Scientific Research Publishing

Open Journal of Respiratory Diseases, 2017, 7, 53-61
http://www.scirp.org/journal/ojrd
ISSN Online: 2163-9418
ISSN Print: 2163-940X

Testing Low Doses of Caffeine on Respiratory Resistance Using the Airflow Perturbation Device

Mary Kate Montgomery, Allen Luk, Arthur T. Johnson, Jafar Vossoughi

Department of Bioengineering, University of Maryland at College Park, College Park, Maryland, USA
Email: artjohns@umd.edu

How to cite this paper: Montgomery, M.K., Luk, A., Johnson, A.T. and Vossoughi, J. (2017) Testing Low Doses of Caffeine on Respiratory Resistance Using the Airflow Perturbation Device. *Open Journal of Respiratory Diseases*, **7**, 53-61.
https://doi.org/10.4236/ojrd.2017.72006

Received: March 15, 2017
Accepted: May 6, 2017
Published: May 9, 2017

Abstract

Research reports on pulmonary function measurements often mention caffeine abstinence as a condition for testing subjects. Yet, the effects of caffeine on respiration are not well documented. This study was intended to investigate the physiological effects of caffeine on respiratory resistance measurements and the necessity of caffeine avoidance in such testing. Thirty-one subjects were administered caffeine in pill form for dosages in the range of 3 - 4.5 mg/kg body weight. Respiratory resistance was measured with the Airflow Perturbation Device every 15 minutes after caffeine ingestion until a full hour of elapsed time. No changes were noted in inhalation, exhalation, and average respiratory resistances during the times of measurements. The conclusion is that for low dosages of caffeine, respiratory resistance measurements are not affected by caffeine ingestion prior to testing.

Keywords

Respiratory Resistance, Caffeine

1. Introduction

Caffeine is a drug of the methylxanthine class. It is widely consumed to provide energy, to improve focus, or to stave off sleep. It is most commonly found in coffee, tea, soda, and chocolate. The average rate of consumption in the United States is 200 mg per day. Caffeine is primarily a non-specific adenosine receptor antagonist and a stimulant of the central nervous system. It binds to all types of adenosine receptors [1], competitively inhibiting the receptors and preventing adenosine, a depressant, from binding to its receptor and triggering "sleepiness" [2]. Unlike many other functions of caffeine, adenosine receptor antagonism occurs even at low plasma concentrations of caffeine, and thus is likely to be the

main cause of the observed effects of caffeine consumption [3].

Effects of caffeine consumed through coffee have been studied in the past and the results have been ambiguous, largely because the magnitude of the effects of caffeine varies greatly depending on the person who consumes it [4]. Most caffeine consumed by humans is ingested in coffee, yet coffee has many other ingredients that could factor into the effects perceived to be caused by caffeine. Additionally, long term studies with caffeine are extremely difficult because subjects build up a tolerance to the drug, and its effect at the beginning of a study could be quite different from its effect at the end [5].

Some studies have shown that adenosine, the effect of which is lessened by caffeine consumption, can cause bronchoconstriction [6]. This would suggest that caffeine ingestion could ease tension on the lungs, making it easier for a person to breathe. Perhaps for this reason, some past studies of respiratory effects have made sure that caffeine had not been ingested prior to testing. Some past experiments on the effect of caffeine had subjects abstain from caffeine for 24 hours beforehand, for example [7] and [8], but several others only required their subjects to abstain from caffeine for 12 hours, such as [9], [10], and [11].

Respiratory resistance, meanwhile, is a measure of the effort to cause air to flow in the respiratory tract. A higher respiratory resistance requires more effort to breathe. Resistance is calculated using the pressure driving airflow divided by the rate of the airflow. The Airflow Perturbation Device (APD), a medical instrument that measures respiratory resistance noninvasively, was used in this study to measure respiratory resistance separately during inhalation, during exhalation, and as the average of the two. It requires the subject to breathe normally through the device while a segmented wheel rotates in the flow pathway. The wheel modifies, or perturbs, flow rates and mouth pressures, the amounts of which depend on respiratory resistance and device resistance [12] [13]. Device resistance is measured, so respiratory resistance can be obtained. The advantage of using the APD is that the values for inhalation and exhalation can be measured distinctly during spontaneous breathing. In this experiment, the APD was used to investigate if there is a correlation between caffeine ingestion and respiratory resistance.

