
- 27
28 14 ● The technical limitations include the difficulty in fitting the ultrasound probe to the
29
30 15 surface of prominent Adam's apple and 5 to 8 min to complete the examination
31
32 16 procedure.

33 34 35 18 **Introduction**

36 19 Tracheal intubation is a routine procedure of resuscitation and general anaesthesia.
37
38 20 The appropriate depth of endotracheal intubation should be confirmed after intubation
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40 21 and during surgery because a malposition of endotracheal tube (ETT) can lead to
41
42 22 serious complications. Placing the tube too deeply may stimulate the carina, and
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44 23 unrecognized endobronchial intubation may result in single-lung ventilation,
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46 24 hypoxemia, and atelectasis of the nonventilated lung.¹ On the other hand, if the ETT is
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48 25 placed too shallowly, the tube cuff's impingement on the vocal cords may lead to vocal
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50 26 cords injury, compression of the recurrent laryngeal nerve, and even accidental
51
52 27 extubation.²

53
54 29 An optimal ETT placement should ensure sufficient distance (2–5 cm) between the tip
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56 30 of the ETT and the carina³ and sufficient distance (1.5–2.5 cm) between the proximal

1 margin of the cuff to the vocal cords.² ⁴ Most ETTs for the adults have two black
2 insertion guide marks at 2 and 4 cm above the cuff or one mark at 2 to 3 cm above the
3 cuff. ⁵ Alignment of the marks with the vocal cords helps to place the ETT at the correct
4 depth. ⁶ However, this technique relies on visualization of the vocal cords with a
5 laryngoscope (i.e., grade I or II view). A large tongue, prominent teeth, a short neck, or
6 blood and secretions may make visualization of the ETT's position within the glottis
7 difficult. Besides, under some circumstances, such as using blind intubation or a Shikani
8 or Bonfil optical stylet to guide intubation, the depth markers cannot be observed.

9
10 Under such circumstances, intubation depth is commonly determined according to
11 experience, usually 23 cm for male and 21 cm for female patients.⁷⁻⁹ After intubation,
12 auscultation of breath sounds is routinely performed to confirm the location of the tube.
13 If endobronchial intubation is suspected, the tube must be withdrawn until bilateral
14 breath sound can be heard. However, auscultation of breath sounds can be unreliable,¹⁰
15 and blind withdrawal of the tube can be hazardous for patients with short tracheas. In
16 some patients the distance from the vocal cords to the carina is identical to or even
17 shorter than the distance from the ETT tip to the insertion guide mark. ⁶ This means
18 that there would not be enough cuff free zone below the vocal cords when breath
19 sounds can be heard from both sides in patients with short tracheas.

20
21 Cuff palpation has been suggested as a tactile method to estimate the position of the
22 EET, ^{11 12} but its accuracy is influenced by the thickness of the soft tissue of the anterior
23 neck and the experience of the operator.¹³ Furthermore, a high-volume low-pressure
24 cuff may not be palpable despite correct placement. One study has shown that cuff
25 palpation has only a 26% specificity for indicating incorrect ETT placement. ¹⁴ The
26 development of ultrasonography has made it possible to identify the ETT cuff more
27 accurately. In 1987, Raphael et al., for the first time, obtained a clear image of a
28 saline-inflated cuff by ultrasound.¹⁵ Previous studies used ultrasonic images of
29 saline-inflated cuffs at or above the suprasternal notch as indicators of appropriate ETT

1 insertion depth.¹⁶ However, as in the case of auscultation, observing the cuff at or above
2 the suprasternal notch can rule out too deep intubation but not too shallow intubation.
3
4 Since both the vocal cords and the ETT cuff can be visualized using ultrasound, a safe
5 distance between the vocal cords and the ETT cuff can potentially be guaranteed by
6 ultrasonography. We hypothesized that ultrasound can be used to estimate the
7 distance between the upper edge of the ETT cuff and the vocal cords in adults so that
8 the depth of the ETT can be adjusted accordingly. The purpose of this study was to
9 review instances of endobronchial intubation and estimate the occurrence of too short
10 a distance between the cuff and vocal cords in adult Chinese using the 23/21 rule and
11 also to determine the feasibility of using ultrasound to measure the distance between
12 the upper edge of saline-inflated cuff and the vocal cords.

14 Materials and methods

15 Study participants

16 Following approval from the institutional review board (Peking University Third
17 Hospital Ethics Committee, IRB00006761-2016163), patients aged 18 to 70 who were
18 scheduled for elective cervical surgery under general anaesthesia from 2016.10 to
19 2017.5 were recruited in this prospective case control study. Written informed consent
20 was obtained from all patients. The exclusion criteria included difficult airway
21 (Mallampati classification 3 and 4, mouth opening <3 cm), abnormal airway or chest
22 anatomy, and a history of cervical trauma or cervical surgery.

