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Running Head: Airflow dynamics following cold-water ingestion

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Declarations of interest: None.

ABSTRACT

Introduction. Drinking cold water evokes decreases in spirometric indices of lung function. We studied whether this could be explained by changes in exhaled-breath temperature (EBT), airflow dynamics, and spirometer measurement sensitivity. **Methods**. In a randomized/crossover design, 10 healthy adults consumed 1,000 mL refrigerated water (2.1±0.64 ºC) or water at room temperature (19.4±0.5 ºC), with EBT assessed at baseline and at 5,10,15 and 30-min post-ingestion. The influence of EBT on pneumotachograph measurement characteristics was modelled using computational fluid dynamics (CFD). **Results**. At 5-min post-ingestion, EBT was lower (p<0.001) following the ingestion of cold water versus water at room-temperature (31.7±1.1 vs. 33.0±0.9 °C), and remained lower until 30-min post-ingestion. At a flow of 8 $L*s^{-1}$, a decrease in EBT of 2.1 $^{\circ}C$ (observed following cold-water ingestion) was modelled to underpredict lung volume by 0.7%. **Conclusions**. Cold water reduces EBT below baseline but effects pneumotachograph measurements only negligibly; thus, decreased lung function following cold-water ingestion likely has a physiological explanation which warrants further study.

Keywords: airflow; lung function; spirometry.

1.0 INTRODUCTION

Spirometry is a common pulmonary function test (PFT) used in the diagnosis and monitoring of respiratory disorders (Miller *et al.* 2005; Graham *et al.* 2019). In addition to providing standardized criteria for maneuver quality, the ATS/ERS suggest that optimal and repeatable results are more likely if a patient abstains from vigorous exercise for 1 h, smoking or vaping for 1 h, large meals for 2 h, and alcohol for 4 h before a given test. There are no clear guidelines pertaining to fluid ingestion as it relates to spirometry, aside from the recommendation that "drinking water should be available" (Graham et al., 2019).

Two recent studies from our group suggest that water, ingested up to 30 min before spirometry, may negatively impact on lung function. In the first of these studies, 500 – 700 mL tap-water evoked significant decreases in forced vital capacity (FVC, –2.3%) and forced expiratory volume in 1 second (FEV_1, –2.9%) in healthy subjects (Turner *et al.* 2015). We observed no such changes with a volume-matched food bolus, indicating that the decreases in lung function following fluid ingestion were independent of gastric load, *per se*. In the second study, we showed that 1,000 mL of refrigerated water (~3 °C) significantly reduced FVC, FEV_1, FEV_1/FVC, and forced expiratory flow measured between 25 and 75% of the exhalation (FEF_{25-75}) in the range of 5 – 10%. Furthermore, the decreases were significantly greater than those observed with an equivalent volume of water at room-temperature (Turner *et al.* 2016). We thereby concluded that ingesting a large bolus of water had the potential to reduce lung function via a mechanism that was likely temperature-dependent.

We can conceive two potential physiological explanations for these findings. First, the autonomic nervous system plays an important role in regulating airway function (van der Velden and Hulsmann 1999). Ingesting cold water has been shown to increase vagal tone (Chiang *et al.* 2010), which might trigger airway mucous production and bronchoconstriction in susceptible groups (Undem and Kollarik, 2005). Second, cold air can evoke a pro-inflammatory hyper-responsiveness in the airway (Cockroft and Davis, 2006), and it is plausible that the ingestion of cold water may exert a similar effect

due to the trachea's close anatomical proximity to the upper-GI tract (laryngopharynx and oesophagus). Both of these hypotheses are yet to be tested.

