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Laboratory Evaluation of the CReSSmicro™ Portable Topography Device: Implications for Clinical Research*

by

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SUMMARY

Performance of the CReSSmicro™ v.2.0.0 portable smoking topography device was evaluated in a controlled laboratory environment using a calibrated smoking machine to generate known, reproducible smoking topographies. Device performance was evaluated using unlit and lit cigarettes over a range of puff volumes (25 to 100 mL) at 2 s puff duration using a sine wave profile. The device missed 93% and 100% of the 25 mL/2 s puffs for unlit and lit cigarettes, respectively. The device underreported puff durations for the entire volume range, i.e., from 40 mL (0.9 ± 0.17 s) to 100 mL (1.6 ± 0.11 s) for both unlit and lit cigarettes. Puff volumes were under reported for lower volumes from 40 mL (25.6 ± 5.5 mL) to 70 mL (68.8 ± 3.7 mL) for both unlit and lit cigarettes and slightly over reported for higher volumes from 85 mL (89.4 ± 7.6 mL) to 100 mL (103.4 ± 9.8 mL) for lit cigarettes. Experimental results indicated that a 12.5–20mL/s (750–1,200 mL/min) flow threshold for puff recognition was responsible for the observed results. This study reinforces the importance of fully understanding device performance prior to performing clinical studies of human smoking topography. [Beitr. Tabakforsch. Int. 26 (2014) 19–25]

ZUSAMMENFASSUNG

Die Leistungsfähigkeit des mobilen Rauchtopographiegerätes CReSSmicro™ v.2.0.0 wurde in einer kontrollierten Laborumgebung untersucht. Dabei wurde eine kalibrierte Abrauchmaschine eingesetzt, um bekannte, reproduzierbare Rauchtopographien zu erzeugen. Die Maschinenleistung wurde mit Hilfe von angezündeten und nicht angezündeten Zigaretten mit unterschiedlichen Zugvolumina (25 bis 100 mL) mit einer Zugdauer von 2 s und einem Sinusprofil untersucht. Bei den nicht angezündeten bzw. angezündeten Zigaretten wurden jeweils 93 % bzw. 100 % der 25 mL/2 s-Züge vom Gerät nicht gezählt. Das Gerät wies in allen gewählten Volumina, d.h. von 40 mL (0,9 ± 0,17 s) bis 100 mL (1,6 ± 0,11 s), für sowohl nicht angezündete als auch angezündete Zigaretten eine zu geringe Zugdauer aus. Die Zugvolumina wurden bei den niedrigeren Volumina von 40 mL (25,6 ± 5,5 mL) bis 70 mL (68,8 ± 3,7 mL) für sowohl nicht angezündete als auch angezündete Zigaretten geringer als tatsächlich angegeben und bei den höheren Volumina von 85 mL (89,4 ± 7,6 mL) bis 100 mL (103,4 ± 9,8 mL) für angezündete Zigaretten etwas zu hoch angegeben. Die Versuchsergebnisse zeigten, dass ein Durchflussschwellenwert von 12,5–20 mL/s (750–1.200 mL/min) bei der Bestimmung der Züge für die beobachteten Ergebnisse verantwortlich war. Diese Studie unterstreicht, wie wichtig es ist, die Leistungsfähigkeit der Maschinen genau zu kennen, bevor klinische Studien zur Rauchtopographie beim Menschen durchgeführt werden können. [Beitr. Tabakforsch. Int. 26 (2014) 19–25]

RESUME

La performance de l'appareil portable de topographie du fumage CReSSmicro™ v.2.0.0 a été évaluée en milieu contrôlé dans un laboratoire, en utilisant une machine à fumer étalonnée pour générer des topographies du fumage reproductibles connues. La performance de l'appareil a été évaluée au moyen de cigarettes non-allumées et allumées,

