

## Total Liquid Ventilation: Dynamic Airway Pressure and the Development of Expiratory Flow Limitation

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**Expiratory flow limitation occurs during total liquid ventilation (TLV), and is characterized by the sudden development of excessively negative intratracheal pressures without increases in flow. The purpose of this study was to identify a dynamic signal for the servoregulation of expiratory flow ( $\dot{V}_e$ ), by determining the range of dynamic intratracheal pressures [P(T)], which mark the onset of flow limitation during liquid expiration, where choke occurs at the critical pressure ( $P_c$ ). The lungs of rabbits were filled with perfluorocarbon to an end-inspiratory lung volume (EILV) of 20, 30, or 40cc/kg and connected to a piston driven liquid ventilator, which removed perfluorocarbon at a rate ( $\dot{V}_s$ ) of 2.5, 5.0, or 7.5 ml/s. Nine animals per EILV group were used (27 animals total), and within each EILV group each ( $\dot{V}_s$ ) was used three times. P(T) and ( $\dot{V}_e$ ) (T) were measured at the tracheostomy tube, and dP/dT was calculated from P(T).  $P_c$  was determined within each EILV/( $\dot{V}_s$ ) group by examining the average dP/dT curve for the first significant change from baseline.  $P_c$  ranged from  $-6.02 \pm 1.83$  to  $-9.02 \pm 3.2$  mm Hg. In general, the higher the EILV, the more negative the  $P_c$ . We conclude that  $P_c$  during TLV varies within a limited range in rabbits. These data may be used to maximize expired volume during TLV by sequentially tapering flow rates as this critical range of pressures is approached. *ASAIO Journal* 2004; 50:485–490.**

Total liquid ventilation (TLV) with perfluorocarbons has been demonstrated to improve gas exchange, pulmonary mechanics, and lung injury in animal models of acute respiratory failure.<sup>1–4</sup> Despite the laboratory evidence that would support the use of TLV in the setting of both neonatal and adult respiratory failure, the clinical application of this technique has been hindered by several factors. These include the complexity of currently developed liquid ventilators, the flow limitation of liquids in the lung during expiration, and diffusion limitation of respiratory gases within those liquids.

Whereas expiratory flow during air breathing and gas ventilation is largely a passive event, the increased time constant for liquid filled lungs caused by higher fluid viscosity and lung

compliance do not allow their effective passive drainage. Early liquid breathing experiments demonstrated that spontaneously breathing animals face a dramatically increased work of ventilation during TLV, rapidly developing hypercarbia and acidosis.<sup>5,6</sup> Although the application of a downstream driving force (mechanical liquid ventilator) has improved minute ventilation and carbon dioxide clearance to acceptable levels in normal animal studies,<sup>7,8</sup> maximum expiratory flow during TLV is still limited, with CO<sub>2</sub> elimination further hindered by the slow diffusion of this molecule into perfluorocarbon (approximately 2,500 times slower than in air).<sup>9</sup> Dawson and Elliot, as well as Shapiro, have shown that the maximum flow of a fluid medium through an elastic tube is limited to the speed of propagation of pressure pulse waves along the tube, which is defined as

$$\dot{V}_c = \left( \frac{A^3 \times dB/dA}{q\rho} \right)^{1/2}$$

where  $A$  = cross sectional area of any point along the tube,  $dB/dA$  = stiffness of the tube at that point,  $\rho$  = density of the fluid medium, and  $q$  = a correctional constant for departure from blunt velocity profiles (1.33 for Poiseuille flow).<sup>10–13</sup> Because the densities of perfluorocarbons greatly exceed those of air, the wave speeds of these media in the respiratory tree are much lower, resulting in maximal expiratory flow rates that have been shown to be 20–100 times lower during assisted liquid expiration when compared with gas ventilation.<sup>14</sup>

During forced liquid expiration, a flow limited state occurs when the set flow of the downstream ventilator ( $\dot{V}_s$ ) equals the maximal flow possible based on the wave speed ( $U_c$ ) at the point in the airways where the product of cross sectional area ( $A$ ) and wall stiffness ( $dP/dA$ ) is a minimum. At this point, any further attempts to increase  $\dot{V}_e$  result in excessively negative intratracheal pressures [P(T)] and, presumably, airway collapse. To avoid this phenomenon,  $\dot{V}_s$  has traditionally been held at a constant low level during TLV, which in turn limits respiratory rate (3–9 breaths/min),<sup>1–4,7,14</sup> minute ventilation, and carbon dioxide clearance. However, because tube wave speed, and hence maximal flow, is directly coupled to the cross-sectional area ( $A$ ) at any point along the tube, it follows that flow limitation would occur at lower  $\dot{V}_e$  as expiration continues and less volume remains in the lungs. Experiments from our laboratory have demonstrated this phenomenon and suggest that  $\dot{V}_e$  could be better maximized by tapering  $\dot{V}_s$  from high to low flow rates as more volume is exhaled from the lungs.<sup>15,16</sup> Efficient dynamic flow adjustments would require a measurable signal of the impending flow limited state.