A third possible explanation for a decrease in spirometric values following cold-water ingestion is a decrease in exhaled-breath temperature (EBT) (via indirect cooling of the upper-airway), and the consequent effect of gas temperature on spirometer measurement (Miller and Sigsgaard, 1994). The pneumotachograph is the most widely-used device in laboratory-based lung function testing (de Jongh, 2008). During an expiratory maneuver, a transducer measures pressure differentials (ΔP) across a capillary tube bank. On the basis that pressure and laminar flow are proportional (Button, 2015), an analogue ΔP signal is used to calculate flow, which is integrated to volume. The ΔP is dependent on gas viscosity which increases with temperature (Miller *et al.* 2005). As a result, a potential source of error is that a change in the temperature of expired gas (from ingesting cold fluids) may alter airflow dynamics, and disrupt the flow-pressure relationship on which the pneumotachograph output is based.

There is also a large discrepancy between the ambient temperature (that at which the pneumotachograph is calibrated) and that of the exhaled gas; this, in turn, would be expected to influence the calculated flows and volumes. Accordingly, a BTPS correction factor (which assumes that gas temperature in the measuring device is equivalent to body temperature; i.e., 37 °C) is applied to the outcome variables. A second potential source of error, therefore, is a cold-water-induced decrease in the exhaled gas temperature below the anticipated 37 °C, thereby invalidating one of the assumptions of the BTPS equation.

To further elucidate the mechanical factors by which cold-water ingestion might influence spirometry, several questions need to be addressed. First, is whether ingesting cold water reduces exhaled-breath temperature (EBT) in healthy subjects. Second, is whether the reduction in EBT induced by cold water ingestion is sufficient to influence airflow dynamics and, therefore, the measurement characteristics of a commercially-available pneumotachograph. Data to this effect would edify standardization guidelines for PFTs, and inform further mechanistic studies into the nature of lung function decline following cold-water ingestion. Given that EBT is widely utilized as a means of monitoring day-to-day perturbations in airway inflammation (Popov *et al.* 2017), data on cold-water ingestion as a potential confounding factor in the assessment of EBT may also prove insightful.

Accordingly, the aims of this randomized, cross-over trial were to evaluate the effects of fluid ingestion on EBT in healthy adults, and to use computational fluid dynamics (CFD) to model the effect of perturbations in gas temperature (and pressure) on pneumotachograph measurements.

2.0 METHODS

2.1 Subjects

Ten healthy, recreationally-active adults (5 male/5 female) volunteered to participate (age = 36 ± 7 y; mass = 87.4 ± 31.8 kg; stature = 1.74 ± 0.80 m). After providing written, informed consent, subjects were instructed to attend the laboratory following an overnight fast, and to abstain from taking any fluid the morning of their visits. The study was approved by the institution's Research Ethics Committee, and performed in accordance with the 1964 Declaration of Helsinki.

2.2 Experimental Overview

Subjects attended the laboratory on three occasions separated by at least 24 h. At the first visit, they performed basic anthropometry, baseline spirometry, and were accustomed to measures of exhaled-breath temperature (EBT). At the second and third visits, subjects performed baseline tests of EBT, after which they consumed a single bolus of cold- or room-temperature water with follow-up tests of EBT performed periodically for 30 min. The order of trials was randomised and counterbalanced, and performed at the same time of day to eliminate the influence of circadian variance. The effect of exhaled gas temperature on measurement characteristics of the pneumotachograph was modelled using CFD (see below).

2.3 Spirometry

Baseline pulmonary volumes, capacities, and flows were assessed via spirometry. Subjects performed between three and eight FVC maneuvers into a two-way disposable mouthpiece connected to a portable pneumotachograph (Alpha Touch; Vitalograph Ltd., Buckingham, England). Subjects were seated, had the nose occluded, and verbal encouragement was given to ensure consistent efforts. Spirometry was performed in accordance with ATS/ERS guidelines (Miller *et al.* 2005), and all values were expressed in absolute terms and as percentages of predicted norms (Quanjer *et al.* 2012).

