Section 12: Substantial Data Equivalence Discussion

Laboratory Studies comparing OptiPillows EPAP Mask versus the predicate device Theravent

We have completed 4 types of bench top studies in the laboratory to substantiate the equivalence to the predicate device. EPAP devices have been tested in clinical trials and found to be safe and effective (references). I have emails from people who tried the EPAP mask, saying that they like it. I have a couple of studies on patients showing that snoring and perhaps obstructive sleep apnea were alleviated. Bench data are shown below.

Part 1: Calibration of the EPAP valve

Conclusion from Part 1: The EPAP valve can be adjusted gradually, easily, and reproducibly to create variable expiratory pressure.

The diagram in Fig 1 illustrates the set up that was used to assess the resistance of the EPAP valve. The valve was connected to an air flow system and the pressure was measured from side port in the connector that attaches to the valve. Air flow was generated using a flow generator (Philips Respironics, Cleveland, Ohio), and the flow was adjusted as needed and measure using a tube flow meter with a range of 0 to 10 l/min (Swingline Co, Ann Arbor, Michigan). The Flow meter had a fine adjustment valve to allow us to generate the required flow. Air flow went through the flow meter into the resistance valve and exited through the side opening (0.07x0.5 inch). The resistance of the opening could be adjusted by rotating the sleeve to open or close the side opening thus adjusting the expiratory resistance. In this series of experiments, the expiratory resistance opening was marked such that it could be closed in steps of 12.5%. The pressure was measure using a pressure transducer (Grass Instruments, Warwick, RI). The signal from the pressure transducer was fed through a data acquisition system (Biopac Systems UM100A, Goleto, CA) and displayed on a computer monitor. Flow of 6 l/min (100 ml/sec) was generated and pressure was recorded as the expiratory resistance was increased in steps. The side opening was closed in steps as mentioned above and the pressure was recorded at each step. The flow was fine adjusted to make sure flow remained at approximately 6 L/min (100 ml/sec). The data acquisition software allowed us to save the data or obtain the average pressure at each flow rate. The pressure was calibrated such that the pressure could be read directly on the monitor or an average value could be obtained at each flow level.

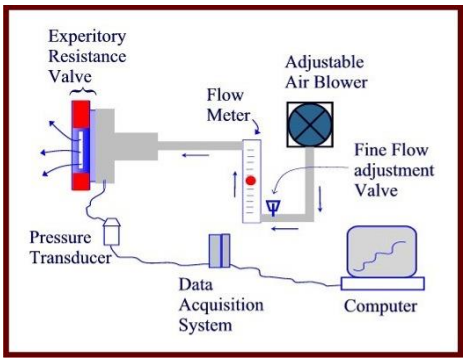
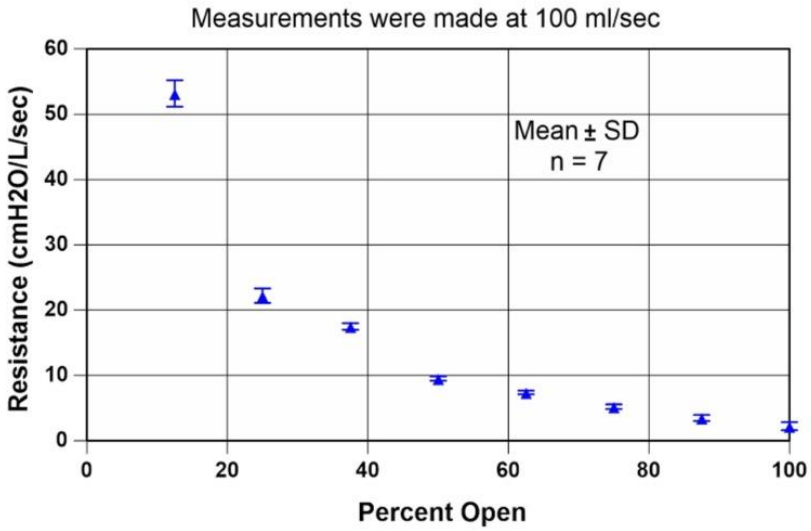


Figure *1*

Results

There was very little difference among the valves, but 7 were selected randomly and tested as described above. The mean data are plotted in Figure 2 and values are shown in the table.

Figure 2



The mean values of 7 measurements and standard deviations.