24 Equipment and researchers

25 A reinforced ETT with a 7.0- or 8.0-mm inner diameter (ID) (Covidien Mallinckrodt,
26 USA), with two insertion guide marks was used in the present study, which involved
27 four investigators: an anesthesiologist experienced in airway ultrasonography using a
28 38-mm 6-13 MHz linear ultrasound probe (Turbo SonoSite HFL, Bothell, WA), an
29 anesthesiologist experienced in fiberoptic bronchoscopy (FOB), a senior resident, and

1 an anesthetic assistant. The two anesthesiologists who performed the ultrasound and
2 FOB examinations were blind to the results of laryngoscopy.

3 4 Ultrasound assessment of vocal cords

5 When the patient reached the operation room, routine monitors (pulse oximeter,
6 noninvasive blood pressure cuff, and electrocardiogram) were placed. The patient was
7 in a neutral position. The ultrasound probe was placed transversely on the neck
8 perpendicular to the skin. The probe was moved cranially or caudally until the true
9 vocal cords could be identified (Figure 1). Along the midpoints of the short axis of the
10 probe, line A was drawn on the patient's skin (Figure 2) to mark the position of true
11 vocal cords. If the vocal cords could not be clearly identified, the patient was excluded.

12 13 Intubation

14 Following the induction of anaesthesia, an ETT (7.0-mm ID for females, 8.0-mm ID for
15 males) was inserted by the resident and the insertion depth was determined using the
16 23/21 cm rule (23 cm at the upper incisor teeth in men and 21 cm in women) using a
17 video-assisted laryngoscope (Zhejiang UE Medical Corporation, Tai Zhou, China). The
18 ETT was held in place by the assistant, then the position of the vocal cords relative to
19 the depth markers was verified under video laryngoscopy. If the vocal cords could not
20 be seen, the patient would be excluded. Once the vocal cords were seen, the ETT was
21 connected to the ventilator for mechanical ventilation and anaesthesia was maintained
22 with propofol 6 to 8 mg/kg per hour.

23 24 Measurements

25 The ultrasound probe was placed sagittal on the neck, perpendicular to the skin, and
26 above the suprasternal notch. The ETT cuff was then inflated with 8 mL of saline. A
27 pressure gauge was used to measure the cuff pressure; if the pressure exceeded 30
28 cmH₂O, the patient would be excluded. After the injection of saline, two parallel
29 hyperechogenic lines would appear on ultrasound screen, as shown in Figure 3. The

1 upper line represented the anterior wall of cuff, and the lower line represented the
2 anterior wall of ETT. The junction of these two lines or the proximal starting point of
3 the upper line represented the proximal margin of the cuff. Then the probe was moved
4 along the midline of the neck until an image of the proximal margin of the cuff appeared
5 at the center of the screen. Line B (Figure 2) was then drawn on the skin along the
6 midpoints of the long axis of the probe. The distance between lines A and B (AB),
7 representing the distance between the vocal cords and the proximal edge of the cuff
8 (VCD), was measured. Then a towel was placed to cover the neck. With the ventilator
9 disconnected, the tip-carina distance and the incisors-carina distances were measured
10 ¹⁷ by the anesthesiologist, who was blind to the marks on patient's neck, using a
11 2.8-mm FOB (TIC-SD-I, Zhejiang UE Medical Corporation, Tai Zhou China). For patients
12 with suitable VCDs (1.9–4.1 cm), the saline was drawn out of the cuff and the cuff filled
13 with the proper amount of air. Finally, the tube was secured with tape. For patients
14 with unsuitable VCDs (<1.9 cm or >4.1 cm), the saline was drawn out of the cuff and the
15 tube moved cephalad or caudally based on the calculated distance to get the desired
16 VCD. Then the video-assisted laryngoscope was again used to confirm the relative
17 position of the glottis and the two insertion guide marks.

19 Patient and public involvement

20 No patients were involved in setting the research question or the outcome measures,
21 nor were they involved in developing plans for design or implementation of the study.
22 No patients were asked to advise on interpretation or writing up of results. Study
23 reports will be disseminated to investigators and patients through this open-access
24 publication.

26 **Statistical analysis**

27 The primary outcome was the accuracy of the ultrasound image confirming the proper
28 depth of the ETT. The distance between the proximal margin of the cuff and the first
29 and second insertion guide marks of the ETT was 2 ± 0.1 cm and 4 ± 0.1 cm

1 respectively. The depth by ultrasound was defined as correct (AB distance between 1.9
2 and 4.1 cm), too shallow (AB distance <1.9cm), or too deep (AB distance >4.1 cm). The
3 depth was also defined by video-assisted laryngoscopy as correct (vocal cords lying
4 between the two insertion guide marks), too shallow (both marks above vocal cords),
5 or too deep (both marks below vocal cords). Both too shallow and too deep placements
6 were considered to be incorrect.