2. Methods and Materials

2.1. Subjects and Materials

Thirty-one healthy subjects volunteered to participate in the experiment. All volunteers were in good health, with no recurring respiratory problems, no recurring sinus problems, and no congestion on the day of testing. The subjects represented a diverse group of students and nonstudent volunteers. As representatives of the entire population, they had a range of ages, heights, weights, and health conditions. All volunteers weighed between 50 and 105 kg (110 and 230 pounds), and were over the age of 18. Any potential subject who weighed below 50 kg was excluded from the experiment for safety reasons, and any subject above 105 kg was excluded to maintain a narrow range of dosages in testing.

Potential subjects with moderate to severe asthma or a similar respiratory condition or with a suspected allergy to caffeine were prohibited from participating as well. They were provided with information on the experimental procedure and any risks associated with it, as well as information on how the data would be used. They were required to read and sign a consent form as well as to fill out a health questionnaire to ensure that they were viable candidates for the experiment. The testing protocol received previous University of Maryland IRB approval.

In preparation for the experiment, subjects abstained from consuming caffeine, including that from coffee (including decaf), tea, soft drinks, or chocolate, for at least 12 hours (overnight) before completing the experiment. Because these subjects were not being paid for their service, it was unreasonable to expect them to abstain from caffeine for a full day, so this particular experiment was conducted with subjects who had not had caffeine in over 12 hours. Subjects were also asked to refrain from consuming any non-essential medications such as aspirin or ibuprofen for 12 hours beforehand to ensure that such medications would not skew the results of the test.

The caffeine pills given to the subjects were Jet Alert TM regular strength caffeine pills (Bell Pharmaceuticals, Bell Plaine, MN). They are widely available, over-the-counter, 100 mg tablets. They are small, tasteless, and easy to swallow. Two, three, or four pills, depending on the subject's body weight, were administered in consumer-available paper cups, along with water. This corresponded to a dosage of 3 - 4.5 mg/kg body weight. Previous caffeine studies have been conducted at a wide variety of dosages, ranging from 3 [14] to 13 [8] mg/kg. Some studies chose to use a specific mass of caffeine rather than a dosage per body weight [9], [11], and [15]. 3 - 4.5 mg/kg was selected for this experiment because it is at the lower, and therefore safer, end of this range.

The placebo pills used in the experiment were 100% lactose pills obtained via online order from Placebo World (in UK, placebo-world.com). They were chosen because they are the same size, shape, and color as the caffeine pills.

In the event that subjects were lactose intolerant, they were warned that the caffeine pills contained a small amount of lactose as an inactive ingredient and that the placebo pills, if they were completing the placebo trials, were 100% lactose. Subjects were then reminded that they could back out of the experiment at any time, and were asked if they would like to do so as a result of their lactose intolerance. If they wanted to continue, they were allowed to do so.

Subjects were offered no reward in exchange for participation, which, along with test length and the necessity for the subject to refrain from drinking coffee that morning, provided a barrier to subject recruitment. As a result, subject demographics such as gender were not evenly distributed, and the subjects were of a wide range of ages (see **Table 1**).

2.2. Experimental Protocol

Each subject was given their own disposable, removable mouth piece for the

Table 1. Subject demographics (Values given are means ± std dev (range)).

	Female	Male	Total
Number of Participants	23	8	31
Weight (kg) (1 bs)	67.6 ± 9.3 (39.3) 148.8 ± 20.5 (86.5)	84.0 ± 16.4 (45.5) 184.8 ± 36.0 (100)	71.9 ± 13.4 (54.5) 158.1 ± 29.4 (120)
Height (cm) (in)	170.7 ± 7.9 (25.4) 67.2 ± 3.1 (10)	179.9 ± 8.9 (27.9) 70.8 ± 3.5 (11)	173.0 ± 8.9 (33.0) 68.1 ± 3.5 (13)
Age (yrs)	38.4 ± 20.3 (52)	36.5 ± 20.4 (47)	37.9 ± 20.0 (52)
Est. Daily Caffeine Consumption (mg)	233.4 ± 162.4 (540)	169.4 ± 156.3 (450)	216.9 ± 160.8 (540)
Est. Weekly Exerciser (hr)	6.4 ± 3.7 (14)	5.0 ± 4.0 (12)	6.1 ± 3.8 (15)

APD to maintain proper hygiene. Subjects were also given disposable nose clips, which prohibited air from escaping through the subjects' noses, forcing all inhalation and exhalation flow through the mouth, and therefore through the APD. Subjects took practice measurements with the APD to ensure that they were comfortable using the device, and any questions the subjects had were answered before beginning the experiment.

