

**1-D Network Simulations for Evaluating Regional Flow and Pressure Distributions
in the Healthy and Asthmatic Human Lungs**

Sanghun Choi¹, Sujin Yoon¹, Jichan Jeon¹, Chunrui Zou^{2,6}, Jiwoong Choi⁶, Merryn H.
Tawhai⁷, Eric A. Hoffman^{3,4,5}, Renishkumar Delvadia⁸, Andrew Babiskin⁸, Ross Walenga⁸, and
Ching-Long Lin^{2,3,4,6*}

¹School of Mechanical Engineering,

Kyungpook National University, Daegu, South Korea

Department of ²Mechanical Engineering, ³Biomedical Engineering,

⁴Radiology, and ⁵Internal Medicine,

⁶IIHR-Hydroscience and Engineering, University of Iowa, Iowa City, Iowa, USA

⁷Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand

⁸Office of Research and Standards, Office of Generic Drugs,

Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Silver Spring, Maryland, USA

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*Corresponding author: Ching-Long Lin, Address: 2406 Seamans Center for the

Engineering Arts and Sciences, Iowa City, Iowa, 52242, USA

(e-mail: ching-long-lin@uiowa.edu), Tel: +1-319-335-5673, Fax: +1-319-335-5669

ABSTRACT

This study aims to introduce a 1-D computational fluid dynamics (CFD) model for airway resistance and lung compliance to examine the relationship between airway resistance, pressure, and regional flow distribution. We employed five healthy and five asthmatic subjects who have dynamic CT scans (4-D CT) along with two static scans at total lung capacity and functional residual capacity. Fractional air-volume change (ΔV_{air}^f) from 4-D CT was used for a validation of the 1-D CFD model. We extracted diameter ratio from existing datasets of 61 healthy subjects for computing mean and standard deviation (SD) of airway constriction/dilation in CT-resolved airways. The lobar mean (SD) of airway constriction/dilation was used to determine diameters of CT unresolved airways. A 1-D isothermal energy balance equation was solved, and pressure boundary conditions were imposed at the acinar region (Model A) or at the pleural region (Model B). A static compliance model was only applied for Model B to link acinar and pleural regions. The values of 1-D CFD-derived ΔV_{air}^f for Model B demonstrated better correlation with 4-D CT-derived ΔV_{air}^f than Model A. In both inspiration and expiration, asthmatics with airway constriction show much greater pressure drop than healthy subjects without airway constriction. This increased transpulmonary pressures in the asthmatics, leading to an increased work-load (hysteresis). The 1-D CFD model was found to be useful in investigating flow-structure, lung hysteresis, and pressure distribution for healthy and asthmatic subjects. The derived flow distribution could be used for imposing boundary condition of 3-D CFD.

45 **NEW & NOTEWORTHY**

46 A 1-D computational fluid dynamics model for airway resistance and lung compliance
47 was introduced to examine the relationship between airway resistance, pressure, and regional
48 flow distribution. The 1-D CFD model investigated differences of flow-structure, lung hysteresis,
49 and pressure distribution for healthy and asthmatic subjects. The derived flow distribution could
50 be used for imposing boundary condition of 3-D CFD.

51

52 **KEY WORDS**

53 Airway Resistance, Lung Hysteresis, Boundary Condition, Airway Diameter, and Lung
54 Compliance

55 **ABBREVIATIONS USED**

56	ADI: Anisotropic Deformation Index
57	AS: Asthmatic Subject
58	BMI: Body Mass Index
59	CFD: Computational Fluid Dynamics
60	EE: End Expiration
61	EI: End Inspiration
62	FEF 25-75: Forced Expiratory Flow 25-75%
63	FEV ₁ : Forced Expiratory Volume in 1 second
64	FRC: Functional Residual Capacity
65	FVC: Forced Vital Capacity
66	GMRES: Generalized Minimal Residual Method
67	HS: Healthy Subject
68	LLL: Left Lower Lobe
69	LUL: Left Upper Lobe
70	MDCT: Multi-detector Computed Tomography
71	PEF: Peak Expiratory Flow
72	PET: Positron Emission Tomography
73	PFT: Pulmonary Function Test
74	QCT: Quantitative Computed Tomography
75	RLL: Right Lower Lobe
76	RML: Right Middle Lobe
77	RMS: Root Mean Square

78 RUL: Right Upper Lobe
 79 RV: Residual Volume
 80 SD: Standard Deviation
 81 SEM: Standard Error of the Mean
 82 TLC: Total Lung Capacity

83

84 **PARAMETERS USED**

85 C_L : Global static compliance
 86 C_l : Local static compliance
 87 d : Average diameter of branch
 88 L : Length of branch
 89 P : Pressure
 90 P_{tp} : Transpulmonary pressure
 91 Q : Flow rate
 92 Re: Reynolds number
 93 t : Time
 94 U : Velocity magnitude
 95 u_i : Velocity vector
 96 μ : Fluid dynamic viscosity
 97 ν : Fluid kinematic viscosity
 98 ρ : Fluid density

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INTRODUCTION

Asthma is a disease associated with bronchial narrowing due to hyper-responsiveness and chronic airway inflammation (3). Airway narrowing of segmental airways can be assessed with airway diameter measurements by quantitative computed tomography (QCT) images. On the other hand, small airways can be assessed with air-trapping measurements by QCT (2, 8) and/or ventilation heterogeneity by functional imaging including positron emission tomography (PET) (36, 37) and magnetic resonance imaging (MRI) (4, 13). With the advantage of detailed structures in quantitative computed tomography (QCT), van de Moortele et al. (35) have recently investigated branching structures including homothetic ratios in segmental healthy airways, and Choi et al. (7) have demonstrated airway narrowing, elliptic airway shape, and wall thickening in segmental asthmatic airways. Existing studies have demonstrated correlations between bronchial structure and lung function, but have yet to explain the pathological mechanisms associated with regional ventilation, airway resistance, pressure and lung compliance that can be altered by the airway narrowing. Recently, a population-based analysis (7) and computational techniques such as image registration (9) and computational fluid dynamics (CFD) (10) have allowed us to develop a computational resistance model for understanding the structural and functional relationship.

Image registration techniques (18, 43, 45) have been used to derive functional air-volume changes and regional strains by matching CT images acquired at different volumes. For instance, using two different static images at total lung capacity (TLC) and functional residual capacity (FRC), Choi et al. (9) have shown that severe asthmatics have relatively smaller air-volume change in the lower lobes and larger air-volume change in the upper lobes. In addition, CFD simulations using subject-specific CT-based images (5, 22, 41, 42) have proven to be useful tools

for predicting flow structure, pressure drop, wall shear stress, water loss, humidity and preferential particle deposition. An accurate prediction of particle deposition is significantly associated with boundary conditions imposed at CT-resolved ending branches (11). Yin et al. (44) used an image registration technique to impose physiologically consistent boundary condition at CT-resolved ending branches. The study further showed that imposing constant pressure or constant velocity conditions to CT-resolved ending branches is less reliable because regional flows are variable depending on the manner in which ending branches are treated. Thus, the boundary condition derived by the image registration technique has been widely used for CFD simulations in healthy subjects without airway narrowing (22, 41, 42). However, it is of recent debate whether two static scanned images can illustrate regional ventilation of the subjects with airway narrowing. A study by Wongviriyawong et al. (40) using PET images has demonstrated that static air-volume change may not reflect regional ventilation.

Several groups have used airway network models to examine the relationship between airway pressure, tissue compliance, and flow distribution (16, 19, 31). In the current study, we use a modification of existing model (31) to investigate the relationship of airway narrowing with regional airflows. To validate the current model, the 1-D derived fractional air-volume changes (ΔV_{air}^f) were compared with dynamic CT (4-D CT)-derived (ΔV_{air}^f) (17, 18). The rationale behind the network model is that lung has a compensatory mechanism, so that an isolated airway may not explain global lung response (37). More specifically, airway narrowing in a branch may create a ventilation defect, leading a compensative ventilation of another region. To construct a whole lung model, we employ Tawhai et al. (32, 34)'s model for branching patterns, and develop a stochastic airway narrowing model to reproduce small airways for CT

unresolved airways. Next, we employ an empirical airway resistance model (6, 25-27), as well as a compliance model equivalent to the model by Wongviriyawong et al. (40).

METHODS

Human Subjects and QCT Imaging

Five healthy and five asthmatic subjects were employed in this study (**Table 1**). For each subject, we obtained 4-D CT scans during tidal breathing, and static scans at TLC and FRC. 4-D CT scans were previously collected to investigate regional ventilation, nonlinearity, and hysteresis of human lungs during dynamic breathing (18). Asthmatic subjects were also gathered to see the difference of regional ventilation and lung deformation (17). The previous studies with imaging protocol (17,18) were approved by the institutional review board and radiation safety committee at the University of Iowa. Siemens Somatom Definition Flash dual-source 128-slice MDCT scanner was utilized for the scanning with detailed setting (17). The acquired CT images were previously processed using a commercial segmentation software (Apollo, VIDA Diagnostics, Coralville, IA), and a published mass-preserving image registration method in existing studies (17, 18). Demographic and pulmonary function test (PFT) results of the healthy subjects and asthmatic subjects are available in **Table 1**. Gender, age, race and body mass index (BMI) were similarly distributed. Means of PFT-based FRC and residual volume (RV) % predicted values were slightly larger in asthmatic subjects than those in healthy subjects, but it did not reach the statistical significance possibly due to the lack of samples. Compared with healthy subjects, asthmatic subjects had significantly smaller forced expiratory volume in one second (FEV₁) % predicted values, FEV₁/forced vital capacity (FVC), and forced expiratory flow

at 25%-75% of FVC (FEF25-75), among which FEF25-75 values suggested that small airways were significantly narrowed in the asthmatic group ($P=0.012$).

Governing Equations for 1-D Airway Flows

We employed incompressible isothermal energy balance equations (25-27) to solve 1-D airflows with successive bifurcation and trifurcation structures (**Figure 1A**). The continuity and energy balance equations in a control surface (Γ) and a control volume (Ω) are as follows:

$$\int_{\Gamma} u_i n_i dS = 0, \quad (1-a)$$

$$\int_{\Omega} \left\{ \frac{\partial}{\partial t} \left(\frac{\rho U^2}{2} \right) + \nabla \cdot \left[P u_i + \frac{\rho U^2}{2} u_i \right] - \mu \mu_i \frac{\partial^2 u_i}{\partial x_j \partial x_j} \right\} dV = 0, \quad (1-b)$$

where u_i , n_i , ρ , U , P , and μ are velocity vector, outward normal vector to the control surface, fluid density, velocity magnitude, pressure, and fluid dynamic viscosity, respectively. By the definition of flow-rate ($Q = \int_{\Gamma} u_i n_i dS$), 1-D form of **Eq. (1-a)** was expressed as $Q_{in} -$

$\sum_{k=1}^m Q_{out,k} = 0$ in bifurcation ($m=2$) and trifurcation ($m=3$) systems of inspiration. For instance, in the control volume of **Figure 1B**, the continuity equation can be expressed as follows:

$$Q_{(1-2)} - Q_{(2-3)} - Q_{(2-4)} = 0. \quad (2)$$

Eq. (1-b) could be divided into four effects of pressure drop due to unsteady effect (ΔP_{uns}), total effect (ΔP_{tot}), kinetic energy (ΔP_{kin}), and viscous dissipation (ΔP_{vis}), respectively. Among four effects, ΔP_{uns} , ΔP_{tot} and ΔP_{kin} were simplified as 1-D forms:

$$\Delta P_{uns} = \frac{1}{Q_{(1-2)}} \int_{\Omega} \rho U \frac{\partial U}{\partial t} dV \approx \rho L \frac{\partial U}{\partial t}, \quad (3-a)$$

$$\Delta P_{tot} = \frac{1}{Q_{(1-2)}} \left[\int_{\Gamma_2} P u_i n_i dS - \int_{\Gamma_1} P u_i n_i dS \right] \approx P_2 - P_1, \quad (3-b)$$

$$\Delta P_{kin} = \frac{1}{Q_{(1-2)}} \left[\int_{\Gamma_2} \frac{1}{2} \rho U^2 u_i n_i dS - \int_{\Gamma_1} \frac{1}{2} \rho U^2 u_i n_i dS \right] \approx K_2 \rho U_2^2 - K_1 \rho U_1^2, \quad (3-c)$$

where L is a branch length between proximal and distal nodes, and K is an empirical constant, depending on Reynolds number (Re) and generation for inspiration and expiration. For a 1-D approximation, we replaced the velocity magnitude U with $4Q/(\pi d^2)$. Thus, in **Eq. (3-a)** ΔP_{uns} was expressed as $\frac{4\rho L}{\pi d^2} \frac{\partial Q}{\partial t}$, and an unsteady coefficient [**Uns**] was defined as $\frac{4\rho L}{\pi d^2}$, being a function of airway geometry and fluid property. In **Eq. (3-c)**, P_{kin} due to the kinetic energy was simplified as $\frac{16K\rho}{\pi^2 d^4} Q^2$, so the kinetic energy coefficient [**Kin**] was defined as $\frac{16K\rho}{\pi^2 d^4}$. Similar to [**Uns**], [**Kin**] was a function of airway geometry and fluid property. Next, ΔP_{vis} was expressed as follows:

