Comparison of Collapsibility of the Human Upper Airway During Anesthesia and During Sleep

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ABSTRACT

Background The propensities for the upper airway (UA) to collapse during anesthesia and sleep are related, although much of our understanding of this relationship has been inferred from clinical observation and indirect measures such as the apnea hypopnea index. The aim of this study was to use an identical, rigorous, direct measure of UA collapsibility (UA critical closing pressure (Pcrit)) under both conditions to allow the magnitude of UA collapsibility in each state to be precisely compared.

Methods Ten subjects (8 males, 2 females; mean±SD; age 40.4±12.1years; body mass index 28.5±4.0kg.m^{-2}) were studied. Pcrit was measured in each subject on separate days during: (i) propofol anesthesia; and (ii) sleep.

Results Pcrit measurements were obtained in all 10 subjects during non-rapid eye movement (NREM) sleep and, in 4 of these 10 subjects, also during rapid eye movement (REM) sleep. Pcrit during anesthesia was linearly related to Pcrit during NREM sleep (r=0.64 [95%CI: 0.02, 0.91], n=10, *p*=0.046) with a similar tendency in REM sleep (r=0.80 [95%CI: -0.70, 0.99], n=4, *p*=0.200). However, Pcrit during anesthesia was systematically greater (indicating increased collapsibility) than during NREM sleep (2.1±2.2 vs. -2.0±3.2cmH_2O respectively, n=10; within-subject mean difference 4.1cmH_2O [95%CI: 2.32, 5.87], *p*<0.001) with a similar tendency during REM sleep (1.6±2.4 vs -1.9±4.3cmH_2O respectively, n=4; unadjusted difference 3.5cmH_2O [95%CI: -0.95, 7.96], *p*=0.087).

Conclusion These results demonstrate that the magnitude of UA collapsibility during

anesthesia and sleep are directly related. However, the UA is systematically more collapsible during anesthesia than sleep, suggesting greater vulnerability to UA obstruction in the anesthetized state.

KEY POINTS

Question: Are upper airway (UA) collapsibilities during anesthesia and sleep related?

Findings: Using the same metric, Pcrit, under each condition we have demonstrated that UA collapsibility during propofol anesthesia and sleep are correlated but that the UA is systematically more collapsible during anesthesia.

Meaning: Collapsibilities of the UA during anesthesia and sleep are related but systematically greater during anesthesia, suggesting that individual vulnerability to UA obstruction in one state indicates vulnerability in the other, but that the UA is particularly prone to obstruction during anesthesia.

Key words: anesthesia; sedation; propofol; Pcrit; sleep; non-rapid eye movement sleep; rapid eye movement sleep.

INTRODUCTION

Indirect comparisons suggest that the tendencies to upper airway (UA) obstruction during anesthesia and sleep are related.[1] In both states the transition to unconsciousness is associated with a decrease in UA dilator muscle activity and an increase in pharyngeal collapsibility,[2,3] the degree of which varies between individuals and depends on several factors including anatomy and posture.[4] However, while a general relationship is evident between the degree of UA collapsibility in both states,[1] anesthesia appears to be associated with more profound collapsibility, as evidenced by the high occurrence of UA obstruction in supine anesthetized subjects (if a mechanical aid to maintain patency is not deployed), including in individuals without obstructive sleep apnea (OSA).[1] Furthermore, anesthesia abolishes the arousal responses that protect the sleeping subject from asphyxia in the case of UA obstruction during sleep.

To date, much of our understanding of the relationship in UA behavior between anesthesia and sleep has been inferred[5,6] or based on relating an indirect measurement of UA collapsibility during sleep (the apnea hypopnea index (AHI)) to a direct measure of UA collapsibility during anesthesia (e.g. UA critical closing pressure (Pcrit), a rigorous direct measure of UA collapsibility).[1]

The lack of a direct comparison of UA collapsibility between the states, using an identical, rigorous assessment of UA collapsibility (such as Pcrit) in the same subjects in both states, is

a deficiency. It leaves the bedrock assumption of a relationship in UA collapsibility between the states (that underpins a large literature relating to sleep disordered breathing and anesthesia) inadequately defined. Defining this relationship is important in determining how directly information regarding UA behavior in one state can be transposed to the other. For example, it is remains unclear how accurately observation of UA behavior during drug induced sedation endoscopy (DISE),[7] a procedure commonly undertaken to inform surgery for OSA, relates to behavior during sleep.[8]

The reason for this deficiency is likely to relate to the logistic and technical challenges in making Pcrit measurements in the same individuals in both states. The aim of this study was to address this gap in knowledge by comparing, for the first time, Pcrit in the same individuals during both deep sedation/anesthesia and sleep. We hypothesized that the degree of UA collapsibility in each state would: (i) be related; and (ii) would be greater during anesthesia than during sleep.