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Submitted for consideration March 2004; accepted for publication June 2004.

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DOI: 10.1097/01.MAT.0000139305.89565.4A

The occurrence of flow limitation during liquid expiration with a downstream driving force is characterized at the level of the trachea by an abrupt transition from gradually to rapidly declining P(T) and a reduction in  $\dot{V}_e$ .<sup>15,16</sup> This transition is, therefore, also marked by an abrupt change in the slope of the (P)T curve (dP/dT). The purpose of this study was to obtain a signal for the future servoregulation of expiratory flow during TLV by identifying the range of dynamic intratracheal pressures that occur at the transition point on the P(T) curve across various  $\dot{V}_e$  and end-inspiratory lung volumes (EILV).

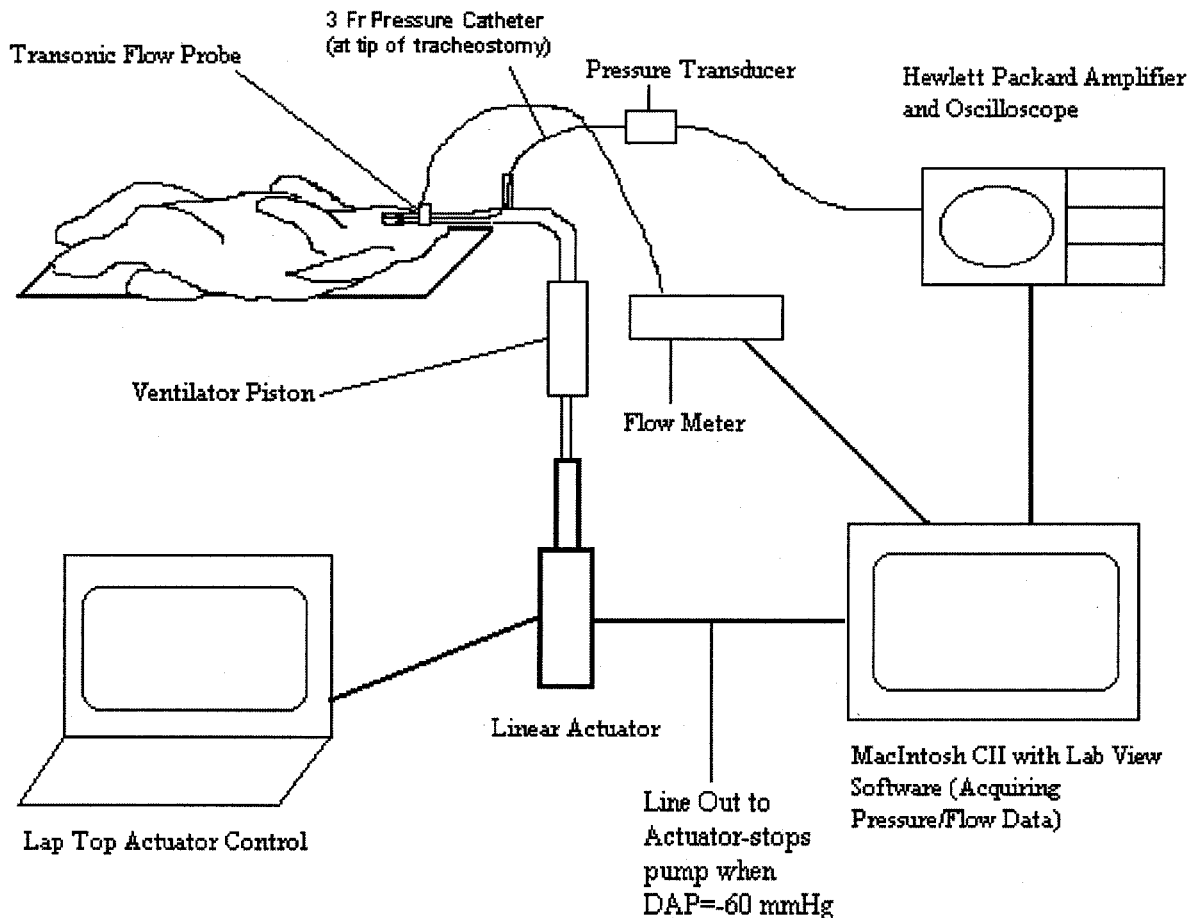
### Materials and Methods

New Zealand White rabbits (weight 2.8–3.2 kg) were anesthetized with 25 mg/kg intramuscular (IM) ketamine and 5 mg/kg IM xylazine and placed supine. Each animal underwent placement of a 24 gauge peripheral IV, subcutaneous local anesthesia with 1% xylocaine, and placement of a handmade, thin walled,  $\frac{3}{16}$  inch diameter steel tracheostomy tube midway between the thyroid cartilage and thoracic inlet. After the administration and circulation of 100 u/kg IV heparin, each animal was euthanized with 2–3cc IV Beuthanasia-D solution (Schering-Plough Animal Health, Kenilworth, NJ.). Previous studies from our laboratory have confirmed that there is minimal alteration in the choke point in the first 40 minutes after animal death.<sup>16</sup> In view of these data, the experimental proto-

col was completed within 30 minutes of euthanasia in all cases. It should also be noted that in an additional study no differences in choke flow were noted in rabbits over a wide range of  $\dot{V}_s$  1 hour before and 1 hour after kill.<sup>17</sup> After death, a volume of perflubron (LiquiVent, Alliance Pharmaceutical Corp., San Diego, CA.) approximately equal to functional residual capacity (FRC = 20 cc/kg) was instilled into the lungs of each rabbit through the tracheostomy tube while varying the position of the animal to achieve more homogenous distribution of the liquid. After postural manipulation to remove trapped air, the liquid filled tracheostomy tube (a liquid meniscus was visible) was clamped to prevent any further air entry into the lungs.

