

The Strain on Airway Smooth Muscle During a Deep Inspiration to Total Lung Capacity

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The deep inspiration (DI) maneuver entices a great deal of interest because of its ability to temporarily ease the flow of air into the lungs. This salutary effect of a DI is proposed to be mediated, at least partially, by momentarily increasing the operating length of airway smooth muscle (ASM). Concerningly, this premise is largely derived from a growing body of in vitro studies investigating the effect of stretching ASM by different magnitudes on its contractility. The relevance of these in vitro findings remains uncertain, as the real range of strains ASM undergoes in vivo during a DI is somewhat elusive. In order to understand the regulation of ASM contractility by a DI and to infer on its putative contribution to the bronchodilator effect of a DI, it is imperative that in vitro studies incorporate levels of strains that are physiologically relevant. This review summarizes the methods that may be used in vivo in humans to estimate the strain experienced by ASM during a DI from functional residual capacity (FRC) to total lung capacity (TLC). The strengths and limitations of each method, as well as the potential confounders, are also discussed. A rough estimated range of ASM strains is provided for the purpose of guiding future in vitro studies that aim at quantifying the regulatory effect of DI on ASM contractility. However, it is emphasized that, owing to the many limitations and confounders, more studies will be needed to reach conclusive statements. [DOI: 10.1115/1.4042309]

Keywords: airway wall, breathing maneuvers, airway distensibility, airway compliance, strain

1 Introduction

The beneficial effect of a deep inspiration (DI) on respiratory mechanics has long been an important topic of discussion among lung physiologists [1–8]. However, the mechanism accountable for the respiratory relief that is normally afforded by a DI is still not clear [7,9]. Several mechanisms are likely involved and each mechanism may contribute to various extents in different individuals. However, one mechanism that arguably received the most attention is the transient change of length (i.e., strain or stretch) that airway smooth muscle (ASM) undergoes during the DI [10–48].

Indeed, the expansion of lung volume during a DI modifies the caliber of the airways (Table 1); the word “caliber” herein refers to the cross-sectional area of the airway lumen. The increase in caliber during a DI results from increasing radial stress that stems from the tethering force of the lung parenchyma. Since ASM is embedded within the airway wall in an orientation that is nearly orthogonal to the long axis of the airways [97,98], an increase in airway caliber necessarily implies that ASM is transiently elongated.

The question of whether, and to what extent, strain affects the contractility of ASM is easier to investigate in vitro. This is because in vitro experiments can specifically control or monitor the length of ASM. Several types of ASM preparations derived from resected or postmortem lung specimens are used to study ASM mechanics. They include rings, spirals and segments of bronchi; strips and segments of tracheas; precision cut lung slices; and strips of lung parenchyma. Our understanding of ASM mechanics evolves quickly due to the use of these in vitro preparations. They can truly address questions that would otherwise be impossible to investigate in vivo. Nowadays, the tools to study

ASM mechanics in vitro can recreate the dynamic lung movements that occur during breathing maneuvers [10–48]. They thus emulate the in vivo environment within which ASM normally resides and operates. This was a steppingstone in the field of ASM mechanics. It has provided instrumental insights regarding the response of ASM to stress and strain.

These in vitro studies demonstrated that perturbing the length of ASM greatly affects its contractile capacity. This effect is certainly relevant to the bronchodilator effect of a DI. However, the reported in vitro results are also plagued with a lack of consistency. The main concern relates to the size of the effect, i.e., the magnitude by which strain decreases the contractile capacity of ASM. However, the discrepancies go as far as being contradictory, as some studies reported that strain increases both airway responsiveness in vivo [99–101] and the contractile capacity of ASM in vitro [102]. The controversy also extends to studies performed with isolated ASM cells, where it was shown that strain can both decrease and increase surrogates for ASM contractility [31,103–107]. All together, these findings are conducive to alternative conclusions regarding the potential contribution of ASM strain to the bronchodilator effect of DI.

The purpose of the present review is not to discuss the variety of factors that may be responsible for the inconsistencies reported in in vitro studies, but rather to focus on one possible source of error, namely the magnitude by which ASM is strained during a DI. I attempted, based on published studies on human subjects in vivo, to determine the physiological range of strains that ASM undergoes in vivo during a DI from functional residual capacity (FRC) to total lung capacity (TLC). The first section describes the methods that can be used to estimate ASM strain. The second section discusses the limitations associated with those methods and to which extent they may affect the accuracy of the reported strain. Finally, the third section describes the confounders that affect ASM strain and that inevitably contribute to its variability.

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Table 1 Estimated strain on ASM during a DI from FRC to TLC

Methods	Sample size and health status	State of ASM activation	Breathing maneuvers	Airways	Estimated ASM strain from FRC to TLC ^{a,b,c}	Reference
V_D (using N_2 as the tracer gas)	2 healthy	Baseline	A normal tidal breath from FRC and a tidal breath to TLC	All	27.5%	[49]
V_D (using CO_2 as the tracer gas)	5 healthy	Baseline	Exercise, CO_2 inhalation (3–6%) or both	All	13.9%	[50]
V_D (using CO_2 as the tracer gas)	1 healthy	Baseline	Always from TLC, expired to a given lung volume, and then inhaled different allocated tidal volume to subsequently measure V_D on the subsequent expiration.	All	20.8%	[51]
Whole-body plethysmography	24 healthy	Baseline	Panting at different lung volumes	All	Overall: 23.2% Children: 19.3% Women: 29.3% Man: 21.5%	[52]
V_D (using N_2 as the tracer gas)	3 healthy	Baseline	From FRC to different end-inspiratory volumes	All	13.0%	[53]
Whole-body plethysmography	12 healthy and 1 asthma	Baseline	Panting at different lung volumes while being seated upright	All	Healthy: 44.2% Asthmatic: 43.3%	[54]
Bronchography	10 patients	The airways were coated with Dionosil Oily	FRC and on full inspiration in supine position	The airways were divided in four groups according to their diameter: - >7 mm - 3.5–7 mm - 1.7–3.5 mm - <1.7 mm	>7 mm: 28% 3.5–7 mm: 14% 1.7–3.5 mm: 15% <1.7 mm: 5%	[55]
-Whole-body plethysmography -Two lateral pressure taps to measure upper Raw	15 healthy, 7 asthma and 6 COPD	Baseline	Panting at different lung volumes while being seated upright	-All the airways from plethysmography -Upper airways from the lateral taps	Healthy: 34.3% Asthma: 47.3% COPD: 39.0%	[56]
V_D (using CO_2 as the tracer gas)	6 healthy	Baseline	From TLC down to different lung volumes	All	34.3%	[57]
FOT at 4 Hz Total (G_L) and lower (down the trachea; G_{LP}) pulmonary conductance were calculated (the excess elastic pressure was subtracted to bring pressure and flow into phase).	G_L : 9 healthy G_{LP} : 4 healthy	Baseline and after atropine (i.v., 1.2 mg)	G_L : Maneuvers from either RV (inflation maneuver) or TLC (deflation maneuver) along which shallow and fast breathing was interspersed at 8–15 lung volumes. G_{LP} : VC maneuvers from either RV (inflation maneuver) or TLC (deflation maneuver)	-All -The upper airways are excluded with G_{LP} (upstream from the second or third tracheal cartilage ring).	G_L -Baseline Inflation: 27.0% Deflation: 30.2% -Postatropine Inflation: 24.9% Deflation: 21.8% G_{LP} -Baseline Inflation: 36.7% Deflation: 24.4% -Postatropine Inflation: 33.0% Deflation: 16.1%	[58]
Pulmonary conductance (flow/ ΔP_L)	10 healthy, 10 asthma and 10 emphysematous	-Baseline for all subjects -Also after isoproterenol (1%) in asthmatics	Interrupted deflation from TLC (after three maximal inspirations)	All	Healthy: 42.8% Emphysema: 48.2% Asthma: 36.2% Asthma postisoproterenol: 36.8%	[59]
Fluoroscopy	10 healthy and 35 cases of acquired tracheomalacia	Baseline	Suspended breathing and coughing	Trachea	Healthy: < 41.4% Cases: > 41.4%	[60]
CT	15 healthy	Baseline	FRC and TLC	Intrathoracic trachea	8.1%	[61]
Acoustic reflection technique	8 healthy	Baseline	Slow maneuver from TLC to RV and back to TLC	-Extrathoracic trachea -Intrathoracic trachea -Bronchial segments	-Extrathoracic trachea Expiration: 10.4% Inspiration: 10.6% -Intrathoracic trachea Expiration: 8.0% Inspiration: 10.2% -Bronchi Expiration: 16.7% Inspiration: 16.6%	[62]
Acoustic reflection technique	11 healthy and 11 cystic fibrosis	Baseline	Slow maneuver from FRC to TLC	The middle one third of the trachea	Healthy: 0.3% Cystic fibrosis: 11.4%	[63]
V_D (using N_2 as the tracer gas)	10 healthy and 10 asthma	After albuterol	From RV and at 0.5L increments up to maximum	All	Healthy: 20.7% Asthma: 13.8%	[64]

Table 1 (Continued)

Methods	Sample size and health status	State of ASM activation	Breathing maneuvers	Airways	Estimated ASM strain from FRC to TLC ^{a,b,c}	Reference
MRI	13 healthy and 6 cases of tracheomalacia	Baseline	Forced inspiration, forced expiration and coughing	A 12-cm long tracheal segment downstream from 1 cm below the upper margin of the aortic arc	Healthy: 14.8% Cases: 31.3%	[65]
Pitot static probe	14 healthy and 10 moderate-to-severe asthma	-Premedicated with 0.5 mg atropine i.m. 30 min before measurements and received topical anesthetic -For asthmatics only: 10-day tapering course of prednisolone in addition to regular treatment and inhaled terbutaline (generally 1 mg) within 1.5 h before measurements	Maximal expiratory maneuvers	5 positions: 1—above the entrance of lower lobe; 2—entrance of middle lobe; 3—midmain stem bronchus; 4—above the carina; 5—midtrachea	Healthy 1—29.6% 2—32.9% 3—16.5% 4—17.2% 5—6.3% Asthma 1—11.5% 2—13.2% 3—7.0% 4—2.5% 5—10.3%	[66]
V_D (using CO ₂ as the tracer gas)	16 healthy and 16 mild asthma	For asthmatics only: After albuterol (200 µg)	3 breathing regimens: 1- low, medium and high volumes 2- TLC to RV 3- RV to TLC	All	1-Healthy: 17.7% Asthma: 14.9% 2-Healthy: 17.1% Asthma: 13.4% 3-Healthy: 16.5% Asthma: 13.4%	[67]
HRCT	9 healthy and 10 asthma	Baseline and following MCh using two protocols <i>Protocol 1</i> : FRC and TLC at baseline followed by FRC and TLC with MCh <i>Protocol 2</i> : FRC at baseline followed by FRC and TLC with MCh	FRC and TLC	Ranged in size from 1.2 to 12.2 mm (191 airways) in diameter for the first protocol and 1.6 to 11.4 mm (195 airways) in the second protocol	-Baseline Healthy: 21% Asthma: 25% -MCh (protocol 1) Healthy: 14% Asthma: 12% -MCh (protocol 2) Healthy: 11% Asthma: 10%	[68]
V_D (using CO ₂ as the tracer gas)	22 healthy and 35 mild-to-moderate asthma	-After albuterol (300 µg)	TLC to FRC	All	Healthy: 11.7% Asthma: 10.3%	[69]
FOT at 8 Hz	9 healthy and 14 asthma (classified as severe or mild-to-moderate according to baseline constriction and reactivity)	-Baseline -Activated with MCh (to a maximal dose of 25 mg/ml or a dose causing at least 20% decline in FEV ₁) using two different challenges, 1 standard and 1 modified (viz., with no DI) -Albuterol and caffeine were withheld for 12 h	FRC and TLC	All	-Baseline Healthy: 23.6% Mild-to-moderate Asthma: 25.7% Severe asthma: 28.1% -Standard MCh Healthy: 27.0% Mild-to-moderate Asthma: 25.6% Severe asthma: 25.0% -Modified MCh Healthy: 24.5% Mild-to-moderate Asthma: 27.0%	[70]
FOT at 8 Hz	7 healthy and 6 asthma	-Baseline -Post-MCh (until they reached PC ₂₀) -Albuterol and caffeine were withheld for 8 h	FRC and TLC	All	-Baseline Healthy: 28.1% Asthma: 21.4% -Post-MCh Healthy: 29.5% Asthma: 21.4%	[71]
FOT at 6 Hz	18 healthy and 25 asthma	-After MCh (average of 1.8 and 95.5 µmol in asthmatic and control group, respectively; same increase in Rrs was achieved in both groups) -SABA and LABA were withheld for 6 and 24 h, respectively	FRC and TLC	All	Healthy: 45.3% Asthma: 33.2%	[72]