Subjects were tested over one hour, for a total of 30 measurements. These measurements were split into 6 sets, each with 5 measurements taken over a 3 - 5 minute time period. The first set was completed before consumption of any pills, and each subsequent set was completed at specific time points, corresponding to 0, 15, 30, 45, and 60 minutes after caffeine intake. The measurements consisted of breathing into the APD for approximately 15 - 30 seconds, while wearing the nose clip, until the device produced a reading on the subject's inhalation, exhalation, and average respiratory resistance.

In between measurements, the subjects were allowed to remove the nose clip while the person administering the test recorded the data, so that the subject was more comfortable during the test. To further ensure comfort, the subject was also given a few extra seconds in between tests to breathe without the hindrance of the nose clip or APD. The subject was also given water during the test to alleviate any other discomfort.

To ensure that no "placebo effect" was taking place, eight subjects who were willing to volunteer more of their time performed the test three times, rather than once. Some of the times, the subject took a caffeine pill, and some of the times, the subject took a placebo. This was to determine if just the act of taking a pill causes the subject to change, whether voluntarily or involuntarily, his or her respiratory resistance. The subject was not told whether they were taking the caffeine or the placebo. Taking the test three times limited the likelihood that the subject would know whether they were being given caffeine or a placebo.

Four subjects who were willing to contribute even more of their time also completed a "Nocebo" test, in which no pills were taken, but the rest of the experimental procedure remained exactly the same.

2.3. Data Analysis

Measurements for each subject were recorded and used to determine larger trends. All five samples taken at a given time were averaged. The purpose of taking multiple samples was to limit the effect of the natural variation of a person's respiratory resistance on the results of the experiment [16]. The values taken at each time were compared with those at every other time, so as to determine if the caffeine had any effect, and if so, at what point. This was done for the placebo and "nocebo" trials as well. Additionally, the values at each time for the caffeine trials were compared to those for the placebo and "nocebo" trials to determine more directly if there was any significant difference between the trials with caffeine and those without it. When doing this, only the caffeine trials of subjects who also completed placebo trials were used. When comparing values taken at different times, the separate inhalation and exhalation values were compared, as well as those for the average resistance.

Each statistical comparison made was tested for statistical relevance using a two-tailed, paired t-test at $\alpha = 0.05$, as well as a Wilcoxon Sign-Rank test at $\alpha = 0.05$.

3. Results

No significant change was observed in respiratory resistance after ingestion of caffeine, placebo, or nothing. No significant change was observed for either inhalation values, exhalation values, or average values.

Table 2 provides values for inhalation, exhalation, and respiratory resistance at regular time intervals after caffeine consumption. Resistance values did not noticeably increase or decrease over time after caffeine ingestion. These data are visualized in Figure 1 below, which shows the distribution of the resistance values for each subject. For some subjects, respiratory resistance varies considerably, while for others, the values are rather consistent. Outliers in the measurements appear to be rare.

There was also no major difference found between the effects of caffeine and those of a placebo. Table 3 provides values for resistances at regular time intervals for both caffeine and placebo. These values come only from those subjects who participated in the placebo trials.

The resistance values for trials with placebo appear to generally be higher. This trend is visible in Figure 2. However, a statistical comparison did not find

Table 2. Respiratory resistance values for all thirty-one caffeine trials. Values are split into inhalation, exhalation, and average resistance. Resistance values were measured in $cmH_2O \cdot sec/L$.

	Before	0 min	15 min	30 min	45 min	60 min
In	3.19 ± 0.78	3.19 ± 0.75	3.17 ± 0.71	3.19 ± 0.73	3.25 ± 0.72	3.20 ± 0.71
Ex	3.00 ± 0.79	2.94 ± 0.78	2.92 ± 0.77	2.87 ± 0.79	2.89 ± 0.79	2.87 ± 0.83
Avg	3.10 ± 0.74	3.06 ± 0.73	3.04 ± 0.71	3.03 ± 0.72	3.07 ± 0.71	3.04 ± 0.72