### Experimental Protocol

After initial filling, each animal was connected to a piston driven, linear actuator powered (Smart Motor, Animatics Corp., Santa Clara, CA) liquid ventilator (**Figure 1**). The piston was advanced to deliver 0, 10, or 20 cc/kg of additional perflubron (in addition to the original 20 cc/kg) to the lungs so that a randomly selected EILV of 20, 30, or 40 cc/kg was achieved. Nine animals for each of three EILV groups, for a total of 27 animals, were used. Baseline static end-inspiratory airway pressure was measured at the tip of the tracheostomy tube for all animals, using a perflubron-coupled 3 French



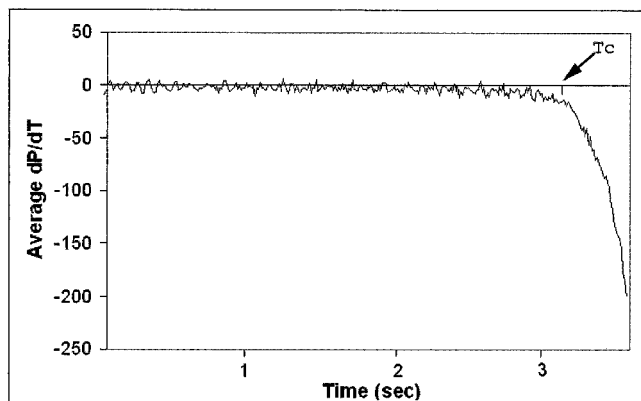
**Figure 1.** A schematic representation of the piston-configured liquid ventilator and data acquisition apparatus.

polyurethane catheter inserted through a side port on the ventilator tubing, and recorded using Lab View software (National Instruments Corp., Austin TX). The piston was then withdrawn to produce expiration at a randomly selected  $\dot{V}_s = 2.5, 5.0, \text{ or } 7.5 \text{ cc/sec}$ . In each animal, all three expiratory flow rates were used, and the process was repeated three times per flow rate for a total of nine expirations per animal. All nine flow rates per animal were randomized by blind card selection.  $P(T)$  was measured during expiration with the same pressure catheter used to obtain the static measurements and was recorded at 0.01 second intervals into Lab View. No correction for a Bernoulli or Pitot effect upon pressure measurements was applied, although we estimated the error caused by ignoring these phenomena at approximately 5% based upon estimates of the dynamic pressure. Flow was measured adjacent to the tracheostomy tube using a perflubron calibrated flow probe (HT 110 Bypass Flow Meter, Transonic Systems, Inc., Ithaca, NY) and was similarly recorded. The piston was servoregulated to stop at an intratracheal pressure of  $-60 \text{ mm Hg}$ , which was considerably more negative than  $P_c$  based upon our preliminary experiments, and was then repositioned to achieve the original EILV. Small amounts of air that may have entered into the system during the previous negative expiratory pressure condition were removed through a nondependent port on the ventilator tubing. Expiration was then repeated at each of the remaining flow rates. At the conclusion of the procedure the thorax was opened, and the lungs were examined for the presence of perfluorothorax.