Table 1 (Continued)

Methods	Sample size and health status	State of ASM activation	Breathing maneuvers	Airways	Estimated ASM strain from FRC to TLC ^{a,b,c}	Reference
-FOT at 6 Hz - V_D (using N_2 as the tracer gas)	4 healthy and 3 mild asthma	Baseline	-FOT: TLC to FRC or FRC to TLC -SBNW: V_D assessed at FRC+500 ml and near TLC	All	-FOT Healthy: 16.4% Asthma: 27.8% -SBNW Healthy: 13.7% Asthma: 23.0%	[73]
Multidetector row helical CT	14 patients with respiratory illnesses	Baseline	End of DI, end of maximal expiration and during forced expiration	-Trachea at the level of aortic arc -Carina -Bronchus intermedius	Aortic arc: 18.8% Carina: 15.4% Bronchus intermedius: 13.9% -During forced expiration Aortic arc: 47.3% Carina: 46.8% Bronchus intermedius: 53.4%	[74]
FOT at 6 Hz	19 healthy and 18 asthma	-Baseline -Relaxed with albuterol (200 μ g) -SABA and LABA were withheld for 6 and 12 h, respectively	Slowly to TLC and then breathed at approximately tidal volume except that the end-expiratory lung volume had to decrease progressively after each breath until the volume was back to FRC.	All	-Baseline Healthy: 26.1% Asthma: 25.1% -Postalbuterol Healthy: 26.3% Asthma: 20.1%	[75]
HRCT	15 COPD	Baseline	RV and TLC	-233 airways ranging from 2.0 to 17.8 mm in diameter at RV -Also segregated the airways into small, medium and large (<3, 3-5 and >5 mm in diameter, respectively)	All airways: 14.6% Small airways: 21.1% Medium size airways: 15.4% Large airways: 5.4%	[76]
CT	50 COPD	Baseline	At DI and at deep expiration	Right B1, right B10 and left B3 -Airway generation 3 -Airway generation 4 -Airway generation 5	Generation 3: 15.5% Generation 4: 19.9% Generation 5: 25.8%	[77]
MDCT	70 patients suspected of tracheobronchomalacia	Baseline	End of DI, end of maximal expiration and during a forced expiration	-At three levels in the trachea (cervical, upper, lower) -Right main bronchus -Left main bronchus	Cervical trachea: 5.4% Upper trachea: 7.6% Lower trachea: 7.2% Left bronchus: 5.9% Right bronchus: 5.6% -During forced expiration Cervical trachea: 6.9% Upper trachea: 13.7% Lower trachea: 16.2% Left bronchus: 15.7% Right bronchus: 15.3%	[78]
Dynamic cine multidetector CT and regular CT	10 healthy and 40 cystic fibrosis	Baseline	-Forced expiration from TLC and coughing -For cystic fibrosis only, CT at the end of a maximal expiration	A 2 cm-long segment of the trachea	Cystic fibrosis: 9.1% -During forced expiration Healthy: 14.8% Cystic fibrosis: 44.3% -Coughing Healthy: 59.5% Cystic fibrosis: 80.3%	[79]
HRCT combined with esophageal pressure	2 healthy	Baseline	TLC and FRC	1.4-7.7 mm in diameter	20.6-59%	[80]
FOT at 8 Hz	11 healthy and 15 COPD (moderate to severe)	-Baseline -Relaxed with albuterol (400 μ g) -SABA were withheld for 12 h	FRC and TLC	All	-Baseline Healthy: 19.9% COPD: 15.2% -Postalbuterol Healthy: 24.9% COPD: 17.1%	[81]
FOT at 6 Hz	19 asthma	-Prior to and after a 12 weeks of inhaled corticosteroid + LABA (two puffs per day of fluticasone + salmeterol; 250/25 μ g) -SABA and LABA were withheld 2 and 24 h, respectively	Slowly to TLC and then breathed at approximately tidal volume except that the end-expiratory lung volume had to decrease progressively after each breath until the volume was back to FRC.	All	Prior treatment: 22.4% After treatment: 26.5%	[82]
FOT at 8 Hz	34 healthy and 35 asthma	SABA and LABA were withheld for 6 and 24 h, respectively	End tidal inspiratory volume to TLC	All	Healthy: 23.9% Asthma: 26.5%	[83]

Table 1 (Continued)

Methods	Sample size and health status	State of ASM activation	Breathing maneuvers	Airways	Estimated ASM strain from FRC to TLC ^{a,b,c}	Reference
HRCT combined with esophageal pressure	9 asthma	-Baseline -After albuterol (200 µg)	TLC and FRC	Airways of 1.1–10.7 mm internal diameter	-Baseline 12.3–93.4% -Postalbuterol 12.0–106.2%	[84]
aOCT	10 healthy, 16 asthma, 9 COPD and 8 bronchiectasis	-Relaxed with salbutamol (5 mg) -Anesthetized with continuous infusion of propofol and remifentanyl	Airway pressure from -10–20 cmH ₂ O	Airway generations 0, 1, 3, 4 and 5	-Generation 0 Healthy: 21% Asthma: 32% COPD: 27% Bronchiectasis: 28% -Generation 1 Healthy: 25% Asthma: 29% COPD: 35% Bronchiectasis: 34% -Generation 3 Healthy: 17% Asthma: 14% COPD: 17% Bronchiectasis: 21% -Generation 4 Healthy: 16% Asthma: 18% COPD: 24% Bronchiectasis: 23% -Generation 5 Healthy: 13% Asthma: 21% COPD: 35% Bronchiectasis: 28%	[85]
HRCT	15 asthma	-Baseline -After albuterol (sequential nebulizations until a plateau of bronchodilation was achieved) -SABA and LABA were withheld for 12 and 48 h, respectively	FRC and TLC (breath holding ~24 s)	Airways of 2.2–17.4 mm internal diameter	Baseline: 16% Postalbuterol: 7.7%	[86]
CT	44 COPD with α-1-antitrypsin	-Relaxed with salbutamol (5 mg) and ipratropium bromide (500 mg)	TLC and FRC	3 segmental bronchi -RB1 -RB10 -LB10	RB1: 6.0% RB10: 15.5% LB10: 15.5%	[87]
HRCT	46 healthy smokers, 23 COPD 2-AP, 23 COPD 2-EP, 23 COPD 4-AP and 23 COPD 4-EP. The numbers referred to GOLD stages, AP and EP stand for airway-predominant and emphysema-predominant, respectively	May or may not have been treated with albuterol	End-tidal expiration and TLC	The right apical bronchi (RB1) - Third generation - Fourth generation The posterior basal (RB10) bronchi - Third generation - Fourth generation	-RB1 third Healthy: 16.8% COPD 2-AP: 11.5% COPD 2-EP: 8.0% COPD 4-AP: 7.2% COPD 4-EP: 10.5% -RB1 fourth Healthy: 20.4% COPD 2-AP: 14.6% COPD 2-EP: 8.8% COPD 4-AP: 7.9% COPD 4-EP: 4.5% -RB10 third Healthy: 28.0% COPD 2-AP: 20.8% COPD 2-EP: 24.0% COPD 4-AP: 11.9% COPD 4-EP: 14.9% -RB10 fourth Healthy: 38.8% COPD 2-AP: 21.3% COPD 2-EP: 28.8% COPD 4-AP: 20.0% COPD 4-EP: 17.7%	[88]
Acoustic reflection technique	20 healthy and 20 cystic fibrosis	Baseline	During spontaneous breathing and at forced inspiration	Trachea	-Trachea Healthy: 0% Cystic fibrosis: 0% -Raw Healthy: 0% Cystic fibrosis: 0.6%	[89]

Table 1 (Continued)

Methods	Sample size and health status	State of ASM activation	Breathing maneuvers	Airways	Estimated ASM strain from FRC to TLC ^{a,b,c}	Reference
FOT at 5 Hz	28 patients with hematological malignancies before and after allogeneic haematopoietic stem-cell transplantation (HSCT)	-Baseline -After albuterol	FRC and TLC	All	-Baseline Pre-HSCT: 14.3% Post-HSCT: 19.3% -Post-albuterol Pre-HSCT: 19.3% Post-HSCT: 16.2%	[90]
HRCT	12 asthma and 8 COPD	Baseline	FRC and TLC	Airways of 2–23.1 mm internal diameter	5–29%	[91]
HRCT	961 smokers or ex-smokers with normal lung function	Baseline	Supine, during breath holding, aiming for TLC after 3 DIs, annually for up to 5 years	All measurable airways from generation 0 to 7 and all segmental bronchi	Generation 0: 16.1% Generation 1: 16.9% Generation 2: 19.4% Generation 3: 26.9% Generation 4: 29.2% Generation 5: 36.6% Generation 6: 41.2% Generation 7: 46.1% -Segmental bronchi R1: 25.8% R2: 28.0% R3: 18.5% R4: 20.2% R5: 20.1% R6: 34.6% R7: 27.4% R8: 41.4% R9: 51.1% R10: 45.8% L1: 30.0% L2: 31.9% L3: 21.7% L4: 21.5% L5: 29.3% L6: 37.6% L7: 47.0% L8: 41.5% L9: 46.7% L10: 44.8%	[92]
HRCT	12 cystic fibrosis with the G551D-CFTR mutation	-Before and after 48 h of treatment with ivacaftor -Inhaled bronchodilators were withheld the morning of the visits.	Supine RV and TLC during breath holding preceded by 3 DIs	Airways with internal diameter of 2.4–20.8 mm	-Before ivacaftor Airways < 4.5 mm: 14.7% Airways 4.5–6.5 mm: 24.3% Airways > 6.5 mm: 22.6% -After ivacaftor Airways < 4.5 mm: 22.0% Airways 4.5–6.5 mm: 21.6% Airways > 6.5 mm: 20.3%	[93]
HRCT	9 healthy and 19 asthma	-Baseline -After albuterol (sequential doses were inhaled until maximal FEV ₁ was attained)	FRC and TLC	Airway generations 2–6	-Baseline Healthy: 16% Asthma: 14% -Postalbuterol Healthy: 3% Asthma: 10%	[94]
FOT at 5 Hz	Healthy (<i>n</i> = 13)	Baseline	Slowly to TLC and then breathed at approximately tidal volume except that the end-expiratory lung volume had to decrease progressively after each breath until the volume was back to RV.	All	32.0%	[95]