MATERIALS AND METHODS

Subjects

All subjects provided written informed consent prior to participation in the study, which was approved by the Human Research Ethics Committee at Sir Charles Gairdner Hospital (SCGH 2009-037). The present observational study is a component of a larger study examining the effect of head posture on the human UA during sleep, sedation and anesthesia in participants with and without OSA.

Subjects with and without OSA were recruited by advertisement in a hospital sleep clinic or the community. Subjects were excluded if they were morbidly obese (body mass index (BMI)>35kg.m^{-2}) or had a history of cardiovascular or respiratory disease or other significant medical co-morbidity.

Experimental Procedures

Study Design

On separate occasions (at least 48 hours apart) subjects underwent: (i) a standard in-laboratory diagnostic sleep study to establish the baseline level of sleep disordered breathing ("*Diagnostic sleep study*"); (ii) a second overnight sleep study to measure UA collapsibility during NREM and REM sleep ("*Research sleep study*"); and (iii) a brief daytime study to measure UA collapsibility during general anesthesia ("*Anesthesia study*"). In all but one instance (Subject #1) the *Research sleep study* preceded the *Anesthesia study*.

Diagnostic Sleep Study

In-laboratory polysomnography was undertaken according to American Academy of Sleep Medicine recommendations.[9] Data were collected on a computerized data acquisition system (E-series, Compumedics, Abbotsford, Victoria, Australia). Standard criteria were used to determine AHI in each subject.[9]

Research Sleep Study

Subjects arrived 2 hours before their usual bedtime to be instrumented as described for the baseline *Diagnostic sleep study*. Topical lignocaine spray was applied to the nares and posterior-pharynx and a pressure-tipped catheter (Millar MPC-550, Millar Instruments, Houston TX, USA) was inserted via the nares to the level of the epiglottis. Subjects were instrumented for Pcrit assessment (see below, *Specific Techniques)*.

Approximately 30 minutes prior to lights out subjects were administered a hypnotic (10-20mg Temazepam) to aid with wake-sleep transition (n=9). CPAP was applied to ensure UA patency during sleep and to facilitate assessment of Pcrit. Head and body posture were carefully controlled during all measures of UA collapsibility. Specifically, subjects were positioned supine with the head in a neutral position (Frankfort plane perpendicular to the horizon) on a modified Shea headrest. An infrared camera enabled visual confirmation of head posture throughout the study, with adjustments made by intervention of the

attending scientific staff where neutral posture was lost. Pcrit measurements were made (see below, *Specific Techniques*) during periods of stable NREM sleep and, where possible, REM sleep.

Anesthesia Study

No premedication was administered. Standard monitoring was applied, and a vein cannulated. Subjects were instrumented for Pcrit assessment (see below, *Specific Techniques*) including application of CPAP administered via a nasal mask with the mouth occluded and head supported in a neutral posture using a Shea headrest, according to our previously described techniques.[2,4] Topical lignocaine spray was applied to the nares and posterior-pharynx and an esophageal-pharyngeal pressure transducer catheter (Gaeltec, CTO-4; Dunvegan, Isle of Skye, Scotland) inserted via the nares as previously described.[4,10] Anesthesia was then induced with propofol (Diprivan, AstraZeneca, Alderley Park, Cheshire, UK) administered via a target-controlled infusion system (Diprifusor, Alaris PK, Cardinal Health, Switzerland).[11,12] Anesthetic depth was monitored using the bispectral index score (BIS) derived from a frontal electroencephalogram (Aspect Medical Systems, Newton, MA). The propofol infusion rate was adjusted to attain an anesthetic depth associated with a BIS≤50. Pcrit measurements were performed only when stable breathing was observed.