#### Data Analysis

Baseline end-inspiratory pressures were averaged for each EILV, and between group comparisons were made using ANOVA with *posthoc* Tukey analysis.  $\dot{V}_e(T)$  was examined at each flow rate in each animal. Plateau flow rate, which was identified by the steady state of the flow meter; time at plateau flow, which was defined from the point of achieving maximal flow to the first point of diminishment from that flow; and  $\dot{V}_e$  at

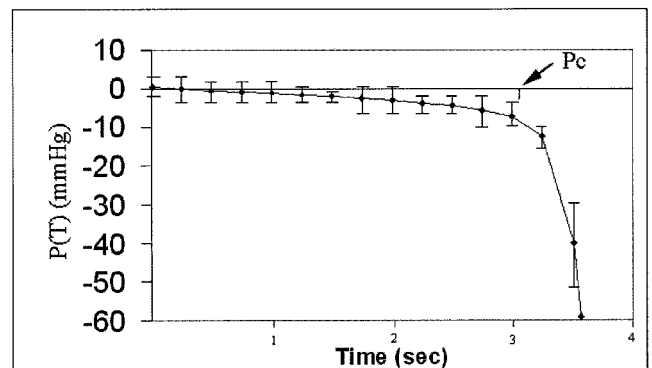
$$P(T = T_{-60}) = -60 \text{ mm Hg}$$



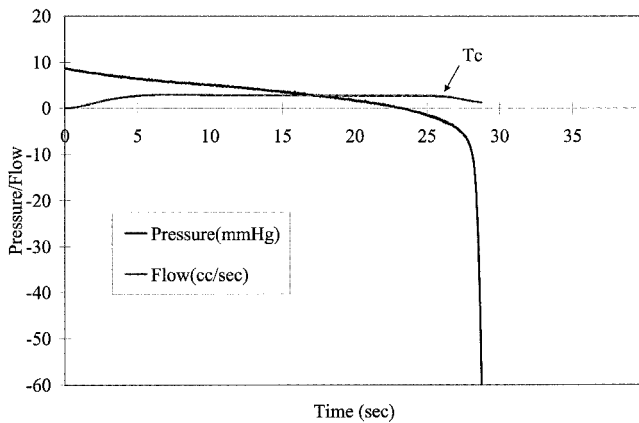
**Figure 2.** Example of an average  $dP/dT$  vs time curve (EILV =  $30 \text{ cc/kg}$ ;  $V_s = 5.0 \text{ cc/sec}$ ).  $T = T_{-200}$  was assigned for all data where  $dP/dT = -200 \text{ mmHg/sec}$  and labeled as  $t = 0$ . The critical time point ( $T_c$ ) is identified as the earliest time point where  $dP/dT$  was significantly different from  $\langle dP/dT \rangle_1$ .

were averaged for the animals within each EILV/ $\dot{V}_s$  group. The time required for each animal to achieve a flow limited state, defined at  $T_{-60}$ , was determined, and average values for each  $\dot{V}_s$  and EILV combination were calculated. Between group comparisons were again made using ANOVA with *posthoc* Tukey analysis.