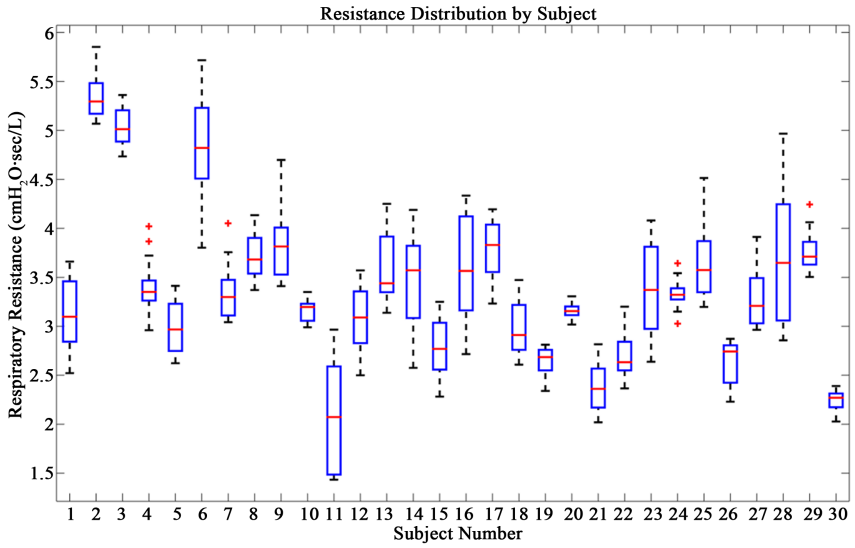

Figure 1. Box-and-whisker plot showing distribution of respiratory resistance values for every subject in caffeine trials. Each subject's inhalation, exhalation, and average values for all time points are represented in the boxes. The red lines show the location of the median resistance value for each subject, and the boxes show the first and third quartiles of the subjects' readings. The minimum and maximum are shown at the ends of the whiskers, unless they are qualified as an outlier, in which case, they are shown with a red +.

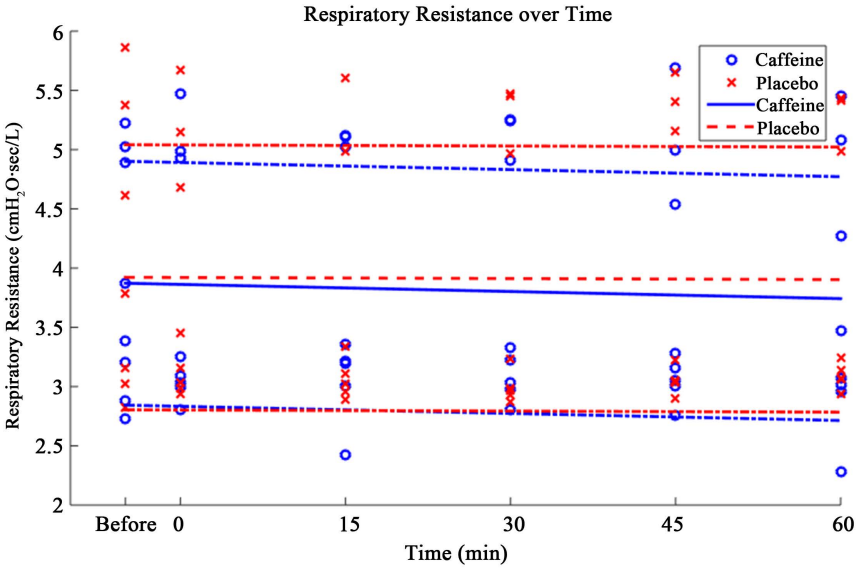

Figure 2. Average respiratory resistance over time for caffeine and placebo for eight subjects who participated in placebo trials. Only average values are shown in the figure. Upper and lower bounds of error range (± Std Dev) are shown in dot-dashed lines that correspond in color to the trend line itself. This trend shows no significant difference between the caffeine and placebo treatments.

any significant difference between the placebo data and the caffeine data for any time point.

Finally, the resistance values for subjects who participated in the nocebo trials are provided in Table 4. These subjects completed trials with caffeine, placebo, and nocebo, which involved no pill.

Table 3. Respiratory resistance values for caffeine and placebo for eight subjects who participated in placebo trials. Values are split into inhalation, exhalation, and average resistance. Resistance values were measured in $cmH_2O \cdot sec/L$.