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dans une plage de volumes de bouffées (de 25 à 100 mL) pour une durée de bouffée de 2 s en utilisant un profil d'onde sinusoïdale. L'appareil s'est trompé pour 93% et 100% des bouffées de 25 mL/2 s avec les cigarettes non-allumées et allumées respectivement. L'appareil a sous-estimé les durées de bouffées sur toute la plage de volumes, c'est-à-dire de 40 mL (0,9 ± 0,17 s) à 100 mL (1,6 ± 0,11 s), tant pour les cigarettes non-allumées que pour les cigarettes allumées. Les volumes de bouffées ont été sous-estimés pour les volumes inférieurs de 40 mL (25,6 ± 5,5 mL) à 70 mL (68,8 ± 3,7 mL), à la fois pour les cigarettes non-allumées et allumées et ils ont été légèrement surestimés pour des volumes plus élevés de 85 mL (89,4 ± 7,6 mL) à 100 mL (103,4 ± 9,8 mL) pour les cigarettes allumées. Les résultats expérimentaux ont indiqué qu'un seuil de flux de 12,5–20 mL/s (750–1200 mL/min) pour la reconnaissance des bouffées était responsable des résultats observés. Cette étude confirme l'importance de parfaitement bien comprendre la performance de l'appareil avant d'effectuer des essais cliniques de topographie du fumage humain. [Beitr. Tabakforsch. Int. 26 (2014) 19–25]

INTRODUCTION

Measurement of human smoking behavior has been of interest for over eighty years (1, 2) and studies measuring human smoking behavior have used various invasive and non-invasive techniques. Invasive techniques include measurement of tobacco specific (tobacco specific nitrosamines) and non-tobacco specific (carboxyhemoglobin, thiocyanate, 1-hydroxypyrene, 3-hydroxypropylmercapturic acid, S-phenylmercapturic acid) biomarkers of exposure in serum and urine (3–8). Non-invasive techniques have been used to measure "mouth level exposure" and include analysis of cigarette butts (9–12) or measurement of smoking topography (13–15). Smoking topography assesses puffing parameters such as the number of puffs, puff volume, puff duration, inter-puff interval, as well as, derived values (mean puff velocity, total puff volume, etc.). Over the years several techniques including trained observers (16), video cameras (17), flowmeters (18–20), pneumotachographs (21, 22) and pressure transducers (23, 24) have been used to measure smoking topography. Currently, the most widely reported human smoking topography measurement device in the literature is the portable version (CReSSmicro™) of the Clinical Research Support System (bench-top device) manufactured by Plowshare Technologies, Inc. (Baltimore, MD, USA; subsequently acquired by Borgwaldt-KC, Richmond, VA, USA and called the CReSS Pocket) (14, 15, 25–28). This battery-operated portable device (2.5" × 2.2" × 1.2") is lightweight and uses differential pressure measurements between orifices to derive puff volume, puff duration, number of puffs and inter-puff interval (27, 28). A cigarette is inserted into one side of the device and the user puffs from the opposite side of the device.