2.4 Exhaled-Breath Temperature

Exhaled-breath temperature was assessed during tidal breathing using a hand-held thermometer (X-Halo; Delmedica Investments, Singapore) using protocols previously described (Popov *et al.* 2007). Briefly, participants were required to inhale through the nose and exhale through the mouth into a one-way antimicrobial filter. The EBT device comprised a metal core containing a high-precision thermal sensor housed within a 300 mL thermo-insulated chamber. Participants were asked to maintain normal tidal breathing until the metal core reached a thermal balance in the mixing chamber (3 – 6 min), at which point peak-EBT was recorded. Following two baseline measures spaced 10 min apart to deduce reproducibility, participants were given 10 min to consume 1,000 mL of refrigerated cold water (2.1 ± 0.6 ºC) or water at room temperature (19.4 ± 0.5 ºC). Exhaled-breath temperature measures were repeated at 5, 10, 15, and 30 min post-ingestion.

2.5 Within- and Between-Day Reproducibility of Measures

Within-day reproducibility of EBT was determined by comparing two sets of baseline measures recorded before and after 10 min passive rest. Between-day reproducibility was determined by re-assessing baseline values at the second visit > 24 h later. There were no systematic differences in measurements ($p > 0.05$), and the between-occasion reliability was excellent (CV = 0.66%; SEM = 0.09 ºC; ICC = 0.84). Using similar procedures and identical apparatus to the present study, we recently published strong within- and between-day reproducibility of our spirometric assessments (all CV < 5%; all SEM < 5%; all ICC > 0.94) (Tiller *et al.* 2019).

2.6 Computational Fluid Dynamics

Computational fluid dynamics was used to model the influence of exhaled-breath temperature on spirometer measurements. The numerical calculation of flow was accomplished through solution of continuity, Navier-Stokes, energy and turbulence model equations (Versteeg and Malalasekera, 1995). Calculations were performed using commercially-available software (Fluent version 17.1.0; ANSYS, Pennsylvania, U.S.A.). A geometric representation of the pneumotachograph and associated equipment, suitable for simulation, was first created with a 22.5 º rotational periodic geometric assumption using computer-aided design (Fig. 1). This was subsequently discretized into 15.3 million polyhedral

elements, and the geometry represented with finite volumes in which flow calculations were iteratively performed.

With the body temperature of the pneumotachograph held at a constant 20 ˚C (i.e., that at which it was calibrated), the effect of various gas temperatures (20, 22, 24, 26, 28, 30, 32, 34 ºC) on the measured pressure drop (ΔP) across the capillary tube bank was simulated at fixed physiological flow rates of 1, 4, 8, 12, and 16 $L*s^{-1}$. Physical gas properties were specified using temperature-dependent polynomials. A pneumotachograph operates on the principle that pressure drop and laminar flow through the body are proportional. For a known ΔP signal, it is possible to calculate flow rate as a factor of time, and thereby interpolate volume. However, because ΔP is affected by temperature of the gas passing through the device, a discordance between the calibration gas temperature and the exhaled gas temperature will introduce discrepancies in the calculated flow (that is, unless a temperature correction has been applied). Through the simulation process (based on a representative flow-volume curve in a healthy subject with normal lung function), a series of ΔP-flow curves were obtained for each gas temperature. From these curves, it was possible to calculate the discrepancy in reported flow and volume that would result from a pneumotachograph calibrated at room temperature (20 ºC). Accordingly, we determined the effect of changes in gas temperature alone, as evoked by cold-water ingestion, on predicted pneumotachograph flow/volume metrics.

2.7 Data Analysis

Descriptive and inferential statistics were calculated using SPSS 24 for Windows (IBM; Illinois, U.S.A.). Reproducibility was assessed using coefficient of variation (CV), standard error of measurement (SEM), and intra-class correlation coefficients (ICC). Exhaled breath temperature following the ingestion of cold- and room-temperature water was compared using a two-factor (condition × time) repeated-measures ANOVA, with a critical alpha level of 0.05. The assumption of equal variance was assessed via Mauchly's Test of Sphericity and, if violated ($p < 0.05$), a Greenhouse-Geisser correction was applied. On significant interactions, follow-up pairwise comparisons were performed using a Bonferroni-adjusted alpha level of 0.01. Effect size (Cohen's *d*) was used to quantify

the magnitude of the difference between group means (0.2 = small; 0.5 = medium; 0.8 = large effect) (Cohen, 1977). Data were presented as mean ± standard deviation (SD).

