Supplementary Material for:

"A Multicompartment Lung Model for Pulmonary Uptake of Sevoflurane in a Physiologically Based Pharmacokinetic Model"

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Supplementary Material – Physiologically Based Pharmacokinetic Model Structure, Parameters, and Mathematical Formulations

This supplementary material provides a comprehensive description of the physiologically based pharmacokinetic (PBPK) model developed to simulate the pulmonary uptake and systemic distribution of sevoflurane during general anesthesia. While detailed information on the lung model configuration, respiratory mechanics, and simulation scenarios is presented in the main manuscript, this document focuses on the overall system architecture and the mathematical formulations governing each subsystem. In the main manuscript, the model was adapted to match the patient population in the referenced clinical study, whereas in this supplementary material, parameters are presented for a 70-kg reference man. All compartments of the model — the anesthesia machine and circle system, the lung subsystem, and the systemic circulation–organ perfusion network — are described together with the corresponding mass-balance equations, parameters, and symbolic definitions.

Model Subsystems

The overall system model is composed of three interconnected subsystems:

- **Anesthesia Machine and Circle System** – Represents the closed-loop breathing circuit, including inspiratory and expiratory pathways, fresh gas inflow, carbon dioxide absorbent, and bellows-driven tidal ventilation. It incorporates a modeled dead space arranged in parallel with alveolar ventilation, retaining 150 mL of the inspiratory tidal volume during the early phase of inspiration and returning this volume to the circuit during early expiration.
- **Lung Subsystem** – Comprises alveolocapillary exchange (ACEL) and non-exchange (ACNEL) compartments, along with an intrapulmonary dead space in series with the alveoli that functions as a rebreathing reservoir by capturing 150 mL during late expiration and releasing it during early inspiration.
- **Systemic Circulation and Organ Perfusion Network** – Receives arterial blood from the pulmonary capillary bed (PCB), distributes it through parallel organ circulations (including a peripheral shunt), and reconverges into a common systemic vein that returns to the PCB, completing the closed-loop circulation. This configuration allows controlled distribution and exchange of sevoflurane between blood and tissue across all organ systems.

1. Anesthesia Machine and Circle System Model

The model chosen is the Anesthesia 7850 standing bellows ventilator (Datex-Ohmeda), for which the compartment volumes have previously been measured [6]. The anesthesia circle system is a closed-loop circuit in which compartments are arranged in series. These include the inspiratory compartment, expiratory compartment absorbent, and expiratory compartment bellows.

The system contains three ports that serve as inlet and outlet points. Fresh gas flow (FGF), composed of a higher concentration of oxygen and sevoflurane, enters the circuit through the FGF inlet. Waste gases are expelled from the circuit to the hospital scavenging system via the spill valve outlet.

The Y-piece, together with the inspiratory and expiratory valves as a combined unit, functions as both an inlet and an outlet. During inspiration, tidal volume flows from the anesthesia circuit

into the lungs; during expiration, it returns from the lungs back into the circuit via the same unit.

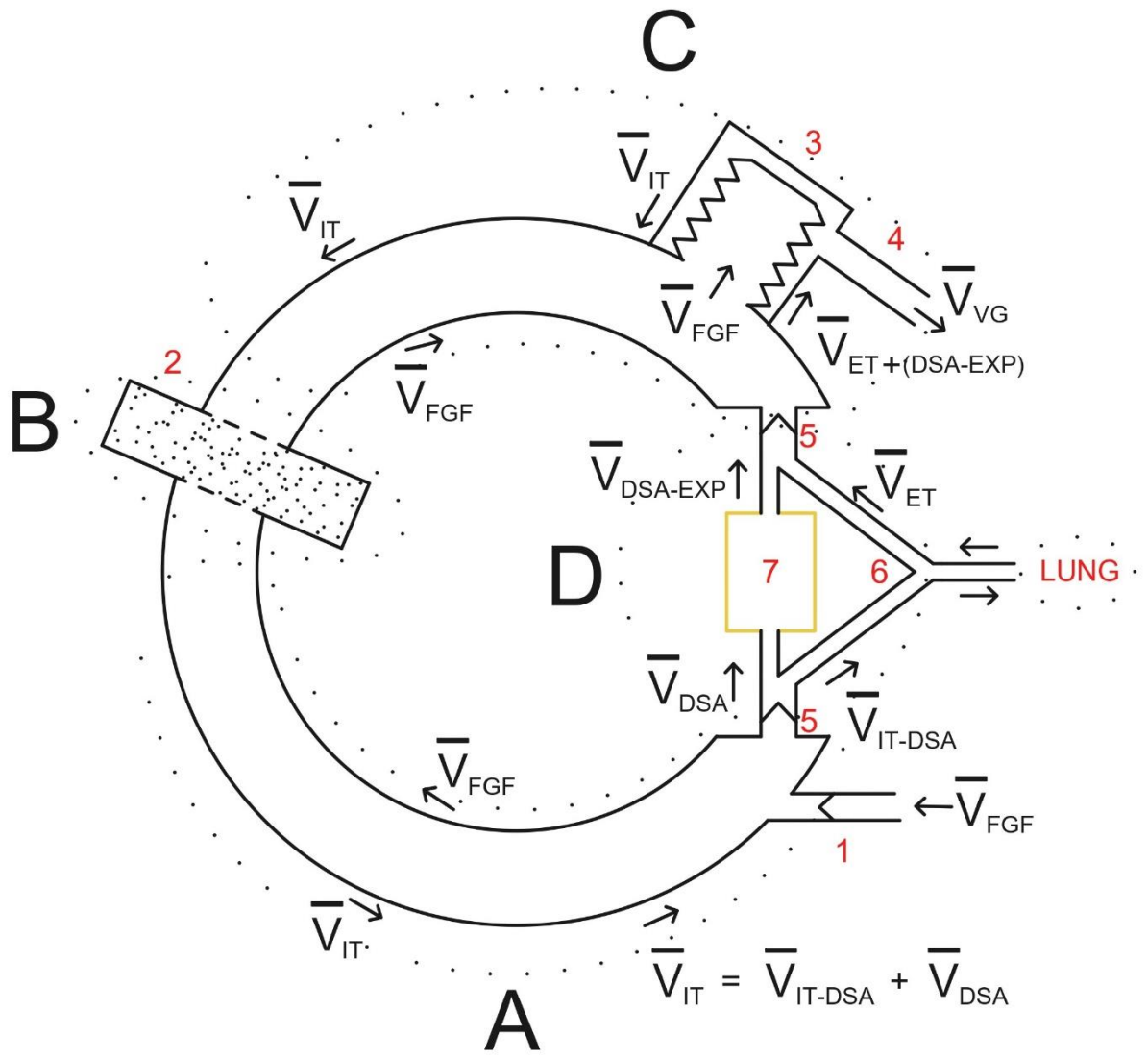

Figure S1. The Anesthesia Circle System.

(A) The inspiratory compartment, located closest to the lung, delivers the inspiratory tidal volume ($\bar{V}_{IT}$) toward the lungs. Fresh gas enters the compartment via the fresh gas flow (FGF) inlet (1) and flows in the opposite direction to the tidal volume ($\bar{V}_{FGF}$).

