

NON-INVASIVE MONITORING OF CARDIAC OUTPUT USING THE INSPIRED SINEWAVE TECHNIQUE

Supplementary material

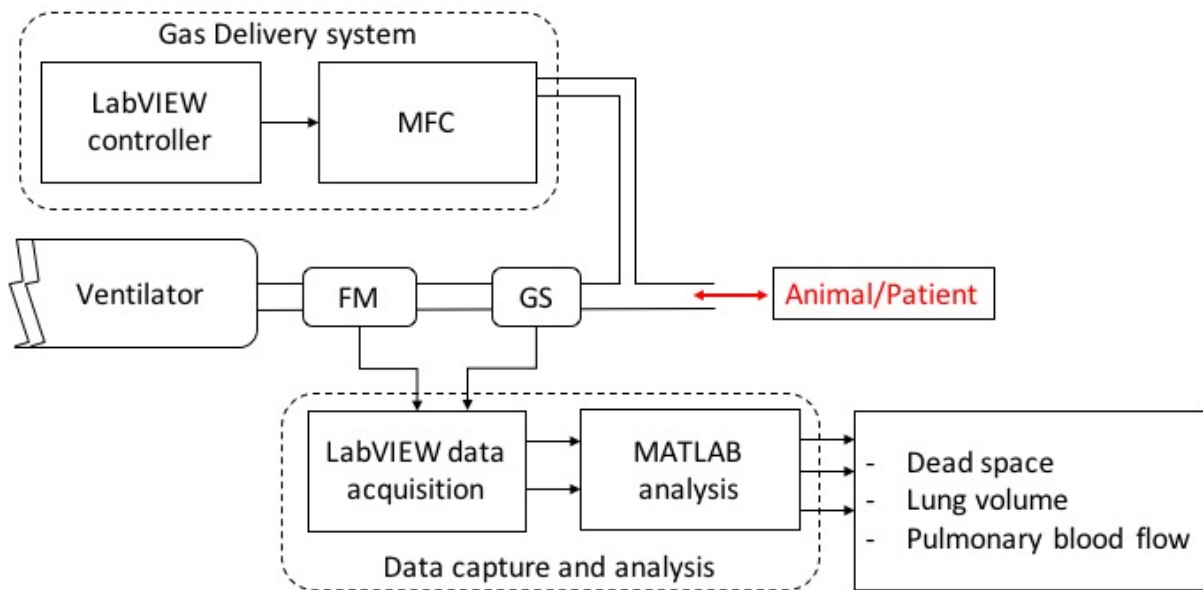


Figure 1S. Schematic representation of the Inspired Sinewave Device. Air is inhaled and exhaled through the flow meter (FM) and gas sensor (GS). Small volumes of N₂O are delivered into inspired gas at the beginning of each inspiration via a mass flow controller (MFC). Flow and gas concentration data are recorded, and cardiorespiratory variables are recovered using a mathematical model of the lung.

Mathematical principles of the IST

The oscillating inspired N_2O concentration can be defined by the equation:

$$F_I(t) = \bar{F}_I + \Delta F_I \sin\left(\frac{2\pi}{T}t + \phi\right) \quad (eq. 1)$$

where \bar{F}_I is the mean amplitude, ΔF_I is the oscillation amplitude, T is the time period (60 seconds) and ϕ is the phase shift.

Figure 2S illustrates the lung model used for parameter recovery. The lung consists of one dead space compartment (V_D) and one lung compartment $V_A(t)$. The body is also considered as one compartment. The total pulmonary capillary blood flow through the lung is $\dot{Q}_P(t)$. N_2O tracer gas is inhaled through the dead-space into the lung and diffuses into pulmonary blood. After being distributed to different body compartments, the tracer gas reenters the pulmonary circulation in mixed venous blood. It passes through dead space, before being exhaled.