3.0 RESULTS

3.1 Spirometry

Lung function was within normal limits: FVC = 103 ± 18 %Pred; FEV_1 = 87 ± 18 %Pred; FEV_1/VC = 85 ± 8 %; peak expiratory flow = 106 ± 22 %Pred.

3.2 Exhaled Breath Temperature

Exhaled-breath temperature at baseline and in response to the ingestion of cold- and room-temperature water is shown in Table 1.0. Baseline EBT was not different between the two experimental visits (p = 0.269, d = 0.25). Mean drink temperature was 2.1 ± 0.6 °C in the cold-water condition (range 1 – 3 °C) and 19.4 ± 1.5 °C in the room-temperature condition (range 17 – 21.5 °C). Relative to baseline, EBT at 5 min post-ingestion had decreased significantly with both cold water (p < 0.001, d = 2.57) and room-temperature water (p = 0.005, d = 0.94), and in both cases remained below baseline until the final measurement at 30 min (p < 0.01). When comparing between the conditions, there were main-effects showing a lower EBT with cold water (F[1,9] = 62.90, p < 0.001), and a condition × time interaction (F[2.21,36] = 10.72, p = 0.001). Pairwise comparisons revealed that EBT was significantly lower following the ingestion of cold water relative to room-temperature water at 5, 10, and 15 min (p < 0.001; Table 1.0). Differences at 30 min were worthy of note, but did not reach statistical significance (p = 0.059).

3.3 Computational Fluid Dynamics

The influence of gas temperature on pressure differentials across the tube bank is shown in Table 2. The magnitude of the pressure drop increased congruent with flow rate and, at each of the five flow rates (1, 4, 8, 12, and 16 $L*s^{-1}$), ΔP was lower at higher gas temperatures. From these data, we were able to model the influence of EBT perturbations on ΔP and the subsequent expiratory flow-volume curve. In a pressure transducer calibrated with an ambient gas of 20 °C, an EBT of 33.8 °C (baseline) and 31.7 °C (post- cold-water ingestion) would result in the underprediction of volume by 5.2 and 4.5%, respectively (Fig. 2). At an example flow rate of 8 $L*s^{-1}$, a decrease in gas temperature from 33.8 to

206 31.7 ˚C attenuated ΔP by 3.2 Pa (0.8%). Thus, in this scenario, a cold-water-induced decrease in EBT
207 of 2.1 ºC results in a difference between predicted volumes of 0.7%.
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4.0 DISCUSSION

The aims of this study were to evaluate the effects of fluid ingestion on EBT in healthy adults, and to use computational fluid dynamics to model the effect of perturbations in gas temperature (and pressure) on pneumotachograph measurement sensitivity. We made several observations: i) the ingestion of both cold water and room-temperature water resulted in significant decreases in EBT, with values remaining below baseline for at least 30 min; ii) cold water ingestion decreased EBT to a significantly greater magnitude than water at room temperature; and iii) the decrease in EBT following cold-water ingestion was calculated to influence the pneumotachograph flow-volume measurement by < 1%. These data have implications for the clinical assessment of both spirometry and EBT.

4.1 Technical considerations

There are several considerations that should predicate the interpretation of our data. First, as discussed below, certain factors might confound the measurement of EBT, including food, exercise, cigarette-smoking, and circadian variance (Carpagnano *et al.* 2016, 2017; Kralimarkova *et al.* 2012, 2014; Svensson *et al.* 2012). To mitigate these factors, we recruited non-smokers, instructed our subjects to attend the laboratory having abstained from food, fluid, and exercise on the morning of the test, and we assessed EBT at the same time of day in both experimental trials (i.e., 08:00 – 09:00). We also demonstrate excellent within- and between-day reliability of our EBT measures: no systematic differences in measurements ($p > 0.05$); CV = 0.66%; SEM = 0.09 ºC; ICC = 0.84. As such, we are confident that our data reflect the *true* EBT responses to cold-water ingestion.

