RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Effect of mask dead space and occlusion of mask holes on delivery of nebulized albuterol

Ariel Berlinski, MD[1,2]

[1]University of Arkansas for Medical Sciences, Department of Pediatrics, Pulmonology Section

[2]Pediatric Aerosol Research Laboratory, Arkansas Children's Hospital Research Institute

Little Rock, Arkansas.

The study was performed at the Pediatric Aerosol Research Laboratory (Arkansas Children's Hospital Research Institute).

Partial data were presented in poster format at 2012 American Thoracic Society International Meeting, San Francisco CA by Dr. Ariel Berlinski.

Corresponding Author

Ariel Berlinski, MD

Associate Professor

University of Arkansas for Medical Sciences

Department of Pediatrics, Pulmonary Medicine

1 Children's Way, Slot 512-17

Phone: 501-364-1006

Fax: 501-364-3930

Little Rock, Arkansas 72202

E-mail: BerlinskiAriel@uams.edu

Financial support: Supported in part by the University of Arkansas for Medical Sciences College of Medicine Children's University Medical Group Fund Grant Program (#036072). The Pediatric Aerosol Research Laboratory at Arkansas Children's Hospital Research Institute was partially established and receives partial support from the George Endowment for Asthma.

Conflict of interest for Ariel Berlinski: Dr. Berlinski served as Principal Investigator in clinical trials sponsored by Johnson & Johnson, MPEX Pharmaceutical, Gilead, Philips, Genentech, Vertex, Abbvie, Aptalis, Janssen and Therapeutic Development Network, and was recipient of an unrestricted educational grant from S&T Technologies. None of their products are discussed in this manuscript.

Running head: Mask Dead Space and Nebulized Albuterol

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Abstract

Background

Infants and children with respiratory conditions are often prescribed bronchodilators. Face masks are used to facilitate the administration of nebulized therapy in patients unable to use a mouthpiece. Masks incorporate holes to their design and their occlusion during aerosol delivery has been a common practice. Masks are available in different sizes and different dead volumes. The aim of this study was to compare the effect of different degrees of occlusion of the mask holes and different mask dead space on the amount of nebulized albuterol available at the mouth opening in a model of a spontaneously breathing child.

Methods

A breathing simulator delivered infant (VT=50ml; breathing frequency=30/min; I:E=1:3), child (VT=155ml; breathing frequency=25/min; I:E=1:2) and adult (VT=500ml; breathing frequency=15/min; I:E=1:2) breathing patterns was connected to a collection filter hidden behind a face plate. A pediatric and an adult size mask connected to a continuous output jet nebulizer were sealed to the face plate. The nebulizers (n=3) were loaded with albuterol sulfate (2.5mg/3ml) and operated with 6 L/min of compressed air for 5 min. Experiments were repeated with different degrees of occlusion (0%, 50%, and 90%). Albuterol was extracted from the filter and measured with a spectrophotometer at 276 nm.

Results:

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

The occlusion of the holes of the large mask did not increase the amount of albuterol in any of the breathing patterns. The amount of albuterol captured at the mouth opening did not change when the small mask was switched to the large mask except with the breathing pattern of a child and the holes of the mask were 50% occluded ($p = .02$).

Conclusions

Neither decreasing the dead space of the mask nor occluding the mask holes increased the amount of nebulized albuterol captured at the mouth opening.

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Background

Wheezing illnesses are very frequent in younger children with almost 50% of them experiencing a wheezing episode between birth and 6 years of age.[1] Infants and children with respiratory conditions are often prescribed nebulized bronchodilators. Bronchodilators are used in the treatment of asthma, bronchiolitis and croup.[2-3]

Clinical studies have demonstrated equal efficacy of inhaled corticosteroids when inhaled either with mouthpiece or mask.[4-5] Other studies performed in pediatric patients experiencing an acute exacerbation showed either no difference or better outcomes with mouthpiece compared to facemask.[6-7] The use of a mouthpiece is preferred over a mask because it reduces ocular and facial exposure to inhaled drugs.[8-9] However, face masks are used to facilitate the administration of nebulized therapy to patients who unable to use a mouthpiece. Masks of different designs and sizes are commercially available. A previous study demonstrated that the larger the dead space of the mask the lower the amount of albuterol delivered by pressurized metered-dose inhaler (pMDI) that is available at the mouth opening.[10] Therefore, masks designed to be used with pMDI should ideally have a low dead space. However, no data are available regarding the effect of face mask dead space and nebulized drug delivery. Acquisition of this knowledge gap will provide manufacturers of face masks with guidance for future mask designs.