Specific Techniques

Evaluation of Upper Airway Collapsibility – Pcrit technique

Measures of UA collapsibility were obtained as previously described.[1,4,13] Briefly, stable breathing was established with a CPAP level ("maintenance pressure") sufficient to abolish inspiratory flow limitation (the presence of which was recognized by appearance of a plateau in the inspiratory flow profile).[13,14] Nasal mask pressure (Pmask) was controlled using a custom made device (Resmed, Bella Vista, Australia) capable of delivering both positive and negative pressures. Pmask was reduced from maintenance pressure to a range of positive and, where necessary, negative pressures to induce variable degrees of inspiratory flow limitation over a 5-breath sequence before return to maintenance pressure (Figure 1A). A minimum of three pressure drops to levels associated with flow limitation were obtained, with care taken to get close to zero flow with at least one of the drops during this sequence. Pcrit was derived from the extrapolation of the linear Pmask - plateau flow rate relationship obtained during these pressure drops to zero flow. Pmask at this point = Pcrit (Figure 1B). Where multiple pressure drop sequences were used to determine Pcrit under a given set of conditions, the average Pcrit value was used for analysis. If a momentary arousal occurred during the first 3 breaths of a 5-breath pressure drop sequence or at any stage during the sequence then pressure was restored and the data from that pressure drop were excluded from analysis, with further pressure drops only initiated after restoration of stable sleep and breathing. However, if a momentary arousal occurred during either of the last two breaths of the sequence then breaths 3 and/or 4 were used for analysis. If the subject awoke (>15 seconds of wakeful encephalographic activity)

at any stage during the pressure drop sequence it was terminated and re-initiated after restoration of stable sleep and breathing.

Pmask, esophageal/epiglottic pressure and flow were recorded continuously on a specific data acquisition-analysis system (model 16s; ADInstruments, Sydney, Australia) as well as on the sleep data acquisition system (E-series, Compumedics, Abbotsford, Victoria, Australia).

Statistical Analyses

Where more than one value for Pcrit was obtained from a subject in a particular state the average value was used. Mean±standard deviation (SD) is reported for Pcrit in each state and for the within-person difference between anesthesia and NREM, anesthesia and REM, and NREM and REM states. One-sample, 2- tailed t-tests were used to examine whether the within-subject differences of Pcrit between states were significantly different from zero. Linear regression models were used to estimate the relationship between Pcrit measured during different states. Pearson product-moment correlations (r), and corresponding *p*-values testing whether the correlation differed from zero, are reported. A Bland Altman plot was used to display the difference between states across the range of Pcrit values.

The relationships between Pcrit values obtained during both NREM and REM sleep with baseline AHI values were estimated, using Pearson product-moment correlations to examine the strength of the linear association between these direct and indirect measures

of airway collapsibility. The correlation of the magnitude of the within-subject differences in Pcrit between anesthesia and NREM sleep with baseline AHI was also examined to investigate whether this difference was influenced by OSA severity.

Data were analyzed using the R environment for statistical computing.[15]

Sample Size

Based on previous experience with similar physiology studies we aimed to recruit 10-15 subjects. Thirteen subjects were recruited between November 2012 and September 2013: two were excluded due to an inability to tolerate a nasal mask during sleep; one was excluded because of recurring arousal from sleep during the first 1-2 breaths whenever mask pressure was decreased from the maintenance pressure. Based on reproducibility data from Ong et al.[16], a sample size of 9 was sufficient to detect a clinically meaningful difference in Pcrit (3.3±3.0cmH_2O) between 2 states with 80% power at the 0.05 significance level using a 1-sample, 2-tailed t-test.

RESULTS

Subject and Study Characteristics

Data from 10 subjects were included in the analysis (8 males, 2 females; age 40.4±12.1years; and BMI 28.5±4.0kg.m^{-2}, see Table 1). Inclusion of participants from the sleep clinic and general community ensured a range of AHI scores evident on the *diagnostic sleep study* undertaken following recruitment (1.3 to 44.0events.hr^{-1}). Mean AHI for the 10 subjects was 16.6±15.3events.hr^{-1}. The mean CPAP level required to maintain airway patency during the *anesthesia study* was 12.05±2.33cmH_2O which was significantly greater than that required during NREM sleep (4.23±2.58cmH_2O, p<0.001) and REM sleep (6.38±2.44cmH_2O p=0.002). During the *anesthesia study* it took 7.17±7.08 minutes to complete the Pcrit measurements. Propofol effect site concentration for the 10 subjects ranged from 3.0 to 5.5μg.ml^{-1}.

Upper airway collapsibility

Between 1 and 3 separate measurements of Pcrit were obtained in each subject during NREM sleep (mean 1.5±0.7 measurements per subject, n=10), with each measurement being derived from between 3 and 11 pressure drops. A minimum of 3 pressure drops sufficient to produce varying degrees of flow limitation were used to determine each Pcrit measurement, based on previously described methods.[4,13,17] An average of 2.4±0.5, 2.4±0.4 and 2.7±0.3 breaths were included in each pressure drop during anesthesia, NREM sleep and REM sleep respectively. Pcrit was able to be obtained during REM sleep in 4 subjects,

with between 1 and 4 separate measurements of Pcrit obtained (mean 2.0±1.4 measures per subject, n=4). A single Pcrit measurement was obtained in all subjects during general anesthesia – this was considered adequate given the highly reproducible measurement conditions including well-controlled head, jaw and body posture and the absence of arousals during the measurement of Pcrit.[4] Individual Pcrit data are represented graphically in Figure 2.