Table 1 (Continued)

Methods	Sample size and health status	State of ASM activation	Breathing maneuvers	Airways	Estimated ASM strain from FRC to TLC ^{a,b,c}	Reference
HRCT	Asthma	After the PC ₂₀ of MCh	Mean lung volume to TLC in supine position	Trachea to airway generation 5	Trachea: 10.8% Right: 12.3% Left: 14.7% RMI: 10.7% RU: 19.4% RM: 16.3% RL: 3.9% LU: 11.7% LL: 19.8% -RB1-3 Generation 3: 22.4% Generation 4: 24% Generation 5: 18.5% -RB4-5 Generation 3: 18.6% Generation 4: 18.6% -RB6-10 Generation 3: 23.7% Generation 4: 26.9% Generation 5: 19.9% -LB1-5 Generation 3: 19.8% Generation 4: -0.4% Generation 5: 23% -LB6-10 Generation 3: 27.5% Generation 4: 36.2% Generation 5: 33%	[96]

Note: aOCT—anaomical optical coherence tomography, COPD—chronic obstructive pulmonary disease, *DI*—deep inspiration, FEV₁—forced expiratory volume in 1 s, FOT—forced oscillation technique, FRC—functional residual capacity, HRCT—high-resolution computed tomography, LABA—long-acting β 2-agonist, MCh—methacholine, PC₂₀—the provocative concentration of methacholine causing a 20% decline in FEV₁, Raw—airway resistance, RV—residual volume, SABA—short-acting β 2-agonist, SBNW—single breath nitrogen washout, TLC—total lung capacity, VC—vital capacity, and *V_D*—dead volume.

^aIt was assumed that ASM is arranged orthogonally in relation to the long axis of the airways.

^bIt was assumed that the volume of the airways expands isotropically during an increase in lung volume from FRC to TLC.

^cIt was assumed that the changes in resistance are inversely proportional to the changes in airway luminal radius at the fourth power.

2 Methods Used to Estimate Airway Smooth Muscle Strain In Vivo

The complexity of the question in hand stems from the difficulty to assess ASM strain in vivo. Although refining technologies are currently emerging, no direct measurement of ASM strain during a DI has yet been performed in vivo. However, many technologies provide reliable measures of luminal volume, airway caliber and resistance. These measurements at different lung volumes then allow approximation of the extent to which ASM is strained during a DI from FRC to TLC. This section describes the methods that may be used to assess airway wall strain in vivo in humans. The major strengths of each method are also briefly stated.

2.1 Dead Volume. The measurement of dead volume (*V_D*) is the more archaic [108] but still useful way to estimate the luminal volume of the airway tree at any given lung volume. The change in *V_D* from one lung volume to the other then allows estimation of the strain undergone by the airway tree during such an excursion of lung volume (Table 1). The measurement relies on the fact that the last part of the inspired air in a breath does not reach the zone of gas-exchanging units. That last part is rather contained in the *V_D* (also called the dead space), which includes the upper airways down to the terminal bronchi. Since air in the *V_D* does not mix with the alveolar gas, the composition of gas at the mouth during an expiration suddenly changes when it transitions from the air that was contained in the *V_D* to the air that was contained in the alveolar space. The volume of air that comes out of the lungs before this transition of air composition is *V_D*. Because diffusion inevitably occurs at the boundary between *V_D* and alveolar volume, and that the amount of diffusion is time-dependent,

appropriate timing during the respiratory maneuver is essential to obtain an accurate measure of *V_D*.

Fowler was the first to use the single-breath nitrogen (N₂) wash-out to measure *V_D* [49]. This technique has been adopted and is still used [109–111]. Alternatively, some have used CO₂ as the tracer gas to estimate *V_D* [57]. Johns and coworkers have demonstrated that a breath-by-breath analysis of *V_D* is possible using CO₂ as the tracer [67]. By progressively changing the lung volume, one can then obtain a slope of the relationship between *V_D* and end-inspiratory lung volume. This slope has been abbreviated ΔV_D and has been used to assess airway distensibility (i.e., the ease by which the airways dilate in response to increasing lung volume) [67]. ΔV_D is advantageous because it can be measured quickly in a noninvasive manner.

2.2 Bronchography and Fluoroscopy. Although X-rays in humans may provide enough resolution to detect abnormal size of the trachea [112], it is not sufficient to quantitate the differences that may occur during an excursion of lung volume from FRC to TLC. The resolution can be improved by contrasting agents. For example, Dionosil Oily inserted through the cricothyroid ligament under local anesthesia, has been used successfully to measure the changes in diameter of large and relatively smaller airways during a full inspiration in man [55].

Fluoroscopy is somewhat better, as it allows motion recording. It has been used without contrast agents to monitor changes in airway caliber during breathing maneuvers. It was to assess the degree of collapsibility of the trachea during coughing in controls and in cases of acquired tracheomalacia [60]. Fluoroscopy may be appropriate to diagnose and assign a degree of tracheomalacia, as it was done in that study. However, it does not seem to provide

the resolution to quantitatively evaluate the changes in airway luminal area during a DI.

2.3 Airway Resistance by Whole-Body Plethysmography.

The measurement of airway resistance (R_{aw}) by whole-body plethysmography ($R_{aw(pleth)}$) is routinely performed in laboratories of lung physiology. $R_{aw(pleth)}$ truly represents the resistance attributed to the viscous flow of air passing through the airways. The practical and theoretical principles involved were previously expatiated [113]. Briefly, the subject is enclosed in a hermetic box of known internal volume. The subject is then instructed to pant inside the box into a tube connected to an open shutter and a pneumotachograph. The shutter is then suddenly closed while the subject tries to keep panting. The airflow at the mouth and the pressures at the mouth and inside the box are monitored continuously. The variations of pressure inside the box (ΔP_{box}) when the shutter is open reflect corresponding but opposite changes in alveolar pressure (ΔP_{alv}). Using the law of Boyle–Mariotte ($V_1P_1 = P_2V_2$), the ΔP_{box} are converted into changes in volume (ΔV_{box} ; often called the shift volume). The ΔV_{box} happens to be the mirror image of the changes in thoracic gas volume (TGV) caused by rarefaction and compression of air during the panting, which are required to generate the driving pressure (ΔP_{alv}) that draws air in-and-out of the lungs. When the shutter is closed, the ΔV_{box} can be related to the changes in alveolar pressure (ΔP_{alv}), since ΔP_{alv} are then the same as the changes in mouth pressure. Once the relationships between both airflow/ ΔV_{box} (when the shutter is open) and $\Delta P_{alv}/\Delta V_{box}$ (when the shutter is closed) are known, the ΔP_{alv} required to accommodate any chosen airflow (usually 1 L/s) can be determined. The ratio of $\Delta P_{alv}/\text{airflow}$ is $R_{aw(pleth)}$. Conveniently, the same panting maneuver and Boyle–Mariotte’s law also allow the TGV from which the subject is panting to be measured.

The panting can be performed at different lung volumes to measure the relationship between $R_{aw(pleth)}$ and lung volume. From this relationship, the airway wall strain from FRC to TLC can be roughly estimated (Table 1). The limitations are discussed below. The greatest advantages of the whole-body plethysmography are that it is noninvasive and nonionizing.

2.4 The Interrupted Deflation.

The interrupted deflation can be used to measure pulmonary resistance (R_L) and to estimate airway resistance (or conductance). The subject is instructed to take a DI to TLC and then to expire slowly (sometimes at a controlled rate) while the flow is being interrupted at the mouth for a short period at specified intervals. The flow at the mouth and P_L need to be measured simultaneously. P_L is measured conventionally using an oesophageal balloon to estimate pleural pressure and to subtract it from airway opening pressure. During the measurement, the change in lung volume is being tracked by integrating flow. This is required to relate punctual changes in P_L caused by the interruptions to the lung volumes at which they were measured. The increase in P_L caused by the interruption is the driving pressure required to accommodate the airflow (and the lung tissue flow) just preceding the interruption. Since the resistance attributed to tissue flow (sometimes called tissue viscance) is small [114], especially during deflation, the rise in P_L caused by the interruption of flow is mainly ascribed to the frictional resistance to airflow within the airway tree. By dividing the increase in P_L to the flow at the mouth, airway resistance can then be calculated at every lung volume at which the interruption took place. The change in resistance between FRC and TLC can then be converted to estimate ASM strain the same way it is done for $R_{aw(pleth)}$ (discussed below) (Table 1). The advantage of the interrupted deflation in comparison to the measurement of $R_{aw(pleth)}$ is that the breathing maneuver performed by the subject is much simpler.

2.5 Acoustic Reflection Technique.

The acoustic reflection technique is an especially good tool to diagnose tracheal stenosis

and malacia [115]. The use of this technique to assess large airway caliber has also been validated in glass tube models and in humans [116,117]. Changes in large airway caliber caused by changing lung volumes were also estimated (Table 1). The acoustic reflection technique consists of a sound wave emitted by a loudspeaker that is traveling along the airways where it is reflected and perceived by a recording microphone located on the external device near the subject’s mouth. The time gap between the emitted sound and the reflections is a measure of the distance between the microphone and the points within the airway where those reflections come from. The amplitude of the reflections is a proxy of the change in airway cross-sectional areas at those specified airway locations. The greatest advantages of the acoustic reflection technique are that it is noninvasive, nonionizing, and quick. It is also easy for the subject, as no complicated breathing maneuvers are required.

2.6 High-Resolution Computed Tomography.

High-resolution computed tomography (HRCT) has first been used by Wilson and coworkers in 1983 to assess airway caliber at different lung volumes [64]. Since then, HRCT was used extensively to assess the bronchodilator effect of DI (Table 1). The breathing protocol used varied widely, but a scan is normally taken at FRC and then at TLC and the differences in airway caliber at corresponding airway locations are measured. HRCT is still considered by some the gold standard for imaging the airways. This is because it assesses directly the geometry of individual airways. It is also noninvasive and does not require sedation. The tools to analyze CT scan have also evolved to provide an accurate measure of airway wall thickness. Another important asset is the fact that many airways of different sizes can be assessed simultaneously.

2.7 Hyperpolarized Gas Magnetic Resonance Imaging.

Magnetic resonance imaging (MRI) is a technology that is currently emerging to image the geometry of airways in vivo in humans. The technology has evolved to offer a good temporal resolution (scanning time of 0.2 s), providing images without blurring, even during cough [65]. Although MRI is primarily used in the field of pulmonary medicine to image ventilation defects [118–122], it can now be used to obtain descent three-dimensional reconstruction of the tracheobronchial tree [123]. However, the resolution does not equate HRCT [124]. Despite other limitations that will be discussed in Sec. 3, MRI still represents an appealing noninvasive and nonradiating alternative strategy to image airway caliber. Further developments are awaited before MRI can accurately assess the changes in airway caliber that occur during a breathing maneuver from FRC to TLC (Table 1).

