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4 **It's not breathing through a straw: pediatric extubation readiness tests should not use**
5 **Pressure Support**
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7
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33 Sources of Support

34 National Institutes of Health/NICHD 1K23HL103785
35 Los Angeles Basin Clinical Translational Science Institute
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37
38 Word Count: 2707 (without abstract); 2957 (with abstract)
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40 **Keywords:** Airway Extubation, Work of Breathing, pediatrics, ventilator weaning
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42
43 **Key Points:** By performing direct measures of patient effort of breathing before and after
44 extubation on over 400 mechanically ventilated children, we have found that patient effort of
45 breathing on CPAP of 5cmH₂O alone provides a good estimate of post-extubation effort.
46 Regardless of the endotracheal tube size, pressure support should not be added to CPAP for
47 extubation readiness testing because it results in significant under-estimation of post-
48 extubation effort of breathing.
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55 **Social Network:** Regardless of endotracheal tube size, PS during ERTs significantly under-
56 estimates post-extubation effort of breathing.
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4 **Abstract**

5 **Purpose:** Pressure Support (PS) is often used for extubation readiness testing (ERT), to
6
7
8 overcome perceived imposed work of breathing from endotracheal tubes (ETT). We sought to
9
10 determine whether effort of breathing on Continuous Positive Airway Pressure (CPAP) of
11
12 5cmH₂O is higher than post-extubation effort, and if this is confounded by ETT size or post-
13
14 extubation noninvasive respiratory support (NIV).
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19 **Methods:** Prospective trial in intubated children. Using esophageal manometry we compared
20
21 effort of breathing with Pressure.Rate Product (PRP) under 4 conditions: PS 10/5 cmH₂O (PS),
22
23 CPAP 5 cmH₂O (CPAP), and spontaneous breathing 5 and 60 minutes post-extubation.
24
25 Subgroup analysis excluded post-extubation upper airway obstruction (UAO) and stratified by
26
27 ETT size and post-extubation NIV.
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33 **Results:** We included 409 children. Median PRP on PS was lower than CPAP which was lower
34
35 than post extubation: PS 100 (IQR 60,175), CPAP 200 (120,300), post-extubation 5min 300
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37 (150,500), 60min 255 (175,400) (all p<0.001). Excluding 107 patients with post-extubation UAO
38
39 (where PRP after extubation is expected to be higher), PS still under-estimated post-extubation
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41 effort by 126-147%, and CPAP underestimated post-extubation effort by 17-25%. For all ETT
42
43 subgroups: ≤ 3.5 mmID (n=152), 4-4.5 mmID (n=102), and ≥ 5.0 mmID (n=48) PRP on PS was
44
45 lower than CPAP and post-extubation (all p<0.0001), while CPAP PRP was not different than
46
47 post-extubation (all p>0.05). For patients on NIV, PRP on PS was lower than CPAP and post-
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49 extubation (p<0.0001), while CPAP PRP was not different than post-extubation (n=81).
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Conclusions: Regardless of endotracheal tube size, PS during ERTs significantly under-estimates post-extubation effort of breathing.