With widespread reported use in the literature, it is surprising that there have only been four published studies designed to assess reliability and validity of cigarette puff data collected with the CReSSmicro™ and bench-top devices (29–32). LEE *et al.* (29) conducted two small clinical trials with the first comparing puff volume, puff duration, inter-puff interval and maximum puff velocity as measured by a CReSS device (portable or bench-top device not specified) on four different days in seven smokers. The second trial compared conventional smoking to smoking through the CReSS device using biological endpoints of exhaled carbon monoxide, heart rate, systolic and diastolic blood pressure and plasma nicotine levels in 10 smokers. The first study used Intraclass Correlation Coefficients (ICC; ratio of between smoker variability to the sum of day-to-day variability of the same smoker and between smoker variability) to conclude that values for puff volume, duration and velocity were reliable, however, inter-puff interval was found not to be reliable. In the second study, mean differences from baseline measurements were not different for any of the endpoints measured regardless of whether smoking occurred through the CReSS device or not. SHAHAB *et al.* (30) compared puffs/cigarette, puff volume, puff duration, inter-puff interval, peak puff flow and average puff flow as measured by the CReSSmicro™ (portable device) on two different days for 118 smokers from four countries (Australia, Canada, United Kingdom, and United States). Fair to good reliability was reported (defined by the authors as ICC > 0.6) for puff volume, puff duration, peak puff flow and average puff flow. BLANK *et al.* (31) compared puffs/cigarette, puff duration, average puff volume, total puff volume, and inter-puff interval as measured by the CReSS bench-top, CReSSmicro™ and video recording in 30 smokers who smoked one cigarette/session (two of their own brand and two Merit™ cigarettes) for a total of four sessions. Using a three-factor within-subject analysis of variance (measurement method × cigarette type × cigarette number) and Tukey's honestly significant difference ($p < 0.05$) methods both the CReSS bench-top and portable devices were found to be reliable with two caveats: 1) compared to video recording both the bench-top and CReSSmicro™ devices measured statistically significantly shorter puff durations and; 2) the bench-top CReSS device measured statistically significantly larger average and total puff volumes than the CReSSmicro™ device. More recently, PERKINS *et al.* (32) compared puff number, total puff volume and maximum puff volume measured using a CReSS device (portable or bench-top device not specified) in 94 smokers over four sessions. Using ICC, excellent reliability (ICC > 0.86) was reported for each measured parameter. For total puff volume and maximum puff volume measurements, variability over the four sessions was statistically significant and reduced the reliability of the measurements, however they were still considered reliable with ICC of 0.7 and 0.6 respectively. None of these clinical studies specified the number of devices used so no device-to-device variability information is available. Additionally, the implicit assumption in all four clinical evaluations of CReSS devices is that they accurately measure puff volume and puff flow of a complex aerosol, mainstream tobacco smoke. In order to confirm this assumption and provide device-to-device variability information, a laboratory evaluation of the accuracy of the CReSSmicro™ devices was performed using smoking machines which generate puffs of defined profile, volume and duration.

EXPERIMENTAL

Topography devices

Twenty CReSSmicro™ v.2.0.0 devices were used as received with the manufacturer's recommended default settings. This included the flow threshold for puff recognition set at 20 (the high level). Previous work at the lower threshold setting of 10 resulted in recording of a large number of false puffs. The single point volume calibration was performed daily by pulling a known 55 mL volume through the "mouth-end" of the device using the provided syringe and tubing with an unlit reference cigarette inserted, described as a test puff in the manual. This single point calibration establishes a software scaling factor to correct subsequent volume measurements. Data were retrieved from the handheld device using the CReSShost software and manufacturer's supplied serial cable. Data were not filtered or rejected in any way, such as by using Plowshare's PuffCleanup.exe or by rejecting data outright as nonsensical. The devices were not cleaned during the study.

Smoking machine

A single commercially available 5-port linear smoking machine, operated in single port mode, was used to create standard test puffs (MN G-48, Borgwaldt-KC, Richmond VA). The following puff parameters were used for both unlit and lit cigarettes: sine wave puff profile, 2 s puff duration, 30 s inter-puff interval, and 25, 40, 55, 70, 85, and 100 mL puff volumes. Each puff volume setting was confirmed using a soap bubble flow meter (0–150 mL range, MN 80241530) and the entire system was leak tested using a leakage tester (MN 80206390 Borgwaldt-KC, Richmond, VA, USA). A puff profile analyzer (now called puff recorder), a laboratory-based diagnostic instrument, was used to confirm the correct operation of the smoking machine by measuring the full flow profile (MN H-17, Borgwaldt-KC, Richmond, VA, USA) per ISO standard 7210 (33). A more detailed description of the devices commonly used to ensure accurate and precise smoking machine operation can be found at the vendor's website, http://www.borgwaldt.com.

Depending on puff volume, a different number of puffs were taken to approximate the standard stopping point in puffing cigarettes (34; 3 mm from tipping paper). For puff volumes equal or less than 70 mL, 10 puffs were taken; 8 puffs were taken for 85 mL puff volumes and 7 puffs were taken for puff volumes of 100 mL. Testing was conducted sequentially from low to high volume puffs beginning with unlit cigarettes and concluding with lit cigarettes.