Face masks used for nebulized drug delivery incorporate holes in their design. These holes decrease ocular and facial impaction and they prevent rebreathing of exhaled gases.[8] Many practitioners occlude these holes in an attempt to increase drug delivery despite the lack of evidence that would support this practice.

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

The aim of this study was to evaluate the effect of different degrees of occlusion of the mask holes, different mask sizes (different dead space), and different breathing patterns on the amount of nebulized albuterol available at the mouth opening of a model of a spontaneously breathing child. We hypothesized that the occlusion of the mask holes, the use of a mask with smaller dead space and breathing patterns with larger tidal volumes will increase the amount of nebulized albuterol available at the mouth opening of a model of a spontaneously breathing child.

Material and Methods

Devices and Albuterol Solutions and Measurements

Three units of a continuous output jet nebulizer (UP-DRAFT II® Optineb Nebulizer, Teleflex Medical, Research Triangle Park, NC) were tested. The nebulizers were operated at 6 L/min with wall air.

Two different bottom-loaded masks were studied: Airlife™ Pediatric Aerosol Mask (Model 1261, Cardinal Health, McGaw, IL) (small mask) and Adult Aerosol Mask (Model 1084, Hudson RCI, Teleflex Medical, Research Triangle Park, NC) (large mask). The dimensions of the masks were (dead volume, height, width and depth): 75 ml, 7.5 cm, 7.5 cm and 4 cm for the small mask and 130 ml, 10.5 cm, 9 cm, and 6 cm for the large mask (Figure 1). Dead volume was measured by water displacement technique.[11]

A new ampule of albuterol sulfate 2.5 mg/3 ml (Nephron Pharmaceuticals Corporation, Orlando, FL) was used for each of the runs.

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Albuterol was quantified via spectrophotometer at 276 nm (Biomate 3 UV-Vis Spectrophotometer, Thermo Electron Corporation, Waltham, MA).[10]

Breathing simulation

A PARI Compass Breath Simulator (Pari Pharma, Munich, Germany) was used to mimic different breathing patterns. The device consists of computer-controller syringe that allows programming of tidal volume, inspiratory time, breathing frequency and length of simulation.[10] Three different breathing patterns corresponding to an infant (VT = 50 ml; breathing frequency = 30/min; I:E = 1:3), child (VT = 155 ml; breathing frequency = 25/min; I:E = 1:2) and adult (VT = 500 ml; breathing frequency = 15/min; I:E = 1:2) were tested.

Study Design

The test setup was optimized to minimize confounding factors such as face contour, face mask seal and force applied to the system. Each mask was glued to a face plate that had a "mouth opening" (22 mm diameter connector) followed by a low dead space filter holder that was connected in line with a breathing simulator (Figure 2).[10]

Study Protocol

Nebulizers were weighted on a precision scale before (W_D) and after (W_L) loading 2.5/3 mls of albuterol solution. A new filter (PARI Respiratory Equipment Inc, Midlothian, VA) was placed

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

in the filter holder and a specific breathing pattern was programed in the breathing simulator. The accuracy of the inhaled tidal volume was verified with a mass flow meter (TSI 4043, Shoreview, MN) and its associated software. The nebulizer was connected to the face mask and operated for 5 minutes. The nebulizer was re-weighted upon completion (W_F), 5 mls of ultrapure water were added to the nebulizer and a new weight measurement was obtained (W_{+5}). Albuterol concentration was measured via spectrophotometer in the washings and the albuterol mass remaining in the nebulizer was calculated as follows: *$(W_{+5} – W_D)$*[albuterol concentration determined by spectrophotometry in µg/ml]*. These results were used as quality controls to assure that any differences were not due to a difference in output and are not reported. The filters were placed in a 50 ml plastic tube, 10 mls of ultrapure water were added and after vigorous shacking, the washings were tested for albuterol concentration via spectrophotometer. The mass of albuterol captured at the mouth opening was the outcome variable and it was calculated as follows: *[albuterol] from filters*10*. Nebulizers were thoroughly cleaned with ultrapure water and air dried.