Word Count: 250

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7 **Introduction**
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10 Critical care practitioners commonly add Pressure Support (PS) during extubation readiness
11 tests (ERT) to overcome perceived imposed resistance of the endotracheal tube (ETT) [1-3]. A
12
13 recent survey of pediatric critical care practitioners identified that 94% add PS to Positive End
14
15 Expiratory Pressure (PEEP) when performing ERTs [4]. There is a reluctance to wean patients to
16
17 Continuous Positive Airway Pressure (CPAP) alone (without PS), or to T-piece ventilation,
18
19 hypothesizing patients work harder to breathe on CPAP than they will extubated because of
20
21 small ETT diameters (smaller than the trachea) and imposed resistance from ventilator circuits
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23 [2]. This perception is amplified because the internal diameter of the ETT is often reduced by
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25 secretions or biofilm, further increasing airway resistance [5-7].
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34 However, resistance through a tube depends on flow [8]. Previous in vitro work has
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36 demonstrated that resistance of the smallest ETTs is higher when matched for flow (i.e. 15
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38 L/min through 3.5 ETT has higher resistance than 15 L/min through 6.0 ETT), but children with
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40 3.5 ETT generally breathe at lower flow rates than those who have 6.0 ETT [9]. Several studies
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42 demonstrate that PS or Automatic endotracheal Tube Compensation (ATC) overcome imposed
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44 resistance from the ETT or ventilator circuits [3, 5, 10-13]. However, these studies do not factor
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46 in the resistance of the natural airway, and have not routinely measured the difference
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48 between effort of breathing before and after extubation. There are limited controlled data
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50 demonstrating that ERTs using ATC or PS result in higher rates of successful extubation
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52 compared to CPAP or T-Piece in adults [14-16], and no pediatric data. The increasing use of
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4 non-invasive respiratory support (NIV) after extubation has complicated this picture, as it is
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7 unclear if using NIV after extubation affords patients to be extubated from higher PS because of
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10 a belief that NIV can further lower effort of breathing after extubation.

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12 While we have previously demonstrated that PS underestimates post-extubation effort, our
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14 findings were limited by small sample size, inability to control for post-extubation Upper
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16 Airway Obstruction (UAO), and no subgroup analysis based on ETT size or NIV [17]. We
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18 hypothesized that effort of breathing on CPAP of 5cmH₂O was not higher than post-extubation
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20 values, and that using PS prior to extubation would significantly underestimate post-extubation
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22 effort. We tested this hypothesis by comparing effort of breathing for children before
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24 extubation on PS with PEEP and CPAP alone to effort of breathing post-extubation. We, a-
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26 priori, sought to control for post-extubation UAO and stratify by size of ETT and use of NIV after
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28 extubation. Some of these findings have previously been published in abstract form [18].
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36 **Methods**

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38 We screened intubated children in the pediatric or cardiothoracic intensive care units at
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40 Children's Hospital Los Angeles from July 2012-April 2015. Inclusion criteria: >37 weeks
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42 gestational age - 18 years, intubated \geq 12 hours with planned extubation from 7 am to 5 pm
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44 Monday-Friday. Exclusion criteria: contraindication to an esophageal catheter or Respiratory
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46 Inductance Plethysmography (RIP) bands. Informed consent was obtained from the
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48 parent/guardian, with approval from the Institutional Review Board and the study was
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50 performed in accordance with the ethical standards laid down in the 1964 Declaration of
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4 Helsinki and its later amendments. This was a planned secondary analysis to a study on post-
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7 extubation UAO, which contains further details about methods [19].
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10 Study Protocol

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14 Prior to extubation, each child received an esophageal balloon catheter and had RIP bands
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16 calibrated under tidal breathing on CPAP of 5 cmH₂O [20, 21]. A self-calibrating
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18 pneumotachometer was used prior to extubation to measure peak inspiratory flow during tidal
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21 breathing.
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25 Patients were studied under 4 conditions: Pressure Support 10/PEEP 5 cmH₂O (PS), CPAP 5
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27 cmH₂O (CPAP), and spontaneous breathing, 5 (5min) and 60 (60min) minutes after extubation.
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30 We recorded data during 5 minutes of steady state breathing on each condition, and calculated
31
32 the median Pressure.Rate Product (PRP = peak-to-trough change in esophageal pressure
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34 (cmH₂O) * respiratory rate (breaths per minute)) on each condition. PRP is a surrogate for effort
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36 of breathing [22-25], and unlike work of breathing (calculated from the pressure-volume curve)
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38 PRP does not need to be sub-divided into patient versus ventilator effort. All of the PRP is
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40 attributable to the patient, making it appropriate for comparing patient effort on and off
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42 mechanical ventilation. While Pressure Time Product can also be used, PRP is easier to calculate
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44 and in our experience more robust against artifact, particularly in young children.
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52 If the patient was initiated on non-invasive respiratory support (NIV) within 60 minutes of
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54 extubation (High Flow Humidified Nasal Cannula, Nasal Intermittent Mandatory Ventilation,
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56 CPAP or BIPAP), additional measurements were obtained 15-20 minutes after NIV initiation.
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4 One of two ventilators was used for PS and CPAP: SERVO-I[®] (MAQUET) and AVEA[®]
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6
7 (Carefusion). Automatic endotracheal tube compensation is available on the AVEA[®], but was
8
9 off during measurements.