$$\Delta P_{vis} = \frac{1}{Q_{(1-2)}} \int_{\Omega} \mu u_i \frac{\partial^2 u_i}{\partial x_j \partial x_j} dV = \frac{D_{vis}}{Q_{(1-2)}}, \quad (4)$$

where D_{vis} was viscous dissipation energy. Pedley et al. (25-27) modeled the viscous dissipation D_{vis} based on laminar boundary layer theory as follows:

$$D_{vis} = Z D_p, \text{ where } Z = \gamma \left(\text{Re} \frac{d}{L} \right)^\alpha \text{ and } D_p = 8\pi \mu U^2 L \quad (5)$$

where γ and α were empirical constants of 0.327 and 0.5 by Pedley et al. (25-27). With the aid of 3-D CFD techniques, Choi et al. (6) improved the quantities, which are functions of Re, generation, branching angle, and inspiration vs. expiration. Detailed formulations for K , γ , and α could be found in reference (6). The d , D_p and μ are average diameter, viscous dissipation in Poiseuille flow and dynamic viscosity, respectively. In this study, Re is defined as $\frac{4\rho Q}{\pi \mu d}$. Thus, by

the definition of viscous dissipation coefficient **[Vis]**, the pressure drop due to viscous dissipation is expressed as $\Delta P_{vis} = [\mathbf{Vis}]Q$, where

$$[\mathbf{Vis}] = \frac{128\mu L}{\pi d^4} \left[\frac{2\gamma}{\sqrt{\pi L \nu}} Q^{0.5} \right], \quad Z > 1 \quad (6-a)$$

$$[\mathbf{Vis}] = \frac{128\mu L}{\pi d^4}. \quad Z \leq 1 \quad (6-b)$$

Note that **[Vis]** is a function of flow-rate Q as well as airway geometry when Z is greater than 1. The governing equation for an airway branch (**Figure 1B**) is written as follows:

$$[\mathbf{Uns}]_{(1-2)} \frac{\partial Q_{(1-2)}}{\partial t} + P_2 - P_1 + [\mathbf{Vis}]_{(1-2)} Q_{(1-2)} + [\mathbf{Kin}]_2 Q_2^2 - [\mathbf{Kin}]_1 Q_1^2 = 0. \quad (7)$$

To discretize Eq. (7) temporally, an implicit method was employed for pressure and viscous dissipation terms as follows:

$$P_1^{n+1} - P_2^{n+1} - \left(\frac{[\mathbf{Uns}]}{\Delta t} + [\mathbf{Vis}]^* \right)_{(1-2)} Q_{(1-2)}^{n+1} = ([\mathbf{Kin}]_2 Q_2^{*2} - [\mathbf{Kin}]_1 Q_1^{*2}) - [\mathbf{Uns}] \frac{Q_{(1-2)}^n}{\Delta t}, \quad (8)$$

where $(n+1)^{\text{th}}$, $*$ and n^{th} indicate present time step, nonlinear iteration, and previous time step, respectively. Note that **[Uns]** and **[Kin]** are just functions of airway geometry, **[Vis]** is a function of flow-rate as well as airway geometry, so that a non-linear iteration is required. If we impose constant pressure boundary condition at acinar units (**Figure 1C**), flow-rate in all regions could be governed by pressure constraint between trachea and acinar unit regions. This boundary condition model was considered as Model A in the Result section.

Compliance Model for Static Air-Volume Change

We employed a lung compliance model (40) that describes regional air-volume change between static images, e.g., two static images at TLC and FRC in this study. A previous work

(40) modeled the lumped compliance along with lumped peripheral resistance to be connected to the CT-ending branches (~20 endings), whereas an equivalent compliance model was imposed to the terminal acinar units (~30,000 terminals) in this study. Global and local compliances (C_L and C_l) in a lung are defined as follows:

$$C_L \equiv \frac{\Delta V_L}{P_{tp}}, \quad (9-a)$$

$$C_l = \frac{\Delta V_l}{\Delta V_L} C_L, \quad (9-b)$$

where ΔV_L and ΔV_l are total lung air volume difference and local air volume difference between TLC and FRC, respectively, and P_{tp} is transpulmonary pressure driving peripheral deformation. C_L of individual subjects was estimated by the multiplication of specific compliance (0.1 l/cmH₂O) and lung volume at FRC (liter) (40).

The P_{tp} of **Eq. (9-a)** is the difference between pressure at acinar region (P_{alv}) and pressure at pleural region (P_{pl}). Thus regional air volume change in acinar units at present time step $(n+1)^{th}$ was governed as follows:

$$P_{alv}^{n+1} - P_{pl}^{n+1} = \frac{V_{alv}^{n+1}}{C_l}. \quad (10)$$

P_{pl} and V_{alv} are relative pleural pressure and local volume to the static pressure and local volume at FRC state. In this model, the change of P_{pl} was assumed to be uniform in whole regions, but C_l is non-uniform, so that C_l reflects the local characteristic in air volume change. In actual breathing in lungs, the change of P_{pl} is non-uniform due to the gravity effect, but this approach using varying compliance can mimic the effect of regional volume change due to body posture. To obtain V_{alv} at current time step $(n+1)^{th}$, the second order time integration method was

243 used as $V_{alv}^{n+1} - V_{alv}^n \approx 0.5(Q^{n+1} + Q^n)\Delta t$. Thus, final form of compliance model was expressed as
 244 follows:

$$245 \quad P_{alv}^{n+1} = P_{pl}^{n+1} + \frac{V_{alv}^n + 0.5(Q^{n+1} + Q^n)\Delta t}{C_l}. \quad (11)$$

246 This compliance model was coupled with airway resistance model of acinar units to
 247 explain the relationship between P_{alv} and P_{pl} (**Figure 1C**), as follows:

$$248 \quad \begin{aligned} & P_1^{n+1} - P_{pl}^{n+1} - \left(\frac{[\mathbf{Uns}]}{\Delta t} + [\mathbf{Vis}]^* + \frac{\Delta t}{2C_l} \right)_{(1-alv)} Q_{(1-alv)}^{n+1} \\ & = \left([\mathbf{Kin}]_{alv} Q_{alv}^{*2} - [\mathbf{Kin}]_l Q_l^{*2} \right) + \left(\frac{\Delta t}{2C_l} - \frac{[\mathbf{Uns}]}{\Delta t} \right)_{(1-alv)} Q_{(1-alv)}^n + \frac{V_{alv}^n}{C_l}. \end{aligned} \quad (12)$$

249 This resistance model with compliance model is referred to as Model B in the Result
 250 section. Kinetic energy terms were neglected when comparing Model A and Model B, because –
 251 unlike Model B - the numerical simulations were not converged when adding the kinetic energy
 252 term to Model A.

253

254 *Computational Simulation*

255 Pressure drop of Poiseuille flow is only a function of fluid properties and airway
 256 structures (diameter d and length L), but that of bifurcating flow is a function of flow
 257 characteristics, as a function of Re, as well as airway structures. Thus, if one considers that
 258 resistance is a constant property in bifurcation systems, it yields an erroneous estimation of
 259 pressure drop. Consequently, as shown in **Figure 1**, a bifurcation structure includes one
 260 continuity and three energy balance equations as follows:

$$Q_{1-2}^{n+1} - Q_{2-3}^{n+1} - Q_{2-4}^{n+1} = 0, \quad (12-a)$$

$$\begin{aligned} P_1^{n+1} - P_2^{n+1} - \left(\frac{[\mathbf{Uns}]}{\Delta t} + [\mathbf{Vis}]_{1-2}^* \right) Q_{1-2}^{n+1} &= \left(-[\mathbf{Kin}]_1 Q_1^{*2} + [\mathbf{Kin}]_2 Q_2^{*2} \right)^n + \frac{[\mathbf{Uns}]}{\Delta t} Q_{1-2}^n \\ P_2^{n+1} - P_3^{n+1} - \left(\frac{[\mathbf{Uns}]}{\Delta t} + [\mathbf{Vis}]_{2-3}^* \right) Q_{2-3}^{n+1} &= \left(-[\mathbf{Kin}]_2 Q_2^{*2} + [\mathbf{Kin}]_3 Q_3^{*2} \right)^n + \frac{[\mathbf{Uns}]}{\Delta t} Q_{2-3}^n \\ P_2^{n+1} - P_4^{n+1} - \left(\frac{[\mathbf{Uns}]}{\Delta t} + [\mathbf{Vis}]_{2-4}^* \right) Q_{2-4}^{n+1} &= \left(-[\mathbf{Kin}]_2 Q_2^{*2} + [\mathbf{Kin}]_4 Q_4^{*2} \right)^n + \frac{[\mathbf{Uns}]}{\Delta t} Q_{2-4}^n \end{aligned} \quad (12-b)$$

Since human airways have consecutive network structures with ~60,000 conducting airways (34, 39), we can construct a matrix with ~100,000 equations and unknowns as below.

$$\begin{bmatrix} \tilde{P} & \tilde{R} \\ 0 & \tilde{C} \end{bmatrix} \begin{bmatrix} \mathbf{P}^{n+1} \\ \mathbf{Q}^{n+1} \end{bmatrix} = \begin{bmatrix} \tilde{K} \\ 0 \end{bmatrix} \quad (13)$$

A GMRES iterative solver was employed to compute pressure $\mathbf{P}^{n+1}$ and flow rate $\mathbf{Q}^{n+1}$ in a strongly coupled manner. In addition, a Picard iterative solver was performed because of nonlinearity of flow rate (Q), because the matrix terms $\tilde{R}$ and $\tilde{K}$ consist of Q .

From 4-D CT images, subject-specific breathing patterns, tidal volumes V_{tidal} , and the periods of a cycle (**Table 2**) were available. Thus, we imposed the temporal derivative of lung volume as the mouth flow-rate to the inlet condition of 1-D CFD simulations. In addition, an iteration number of 400 was chosen for all simulations, equivalent to the time step of ~0.01 s, because numerical results were not sensitive to the time step unless it is greater than 0.01 s.

Population-Based Stochastic Airway Diameter for CT Unresolved Airways

Due to the current resolution of QCT imaging, reliable branching patterns including branching angle, branch length and airway diameter were not available if airway diameter is less than ~2 mm. To perform an airflow simulation for whole lungs, it is necessary to create physiologically reasonable branching patterns in the region beyond CT resolved airways. To

create branching angle and length, we employed a volume filling method introduced by Tawhai et al. (32, 34), and Horsfield ordering (15) was used to create diameter based on healthy homothetic ratio (33). After generating healthy diameters, we introduced a stochastic random heterogeneity model measured from CT resolved airways. In a previous population-based CT imaging study (7), an equation that predicts tracheal diameters for healthy subjects ($D_{\text{trachea,pred}}$) was derived using multiple linear regression for 61 healthy subjects, to give

$$D_{\text{trachea,pred}} (\text{mm}) = 16.446 - 2.4019 \text{ gender} - 0.29881 \text{ gender} \times \text{age} + 0.028484 \text{ age} \times \text{height} + 0.17866 \text{ gender} \times \text{age} \times \text{height}, \quad (14)$$

where [gender, age, height] take the value/unit of [0 (male) or 1 (female), year, meter]. The equation was significantly correlated with gender, age, and height, so it was used to normalize airway diameter to comparing between healthy and asthmatic subjects. In this study, we further computed the healthy diameter ratio (D_{ave}^r) of airway diameter to $D_{\text{trachea,pred}}$ depending on generation number for the respective five lobes (**Figure 2A** and **Table 3**). The five lobes are the left-upper lobe (LUL), the left-lower lobe (LLL), the right-upper lobe (RUL), the right-middle lobe (RML), and the right-lower lobe (RLL). Based on **Figure 2A**, average predicted diameter for respective lobes and generations was derived as follows:

$$D_{\text{ave,pred}} = D_{\text{trachea,pred}} \times D_{\text{ave}}^r. \quad (15)$$

$$D_{\text{ave}}^* = D_{\text{ave}} / D_{\text{ave,pred}}, \quad (16)$$

where D_{ave} was diameter averaged from the middle region (30%-70%) of an airway segment (7). As in Eq. (16), by dividing D_{ave} of individual subjects with $D_{\text{ave,pred}}$, the degree of airway constriction/dilation from CT-resolved airways could be estimated. Thus, this quantity can be used to evaluate airway constriction or dilation in any of local airway segments. We then computed mean and standard deviation (SD) of D_{ave}^* depending on each lobe to estimate the

degree of airway narrowing in each lobe. In our 1-D modeling for CT unresolved airways, we initially created an airway diameter based on Horsfield ordering (32), and the random numbers of D_{ave}^* were extracted based on the mean (SD), and multiplied to the initial diameter for modifying diameters of CT unresolved airways. This modeling is a stochastic spatial approach with the assumption that alteration of the segmental airways, e.g. constriction or dilation, is proportional to that of the peripheral airways.