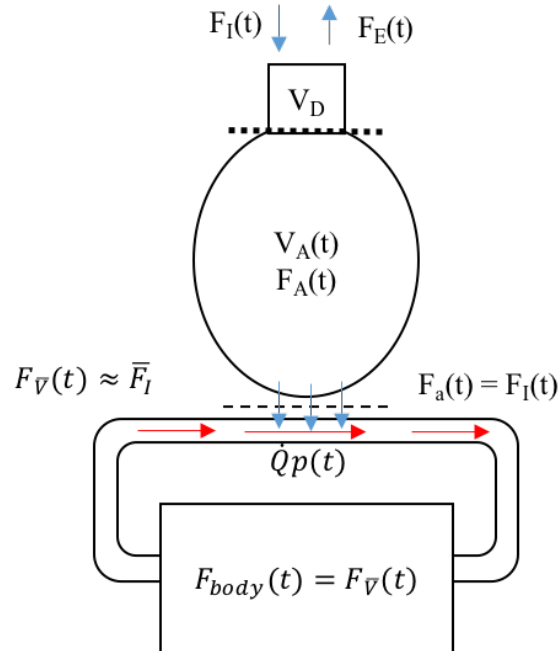


Figure 2S: The single compartment “balloon and straw” model of the lung and circulatory system

During the IST test, the $F_I(t)$ follows the sinewave pattern described by equation (eq.1). After an initial transient period, the alveolar concentration $F_A(t)$, the arterial concentration $F_a(t)$ and the mixed venous concentration $F_{\bar{v}}(t)$ all reach steady-state and follow sinusoidal patterns. The mixed venous concentration can then be described as:

$$F_{\bar{v}}(t) = \bar{F}_I + \Delta F_{\bar{v}} \sin\left(\frac{2\pi}{T}t + \phi_{\bar{v}}\right) \quad (eq. 2)$$

From Figure 2S, the mass balance of the N_2O in the lung can be written as:

$$\begin{aligned} & \text{Change of mass in lung} \\ & = \text{mass inhaled} - \text{mass exhaled} - \text{mass exchanged with the blood} \end{aligned}$$

So, the mass balance equation of the tracer gas of two consecutive breaths ($n-1$ and n) is:

$$\begin{aligned} & F_{E,n-1} \times V_A + \bar{F}_{I,n} \times (V_{T,n} - V_D) + F_{E,n-1} \times V_D - \lambda \times \dot{Q}_P \times (F_{E,n} - F_{\bar{v}}) \times \Delta t_n \\ & = V_A \times F_{E,n} + V_{T,n} \times F_{E,n} \end{aligned} \quad (eq. 3)$$

in which:

V_A : the alveolar lung volume;

\dot{Q}_P : the pulmonary blood flow;

V_D : the deadspace, estimated from the Bohr method;

$\bar{F}_{I,n}$: the mean inspired concentration of breath n^{th} ;

$F_{E,n-1}, F_{E,n}$: the end expired concentrations of breath ($n-1$) and n ;

λ : the solubility of N_2O , 0.47;

$F_{\bar{v}}$: the mixed venous concentration, assumed to equal to the mean of the inspired sinewave concentration at steady state F_I^0 ;

Δt_n : the duration of breath n^{th} ;

$V_{t,n}$: the tidal volume of breath n^{th} .

The mixed-venous concentration, $F_{\bar{v}}$, is assumed to be heavily damped by the body compartments and so to oscillate only negligibly at periods less than 3 minutes. Therefore, it can be considered as a constant $F_{\bar{v}}$ which approximates to the mean inspired concentration, \bar{F}_I .

The mass balance equation then becomes:

$$\begin{aligned} &\Leftrightarrow V_A \times (F_{E,n} - F_{E,n-1}) + \lambda \times \dot{Q}_P \times (F_{E,n} - \bar{F}_I) \times \Delta t_n \\ &= V_D \times (F_{E,n-1} - F_{\bar{I},n}) + V_{T,n} \times (F_{\bar{I},n} - F_{E,n}) \quad (eq. 4) \end{aligned}$$

The volume of dead-space was calculated using Bohr method:

$$V_D = V_T \frac{F_E - F_{\bar{E}}}{F_E - \bar{F}_I}$$

where $F_{\bar{E}}$ is the average expired tracer gas concentration and \bar{F}_I is the mean inspired concentration. A modified Bohr method has also been proposed to further improve the accuracy and repeatability of the airway dead space estimation¹⁷. This method also increases the accuracy of \dot{Q}_P and V_A estimation. With V_D and all the other parameters determined, effective lung volume ($ELV = V_D + V_A$) and \dot{Q}_P (i.e. \dot{Q}_{IST}) are estimated by solving a set of mass balance equations (eq.4).