7
8 According to the results of preliminary tests, an accuracy of 90% was considered
9 acceptable; to obtain an α error of 0.05 and a statistical power of 0.8, the calculated
10 sample size was 102 patients using PASS11.0 (NCSS LLC, Utah) software. A total of 120
11 patients were recruited to provide for potential dropouts. SPSS version 20.0 (SPSS, Inc.,
12 Chicago, IL) was used for data management. The normality of data was assessed using
13 the Shapiro-Wilk test. Normally distributed variables were expressed as the mean \pm SD
14 and compared between genders using Student's *t*-test. Non-normally distributed
15 variables were expressed as the median (range) and analyzed using the Mann-Whitney
16 U test. Ultrasound was compared with the gold standard of HC video-assisted
17 laryngoscopy as a diagnostic test; accuracy, sensitivity, specificity, positive predictive
18 value (PPV), and negative predictive value (NPV) were calculated. The corresponding
19 95% confidence intervals (CIs) were calculated based on the Clopper-Pearson method
20 in SAS 9.4 (SAS Inc., NC). Agreement between ultrasound and video-assisted
21 laryngoscopy was evaluated by the kappa consistency test. $P < .05$ was considered to be
22 statistically significant.

23 24 **Results**

25 A total of 120 patients were initially enrolled in the study and 105 were included in the
26 final analysis. Figure 4 presents the allocation process. The demographic data of the
27 105 patients who completed the trial are presented in Table 1. The differences in
28 height, weight, and thyromental distance between males and females were statistically

1 significant ($P < .05$). There was no significant difference in VCD detected by ultrasound
2 and the tip-carina distance detected by FOB between males and females (Table 1).

3
4 Table 1 Patient Demographics

	Total (n=105)	Female (n=62)	Male (n=43)	P (Male vs Female)
Age (yr)	53 (20, 69)	53 (20, 69)	54 (20, 65)	0.757
Weight (kg)	64.0 ± 9.8	60.6 ± 8.9	68.9 ± 8.7	<0.001
Height (cm)	164.8 ± 8.5	160.0 ± 6.6	171.7 ± 5.9	<0.001
BMI	23.0 (17.0, 33.7)	22.8 (18.8, 33.7)	23.1 (17.0, 30.9)	0.669
VCD (cm)	2.9 ± 0.6	2.9 ± 0.6	3.0 ± 0.6	0.607
TCD (cm)	3.6 (1.3, 6.4)	3.4 (1.3, 6.4)	3.6 (1.9, 6.4)	0.124

5 Variables are presented as mean ± SD (range) or median (range), VCD: vocal cords -cuff
6 -distance, TCD: tip- carina distance, P- comparison between male and female

7 It took about 30 sec to 1 min to find the vocal cords and mark on the skin, and it took
8 another 3 to 5 min to finish the rest of the procedure, from filling the cuff with saline to
9 withdrawing FOB. The ventilator was stopped for no more the 20 seconds during FOB
10 examination, and no change in SpO₂ was found. The diagnoses of too shallow an
11 intubation for one female and one male and too deep an intubation for one female
12 made by ultrasound was in agreement with the diagnoses made by direct laryngoscopy.
13 The data on these patients are shown in Table 2. After inserting the tube forward for
14 about 1.5 cm, the glottis in each of the two shallow intubation patients lay between the
15 two depth makers as confirmed by video-assisted laryngoscopy. After pulling the tube
16 up about 1cm, the glottis position of the deep intubation patient was also corrected.
17 The distances from the ETT tip to the carina measured by FOB were between 1.3 to 6.4
18 cm with no statistical difference between males and females. This distance was less
19 than 2 cm for a total of 1 male and 8 female patients. Except for the No.3 patient in

1 Table 2, the tubes were not withdrawn. For these 8 patients, fibreoptic bronchoscopy
 2 was performed during surgery to ensure no endobronchial intubation occurred.

3
 4 Table 2. Data of the three patients with incorrect insertion depth

Patient	VCD (cm)	Sex	Age (y)	Height(cm)	Weight (kg)	BMI (kg/m ²)	TCD (cm)
1	1.1	M	20	188	80	22.6	6.4
2	1.4	F	61	162	60	22.8	3.3
3	4.4	F	61	152	52	22.5	1.3

5 VCD: vocal cords-cuff distance, TCD: tip- carina distance,

6 Using video-assisted laryngoscopy as the standard criterion (Table 3), the overall
 7 accuracy of ultrasound was 100.0% (95% confidence interval [CI]:96.6–100%), with a
 8 sensitivity of 100% (95% CI: 96.5%–100%), a specificity of 100% (95% CI: 29.2%–
 9 100%), PPV 100% (95% CI: 96.5%–100%), and NPV 100% (95% CI: 29.2%–100%),
 10 and 100.0% (95% confidence interval [CI]:96.6–100%) in detecting the correct
 11 position of the ETT. Overall, the correct identification of tracheal versus bronchial
 12 intubation was 100.0% (95% confidence interval [CI]:96.6–100%). The kappa value
 13 was 1.