2.8 Pitot Static Probe.

The pitot static probe is a device used to measure the velocity of a moving fluid. It has several applications in modern world. A miniature pitot static probe (few centimeters long and 3 mm external diameter) can be inserted into the airway tree to assess airway caliber on the basis of physiological measurements. The probe is positioned at desired heights down the airway tree, which is determined prior the measurements using a bronchoscope. The probe has an opening at the distal end leading to a first catheter coming out at the mouth, which is used to measure impaction pressure (also called total pressure or Ptot). The probe also has side holes that merge into a distinct catheter to measure lateral pressure (Plat). The difference between impaction pressure and lateral pressure is the drop of pressure due to convective acceleration (i.e., the kinetic energy of the gas passing the cross-sectional area). Assuming incompressible air flowing in a tube with a blunt velocity profile, Bernoulli equation can then be used to estimate air velocity ($P_{tot} = P_{lat} + \rho V^2/2$, where ρ is air density and V is velocity). The flow at the pitot static probe can also be calculated from the mouth flow and correcting for difference in air pressure at that location (barometric pressure + plat) using Boyle’s law. With this local flow and velocity, one can than

calculate the cross-sectional area at the location of the pitot static probe ($A = 10 \dot{V}/V$, where A is area in cm^2 , \dot{V} is flow in L/s and V is velocity in m/s). Calculating the cumulative expelled volume by integrating the flow at the mouth allows for changes in airway caliber to be related to changes in lung volume. Theoretically, one maneuver would allow the measurement of airway caliber at every lung volume. The greatest advantage of the pitot static probe is thus to follow the kinetics of change in airway caliber. The insertion of an esophageal balloon as a proxy of pleural pressure (Ppl) can also provide additional insights. For example, by relating airway caliber to transmural pressure (Ptm, which is Plat-Ppl), airway compliance (Caw) can be obtained.

The pitot static probe is not often used to assess airway caliber at different lung volumes. In fact, only one study documented the utility of the pitot static probe for that purpose. In that study, the measurement was made during a maximal expiratory flow-volume maneuver (MEFV), i.e., the subject was instructed to inhale to TLC and then provide a maximal expiratory effort to RV. Several limitations are associated with this method. Of special concern is the instability of the probe during the maneuver. The plugging of the end and side holes by mucus and secretions is also common. Maximal reproducible efforts are also required, which can be demanding for the subject. These limitations, together with the other limitations discussed in Sec. 3, may have dissuaded many investigators from using this method.

2.9 Forced Oscillation Technique. This technique consists of forcing the movement of air in or out the respiratory track using different devices and to then calculate impedance from the resulting flow and pressure that are measured at different locations in relation to the subject (reviewed in Ref. [125]). The most common devices force air directly into the subject's mouth and the resulting flow and pressure within the mouth are used to calculate impedance (input impedance). The motion of air imposed by the device can also take different shapes, but sinusoidal forcing at one or several simultaneous frequencies are often used. During the measurement, the subject is usually instructed to keep breathing normally at tidal volume. The forced oscillation is thus simply superimposed on top of the natural motion of air resulting from breathing. The forced oscillation technique (FOT) has gained tremendous momentum in human respiratory research. This is because it provides valuable readouts pertaining to the mechanics of the respiratory system, including respiratory system resistance (Rrs) and reactance (Xrs) at every tested frequencies. These measurements allow one to infer on phenomena as complex as recruitment-derecruitment and airway caliber heterogeneity. One of the greatest advantages of the FOT is its fine time resolution. Because of this fine time resolution, it is possible to measure the kinetics of events happening over a short time-scale, e.g., such as the extent and dynamics of airway dilatation during a DI. Its usefulness is also ascribed to its noninvasiveness, the ease with which it is operated and the very low level of cooperation that is required from the tested subjects.

Forced oscillation technique can be used to estimate ASM strain during a DI from FRC to TLC because Rrs and its inverse, respiratory system conductance (abbreviated Grs), represent proper proxies of airway caliber when measured near the resonant frequency (6–10 Hz) [70]. This is especially true at zero flow, when the resistance is not affected by frictional airway resistance to airflow. Many have measured Rrs (or Grs) to assess the changes in airway caliber during a DI (see Table 1).

2.10 Anatomic Optical Coherence Tomography. Anatomic optical coherence tomography (aOCT) is an in vivo imaging technology that broadcasts live the interior of the airways [126]. aOCT uses a fiber-optic probe that passes through a bronchoscope and emits a beam of near-infrared light toward the airway wall. The resulting reflections are detected and analyzed using low-coherence interferometry, which allows the measurement of the

position of the airway wall in relation to the probe. By rotating the probe, one can obtain two-dimensional cross-sectional images of the lumen, and by moving the probe forward or backward, these serial two-dimensional images can provide a full 3D representation of the airway lumen. Although not used extensively so far, aOCT is likely to provide insightful information regarding the excursion of airway caliber during a DI. I am aware of only one published study that has used aOCT for that purpose [85] (Table 1).

A new cousin of OCT has also recently been developed, called orientation-resolved OCT (OR-OCT) [127]. OR-OCT uses the birefringent property of ASM to capture its exact localization within the wall of large airways. ASM in humans in vivo can be visualized with a sensational level of resolution by this method [127]. OR-OCT should ultimately enable the direct measurement of ASM strain during a DI from FRC to TLC.

3 Limitations

None of the aforementioned methods directly measure ASM strain. They rather reported a change in the cross-sectional area of the lumen in individual airways, a change in luminal volume of the entire airway tree or a change in resistance to airflow in the airways or to the whole respiratory system. This obliges the transformation of the original data into radial airway wall strain. For the sake of this review, it was then assumed that the airway wall strain can be used as an appropriate proxy of ASM longitudinal strain. This section describes the limitations associated with several methods, as well as the limitations associated with the transformations and assumptions that were made to convert the original data into ASM strain.

3.1 Lumen Versus Airway Smooth Muscle. The strain on the airway wall reported by most methods during the DI refers to the change in perimeter at the apical surface of the epithelium (i.e., the size of the lumen). This is true for imaging methods such as bronchography, HRCT, MRI, and aOCT, but also for the methods relying on physiological measurements, such as V_D and resistance (plethysmography, interrupted deflation, acoustic reflection technique, pitot static probe, and FOT). It is important to understand that the change in luminal geometry does not represent precisely the change in perimeter occurring at the middle of ASM. Due to the combined thickness of the epithelium, the lamina propria, and the ASM, the extent by which ASM is stretched during a DI is slightly overestimated when the luminal geometry (radius, diameter, perimeter, and cross-sectional area) is used to calculate the change in ASM length (Fig. 1). The size of this effect is more prominent in smaller airways. In fact, the size of this effect increases as the ratio of the perimeter measured at the middle of ASM to the perimeter of the lumen increases. The thickening of the airway wall observed in some respiratory disorders also amplifies the size of this effect (Fig. 1).

3.2 Airway Smooth Muscle Alignment. The reported strain (the one estimated in Table 1) represents more accurately the radial strain on the airway wall than the longitudinal strain on the ASM. This is because the orientation of ASM within the airway wall varies. Here, I assumed that ASM is arranged in an orthogonal fashion in relation to the long axis of the airways. This assumption is correct for the trachea and the main stem bronchi. However, ASM is oriented differently in smaller airways. The angle of orientation of ASM relative to the long axis of the airways is on average 75 deg [98]. However, this angle is obviously another parameter that is variable from one airway generation to another, as well as from one ASM bundle to another. The implication here is that the strain reported is somewhat overestimated compared to the real strain on the long axis of the ASM bundle. For example, when one assumes a radial airway wall strain (viz., an increase of airway perimeter) of 25% with no longitudinal

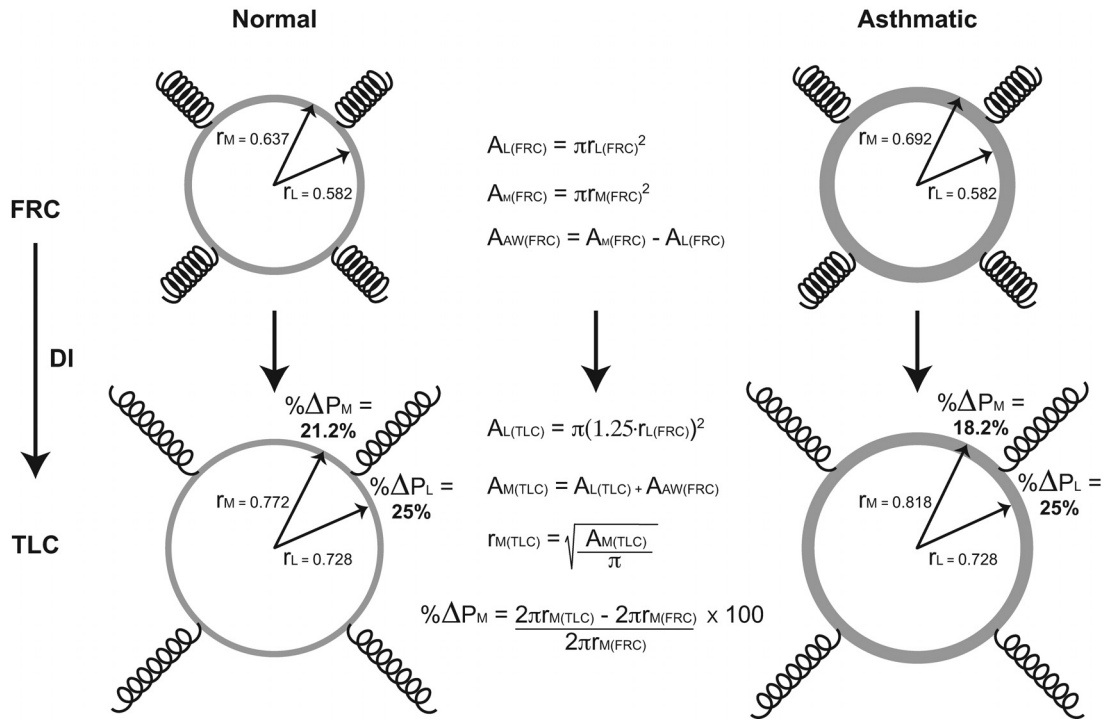


Fig. 1 The changes in luminal geometry overestimate the stretch the ASM undergoes during a deep inspiration (DI). The schematic illustrates a normal (left) and an asthmatic (right) airways at FRC and after a DI to TLC. The dimensions are zoomed but at scale to an average airway of the ten generation. The springs represent lung recoil. They are stretched at TLC relative to FRC. The arrow at approximately 2 o'clock is the radius (in mm) of the airway lumen (r_L). The arrow at approximately 1 o'clock is the radius up to the middle of the airway smooth muscle layer (r_M). The material composing the airway wall was considered inextensible. Notice the thinning of the airway wall when the lungs are inflating to TLC. In this schematic it was assumed that the luminal geometry at FRC was equal between normal and asthmatic. It was further assumed that the DI was increasing luminal radius by 25% in both normal and asthmatic, so that the luminal geometry at TLC was also equal between normal and asthmatic. The schematic demonstrates that a 25% increase of luminal perimeter (P_L) only causes a 21.2% increase of the perimeter at the middle of the ASM layer (P_M). This effect is further amplified in asthmatic because of a thicker airway wall (25 versus 18.2%). The mathematics is developed in the middle. Other abbreviations: A_{AW} —area of the airway wall from the lumen to the middle of the ASM layer, A_L —luminal area, A_M —area internal to the middle of the ASM layer, and % Δ —change in percentage.

airway strain (viz., no lengthening of the airway) and an ASM bundle oriented 75 deg off the long axis of the airway, the strain on the long axis of the ASM bundle is 23.5% (Fig. 2). The magnitude by which ASM strain is overestimated depends on how far off the angle of orientation deviates from 90 deg. The reality, however, is that the airway is also strained on its longitudinal axis (this is discussed below). If both the radial strain and the longitudinal strain of the airway increase by 25%, the ASM are then also strained by 25% regardless of the orientation of the ASM bundle in relation to the long axis of the airway (Fig. 2).