Second, our model of EBT and airflow dynamics is only relevant when assessing lung function via the Fleisch or Lilly pneumotachograph (i.e., those deriving flow via pressure differentials across a screen or capillary tube bank). Other frequently-used devices include wet/dry volume-measurement spirometers, and flow measurement devices operating under different principles (e.g., mass flow meters), and there are systematic differences in the data obtained among the various spirometers (Brouwer *et al.* 2007; Gerbase *et al.* 2013; Stwart *et al.* 2003). As such, although pneumotachographs are generally considered to be the best (Miller *et al.* 1997) and most widely-used (de Jongh, 2008)

means of measuring forced expiratory maneuvers, further studies are needed to assess the effects of cold-water-induced changes in airflow dynamics with other devices.

Finally, it is worth noting that our airflow model is based on the standard, non-heated pneumotachograph that is in widespread clinical use (Miller and Sigsgaard, 1994). Some devices contain a heated element that conditions the expired air in order to reduce surface condensation in the tube bank that may occur during repeated expiratory maneuvers, but this is unlikely to reduce measurement inaccuracies that result from changes in gas temperature.

4.2 Exhaled-breath Temperature and Computational Fluid Dynamics

The bronchial microvasculature plays an important role in the response to airway disease (Paredi and Barnes, 2009), and the assessment of EBT has become commonplace in monitoring day to-day perturbations in airway blood flow resulting from inflammation and exacerbation (Popov *et al.* 2012). Indeed, acute exacerbations in asthmatic patients (resulting from hyperreactivity and vascularization of the bronchial smooth muscle) transiently increase EBT; by contrast, chronic airway damage and reduced vascularization which characterize COPD results in lower baseline EBT values (Popov *et al.* 2012).

Several factors are thought to confound the measurement of EBT. Circadian variance was shown to result in EBT fluctuations of ~1.33 °C (Carpagnano *et al.* 2017), while smoking a cigarette and eating snack foods have been shown to influence baseline measurements by ~0.19 °C (Kralimarkova *et al.* 2014) and ~0.48 °C (Kralimarkova *et al.* 2012), respectively. Following exercise, asthmatics and healthy controls exhibited increases in EBT of <1.0 °C, with no significant difference between groups (Scvensson *et al.* 2012). To our knowledge, ours is the first study to evaluate the effect of fluid ingestion on EBT measurement. The data show that a bolus of refrigerated water decreased EBT to a far greater magnitude (-2.1 °C) than that observed from other confounders. Moreover, the decrease had only partially recovered (to -1.0 °C) at 30 min post-ingestion (Table 1.0). Accordingly, patients using EBT as a means of monitoring airway inflammation should abstain from drinking large volumes of fluid, particularly cold fluid, for at least 30 - 60 min before a given assessment.

To evaluate the effect of cold-water ingestion on spirometer measurement, we first modelled the broad effects of gas temperature on airflow dynamics in a standard, non-heated pneumotachograph. The model assumed that the device was calibrated using an ambient gas at 20 ºC. At an expiratory flow of 8.0 $L*s^{-1}$, we calculated that an exhaled gas temperature of 33.8 °C (baseline EBT) would result in a ΔP across the tube bank that is 22.4 Pa (5.5%) larger than that elicited by an ambient temperature exhalate. The result would be a flow underprediction of 5.2% (Table 2). To accommodate this considerable error, a BTPS correction factor is applied which assumes that gas temperature in the measuring device is equivalent to body temperature (i.e., 37 °C). However, there are numerous studies showing baseline EBT to be below 37 °C in various subgroups, including healthy controls (33.2 - 34.8 °C, Popov *et al*. 2007; Garcia *et al.* 2013; Svensson *et al.* 2012), asthmatics (33.7 - 35.5 °C, Popov *et al.* 2007; Svensson *et al.* 2012, 2014; Garcia *et al.* 2013), and patients with COPD (34.0 - 34.6 °C, Lázár *et al.* 2014). We presently report a baseline EBT in our healthy cohort of ~33.8 ± 0.4 °C, which mirrors data from Svensson *et al.* (2012), and corroborates the general consensus. As such, to mitigate unnecessary errors in spirometric measurement, we concur with others who suggest that the BTPS correction factor for expiratory gas should be adapted to the actual gas conditions in the pneumotachograph (Normand *et al.* 2007).