(B) The expiratory compartment absorbent houses a canister (2) filled with carbon dioxide–absorbent granules.

(C) The expiratory compartment bellows contains the bellows (3), which generate the inspiratory tidal volume by compressing into the compartment. Excess gas ($\bar{V}_{VG}$) is vented through the outlet (4).

(D) The Y-piece (6) serves as the interface between the anesthesia circuit and the lungs. Unidirectional valves (5) ensure that inspiratory and expiratory tidal volumes flow in a single, defined direction.

In the model, the first quarter of the inspiratory tidal volume ($\bar{V}_{DSA}$) accumulates in a conceptual dead space within the circuit (7, gold, V_{DSA}), and subsequently mixes with the expiratory volume returning from the lungs ($\bar{V}_{DSA-EXP}$+$\bar{V}_{ET}$).

Table S1. Selected Symbols and Parameter Values Used in the Model

Symbol	Description	Value
C_{IC}	sevoflurane concentration in the inspiratory compartment	
V_{IC}	volume of the inspiratory compartment	2240 mL
C_{FGF}	sevoflurane concentration in the fresh gas flow (FGF)	3.5%
$\bar{V}_{FGF}$	flow rate of the fresh gas flow (FGF)	104.16 mL/s 5 L/min
$\bar{V}_{IT}$	inspiratory tidal volume flow rate (1-second inspiration)	560 mL/s
$\bar{V}_{IT\text{-}DSA}$	inspiratory tidal volume flow rate (last ¾ of inspiration)	546.66 mL/s 410 mL in period
$\bar{V}_{DSA}$	inspiratory tidal volume flow rate (first ¼ of inspiration)	600 mL/s 150 mL in period
C_{ECA}	sevoflurane concentration in the expiratory compartment absorbent	
V_{ECA}	volume of the expiratory compartment absorbent	560 mL
C_{ECB}	sevoflurane concentration in the expiratory compartment bellows	
V_{ECB}	volume of the expiratory compartment bellows	1940 mL to 2500 mL
$\bar{V}_{ET\text{-}1}$	expiratory tidal volume flow rate (first second)	390 mL/s
$\bar{V}_{ET\text{-}2}$	expiratory tidal volume flow rate (second second)	40 mL/s in half a second
C_{DSA}	sevoflurane concentration in anesthesia circle dead space	
$\bar{V}_{DSA\text{-}EXP}$	flow rate of the expiratory tidal volume of the dead space in the anesthesia circle during first half second of the expiratory period	300 mL/s in half a second
C_{VG}	sevoflurane concentration of the vented gas	
$\bar{V}_{VG}$	flow rate of gas through the venting outlet	208.33 mL/s 5 L/min
$V_{ECB\text{-}ONSET}$	initial volume of the bellows compartment	2500 mL
Δt_{ins}	duration of inspiratory phase	1 s
Δt_{eks1}	duration of first second of expiratory phase	1 s
Δt_{eks2}	duration of second second of expiratory phase	1 s
$\Delta t_{DSA\text{-}EXP}$	duration of dead space expiration (anesthesia circle)	0.5 s
V_{DSA}	volume of dead space in the anesthesia circle	150 mL
C_{ACNEL}	sevoflurane concentration in the ACNEL compartment	
V_{ACNEL}	volume of the ACNEL compartment	900 mL or 450 mL or 90 mL or 10 mL in different models
F_{ACEL}	fraction of tidal volume allocated to ACEL compartment	1.0 or 0.9 or 0.8 in different models
C_{ACEL}	sevoflurane concentration in the ACEL compartment	
V_{ACEL}	volume of the ACEL compartment	1200 mL or 1650 mL or 2010 mL or 2090 mL
C_{DSL}	sevoflurane concentration in the dead space within lung	
V_{DSL}	volume of the pulmonary dead space	1 mL to 151 mL
$\bar{V}_{DSL\text{-}INS}$	inspiratory tidal volume flow (from dead space within lung to ACNEL)	600 mL/s 150 mL in period
$\bar{V}_{DSL\text{-}EXP}$	expiratory tidal volume flow (from ACNEL to the dead space within lung)	300 mL/s 150 mL in period
C_{PCB}	sevoflurane concentration in pulmonary capillary bed	
V_{PCB}	volume of the pulmonary capillary bed	108 mL
Q_{PCB}	blood flow rate through pulmonary capillary bed	108 mL/s
C_{ART}	sevoflurane concentration in arterial blood	
Q_{ART}	flow rate of arterial blood	108 mL/s
C_{VEIN}	sevoflurane concentration in venous blood	
Q_{VEIN}	flow rate of venous blood	108 mL/s
S_{BLOOD}	relative solubility of sevoflurane in blood	
S_{AIR}	relative solubility of sevoflurane in air	
$K_{S\text{-}BLOOD\text{-}GAS}$	blood–gas partition coefficient of sevoflurane	0.65

1.1. The Inspiratory Compartment

The inspiratory compartment is a fixed-volume space with a volume of 2240 mL. In the model, ventilation is cyclic rather than continuous. During the one-second inspiratory phase, the tidal volume flows from the inspiratory compartment into the lungs, while gas simultaneously moves from the expiratory compartment absorbent into the inspiratory compartment. This unidirectional flow is ensured by pressure differentials and the presence of unidirectional valves within the anesthesia circuit.

During this phase, the FGF inlet is deactivated, meaning that no sevoflurane enters the inspiratory compartment from the FGF line. Consequently, any sevoflurane entering the compartment during this period originates solely from the expiratory compartment absorbent.

The change in the quantity of sevoflurane within the inspiratory compartment over this one-second inspiratory phase, modeled at each time step, is mathematically expressed as follows:

$\overline{V}_{FGF}=0$

$$\left(\frac{dC_{IC}}{dt}\times V_{IC}\right)=(C_{ECA}\times\overline{V}_{IT\text{-}DSA})+(C_{ECA}\times\overline{V}_{DSA})-(C_{IC}\times\overline{V}_{IT\text{-}DSA})-(C_{IC}\times\overline{V}_{DSA}) \quad (S1)$$

The FGF inlet is connected to the inspiratory compartment, allowing oxygen- and sevoflurane-rich gas to enter the compartment through this route. In the model, the FGF inlet is activated during a four-second interval both before and after the inspiratory tidal volume phase.

The total FGF is set at 5 liters per minute, corresponding to a flow rate of 104.16 mL/s during each second that the FGF inlet is active.

During this four-second period, the FGF-rich contents of the inspiratory compartment flow into the expiratory compartment absorbent in the direction opposite to tidal ventilation, at a rate equal to the FGF.

The change in the quantity of sevoflurane within the inspiratory compartment over this four-second FGF-on period, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{IT\text{-}DSA}=0$, $\overline{V}_{DSA}=0$

$$\left(\frac{dC_{IC}}{dt}\times V_{IC}\right)=(C_{FGF}\times\overline{V}_{FGF})-(C_{IC}\times\overline{V}_{FGF}) \quad (S2)$$

1.2. The Expiratory Compartment Absorbent

The expiratory compartment absorbent is positioned between the expiratory compartment bellows and the inspiratory compartment. It contains carbon dioxide–absorbent granules and is modeled as a fixed-volume space. The total volume of air between the absorbent granules and within the connecting tubes is set at 560 mL in the model.

