GAS TRANSPORT MECHANISMS DURING HIGH-FREQUENCY VENTILATION

Online Supplement

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Table 1. Glossary of gas exchange mechanisms and terminology.

Term	Definition
Advection	The transport of a substance due to bulk fluid motion (such as occurs during conventional tidal ventilation).
Capacitor	In the context of HFV, the component of the RLC circuit used to represent the elastic loads acting on the airway-lung system.
Corner frequency	In the context of HFV, and based on RLC-type modelling, it is the frequency where the pressure cost of flow is lowest for a system with high airway resistance (overdamped). In general, it might be considered the frequency of a system at which the energy might be lowest.
Inductor	In the context of HFV, the component of the RLC circuit used to represent the inertial loads acting on the airway-lung system.
Molecular diffusion	Diffusion of matter, from a region of high concentration to a region of low concentration, due to random molecular motion.
Natural frequency	In the context of HFV, and based on RLC-type modelling, it is the frequency where the pressure cost of flow is lowest. In general, it is the frequency at which a system naturally vibrates.
Nonlinear mean streaming	A non-zero average velocity of gas flow at a given location that can occur in the middle to upper generations of the airway during high-frequency ventilation.
Pendelluft	Gas transport between adjacent lung compartments due to varying compliance.
Resistor-Inductor-Capacitor (RLC-type) model	In the context of HFV, the modelling technique currently used to understand the dynamics of the airway-lung system during high-frequency ventilation. In general, an electrical analogy used to model a dynamical system.
Resistor	In the context of HFV, the component of the RLC circuit used to represent the viscous losses in the airway-lung system.
Taylor dispersion	Enhanced transport of a gas in the axial direction (along a tube) that is induced by a radial concentration gradient (across the tube).
Turbulent diffusion	The mixing, transport and diffusion of gas due to turbulent motion that can occur in the upper generations of the airway during high-frequency ventilation.
Womersley parameter	A dimensionless parameter used in biofluid mechanics to quantify the relative importance of viscous effects in pulsatile and oscillatory flows.

Definitions of gas transport mechanisms and terms associated with current modelling that are used throughout this manuscript.

Table 2. Baseline ventilation protocols for the treatment of infants born at or near term with severe pulmonary dysfunction and the treatment of infants born preterm with acute pulmonary dysfunction.

Study†	Starting Frequency (Hz)	Mean Airway Pressure	Pressure Amplitude
Studies from infants born at or near term [16]			
Clark *et al.* 1994 [46]	10	"Our goals were to maintain the lowest $F_iO_2$and normal lung inflation"	"a pressure amplitude sufficient to produce visible chest wall motion"
Rojas *et al.* 2005 [47]	10	"$2\mathrm{cmH_2O}$ above $\overline{\mathrm{Paw}}$ on CV at the time of enrolment"	"amplitude adjusted to obtain visual vibration of the chest wall and desired levels of $\mathrm{P_aCO_2}$"
Studies from infants born pre-term [17]			
Clark *et al.* 1992 [48]	10	"$\overline{\mathrm{Paw}}$ (measured proximal to the endotracheal tube) 1 to $2\mathrm{cmH_2O}$ greater than that being used on CV at the time of entry in the study"	"pressure amplitude that produced visible chest wall movement"
Courtney *et al.* 2002 [49]	10 – 15	"the initial mean airway pressure was at least 2 cm of water higher than that received during conventional ventilation"	NA
Craft *et al.* 2003 [50]	10 – 12	"Mean airway pressure was adjusted to maintain an optimal lung volume strategy as measured by a chest radiograph demonstrating expansion to eight to nine ribs and oxygenation saturation between 88% and 92% on an $\mathrm{F_iO_2}$ less than 0.40"	"Amplitude was adjusted to meet the goal $\mathrm{P_ACO_2}$"
Dani *et al.* 2006 [51]	10	$8\mathrm{cmH_2O}$	$30\mathrm{cmH_2O}$
Durand *et al.* 2001 [52]	10 – 15	"Mean airway pressure $(\mathrm{P_{AW}})$ at least $2\mathrm{cmH_2O}$ greater than patient was receiving on conventional ventilation."	"Amplitude $(\Delta\mathrm{P})$ adjusted based on physical examination and/or transcutaneous monitoring."
Gerstmann *et al.* 1996 [53]	10 – 15*	"The HFOV strategy was to begin CDP at $1-2\mathrm{cmH_2O}$ above $\mathrm{P_{AW}}$ used during the stabilisation period on CV"	"Ventilation was controlled by adjusting the power output to increase or decrease ΔP"
HiFi Group 1989 [54]	15	"The initial fraction of inspired oxygen and mean airway pressure were specified by the protocol to be the same as those required during stabilization on conventional mechanical ventilation. If the	"the oscillatory amplitude was increased until chest-wall oscillations were rapidly apparent, and it was then adjusted as needed to correct hypocapnia or hypercapnia."