14
 15 Table 3. Results of Ultrasound vs. Video assisted laryngoscope

Ultrasound	Video assisted laryngoscope	
	Positive	Negative
Correct	102	0
Incorrect	0	3

16 Video assisted laryngoscope: identifying the relationship of vocal cords and depth
 17 markers. Positive: vocal cords lied between two depth markers; otherwise it is negative.
 18 Ultrasound: identifying the distance between upper edge of cuff and the glottis. Correct:

1 the distance between upper edge of cuff and glottis was in the range of 1.9 to 4.1cm;
2 otherwise it is incorrect.

3 **Discussion**

4 Among the 105 cases using the 23/21 rule, two cuffs were too close to the vocal cords
5 and one too far away from the vocal cords. The diagnoses of too deep intubation and
6 too shallow intubation made by ultrasound were in agreement with direct
7 laryngoscopy. The distances measured by ultrasound had high accuracy, sensitivity,
8 specificity, PPV, and NPV for identifying the position of ETT at the level of the glottis. It
9 was also found that malposition of the ETT could be corrected based on the results of
10 ultrasound.

11
12 Unlike previous studies, which were mainly focused on the avoidance of too deep an
13 intubation, the safety of the vocal cords was concerned as a priority in our study. We
14 believe that for most adults, ETT cuff impingement on the vocal cords or compression
15 of the recurrent laryngeal nerve are more harmful—and more readily ignored—than
16 endobronchial intubation.

17
18 In an early study, Cavo et al.² pointed out that the rigid thyroid lamina was lateral to the
19 anterior branch of the recurrent laryngeal nerve; they suspected that the vulnerable
20 point of the recurrent laryngeal nerve lay between 6 and 10 mm below the posterior
21 end of the free edge of the vocal cord. Several studies have shown that extension of the
22 neck and concomitant movement of the ETT was a risk factor for vocal cord injury
23 owing to neck extension during withdrawal of the ETT from the trachea (1.9 cm in
24 Conrardy's study,³ 1.7 ± 0.8 cm in Kim's study,¹⁸ and 0.9 ± 0.9 cm in Hartrey's study⁵).
25 Under external force, the withdrawal distance of the ETT is increased.¹⁹ Since the
26 cuff-free area of 2 to 4 cm below the vocal cords can be guaranteed by observing the
27 insertion guide marks, this criterion was adopted as the standard for correct ETT
28 positioning in the present study.

29

1 Our study showed that in using 23/21 rule, the rate of correct ETT positioning was as
2 high as 97.1%. In only one male patient and one female, the tube insertion was
3 considered to be too deep. Some anesthesiologists suggested that it would be safer to
4 use a 22/20 rule for Asian people to avoid endobronchial intubation.^{9, 20} However, if the
5 22/20 rule had been used in our study, the number of patients with a VCD less than 1.9
6 cm would have increased to 12, with a greater risk of harmful impingement of the cuff
7 on the vocal cords.

8
9 In our study, the VCD was measured with ultrasound. Although some studies have used
10 FOB to make sure that the ETT cuff was 2 to 3 cm below the vocal cords,^{21, 22} we found
11 it difficult to identify the cuff and the vocal cords via FOB when the ETT was already in
12 place. We used direct video-assisted laryngoscopy to verify the position of the vocal
13 cords with respect to the ETT cuff. Although a quantitative measurement could not be
14 achieved with laryngoscopy, agreement on correct position of ETT using two these two
15 methods can still be justified.

16
17 With the increasing popularity of ultrasound use in the field of anaesthesia, several
18 studies have used ultrasound to help confirm the depth of intubation. McKay et al.²³
19 observed an ultrasound image of tracheal ring undulation caused as the ETT was
20 advanced and considered it as an indication of proper ETT depth. Actually, such an
21 image can only be regarded as a sign of endotracheal intubation. Uya et al.²⁴ defined
22 adequate ETT placement as complete visualization of the saline-injected ETT cuff at the
23 suprasternal notch. Similarly, Tessaro et al.¹⁶ considered that ultrasonography of the
24 saline-inflated cuff at the suprasternal notch represented correct ETT insertion depth.
25 Some concern has been raised about how far above the suprasternal notch the cuff
26 should be located.²⁵⁻²⁷

27
28 Our study was the first to use ultrasound to measure VCD. In awake patients, in the
29 ultrasound transverse view, the hyperechoic vocal ligaments can easily be visualized.