We next assessed the effects of a change in EBT on spirometer airflow dynamics. We showed that a cold-water-induced decrease in EBT of 2.1 °C would alter the linear flow-pressure relationship, and decrease the volume output by 0.7%. Our earlier studies show a decrease in FVC, FEV_1, and MEF_{25-75} in the region of 5 – 10% following cold-water ingestion (Turner *et al*. 2015; 2016). These decreases are of a far greater magnitude than can be explained by our current model of pneumotachograph airflow temperature considerations. At present we can only speculate on the physiological mechanisms that underpin lung function decline following cold-water ingestion. It was initially thought that cold-water ingestion may evoke a pro-inflammatory hyperresponsiveness in the airway, in a similar fashion to that observed with cold air (Cockroft and Davis, 2006). However, Svensson *et al.* (2012) reported larger post-exercise decreases in FEV_1 in those individuals with higher EBT, suggesting that EBT increases under conditions of acute airway inflammation. We currently report decreases in EBT following cold-water ingestion, thereby potentially discounting airway inflammation and/or hyperresponsiveness as a

causative factor. Further research into these mechanisms may have important implications for routine pulmonary function testing guidelines.

In conclusion, we observed large and sustained decreases in exhaled breath temperature following the ingestion of cold water. The magnitude of the decrease exceeds that seen with other confounding variables and, as such, abstaining from fluid ingestion for at least 30 min prior to a test should be integrated into standard EBT assessment guidelines. However, the decreases in EBT influenced spirometer measurements only negligibly (<1%), suggesting that cold-water-induced decreases in spirometric output likely have a physiological mechanism, which warrants further study.

Acknowledgements

The authors would like to thank the subjects who volunteered their time to participate in this research.

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FIGURES & TABLES

Table 1. Exhaled-breath temperature at baseline and following the ingestion of cold or room-temperature water.

Table 2. The modeled influence of gas temperature on pressure changes (ΔP) across the pneumotachograph tube bank.

Fig. 1. Modelled pneumotach geometry with a rotational periodicity of 22.5º. The geometry of the pneumotach can be approximated as axially repeating, allowing the use of rotational periodic boundary assumptions that reduce overall computational expense of the simulation.

Fig. 2. Modelled influence of gas temperature on a typical expiratory flow-volume curve. In a pressure transducer calibrated with a gas of 20 ºC (standard room temperature), an EBT of 33.8 ºC (baseline) and 31.7 ºC (post- cold-water ingestion) result in an underestimation of the calculated volume by 5.2 and 4.5%, respectively. The EBT decrease following cold-water ingestion (2.1 ºC) results in a 0.7% underprediction of volume.

444 **Table 1.** Exhaled-breath temperature at baseline and following the ingestion of cold- or room-
445 temperature water.

	Cold (2.1 ◦C)	Room (19.4 ◦C)	*p	d
Baseline	33.8 ± 0.4	33.7 ± 0.5	0.269	0.25
+5 min	31.7 ± 1.1*	33.0 ± 0.9*†	<0.001	1.34
+10 min	32.6 ± 0.6*	33.2 ± 0.6*†	<0.001	1.06
+15 min	32.5 ± 0.6*	33.3 ± 0.5*†	<0.001	1.46
+30 min	32.8 ± 0.5*	33.3 ± 0.8*	0.059	0.74

446

447 Mean ± SD, n=10. *d* = Cohen's *d* effect size (0.2 = small, 0.5 = medium, 0.8 = large effect) (17).
448 *significantly different versus respective baseline; †significantly different versus cold water.