The relationships between Pcrit during anesthesia and either sleep state are illustrated in Figure 3. Pcrit during NREM sleep was linearly related to Pcrit during anesthesia (r=0.64 [95%CI: 0.02, 0.91], n=10, p=0.046). However, Pcrit during NREM sleep was systematically lower than that during anesthesia (-2.0±3.2 vs. 2.1±2.2cmH_2O, respectively, n=10; unadjusted mean difference 4.1cmH_2O [95%CI: 2.32, 5.86], p<0.001), indicative of a more collapsible UA under anesthesia. For REM sleep, the available number of observations was small and neither significant linear relationships between Pcrit during REM sleep and during anesthesia (r=0.80 [95%CI: -0.70, 0.99], p=0.200; n=4) nor differences in their values (-1.9±4.3 vs. 1.6±2.4cmH_2O, respectively, n=4; unadjusted mean difference 3.5±2.8cmH_2O [95%CI: -0.95, 7.96]); p=0.087) were observed. For the 4 subjects in whom Pcrit measurements were completed in both NREM and REM sleep, their values were similar in either state (within-subject mean difference -0.7cmH_2O [95%CI: -2.40, 0.91]; p=0.247) (Figure 3).

Pcrit during both NREM and REM sleep, obtained during the *research sleep study*, were linearly related to baseline AHI determined on the *diagnostic sleep study* (r=0.69 [95%CI: 0.11, 0.92], p=0.027, n=10 and r=0.98 [95%CI: 0.23, 1.00], p=0.025, n=4, respectively).

There was also a linear relationship between this baseline AHI and the magnitude of the difference in Pcrit between anesthesia and NREM sleep (r=-0.75 [95%CI: -0.94, -0.22]; p=0.013), with lesser differences at higher AHI. At AHI values <25events.hr^{-1} these differences were consistently greater than 3.5cmH_2O. In the two subjects with most severe OSA, subjects #1 (AHI=35 events.hr^{-1}) and #10 (AHI=44 events.hr^{-1}), these differences were 1.1 and -0.1cmH_2O respectively (Table 1).

DISCUSSION

Measurement of Pcrit during both general anesthesia and sleep allows, for the first time, a direct comparison between stability of the human UA in these two states. This study reveals that the magnitude of individual UA collapsibilities is correlated between the states but is systematically greater during anesthesia than sleep. Notably, sleep Pcrit – a direct measure of UA collapsibility – was correlated with AHI, a measure of OSA severity.

The nature of this relationship in UA collapsibility between anesthesia and sleep appeared relatively unaffected by sleep stage, with the magnitude of difference between Pcrit during anesthesia and sleep being similar for both NREM and REM sleep. While the small number of measurements able to be obtained during REM limits the capacity to make comparisons between these sleep stages, the lack of difference in Pcrit between REM and NREM is consistent with other studies with larger sample sizes.[16] Given the more variable circumstances of sleep, with its potential for subtle state and posture changes, we obtained several Pcrit values in each subject for each sleep state using the average value for subsequent analysis. Only one measurement of Pcrit was required during anesthesia given the relative stability of state and posture during it.

Although correlated, Pcrit was systematically greater during anesthesia than sleep, indicative of a more collapsible UA in that state. Specifically, during anesthesia mean Pcrit was approximately 4cmH_2O greater than that observed during either NREM or REM sleep,

which is a meaningful difference.[16,18] Although variable in degree, the difference was evident across the range of Pcrit values examined (Figure 3). However, when the differences in Pcrit values between anesthesia and NREM sleep were examined in relationship to baseline AHI, they were found to be greatest in those with low AHIs (indicative of nil or milder OSA) with little difference in individuals with severe OSA (Table 1). This suggests that while those with severe OSA are highly vulnerable to obstruction in either state, individuals with less problematic sleep may still obstruct during anesthesia. These observations are consistent with previous observations that the propensity of the unprotected UA to obstruct is common during anesthesia but less so during sleep.[1]

Several potential mechanisms could account for this difference including state-related differences in pharyngeal muscle dilator activity, head and/or body posture and lung volume. We have previously shown that propofol anesthesia at a level sufficient to decrease the BIS to <50 is accompanied by marked muscle hypotonia.[2,11] While we did not measure it in the present study, it is plausible that UA muscle activation is less during anesthesia than sleep, particularly NREM sleep where persisting skeletal muscle activity is evident. However, residual UA muscle activity is relatively low following sleep onset.[3] Furthermore, the use of CPAP during the Pcrit technique induces a hypotonic state in the UA muscles, so when applied during sleep should induce a comparable level of UA muscle activity to that during anesthesia. Indeed, data from our group[16] and others[17,19,20] have demonstrated similar Pcrit values during NREM and REM sleep, despite REM sleep being

accompanied by profound skeletal muscle hypotonia. Thus, we believe it unlikely that differences in UA muscle activation account for the difference in collapsibility observed between anesthesia and sleep in the present study.