SUPPLEMENTARY FIGURES

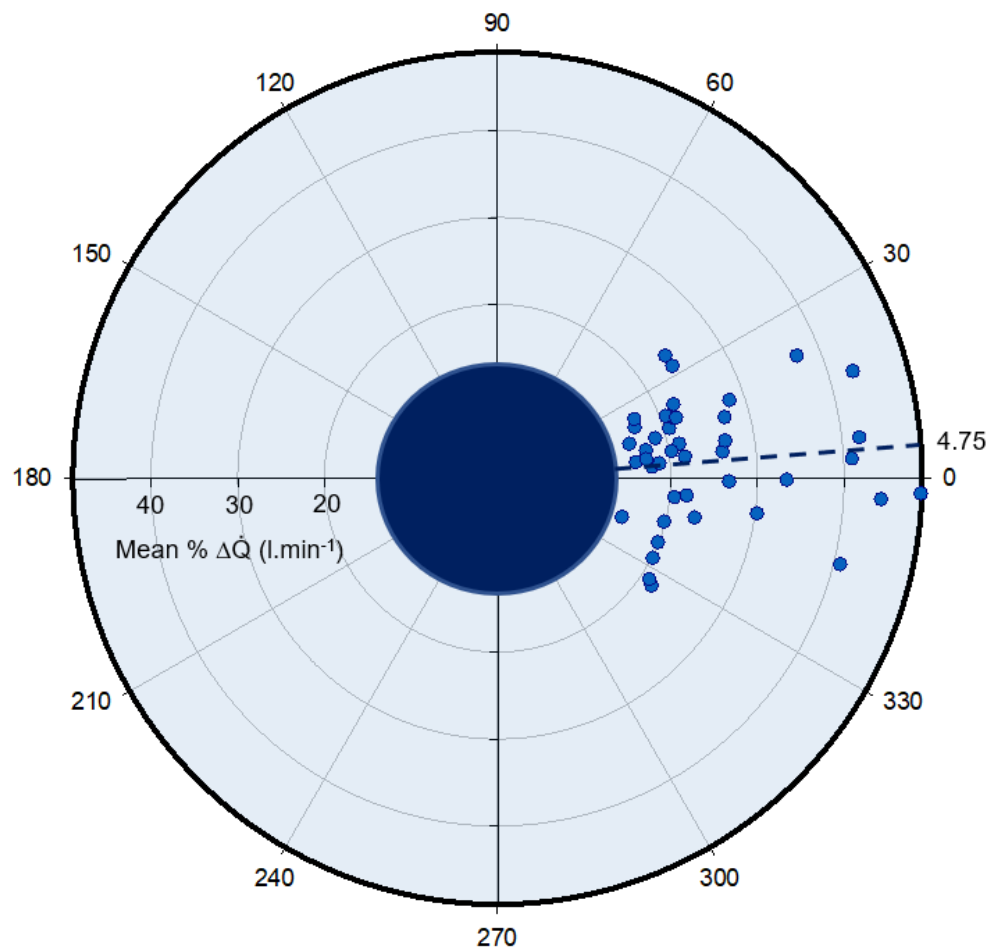


Figure 3S. Half circle polar-plot analysis of $\% \Delta \dot{Q}_{IST}$ vs. $\% \Delta \dot{Q}_T$ throughout the protocol pre-saline lung lavage, with an exclusion zone of 15% mean \dot{Q} . Mean angular bias = 4.75° (-26.8° , 36.3°). Data points located within $\pm 30^\circ$ limits were considered concordant (90.5%). Data points distributed near the polar axis (0°) indicate good trending.

SALINE LAVAGE MODEL TABLES/FIGURES

Injured									
Parameter	Animal Number								Mean
	1	2	3	4	5	6	7	8	
Weight (kg)	46.5	45	39	53	37	37	47	44.5	43.0
HR	78	73	84	72	104	96	78	69	81
SBP (mmHg)	94	105	97	70	77	84	103	15	83
DBP (mmHg)	69	47	72	46	40	54	59	47	54
\dot{Q}_T (l min ⁻¹)	2.7	7.2	5.6	3.5	5.2	4.1	4.1	3.3	4.5
\dot{Q}_{IST} (l min ⁻¹)	2.8	6.6	6.1	3.2	4.7	4.6	6.7	9.1	5.5
PAP (mmHg)	37	27	27	35	21	32	24	29	29.1
Hb (g dl ⁻¹)	7.2	6.7	7.7	8.3	8	6.9	7.6	8.8	7.6
FiO ₂	0.6	0.7	0.7	0.8	0.7	0.7	0.9	0.9	0.8
SaO ₂ (%)	93	99	100	93	100	99	99	100	98
pH	7.17	7.33	7.25	7.39	7.19	7.21	7.23	7.15	7.23
PaO ₂ (mmHg)	92	178	232	93	249	169	221	298	193
PaCO ₂ (mmHg)	78	50	69	80	78	73	73	85	73
PFR	153	255	331	116	355	241	245	331	250
Paw Peak (cmH ₂ O)	38	28	26	39	18	28	26	33	29