During the one-second inspiratory phase, the tidal volume flows into the absorbent compartment from the expiratory compartment bellows and simultaneously continues into the inspiratory compartment.

The change in the quantity of sevoflurane within the expiratory compartment absorbent over this one-second period, calculated in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{FGF}=0$

$$\left(\frac{dC_{ECA}}{dt}\times V_{ECA}\right)=(C_{ECB}\times\overline{V}_{IT\text{-}DSA})+(C_{ECB}\times\overline{V}_{DSA})-(C_{ECA}\times\overline{V}_{IT\text{-}DSA})-(C_{ECA}\times\overline{V}_{DSA}) \quad (S3)$$

During the four-second FGF-active period, the sevoflurane-rich contents of the inspiratory compartment flow into the expiratory compartment absorbent, while the absorbent compartment simultaneously transfers its contents into the expiratory compartment bellows.

The change in the quantity of sevoflurane within the expiratory compartment absorbent over this four-second period, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{IT\text{-}DSA}=0$, $\overline{V}_{DSA}=0$

$$\left(\frac{dC_{ECA}}{dt}\times V_{ECA}\right)=(C_{IC}\times\overline{V}_{FGF})-(C_{ECA}\times\overline{V}_{FGF}) \quad (S4)$$

1.3. The Expiratory Compartment Bellows

The expiratory compartment bellows is a variable-volume space, initially assigned a volume of 2500 mL. During the one-second period of controlled inspiration, the bellows plate moves inward at a constant rate, progressively reducing the compartment's volume. This decrease in volume leads to a rise in internal pressure, driving the pressurized gas in one direction through the circuit tubing. This unidirectional movement is facilitated by valves that ensure flow toward the path of least resistance. The resulting airflow constitutes the inspiratory tidal volume.

The sevoflurane concentration within this tidal volume is equivalent to the concentration in the expiratory compartment bellows and flows into the expiratory compartment absorbent. The inspiratory tidal volume is modeled as consisting of two sequential components delivered at constant flow: the first quarter is assigned to dead space ventilation, while the remaining three quarters represent the volume participating in alveolar gas exchange.

The change in the quantity of sevoflurane within the expiratory compartment bellows over the five-second modeling period is mathematically expressed as follows:

$$\left(\frac{dC_{ECB}}{dt}\times V_{ECB}\right)=(C_{ACNEL}\times\overline{V}_{ET\text{-}1})+(C_{ACNEL}\times\overline{V}_{ET\text{-}2})-(C_{ECB}\times\overline{V}_{IT\text{-}DSA})-(C_{ECB}\times\overline{V}_{DSA})$$
$$-(C_{VG}\times\overline{V}_{VG})+(C_{ECA}\times\overline{V}_{FGF})+(C_{DSA}\times\overline{V}_{DSA\text{-}EXP}) \quad (S5)$$

The time-dependent variation in the volume of the expiratory compartment bellows, synchronized with the respiratory cycle, is given by:

$$V_{ECB}=V_{ECB\text{-}ONSET}-(\overline{V}_{IT}\times\Delta t_{ins})+(\overline{V}_{ET\text{-}1}\times\Delta t_{eks1})+(\overline{V}_{ET\text{-}2}\times\Delta t_{eks2})+(\overline{V}_{DSA\text{-}EXP}\times\Delta t_{DSA\text{-}EXP}) \quad (S6)$$
$$(\overline{V}_{IT}\times\Delta t_{ins})=(\overline{V}_{IT\text{-}DSA}\times\Delta t_{IT\text{-}DSA})+(\overline{V}_{DSA}\times\Delta t_{DSA})$$

Accordingly, the volume of the expiratory compartment bellows is modeled as a periodic function, repeating identically every five seconds.

During the inspiratory phase, the change in the quantity of sevoflurane within the expiratory compartment bellows over the one-second period is computed in discrete time steps and mathematically expressed as follows:

$\overline{V}_{ET\text{-}1}=0$, $\overline{V}_{ET\text{-}2}=0$, $\overline{V}_{VG}=0$, $\overline{V}_{FGF}=0$

$$\left(\frac{dC_{ECB}}{dt}\times V_{ECB}\right)=-(C_{ECB}\times\overline{V}_{IT\text{-}DSA})-(C_{ECB}\times\overline{V}_{DSA}) \quad (S7)$$

During the two-second expiratory phase following inspiration, the bellows returns to its initial position, and the internal pressure within the compartment begins to decrease. This phase coincides with both the two-second expiratory period in the lungs and the first two seconds of the four-second FGF period in the inspiratory compartment.

As the volume of the bellows expands and the internal pressure drops, the compartment becomes a region of lower pressure relative to the adjacent compartments. Consequently, two flows enter the bellows: one from the expiratory compartment absorbent at a rate equal to the FGF, and the other from the lungs at a rate equal to the expiratory tidal volume.

Additionally, during the first second of this two-second expiratory phase, the dead space volume from the anesthesia circle also enters the bellows.

The change in the quantity of sevoflurane in the expiratory compartment bellows during this initial one-second period of expiration, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{ET\text{-}2}=0$, $\overline{V}_{VG}=0$, $\overline{V}_{IT\text{-}DSA}=0$, $\overline{V}_{DSA}=0$

$$\left(\frac{dC_{ECB}}{dt}\times V_{ECB}\right)=(C_{ACNEL}\times\overline{V}_{ET\text{-}1})+(C_{ECA}\times\overline{V}_{FGF})+(C_{DSA}\times\overline{V}_{DSA\text{-}EXP}) \quad \text{(S8)}$$

The change in the quantity of sevoflurane within the expiratory compartment bellows during the second second of the two-second expiratory period, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{ET\text{-}1}=0$, $\overline{V}_{VG}=0$, $\overline{V}_{IT\text{-}DSA}=0$, $\overline{V}_{DSA}=0$, $\overline{V}_{DSA\text{-}EXP}=0$

$$\left(\frac{dC_{ECB}}{dt}\times V_{ECB}\right)=(C_{ACNEL}\times\overline{V}_{ET\text{-}2})+(C_{ECA}\times\overline{V}_{FGF}) \quad \text{(S9)}$$

During the two-second period following expiration in the expiratory compartment bellows—corresponding to the final two seconds of the four-second FGF delivery phase—the venting gas outlet valve opens, allowing waste gas to be released into the hospital scavenging system.

To maintain system equilibrium, the total volume of waste gas vented over each five-second cycle must equal the total FGF volume. Since the venting duration is half the length of the FGF delivery period, the venting rate must be twice the FGF rate. Accordingly, the waste gas outflow rate is 208.33 mL/s, compared to the FGF rate of 104.16 mL/s.

During this two-second venting phase, the contents of the expiratory compartment absorbent flow into the bellows at the FGF rate, while the contents of the bellows are simultaneously vented to the scavenging system.