Cigarettes

A popular commercially available cigarette with a "tar" yield of 10 mg (measured using the Cambridge Filter Method - previously known as the FTC method - 35) was used in the unlit and lit cigarette puffing test. The cigarettes were lit using a standard electric lighter (MN 70291190, Borgwaldt-KC, Richmond, VA, USA).

Table 1. Percent of two second puffs recorded by CReSSMicro™ devices.

Puff volume (mL)	Linear smoking machine generated puffs/device	Percent missed puffs [a]	
		Unlit cigarette [b]	Lit cigarette [c]
25	10	93	100
40	10	0	1.5
55	10	0	0.5
70	10	0	0
85	8	0	0
100	7	0	8.8

[a] Number of detected puffs ÷ total number of puffs for all devices (e.g., at 25 mL setting, only 7 of 200 (20 CReSSmicro devices × 10 puffs/device) total puffs were detected).
[b] N = 20 devices.
[c] N = 15 devices, 5 devices failed to function after unlit cigarette testing.

RESULTS

Testing started with 20 CReSSmicro™ devices, 5 devices stopped responding during testing with lit cigarettes, therefore testing with lit cigarettes reflects data from only 15 devices. Not all puffs generated by the linear smoking machine were recorded by the CReSSmicro™ devices tested (Table 1). Mainstream cigarette smoke aerosol affected the CReSSmicro™ device's ability to detect 25 mL and 100 mL volume puffs over a two-second time duration. For puffs that were detected using unlit and lit cigarettes, puff volumes below 70 mL were underestimated (Table 2). No practical differences in puff volumes were seen between the response with lit and unlit cigarettes. This data confirmed previous laboratory studies that indicated the lack of device cleaning did not affect measurement accuracy and precision for the smoking parameters studied during use of the devices in this study. The puff duration measured by the CReSSmicro™ devices also was underestimated (Table 2). The measured duration asymptotically approaches the target with increasing puff volumes but never reaches the target duration. Puff volume and duration variability represented by the standard deviation of the mean measurements varied as a function of puff volume and duration (Table 2).

DISCUSSION

The tested puff volumes and duration were chosen to encompass standard machine smoking regimens, such as Cambridge Filter Method (35), Massachusetts Department of Health (36), and Health Canada (37), and the range of values reported in the literature (29, 31). The CReSSmicro™ device uses a fixed orifice design in which airflow creates a pressure difference which is detected by a pressure transducer. The relationship between puff flow rate and percent of missed puffs demonstrates that at the manufacturer's recommended sensitivity setting (high), a flow rate between 12.5–20 mL/s is required to generate a large enough pressure differential for puff recognition. A

Table 2. Variability (standard deviation – SD) in puff volume and duration measurements by CReSSmicro™ devices.

Smoking machine puff volume [a] (mL)	CReSS measured volume (mL)				CReSS measured duration (ms)			
	Unlit cigarettes [b]		Lit cigarettes [c]		Unlit cigarettes [b]		Lit cigarettes [c]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
25	17.5	5.1	ND [d]		803	204	ND	—
40	28.3	5.3	25.6	5.5	979	175	871	171
55	48.9	2.0	48	2.9	1331	51	1288	63
70	66.5	2.8	68.8	3.7	1505	63	1495	47
85	82.3	2.3	89.4	7.6	1611	43	1636	52
100	95.6	9.1	103.4	9.8	1630	91	1647	107

[a] All puffs were 2000 milliseconds in duration
[b] N = 20 devices
[c] N = 15 devices
[d] ND = Not detected

threshold value for puff recognition also explains the results for puff volume and duration using an idealized sine wave puff profile (Figure 1) and the two caveats noted by BLANK *et al.* (31). Obviously, a threshold for puff recognition must be set high enough so as to not falsely trigger or detect puffs from ambient motion of the CReSSmicro™ device and any electrical noise on the signal, but low enough so as not to miss puffs with low flows. Thus the differential pressure must be set at some finite value greater than zero in order to register the beginning and end of each puff. Changing the sensitivity setting from the manufacturer's recommended "high" sensitivity setting to "low" resulted in recording a significant number of false puffs that precluded testing.