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12 UAO (either subglottic or supraglottic) was labeled as present after extubation when there was
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15 inspiratory flow limitation on the plot of flow from calibrated RIP and esophageal pressure, as
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18 previously published using this cohort [19]. A priori subgroup analysis was planned excluding
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21 children with post-extubation UAO, stratifying by ETT size. Additional subgroup analysis was
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24 planned for those on NIV within 60 minutes of extubation. Average peak inspiratory flow
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26 (L/min) was measured from spirometry during 2-3 minutes of steady state breathing on CPAP of
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29 5 cmH₂O. Peak inspiratory resistance (cmH₂O/L/sec) was calculated using the patient's ETT size
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31 and measured peak inspiratory flow, using formulae derived from in-vitro studies [9].
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33 34 Analysis

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38 We hypothesized that effort of breathing on CPAP of 5cmH₂O was not higher than post-
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41 extubation effort, and attempting to “overcome endotracheal tube resistance” with PS would
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44 underestimate post-extubation effort of breathing. Secondary objectives were to determine
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47 whether this relationship was confounded by size of ETT, or use of post-extubation NIV. For all
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50 subgroup analyses, we excluded patients with post-extubation UAO because post-extubation
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53 PRP is expected to be significantly higher than pre-extubation PRP, and including these patients
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56 may bias results in favor of our hypothesis. Three ranges of ETT sizes were used for subgroup
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59 analysis (≤ 3.5 mmID, 4.0-4.5 mmID, and ≥ 5.0 mmID), ensuring sufficient patients per group for
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62 analysis. Separate subgroup analysis was performed for patients on NIV within 1 hour of
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4 extubation, comparing pre-extubation PRP with PRP 15-20 minutes after NIV initiation.
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7 Descriptive statistics are reported using median (interquartile range) or number (percent). Box
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9 and whisker plots demonstrate differences in PRP under the 4 study conditions. For analysis,
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11 PRP was log transformed for repeated measures ANOVA with Scheffe's test for post-hoc
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13 multiple comparisons. Statistical analysis was performed in Statistica 10 (Dell, Tulsa, Oklahoma)
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15 and Stata 10 (Stata-Corp, College Station, Texas).
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20 **Results**

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24 A total of 1159 patients were eligible and 409 were included, with a median age of 5 months
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26 (IQR 1, 16) and 55% male. The most common reasons eligible patients were not enrolled were:
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28 (a) parents unavailable for consent and (b) extubation during a night or weekend when the
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30 study team was unavailable. Demographics and reasons for non-enrollment have been
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32 previously published [19]. Approximately half were intubated for cardiac surgery. Median
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34 length of mechanical ventilation was 4.1 days (IQR 1.4, 8.0 days). Thirty-four patients were re-
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36 intubated (8.3%), and 107 (26%) had post-extubation UAO (subglottic or supraglottic) within 1
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38 hour of extubation. One hundred and seven (26%) children were on NIV within 1 hour of
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40 extubation (mostly HFNC).
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48 **Resistance as a function of flow and endotracheal tube size**

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51 For the entire cohort, 209 (51%) had an ETT \leq 3.5 mmID, 143 (35%) were 4.0 or 4.5 mmID, and
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53 57 (14%) were \geq 5.0 mmID. Peak inspiratory flow increased as ETT size increased (Figure 1).
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56 While peak inspiratory resistance was higher for smaller ETTs, median peak inspiratory
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4 resistance was lower in intubated children compared to expected values while extubated, even
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6 with a 3.0 ETT on CPAP of 5 cmH₂O [26-29] (Figure 1). The flow rates used by most infants and
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8 children while intubated on CPAP are in a range in which significant increases in resistance are
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10 not expected (Figure 2).
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15 Effort of breathing before and after extubation