The change in the quantity of sevoflurane in the expiratory compartment bellows during this two-second period, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{ET\text{-}1}=0$, $\overline{V}_{ET\text{-}2}=0$, $\overline{V}_{IT\text{-}DSA}=0$, $\overline{V}_{DSA}=0$, $\overline{V}_{DSA\text{-}EXP}=0$

$$\left(\frac{dC_{ECB}}{dt}\times V_{ECB}\right)=-(C_{VG}\times\overline{V}_{VG})+(C_{ECA}\times\overline{V}_{FGF}) \quad \text{and as} \quad C_{VG}=C_{ECB},$$

$$\left(\frac{dC_{ECB}}{dt}\times V_{ECB}\right)=-(C_{ECB}\times\overline{V}_{VG})+(C_{ECA}\times\overline{V}_{FGF}) \quad \text{(S10)}$$

1.4. Dead Space within the Anesthesia Circle

The change in the quantity of sevoflurane within the dead space of the anesthesia circle during the first quarter of the inspiratory phase, modeled in discrete time steps, is mathematically expressed as follows:

$$\left(\frac{dC_{DSA}}{dt}\times V_{DSA}\right)=(C_{IC}\times\overline{V}_{DSA}) \tag{S11}$$

The change in the quantity of sevoflurane within the dead space during expiration, modeled in discrete time steps, is expressed as follows:

$$\left(\frac{dC_{DSA}}{dt}\times V_{DSA}\right)=-(C_{DSA}\times\overline{V}_{DSA\text{-}EXP}) \tag{S12}$$

2. The Lung Subsystem

2.1. Alveolocapillary Non-Exchange Air Compartment (ACNEL)

The change in the quantity of sevoflurane within the alveolocapillary non-exchange air compartment of the lung over the five-second respiratory cycle, modeled in discrete time steps, is mathematically expressed as follows:

$$\begin{aligned}\left(\frac{dC_{ACNEL}}{dt}\times V_{ACNEL}\right)=&(C_{IC}\times\overline{V}_{IT\text{-}DSA})-(C_{ACNEL}\times\overline{V}_{IT}\times F_{ACEL})+(C_{ACEL}\times\overline{V}_{ET\text{-}1}\times F_{ACEL})\\&+(C_{ACEL}\times\overline{V}_{ET\text{-}2}\times F_{ACEL})\\&-(C_{ACNEL}\times\overline{V}_{ET\text{-}1})-(C_{ACNEL}\times\overline{V}_{ET\text{-}2})+(C_{DSL}\times\overline{V}_{DSL\text{-}INS})-(C_{ACNEL}\times\overline{V}_{DSL\text{-}EXP})\end{aligned} \tag{S13}$$

The volume of this compartment is modeled as a periodic function that repeats identically every five seconds and it is expressed as follows:

$$\begin{aligned}V_{ACNEL}=&V_{ACNEL\text{-}RESIDUAL}+(\overline{V}_{DSL\text{-}INS}\times\Delta t_{DSL\text{-}INS})+(\overline{V}_{IT\text{-}DSA}\times\Delta t_{IT\text{-}DSA})-(\overline{V}_{IT}\times F_{ACEL}\times\Delta t_{ins})\\&+(\overline{V}_{ET\text{-}1}\times F_{ACEL}\times\Delta t_{exp1})+(\overline{V}_{ET\text{-}2}\times F_{ACEL}\times\Delta t_{exp2})\\&-(\overline{V}_{ET\text{-}1}\times\Delta t_{exp1})-(\overline{V}_{ET\text{-}2}\times\Delta t_{exp2})-(\overline{V}_{DSL\text{-}EXP}\times\Delta t_{DSL\text{-}EXP})\end{aligned} \tag{S14}$$

For alternative lung air compartment model transforming from a double compartment one to a single compartment one by a permanent transfer of a certain amount of blank volume ($\breve{V}_{PERMANENT}$) from ACNEL to ACEL, the change of residual volume of ACNEL ($V_{ACNEL\text{-}RESIDUAL}$) during transformation process in a discrete step time is expressed as follows:

$$\Delta V_{ACNEL\text{-}RESIDUAL}=-\breve{V}_{PERMANENT}\times\Delta t \tag{S15}$$

During the one-second inspiratory phase, the change in the quantity of sevoflurane within this compartment, modeled in discrete time steps, is expressed as follows:

$$\overline{V}_{ET\text{-}1}=0\ ,\ \overline{V}_{ET\text{-}2}=0\ ,\ \overline{V}_{DSL\text{-}EXP}=0$$

$$\left(\frac{dC_{ACNEL}}{dt}\times V_{ACNEL}\right)=(C_{IC}\times\overline{V}_{IT\text{-}DSA})-(C_{ACNEL}\times\overline{V}_{IT}\times F_{ACEL})+(C_{DSL}\times\overline{V}_{DSL\text{-}INS}) \tag{S16}$$

The change in the quantity of sevoflurane within the alveolocapillary non-exchange air compartment during the first second of the expiratory phase, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{IT}=0$, $\overline{V}_{ET\text{-}2}=0$, $\overline{V}_{DSL\text{-}INS}=0$, $\overline{V}_{DSL\text{-}EXP}=0$

$$\left(\frac{dC_{ACNEL}}{dt}\times V_{ACNEL}\right)=(C_{ACEL}\times\overline{V}_{ET\text{-}1}\times F_{ACEL})\text{-}(C_{ACNEL}\times\overline{V}_{ET\text{-}1}) \quad \text{(S17)}$$

The change in the quantity of sevoflurane within the alveolocapillary non-exchange air compartment of the lung during the second second of the expiratory phase, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{IT}=0$, $\overline{V}_{ET\text{-}1}=0$, $\overline{V}_{DSL\text{-}INS}=0$

$$\left(\frac{dC_{ACNEL}}{dt}\times V_{ACNEL}\right)=(C_{ACEL}\times\overline{V}_{ET\text{-}2}\times F_{ACEL})\text{-}(C_{ACNEL}\times\overline{V}_{ET\text{-}2})\text{-}(C_{ACNEL}\times\overline{V}_{DSL\text{-}EXP}) \quad \text{(S18)}$$

During the first half of this phase, the sevoflurane dynamics are governed by:

$$\left(\frac{dC_{ACNEL}}{dt}\times V_{ACNEL}\right)=(C_{ACEL}\times\overline{V}_{ET\text{-}2}\times F_{ACEL})\text{-}(C_{ACNEL}\times\overline{V}_{ET\text{-}2\text{-}1}) \quad \text{(S19)}$$

The change in the quantity of sevoflurane during the second half of this period is modeled in discrete time steps as follows:

$$\left(\frac{dC_{ACNEL}}{dt}\times V_{ACNEL}\right)=(C_{ACEL}\times\overline{V}_{ET\text{-}2}\times F_{ACEL})\text{-}(C_{ACNEL}\times\overline{V}_{DSL\text{-}EXP}) \quad \text{(S20)}$$

$$(\overline{V}_{ET\text{-}2}\times\Delta t_{ET\text{-}2})=(\overline{V}_{ET\text{-}2\text{-}1}\times\Delta t_{ET\text{-}2\text{-}1})+(\overline{V}_{DSL\text{-}EXP}\times\Delta t_{DSL\text{-}EXP})$$

2.2. Dead Space within the Lung

The change in the quantity of sevoflurane in the dead space within lung over the five-second respiratory cycle, modeled in discrete time steps, is mathematically expressed as follows:

$$\left(\frac{dC_{DSL}}{dt}\times V_{DSL}\right)=(C_{ACNEL}\times\overline{V}_{DSL\text{-}EXP})\text{-}(C_{DSL}\times\overline{V}_{DSL\text{-}INS}) \quad \text{(S21)}$$

The volume of the dead space within lung is modeled as a periodic function that repeats identically in each five-second respiratory cycle.