The implication of this finite non-zero differential pressure threshold for puff recognition may be significant for clinical measurements intended to evaluate human smoking behavior, especially if total puff volume is less than 25 mL. For example, corrections based upon the current study for three different mean puff volumes and puff durations reported in the literature are given in Table 3. Corrected puff volumes were estimated using linear regression of the relationship between the puff volume measured by the CReSSmicro™ device and the actual puff volume (Table 2). Corrected puff durations were estimated using a ratio of the puff duration measured by the CReSSmicro™ device and the actual puff duration (Table 2). As expected larger discrepancies occurred with smaller puff volumes. Missed puffs (Table 1) and device variability (Table 2) were not incorporated into these corrections. Two authors (15, 25) have noted limitations in puff volume data measured by CReSS devices by stating their puff volume rejection criteria (< 5mL puff volume; > 1000 mL puff volume; puff duration > 30 s).

The results reported here used machine-generated idealized sine wave puff profiles. Although the single smoking

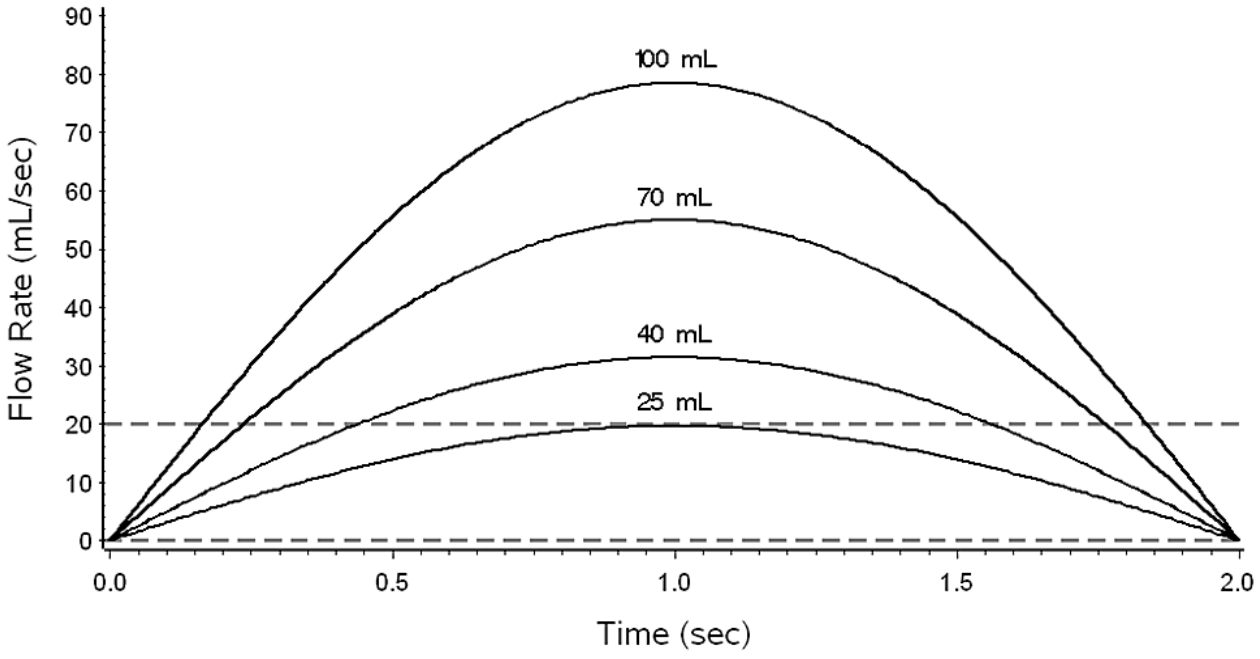

Figure 1. Effect of a threshold value (horizontal dotted line at 16 mL/s) for puff recognition on measurements of puff volume and duration using an idealized sine wave puff profile.