Resistance and Work-Load During Breathing

To compare global features of 1-D airflow simulations between healthy and asthmatic subjects, total airway resistance in a global lung (Res_{Total}) was computed with an average intrapulmonary pressure ($\Delta P_{ave,intra}$) divided by $Q_{trachea}$ as follows:

$$Res_{Total} = \frac{\Delta P_{ave,intra}}{Q_{trachea}}. \quad (17)$$

The $\Delta P_{ave,intra}$ was estimated by subtraction of an average of P_{alv} measured at terminal airways from the inlet pressure at the trachea. In addition, we computed area for lung pressure-volume hysteresis, being considered as a work-load ($W_{cycle} = \oint P_{tp} dV$) during breathing. Mean effective pressure (MEP) was additionally computed as the work-load divided by V_{tidal} as follows:

$$MEP = \frac{W_{cycle}}{V_{tidal}}. \quad (18)$$

RESULTS

Generation of Stochastic Diameter of CT unresolved Airways

Figure 2A shows the ratio of generational diameter (D_{ave}^r) to the predicted tracheal diameter ($D_{trachea,pred}$) of 61 healthy subjects depending on respective lobes. Note that the quantities of D_{ave}^r were newly computed in this study. The error bar was presented with standard error of the mean (SEM), indicating the reliability of mean values. The generational number was counted as 0 at trachea. For the convenience of using current diameter ratio, quantitative values were also reported in **Table 3**. It was found that diameters of branches in lower lobes (LLL and RLL) were larger than those of upper and middle lobes (RUL, LUL, and RML) when compared in the same generation. We employed these quantities to estimate the degree of airway constriction/dilation of the individual airways such as D_{ave}^* (see the method section). **Table 4** shows mean (SD) of D_{ave}^* for respectively five healthy subjects and five asthmatic subjects. D_{ave}^* of healthy subjects were close to normal ranges, whereas those of asthmatic subjects demonstrated significant airway constrictions ($D_{ave}^* < 1.0$). The quantities of asthmatic subjects were significantly smaller than those of healthy subjects in right lower lobe (RLL, $P=0.022$). The subject- and lobe- specific mean (SD) of D_{ave}^* was randomly imposed to generate diameters of CT-unresolved airways in respective lobes (**Figure 2B**).

Validation of the Flow-rate Distribution using 4-D CT

We evaluated two different boundary conditions (Model A vs. Model B). For simplicity, in experimental settings, atmospheric pressure boundary conditions were usually imposed to the ending airways (29). Model A is an equivalent model of such experiment, because it imposes constant pressure boundary condition at acinar units. In contrast, Model B included a compliance

effect estimated by two static images (TLC vs. FRC). Using two different models, fractional air-volume changes (ΔV_{air}^f , 1-D CFD) between end inspiration (EI) and end expiration (EE) were estimated at the CT resolved ending branches. Since we obtained 4-D CT images, we extracted fractional air-volume change between EI and EE (ΔV_{air}^f , 4-D CT) derived by Jahani et al. (17). This was considered as a gold standard. Then ΔV_{air}^f 1-D CFD and ΔV_{air}^f 4-D CT were compared by imposing the same breathing patterns. **Figure 3A** shows boundary condition effects of Model A and Model B (See method section). Model B including a compliance model shows better correlations of 1-D CFD derived ΔV_{air}^f vs. 4-D CT derived ΔV_{air}^f , compared with Model A without the compliance effect. **Figure 3B** demonstrated correlations of ΔV_{air}^f (1-D CFD model) vs. ΔV_{air}^f (4-D CT) between healthy and asthmatic subjects when using Model B. While correlations of ΔV_{air}^f between 1-D CFD and 4-D CT were significant for both healthy and asthmatic subjects, deviation from the identity line was more noticeable in asthmatic patients (RMS error = 0.0067) than healthy subjects (RMS error = 0.0049). The correlation coefficient in asthmatics was significantly smaller than that in healthy subjects (Fisher Z transformation: $Z = 5.062$; $P < 0.001$). Lower correlations were especially observed in three asthmatic subjects (AS 1, AS 3, and AS 4), relative to other subjects (**Table 2**), possibly due to airway narrowing in CT unresolved regions. Among them, only AS 4 was severe asthmatic subject. Note that the correlation coefficients were significantly smaller in asthmatic subjects than healthy subjects ($P \approx 0.02$).

Pressure Distributions and Resistance at Peak Inspiration vs. Peak Expiration

Figure 4 shows pressure distributions between a healthy subject (HS 4, top row) and an asthmatic subject (AS 2, bottom row) at peak inspiration (left column) and peak expiration (right

column). In the CT resolved airways, HS 4 has a relatively normal diameter ratio, whereas AS 2 has a reduced diameter ratio (**Table 4**), so we assumed that subjects HS 4 and AS 2 may demonstrate the most extreme difference of lung function. The significant airway constriction of CT resolved airways in the asthmatic subject were stochastically applied to diameters of CT unresolved airways. Pressure drops were more significant in both inspiration and expiration of asthmatic subjects, compared with healthy subjects, possibly due to airway constriction. Note that total pressure drops were much greater in the asthmatic subject (**Figure 4**). This comparison between HS 4 and AS 2 demonstrates that ~21% constricted airways increase ~3 times and ~2 times for pressure and resistance in the global lung, respectively.

Temporal Histories between Pressure, Volume, and Flow

Table 2 shows breathing conditions including tidal volume, period of the cycle, and minute ventilation for respective five healthy subjects and five asthmatic subjects. The three quantities were not statistically different between healthy and asthmatic subjects. Thus, in the similar breathing condition, we investigated the relationship among Q_{trachea} , V_{tidal} and P_{pl} (**Figure 5**). We obtained the lung volume change pattern from the volume controller in acquiring 4-D CT images (blue-dashed line). The mouth flow rate was computed by the derivative of lung volume change. With the aid of a 1-D-CFD simulation, pleural pressure was dynamically computed during breathing, which was found to be consistent with volume change pattern in healthy subject without airway narrowing. On the other hand, the curve of pleural pressure was somewhat shifted from volume change (blue-dashed) curve to flow-rate curve (black-solid) in asthmatic subjects, indicating that resistance becomes important when breathing in asthmatic airways. Based upon these features, we plotted $P_{\text{pl}}-V_{\text{tidal}}$ curve, which is physiologically well-

known hysteresis curve that indicates the degree of airway resistance. **Figure 6** shows different hysteresis between healthy (top row) and asthmatic subjects (bottom row). While the healthy subjects require minimum work to breathe, the asthmatic subjects require larger work to breathe. The positive pleural pressure was only observed around the end of expiration in asthmatics, being consistent with existing pathophysiology of asthma (38).

To see the effect of peripheral airway resistance, we performed additional simulation for “without stochastic airway constriction” for CT unresolved airways (the green solid line with triangle). In the healthy subjects, peripheral airway constriction demonstrates little effect on global hysteresis, whereas in the asthmatic subjects, it increased the area of hysteresis curve. We further quantified work-load and mean effective pressure (work-load over tidal volume) (**Table 5**). Mean effective pressure values of asthmatic subjects were overall greater than those of healthy subjects ($P \approx 0.06$). This implies that the asthmatic subject requires more work per unit volume than healthy subject during normal breathing.

DISCUSSION

Standard pulmonary function tests (PFTs) include a measure of global lung resistance, but this cannot explain local structure and function. Several other experimental approaches including forced oscillation (1), multi-breath inert gas washout (28) and imaging techniques (12, 14, 24) can provide some information on global and/or local lung ventilation or resistance. In addition, as a computational approach, the 3-D computational fluid dynamics (CFD) technique is a popular method for demonstrating mechanical relationships regarding flow structure, pressure distribution, and aerosol delivery. However, 3-D CFD is relatively expensive due to large numbers of computational elements that resolve a multiscale airflow structure. As a surrogate to

3-D CFD technique, in this study we introduced a 1-D network CFD model including the effects of airway resistance and lung compliance. The 1-D network CFD model has successfully derived a physiological air-volume change (ΔV_{air}^f) consistent with 4-D CT image-derived ΔV_{air}^f . We employed a concept of lung compliance to consider the effect of static lung volume change, being a critical step to match with 4-D CT ΔV_{air}^f . The temporal histories obtained from 1-D simulations for flow-rate vs. lung volume vs. pressure can help explain a global lung mechanism due to resistance and compliance. It further demonstrates the relationship between pleural pressure, and lung volume to mimic lung hysteresis that can estimate work-load during breathing.

It is challenging to derive physiologically reasonable CFD boundary conditions for airflow simulations of CT-resolved branches. These boundary conditions are important when designing for efficient drug delivery and targeting hot spots. For convenience, pressure or velocity-based boundary condition have been usually imposed at CT-resolved ending branches. Yin et al. (45) derived a two-image based boundary condition with the aid of image registration technique. Unlike pressure or velocity boundary conditions, the imaging-based boundary condition was less sensitive for determining how to treat CT ending branches. Later, Yin et al. (43) and Miyawaki et al. (21) extended the current method to three static images and 4-D CT images, respectively. While the current approach was successful for healthy subjects, there was room for improvement with asthmatic subjects because static air-volume change may not reflect dynamic ventilation in the case of severe airway narrowing (40). In this study, we used CT images at TLC to determine airway diameters and used two images at TLC and FRC to derive local compliance. An airway resistance model considering kinetic energy and viscous dissipation was employed. Using this 1-D CFD model, we derived physiologically reliable airflows both for

436 healthy and asthmatic subjects. Thus, it is our hypothesis that the obtained airflows from 1-D
437 CFD can be possibly applied to the 3-D CFD simulation with subjects with constricted airways.

438 Lutchen and Gillis (20) previously demonstrated that most of the functional impairment
439 in asthma is caused by heterogeneous constriction of peripheral airways. Thus, methodology for
440 how to construct diameters of small airways beyond CT resolved airways is critical for
441 realistically mimicking 1-D CFD simulations. We used Tawhai et al.'s model (32, 34) to
442 construct airway trees known to be an anatomically consistent three-dimensional model. Then,
443 we generated healthy diameters with Horsfield ordering (15) as an initial guess. In this study,
444 with 61 healthy subjects, we investigated generational diameters between five lobes, showing
445 that lower lobes have larger diameters than upper lobes at the same generation. Smith et al. (30)
446 have found that airway diameters should be compared location by location because of regional
447 variability, being consistent with lobar distribution of airway diameter in the current study. We
448 estimated random heterogeneity of individual subjects and imposed these values to construct
449 subject-specific diameters due to airway constriction/dilation. An existing 1-D model by Kim et
450 al. (19) considered uniform constriction of diameters for the CT-unresolved airways, whereas we
451 imposed random heterogeneity based on lobar mean and standard deviation. It may be argued
452 that airway diameters in peripheral regions cannot be estimated by the diameters from segmental
453 airways. However, unless CT scans with increased resolution are available to capture very small
454 airways, the proposed diameter model for CT unresolved airways could be considered as a good
455 approximation.

456 To examine a potential of the current 1-D resistance model, computational simulations
457 were performed with healthy and asthmatic subjects. One finding of these simulations is that a
458 phase mismatch in asthmatics between lung volume and pleural pressure is observed. The

curve tends to show this flow-dominant feature in asthmatics, leading to a severe increase of hysteresis in pressure vs. volume. Thus, significant mechanical force is required for this stable asthmatic subject even during normal breathing. With the same 4-D CT imaging data, Jahani et al. (17) demonstrated a relationship of anisotropic deformation index (ADI) vs. lung volume. The ADI was an indicative metric of shear force (18). In their study, ADI in asthmatics was increased during expiration, relative to healthy subjects, possibly due to an increase of shear force. Thus, smaller hysteresis of ADI vs. volume was observed in asthmatic subjects compared with healthy subjects. In this study, larger hysteresis of pressure vs. volume was observed in asthmatic subjects than in healthy subjects. The airway narrowing in asthmatics possibly induces an increase of work, i.e. increased hysteresis in the pressure-volume loop, and an increase of shear force, i.e. reduced hysteresis area in the ADI-volume loop.

This model also provides local pressure distribution of entire lungs between inspiration and expiration. Although the diameter difference is 21%, pressure drop magnitude is about 3 times larger between HS 4 and AS 2. This demonstrates the potential of using method developed for this study in a clinical setting. However, this model has several limitations. Fixed airway diameter and airway skeleton during breathing were considered. Second, diameters of CT unresolved airways were stochastically imposed. We employed specific compliance of a constant value ($0.1 \text{ l/cmH}_2\text{O}$) for both healthy and asthmatic subjects, but the specific compliance could be varied depending on subject-specific disease states. It is known to be increased in diseases of asthma and emphysema, so a future study would be necessary to better estimate specific compliance. Furthermore, we did not consider the effect of the upper airways which cause complex flow phenomena, leading to a large pressure drop (23). A complete model is necessary to consider the effect of the upper airways. Although dynamic

local compliance could be directly derived from 4-D CT images, we derived static compliance using static CT, because 4-D CT data is generally not available due to high exposure of radiation. Furthermore, this study aims to mimic dynamic ventilation using static compliance coupled with a 1-D resistance computational method. While we validated our regional airflows by comparing with 4-D CT data, it is not currently possible to confirm that the pressure or airway resistance distributions are accurate. This remains a challenge for this field, and will need to be addressed in future studies once experimental data is available.