3.3 Circumferential Proportion of the Airway Wall Containing Airway Smooth Muscle. Although the bundles of ASM completely encircle the small airways, it is not the case for the trachea and the main stem bronchi. In fact, ASM occupies approximately 1/3 and 2/3 of the total airway wall circumference in the trachea and the main stem bronchi, respectively. The remaining circumference is made up of cartilage. Since the cartilage is stiffer than the ASM, the strain is not distributed homogeneously along the entire circumference of the airway. In reality, near 100% of the change in circumference is taken up by 1/3 to 2/3 of the airway wall; the portion occupied by ASM and free of cartilage. ASM strain during a DI in the trachea and the main stem bronchi may thus be well beyond the one estimated based on the change in airway caliber.

3.4 Two Versus Three Dimensions. The estimation of ASM strain during a DI from FRC to TLC is sometimes accomplished by measuring a change in volume. This is the case for the methods measuring and comparing V_D at different lung volumes. To convert a change in volume into radial airway wall strain (or \sim ASM longitudinal strain), an additional step is required. This is because not only the caliber but also the length of the airways fluctuates during breathing maneuvers [128]. The relative extent by which the length of the airways elongate and shorten during breathing maneuvers compared to the extent by which they dilate and narrow have been poorly studied. One can assume that the percentage change is equal in every directions; so that the luminal airway volume expands or shrinks isotropically without changing shape during both inflation and deflation. Some experimental data support this assumption [58,129–131]. Studies showing that ΔV_D is linearly related to Δ lung volume also support this assumption [64,67]. However, other evidences suggest that it is not always the case [132]. In fact, the accuracy of this assumption seems greatly affected by the starting lung volume and the magnitude of the lung volume excursion [80,84,130]. The strain in one direction relative to the other directions is also likely to vary between airways from different individuals and between airways within the same individual. Regardless, the degree by which the deformation of the airways deviates from isotropy obviously affects the precision with which ASM strain can be estimated by these methods.

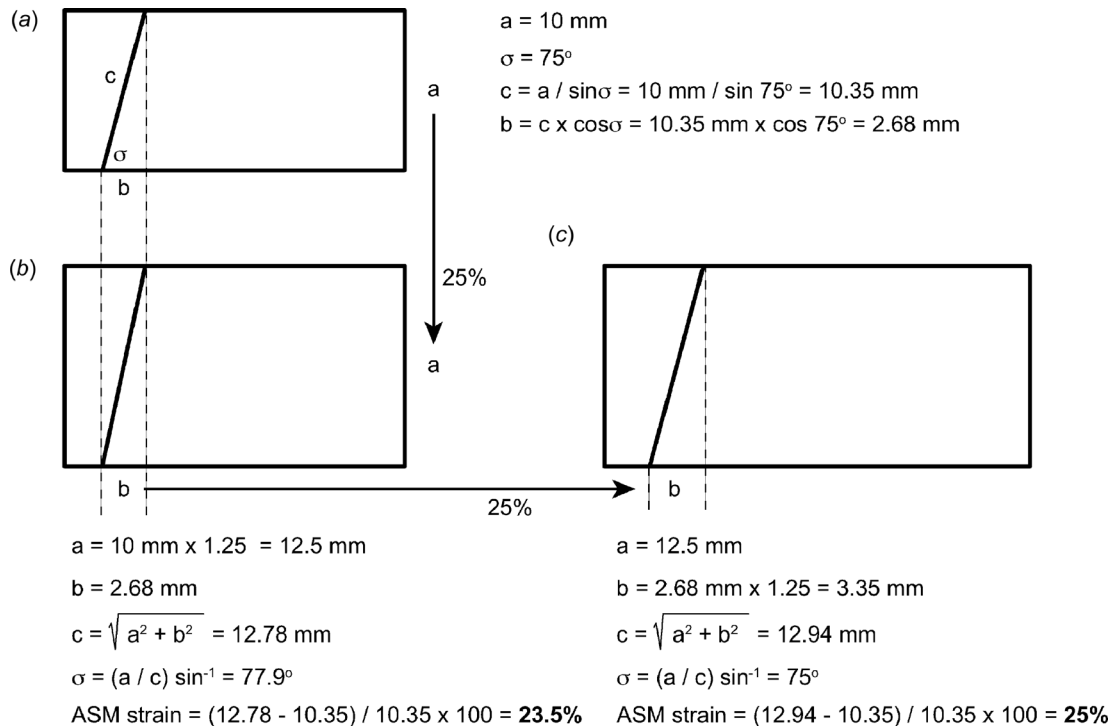


Fig. 2 Imagine an airway cut open longitudinally and unfolded to form the rectangle on top (a). The letter *a* represents the airway perimeter and, in this example, is set to 10 mm. The letter *b* is the airway longitudinal distance covered by the ASM bundle going around the full circumference of the airway. Finally, the letter *c* represents the length of the ASM bundle and, in this example, is set at an angle 75 deg off the long axis of the airway. Using trigonometry, *b* and *c* can be determined. Now imagine that this airway is stretched radially to increase its perimeter by 25%. On the flattened airway shown in (a), this would increase the height of the rectangle by 25% without changing its length (*b*). Compared to (a), the length of *a* would increase by 25%, the length of *b* would remain unchanged and the length of *c* would increase by 23.5%. The angle of *c* would also change to 77.9 deg. Therefore, a radial stretch to the airway increasing its perimeter by 25% is expected to strain the ASM bundle by only 23.5%. Now imagine that the airway length is also strained by 25%. On the flattened airway shown in (b), this would increase the length of the rectangle by 25% (c). Compared to (a), the length of *a*, *b*, and *c* would all increase by 25%. In contrast to (b), the angle of *c* would remain unchanged. Therefore, when both radial and longitudinal strains are applied simultaneously at the same magnitude on an airway, the strain on the ASM is also of this magnitude.

3.5 Vertical Displacement. Due to the elongation of the airway tree during a DI, the relative distance of a specific point within an airway to a recording device at the mouth increases. This is an issue for several methods. This vertical displacement is important to consider in order to allocate a change in caliber from FRC to TLC at specific airway locations. Otherwise, erroneous changes are caused by comparing a upper (and larger) part of the airway to a lower part due to lung and airway elongation at TLC. For the acoustic reflection technique, coronal radiographs can be acquired. The radiograph allows the identification of the carina and to subsequently measure its distance from the microphone. The other measured areas can then be allocated to specific airway locations. Since the carina is moving at different locations during a breathing maneuver, several radiographs for monitoring its location at different lung volumes is ideally required. However, this is not always done [62]. It is thus likely that a small variability arises due to a vertical displacement of the airways relative to the recording microphone. To limit this problem, the cross-sectional area is usually averaged over a few centimeter-long segment.

The vertical displacement is also an issue for the pitot static probe. Indeed, the distance of the probe from the mouth is always the same, as the catheter is fixed at the mouth. This means that the probe is actually moving in relation to the airway tree during the forced expiratory maneuver. This is not taken into account with the pitot static probe.

The issue of vertical displacement is more easily overcome by HRCT. This is because an image of the entire (or a major portion

of the) lungs is obtained. Landmarks can thus be identified to assess the vertical displacement of the lungs during the DI.

3.6 Strain in Different Dimensions and Directions. The strain can be applied in the three dimensions, as well as in two directions (stretch or compress). The focus of this review is on the expansion of airway caliber during a DI causing a stretch to ASM. However, the elongation of the airways during a DI also implies that ASM is strained in at least another dimension, namely on its transversal axis. The effect of transversal strain on ASM contractility has not been studied sufficiently. One study demonstrated that cyclical lengthening of isolated airways mainly increases their contractile capacity [133].

The third dimension (thinner versus thicker airway wall) is also important to consider. One may think that an increase in P_L should thicken the airway wall, for the same reasons as it increases the length and the perimeter of the airways. However, the materials constituting the airway wall hardly change in volume during a DI compared to the air-filled compartments (i.e., the lumen of the airways and the alveoli). Increasing the length of an airway and its caliber during a DI to TLC should thus exert a tensile stress on the airway wall, which tends to make it thinner. Many CT studies actually reported that the airway wall is thinner at TLC, supporting that the airway wall is compressed in this dimension during a DI [92,94]. This was also shown in cat lobes frozen at different volumes [131], as well as in isolated airways stretched to

elongated lengths [133]. Overall, these suggest that the airway wall is stretched in two dimensions and compressed in one dimension during a DI to TLC. The ASM should thus be longer and wider but thinner at TLC. This is different from stretching an ASM bundle in vitro, where it becomes longer but consequently less wide and less thick. Thus, in contrast to in vivo, the ASM in vitro is stretched in only one dimension and compressed in two directions. The effects of varying the orientation and the direction of strain on ASM contractility have been largely overlooked. Only few studies conducted with isolated cells have examined the effect of strain orientation on ASM contractility [31,103–107]. The findings suggest that strain orientation has a major impact on the outcome. To the best of our knowledge, no study has yet investigated the impact of strain orientation and direction, as well as their different combinations, on the contractility of ASM tissues. These studies are clearly warranted.

3.7 Upper Airways. The effect of the upper airways (mouth, larynx, and pharynx) cannot always be discounted. Whether the upper airways can be considered a mere extension of the lower airways can be justifiably questioned. Some evidence suggests that the cross-sectional area of upper airways is also dependent on lung volume [134]. However, the upper airways also have an intricate geometry. The concepts of fluid mechanics that apply to a single rigid cylindrical tube in which the flow regime is laminar might not be relevant. For example, the flow path during an expiration bends when it reaches the larger space of the mouth. The flow path also encounters many protruding structures and diverticula that can alter its flow regime such as the vocal cords, the uvula, the epiglottis, the tongue, and the alimentary and nasal canals. All these structure are likely to foster turbulent flow.

The measurements of resistance by the FOT, the interrupted deflation, and the whole-body plethysmography are affected by upper airways. In the case of $R_{aw(pleth)}$, attempts were made to subtract upper airway resistance from R_{aw} in order to obtain lower R_{aw} [56]. In these experiments, the pressure difference between two lateral taps, one at the mouth and one inserted mid-stream in the tracheal lumen via a puncture 2–3 cm below the cricoid cartilage, was measured. This difference in pressure over the mouth flow was then used to estimate upper R_{aw} and to subtract it from $R_{aw(pleth)}$ [56].