These measurements were repeated while occluding 50% and 90% of the surface of the mask holes.

Three different nebulizers were tested with each mask size (small and large), with all three breathing patters (infant, child, and adult) and with 3 different degrees of obstruction of the mask holes (0%, 50%, and 90%).

Statistics

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Comparison among different breathing patterns and among different degrees of obstruction of the mask holes was done with analysis of variance for repeated measures followed by Bonferroni test for when multiple comparison analysis was required. Comparison between mask sizes for each breathing pattern was done with paired T-test. A p value < .05 was considered statistically significant.

Results

Occlusion of the Mask Holes (Table 1)

The occlusion of the holes of the large mask did not increase the amount of albuterol in any of the breathing patterns (P = .74, P = .97, and P = .80 for adult, child, and infant respectively).

The occlusion of the holes of the small mask did not increase the amount of albuterol in any of the breathing patterns (P = .10, P = .02 but NS after Bonferroni adjustment and P = .90 for adult, child, and infant respectively).

The amount of albuterol available at the mouth was 100% larger for the child and adult breathing patterns than for the infant one.

Mask Size (Figure 3)

The amount of albuterol captured at the mouth opening did not change when the small mask was switched to the large mask for almost all breathing patterns and degrees of obstruction. The only

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

exception was with the breathing pattern of a child and the holes of the mask occluded 50% ($p = .02$).

Discussion

In this study we found that neither decreasing the dead space of the mask nor occluding the mask holes increased the amount of nebulized albuterol captured at the mouth opening.

The occlusion of the holes of the mask did not increase the amount of nebulized albuterol available at the mouth opening. These findings reject our first hypothesis. We speculate that the occlusion might have increased the pressure inside the mask negating any potential improvement that the mask behaving like a spacer would provide. The increase in pressure is inferred by the fact that during design stage of this study full occlusion was not possible. In addition, the same amount of exhaled aerosol had to pass through smaller orifices, thus increasing impaction. We speculate that the occlusion might have led to an increase in facial deposition. Unfortunately we did not measure the amount of albuterol deposited on the face plate. Also, the occlusion of the holes of mask could produce CO2 rebreathing.[12] Therefore, the practice of occluding the holes of the mask should be abandoned.

The amount of albuterol captured at the mouthpiece was lower for the infant breathing pattern as expected. However, we would have expected the amount of albuterol to be higher with the adult breathing pattern than with the child one. The inspiratory flow (tidal volume/inspiratory time

*60) was 6, 11.6, and 22.5 L/min for the infant, child and adult breathing patterns respectively. The minute ventilation (tidal volume * breathing frequency) was 1.5, 3.9, and 7.5 L for the infant, child and adult breathing patterns respectively. However, the amount of time per minute the aerosol was inhaled (inspiratory time * breathing frequency) was 15, 20, and 20s for the infant, child and adult breathing patterns respectively. Therefore, since all inspiratory flows were equal or larger than the nebulizer flow, the difference in the amount of albuterol captured at the mouth was dependent on the exposure time. This would explain why the child and adult breathing patterns rendered similar results. These results are limited to the combination of device and mask most commonly used (continuous output jet nebulizer and bottom loaded mask). This is in agreement with findings reported by Bauer et al. who compared nebulized arformoterol output using different breathing patterns.[13] They also found that the largest the exposure time the largest the drug output. We anticipate that results would have been different for other type of nebulizers such as vibrating mesh nebulizers.[14] We think that due to the slow speed of the aerosol produced by the vibrating mesh nebulizer, the breathing pattern plays a major role in drug delivery when this technology is used.