In conclusion, we introduced a network CFD model to understand structural and functional mechanism. The 1-D CFD model developed for this study is original in three aspects: 1) a population-based airway constriction model; 2) an integrated unsteady incompressible isothermal energy balanced 1-D solver; and, 3) a modification of 1-D airflow resistance with lung compliance model. The developed 1-D network airway resistance coupled with a compliance model is evaluated for five healthy and five asthmatic subjects with 4-D CT and two static CT images. In both inspiration and expiration, asthmatic subjects with airway constriction exhibit much greater pressure drop than those of healthy subjects. This further increased transpulmonary pressures in the asthmatic subject, leading to an increase of work load (hysteresis) compared with that in the healthy subject. The current 1-D CFD model was found to be useful in investigating flow-structure, lung hysteresis, and pressure distribution for both healthy and asthmatic subjects. The derived flow distribution could be used for imposing boundary conditions of a 3-D CFD model. Furthermore, the advanced 1-D CFD model could be potentially utilized for evaluation of lung function in a clinical setting.

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AUTHOR DISCLOSURE STATEMENT

Eric A. Hoffman is a shareholder in VIDA diagnostics, a company that is commercializing lung image analysis software derived by the University of Iowa lung imaging group. He is also a member of the Siemens CT advisory board.

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TABLES

Table 1. Demographic and pulmonary function test results of five healthy subjects and five asthmatic subjects

	Healthy subjects	Asthmatic subjects	<i>P</i> value
Demographics			
Subjects, <i>n</i> (Female)	5 (2)	5 (2)	-
Age, <i>yr</i>	43.4 (13.6)	41.0 (14.0)	0.675
Race, <i>n</i> (Caucasian/ Hispanic/Asian)	4/1/0	4/0/1	-
BMI (kg/m ²)	27.5 (3.4)	26.2 (4.2)	0.835
Pulmonary function tests			
FEV ₁ (% predicted)	90.7 (5.7)	66.5 (20.8)	0.022
FVC (% predicted)	92.2 (7.5)	86.7 (15.8)	0.531
FEV ₁ /FVC (%)	78.7 (2.6)	60.4 (12.5)	0.012
FEF 25-75 (% predicted)	88.3 (10.0)	38.7 (18.4)	0.012
PEF (% predicted)	96.0 (9.9)	78.7 (20.0)	0.095
TLC (% predicted)	95.6 (5.2)	96.0 (7.7)	1.000
FRC (% predicted)	79.0 (14.0)	102.6 (21.7)	0.095
RV (% predicted)	80.7 (13.7)	102.5 (29.1)	0.060
RV/TLC (%)	26.7 (6.7)	32.5 (13.0)	0.676

Values are expressed as mean (standard deviation, SD) except gender and race. Mann-Whitney U tests were performed for continuous variables.

Table 2. The subject-specific tidal volume, the period of the cycle, correlation coefficients and mean effective pressure

	Tidal volume [mL]	Period of the cycle [s]	Coefficient of correlation	Minute ventilation [mL/min]
Healthy subjects				
1	993	4.5	0.942	13136
2	825	3.9	0.869	12594
3	732	4.7	0.858	9366
4	829	4.9	0.779	10150
5	1012	4.3	0.923	13997
Asthma subjects				
1	740	3.6	0.675	12394
2	865	4.4	0.770	11905
3	1013	4.2	0.560	14335
4	659	3.6	0.668	10998
5	859	4.2	0.841	12320
Mann-Whitney U test (<i>P</i> value)				
	1.00	1.00	0.02	1.00

Mann-Whitney U tests were performed between five healthy subjects and asthmatic subjects *

LUL: Left upper lobe, LLL: Left lower lobe, RUL: Right upper lobe, RML: Right middle lobe,

RLL: Right lower lobe

Table 3. The generational mean (Standard error of the mean, SEM) of D_{ave}^r ($D_{ave,pred}/D_{trachea,pred}$) in respective lobes from 61 healthy subjects (Choi et al. 2015, *J Appl Physiol*)

Generat ion	2	3	4	5	6	7	8	9	10
LUL	0.610 (0.016)	0.451 (0.010)	0.299 (0.005)	0.224 (0.002)	0.190 (0.003)	0.170 (0.002)	-	-	-
LLL	0.586 (0.008)	0.453 (0.008)	0.335 (0.007)	0.245 (0.004)	0.206 (0.003)	0.185 (0.002)	-	-	-
RUL	0.573 (0.011)	0.390 (0.009)	0.257 (0.003)	0.198 (0.003)	0.171 (0.002)	0.161 (0.002)	-	-	-
RML	-	0.398 (0.007)	0.294 (0.005)	0.217 (0.003)	0.189 (0.003)	0.175 (0.003)	-	-	-
RLL	-	0.580 (0.016)	0.420 (0.011)	0.307 (0.007)	0.232 (0.004)	0.207 (0.004)	0.198 (0.003)	0.185 (0.002)	0.175 (0.002)

664 **Table 4.** Lobar mean (SD) of D_{ave}^* ($D_{ave}/D_{ave,pred}$) estimated by CT-resolved airways of
 665 respective subjects

	LUL	LLL	RUL	RML	RLL
Healthy subjects					
1	1.018 (0.247)	1.054 (0.356)	1.020 (0.188)	1.178 (0.176)	1.144 (0.410)
2	0.869 (0.210)	0.810 (0.229)	0.807 (0.135)	0.793 (0.124)	0.874 (0.313)
3	0.937 (0.164)	1.086 (0.341)	1.079 (0.176)	0.992 (0.103)	0.957 (0.271)
4	1.019 (0.166)	1.106 (0.424)	1.068 (0.185)	1.055 (0.109)	1.006 (0.320)
5	0.846 (0.142)	0.866 (0.228)	0.933 (0.196)	0.807 (0.170)	0.912 (0.256)
Asthma subjects					
1	0.846 (0.378)	0.894 (0.395)	0.850 (0.236)	0.693 (0.119)	0.702 (0.243)
2	0.757 (0.121)	0.777 (0.240)	1.066 (0.386)	0.799 (0.086)	0.756 (0.301)
3	0.754 (0.164)	0.897 (0.305)	0.866 (0.170)	1.066 (0.263)	0.674 (0.166)
4	0.838 (0.180)	0.823 (0.228)	0.859 (0.296)	0.763 (0.062)	0.893 (0.260)
5	1.120 (0.472)	0.987 (0.337)	0.885 (0.224)	0.898 (0.143)	0.772 (0.151)
Mann-Whitney U test (<i>P</i> value)					
	0.144	0.296	0.296	0.296	0.022

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Table 5. Work-load depending on computational conditions, intrapulmonary pressure drops and resistance for respective subjects

	Work-load [J]		Mean effective pressure [Pa]		Intrapulmonary pressure drops [Pa]		Resistance [Pa·s/m ³]	
	Resistance model	No peripheral constriction	Resistance model	No peripheral constriction	PI	PE	PI	PE
Healthy subjects								
1	0.11	0.07	112	68	57	95	74604	110852
2	0.15	0.05	178	62	120	117	138990	134545
3	0.04	0.02	60	29	30	40	48476	76787
4	0.04	0.02	51	27	19	51	39808	54268
5	0.10	0.06	95	56	58	75	79146	105349
Asthma subjects								
1	0.20	0.07	268	93	159	183	163703	185315
2	0.14	0.06	158	73	59	158	89502	121217
3	0.12	0.06	120	59	52	104	76248	101969
4	0.08	0.04	126	58	127	83	123069	145548
5	0.20	0.12	228	137	112	207	151201	186644
Mann-Whitney U test (<i>P</i> value)								
	0.14	0.14	0.06	0.10	0.14	0.06	0.09	0.09

FIGURE CAPTIONS

Figure 1. A: Airway generation by a volume filling method (Tawhai et al. 2004 *J Appl Physiol*); B: A schematic of bifurcation structure for continuity; C: A schematic of an acinar unit for two different pressure boundary conditions (P_{alv} vs. P_{pl}); P_{alv} and P_{pl} indicate pressure at acinar region and pleural cavity, respectively.

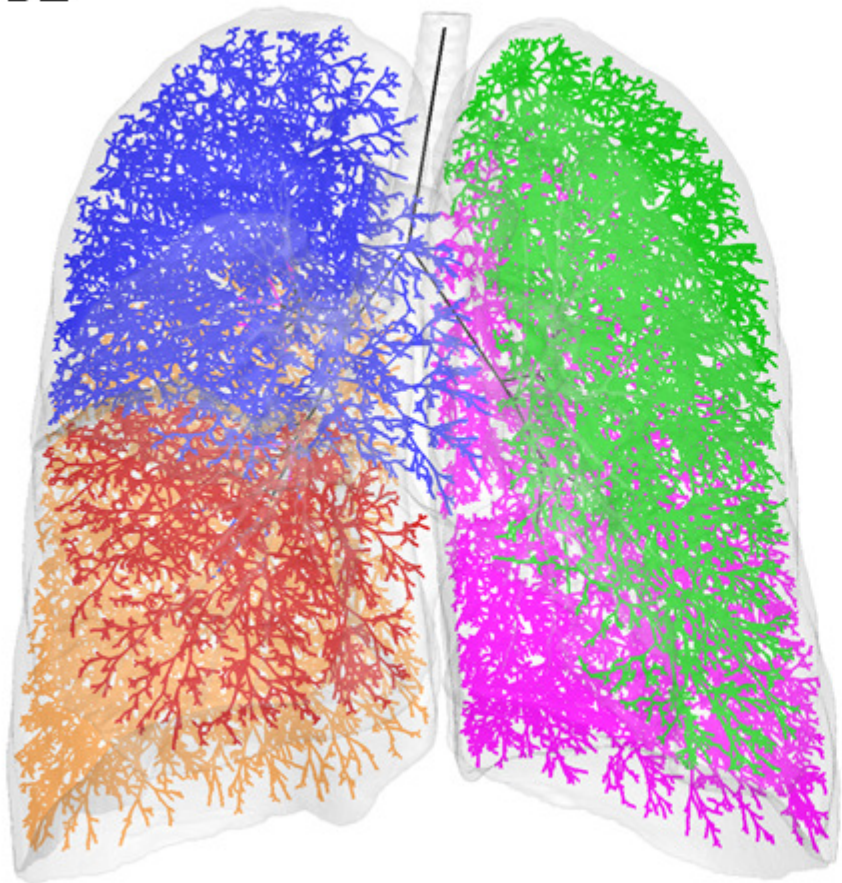
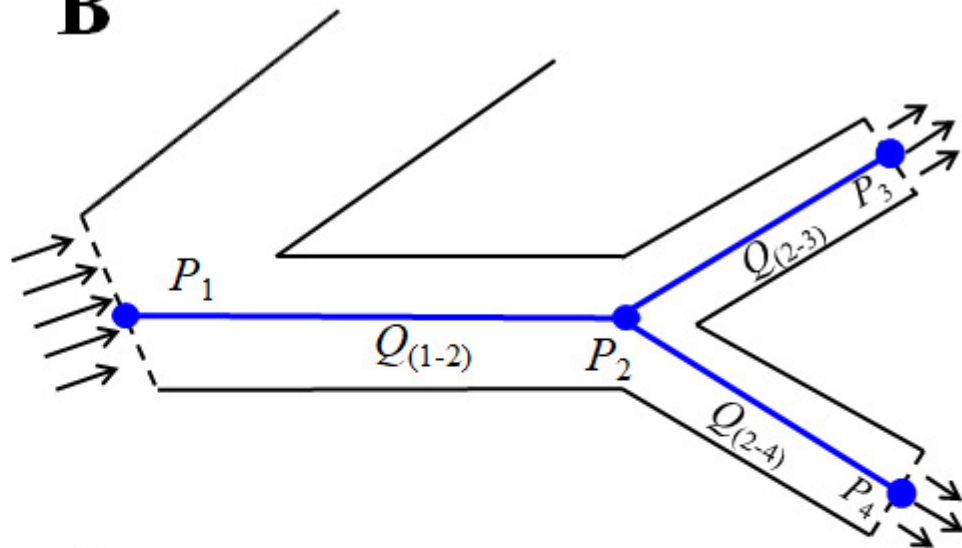
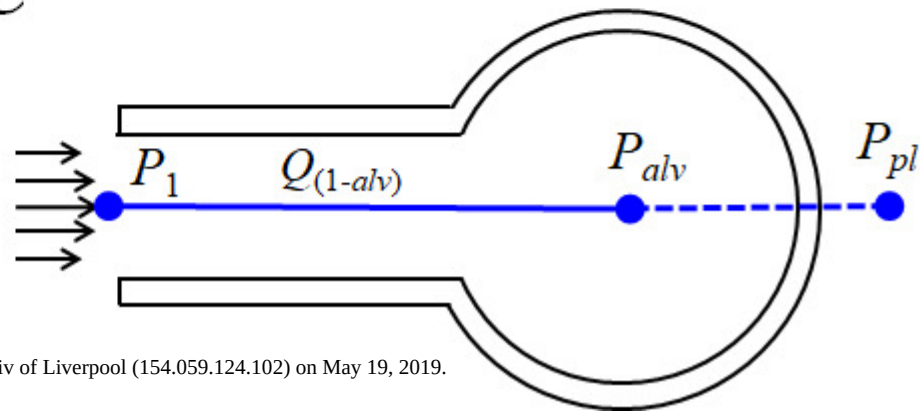
Figure 2. A: Generational mean (SEM) of D_{ave}^r ($D_{\text{ave}}/D_{\text{trachea,pred}}$) in five lobes with 61 healthy subjects (Choi et al. 2015 *J Appl Physiol*), and B: Random heterogeneity to create stochastic airway diameters for CT unresolved airways