The acoustic reflection technique is one convenient method to assess upper airways. This is because the time at which the signal is collected can be allocated to a specific distance from the mouth. The intensity of the signal is thus dictated only by the structural features that are in place at that distance. However, it does not provide information regarding the structural features altering the signal. Therefore, a notch, a dent or a circular decrease in caliber are equally detected.

3.8 Small Airways. Capturing the excursion of small airway caliber during a DI is a challenge. Indeed, many methods described in Sec. 2 are restricted to the assessment of large airways. This is probably the main limitation of the acoustic reflection technique. According to the results obtained with rigid casts of the airway tree, the areas determined acoustically agreed well with the real areas for airway segments extending up to 6 cm past the carina [135]. Therefore, the airways further down the main bronchi cannot be assessed. This obviously restrains the use of the acoustic reflection technique for the assessment of airway wall strain during DI. Also, only one measurement per distance can be obtained. So beyond the branching point, the signal emanates from the cumulative effect of the two main bronchi and their respective contribution cannot be distinguished.

The pitot static probe is also limited to the assessment of the large airways. The lowest position measured in Brackel and coworkers' study was at the entrance of the middle lobe [66]. In this case, the penetration depth of the device is limited by its size in relation to airway caliber. The same constraints apply to aOCT.

High-resolution computed tomography is probably the best method to assess the small airways. Yet, adequate resolutions are restricted to airway size over ~ 1 mm of internal diameter.

The contribution of the small airways is certainly embodied in measurements such as V_D , $R_{aw(pleth)}$, and FOT. However, the extent by which the small airways contribute to the overall signal cannot be quantified. FOT was initially suggested by some to distinguish the small from the large airways. The rationale lies in the traveling distances of the oscillations at different frequencies. While oscillations at low frequencies travel far down into the lungs, the traveling distance of high frequencies are shorter. Therefore, while the low frequencies should probe the entire airway tree, the high frequencies should only probe the large airways. By looking at the frequency-dependence of R_{rs} , or by using a simpler readout such a R_{5-19} (which is the subtraction of R_{rs} at 19 Hz from the R_{rs} at 5 Hz), it was suggested that the degree of obstruction of the small airways can be deduced. Although this line of reasoning is logical, this is no longer the prevailing belief. First, the penetration depth of the forced oscillations at different frequencies cannot be ascertained. It is thus not sure from how far deep into the lungs the signals used to calculate R_{rs} at different frequencies emanate. Second, and most importantly, computational models have clearly demonstrated that the frequency-dependence of resistance is particularly sensitive to the pattern of constriction in peripheral airways [136–138]. On one hand, a homogeneous pattern of small airway constriction increases R_{rs} equally throughout the frequency range. On the other hand, a heterogeneous pattern of small airway constriction increases R_{rs} way more at low than at high frequencies. Therefore, the frequency-dependence of R_{rs} (or R_{5-19}) is now considered a readout that is more useful to quantify the degree of airway narrowing heterogeneity in the periphery than to assess the degree of small airway obstruction.

3.9 Measurements Near Total Lung Capacity. The measurements made at TLC are sometimes difficult and sometimes just not possible. $R_{aw(pleth)}$, for example, cannot be measured at TLC but only near TLC. The measurement requires a certain amount of air to flow in-and-out of the lungs to calculate $R_{aw(pleth)}$. This panting maneuver near TLC is also difficult for the subject. The measurement of R_L with the interrupted deflation also required a certain amount of air to evacuate the lungs in order to measure the change of P_L caused by the interruption. Therefore, the value at TLC cannot be determined. Holding the breath at TLC during HRCT can also be difficult, especially for older and/or sicker patients. Concerning the pitot probe, the airway caliber at different positions were grouped in volume range (e.g., the caliber between 100% and 80% of FVC). The total strain experienced by ASM may thus have been underestimated because many measurements were not at TLC. Notwithstanding this possibility, the error associated with not assessing airway caliber at TLC compared with near-TLC would be small since the airways are stiffer in that range of lung volume. The variation in transmural pressure may disproportionately exceed the strain on ASM. In fact, submaximal volumes and/or P_L are generally sufficient to achieve maximal dilation [130,139].

Other issues are also more common at or near TLC than other lung volumes and can affect the accuracy of the measurement. For example, glottic closure commonly occurs at extreme volumes (RV and TLC). Therefore, the changes in airway caliber sometimes need to be assessed within these volumes (i.e., a little above RV and a little below TLC), which may slightly underestimate the full range of airway wall excursion that occurs during a DI from FRC to TLC.

3.10 Bronchial Tree Geometry. The estimation of ASM strain during a DI from FRC to TLC is often accomplished by measuring the changes in resistance at different lung volumes. This is the case for the whole-body plethysmography, the

interrupted deflation, and the FOT. To convert resistance into ASM strain, some arithmetics are needed. The calculation is based on Poiseuille's equation. This equation states that within a tube with a perfect cylindrical geometry in which flow is running in a laminar fashion, airway resistance is inversely proportional to the luminal radius at the fourth power. A change in airway resistance at different lung volumes can thus be converted into ASM strain, as the percent change in radius is the same as the percent change in airway perimeter (viz., \sim ASM length). As aforementioned, the airways also elongate during a DI. According to Poiseuille's equation, resistance to airflow is proportional to the length of the airway. So while the increase in caliber at TLC decreases resistance, the elongation increases resistance. As resistance is related to the radius at the fourth power, the effect of changing caliber largely predominates over the effect of changing the length of the airway. However, the estimation of ASM strain based on measurements of resistance might be slightly underestimated because the increase in airway length is usually not taken into account.

It is understood that the airway tree is way more complicated than a single cylindrical tube with identical size on both ends. It is also understood that the flow is not always laminar. The airway tree branches in different directions, contains numerous bifurcations, and many bronchi are bending and exhibit a tapered end. All these elements obviously disturb flow and increase the degree of turbulence. Notwithstanding this complexity, the most accurate computational model of the human lungs is the single-compartment model [140]. This model is merely constituted of a single airway with a perfectly cylindrical geometry that runs into a single elastic compartment. The resistance that stems from the viscous flow of air within the airways in a real airway tree, as well as its response to different interventions, thus seem to be predicted quite precisely just by altering the caliber of a single conducting airway in the modeled lungs. It seems that, sometimes, the gestalt behaves as a simple element. There is thus no reason to treat it differently as such in order to extract information that would otherwise be impossible to infer.

The presence of chokepoints (sometimes called stenosis) is also important to consider. The excursion of ASM length at these chokepoints during breathing maneuvers can be greatly altered [141]. Chokepoints also obstruct the dynamics of fluid. Consequently, they severely increase resistance without necessarily affecting the caliber along the entire airway. The presence of chokepoints is thus likely to insert inaccuracies in the estimation of ASM strain in methods using measures of resistance. In addition, chokepoints affect the regional transmural pressures, especially during forced maneuvers. While the transmural pressure downstream of the chokepoint increases during expiration (as the luminal pressure increases in the airways and alveoli subtended by the choked airway), it decreases upstream of the chokepoint. The opposite occurs during inspiration. Either way, the transmural pressures are altered. The strain ASM undergoes is thus attended to be affected in these regions. Also, these chokepoints are usually not present at every lung volume. The chokepoint may thus affect resistance at low lung volumes but not at high lung volumes, and thus affect the change measured between two lung volumes. More generally, the entire geometry of the airway tree (not only chokepoints) is likely to change at different lung volumes, which inevitably affects differently the resistance to airflow.

3.11 Chest Wall. The chest wall can also affect some measurements. This is the case for the FOT. The estimated change in airway caliber calculated from the change in R_{rs} from FRC to TLC needs to be taken with caution. This is because R_{rs} at volumes surrounding FRC is compounded by the resistance of the chest wall (R_{cw}), which is not the case at TLC [71]. Consequently, the delta of R_{rs} from FRC to TLC overestimates ASM strain. This is consistent with Brown and coworkers' study, in which the estimated ASM strain by FOT using R_{rs} was greater than the one predicted based on delta V_D assessed by the single-

breath nitrogen washout [73]. R_L estimated with the esophageal balloon can remedy this overestimation by discarding the effect of the chest wall.

3.12 Ionizing Radiation. The exposure to ionizing radiation is obviously a major concern. It is probably the most important downside of HRCT. Repeated measures should absolutely be avoided. Unfortunately, the investigators are left with a few snapshots at a few chosen lung volumes to quantify the excursion of airway caliber, which is far from ideal. Radiation is also a concern with bronchography, although the doses used are lower.

4 Confounders

Many factors influence the estimated strain ASM undergoes during a DI from FRC to TLC and should thereby be considered as confounders. The confounders can be related to methodological procedures (an intervention or the breathing maneuvers during and preceding the measurement), which can either be controlled or not. Alternatively, some confounders are inherent biological factors that cannot be controlled. This section describes the many procedural and biological confounders that are known to affect airway wall strain during a DI.

4.1 Driving Pressure and Volume. The magnitude by which the airways are strained during a DI is dictated in great part by the swing in transmural pressure (i.e., the pressure across the airway wall). The swing in transmural pressure during a DI depends on the extent by which the lung parenchyma is pulling the airway open, which, in turn, depends on the transpulmonary pressure (P_L). A greater swing in P_L and/or lung volume during a DI inflicts a greater excursion of airway caliber and, thereby, a greater stretch to ASM.

P_L and the lung volume attained at TLC are variable between individuals. These biological factors thus affect ASM strain during a DI and should thus be considered as important confounders. As discussed above, many methods that are used to estimate ASM strain from FRC to TLC rely on tricky breathing maneuvers near TLC (e.g., $R_{aw(pleth)}$) or a holding maneuver at TLC (e.g., HRCT). The level of inspiration that is achieved/maintained by the subjects during such maneuvers relative to their maximum also contributes to variability [141]. It is also important to mention that considerable regional differences in P_L exist within the lungs. During the same breathing maneuvers, the airways in lower lobes are more strained than airways of the same generation in the apical lobes [87,88,92,96]. The estimated strain ASM undergoes is thus highly influenced by the region of the lungs in which the airways are embedded.

4.2 Starting Pressure and Volume. The pressure–volume curve of the lungs is not linear, so as the curve defining the relationship between transmural pressure and airway radius. By changing the starting (FRC) transpulmonary pressure or lung volume not only the swing in pressure and/or volume from FRC to TLC may be affected [86] but it also implies that the airways are now operating on a different part of the transmural pressure–radius curve. This is important as it indicates that the same swing in pressure now translates to different changes in radius and thus to different degrees of ASM strain. This was predicted by computational modeling [142] and clearly shown in vitro [29,39].

An increase in FRC (i.e., hyperinflation) also impairs the ability to generate high P_L [59]. Consequently, it reduces the pressure distending the airways during a DI. In fact, hyperinflation is a strong predictor of the bronchodilator effect of DI [86]. More severe is the hyperinflation, smaller is the excursion of airway caliber from FRC to TLC and less efficient is the bronchodilator effect of a DI [86].

Lung volume and P_L at FRC also vary between individuals. These biological factors are thus important confounders that affect

the strain ASM undergoes during a DI. All the methods used to estimate ASM strain during a DI rely on measurements made at FRC. They are thus influenced by the starting lung pressure and volume.