The change in the quantity of sevoflurane within the pulmonary dead space during the first quarter-second of the inspiratory phase, modeled in discrete time steps, is mathematically expressed as follows:

$$\left(\frac{dC_{DSL}}{dt}\times V_{DSL}\right)=\text{-}(C_{DSL}\times\overline{V}_{DSL\text{-}INS}) \quad \text{(S22)}$$

During the final half-second of the second second of the expiratory phase, the change in the quantity of sevoflurane in the dead space within lung, modeled in discrete time steps, is mathematically expressed as follows:

$$\left(\frac{dC_{DSL}}{dt}\times V_{DSL}\right)=(C_{ACNEL}\times\overline{V}_{DSL\text{-}EXP}) \quad \text{(S23)}$$

2.3. Alveolocapillary Exchange Air Compartment (ACEL), Pulmonary Capillary Bed, and Air–Blood Sevoflurane Exchange

The change in the quantity of sevoflurane within the alveolocapillary exchange unit of the lung over the five-second respiratory cycle, modeled in discrete time steps, is mathematically expressed as follows:

$$\left(\frac{dC_{ACEL}}{dt}\times V_{ACEL}\right)+\left(\frac{dC_{PCB}}{dt}\times V_{PCB}\right)=(C_{ACNEL}\times\bar{V}_{IT}\times F_{ACEL})-(C_{ACEL}\times\bar{V}_{ET\text{-}1}\times F_{ACEL})$$
$$-(C_{ACEL}\times\bar{V}_{ET\text{-}2}\times F_{ACEL})-(C_{ART}\times Q_{ART})+(C_{VEIN}\times Q_{VEIN}) \quad (S24)$$

$Q_{VEIN} = Q_{ART} = Q_{PCB}=V_{PCB}$, $C_{ART} = C_{PCB}$

If the blood–gas partition coefficient is denoted as,

$$\frac{C_{PCB}}{C_{ACEL}} = \frac{S_{BLOOD}}{S_{AIR}} = K_{S\text{-}BLOOD\text{-}GAS}$$

$C_{PCB} = C_{ACEL} \times K_{S\text{-}BLOOD\text{-}GAS}$ and $\frac{dC_{PCB}}{dt} = \frac{dC_{ACEL}}{dt} \times K_{S\text{-}BLOOD\text{-}GAS}$, where the sevoflurane concentration is initially zero in both the air and blood compartments.

The volume of the alveolocapillary exchange air compartment in the lung is modeled as a periodic function that varies according to the inspiratory and expiratory tidal volumes. This pattern repeats identically in each five-second respiratory cycle. Whereas, the pulmonary capillary bed is a constant volume compartment. The volume of the alveolocapillary exchange air compartment over five-second-long cycle is expressed as follows:

$$V_{ACEL}=V_{ACEL\text{-}RESIDUAL}+(\bar{V}_{IT}\times F_{ACEL}\times\Delta t_{ins})-(\bar{V}_{ET\text{-}1}\times F_{ACEL}\times\Delta t_{exp1})$$
$$-(\bar{V}_{ET\text{-}2}\times F_{ACEL}\times\Delta t_{exp2}) \quad (S25)$$

For alternative lung air compartment model transforming from a double compartment one to a single compartment one by a permanent transfer of a certain amount of blank volume ($\breve{V}_{PERMANENT}$) from ACNEL to ACEL, the change of residual volume of ACEL ($V_{ACEL\text{-}RESIDUAL}$) during transformation process in a discrete step time is expressed as follows:

$$\Delta V_{ACEL\text{-}RESIDUAL}= +\breve{V}_{PERMANENT}\times\Delta t \quad (S26)$$

During the inspiratory phase, the change in the quantity of sevoflurane within this compartment, modeled in discrete time steps, is mathematically expressed as follows:

$\bar{V}_{ET\text{-}1} = 0$, $\bar{V}_{ET\text{-}2} = 0$

$$\left(\frac{dC_{ACEL}}{dt}\times V_{ACEL}\right)+\left(\frac{dC_{PCB}}{dt}\times V_{PCB}\right)=(C_{ACNEL}\times\bar{V}_{IT}\times F_{ACEL})$$
$$-(C_{ART}\times Q_{ART})+(C_{VEIN}\times Q_{VEIN}) \quad (S27)$$

And after performing the necessary substitutions, the resulting expression for the change in the quantity of sevoflurane is:

$$\frac{dC_{ACEL}}{dt}\times[V_{ACEL}+(K_{S\text{-}BLOOD\text{-}GAS}\times V_{PCB})]=(C_{ACNEL}\times\bar{V}_{IT}\times F_{ACEL})$$
$$-(C_{ACEL}\times K_{S\text{-}BLOOD\text{-}GAS}\times Q_{ART})+(C_{VEIN}\times Q_{VEIN})$$

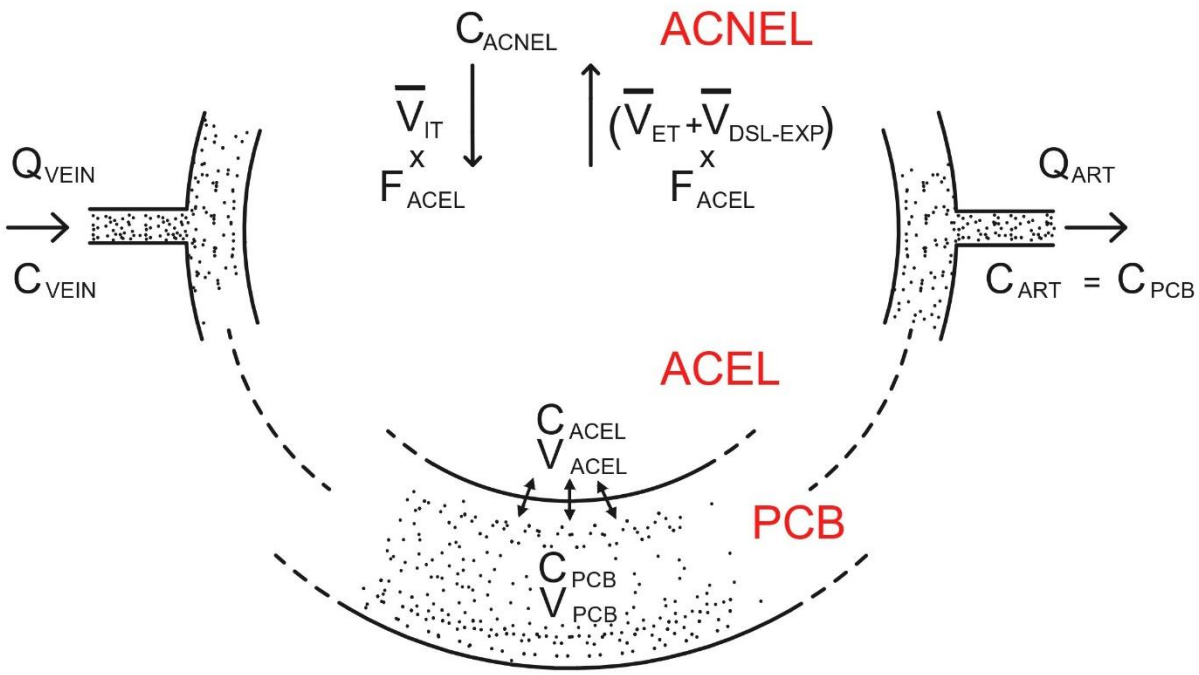

Figure S2. Schematic representation of the alveolocapillary exchange unit and its functional components.