Other influences on UA collapsibility include head posture and body posture. Supine sleep is associated with a higher Pcrit and more severe OSA than that observed in the lateral posture.[16,19-21] Head flexion relative to extension has also been shown to increase UA collapsibility.[4] However, head and body posture were tightly controlled in the present study and are therefore unlikely to explain the observed differences in Pcrit between anesthesia and sleep.

Lung volume, specifically functional residual capacity (FRC), is also an important contributing factor to UA collapsibility.[22] A lower FRC relative to wakeful levels, as occurs during both sleep and anesthesia, decreases UA longitudinal traction forces and increases pressure gradients at the thoracic inlet, increasing propensity for UA collapse.[22-25] Given the dose-related relaxant effect of propofol on skeletal muscles,[26,27] including respiratory and chest wall muscles, it is possible that FRC is lower during anesthesia than sleep. Indeed, dose-related decreases in ventilation occur with increasing anesthetic depth; deep anesthesia can induce profound hypoventilation in spontaneously breathing healthy subjects, of a degree not seen during natural sleep. This suggests that anesthesia has a substantially greater potential depressant effect on respiratory/chest wall muscle activation, likely resulting in a

lower FRC and associated greater increase in UA collapsibility in this state than during sleep. However, because we did not directly measure lung volume during either sleep or anesthesia, this mechanism remains speculative.

Our findings are relevant to the use of drug induced sedation to simulate natural sleep during endoscopic evaluation for UA surgery for OSA (i.e. drug induced sedation endoscopy, DISE). Our data suggest that despite a correlation between UA collapsibility during propofol anesthesia (BIS<50) and sleep, the states are not entirely equivalent with the UA likely to collapse more readily during deep sedation/anesthesia than during sleep.

There are potential limitations to this study. Firstly, nine of the ten subjects were administered a hypnotic (10-20mg of Temazepam) to assist with wake-to-sleep transition. However, where such modest doses of benzodiazepines are used UA collapsibility is similar to that seen in natural sleep[16,28] and AHI, oxygen desaturation index and respiratory disturbance index do not change significantly.[29-31] Consistent with this, the one subject who did not receive Temazepam in the present study behaved comparably to those that did. Secondly, supplemental oxygen was applied during anesthesia but not the sleep studies. However, hyperoxia has been shown to have little impact on UA collapsibility[32] although hypoxia marginally increases UA collapsibility. However, as UA patency was maintained with therapeutic CPAP for most of each study significant desaturation was not observed during these studies. Thirdly, low subject numbers in REM sleep (n=4), because of the well-

recognized difficulties in making Pcrit measurements in this sleep stage due to unstable breathing patterns and arousals when attempting them,[33] make it prudent to interpret analyses from this state with caution, although they are consistent with behavior during NREM sleep. Fourthly, measures of lung volume and chest wall muscle and UA dilator muscle activity in both states would have allowed the mechanisms behind the observed changes in UA collapsibility to have been more directly addressed. Finally, for logistical reasons in all but one instance (subject #1) the research study preceded the anesthesia study, rather than the order being randomized.

In summary, this study shows that the propensities for the UA to collapse during general anesthesia and sleep are related but that the UA is systematically more collapsible during anesthesia than sleep. This finding is relevant to DISE, which is widely used to evaluate patients in a state that approximates natural sleep, as the states do not appear to be entirely equivalent in respect to UA collapsibility. More generally, the findings suggest that anesthesia is a “worst case” scenario for maintenance of UA patency. Accordingly, while patients with OSA appear to be at particular risk, patients with apparently normal UA function during sleep are not exempt from obstruction under the influence of anesthetic and sedative drugs.