Table 2. Baseline and respiratory and haemodynamic variables from each animal following repeated saline lavages. HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, \dot{Q}_T = cardiac output from PAC thermodilution, \dot{Q}_{IST} = cardiac output from IST; PAP = mean pulmonary artery pressure, Hb = haemoglobin, FiO₂ = fraction of inspired O₂, SaO₂ = arterial oxygen saturation, PaO₂ = arterial O₂ partial pressure, PaCO₂ = arterial CO₂ partial pressure, PFR = PaO₂:FiO₂ ratio, Paw Peak = peak airway pressure. * Difference between baseline \dot{Q}_{IST} and \dot{Q}_T was 1.0 l.min⁻¹ (-1.1, 3.1), $P = 0.28$).

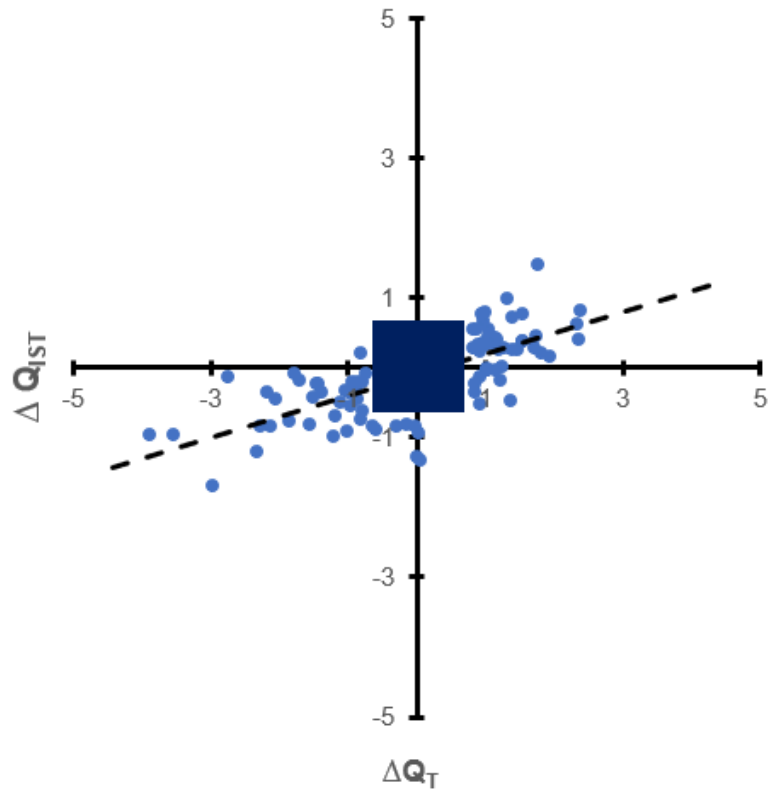


Figure 4S. Four-quadrant plot analysis of $\Delta \dot{Q}_{IST}$ vs. $\Delta \dot{Q}_T$ throughout the protocol post saline lung lavage, with an exclusion zone of 15% mean \dot{Q}_T (0.75 l min^{-1}). Linear regression analysis reveals an equation of $\Delta \dot{Q}_{IST} = 0.3 \times \Delta \dot{Q}_T + 0.1$, with $r = 0.72$. Data points located in either quadrant of agreement were considered concordant (89.4%)