Study†	Starting Frequency (Hz)	Mean Airway Pressure	Pressure Amplitude
		infants had not yet received conventional mechanical ventilation, the initial amount of inspired oxygen was set to be the same as that before intubation and the mean airway pressure was set to be $0.8\ to\ 1.0kPa\ (8-10\text{cm of water}).$"	
Johnson *et al.* 2002 [55]	10	$6-8\text{cm}H_2O$	"the amplitude was increased until the infant's chest was seen to be "bouncing""
Lista *et al.* 2008 [56]	10	$8-10\text{cm}H_2O$	40%
Moriette *et al.* 2001 [57]	15	"Initial mean airway pressure was set at $14\text{cm}H_2O$ when $F_iO_2 > 0.4$ and $2\text{cm}H_2O$ higher than with conventional ventilation when $F_iO_2 \leq 0.4$."	"Peak-to-peak pressure was set according to the PCO_2 level."
Ogawa *et al.* 1993 [58]	15	"lung volume was recruited in high frequency oscillatory ventilation by inflating the lungs fully by manual bagging just before starting and a high mean airway pressure was adopted"	NA
Plavka *et al.* 1999 [59]	15	"The proximal airway distending pressure (PA_WDP) was increased step by step to reach optimum lung inflation and alveolar recruitment and to optimize oxygenation as soon as possible"	"The pressure amplitude (DP) was adjusted to achieve adequate vibration of the thorax"
Rettwitz-Volk *et al.* 1998 [18]	15 – 20	"The initial settings were mean airway pressure and oscillatory amplitude to show good chest movement and F_iO_2 to maintain oxygen saturation as described above."	"The initial settings were mean airway pressure and oscillatory amplitude to show good chest movement and F_iO_2 to maintain oxygen saturation as described above."
Salvo *et al.* 2012 [60]	15	"mean continuous distending pressure (CDP), 6 to $8\text{cm}H_2O$"	"pressure amplitude producing visible chest vibrations"
Schreiber *et al.* 2003 [61]	10 – 15	"2 cm of water above that required during initial stabilization"	"an amplitude sufficient to jiggle the chest wall to the level of the umbilicus"
Sun *et al.* 2014 [62]	10	$6-8\text{cm}H_2O$	"The pressure amplitude was set in such a way that chest oscillations were visible with a frequency of 10Hz."

Study†	Starting Frequency (Hz)	Mean Airway Pressure	Pressure Amplitude
Thome *et al.* 1999 [63]	10	"Paw was initially set 1 to $2\mathrm{cmH_2O}$ above the mean pressure during the previous stabilization with IPPV or, if HFV was started immediately after intubation, Paw was set at 10 to $12\mathrm{cmH_2O}$."	"ventilation was controlled by adjusting the amplitude"
Van Reempts *et al.* 2003 [64]	10	"Randomised infants were started on a MAP of $8\mathrm{cmH_2O}$ for infants < 29 weeks and $10\mathrm{cmH_2O}$ for neonates 29-31 6/7 GA with $\mathrm{F_iO_2}$ as needed."	"The pressure amplitude (delta P) was set at a value that produced visible chest wall movement."
Vento *et al.* 2005 [65]	10	$10\mathrm{cmH_2O}$	"set at 30% at the beginning, was increased, if necessary, until the infant's chest was seen to be "bouncing""

Baseline ventilator protocols obtained from references included in the Cochrane Database of Systematic Reviews: High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term (Review) [16]; and Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants (Review) [17]. †Apart from the Sensormedics 3100A most of these trials were conducted on HFV devices that are now superseded. * "Ventilator frequency was set to $10\mathrm{Hz}$, although in some very small infants this produced overventilation even at low power settings. In these small infants the oscillation frequency was increased to $15\mathrm{Hz}$, which reduced tidal volume output and decreased overventilation" GA: Gestational Age. NA: Not apparent. Note: References listed here are not exhaustive. Only references to studies included in the review have been tabulated here. Where applicable, only the major publication for the study has been included. Unless specified otherwise, tabulated values indicate protocol which high-frequency ventilation was initiated at.

Table 3. Baseline ventilation protocols for the treatment of adults with ARDS.