This figure illustrates the combined alveolar–capillary structure where gas exchange occurs between inhaled sevoflurane and pulmonary blood. The alveolocapillary exchange air compartment (ACEL) and the pulmonary capillary bed (PCB) are represented as a single functional unit in the model.

Sevoflurane enters this unit via two pathways: (1) the venous blood (Q_{VEIN}) carrying sevoflurane at concentration (C_{VEIN}), and (2) the inspiratory tidal volume from the alveolocapillary non-exchange air compartment (ACNEL), with concentration (C_{ACNEL}).

Sevoflurane leaves the unit through: (1) the arterial blood (Q_{ART}) at concentration (C_{ART}), and (2) the expiratory tidal volume returning to the ACNEL compartment with concentration (C_{ACEL}). The direction and rate of gas exchange between air and blood are governed by the blood–gas partition coefficient ($K_{S\text{-}BLOOD\text{-}GAS}$) and the concentration gradient between the two media.

During the first second of the expiratory phase, the change in the quantity of sevoflurane within the alveolocapillary exchange unit, modeled in discrete time steps, is mathematically expressed as follows:

$$\bar{V}_{IT} = 0 \, , \bar{V}_{ET\text{-}2} = 0$$

$$\left(\frac{dC_{ACEL}}{dt} \times V_{ACEL}\right) + \left(\frac{dC_{PCB}}{dt} \times V_{PCB}\right) = -(C_{ACEL} \times \bar{V}_{ET\text{-}1} \times F_{ACEL}) - (C_{ART} \times Q_{ART}) + (C_{VEIN} \times Q_{VEIN}) \quad \text{(S28)}$$

And after substituting the relevant parameters, the resulting expression becomes:

$$\frac{dC_{ACEL}}{dt} \times [V_{ACEL} + (K_{S\text{-}BLOOD\text{-}GAS} \times V_{PCB})] = -C_{ACEL} \times [(\bar{V}_{ET\text{-}1} \times F_{ACEL}) + (Q_{ART} \times K_{S\text{-}BLOOD\text{-}GAS})] + (C_{VEIN} \times Q_{VEIN})$$

During the second second of the expiratory phase, the change in the quantity of sevoflurane within the alveolocapillary exchange unit, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{IT}=0$, $\overline{V}_{ET-1}=0$

$$\frac{dC_{ACEL}}{dt}\times[V_{ACEL}+(K_{S\text{-}BLOOD\text{-}GAS}\times V_{PCB})]=-C_{ACEL}\times\left[(\overline{V}_{ET-2}\times F_{ACEL})+(Q_{ART}\times K_{S\text{-}BLOOD\text{-}GAS})\right]+(C_{VEIN}\times Q_{VEIN}) \quad (S29)$$

During the two-second non-tidal ventilation period, the change in the quantity of sevoflurane within the alveolocapillary exchange unit, modeled in discrete time steps, is mathematically expressed as follows:

$\overline{V}_{IT}=0$, $\overline{V}_{ET-1}=0$, $\overline{V}_{ET-2}=0$

$$\frac{dC_{ACEL}}{dt}\times[V_{ACEL}+(K_{S\text{-}BLOOD\text{-}GAS}\times V_{PCB})]=-(C_{ACEL}\times Q_{ART}\times K_{S\text{-}BLOOD\text{-}GAS})+(C_{VEIN}\times Q_{VEIN}) \quad (S30)$$

3. Systemic Circulation, Organ Perfusion, and Capillary–Tissue Exchange Model

The systemic circulation is composed of serially connected arterial pathways, parallel organ circulations, systemic venous return, and the pulmonary capillary circulation. In this model, blood flow is assumed to occur without longitudinal mixing, in accordance with the description provided by Mapleson for circulation models [12].

This assumption implies that if the transit time between point A and point B is t_n, then the sevoflurane concentration at point B is identical to the concentration at point A exactly t_n seconds earlier. As illustrated:

$$C_A(t-t_n) = C_B(t) \quad (S31)$$

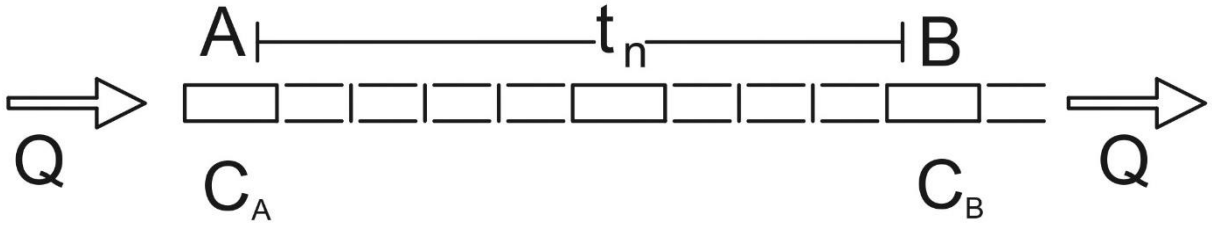

Figure S3. Time-shifted transport of sevoflurane in the systemic circulation based on a non-mixing flow assumption.

This schematic illustrates the plug-flow transport of sevoflurane in the systemic circulation, based on the non-mixing assumption. Blood with concentration C_A flows from point **A** to point **B** with a constant flow rate **Q**, and reaches point **B** after a transit delay of t_n. The box-like segments represent discrete fluid elements maintaining their internal concentration during flow, as assumed in the Mapleson model.

The circulation time through the systemic artery—from the exit of the pulmonary capillary bed to the entry point of the organs—is assigned as 6 seconds. At the distal end of the systemic artery, blood flow branches into ten parallel organ circulations. Each organ is characterized by a specific mean transit time, defined as the duration from the start of its arterial branch to the end of its venous return.

Within each organ circulation, sevoflurane exchange occurs between the capillary blood and surrounding tissue. Blood from all ten organ perfusion pathways then reconverges into the common systemic vein. The circulation time from the organ venous exit to the pulmonary capillary bed via the systemic vein is also assigned as 6 seconds.

As a result, the total central circulation time is approximately 13 seconds, which aligns with Oldendorf's human measurement of 12 seconds from the antecubital vein to the carotid artery [20].

For system stability, the flow rates through the systemic artery, the ten organ circulations, the systemic vein, and the pulmonary circulation must be equal.

3.1. Organ Circulation and Capillary–Tissue Sevoflurane Exchange Model

Each of the ten parallel organ circulations is assigned its own blood flow rate. These circulations represent the brain, heart, thyroid–adrenal glands, minor endocrine glands, adipose tissue, lean tissue (muscle and skin), kidneys, liver and splanchnic region, and peripheral shunt.