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18 For the entire cohort (n=409), median PRP was 100 (IQR 60,175) on PS 10/5 cmH₂O, 200 (IQR
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20 120,300) on CPAP of 5 cmH₂O, 300 (IQR 150,500) 5 minutes after extubation, and 255 (IQR
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22 175,400) 60 minutes after extubation (Figure 3). PS PRP was lower than CPAP and post
23
24 extubation PRP (multiple comparisons p<0.0001) and CPAP PRP was lower than post extubation
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26 PRP (multiple comparisons p< 0.0001). Restricting the analysis to patients without post-
27
28 extubation UAO (n=302), there were similar trends in median PRP values as a function of level
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30 of support, with slightly lower values for the post-extubation PRP (Figure 4). Again, PS PRP was
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32 lower than CPAP and post extubation PRP (multiple comparisons p<0.0001) and CPAP PRP was
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34 lower than post extubation PRP (multiple comparisons p< 0.02).
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43 Excluding patients with UAO, 5 minutes after extubation individual patient's PRP was a median
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45 25% (IQR -5%, 72%) higher than CPAP values and 147% (67, 267%) higher than PS values. By 60
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47 minutes after extubation, individual patient's PRP remained a median 17% (-20%, 60%) higher
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49 than CPAP values, and 126% (40%, 233%) higher than PS values.
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54 Subgroup Analysis: Endotracheal tube size and NIV

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4 We subsequently sub-grouped children without UAO (n=302) by size of ETT. The patterns were
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6 the same for endotracheal tube size groupings of ≤ 3.5 mmID (n=152, Figure 5a), 4-4.5 mmID
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8 (n=102, Figure 5b), and ≥ 5.0 mmID (n=48, Figure 5c). Regardless of ETT subgrouping, PS PRP
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10 was less than CPAP and post-extubation PRP (all multiple comparisons $p < 0.01$), while within
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12 each ETT subgroup CPAP PRP was similar to post extubation PRP (all multiple comparisons $p >$
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17 0.05).

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20 When examining the cohort of 107 children who were placed on NIV within 1 hour of
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22 extubation, 26 had post-extubation UAO. In the remaining 81 patients (2 BiPAP, 74 HFNC, 5
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24 Nasal IMV) the median PRP on PS 135 (IQR 90,220) was significantly lower than PRP on either
25
26 CPAP 270 (200,400) prior to extubation or post-extubation on NIV 320, (220, 420) (multiple
27
28 comparisons $p < 0.0001$). However there was no difference in PRP on CPAP prior to extubation
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30 and PRP post-extubation on NIV (multiple comparisons $p=0.8$).

31 32 33 **Discussion**

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36 We have demonstrated that using PS during ERTs significantly under-estimates post-
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38 extubation effort of breathing in children, regardless of ETT size or use of non-invasive
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40 respiratory support (mostly HFNC) after extubation. Effort of breathing on CPAP of 5 cmH₂O
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42 may still under-estimate post-extubation effort, although on average it is 15-25% lower than
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44 post-extubation, and appears similar to effort of breathing on NIV after extubation. In other
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46 words, if the patient cannot tolerate CPAP 5 cmH₂O alone prior to extubation, they are unlikely
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48 to do well after extubation, even with NIV. While inspiratory resistance increases as ETT size
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50 decreases, prior to extubation children are breathing with flow rates where predicted
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4 inspiratory resistance is actually below extubated values [26-29]. Therefore, we have found no
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7 evidence to support adding any amount of PS to “reduce imposed work of breathing” during
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10 ERTs in children, regardless of the ETT size.