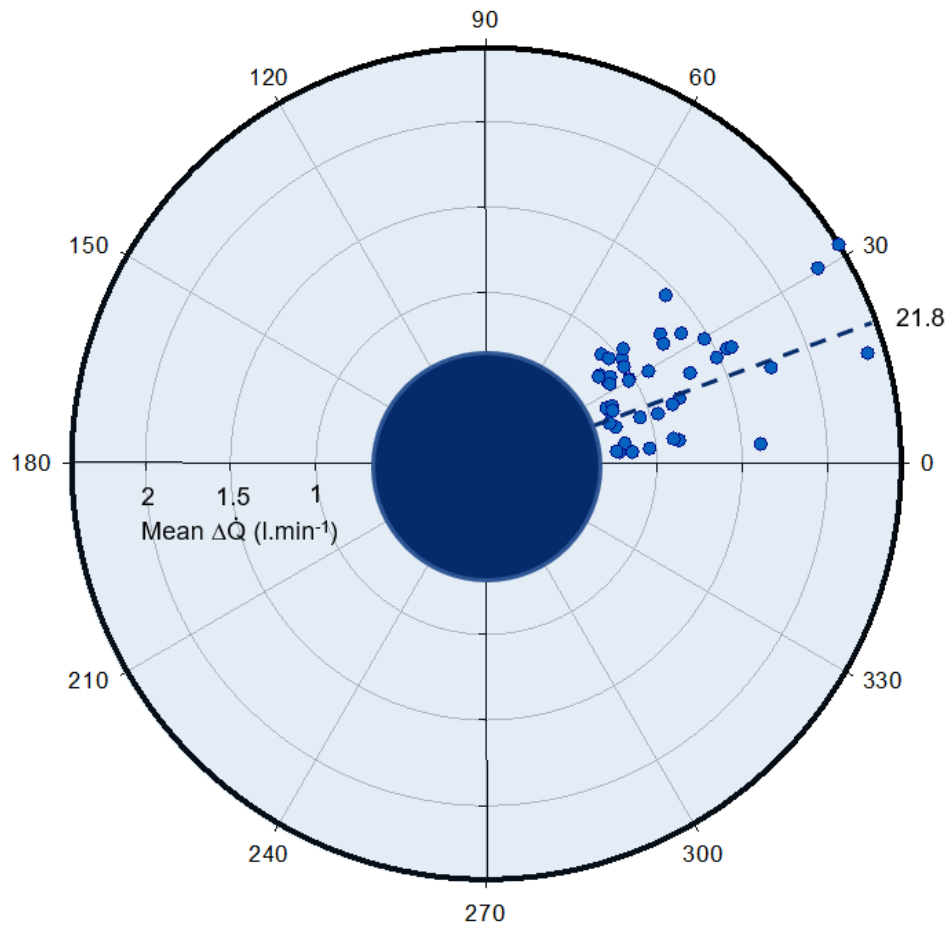


Figure 5S. Half circle polar-plot analysis of $\% \Delta \dot{Q}_{IST}$ vs. $\% \Delta \dot{Q}_T$ throughout the protocol post-saline lung lavage, with an exclusion zone of 15% mean \dot{Q}_T (0.75 l.min⁻¹). Mean angular bias = 21.8° (-4.2°, 47.6°) Data points distributed near the polar axis (0°) indicate good trending.

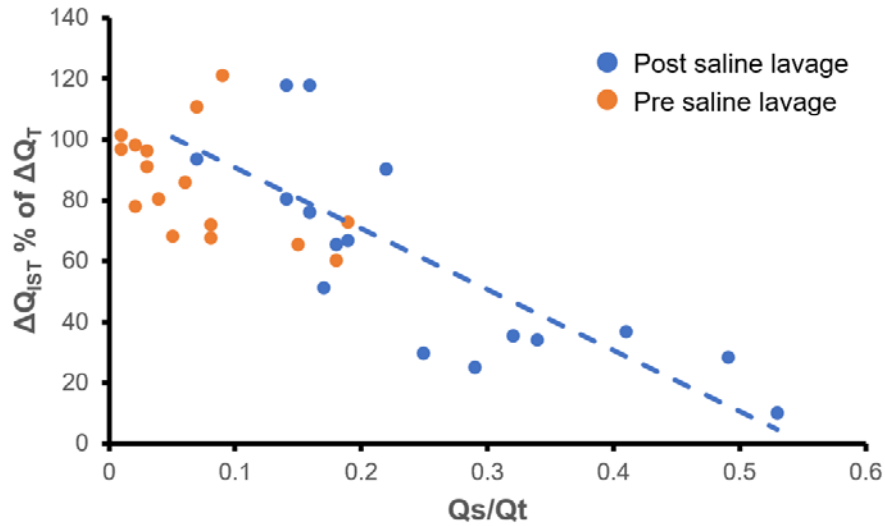


Figure 6S. The correlation, between shunt fraction (\dot{Q}_s/\dot{Q}_t) and the change in \dot{Q}_{IST} expressed as a percentage of the change in \dot{Q}_T ($\Delta\dot{Q}_{IST}$ % of $\Delta\dot{Q}_T$). Orange dots = pre-lavage; Blue dots = Post lavage; $r = 0.79$, $P < 0.05$. Arterial blood gas samples, needed for the calculation of \dot{Q}_s/\dot{Q}_t , were collected on two occasions during each protocol: 1) during the nadir of \dot{Q}_T and 2) during peak \dot{Q}_T . As such, $\Delta\dot{Q}_{IST}$ and $\Delta\dot{Q}_T$ were calculated as 1) the change in \dot{Q} from baseline to nadir and 2) the change in \dot{Q} from nadir to peak.