1 During phonation, the true cords move toward the midline. Surface projection of the
2 vocal cords can then be marked on the skin after obtaining the optimal image of the
3 true vocal cords. Surface projection of the proximal edge of the cuff can also be marked
4 on the skin, as in the present study. Our results show that this is a reliable method for
5 identifying incorrect intubation depth. Also, adjustment of insertion depth can be made
6 based on the VCD obtained with this method. One can argue that it is needless to
7 measure VCD in every patient intubated with the 23/21 rule. However, for patients
8 whose necks are in extension during surgery, pre-surgery evaluation of the relative
9 position of the vocal cords and cuff may be necessary. In the present study, although
10 patients with Mallampati classification 3 and 4 and mouth opening less than 3 fingers
11 were excluded, vocal cords could not be completely exposed using video-assisted
12 laryngoscope on 11 of 120 patients. Measuring the VCD as shown in the present study
13 may serve as an alternative under such circumstances.

14 15 Limitations of the study

16 There are several limitations to our study. Firstly, the number of incorrect tube
17 positions in our study was small. A larger sample size study may be needed to verify
18 our results. Secondly, for some male patients with prominent Adam's apples, the probe
19 could not be fully attached to the skin and the vocal cords could not be completely seen.
20 Three male patients were excluded from the study due to unsatisfactory ultrasound
21 images of the glottis. Putting a specially designed water-filled pad or gel-like pad which
22 fits the surface of the probe between the probe and the skin may increase the contact
23 area and enhance ultrasound imaging. Thirdly, although too shallow an intubation can
24 be avoided using the present method, too deep intubation cannot. Using lung
25 ultrasound technique, endobronchial intubation can be determined, and bronchial
26 intubation avoided.²¹ For patients with extremely short airways, the proper choice is to
27 select an ETT with a short distance from the catheter tip to the upper edge of the cuff.
28 Lastly, although the ultrasound examination was done by experienced
29 anesthesiologists, it still took 5 to 8 min to complete the whole examination procedure.

1 Training is needed for inexperienced anesthesiologists but a study has shown that this
2 technique can be easily learned.²⁴

3 4 **Conclusion**

5 Ultrasonography of the upper edge of a saline-inflated ETT cuff appears to be a simple
6 and reliable method for identifying the distance between the vocal cords and the
7 proximal edge of the ETT cuff, and malposition of the ETT can be corrected according to
8 the results of the ultrasound. Confirmation of a safe distance from the upper margin of
9 the cuff to the vocal cords may prevent injury to the vocal cords and recurrent
10 laryngeal nerve.

11 12 **Uncategorized References**

- 13 1. Owen R, Cheney F. Endobronchial intubation: a preventable complication.
14 *Anesthesiology* 1987;67(2):255-7.
- 15 2. Cavo J, John W. True vocal cord paralysis following intubation. *Laryngoscope*
16 1985;95(11):1352-9.
- 17 3. Conrardy P, Goodman L, Lainge F, et al. Alteration of endotracheal tube position. Flexion
18 and extension of the neck. *Crit Care Med* 1976;4(1):8-12.
- 19 4. Mehta S. Intubation guide marks for correct tube placement A clinical study. *Anaesthesia*
20 1991;46(4):306-8.
- 21 5. Hartrey R, Kestin I. Movement of oral and nasal tracheal tubes as a result of changes in
22 head and neck position. *Anaesthesia* 1995;50(8):682-7.
- 23 6. Chong D, Greenland K, Tan S, et al. The clinical implication of the vocal cords–carina
24 distance in anaesthetized Chinese adults during orotracheal intubation. *British*
25 *journal of anaesthesia* 2006;97(4):489-95. doi: 10.1093/bja/ael186
- 26 7. Stone D, Gal T. Airway management: in Miller's Anesthesia. Airway Management: In
27 Miller's Anesthesia. 6th ed, Philadelphia. *Elsevier Churchill Livingstone* 2005:P1431-2.
28 doi: 10.1097/EJA.0b013e328333a0f0
- 29 8. Dorsch J, Dorsch S. Tracheal tubes: Understanding Anesthesia Equipment. *4th Ed,*
30 *Baltimore: Williams and Wilki* 1999:589. doi: 10.1097/CCM.0b013e31824e68ae
- 31 9. Mitsuda S, Moriyama K, Yorozu T. Optimal insertion depth of endotracheal tube among
32 Japanese. *J Anesth* 2014;28(3):477. doi: 10.1007/s00540-013-1739-9
- 33 10. Vezzani A, Manca T, Brusasco C, et al. Diagnostic value of chest ultrasound after cardiac
34 surgery: a comparison with chest X-ray and auscultation. *Journal of cardiothoracic*
35 *and vascular anaesthesia* 2014;28(6):1527-32. doi: 10.1053/j.jvca.2014.04.012
36 [published Online First: 2014/09/30]