Table 3. Potential effect of CReSSmicro™ measurement errors on reported values for puff duration and volume.

	Reported puff parameters		Adjusted puff parameters [a]	
Author	Mean puff volume [b] (mL)	Mean puff duration [c] (s)	Mean puff volume [b] (mL)	Mean puff duration [c] (s)
LEE *et al.* (29)	30.8	0.9	42.6	1.8
BLANK *et al.* (31)	44.4	1.7	52.9	2.8
CZOGALA *et al.* (39)	60.0	1.7	64.7	2.4

[a] Does not include correction for missed puffs
[b] Estimated puff volume (mL) = Measured puff volume (mL) × 0.7567 + 19.268
[c] Estimated puff duration (s) = 1/(Measured puff duration (s) × 0.14145 × (Measured puff duration (s) – 0.00006957) × Measured puff duration $(s)^2$

machine was set up according to ISO standards and calibrated at each puff volume, there was still a small amount of variability that could be reflected in the measurements by the CReSSmicro™ devices. Variability of the CReSSmicro™ devices measured by relative standard deviation (RSD, (SD/mean) × 100%) for puff volume using lit cigarettes were higher at low (RSD of 21.5% for a 40 mL puff) and high puff volumes (RSD of 9.5% for a 100 mL puff) compared to those in the middle (RSD of 5.4% for a 70 mL puff) demonstrating a "U" shaped profile. A similar "U" shaped profile was seen for puff duration with an RSD of 20% for a 40 mL puff, 3% RSD for a 70 mL puff and 6.5% RSD for a 100 mL puff. These data suggests that if multiple CReSSmicro™ devices are used within a study to compare puff volumes and puff duration, device to device variability could be a significant factor, in addition to the inherent variability in human puffing profiles (Figure 2). There are several limitations of the current study design including lack of randomization of the puffing conditions and use of a fixed puffing duration of 2 s. Because of a lack of randomization of the puffing conditions, differences seen between unlit and lit cigarette puff detection, puff volumes and puff duration could be due to the mainstream cigarette smoke aerosol, a temporal effect (instrument reliability) or