		Before	0 min	15 min	30 min	45 min	60 min
Caffeine	In	3.55 ± 0.99	3.59 ± 1.07	3.55 ± 1.02	3.61 ± 0.98	3.61 ± 1.00	3.46 ± 0.97
	Ex	3.44 ± 0.92	3.29 ± 0.95	3.30 ± 1.00	3.31 ± 1.01	3.25 ± 1.06	3.20 ± 1.10
	Avg	3.51 ± 0.91	3.44 ± 0.99	3.42 ± 0.99	3.46 ± 0.97	3.43 ± 0.99	3.33 ± 1.01
Placebo	In	3.75 ± 1.12	3.69 ± 1.12	3.73 ± 1.20	3.73 ± 1.23	3.73 ± 1.24	3.73 ± 1.11
	Ex	3.54 ± 1.18	3.37 ± 1.08	3.44 ± 1.23	3.33 ± 1.10	3.44 ± 1.14	3.41 ± 1.05
	Avg	3.65 ± 1.11	3.53 ± 1.06	3.59 ± 1.16	3.53 ± 1.12	3.59 ± 1.15	3.56 ± 1.03

Table 4. Respiratory resistance values for caffeine, placebo and nocebo for four subjects who participated in nocebo trials. Values are split into inhalation, exhalation, and average resistance. Resistance values were measured in $cmH_2O \cdot sec/L$.

		Before	0 min	15 min	30 min	45 min	60 min
Caffeine	In	3.30 ± 0.99	3.41 ± 1.26	3.25 ± 1.01	3.34 ± 0.98	3.45 ± 1.24	3.24 ± 1.20
	Ex	3.24 ± 1.01	3.07 ± 1.01	3.03 ± 1.07	3.10 ± 1.06	3.17 ± 1.24	2.99 ± 1.33
	Avg	3.27 ± 0.99	3.24 ± 1.13	3.14 ± 1.03	3.22 ± 1.01	3.31 ± 1.22	3.11 ± 1.24
Placebo	In	3.41 ± 1.01	3.48 ± 1.03	3.40 ± 0.52	3.24 ± 0.99	3.30 ± 0.92	3.35 ± 0.83
	Ex	3.37 ± 1.52	3.29 ± 1.34	3.38 ± 1.39	3.16 ± 1.29	3.17 ± 1.27	3.29 ± 1.30
	Avg	3.39 ± 1.26	3.39 ± 1.16	3.39 ± 1.11	3.22 ± 1.14	3.24 ± 1.09	3.31 ± 1.05
Nocebo	In	3.44 ± 0.83	3.42 ± 0.77	3.31 ± 0.77	3.25 ± 0.88	3.39 ± 0.90	3.36 ± 0.85
	Ex	3.24 ± 0.90	3.25 ± 0.88	3.26 ± 0.94	3.15 ± 1.13	3.45 ± 1.22	3.34 ± 1.08
	Avg	3.34 ± 0.86	3.34 ± 0.81	3.29 ± 0.85	3.20 ± 0.99	3.42 ± 1.05	3.35 ± 0.96

Again, there was no significant difference between resistance values for caffeine, placebo, and nocebo trials for these subjects.

4. Discussion

There was no significant change in respiratory resistance from beginning to end of the caffeine trials. This would imply that respiratory resistance is not affected by caffeine ingestion. The act of taking a pill does not appear to affect respiratory resistance either, as there was no significant difference over time for placebo trials. Additionally, the repeated measurement-taking of the testing process did not appear to have any effect on respiratory resistance, as there was no significant increase or decrease in resistance values over time in the "nocebo" trials. These results were also found to be true for both the inhalation and exhalation phases of the breathing period.

Ingestion of small amounts of caffeine appears to have no effect on respiratory resistance, so pulmonary function laboratory measures of respiratory resistances are not expected to be influenced by drinking caffeine beverages prior to testing. Due to the risk involved in this experiment, very low dosages of caffeine were

used. In order to truly determine if larger doses of caffeine can have an effect on respiratory resistance, further testing with higher caffeine doses would be required.

References

[1] Daly, J.W., Ukena, D. and Jacobson, K.A. (1987) Analogues of Adenosine, Theophylline, and Caffeine: Selective Interactions with A, and A2 Adenosine Receptors. In: Gerlach, E. and Becker, B.F., Eds., *Topics and Perspectives in Adenosine Research*, Springer, Berlin, 23-36. https://doi.org/10.1007/978-3-642-45619-0_3

[2] Neims, A.H. and Von Borstel, R.W. (1983) Caffeine: Metabolism and Biochemical Mechanisms of Action. In: Wurtman, R.J. and Wurtman, J.J., Eds., *Nutrition and the Brain*, Raven Press, New York, l-30.