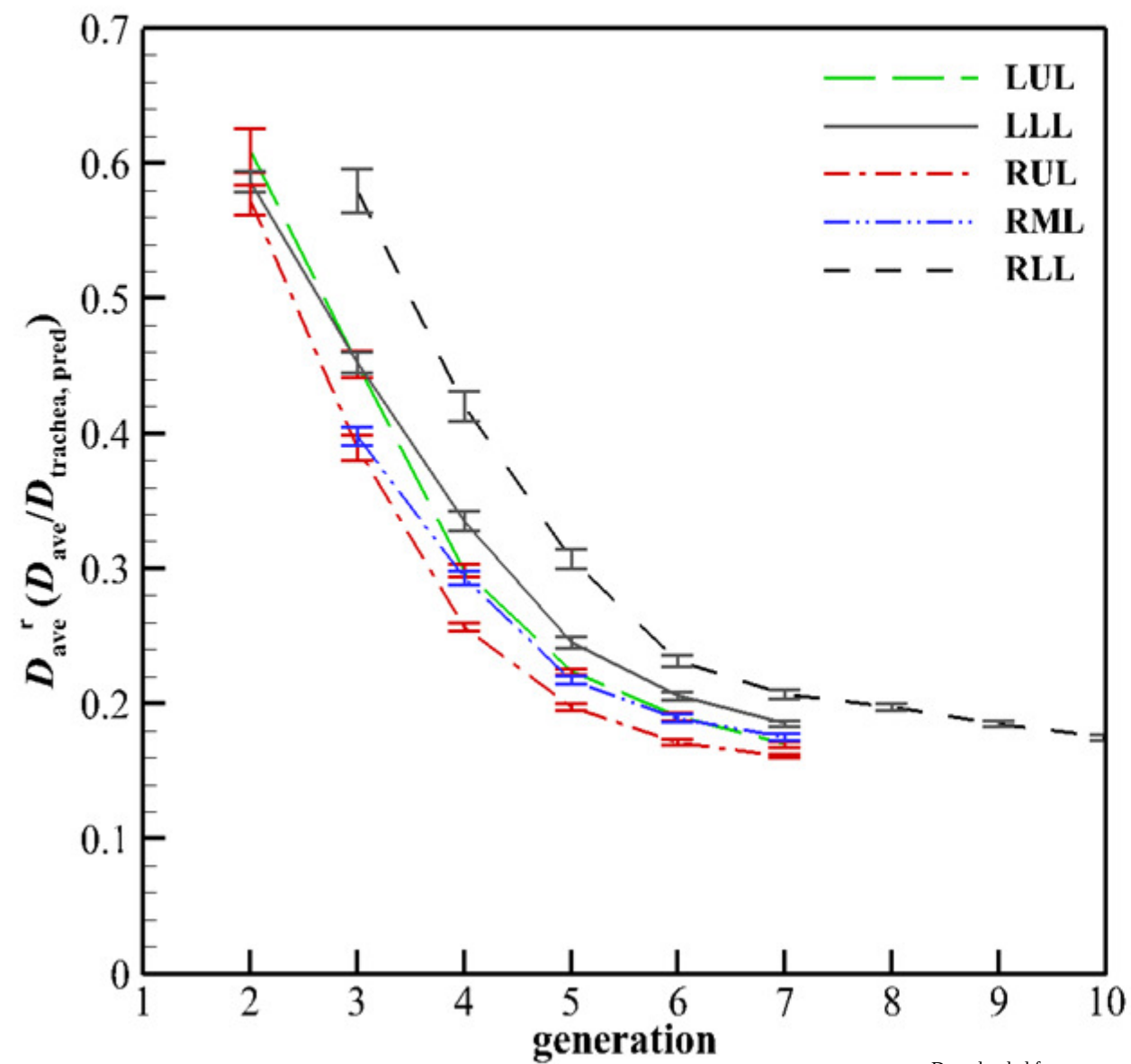
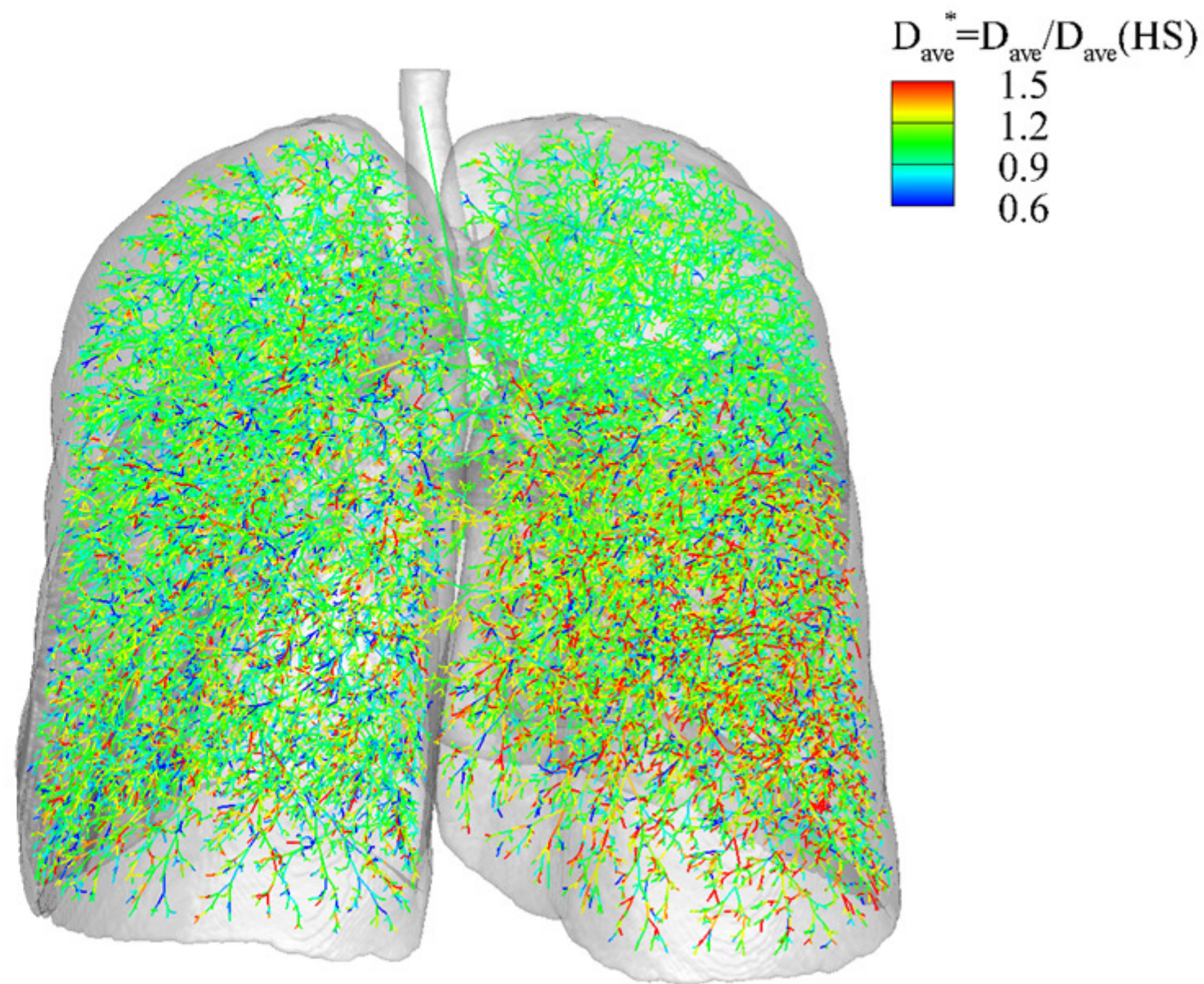
Figure 3. A: Fractional air-volume change ($\Delta V_{\text{air}}^f = \Delta V_{\text{local}} / \Delta V_{\text{total}}$, ΔV_{local} : air volume change at respective ending branches in segmental airways) of dynamic CT images vs. ΔV_{air}^f of 1D CFD model using two different boundary conditions (Model A and Model B) neglecting kinetic energy effect; B: ΔV_{air}^f of dynamic CT images vs. ΔV_{air}^f of 1D CFD model (Model B) between healthy subjects and asthmatic subjects