11. Pattnaik S, Bodra R. Ballotability of cuff to confirm the correct intratracheal position of the endotracheal tube in the intensive care unit. *Eur J Anaesthesiol* 2000;17(9):587-90. doi: 10.1007/s12630-009-9077-y
12. Pollard R, Lobato E. Endotracheal tube location verified reliably by cuff palpation *Anesth Analg* 1995;81(1):135-8.
13. McKay W, Klonarakis J, Pelivanov V, et al. Tracheal palpation to assess endotracheal tube depth: an exploratory study. *Can J Anesth* 2014;61(3):229-34.
14. Ledrick D, Plewa M, Casey K, et al. Evaluation of manual cuff palpation to confirm proper endotracheal tube depth. *Prehosp Disaster Med* 2008;23(3):270-4.
15. Rapheal D, Conard F. Ultrasound confirmation of endotracheal tube placement. *J Clin Ultrasound* 1987;15(7):459-62.
16. Tessaro M, Salant E, Arroyo A, et al. Tracheal rapid ultrasound saline test (T.R.U.S.T.) for confirming correct endotracheal tube depth in children. *Resuscitation* 2015;89(10):8-12. doi: 10.1016/j.resuscitation.2014.08.033
17. Cherg C, Wong C, Hsu C, et al. Airway length in adult :estimation of the optimal endotracheal tube length for orotracheal intubation. *J Clin Anesth* 2002;14(4):271-4.
18. Kim J, Kim H, Ahn W, et al. Head rotation, flexion, and extension alter endotracheal tube position in adults and children. *Can J Anaesth* 2009;56(10):751-6. doi: 10.1007/s12630-009-9158-y
19. Buckley J, Brown A, Shin J, et al. A comparison of the haider tube-guard endotracheal tube holder versus adhesive tape to determine if this novel device can reduce endotracheal tube movement and prevent unplanned extubation. *Anesthesia and analgesia* 2016;122(5):1439-43. doi: 10.1213/ANE.0000000000001222
20. Falzone E, Hoffmann C, Pasquier P, et al. Proper depth placement of oral endotracheal tubes in adults: 21/23 cm or 20/22 cm? *J Clin Anesth* 2012;24(2):165-6; author reply 66. doi: 10.1016/j.jclinane.2011.08.004
21. Ramsingh D, Frank E, Haughton R, et al. Auscultation versus point-of-care ultrasound to determine endotracheal versus bronchial intubation: A diagnostic accuracy study. *Anesthesiology* 2016;124(5):1012-20. doi: 10.1097/ALN.0000000000001073
22. Salem MR. Verification of endotracheal tube position. *Anesthesiol Clin North America* 2001;19(4):813-39.
23. Mckay W, Wang A, Yip K, et al. Tracheal ultrasound to assess endotracheal tube depth: an exploratory study. *Can J Anaesth* 2015;62(6):667-68. doi: 10.1007/s12630-015-0313-3
24. Uya A, Apear D, Patel K, et al. Can novice sonographers accurately locate an endotracheal tube with a saline-filled cuff in a cadaver model? A pilot study. *Acad Emerg Med* 2012;19(3):361-64. doi: 10.1111/j.1553-2712.2012.01306.x
25. Li Y, Wang J, Wei X. Confirmation of endotracheal tube depth using ultrasound in adults. *Can J Anaesth* 2015;62(7):832.
26. Mckay W, Wang A, Yip K, et al. In reply: Confirmation of endotracheal tube depth using ultrasound in adults. *Can J Anaesth* 2015;62(7):833-34. doi: 10.1007/s12630-015-0360-9

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4 1 27. Li Y, Wang J, Wei X. Confirmation of the depth of the endotracheal tube: where should
5 2 the cuff be? *Resuscitation* 2015;88:e7. doi: 10.1016/j.resuscitation.2014.11.032
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8 9 4 **Footnotes**

10
11 5 **Contributors** ML designed the study and revised the final manuscript as submitted. XC
12 6 and WZ contributed equally to this paper, and they were both the first authors. XC, WZ,
13 7 ZY and JG carried out all data collection. XC and WZ carried out data analyses and
14 8 drafted the initial manuscript. All authors approved the final manuscript as submitted.
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26 12 **Disclaimer:** The funders were not involved in the study design, data analysis or
27 13 manuscript preparation.
28

29 14 **Competing interests:** None.
30

31 15 **Patient consent:** Patient consent obtained.
32
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34 16 **Ethics approval:** The study was approved by Peking University Third Hospital Ethics
35 17 Committee (IRB00006761-2016163).
36

37 18 **Provenance and peer review:** Not commissioned; externally peer reviewed.
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40 19 **Data sharing statement:** A full anonymized dataset is available from the
41 20 corresponding author on request.
42

43 21 **Figure legend**

44
45 22 Figure 1. Transverse scan over the glottis. asterisks, thyroid cartilage; V: vocal cords.
46