The reduction of the dead space did not affect the amount of nebulized albuterol available at the mouth opening. These findings reject our second hypothesis and are not in agreement with published data using pMDIs and holding chambers.[10] That study used a similar experimental setup to the one used in this study, thus eliminating the type of model as a confounding factor. We speculate that the different behavior noted for nebulized albuterol is due to the fact that the aerosol produced by the nebulizer is continuously produced while the aerosol produced by the

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

pMDI is only available for inhalation for few seconds. Also, the mask might act as a small reservoir therefore minimizing the negative effect of increasing the dead space.

One of the limitations of this study is the in-vitro nature of the testing. Although widely accepted, the filter overestimates the amount of drug delivered by the aerosol generator because it does not allow exhalation of the aerosols. Also, we tested only one type of nebulizer (continuous output) and one type of mask design. As discussed above results obtained with one type of device/mask should not be extrapolated to others.

Conclusion

Contrary to what happens with pMDIs, the mask dead space does not affect the amount of nebulized albuterol available at the mouth opening when a continuous output jet nebulizer and a bottom loaded mask are used. Also, the occlusion of the holes of the mask does not increase the amount of nebulized albuterol available at the mouth opening when a continuous output jet nebulizer and a bottom loaded mask are used. This practice should be abandoned.

References

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332(3):133-138.
2. Schweich PJ, Smith KM, Dowd MD, Walkley EI. Pediatric emergency medicine practice patterns: a comparison of pediatric and general emergency physicians. Pediatr Emerg Care. 1998 Apr;14(2):89-94.
3. McCulloh RJ, Smitherman SE, Koehn KL, Alverson BK. Assessing the impact of national guidelines on the management of children hospitalized for acute bronchiolitis. Pediatr Pulmonol. 2013 Jul 19. doi: 10.1002/ppul.22835. [Epub ahead of print]
4. Mellon M, Leflein J, Walton-Bowen K, Cruz-Rivera M, Fitzpatrick S, Smith JA. Comparable efficacy of administration with face mask or mouthpiece of nebulized budesonide inhalation suspension for infants and young children with persistent asthma. Am J Respir Crit Care Med. 2000;162(2 Pt 1):593-598.
5. Georgitis JW, McWilliams B, Cruz-Rivera M, Fitzpatrick S, and Smith JA. Effective Once-Daily Administration of Budesonide Inhalation Suspension by Nebulizer with Facemasks or Mouthpieces for Persistent Asthma in Infants and Young Children. Pediatr Asthma Allergy Immunol 2001;15(1):3–13.
6. Lowenthal D, Kattan M. Facemasks versus mouthpieces for aerosol treatment of asthmatic children. Pediatr Pulmonol. 1992;14(3):192-196.
7. Kishida M, Suzuki I, Kabayama H, Koshibu T, Izawa M, Takeshita Y, Kurita F, Okada M, Shinomiya N, Aoki T. Mouthpiece versus facemask for delivery of nebulized salbutamol in exacerbated childhood asthma. J Asthma. 2002;39(4):337-339.

8. Sangwan S, Gurses BK, Smaldone GC. Facemasks and facial deposition of aerosols. Pediatr Pulmonol. 2004;37(5):447-452.
9. Geller DE. Clinical side effects during aerosol therapy: cutaneous and ocular effects. J Aerosol Med. 2007;20(Suppl 1):S100-S108; discussion S109.
10. Chavez A, McCracken A, Berlinski A. Effect of face mask dead volume, respiratory rate, and tidal volume on inhaled albuterol delivery. Pediatr Pulmonol. 2010 Mar;45(3):224-229.
11. Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. Respir Care. 2006;51(2):140-144.
12. Mundt C, Sventitskiy A, Cehelsky JE, Patters AB, Tservistas M, Hahn MC, Juhl G, Devincenzo JP. Assessing Modeled CO(2) Retention and Rebreathing of a Facemask Designed for Efficient Delivery of Aerosols to Infants. ISRN Pediatr. 2012;2012:721295.
13. Bauer A, McGlynn P, Bovet LL, Mims PL, Curry LA, Hanrahan JP. The influence of breathing pattern during nebulization on the delivery of arformoterol using a breath simulator. Respir Care. 2009;54(11):1488-1492.
14. Waldrep JC, Dhand R. Advanced nebulizer designs employing vibrating mesh/aperture plate technologies for aerosol generation. Curr Drug Deliv. 2008;5(2):114-119.