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13 Extubation failure rates are generally low in children, on average 8% [30]. Moreover,
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15 nearly half of extubation failures are from post-extubation UAO [19, 20, 30], which may be
16
17 difficult to predict during standard ERTs [31-33]. With < 5% of patients failing extubation from
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19 causes other than UAO, it is difficult to demonstrate that one mode of ERT results in lower re-
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21 intubation rates. This low extubation failure rate has perhaps lulled pediatric practitioners into
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23 a sense of security about using PS. If < 5% of patients fail extubation when PS is used, why
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25 should we be more restrictive about whom we extubate by mandating ERTs be done on CPAP.
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32 Perhaps our extubation failure rates are too low. This is supported by the > 50% success
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34 rate of unplanned extubations in pediatrics [30], highlighting many patients can be extubated
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36 well before we recognize they are ready. Daily SBTs have been advocated as part routine
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38 practice, but fewer than 25% of pediatric practitioners use them [4]. Perhaps patients can be
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40 successfully extubated sooner [2, 34] if we routinely perform SBTs earlier in the mechanical
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42 ventilation course [8]. Once we start doing this, based on the physiologic data presented in this
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44 paper, it is possible we would have higher extubation failure rates if effort of breathing on PS is
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46 used during ERTs.
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53 From our data, we believe CPAP of 5 cmH₂O alone is sufficient for ERTs in most children,
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55 given effort of breathing after extubation is generally 15-25% higher than values on CPAP of 5
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57 cmH₂O, and is similar to what is provided with NIV post-extubation. While our previous work
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4 did not find major differences in effort of breathing between CPAP and T-piece [17], some
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6 patients may warrant further reductions to T-piece ventilation, or warrant longer SBTs, such as
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8 those with neuromuscular disease. In addition, some patients warrant CPAP > 5 cmH₂O during
9
10 SBTs, such as children with obesity. When extubated, these children may use other mechanisms
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12 to maintain normal trans-pulmonary pressures at end exhalation, and weaning to CPAP of 5
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14 cmH₂O may result in more alveolar collapse than they would have extubated. Ultimately, the
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16 duration of the SBT and level of end expiratory pressure (CPAP or T-piece) should be
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18 determined by an experienced provider mindful of the expected pathophysiology of the
19
20 patient. However, we believe our data support PS should not be added to this end expiratory
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22 pressure, even when extubation is planned to HFNC, as CPAP prior to extubation still best
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24 estimates post-extubation effort. Because of limited number of patients on non-invasive CPAP
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26 or BiPAP post extubation, it is unclear if the same holds when extubating to these modes of
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28 non-invasive positive pressure.
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39 There are several limitations to our study, despite its prospective nature. First, it is
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41 single institution, although we believe generalizability is high given this is a physiologic study.
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43 Second, we obtained a convenience sample because we did not study patients on nights or
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45 weekends, or patients who did not consent. This may introduce a selection bias on types of
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47 patients enrolled. Moreover, these patients were intubated for many reasons (cardiac surgery,
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49 pulmonary disease etc...) and independent of work of breathing, ERTs may use different criteria
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51 based on patient factors. Third, we excluded patients with post-extubation UAO using an
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53 “objective” UAO parameter we have previously reported, but there still may be some
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4 imprecision in labelling patients with UAO. Fourth, we had only 3 patients with size 2.5 mmID
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7 ETTs, precluding subgroup analysis. Our findings may not generalize to premature or small for
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9 gestational age children with 2.5 mmID ETT. Fifth, NIV was mostly HFNC, and the results may
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11 differ with mask CPAP or BiPAP. Unfortunately, this represents institutional preference for
12
13 HFNC as we had only 2 patients without UAO on BiPAP within 60 minutes of extubation. Sixth,
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15 our illustrative calculations of airway resistance were based on measured patient flow with
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17 bench models of ETTs to determine resistance. Actual resistance in vivo could be lower because
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19 of less heat loss when connected to the patient versus exposed to atmosphere, or higher if the
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21 internal diameter of the ETT is reduced from secretions or biofilm. Unfortunately we did not
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23 measure resistance as part of the study, and it is difficult to attribute measured resistances in
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25 vivo to just the upper airway. To that end, there are few published norms for upper airway
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27 resistance in spontaneously breathing infants and children, and there are differences between
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29 peak resistance (used in our study) and mean resistance. This makes precise definitions of
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31 normal values of upper airway resistance complicated [26, 27, 29]. Nevertheless, this will not
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33 influence the effort of breathing results, which clearly illustrate that effort of breathing on CPAP
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35 is lower than when extubated for most patients, regardless of resistance. Seventh, we used
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37 two different ventilators which may deliver CPAP and PS in different ways. Finally, this study
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39 did not examine re-intubation because of the relatively few cases of re-intubation from causes
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41 other than UAO.
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54 In conclusion, Pressure Support should not be added to CPAP to overcome “imposed work of
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56 breathing” from the ETT during SBTs or ERTs in children, regardless of the size of the ETT. Using
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Pressure Support greatly under-estimates post-extubation effort of breathing (125-150% under-estimation), while effort of breathing on CPAP of 5cmH₂O alone may still under-estimate post-extubation effort of breathing by 15-25%.