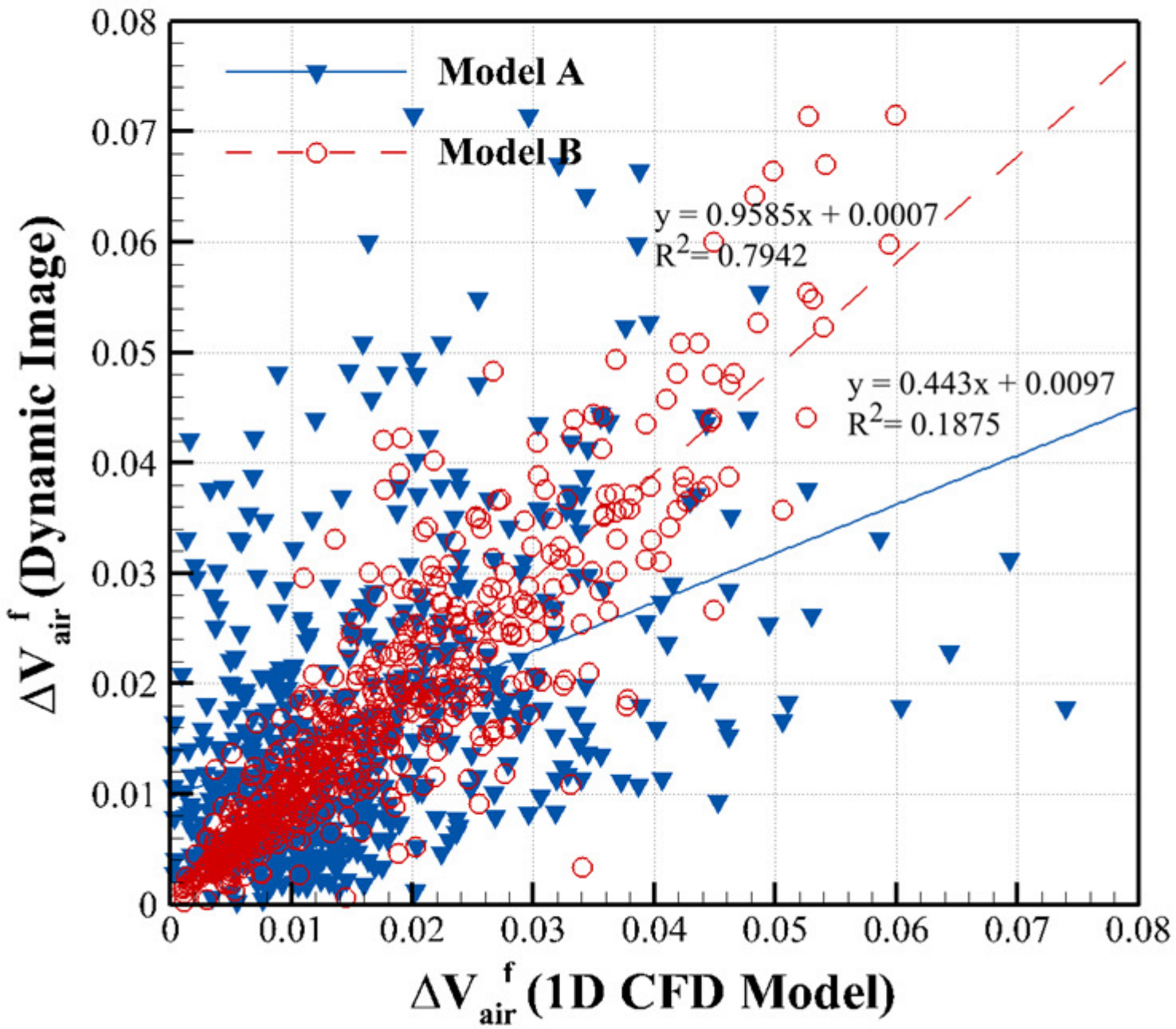
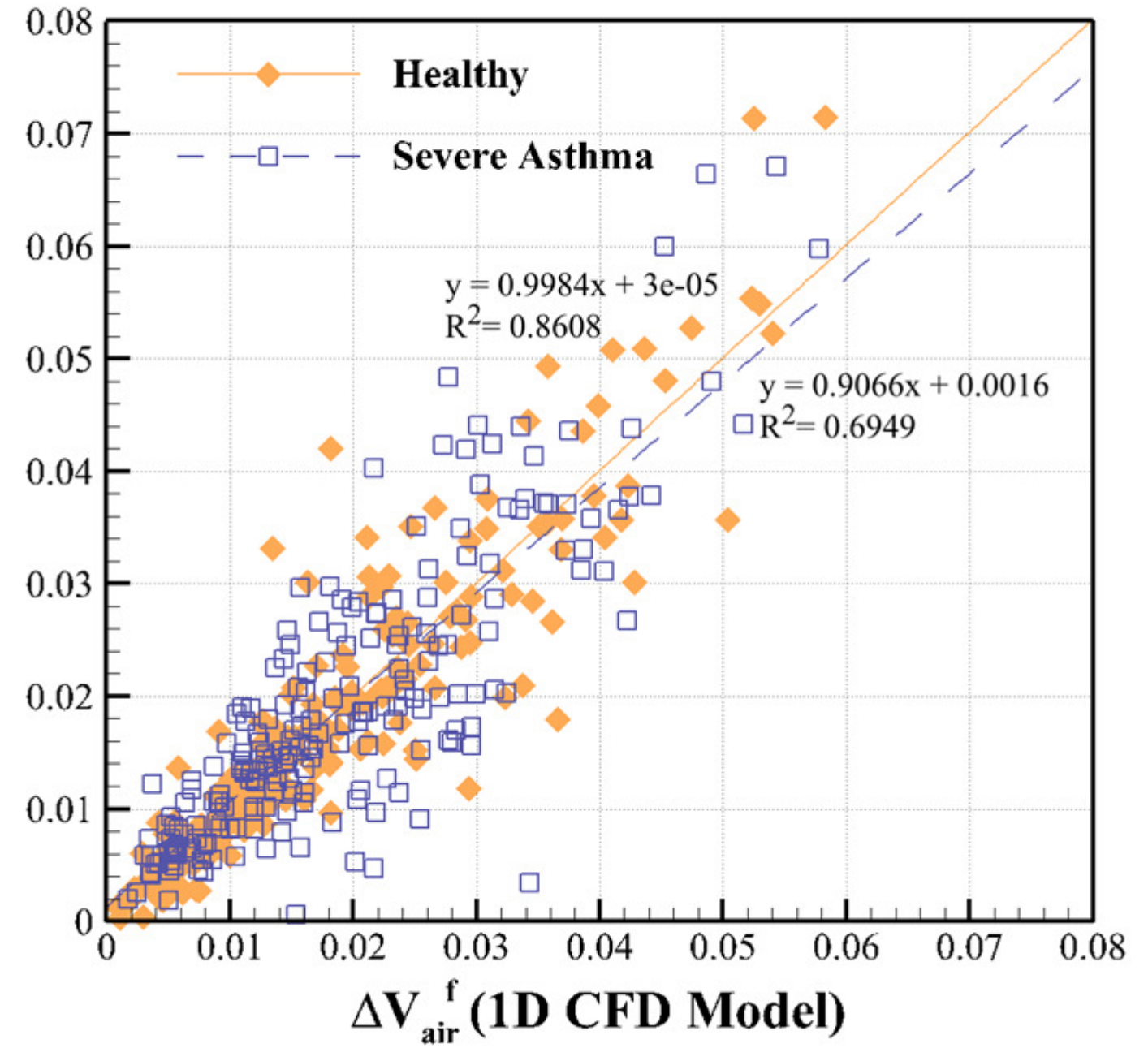
Figure 4. Pressure distributions for A: peak inspiration, and B: peak expiration of a healthy subject (HS 4); Pressure distributions for C: peak inspiration, and D: peak expiration of an asthmatic subject (AS 2)

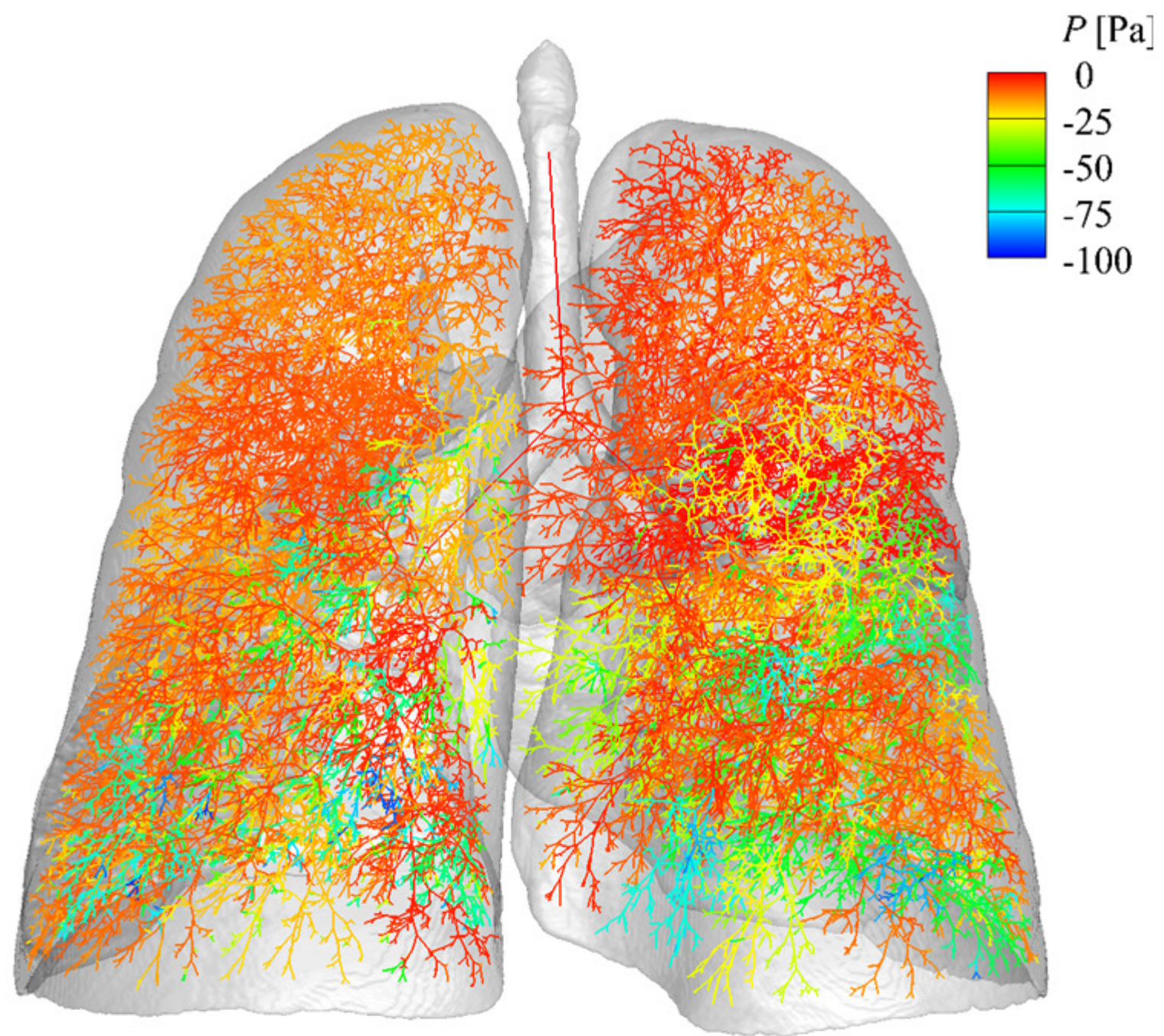
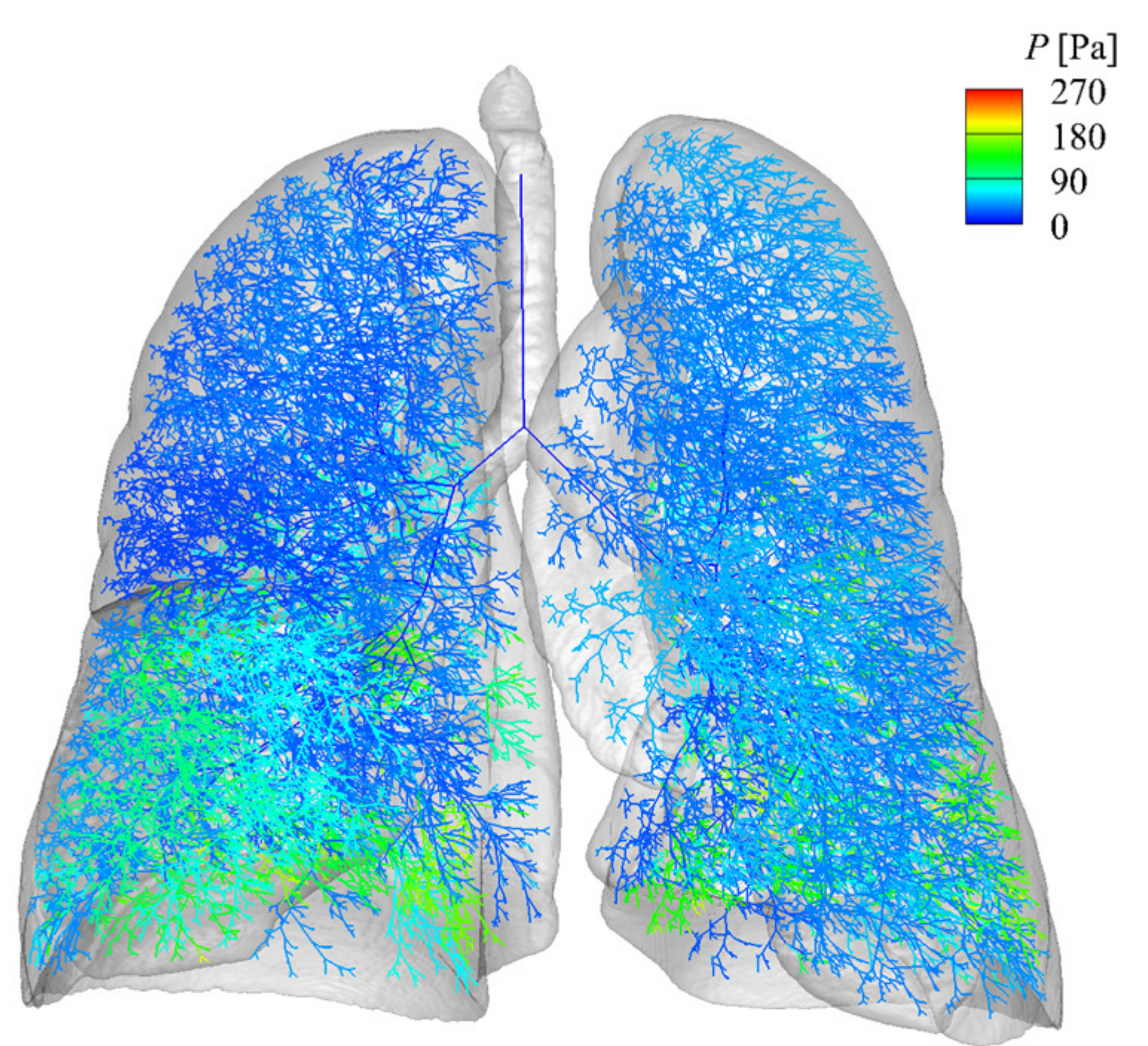
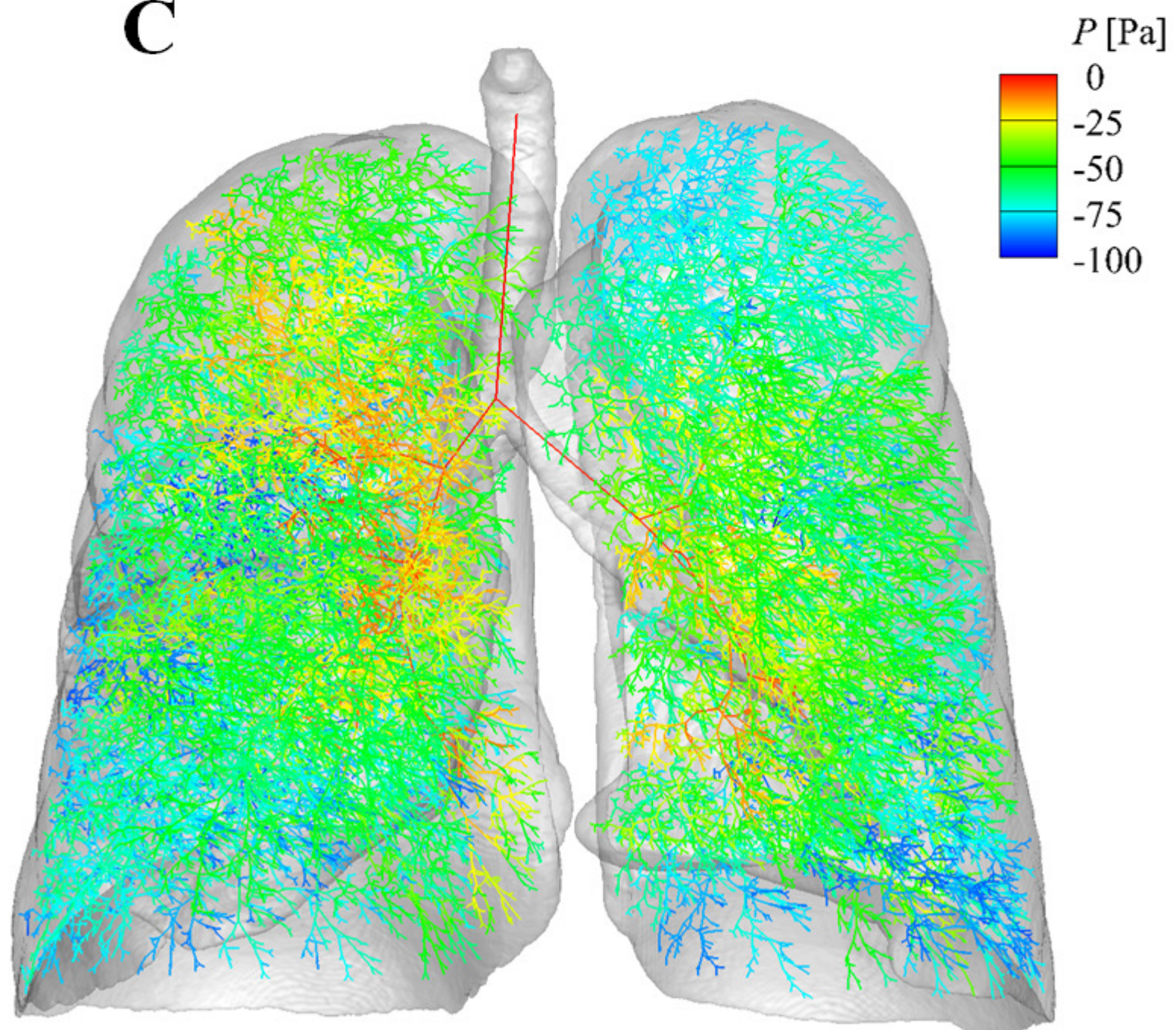
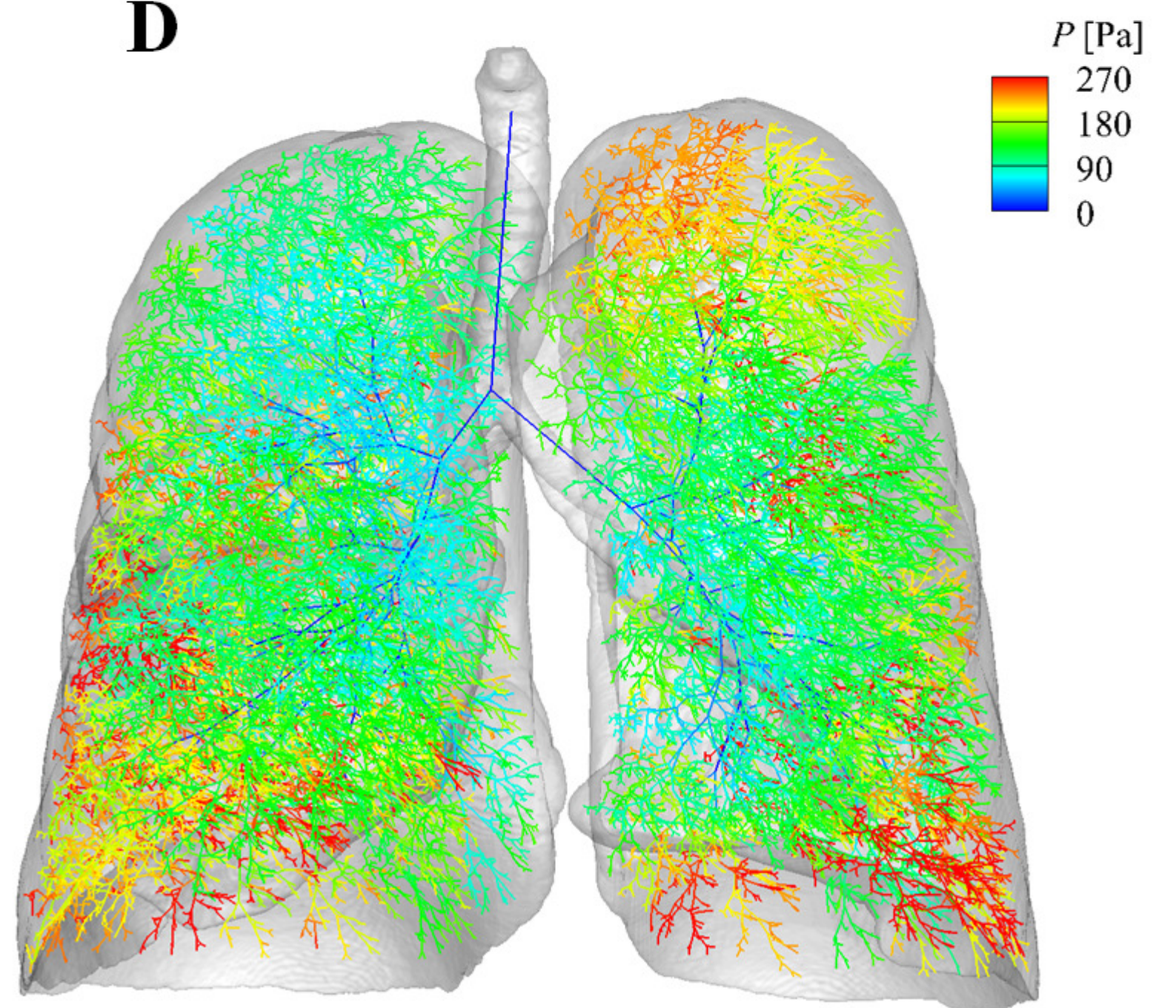
Figure 5. Temporal histories of Q_{trachea} , V_{tidal} , and P_{pl} in A: a healthy subject (HS 4) and B: an asthmatic subject (AS 2); Q_{trachea} , V_{tidal} , and P_{pl} are flow-rate at tracheal inlet, tidal volume, and pressure at pleural cavity, respectively.