The sevoflurane concentration entering each parallel organ circulation is equal to the arterial concentration in the common systemic artery. In the model, each organ receives blood via a dedicated artery connected in series to a single capillary segment. Sevoflurane exchange occurs across this capillary–tissue interface and is driven by the solubility and concentration gradients between the blood and the surrounding tissue.

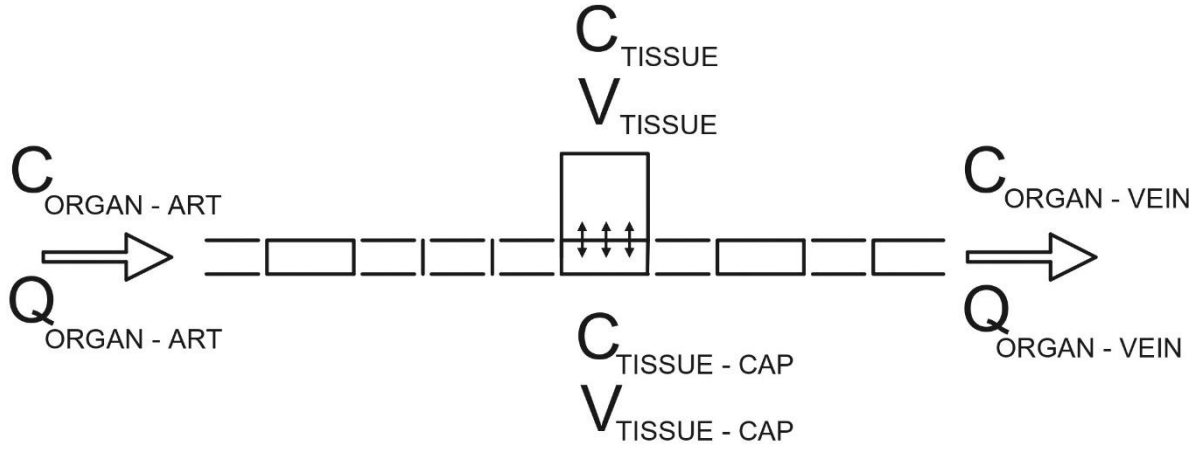

Figure S4. Sevoflurane Transport and Exchange Across the Organ Circulation

Sevoflurane is transported via arterial blood to the organ-specific capillary bed, without longitudinal mixing. At the capillary–tissue interface, passive exchange occurs between the blood and surrounding tissue, governed by the partition coefficient between the two media. Following this exchange, the blood—still assumed to be unmixed—exits the organ as venous outflow.

The circulation time across each organ's capillary bed is assumed to be one second. As initial concentrations of sevoflurane in both compartments (blood and tissue) are zero, the change in sevoflurane concentration in one time step — and the resulting concentration ratio between compartments — must conform to a constant solubility coefficient specific to the two media.

The mathematical expression describing the change in the quantity of sevoflurane in the capillary–tissue unit over one discrete time step is given by:

$$\left(\frac{dC_{ORGAN\text{-}TISSUE}}{dt}\times V_{ORGAN\text{-}TISSUE}\right)+\left(\frac{dC_{ORGAN\text{-}CAP}}{dt}\times V_{ORGAN\text{-}CAP}\right)= (Q_{ORGAN\text{-}ART}\times C_{ORGAN\text{-}ART})-(Q_{ORGAN\text{-}VEIN}\times C_{ORGAN\text{-}VEIN})$$

If the solubility coefficient between tissue and blood is denoted as $K_{TISSUE\text{-}BLOOD}$, and the exchange is assumed to occur instantaneously, then:

$K_{TISSUE\text{-}BLOOD}=\frac{C_{ORGAN\text{-}TISSUE}}{C_{ORGAN\text{-}CAP}}=\frac{\frac{dC_{ORGAN\text{-}TISSUE}}{dt}}{\frac{dC_{ORGAN\text{-}CAP}}{dt}}$, where the sevoflurane concentration is initially zero in both the organ-tissue and organ-capillary compartments.

$C_{ORGAN\text{-}VEIN}=C_{ORGAN\text{-}CAP}$, $Q_{ORGAN\text{-}ART}=Q_{ORGAN\text{-}VEIN}=Q_{ORGAN\text{-}CAP}$

After applying the substitutions, the equation reduces to:

$$\frac{dC_{ORGAN\text{-}CAP}}{dt}\times[(K_{TISSUE\text{-}BLOOD}\times V_{ORGAN\text{-}TISSUE})+V_{ORGAN\text{-}CAP}]= Q_{ORGAN\text{-}ART}\times(C_{ORGAN\text{-}ART}-C_{ORGAN\text{-}CAP}) \quad (S32)$$

The change in the quantity of sevoflurane within the systemic vein, modeled in discrete time steps, is mathematically expressed as follows:

$$(C_{SYS\text{-}VEIN}\times Q_{SYS\text{-}VEIN})=(C_{BR\text{-}VEIN}\times Q_{BR})+(C_{HEART\text{-}VEIN}\times Q_{HEART})+(C_{KID\text{-}VEIN}\times Q_{KID}) +(C_{TYR\text{-}VEIN}\times Q_{TYR})+(C_{LIVER\text{-}VEIN}\times Q_{LIVER})+(C_{LEAN\text{-}VEIN}\times Q_{LEAN})+(C_{END\text{-}VEIN}\times Q_{END}) +(C_{ADI\text{-}VEIN}\times Q_{ADI})+(C_{SHUNT}\times Q_{SHUNT}) \quad (S33)$$

In the model, all tissue volumes, organ perfusion rates, and systemic perfusion parameters are adopted from the "reference man" described by Mapleson [16,17]. The volume of the pulmonary capillary bed is assigned to be equal to the one-second systemic perfusion volume.

3.2. Splanchnic and Hepatic Circulation

Unlike other organ circulations, the splanchnic perfusion drains into the hepatic circulation in series, rather than directly into the common systemic vein. As a result, the liver receives blood from two inflowing vessels—the hepatic artery and the portal vein (draining splanchnic flow) and has a single outflow via the hepatic vein. In contrast, all other organs in the model are supplied by one arterial vessel and drained by one venous vessel.