Study	Frequency (Hz)	Mean Airway Pressure	Pressure Amplitude
Derdak *et al.* 2002 [66]	5	"mPaw was set $5\mathrm{cmH_2O}$ greater than mPaw during CV immediately before conversion to HFOV."	"Pressure amplitude of oscillation (ΔP) was initially set to achieve chest wall vibration to the level of the midthigh."
Bollen *et al.* 2005 [67]	5	"HFOV was started with continuous distending pressure (CDP) at $5\mathrm{cmH_2O}$ higher than mean airway pressure (MAP) on CV and then adjusted to achieve and maintain optimal lung volume."	"Delta P was adjusted according to $\mathrm{P_aCO_2}$ and chest wall vibrations."
Demory *et al.* 2007 [68]	5	"Mean airway pressure was set at $5\mathrm{cmH_2O}$ greater than mean airway pressure measured during the ventilation optimization period."	"The pressure amplitude of oscillation was set to achieve a $\mathrm{P_aCO_2}$ close to the $\mathrm{P_aCO_2}$ measured during the ventilation optimization period."
Ferguson *et al.* 2013 [69]	NA	$30\mathrm{cmH_2O}$	"We minimised HFOV tidal volumes by using the highest possible frequency that would maintain arterial blood pH above 7.25."
Young *et al.* 2013 [31]	10	"$5\mathrm{cmH_2O}$ above the plateau airway pressure at enrolment"	NA
Mentzelopoulos *et al.* 2007 [70]	4 [6]	"mPaw of $3\mathrm{cmH_2O}$ above mean tracheal pressure measured distal to the endotracheal tube" [6]	"$30\mathrm{cmH_2O}$ above initial $\mathrm{P_aCO_2}$ during CV" [6]

Baseline ventilator protocols obtained from HFV trials for the treatment of adults with ARDS originally report in [6]. $\mathrm{P_aCO_2}$: Partial pressure of carbon dioxide. $\mathrm{F_iO_2}$: Fraction of inspired oxygen. IT: Inspiratory time. BF: Bias flow. mPaw: Mean airway pressure. CV: Conventional Ventilation. CMV: Conventional Mechanical Ventilation. NA: Not apparent. Unless specified otherwise, tabulated values indicate protocol which high-frequency ventilation was initiated at.

Table 4. Trachea diameters from various species.

Species	Diameter (mm)	Comments	Source
Rats	2.2	Approximate value of hydraulic diameter, read from Figure 2B	[71] Oakes JM, Scadeng M, Breen EC, Marsden AL, Darquenne C. Rat airway morphometry measured from in situ MRI-based geometric models. J Appl Physiol. 2012;112:1921-31.
Rabbits	3.5	Value from Table 1, group 3 (group 3 to match weight range from data in Venegas), minimum diameter	[72] Arendt TB, Loeber SJ, Schroeder CA, Lasarev MR, Ferreira TH. Computed tomographic laryngotracheal dimensions in adult domestic rabbits (Oryctolagus cuniculus) are positively associated with body weight and the laryngotracheal lumen is narrowest at the level of the thyroid cartilage. Am. J. Vet. Res. 2023;84:8.
Monkeys	9.0	Refer to section "Respiratory system" under subsection "Anatomic features"	[73] Valverde CR, Christe KL. CHAPTER 22 - Radiographic Imaging of Nonhuman Primates. In: Wolfe-Coote S, editor. The Laboratory Primate. Academic Press; 2005. p. 371-386.
Dogs	12.5	Approximate value read from Figure 2A (level A)	[74] Mostafa AA, Berry CR. Radiographic vertical tracheal diameter assessment at different levels along the trachea as an alternative method for the evaluation of the tracheal diameter in non-brachycephalic small breed dogs. BMC Vet Res 2022; doi.org/10.1186/s12917-022-03160-4
Humans	19.2	Value from Table 1, male, age group 30-39, coronal diameter	[75] Breatnach E, Abbott GC, Fraser RG. Dimensions of the normal human trachea. Am J Roentgenol. 1984;142:903-6.
Horses	49.8	Value calculated from: D_pred = 0.47*(body weight)^0.39 (cm), based on weight of 427kg used by Venegas	[76] Carstens A, Kirberger RM, Grimbeek RJ, Donnellan CMB, Saulez MN. Radiographic quantification of tracheal dimensions of the normal thoroughbred horse. Vet Radiol Ultrasoun. 2009;50:492-501.

Trachea diameters from various species used as the length scale for plotting the data shown in Figure 2 of this manuscript.

HFV non-dimensionalisation using Buckingham Pi theorem.