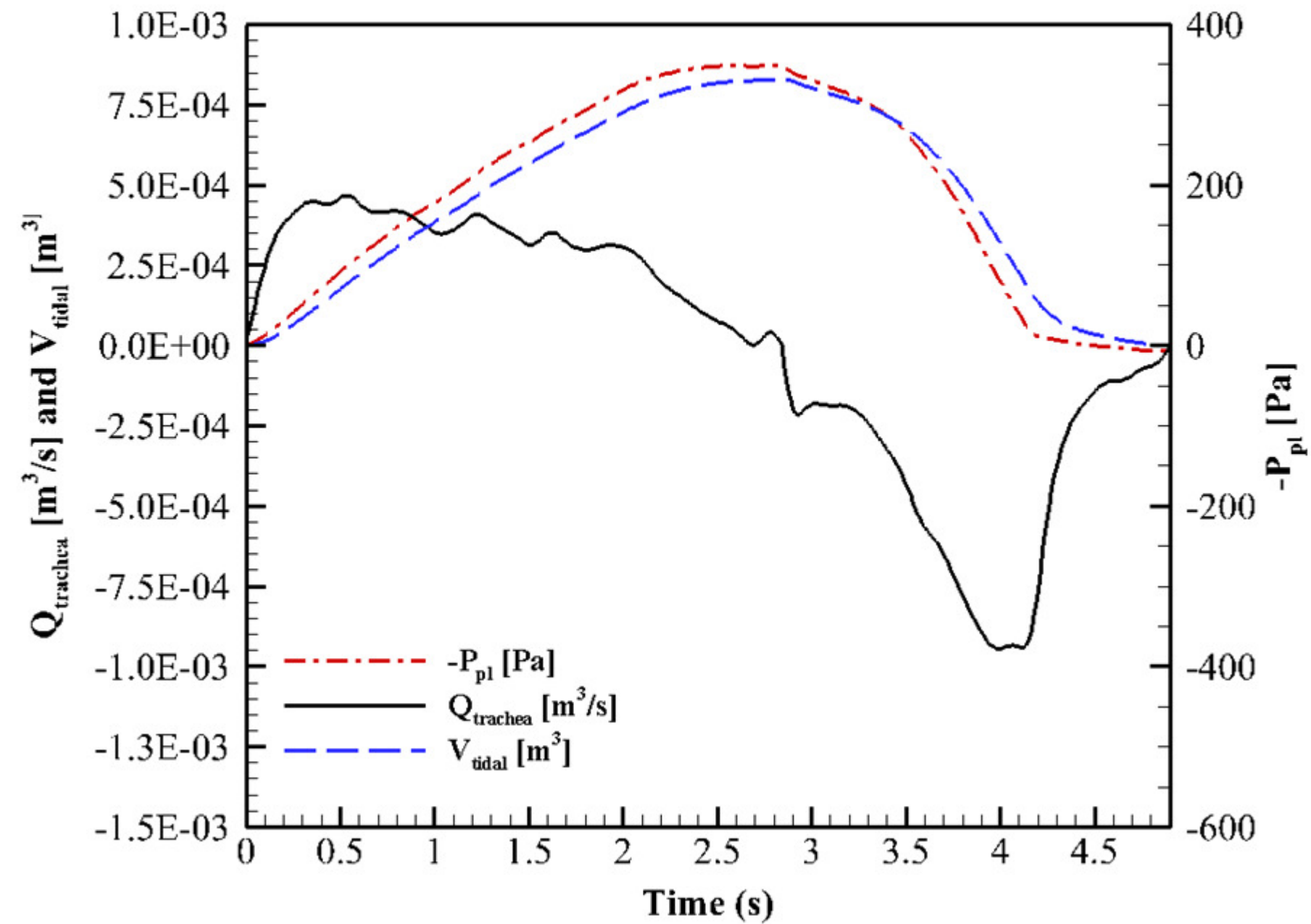
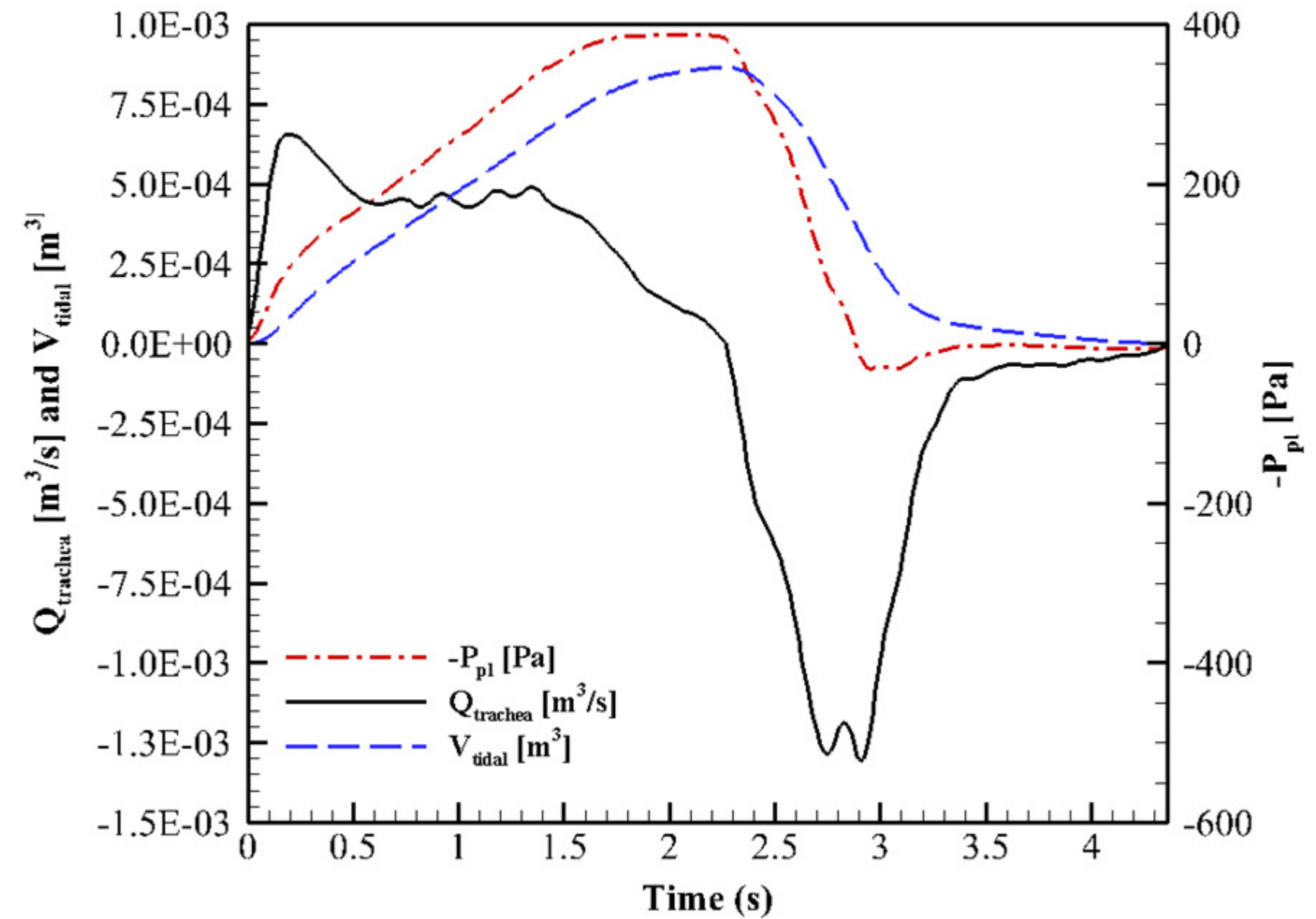
Figure 6. Hysteresis curve of P_{pl} vs. V_{tidal} in A (HS 3) and B (HS 4): healthy subjects and C (AS 1) and D (AS 2): asthmatic subjects depending on computational conditions; P_{pl} and V_{tidal} are pressure at pleural cavity and tidal volume, respectively.