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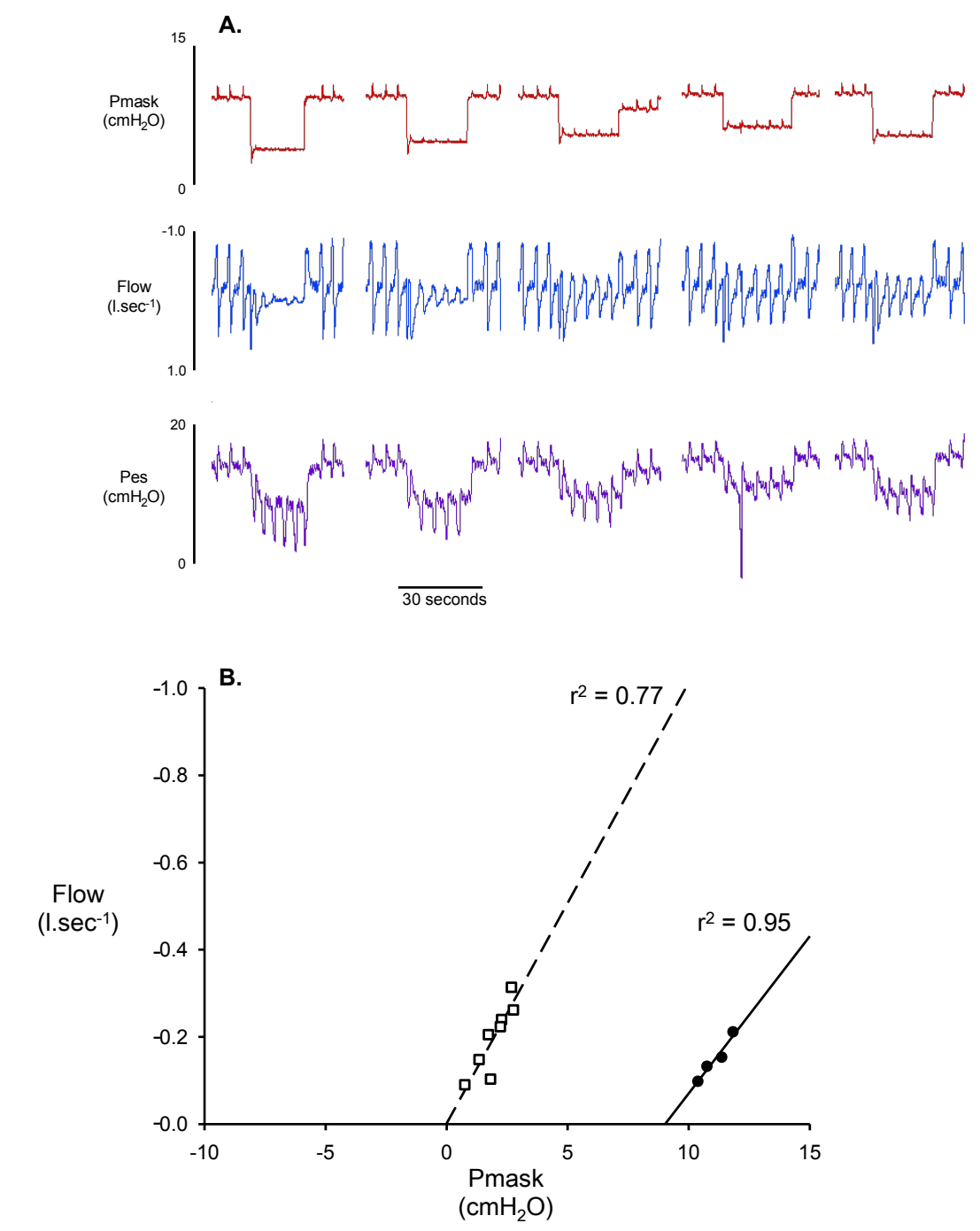
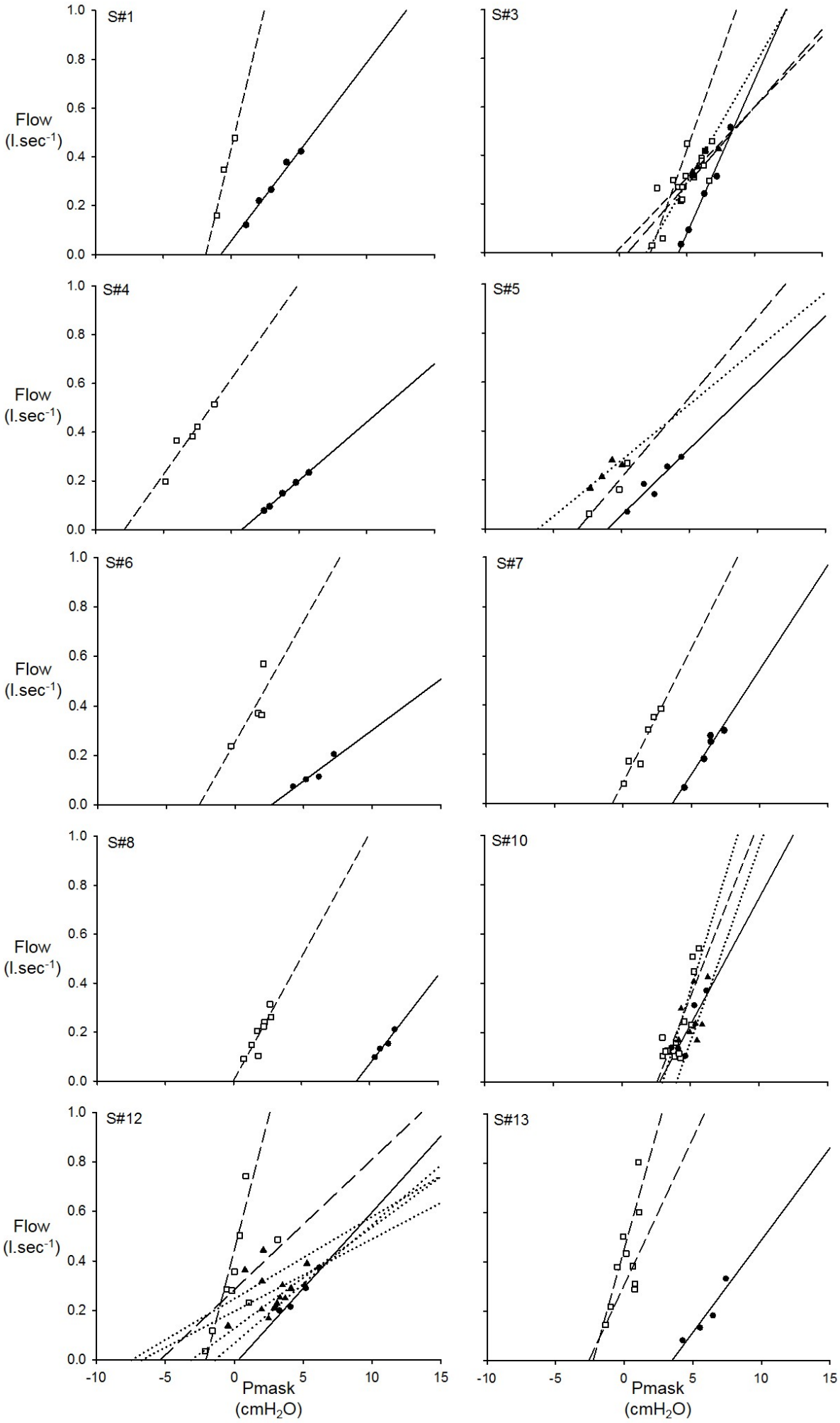
FIGURE LEGENDS