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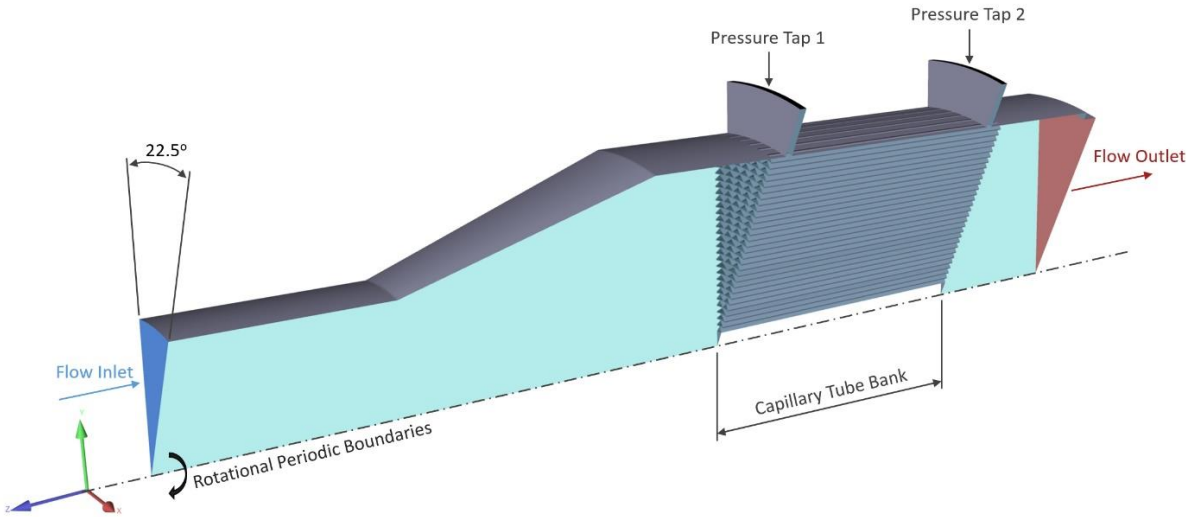
Table 2. The modeled influence of gas temperature on pressure changes across the pneumotachograph tube bank.

	Pressure difference across pneumotachograph (Pa)		
Flow ($L \cdot s^{-1}$)	20 °C	28.5 °C (%Diff.)	34.5 °C (%Diff.)
1	−43.9	−42.6 (3.1)	−41.7 (5.3)
4	−197.9	−191.7 (3.2)	−187.6 (5.5)
8	−426.5	−413.1 (3.2)	−404.1 (5.5)
12	−664.2	−643.5 (3.2)	−629.5 (5.5)
16	−907.4	−877.0 (3.5)	−858.0 (5.8)

%Diff. is relative to pressure at 20 °C.



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461 **Figure 1.**

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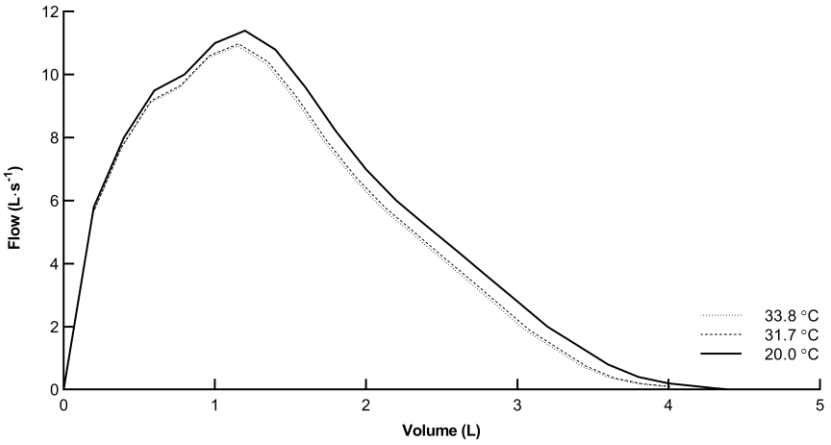

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464 **Figure 2.**