% Open	Mean resistance (cmH2O/L/sec	Standard Deviation
100	2.22	± 0.62
87.5	3.48	± 0.46
75	5.21	± 0.35
62.5	7.38	± 0.28
50	9.52	± 0.32
37.5	17.5	± 0.50
25	22.22	± 1.11
12.5	53.18	± 2.03

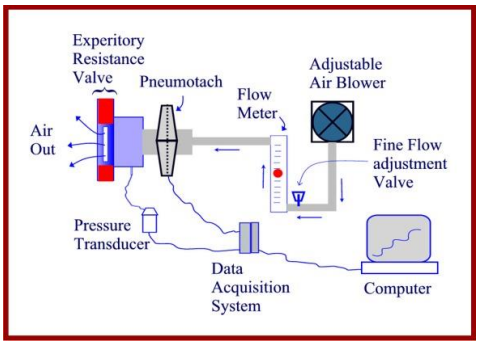
Part 2: Comparison of resistance of the EPAP Valve versus the predicate device Theravent using steady unidirectional flow.

Conclusion from Part 2: Expiratory resistance of the EPAP valve is substantially equivalent to the expiratory resistance of the predicate device Theravent.

The diagrams in Figures 3 and 4 illustrate the experimental set up that was used to compare the two devices. The set up was similar to that used in Part 1 studies with the exception that a Pneumotach (Biopac Systems, Airflow Transducer TSD 117) was added in the system to allow precise recording and

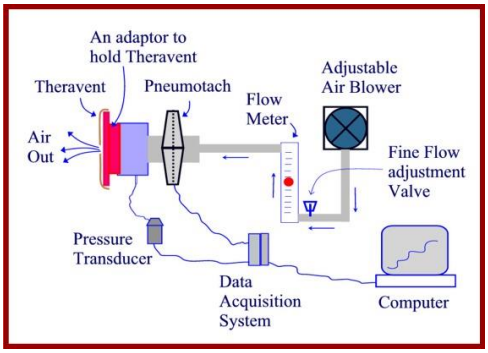
comparison between the two devices. The flow was as in part 1, unidirectional and steady flow. The flow transducer was calibrated daily as recommended by the factory and the flow measurement was verified against the flow rate using the Tube Flow meter. The set up allowed rapid change from using the EPAP mask to using the predicate device Theravent as shown in the figures 3 and 4. The EPAP valve was connected to the experimental set up directly via a wide connector, while the predicate device Theravent was adhered onto the surface of a connecter which was connected directly onto the experimental set up. This arrangement allow a rapid going back and forth from using the EPAP mask and the Predicate device Theravent. The EPAP mask was adjusted to provide 3 levels of expiratory resistance for comparison with Theravent. The EPAP mask was fully open, 50% closed, and 75% closed. The pressure and flow transducer were calibrated and verified prior to each experiment. The measurements were made using two levels of flow rates, 100 ml/sec and 200 ml/sec.

Figure 3



Experimental procedure: After completing calibration and verification of zero levels, the EPAP mask was connected and the flow was set at 100 ml/sec, the resistance on the valve was first left fully open and then adjusted to 50% closed and 75% closed and then returned to fully open. Adequate time was allowed for the pressure to change and reach a steady level at each setting of resistance. The EPAP valve was removed and replaced with the predicate device Theravent and the pressure was measures at flow rate of 100 ml/sec. The predicate device was again replaced with the EPAP mask and the flow rate

Figure 4



was then increased to 200 ml/sec. The pressure was measured while the EPAP mask was fully open, and then while 50% closed and 75% closed. The EPAP valve was then replaced with the predicate device and the pressure was measure at the high flow rate of 200 m/sec. This procedure was done using 12 random samples of EPAP masks and the predicate device Theravent. The flow rates of 100 and 200 ml/sec were

selected because they represent the average expiratory flow rate in human during breathing quietly at rest. Furthermore, the predicate device was calibrated using a flow rate of 100 ml/sec. Differences in pressures were compared using multi-variance analysis with post hoc comparisons of selected pairs using Bonferroni test. The same statistical analysis tests were utilized for comparing all results in this subsequent tests. A p value of less than 0.05 was considered significant. The results are shown below.

Results:

Figure 5 shows the mean pressure and standard deviation of 12 samples. With steady unidirectional flow of 100 ml/sec, the pressures with the EPAP mask were 0.32±0.03, 0.87±0.06, and 3.48±0.82 cmH2O when the expiratory resistance was fully open, 50% closed and 75% closed respectively. In comparison the pressure with the predicate device at 100 ml/sec flow rate was 1.37±0.15 cmH2O. With 200 ml/sec, the pressures with the EPAP mask were 1.11+0.05, 3.07+0.20, and 9.74+0.57 cmH2O when the valve was fully open, 50% closed, and 75% closed respectively. In comparison, the pressure with the predicate device Theravent at this flow of 200 ml/sec was 5.53+0.18 cmH2O. With low and high flow rates, the pressure with Theravent was significantly higher the pressure with the EPAP mask when 50% closed and significantly lower than the pressure when it was 75% closed ($p < 0.05$). The mean flow rate for each condition was kept close to 100 ml/sec and 200 ml/sec as planned.