47
48 23 Figure 2. Demonstration of probe placement. Line A: probe placed at the level of vocal
49 24 cord, Line B: probe placed at the level of proximal edge of tube cuff
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51 25 Figure 3. Longitudinal view of the intubated trachea, with the cuff of the endotracheal
52 26 tube inflated with saline. Arrows pointing downwards - anterior wall of the cuff.
53 27 Arrows pointing upwards - anterior wall of the ETT.
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56 28 Figure 4. Allocation process
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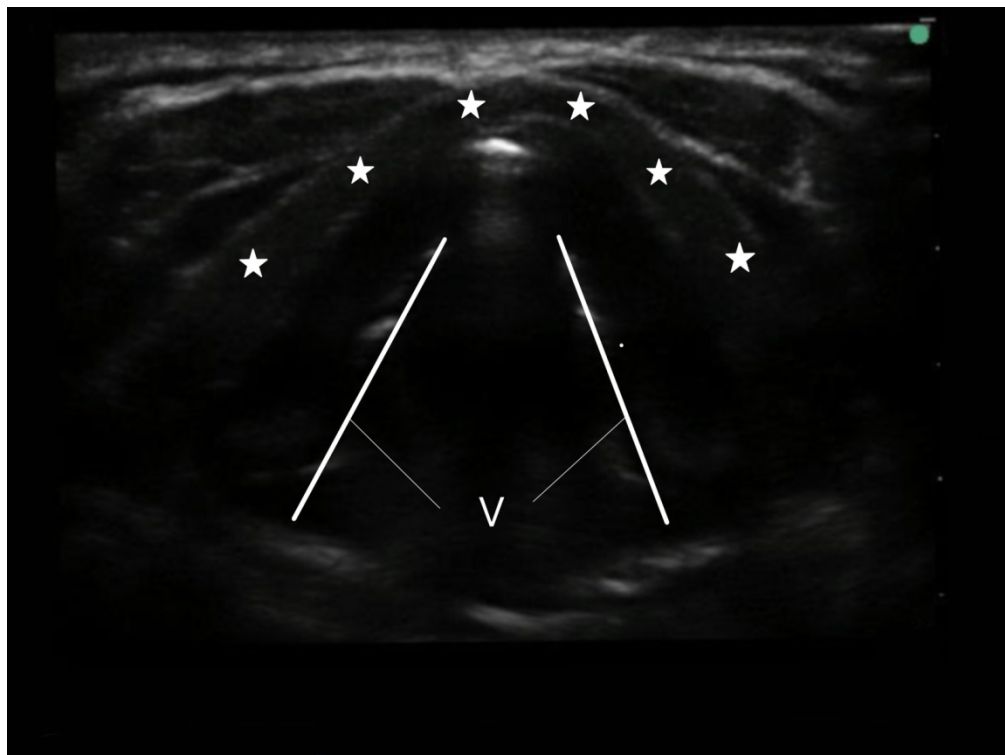


Figure 1. Transverse scan over the glottis. asterisks, thyroid cartilage; V: vocal cords.

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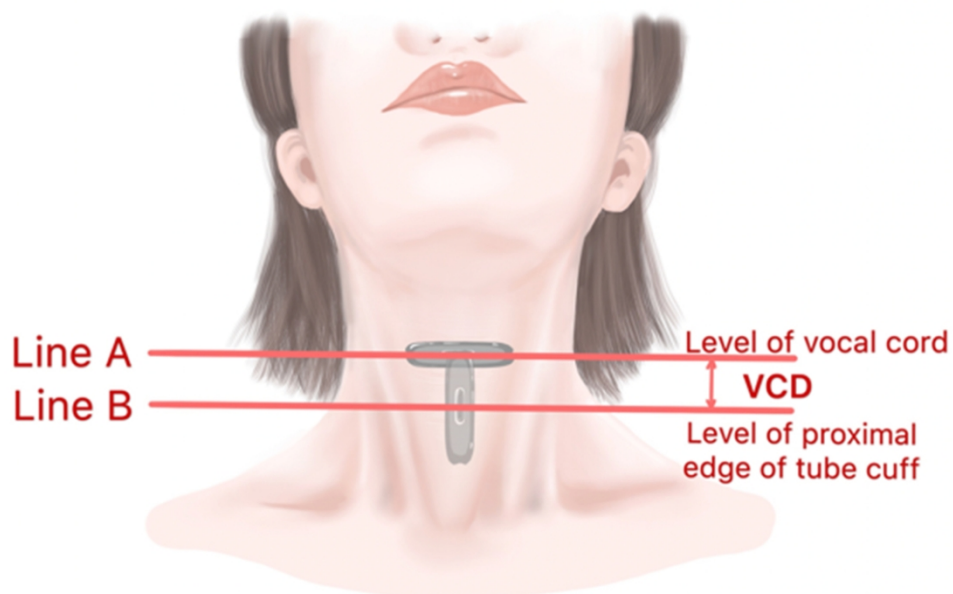