4.3 Hysteresis. The pressure–volume curve of the lungs during inflation and deflation do not overlap. In fact, when the two curves are combined they form a loop that rotates clockwise, meaning that the volume at any given pressure is greater during deflation. This is called hysteresis and is due to the resistive component of the lungs, which is chiefly perceived during inflation but dissipated and barely not perceived during deflation.

This hysteretic behavior also applies independently to both the airways and the lung parenchyma. Therefore, when tracking the transpulmonary pressure and the cross-sectional area of an airway during breathing, a loop is also formed. However, the direction of rotation depends of the relative hysteresis between the airway and the surrounding parenchyma. When the airway is more hysteretic than the parenchyma the loop rotates clockwise. Inversely, when the parenchyma is more hysteretic than the airway the loop rotates anticlockwise. In healthy individuals, airway hysteresis dominates and is largely due to ASM tone [57,58]. This was also shown in isolated airways [132,143].

Hysteresis has important implications. It indicates that the caliber of an airway at a particular lung volume varies according to whether it follows a deflation from a higher lung volume or an inflation from a lower lung volume [58]. After either a deflation or an inflation, the caliber can be larger or smaller depending on whether airway or parenchymal hysteresis predominates. For example, when airway hysteresis predominates, the caliber of the airways at FRC after a DI to TLC is greater than the caliber at FRC prior to the DI. In essence, this is the definition of the bronchodilator effect of a DI.

Hysteresis also implies that the estimated strain ASM undergoes during a DI is not the same when the measurements are made from FRC to TLC than when they are made from TLC to FRC. An important procedural confounder is thus related to whether the change in airway caliber is measured during inflationary maneuvers versus deflationary maneuvers. The methods used to estimate ASM strain described in Sec. 2 involve either types of maneuvers. For example, the measurements of R_L at different lung volumes with the interrupted deflation are performed during deflation. The pitot static probe also takes the measurement during a forced deflationary maneuver. Contrastingly, the change in cross-sectional area of the airway lumen with the MRI is measured during inflation. This is because the image has to be captured during the flow of hyperpolarized gas (^3He or ^{129}Xe) into the conducting airways in order to achieve a better contrast between the airways and the parenchyma. This also implies that the image is not obtained at fixed volumes but rather during a dynamic change in lung volume.

The caliber at which an airway settles after a perturbation, such as a DI, also takes time due to hysteresis. The timing at which the measurements are made can thus affect the results and should thereby be considered as a confounder. Likewise, some methods used to estimate ASM strain require interferences with the normal pattern of breathing. HRCT, for example, requires breath-holding to assess airway caliber at different lung volumes. The breath-hold usually decreases the bronchodilator effect of a DI [3,144]. However, whether the breath-hold overestimates or underestimates airway wall strain depends: 1—on the relative hysteresis between the airways and the parenchyma; 2—at which lung volume it is measured; and 3—whether the lungs were inflating or deflating before the breath-hold. Regardless, the longer time that is allowed for the airways to settle at a new lung volume is likely to affect its caliber. Consequently, the estimated strain excursion undergone by ASM during such a change in lung volume will also be different compared to the one caused by the same change in volume with no breath-hold. All the other methods using

measurements made at static (or quasi-static) lung volumes instead of dynamic lung volumes are likely to be affected by this procedural confounder.

4.4 Forced Maneuvers. Other procedures that clearly affect the estimation of ASM strain include forced breathing maneuvers, such as forced expiratory volume in 1 s (FEV_1) and coughing. The transitory peak of negative airway transmural pressure achieved during these maneuvers can transiently narrow the airway lumen to a level beyond that observed at the end of the maneuver [65,74,78,79]. This phenomenon is also known for causing dynamic collapses and expiratory flow limitation. One method used to estimate ASM strain that can certainly be affected by forced maneuvers is the pitot static probe.

The flow rate (or speed of inspiration) during the DI is also important to consider. A DI at a high flow rate is more effective to bronchodilate the airways than a DI at slow flow rate [3,4,144]. This was also demonstrated with isolated airways [30,145] and ASM strips stretched at different rates [16]. An increase in transmural pressure was proposed to account for the greater bronchodilator effect observed at high flow rate [144]. With regards to the estimation of ASM strain, both inspiratory and expiratory forced maneuvers should be considered as procedural confounders.

4.5 History. Beyond the different breathing maneuvers used during the measurements (inflation versus deflation, static versus dynamic, slow versus forced maneuvers), the sequence of events preceding the measurements should be considered. The most prominent example is the bronchoprotective effect of a DI [146–151]. So a DI, or a series of DIs, prior to a bronchoconstriction elicited by inhaled methacholine, facilitates bronchodilatation induced by a subsequent DI postmethacholine [101]. The time elapsed between the DI pre-methacholine and the subsequent DI under a bronchoconstricted state also affects its bronchodilator effect [148]. The time spent without DI under bronchoconstriction also affects the excursion of airway caliber during a DI because it increases narrowing [149,152]. The bronchodilator effect of a DI is also not the same after a sequence of DIs than after a single DI [149]. All together, these results indicate that the strain ASM undergoes during a DI is affected by lung history.

The geometry of the airways at FRC can also be affected if the preceding measurements were performed at RV compared to if they were performed at TLC [57]. The caliber of the airways at a given lung volume is greater when preceded by measurements done at a higher lung volume [114]. As explained above, part of it is due to hysteresis. Notably, history can affect the measurements in both directions, as it can either increase or decrease the estimated strain ASM undergoes during a DI. Lung history thus represents a serious procedural confounder and should be controlled whenever possible.

4.6 Posture. The lungs undergo important deformation during changes in posture. This is because it changes the direction of the gravitational forces, which then affects the local P_L and the gradient of P_L [153]. A computational model predicted that a change of ~ 10 cmH₂O can occur at specific locations in the lungs during a change in posture from supine to prone [153]. In turn, this can be expected to change lung volume by approximately twofold, depending on which part of the pressure–volume curve this change in pressure occurs. This is then predicted to strain ASM by $\sim 26\%$, assuming that the perimeter of the airways changes proportionally to the changes in the cube root of lung volume. A change in posture also affects the starting (FRC) lung volume, engendering the consequences stated above. For example, FRC is decreased in supine posture [154].

The methods used to estimate ASM strain involved measurements at different postures. The measurements of airway resistance by FOT and plethysmography are usually performed seated upright. Contrastingly, HRCT and MRI are usually performed

supine. The changes in gravitational forces due to these different postures are likely to affect ASM strain differently in different locations of the lungs. The posture should thus be considered a procedural confounder.

4.7 Airway Size and Composition. All the elements that constitute the airway wall can be organized differently, in addition to vary in absolute amount and relative proportion [155]. These elements include the cellular and the extracellular components of the airway wall, as well as other structures such as the cartilages. Any elements constituting the airway wall should thus be considered as biological confounders. This is because any change in the structural composition of an airway is likely to modify its mechanical properties and thereby affects the strain ASM undergoes during a DI from FRC to TLC.

Many of these elements vary in healthy subjects according to airway size. Small airways, for example, has a structural composition that makes them more compliant [66,76,84,85,91,141]. Their percentage of dilation during a DI is thus greater compared to larger airways [55,141]. Interestingly, it was shown in mice that the specific compliance of the small airways are greater than the specific compliance of the lungs [156].

The P_L at which the airway dilation plateaus during an inflation maneuver also varies with airway size. In healthy individuals, the P_L at which this plateau occurs increases progressively with increasing airway size [80,84]. This indicates that maximal airway dilation occurs rapidly in small airways during inflation, while the large airways continue to dilate until later on in the maneuver. This is concerning for the methods that use the change in the entire volume of the airway tree in order to estimate the longitudinal strain on ASM. This is because these methods assume that all the airways expand to the same extent.

As stated above, airways of different size have different compliance. Their compliance also varies according to the pressure range across which they are studied [80,84]. In airway generations 0 (trachea) through 5, the curve that describes the relationship between luminal area and P_L in every generation is sigmoidal. In fact, most of the change in luminal area occurs within a narrowed range of P_L of about 15 cmH₂O [85]. Therefore, a limited window exists where changes in P_L actually cause changes in airway caliber. This implies that no change in airway caliber occurs at either low and high P_L . Contrastingly, in the steeper part of the curve, large changes in caliber occur across a very small range of P_L . Similar to the mouse study stated above [156], the specific compliance of the small airways in dogs and sheep are greater than the specific compliance of the lungs in that steeper part of the curve [130,157]. Collectively, these last observations suggest that the starting P_L , the maximal P_L attained during the DI, and the curve describing the relationship between P_L and the caliber of the airways under scrutiny need to be known in order to allocate an exact amount of strain on ASM during a DI.

4.8 Interdependence With Lung Parenchyma. As mentioned above, the swing in transmural pressure during a DI is a major determinant of ASM strain. Apart from the transpulmonary pressure, the transmural pressure across the wall of any airway is influenced by the stiffness of the surrounding lung parenchyma and the degree of interdependence between the airway and the parenchyma [158]. A more compliant parenchyma may dampen the swing in distending pressure generated by lung inflation and thus limit dilation. A loss of connectivity between the airway and the parenchyma, due to alveolar detachments [159] or geometric decoupling due to thicker adventitia [160], also limits the transmission of pressure across the airway wall. The stiffness of the surrounding parenchyma and the level of interdependence between the airways and the parenchyma are thus biological confounders that are important to consider.

4.9 Age. Aging influences the mechanical properties of the lungs and its constituents [161]. Age should thus be considered a biological confounder. For example, the extensibility (i.e., the ease by which it is elongated) of extraparenchymal airways, such as the trachea, decreases with age [162]. In contrast, intraparenchymal airways and the parenchyma seem to be more distensible [141]. Indeed, loss of lung elastic recoil was reported with aging [163]. The larger percentage change in caliber of small versus large airways during a change in lung volume also seems to vanish with age, probably due to an increase in lung compliance [141]. Age can thus affect ASM strain during a DI from FRC to TLC due to various reasons. These phenomena may account for the attenuated bronchodilator effect of DI with aging [164] and the lack of bronchoprotective effect of DI in infants [151].

4.10 Health Status. Respiratory disorders can influence to various extent and by several ways the strain ASM undergoes during a DI. The driving pressure, the mechanical properties of the airways and the lung parenchyma, as well as the forces of interdependence can all be affected by diseases. In fact, changes in the structural composition of the airways, a process called remodeling, are common in many respiratory disorders and can have a major impact on the mechanical properties of the airway wall [165].

Airway distensibility is decreased in asthma [59,64,66,67,69,70,86], especially at high [75] but also at low lung volumes [166]. This seems to be mainly caused by airway remodeling [69,75] but also inflammation [166,167]. Asthmatic patients also tend to exhibit airways of smaller caliber [68,70,85,168]. The sigmoidal curve that describes the relationship between P_L and airway caliber is also shifted to the left in asthmatic patients, at least when a bronchodilator (salbutamol) is administered prior to measurements [85]. This suggests that the changes in airway caliber due to breathing maneuvers occur at lower P_L in asthma [85]. This may explain why fluctuation of Rrs during tidal breathing is increased in asthma [72]. Interestingly, this increased tidal fluctuation of Rrs also negatively correlates with the bronchodilator effect of DI [72]. This is somewhat logical. By operating at a steeper part of the sigmoidal curve during tidal breathing, less of the total possible strain is available during a DI to TLC. In contrast to asthmatic patients, the lungs of nonasthmatic individuals seem to breath in a range of P_L below the one where airway caliber is greatly affected by small changes in P_L (based on small tidal fluctuation of Rrs [72]). However, for the same reason, the total possible strain the airways can undergo is still available and may occur during a DI to TLC. The benefit is a greater stretch to ASM and, thus, a commensurately greater bronchodilator effect of DI. Finally, a decline in lung elastic recoil was also reported in long-standing asthma [169–171]. All these phenomena may account for the attenuated bronchodilator effect of DI in asthma [70,72,167,172–179], as well as its attenuated bronchoprotector effect [150,172,174].