Figure legends

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Figure 1: Masks used in the study.

Figure 2: Setup used for simulated breathing

Figure 3: Amount of albuterol captured at the mouth opening*

* Results are expressed in µg. The bars represent the mean of 3 measurements and the error bars represent the SD.

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

Table 1: Amount of albuterol captured at the mouth opening with different degrees of occlusion of the mask holes.

Mask Size	Breathing Pattern	Degree of Occlusion		
		0%	50%	90%
Small	Infant	104 ± 10	108 ± 9	104 ± 9
	Child	201 ± 7	225 ± 11	199 ± 12
	Adult	187 ± 5	217 ± 13	203 ± 22
Large	Infant	112 ± 31	108 ± 4	103 ± 4
	Child	198 ± 12	199 ± 18	200 ± 11
	Adult	214 ± 7	217 ± 18	222 ± 21

Results are expressed in µg as mean ± SD of 3 samples.

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

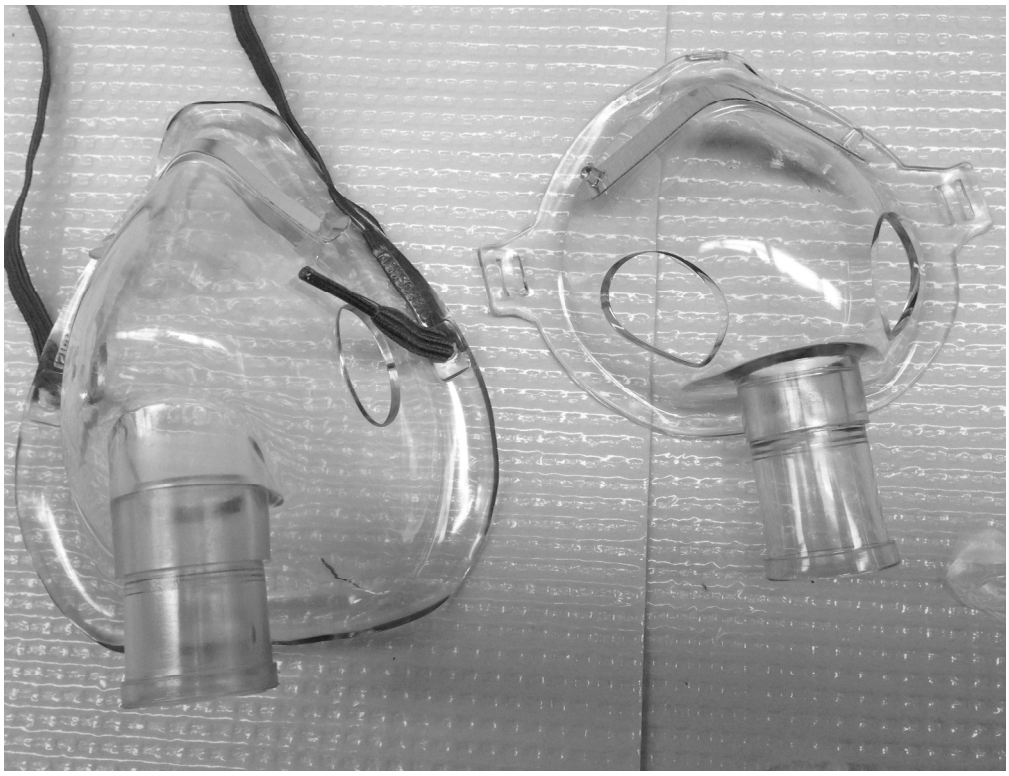

Figure 1: Masks used in the study.