Figure 2. Demonstration of probe placement. Line A: probe placed at the level of vocal cord, Line B: probe placed at the level of proximal edge of tube cuff

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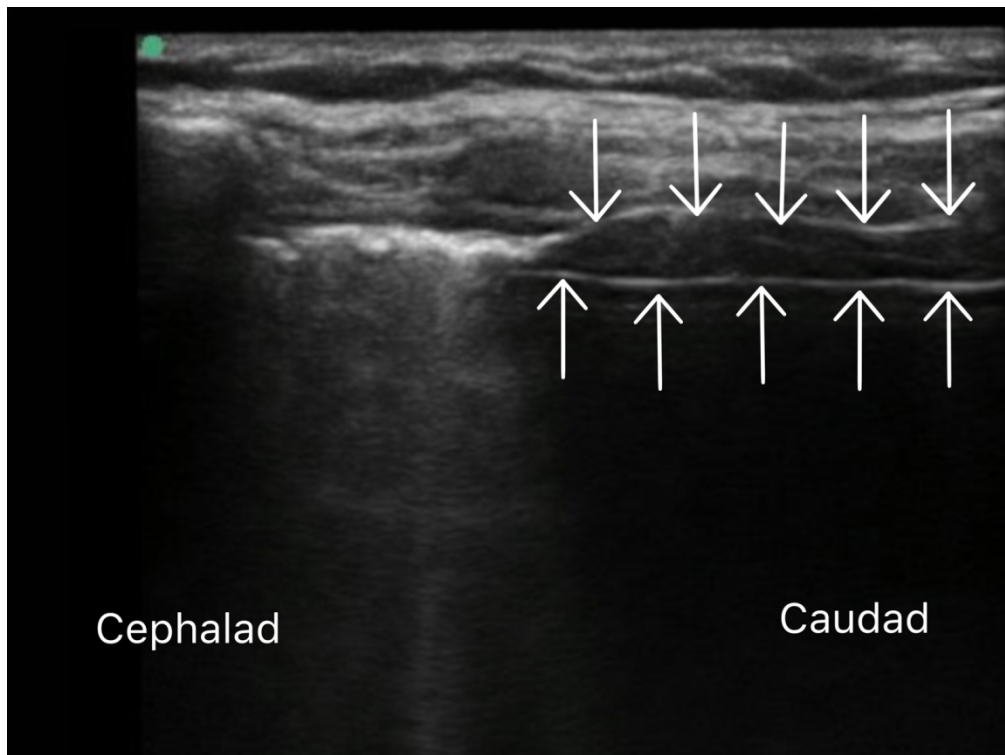


Figure 3. Longitudinal view of the intubated trachea, with the cuff of the endotracheal tube inflated with saline. Arrows pointing downwards - anterior wall of the cuff. Arrows pointing upwards - anterior wall of the ETT.

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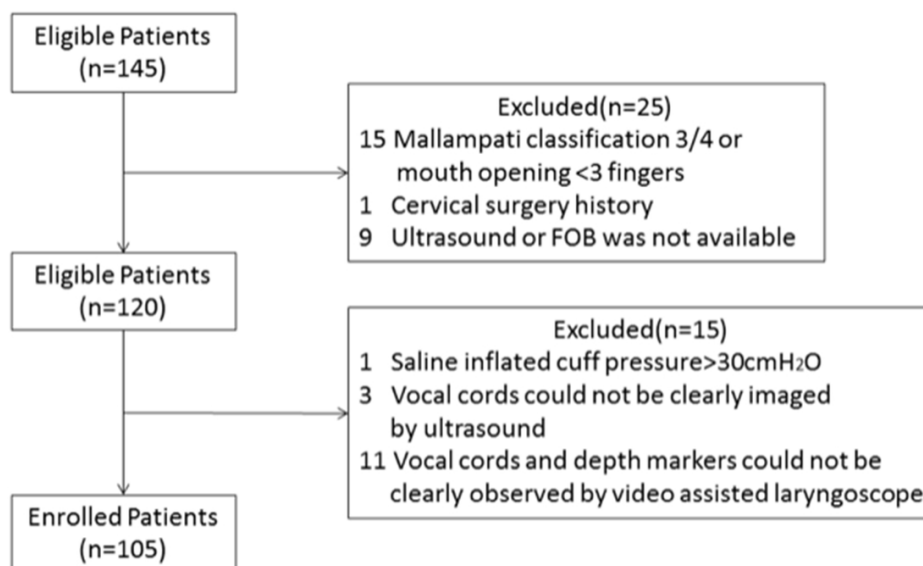


Figure 4. Allocation process

99x63mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up		
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at	8	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.