The total amount of sevoflurane flowing into the liver during a discrete time step is mathematically expressed as follows:

$$\textit{the quantity of sevoflurane flowing into the liver}=(C_{SPL\text{-}VEIN}\times Q_{SPL})+(C_{ART}\times Q_{HEPATIC\text{-}ART}) \quad (S34)$$

$$Q_{LIVER}= Q_{HEPATIC\text{-}ART}+ Q_{SPL} \quad (S35)$$

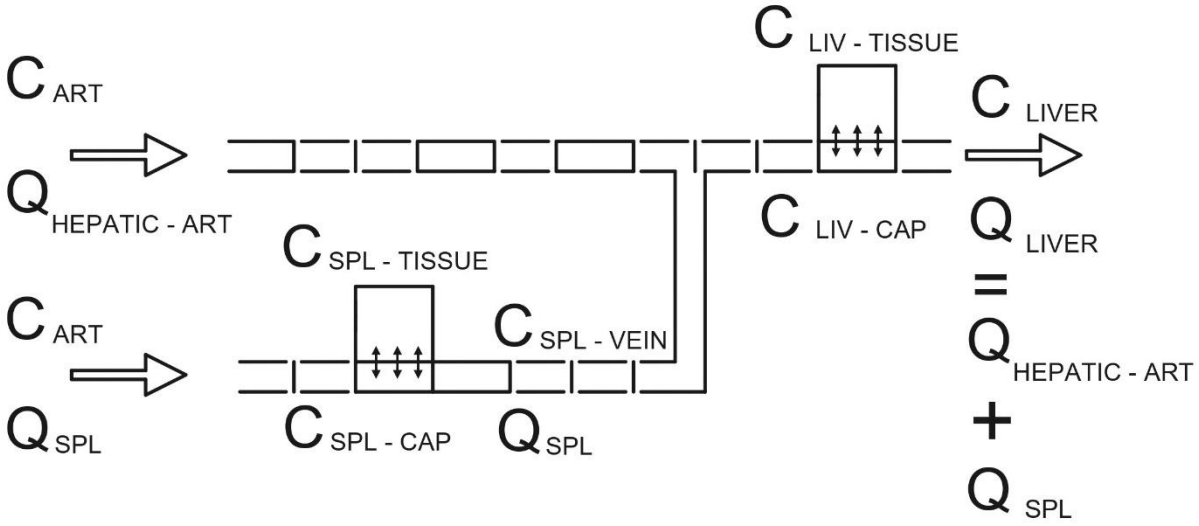

Figure S5. Dual blood supply and sevoflurane exchange in the hepatic circulation.

This schematic illustrates the dual inflow and single outflow configuration of the hepatic circulation. The liver receives blood from two sources: arterial inflow from the systemic circulation via the hepatic artery ($Q_{HEPATIC-ART}$) and venous inflow from the splanchnic circulation via the portal vein (Q_{SPL}). Unlike other organs, the splanchnic venous return bypasses the systemic venous system and enters the liver directly. Sevoflurane exchange occurs at two distinct sites: first within the splanchnic capillary–tissue interface, and subsequently within the hepatic capillary bed. The total hepatic outflow (Q_{LIVER}) equals the sum of both inflows and exits through a single hepatic vein into the systemic venous circulation.

3.3. Hepatic Metabolism

In the model, hepatic metabolism is assumed to follow first-order kinetics and is set to occur in 40% of the blood flowing through the liver, instantaneously. The simulation is designed to replicate a clinical study investigating hepatic metabolism of sevoflurane [11]. Accordingly, the model is run under 2.7% inspiratory sevoflurane concentration for 3 hours, followed by 222 hours at 0% inspiratory concentration.

At the end of the simulation, the difference between the total amount of sevoflurane introduced into the system via the FGF inlet and the total amount eliminated through the venting outlet corresponds to approximately 5.38% of the total sevoflurane input—attributed to hepatic metabolism.

This hepatic metabolic dynamic is applied consistently across all simulation scenarios in the model.

$$C_{LIV-TISSUE}=C_{LIV-CAP}\times K_{LIV-BL}\ ,\ Q_{LIVER}=Q_{HEPATIC-ART}+Q_{SPL}$$

$$\frac{dC_{LIV-CAP}}{dt}\times[(K_{LIV-BL}\times V_{LIV-TISSUE})+V_{LIV-CAP}]=$$

$$\frac{60}{100}\times[(Q_{HEPATIC-ART}\times C_{ART})+(C_{SPL-VEIN}\times Q_{SPL})]-(C_{LIV-CAP}\times Q_{LIVER}) \quad (S36)$$

3.4. Perfusion Dynamics of Adipose Tissue as a Function of Its Increasing Volume [21].

$$\frac{\text{perfusion of new adipose tissue}}{\text{perfusion of the adipose tissue of the reference man}}=\left(\frac{\text{volume of new adipose tissue}}{\text{volume of adipose tissue of the reference man}}\right)^{0.75} \quad (S37)$$

Table S2. Organ volumes, capillary bed volumes, organ-specific and total-body blood perfusion rates, and tissue–blood partition coefficients, along with corresponding symbols. All values are based on a 70-kg, 30–39-year-old reference man as defined by Mapleson [16,17,22–24].

Organ	Mean Transit Time (s)	Organ Volume (mL)	Organ Tissue Volume Symbol	Organ Tissue Concentration Symbol	Organ Capillary Bed Volume (mL)	Organ Capillary Bed Volume Symbol	Organ Capillary Bed Concentration Symbol	Tissue-Blood Partition Coefficient and Symbol		Organ Perfusion (mL\s) and Symbol	
Brain	9	1300	$V_{BR-TISSUE}$	$C_{BR-TISSUE}$	43.33	V_{BR-CAP}	C_{BR-CAP}	1.7	K_{BR-BL}	12.35	Q_{BR}
Kidneys	3	270	$V_{KID-TISSUE}$	$C_{KID-TISSUE}$	9	$V_{KID-CAP}$	$C_{KID-CAP}$	2.3	K_{KID-BL}	20.35	Q_{KID}
Thyroid-Adrenals	2	31	$V_{THY-TISSUE}$	$C_{THY-TISSUE}$	1.03	$V_{THY-CAP}$	$C_{THY-CAP}$	2	K_{THY-BL}	2.85	Q_{THY}
Heart	9	307	$V_{HEART-TISSU}$	$C_{HEART-TISSUE}$	10.23	$V_{HEART-CAP}$	$C_{HEART-CAP}$	1.3	$K_{HEART-BL}$	4.43	Q_{HEART}
Small Endocrines	8	186	$V_{END-TISSUE}$	$C_{END-TISSUE}$	6.2	$V_{END-CAP}$	$C_{END-CAP}$	2	K_{END-BL}	0.95	Q_{END}
Splanchnic	42	1334	$V_{SPL-TISSUE}$	$C_{SPL-TISSUE}$	44.46	$V_{SPL-CAP}$	$C_{SPL-CAP}$	2.4	K_{SPL-BL}	18.51	Q_{SPL}
Liver	12	1639	$V_{LIV-TISSUE}$	$C_{LIV-TISSUE}$	54.63	$V_{LIV-CAP}$	$C_{LIV-CAP}$	2.4	K_{LIV-BL}	7.41	Q_{LIV}
Adipose	98	14786	$V_{ADI-TISSUE}$	$C_{ADI-TISSUE}$	492.86	$V_{ADI-CAP}$	$C_{ADI-CAP}$	48	K_{ADI-BL}	5.7	Q_{ADI}
Lean (Muscle and Skin)	98	33200	$V_{LEAN-TISSUE}$	$C_{LEAN-TISSUE}$	553.33	$V_{LEAN-CAP}$	$C_{LEAN-CAP}$	3.1	$K_{LEAN-BL}$	19.11	Q_{LEAN}
Peripheral Shunt	8	-		C_{SHUNT}	-		C_{SHUNT}	-		16.31	Q_{SHUNT}
Total	**-**	**53053**	**-**		**1215**	**-**		**-**		**108**	

Table S3. Blood volumes across different components of the circulatory system [16].

The total blood volumes of organ arteries, capillaries and veins	The total blood volume of the systemic circulation	Total
3777 mL	1404 mL	5108 mL