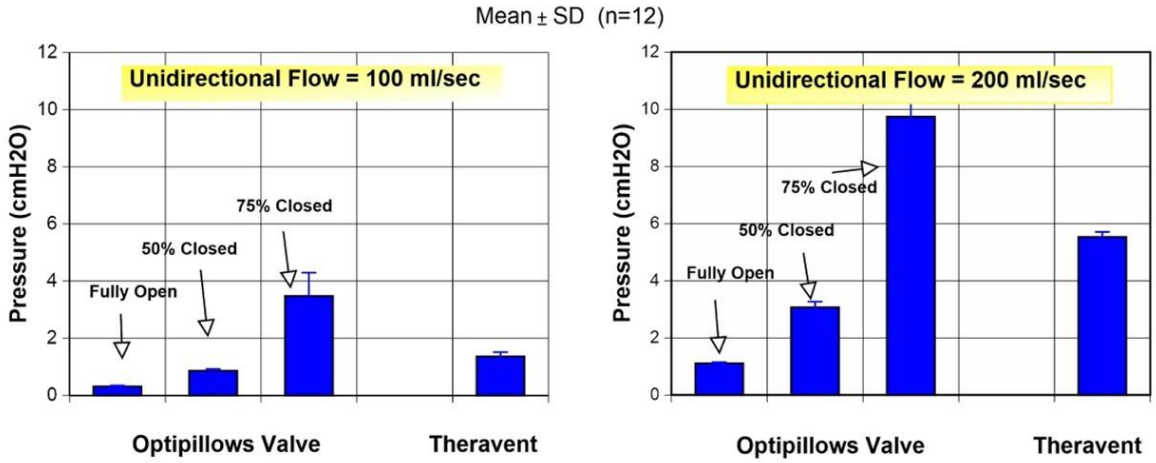


Figure 5

Conclusion: Using a steady unidirectional flow of air through the EPAP mask and the predicate device Theravent, the pressure with the predicate device was well within the range of pressure that the EPAP mask can provide.

Part 4: Comparison of Optipillows EPAP mask with the predicate device Theravent using cyclic breathing that simulated the normal breathing pattern and in a manner that represented the way that the two devices are used in human using a fake rubber nose. Breathing was through the rubber nose and with either Theravent or the Optipillows EPAP mask in place.

Conclusion: Optipillows EPAP mask performs substantially similar to the predicate device Theravent when used as they are designed to be used in humans.

Experimental set-up: We utilized the set up as described in part 3 except that in this part we used the real EPAP mask and applied against the nostrils of the rubber nose. Theravent was also adhered on the rubber nose as it would be in humans. The set up allowed to create breathing through the EPAP mask and through Theravent as it would happen in human. Pressure, flow and volume channels were calibrated and verified as above prior to each experiment. We constructed a rubber nose that resembled a normal nose with nostrils and shape that allowed us to apply the Optipillows EPAP mask or Theravent interchangeably. The set up is shown in Figure 9. Most components of the set up were similar to part 3 with the exception that a rubber nose was added that allowed up to use the EPAP mask or adhere Theravent as it would be done normally in people.

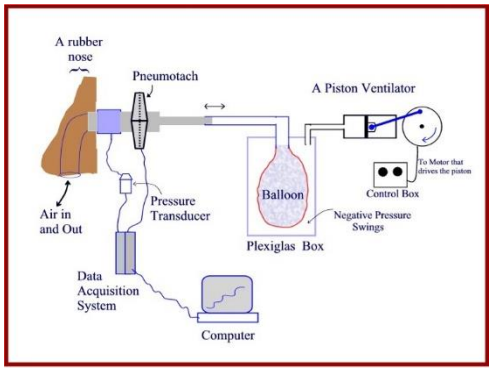


Figure 9

The rubber nose had two nostrils to accept the nasal pillows on the EPAP mask. The opening of the nostrils were joined into a large bore tubing (3/4 inch) at the exit (Figure 10) which allowed us to connect it easily to the experimental set up while allowing us to easily apply either the Optipillows EPAP mask or Theravent to the nose (Figure 11). The headgear from the mask were attached onto a rod above the nose so that a seal can be created between the nasal pillows and the nostrils of the rubber nose.