[3] Boulenger, J.P., Patel, J. and Marangos, P.J. (1982) Effects of Caffeine and Theophylline on Adenosine and Benzodiazepine Receptors in Human Brain. *Neuroscience Letters*, **30**, 161-166. https://doi.org/10.1016/0304-3940(82)90290-7

[4] Dews, P.B. (1984) Behavioral Effects of Caffeine. In: Dews, P.B., Ed., *Caffeine*: *Perspectives from Recent Research*, Springer, Heidelberg, 86-103. https://doi.org/10.1007/978-3-642-69823-1_6

[5] Robertson, D., Wade, D., Workman, R., Woosley. R.I., and Oates, J.A. (1981) Tolerance to the Humoral and Hemodynamic Effects of Caffeine in Man. *Journal of Clinical Investigation*, **67**, 1111-1117. https://doi.org/10.1172/JCI110124

[6] Mohsenin, A. and Blackburn, M.R. (2006) Adenosine Signaling in Asthma and Chronic Obstructive Pulmonary Disease. *Current Opinion in Pulmonary Medicine*, **12**, 54-59. https://doi.org/10.1097/01.mcp.0000199002.46038.cb

[7] Mitchell, P.J. and Redman, J.R. (1992) Effects of Caffeine, Time of Day and User History on Study-Related Performance. *Psychopharmacology*, **109**, 121-126. https://doi.org/10.1007/BF02245489

[8] Pasman, W.J., Van Baak, M.A., Jeukendrup, A.E. and De Haan, A. (1995) The Effect of Different Dosages of Caffeine on Endurance Performance Time. *International Journal of Sports Medicine*, **16**, 225-230.https://doi.org/10.1055/s-2007-972996

[9] Lieberman, H.R., Wurtman, R.J., Emde, G.G., Roberts, C. and Coviella, I.L.G. (1987) The Effects of Low Doses of Caffeine on Human Performance and Mood. *Psychopharmacology*, **92**, 308-312. https://doi.org/10.1007/BF00210835

[10] Bell, D.G., Jacobs, I. and Zamecnik, J. (1998) Effects of Caffeine, Ephedrine and their Combination on Time to Exhaustion during High-Intensity Exercise. *European Journal of Applied Physiology and Occupational Physiology*, **77**, 427-433. https://doi.org/10.1007/s004210050355

[11] Astrup, A., Toubro, S., Cannon, S., Hein, P. and Madsen, J. (1991) Thermogenic Synergism between Ephedrine and Caffeine in Healthy Volunteers: A Double-Blind, Placebo-Controlled Study. *Metabolism*, **40**, 323-329. https://doi.org/10.1016/0026-0495(91)90117-F

[12] Lausted, C.G., and Johnson, A.T. (1999) Respiratory Resistance Measured by an Airflow Perturbation Device. *Physiological Measurement*, **20**, 21-35. https://doi.org/10.1088/0967-3334/20/1/002

[13] Silverman, N.K. and Johnson, A.T. (2005) Design for a Stand-Alone Airflow Perturbation Device. *Journal of Medical Implants and Surgery*, **1**, 139-148.

[14] Zahn, T.P. and Rapoport, J.L. (1987) Autonomic Nervouse System Effects of Acute Doses of Caffeine in Caffeine Users and Abstainers. *International Journal of Psychophysiology*, **5**, 33-41. https://doi.org/10.1016/0167-8760(87)90070-5

[15] Harder, S., Staib, A.H., Beer, C., Papenburg, A., Stille, W. and Shah, P.M. (1988) 4-Quinolones Inhibit Biotransformation of Caffeine. *European Journal of Clinical Pharmacology*, **35**, 651-656. https://doi.org/10.1007/BF00637602

[16] Johnson, A.T., Jones, S.C., Pan, J.J. and Vossoughi, J. (2012) Variation of Respiratory Resistance Suggests Optimization of Airway Caliber. *IEEE Transactions on Biomedical Engineering*, **59**, 2355-2361. https://doi.org/10.1109/TBME.2012.2204055