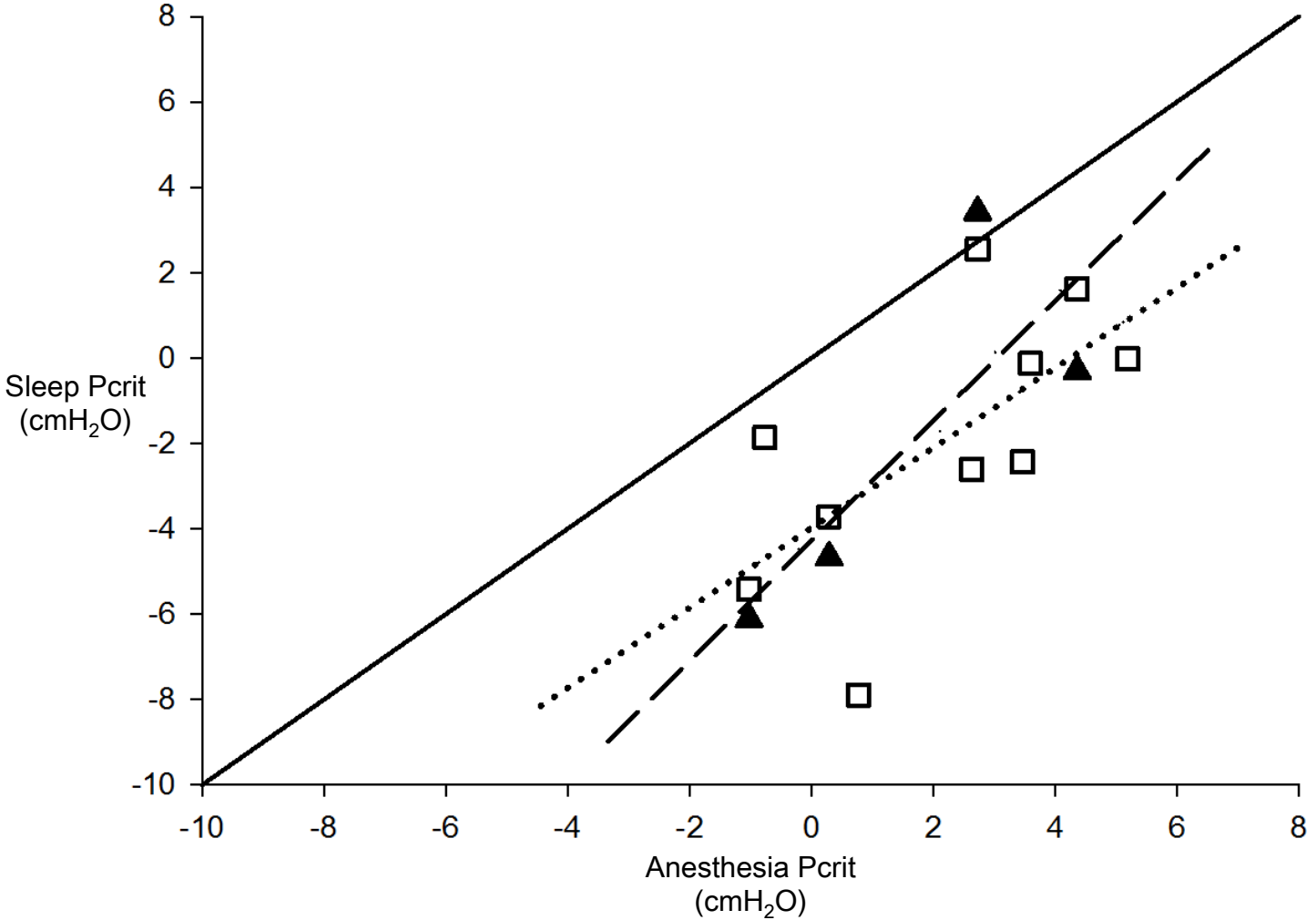
Figure 1 A. Polygraph example from one subject during general anesthesia showing a sequence of drops in mask pressure (Pmask) with accompanying decreases in respiratory flow rates. Note the decrease in peak inspiratory flow rates and flattening of the flow profile observed with the flow limitation induced by these changes. Greater decrements in Pmask are accompanied by greater decrements in peak inspiratory flow. Respiratory effort persists as indicated the negative swings in esophageal pressure (Pes). **B**. The relationship between Pmask and inspiratory flow (Flow) during flow limitation induced by varying decreases in Pmask is illustrated for one subject during anesthesia (*closed circles & solid line*, Pcrit = 8.1cmH_2O) and during sleep (*open squares & dashed line*, Pcrit = 0cmH_2O) and. Note the linear relationship between Pmask and Flow for these flow limited breaths. The pressure at which this relationship interpolates on zero flow is called Pcrit. A more negative Pcrit indicates a less collapsible airway.