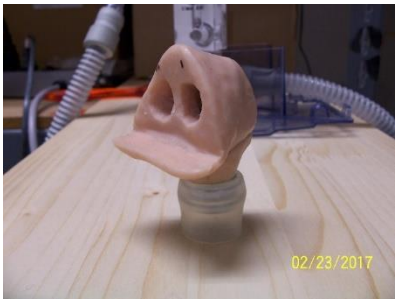


Figure 10

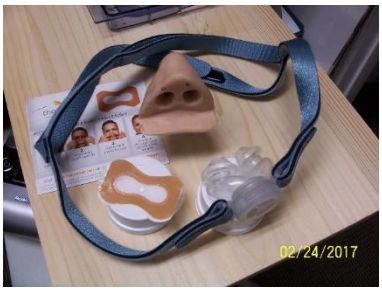


Figure 11

Experimental procedure: The steps in this experimental procedure were very similar to those in part 3 except that Theravent was adhered directly on the rubber nose, and Optipillows EPAP mask was fastened against the rubber nose. The pressure, flow and volume channels were calibrated prior to each experiment and calibrations were verified for accuracy. The breathing pattern, frequency and volume were similar as the setting used in part 3. The low volume breathing (300 ml) was started and the EPAP mask was mounted in place with the valve fully open. Although the EPAP mask and Theravent were applied directly on the rubber nose, a tracing of the experimental procedure was not much different from the one shown above in Figure 7. It took a bit longer for each run because more time was involved in securing the EPAP mask or Theravent onto the nose. In this procedure it was more convenient to test the Optipillows EPAP mask at low and high volumes, and then switch to Theravent , and test it with low and high volumes. Sometimes, Theravent was tested before Optipillows, and sometime the opposite was true. The order of testing with low and high volumes were also done at random.

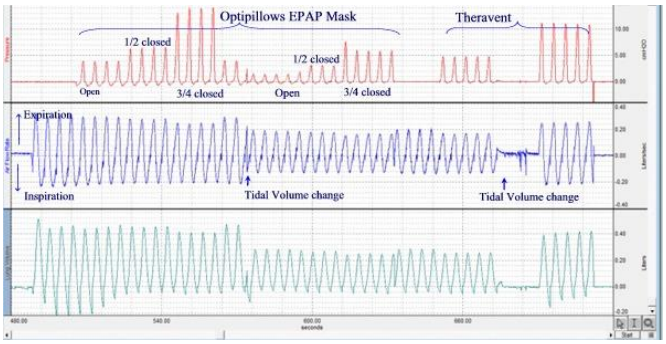


Figure 12

Results: Figure 12 shows a typical tracing from one experimental run. One can see that the tracing does not look very different from the tracing in Figure 7. Peak expiratory pressure, peak expiratory flow, and volume were measured. Peak inspiratory pressure was as before <0.2 cmH2O with low volume breathing and <0.5 cmH2O with high volume breathing and were not significantly different with Optipillows and Theravent (not shown). The mean values of 18 random samples while breathing through the rubber nose using Optipillows EPAP mask or Theravent are shown in Figure 13.

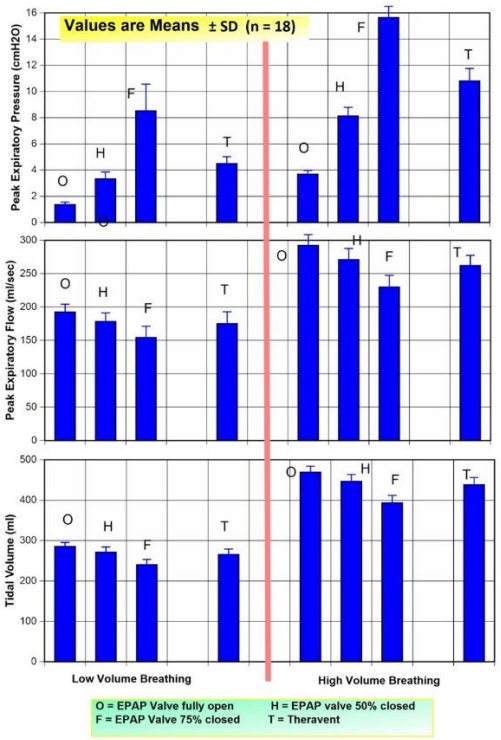


Figure 13

The mean values in the figure show that Peak Expiratory pressure at low volume breathing through the rubber nose and the EPAP mask with pillows were not significanltly different from the mean values obtained with breathing without the rubber nose. This suggested that the nasal pillows do not contribute to the reistance to air flow in or out of the lungs. The mean expiratory peak pressure during breathing through the nose was 1.36±0.19, 3.33±0.52, and 8.52±2.04 cmH2O when the EPAP valve was open, half closed and 75% closed respectively. The peak expiratory pressure with Thervanet was 4.49±0.53 cmH2O and was as before significantly higher than the peak experiratiry pressure when the EPAP valve was hlaf closed and sinificantly lower when the valve was 75% closed ($p<0.05$). Similar results were observed with high volume breathing. Likewise there were small changes in peak expiratory flow, and volume but the values with Theravent were within the range that was obtained with the EPAP mask.

Conlcusion: Using a rubber nose and using cyclic breathing to simulate normal breathing, the EPAP mask perfomed substantially equivalent to the predicate device Theravnet in terms of the peak expiratory pressure and peak expiraory flow and tidal volume.