The idea behind Buckingham's Pi theorem is that a relationship between n independent variables can be reduced to a relationship between m dimensionless groups where

$$m = n - r$$

and r is the number of *dimensions* of the problem. In the standard SI system, there are at most 7 dimensions (see https://www.bipm.org/en/measurement-units/si-base-units). The process to find a set of dimensionless groups is to

1. List the m dimensional variables
2. Identify the r dimensions involved in the problem
3. Choose r dimensional variables that will be used as repeating variables. Each will define the scale being used for each dimension, and so these will appear in all of the dimensionless groups. As such, these repeating variables should not be variables whose impact we wish to isolate. Also, the repeating variables should not be able to be organised into a dimensionless group themselves (if they can be, the scales being used are not unique)
4. Combine each of the remaining m non-repeating variables into a dimensionless group with the repeating variables

Note that in most problems there are multiple sets of m groups that can be formed, depending on the choice of scales and repeating variables. The "right" choice is the one that best collapses the data, or highlights the phenomena being studied. Sometimes this can only be determined after the fact.

For the HFV problem, we consider first a relationship for the rate of alveolar ventilation, $\dot{V}_A$ in terms of the ventilator parameters of the pressure fluctuation ΔP and the frequency f, *the lung parameters* of the natural frequency f_n and inertance m, and the characteristic size of the airway

system D. Note that we have not strictly defined D here; however, in the manuscript we use two, either the cube root of the dead space volume $V_D^{\frac{1}{3}}$, or the tracheal diameter. So, we have a dimensional relationship

$$\dot{V}_A = \emptyset(f, \Delta P, f_N, D, m).$$

This gives six dimensional parameters, so that $n = 6$. Inspection of these dimensional variables shows that they span the three dimensions of length, mass, and time so that $r = 3$. Therefore, we expect $m = n - r = 3$ dimensionless groups. The repeating variables we choose in this case are

- f_N with dimensions T^{-1} to non-dimensionalise time, or f_N^{-1} as the relevant time scale
- D with dimensions L to non-dimensionalise length, or D as the relevant length scale
- m with dimensions M to non-dimensionalise mass, or m as the relevant mass scale

Next, we combine the remaining variables with the repeating variables to form dimensionless groups or ratios

- $\dot{V}_A$ has dimensions of L^3T^{-1} so group 1 is $\pi_1 = \frac{\dot{V}_A}{D^3 f_N}$. No mass is required so m doesn't appear
- f has dimensions of T^{-1}, so group 2 is $\pi_2 = \frac{f}{f_N}$. No mass or length is required so m and D do not appear
- ΔP has dimensions of $ML^{-1}T^{-2}$, so group 3 is $\pi_3 = \frac{\Delta P D}{m f_N^2}$

Therefore, the final dimensionless relationship can be expressed as

$$\pi_1 = \emptyset(\pi_2, \pi_3) \text{ or } \frac{\dot{V}_A}{D^3 f_N} = \emptyset\left(\frac{f}{f_n}, \frac{\Delta P D}{m f_N^2}\right)$$

Note that the *controllable variables,* f and ΔP, each only appear in a single group. Changing one of them has an impact on only a single group.

Now, we consider what can be done if we add a parameter to try to capture the impact of the *flow variation* that is impacted by the viscous stress. We add another parameter, the kinematic viscosity v. No new dimensions are added by the kinematic viscosity, so we simply expect another independent group to be formed

- v has dimensions of L^2T^{-1}, so group 4 is $\pi_4 = \frac{v}{f_N D^2}$. No mass is required so m does not appear

This means that the original dimensional relationship (which includes the kinematic viscosity) expressed as

$$\dot{V}_A = \emptyset(f, \Delta P, f_N, D, m, v)$$

is reduced to the dimensionless relationship

$$\pi_1 = \emptyset(\pi_2, \pi_3, \pi_4) \text{ or } \frac{\dot{V}_A}{D^3 f_N} = \emptyset\left(\frac{f}{f_n}, \frac{\Delta P D}{m f_N^2}, \frac{v}{f_N D^2}\right)$$

This set of parameters is valid, and all use consistent mass, length, and time scales. Note that the final group, π_4, at this point consists of

- Parameters which are beyond the control of a clinician
- A ratio of time scales which are the natural period (the inverse of the natural frequency) f_N^{-1}, and a second time scale related to the time required for momentum to diffuse due to viscosity, $\frac{D^2}{v}$.