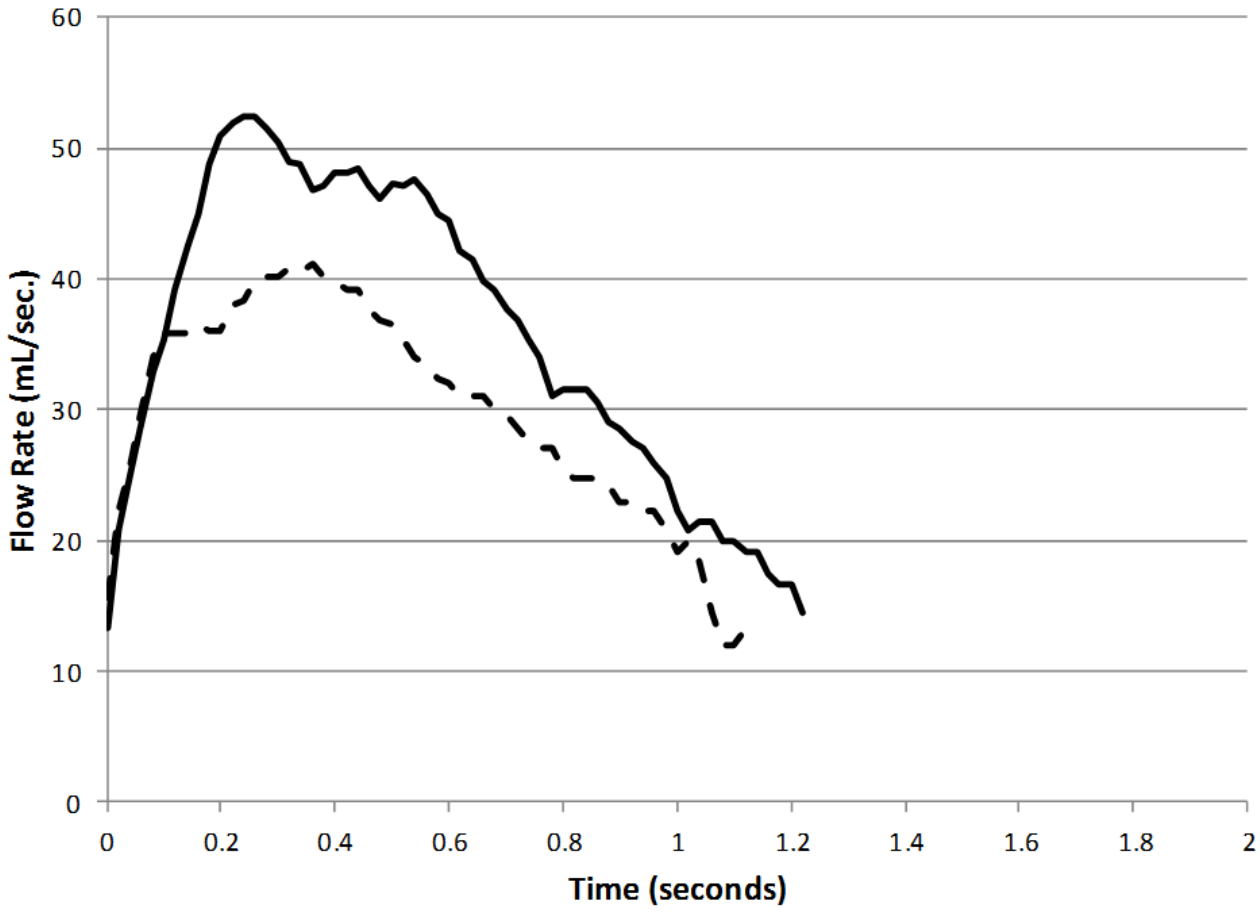

Figure 2. Two sequential puff profiles (after cigarette lighting) using the CReSS laboratory smoking topography device of a smoker smoking their usual cigarette brand. Second puff (first puff after lighting - solid line) has a reported volume of 43.6 ml, puff duration of 1.2 s and maximum flowrate of 53.4 mL/s. Third puff (dashed line) has a reported volume of 33.7 mL, puff duration of 1.1 s and maximum flowrate of 41.5 mL/s.

a combination of both. Variability within a single CReSS-micro™ device was confounded because of the lack of randomization of puffing conditions and therefore was not reported. The use of a fixed puff profile and duration of 2 s to generate different flowrates (cc/s) restricted our ability to precisely define the puff recognition threshold and influenced our estimated effects on clinically reported puff volume and puff duration. The greater the difference between the idealized sine wave puff profile (Figure 1) and actual human puff profiles (Figure 2), the less accurate our regression equations and therefore the estimated effect on clinically reported puff volume and puff duration.

Smoking topography is a non-invasive indirect measure of mouth exposure, which only estimates the puff process and does not encompass the second phase of smoking, the inhalation/exhalation process. Concerns have also been raised about the effect the CReSSmicro™ device has on the behavioral parameters it is measuring (31, 38). More robust measurements of exposure exist (biomarkers of exposure) that reflect both smoking phases, as well as absorption, distribution, (plasma nicotine, carboxyhemoglobin also called COHb) metabolism, (plasma cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides also called total plasma NNAL, 4-ABP-Hb) and excretion of some smoke constituents (urinary: nicotine equivalents; total NNAL; total *N'*-nitrosonornicotine and its glucuronide also called NNN; total 1-hydroxypyrene also called 1-OHP; 3-hydroxylpropyl-mercapturic acid also called 3-HPMA, S-phenylmercapturic acid also called S-PMA). Researchers should carefully evaluate performance of smoking topography devices used in clinical studies to ensure accurate and reliable data are obtained.

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