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Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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4 **Figure Legends**
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11 **Figure 1:** Peak inspiratory flow (dotted) (L/min) and Peak Inspiratory resistance (solid)
12 (cmH₂O/L/sec) as a function of endotracheal tube size. Note, 2.5 endotracheal tube was
13 excluded from graph because there were only 3 measurements. 6.0 endotracheal tube includes
14 all those with ETT ≥ 6.0 mmID. While resistance is nearly 3 fold higher for 3.0 ETT compared to
15 6.0 ETT, these values are lower than peak resistance with a natural airway.
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25 **Figure 2:** Range of peak resistance (cmH₂O/L/sec) expected based on actual patient peak
26 inspiratory flow (L/min), superimposed on bench model of ETT resistance from Manczur et al.
27 Note that for patients with small endotracheal tubes, flow is lower, predicting resistances that
28 are still lower than expected with a natural airway.
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36 **Figure 3:** PRP as a function of pre-extubation support (PS= Pressure Support of 10/PEEP of 5
37 cmH₂O), CPAP (Continuous Positive Airway Pressure=5 cmH₂O), and spontaneously breathing 5
38 and 60 minutes post extubation, for the entire cohort of 409 children. All PRP values were
39 significantly different than one another, with PRP PS < PRP CPAP < PRP post-extubation (log
40 transformed PRP, ANOVA p<0.0001, multiple comparisons all p0.0001).
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50 **Figure 4:** PRP as a function of pre-extubation support (PS= Pressure Support of 10/PEEP of 5
51 cmH₂O), CPAP (Continuous Positive Airway Pressure=5 cmH₂O), and spontaneously breathing 5
52 and 60 minutes post extubation, excluding the 107 patients with post-extubation UAO. All PRP
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4 values were significantly different than one another with PRP PS < PRP CPAP < PRP post-
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7 extubation (log transformed PRP, ANOVA p<0.0001, multiple comparisons all p< 0.02).
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10 **Figure 5 a-c:** PRP as a function of pre-extubation support (PS= Pressure Support of 10/PEEP of 5
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12 cmH₂O), CPAP (Continuous Positive Airway Pressure=5 cmH₂O), and spontaneously breathing 5
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14 and 60 minutes post extubation, excluding the 107 patients with post-extubation UAO,
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16 stratified by endotracheal tube size. The patterns were the same for endotracheal tube size
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18 groupings of ≤ 3.5 mmID (n=152, a, top left), 4-4.5 mmID (n=102, b, bottom left), and ≥ 5.0
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20 mmID (n=48, c, top right). Regardless of endotracheal tube subgrouping, PS PRP was less than
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22 CPAP PRP (log transformed PRP, ANOVA p<0.0001, multiple comparisons all p< 0.01). CPAP PRP
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24 was similar to post-extubation PRP (p>0.05).
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