The goal of these experiments was to identify the pressure at initiation of choked flow. We define the critical pressure as  $P_c = P(T = T_c)$  to be the pressure at which the flow became choked, which occurred at time  $T = T_c$ .  $T_c$  was unknown *a priori* and was determined as the time at which  $P = P_c$ .  $P_c$  was identified in the following manner: time derivative of pressure  $dP/dT$  values were calculated at 0.01 second intervals from the unfiltered  $P(T)$  data and plotted against time. Because the time to choked flow varied from one animal to another, it was more instructive to choose a time origin that was common to all experimental situations, which was based upon a common end-point. As such, a  $T = T_{-200}$  value was assigned for all data where  $dP/dT = -200 \text{ mm Hg/sec}$ , that is,  $dP/dT(T_{-200}) = -200 \text{ mm Hg/s}$ , as this value was achieved in all cases and consistently represented a portion of the  $dP/dT$  vs.  $T$  curve, which was well beyond  $T_c$ . The  $dP/dT$  data for each of the individual animals within each EILV/ $\dot{V}_s$  group were then averaged for each 0.01 second interval before  $T_{-200}$  to create an average  $dP/dT$  vs.  $T$  curve (Figure 2). Points between  $T = -3.0$  and  $-2.0$  seconds were averaged over that 1 second interval and defined as  $\langle dP/dT \rangle_1$ . Values of  $dP/dT$  for the remaining times were compared with  $\langle dP/dT \rangle_1$  by the method of least significance. This consisted of an iterative process in which ever decreasing time intervals were evaluated using *t* tests to identify the instantaneous  $dP/dT$  value that represented the earliest time that was significantly different from  $\langle dP/dT \rangle_1$ . This value of time was considered to be  $T_c$ . A Bonferroni correction was applied for each group to account for multiple comparisons. This analysis in effect determined critical pressure at which flow limitation occurred by determining the time (and pressure) at which the driving pressure increased rapidly (as indicated by a significant change in  $dP/dt$ ) indicating the onset of flow limitation.



**Figure 3.** An example of a  $P(T)$  curve (EILV =  $30 \text{ cc/kg}$ ,  $V_s = 5.0 \text{ cc/sec}$ ).  $P(T)$  values for the animals within each EILV/ $\dot{V}_s$  group were aligned at  $T = 0$  and averaged for each prior 0.01 second interval to obtain an average  $P(T)$  curve. The critical pressure ( $P_c$ ) is identified as the pressure associated with the earliest change in  $dP/dT$  from  $\langle dP/dT \rangle_1$  and indicates the beginning of the choke phenomenon. Standard error bars are shown every .25 seconds although data were averaged every 0.01 seconds.



**Figure 4.** Typical P(T) (black) and  $\dot{V}_e$ (T) (grey) expiratory curves, shown for a single animal (EILV = 30 cc/kg,  $\dot{V}_s = 2.5$  cc/sec). Note the initial transient development of  $\dot{V}_e$  increasing from 0 to  $\dot{V}_s$  (due to the startup of the pump) and the decrease in  $\dot{V}_e$  at  $T = T_c$  (due to the onset of flow limitation).

P(T) values for the animals within each EILV/ $\dot{V}_s$  group were aligned at  $T = T_{-200}$  and averaged for each prior 0.01 second interval to obtain an average P(T) curve (Figure 3). Then  $T = T_c$  was located on this curve and the corresponding pressure identified as  $p = P_c$ .  $P_c$  was obtained independently for each EILV/ $\dot{V}_s$  group. Between group analyses were performed using ANOVA with *posthoc* Tukey analysis. All studies were reviewed and approved by the University Committee on the Care and Use of Animals (UCUCA), and the National Institute of Health guidelines for animal use and care were followed throughout.

### Results

Nine animals comprised each EILV/ $\dot{V}_s$  group, for a total of 81 animals. An example of an individual P(T) and  $\dot{V}_e$  (T) profile is shown in Figure 4 for EILV = 30 cc/kg and  $\dot{V}_s = 2.5$  cc/sec.  $\dot{V}_s$  was confirmed in all cases by the measurement of plateau flow at the level of the distal ventilator tubing.  $\dot{V}_e$  was diminished in all  $\dot{V}_s$  groups at  $T_{-60}$  (Table 1). Baseline static end-inspiratory pressures are also demonstrated in Table 1 for each EILV and  $\dot{V}_s$ .

$P_c$  values varied over a fairly narrow range between  $-6.02$

$\pm 1.83$  mm Hg and  $-9.01 \pm 3.2$  mm Hg and are represented graphically in Figure 5. Between group comparisons demonstrated no significant differences in  $P_c$  as a function of  $\dot{V}_s$  at the same EILV. In contrast, EILV = 20 cc/kg had a statistically increased (less negative)  $P_c$  when compared with EILV = 30 cc/kg at  $\dot{V}_s = 2.5$  cc/sec ( $P_c$ : 30 cc/kg =  $-9.01 \pm 3.2$  mm Hg, 20 cc/kg =  $-6.02 \pm 1.83$  mm Hg;  $p = 0.03$ ) and EILV = 40 cc/kg at  $\dot{V}_s = 2.5$  ( $P_c$ : 40 cc/kg =  $-8.81 \pm 1.32$  mm Hg, 20 cc/kg =  $-6.02 \pm 1.83$  mm Hg;  $p = 0.003$ ) and 7.5 cc/sec ( $P_c$ : 40 cc/kg =  $-8.11 \pm 0.73$  mm Hg, 20cc/kg =  $-7.08 \pm 0.54$  mm Hg;  $p = 0.006$ ). Postmortem examination of the thoracic cavity revealed no evidence of perfluorocarbon leakage from the lungs.