Figure 2. Individual Pcrit data during general anesthesia, NREM and REM (n=10). The relationship between mask pressure (Pmask) and peak inspiratory flow (Flow) during flow limitation induced by varying decreases in Pmask is illustrated for all subjects during anesthesia (*closed circles & solid lines*), NREM sleep (*open squares & dashed lines*) and where available REM sleep (*closed triangles & dotted lines*). A more negative Pcrit indicates a less collapsible airway.

Figure 3. Linear regressions of Pcrit measured during general anesthesia versus Pcrit measured during NREM sleep (*open squares & dashed lines*, r=0.64 [95%CI: 0.02, 0.91], n=10; *p*=0.046) and REM sleep (*closed triangles & dotted lines*, r=0.80 [95%CI: -0.70, 0.99], n=4; *p*=0.200). Four subjects have both NREM and REM data available. The line of identity is represented by a solid line.


A.
15
Pmask
(cmH2O)
0
-1.0
Flow
(l.sec-1)
1.0
20
Pes
(cmH2O)
0
30 seconds
B.
-1.0
-0.8
-0.6
-0.4
-0.2
-0.0
Flow
(l.sec-1)
r2 = 0.77
r2 = 0.95
-10
-5
0
5
10
15
Pmask
(cmH2O)


S#1
S#3
S#4
S#5
S#6
S#7
S#8
S#10
S#12
S#13
Flow (l.sec-1)
Pmask (cmH2O)
1.0
0.8
0.6
0.4
0.2
0.0
-10
-5
0
5
10
15


8
6
4
2
0
-2
-4
-6
-8
-10
Sleep Pcrit
(cmH2O)
-10
-8
-6
-4
-2
0
2
4
6
8
Anesthesia Pcrit
(cmH2O)