We can form a new dimensionless group by simply taking the product of two existing groups. If we take the quotient of group π_2 and π_4, we arrive at

$$\frac{\pi_2}{\pi_4} = \frac{fD^2}{v}.$$

So that the dimensionless relationship amongst the variables can be written as

$$\frac{\dot{V}_A}{D^3 f_N} = \emptyset\left(\frac{f}{f_N}, \frac{\Delta P D}{m f_N^2}, \frac{f D^2}{\nu}\right).$$

Note that when written this way

- The last group is still a ratio of two time scales which are the diffusive time scale $\frac{D^2}{\nu}$, and the ventilation period (the inverse of the ventilation frequency) f^{-1}
- The first group and the last group on the right-hand side of the equation involve the ventilation frequency f. This highlights that the ratio of the ventilation period to the natural period, and the ratio of the ventilation period to the diffusive time scale, cannot both be varied independently. Control of one sacrifices control of the other.

Establishing the relationship between tidal volume and frequency from the expression for the flow cost of ventilation in Equation 14.

Equation 14 presents, non-dimensionally, a relationship between the flow cost of ventilation and the square of the Womersley parameter. From this non-dimensional data, a dimensional relationship can be established showing how the tidal volume is likely to reduce as the frequency is increased.

From the equation for the curve fitted to the "lower branch" of data in Figure 2 which includes the data from dogs, monkeys, humans and horses, this information can be made explicit if the following information is known or attainable:

- The dynamic viscosity of air
- The tracheal diameter
- The required rate of alveolar ventilation

then (V_T) can be calculated as a function of (f). Below are two examples of this:

- A sample infant, assuming a tracheal diameter of $D = 5.5$ mm and a rate of alveolar ventilation of $\dot{V}_A = 10$mL/s
- A sample adult, assuming a tracheal diameter of $D = 19.2$mm and a rate of alveolar ventilation of $\dot{V}_A = 75$mL/s

In both cases, the dynamic viscosity is taken as $\nu = 1.5 \times 10^{-5}$m^2/s.

In the first infant sample, for a specified value of $(\alpha^2 = 300)$, the process is as follows:

1. Calculate (f) from (α^2)

$$\alpha^2 = {2\pi f D^2}/{4\nu}$$

$$\rightarrow f = \frac{\alpha^2 4\nu}{2\pi D^2}$$

$$\rightarrow f = \frac{300 * 4 * 1.5 \times 10^{-5}}{2 * \pi * 0.0055^2}$$

$$\rightarrow f \approx 94\ Hz$$

2. Calculate (Q) from Equation 14

$$Q = 1581.869e^{-0.003357\alpha^2} - 1581.869e^{-0.003465\alpha^2}$$

$$\rightarrow Q = 1581.869e^{-0.003357*300} - 1581.869e^{-0.003465*300}$$

$$Q \approx 18.4$$

3. Calculate (V_T) from Equation 1 noting that the units of (V_T) will be the same as the units of $\left(\dot{V}_A\right)$ without time dependence. I.e., $\left(\dot{V}_A\right)$ in units of ml/s becomes (V_T) in units of ml.

$$Q = \frac{V_T f}{\dot{V}_A}$$

$$\rightarrow V_T = \frac{Q\dot{V}_A}{f}$$

$$\rightarrow V_T = \frac{18.4 * 10}{94}$$

$$V_T \approx 1.9 \text{ ml}$$

The second adult sample is the same, for the same value of $(\alpha^2 = 300)$, the process is as follows:

1. Calculate (f) from (α^2)

$$\alpha^2 = {}^{2\pi f D^2}/_{4v}$$

$$\rightarrow f = \frac{\alpha^2 4v}{2\pi D^2}$$

$$\rightarrow f = \frac{300 * 4 * 1.5 \times 10^{-5}}{2 * \pi * 0.0192^2}$$

$$\rightarrow f \approx 7.8\ Hz$$

2. Calculate (Q) from Equation 14

$$Q = 1581.869e^{-0.003357\alpha^2} - 1581.869e^{-0.003465\alpha^2}$$

$$\rightarrow Q = 1581.869e^{-0.003357*300} - 1581.869e^{-0.003465*300}$$

$$Q \approx 18.4$$

3. Calculate (V_T) from Equation 1

$$Q = \frac{V_T f}{\dot{V}_A}$$

$$\rightarrow V_T = \frac{Q\dot{V}_A}{f}$$

$$\rightarrow V_T = \frac{18.4 * 75}{7.7}$$

$$V_T \approx 179.2 \text{ ml}$$

This process can be repeated with different values of (α^2) to establish a relationship showing how (V_T) is likely to change as (f) is altered for a specific size patient. Shown below is the infant sample on the left and the adult sample on the right.