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

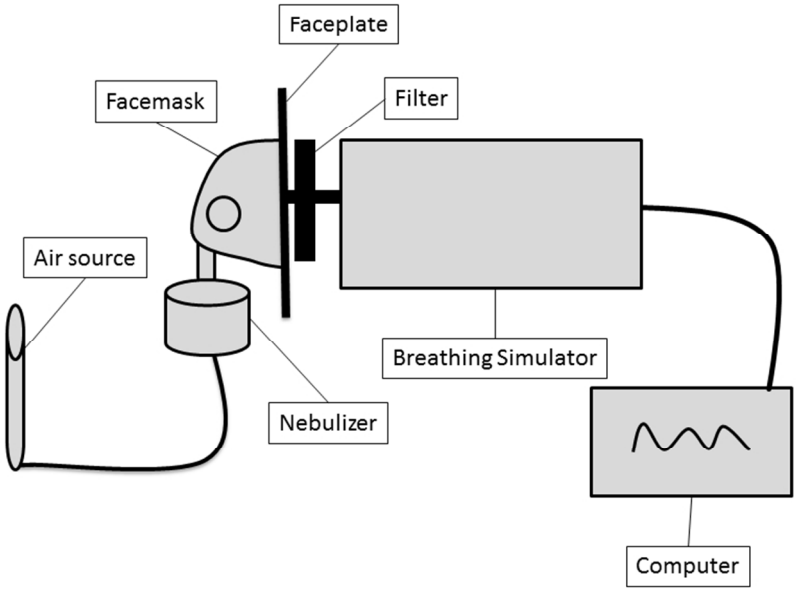

Figure 2: Setup used for simulated breathing
254x190mm (96 x 96 DPI)

RESPIRATORY CARE Paper in Press. Published on December 10, 2013 as DOI: 10.4187/respcare.02978

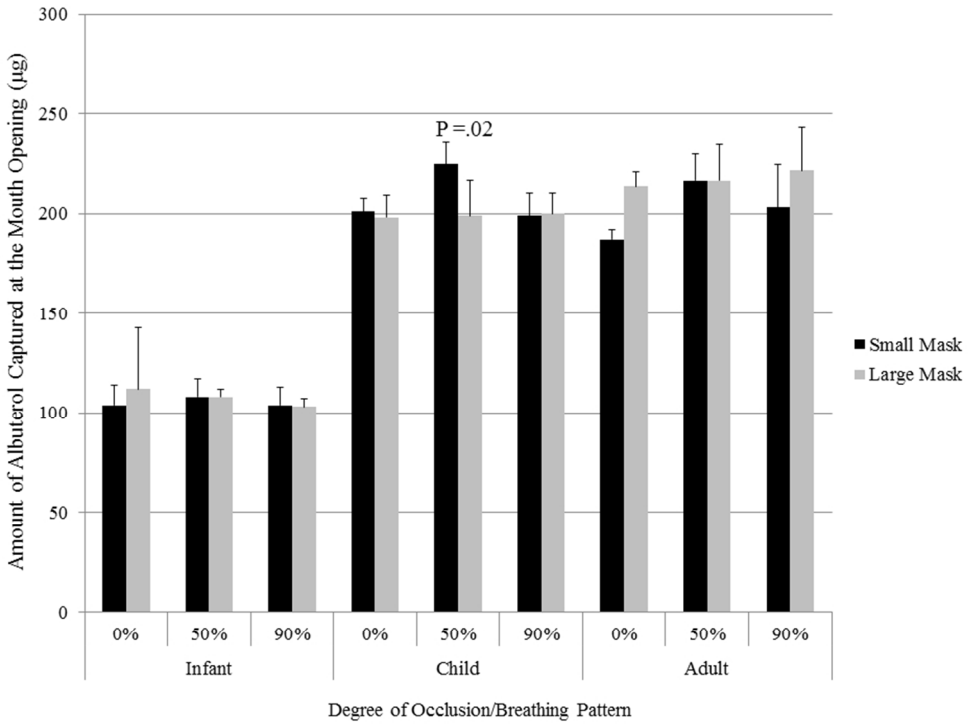

Figure 3: Amount of albuterol captured at the mouth opening*

* Results are expressed in µg. The bars represent the mean of 3 measurements and the error bars represent the SD.

254x190mm (96 x 96 DPI)