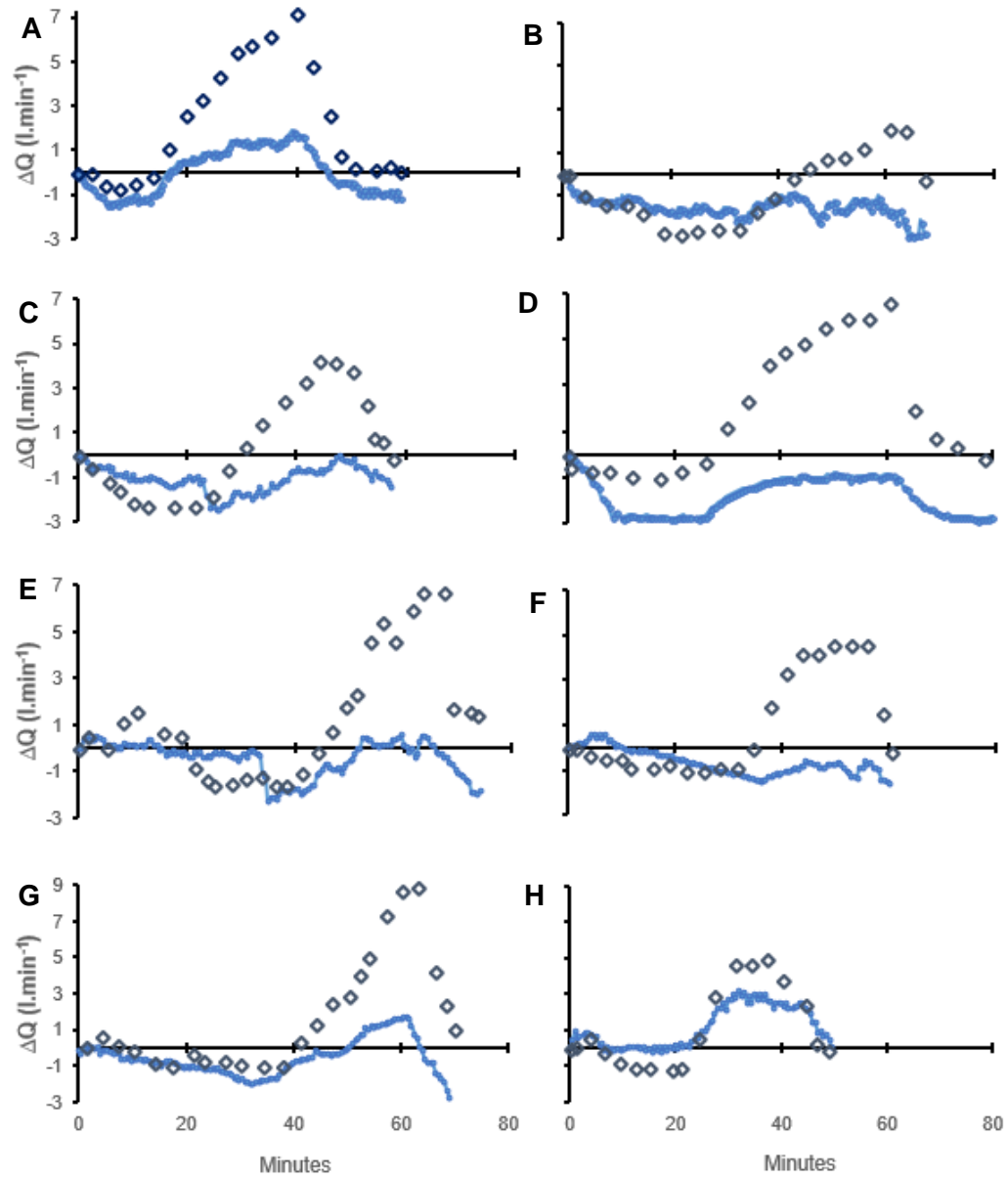


Figure 7S A-H. $\Delta \dot{Q}$ from baseline in all 8 animals throughout the protocol. Dark blue diamonds are \dot{Q}_T measurements, and light blue dots and lines are \dot{Q}_{IST} measurements.