Airway distensibility also seems to be attenuated in COPD patients [76,180], especially in emphysema-predominant compared to airway-predominant subtypes of COPD [88]. In this case, the lower apparent distensibility seems mainly attributed to a loss of recoil due to parenchymal destruction [59,76], as well as hyperinflation, which limits inspiratory capacity and the driving P_L during the DI [76]. These phenomena may account for the attenuated bronchodilator effect of DI in COPD [76,167,180].

In contradistinction, the distensibility of the airways is increased in patients with cystic fibrosis [63]. Lung volume dependence of tracheal cross-sectional area in these patients was calculated to 0.22 cm²/L, compared to almost nil in healthy subjects. Cystic fibrosis patients also demonstrate increased lung compliance [181], which may limit the swing in P_L . Therefore, the reported increase in tracheal distensibility may be attributable to flaccidity, as previously reported in older patients with cystic fibrosis, as well as postmortem on isolated tracheas from patients

with cystic fibrosis [112]. Bronchiectatic bronchi, which are common in cystic fibrosis patients, are also prone to bronchomalacia. It is important to mention though that the incidence of bronchomalacia is high (70%) in patients with bronchiectasis with or without coexistent lung disorders [182].

Even nonrespiratory disorders are sometimes important to consider. Allogeneic haematopoietic stem-cell transplantation, for example, increases the changes in airway caliber during a lung excursion from FRC to TLC [90]. This seems to be entirely related to an increase in lung parenchymal stiffness rather than an increase in airway distensibility. Obesity is another example that can significantly impact ASM strain during a DI, mainly by changing lung volumes [183]. This phenomenon may account for the attenuated bronchodilator effect of DI in obesity [184–186].

Most respiratory disorders also affect the airways nonuniformly [187,188]. The amount of strain the ASM experiences during a DI is thus expected to vary according to this patchy pattern of affection. Overall, diseases can exert a huge and variable impact on the strain ASM undergoes during a DI. They should thus be considered as biological confounders.

4.11 Level of Airway Smooth Muscle Activation. Among all the elements that constitute the airway wall, ASM is one that is very special. This tissue is endowed with the ability to quickly adjust the mechanical properties of the airway wall. Greater is its level of activation, stiffer are the airways. In turn, stiffer airways are intuitively expected to expand less in response to a DI. However, this is not always the case. The change in airway caliber caused by a simulated DI is sometimes greater when ASM is activated by methacholine than when it is relaxed by atropine [130]. This is because increasing the level of ASM activation may also cause airway constriction, which affects ASM strain during a DI for at least two reasons. First, it modifies the length of ASM before the DI, which impacts its contractile capacity. More precisely, shortening the length of ASM decreases its contractile capacity [47,189]. Second, airway constriction also changes the positions over which the airways are operating on the pressure–radius curve [142]. Following airway narrowing, the DI thus takes place on a more compliant part of the pressure–radius curve and thereby increases the strain for any given stress [29]. Therefore, while the maximal distention attained by the airway during a DI is certainly limited by the level of ASM activation, the strain excursion may not. These have important implications for *in vitro* studies that attempt to emulate *in vivo* situations. For example, it may be appropriate to impose an equivalent level of strain on ASM during a simulated DI with or without spasmogen-induced contraction. However, this simulation only recreates adequately the *in vivo* situation if the ASM is also adjusted to a shorter starting length in the presence of a spasmogen.

The intrinsic level of ASM activation is tuned by many spasmogens and bronchodilators that are produced endogenously [190]. The intrinsic level of ASM activation should thus be considered a biological confounder. However, some interventions also affect the level of ASM activation, which consequently changes the stiffness of the airway wall and the strain caused by a DI. On one hand, many methods used to estimate ASM strain during a DI intentionally manipulate the level of ASM activation with bronchoactive substances (bronchoconstrictor such as methacholine or bronchodilator such as salbutamol). Some studies are actually designed to dissociate the active contribution of ASM in determining airway wall stiffness from the passive structural components of the airway wall [58,75,166,191]. These studies investigated the response to DIs before and after the activation or the inhibition of ASM. On the other hand, many methods used to estimate ASM strain during a DI unintentionally manipulate the level of ASM activation by utilizing topical or systemic anesthesia. This is the case for aOCT [85]. For these reasons, the level of ASM activation should sometimes be considered a procedural confounder.

Some patients also take medications with either short or long duration of action. Those are likely to affect the stress–strain relationship of the airway wall and thus the distension of the airways during a DI. They should thus be considered as confounders. The duration of withholding from these medications prior to measurements is also an important confounder to take into account.

Apart from medications, some interventional procedures also have the potential to affect ASM strain during a DI. This is the case for bronchial thermoplasty, which is an alternative treatment for severe refractory asthma. It was demonstrated in dogs that bronchial thermoplasty increases airway caliber at any airway pressure from 0 to 30 cmH₂O [192]. The change in airway caliber though from 0 to 30 cmH₂O was identical pre- versus postbronchial thermoplasty. Based on these observations, geometrical considerations need to be taken into account to understand the impact of bronchial thermoplasty on ASM strain. Airway caliber changes proportionately to the square of airway perimeter (*viz.*, \sim ASM length). The same change in caliber induced by rising the pressure from 0 to 30 cmH₂O in an airway starting at a larger caliber implies that ASM strain was attenuated postbronchial thermoplasty. Therefore, the initial (FRC) length of ASM may be greater after bronchial thermoplasty, but the strain ASM undergoes during the DI may be attenuated.

5 Discussion

The goal of this review was to estimate the strain ASM undergoes *in vivo* in humans during a DI from FRC to TLC. This transient stretch is important to quantify as it was proposed to contribute to the beneficial effect of DI by decreasing the contractile capacity of ASM. However, it remains unclear to what extent ASM is strained during a DI. Despite this gap in knowledge, the effect of strain on ASM contractility has been tested extensively *in vitro*. A variable range of strains at different frequencies and for different durations in a variety of ASM preparations have been tested. We came to learn that the dynamic environment in which ASM operates *in vivo* has the potential to greatly affect its contractile capacity. In general, the *in vitro* results indicate that the decline in contractile capacity is largely dictated by the amount of strain [11–15,17,23,28–30], which is consistent with *in vivo* results in rabbits [24] and humans [3,5,86,139,193,194], as well as with isolated cells [107]. Together, these studies support the hypothesis that the beneficial effect of DI on respiratory mechanics is related to the decrease in the contractility of ASM elicited by the stretch. However, the *in vitro* results are also variable, sometimes contradictory, and it is still uncertain if the strain required to significantly decrease the contractile capacity of ASM is physiologically attainable [29,33]. Incorporating an appropriate range of strains in these *in vitro* studies is obviously essential in order to understand the integrated role of ASM in respiratory mechanics.

As seen in Sec. 2 of this review, many former methods and more recent technological advances can be used to estimate ASM strain in humans *in vivo* during a DI. On one hand, some methods assess the distensibility of the entire airway tree. These methods have the advantage to assess the effect of all the airways combined, but provide little insights on the localized response in any given airway and miss completely in reporting the spatial heterogeneity of the response. They are also unable to distinguish between radial versus longitudinal airway strain. Among those methods, the measurement of V_D , R_{rs} near the resonance frequency with the FOT and R_{aw} by whole-body plethysmography are the most relevant. The FOT is especially appealing and increasingly used in clinical settings. Combined with imaging technique and computational modeling, FOT may eventually be able to document the changes in airway caliber during breathing maneuvers with a tremendous temporal and spatial resolution [195,196].

On the other hand, other methods assess individual airway distensibility. These methods have the advantage to measure

directly the localized response, but usually fail to assess the small peripheral airways. The better being HRCT, which can provide adequate resolution for airways down to ~ 1 mm of internal diameter. The other methods include bronchoscopy, fluoroscopy, acoustic reflection technique, MRI, pitot static probe, and aOCT. These methods were all very useful as they have clearly demonstrated that ASM strain during a DI differs according to airway size and location.

As seen in Sec. 3 of this review, several limitations need to be considered as none of these methods assess ASM strain directly. Each of these limitations can putatively add inaccuracies that are sometimes not negligible. A few assumptions also need to be made in order to transform the original data into ASM strain. The veracity of these assumptions can certainly be argued. Owing to these limitations and assumptions, it is understood that the strains reported in this review are nothing more than estimations.

As seen in Sec. 4 of this review, a single value of ASM strain cannot be attributed to a DI. This is because many procedural and biological confounders contribute to the variability between individuals and between airways within the same individual, as well as to the temporal variability of any given airway of a given individual [96]. At this point, it seems more appropriate to provide a rough estimated range of strains that is physiologically relevant.

Despite the different setbacks of each method and the many confounders, the level of concordance between the methods for predicting the level of ASM strain during a DI is decent (Table 1). This suggests that, although a greater level of temporal and spatial resolution can now be achieved, the new and refined technologies have simply confirmed the estimations made previously with antecedent methods. Set apart the stiffer trachea and main stem bronchi, the longitudinal strain ASM undergoes during a DI from FRC to TLC is estimated to reside within the range of 15–30%. These values should assist investigators who attempt to impose a physiologically relevant level of strain to different ASM tissues in *in vitro* settings in order to mimic a DI.

It is also important to realize that the value of strain that I was chasing in this review is the maximal attainable strain, i.e., the one achieves at TLC. Involuntary DIs, or should I call them sighs, which occur spontaneously every few minutes [194,197,198], do not reach TLC. Provided that an *in vitro* study is interested to investigate the regulatory effect of these sighs on ASM contractility, the range of acceptable strains is quite large. This is because beyond all the factors discussed in this review, the size of the breath during a sigh is obviously variable. The strain ASM undergoes during sighs is thus commensurately variable. Any intermediate values of strain occurring between FRC to another higher lung volume anywhere from end-tidal inspiration to TLC can justifiably be used to simulate these spontaneous respiratory motions of the lungs. I think the one advice to take from this review is to stay within the reported range of strains and, more importantly, to never exceed the limit of what is physiologically attainable.

To simulate more accurately particular *in vivo* situations, more data will be needed. Indeed, owing to the number of biological confounders affecting the variability, more studies using different populations of patients and controlling for as many confounders as possible are required. These studies will allow us to adjust the strain in our *in vitro* settings according to the particular real-life situations that we are trying to model. In turn, applying a correct range of strains in our *in vitro* settings should: 1—ameliorate the validity of these *in vitro* simulations; 2—justify the incorporation of those *in vitro* results in computational models that attempt to predict the consequences of those findings at higher biological length scales; 3—leap forward our understanding of the regulatory role of lung movements on the contractile capacity of ASM; and 4—allow to correctly infer on the potential contribution of ASM strain to the bronchodilator effect of a DI.

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