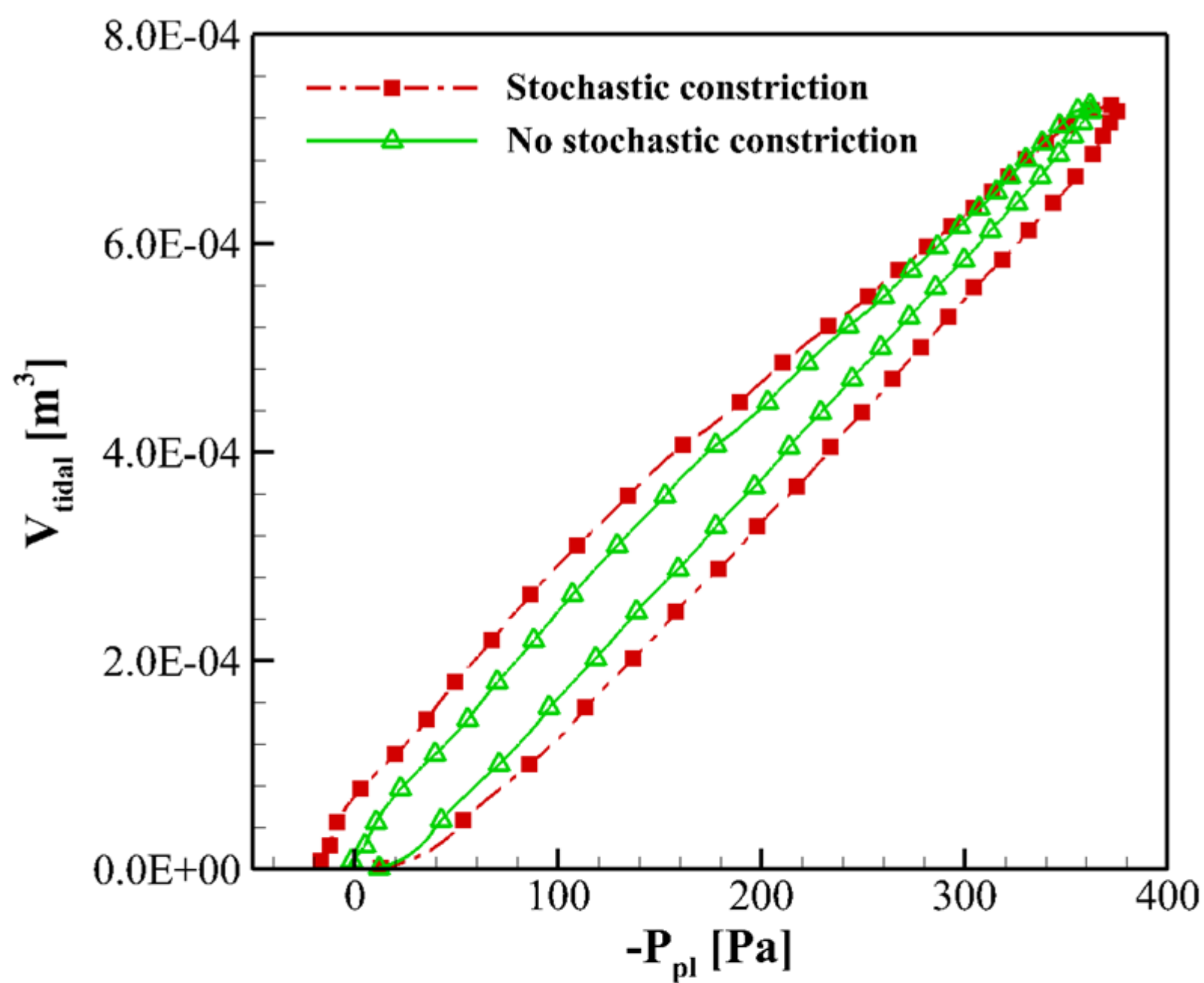
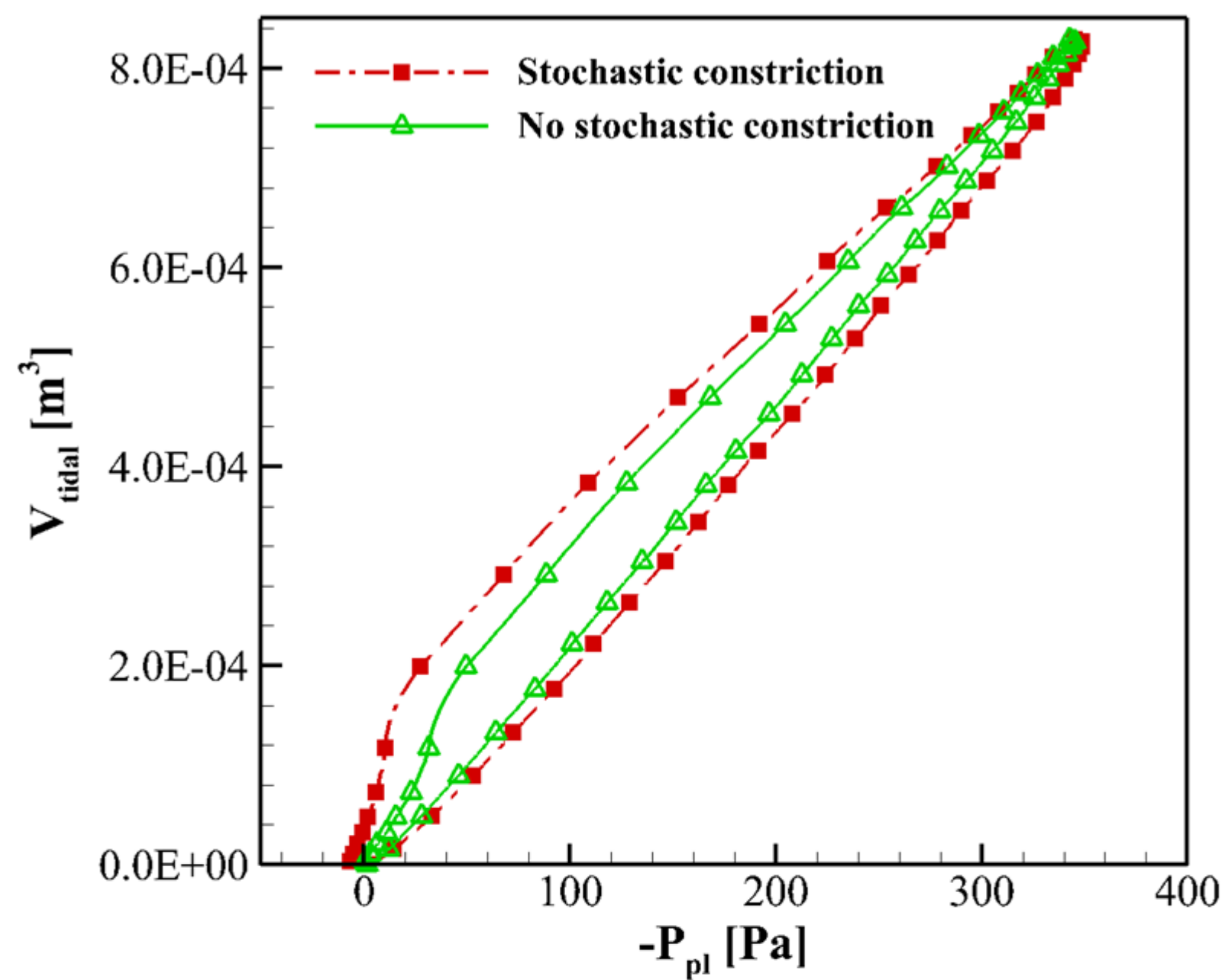
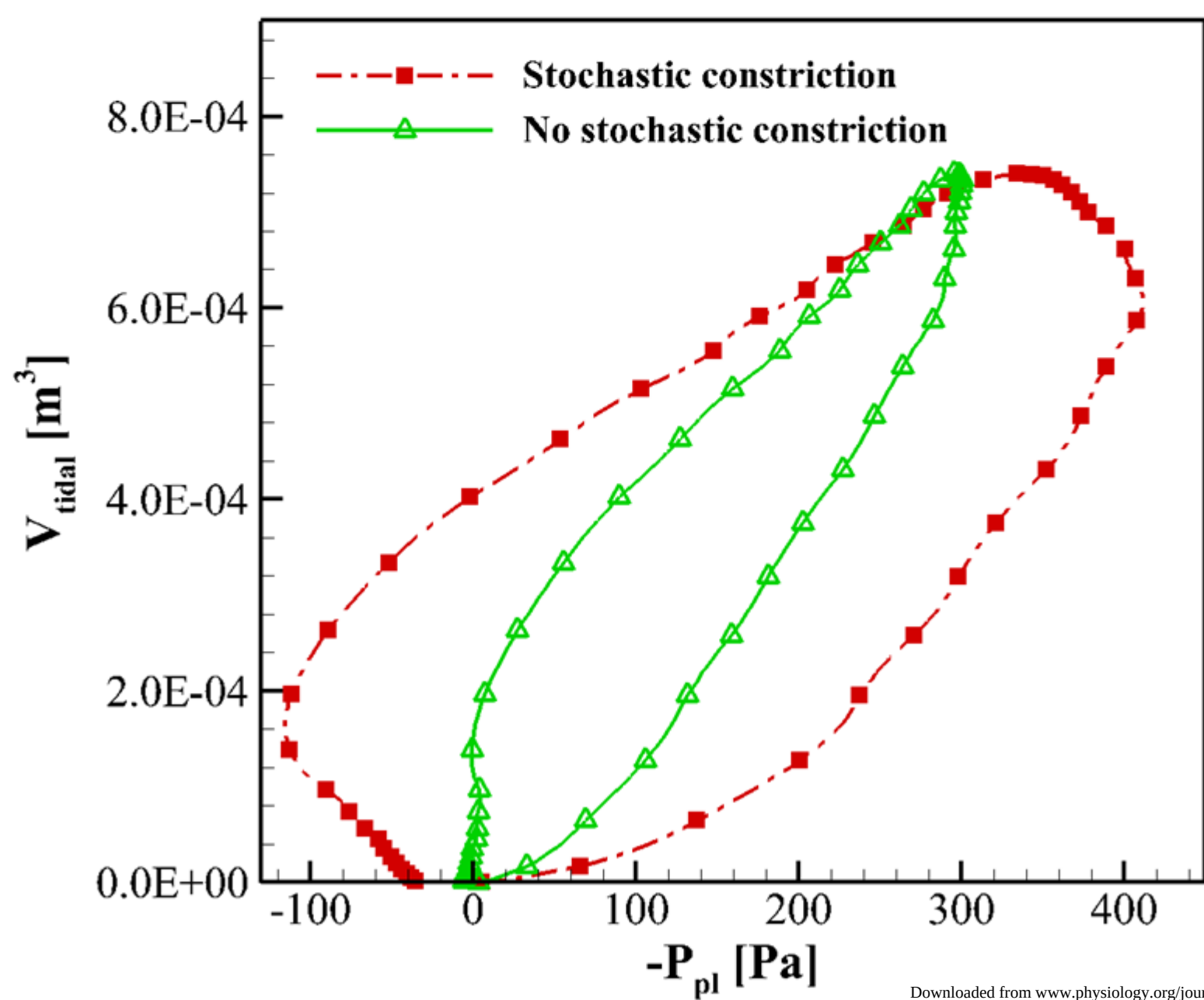
A**B****C**

A**B**

A**B**

A**B****C****D**

A**B**

A**B****C****D**