### Discussion

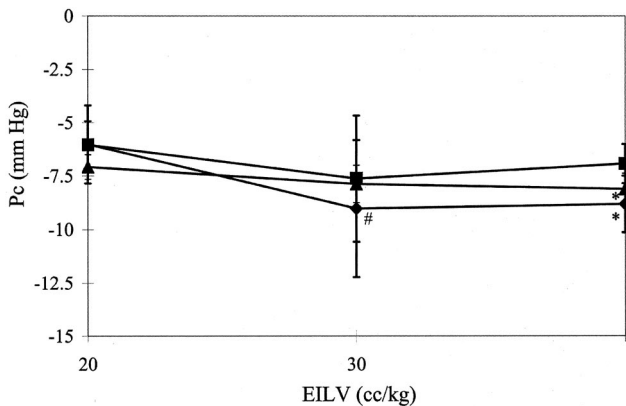
Previous experiments from our laboratory have demonstrated that P(T) decreases gradually during expiration of liquids at a constant  $\dot{V}_s$ .<sup>15,16</sup> After a reduction of lung volume under these conditions, the slope of the P(T) curve decreases abruptly indicating the onset of flow limitation. In this experiment, the decrease in P(T) that marks the flow limited state was defined by examining the corresponding  $dP/dT$  vs. time curves for a significant change from  $<dP/dT>_1$ . Using this approach,  $P_c$  values varied over a fairly narrow range despite variations in EILV and  $\dot{V}_s$ .

The results of this study suggest that tapering of expiratory flow in TLV has the potential to reduce expiratory time while avoiding flow limitation. The development of excessively negative airway pressures and choked flow has traditionally been avoided during mechanical liquid breathing through limitation of expiratory flow rates or by increasing FRC and thus EILV.<sup>1,2,7,8</sup> Whereas this combination of techniques is effective at reducing the effect of flow limitation upon performance of TLV, minute ventilation and carbon dioxide clearance are affected at the low respiratory rates dictated by these conditions or by the increased anatomic dead space associated with an increase in liquid FRC. In addition, cardiovascular compromise can occur during TLV at increased FRC as a result of the compressive effects of the perfluorocarbon filled lungs on the heart and pulmonary vasculature.<sup>18,19</sup> Expiratory flow profiles during TLV have typically been square waves, with liquid flow throughout expiration being maintained at levels below the end-expiration  $\dot{V}_c$  where airway cross-sectional area and stiff-

**Table 1. Measured End-Inspiratory Pressure,  $\dot{V}_e$ , Time at Plateau Flow, and  $\dot{V}_e$  ( $T = T_{-60}$ ) for Each EILV/ $\dot{V}_s$  Group**

EILV (cc/kg)/ $\dot{V}_s$ (cc/sec) group	End Inspiratory Pressure (mm Hg)	Measured plateau flow rate (cc/sec)	Time at plateau flow (sec)	$\dot{V}_e$ ( $T = T_{-60}$ ) (cc/sec)
20 cc/kg, 2.5 cc/sec	7.1 $\pm$ 0.7	2.55 $\pm$ 0.09	5.87 $\pm$ 2.45	1.51 $\pm$ 0.49**
20 cc/kg, 5.0 cc/sec	8.2 $\pm$ 0.6	5.13 $\pm$ 0.35	2.67 $\pm$ 0.51	3.98 $\pm$ 0.73*
20 cc/kg, 7.5 cc/sec	8.16 $\pm$ 0.5	7.53 $\pm$ 0.12	1.32 $\pm$ 0.28	6.53 $\pm$ 0.70*
30 cc/kg, 2.5 cc/sec	13.1 $\pm$ 2.2	2.55 $\pm$ 0.11	16.60 $\pm$ 6.38	1.51 $\pm$ 0.70*
30 cc/kg, 5.0 cc/sec	12.6 $\pm$ 1.3	5.09 $\pm$ 0.16	7.27 $\pm$ 1.37	3.38 $\pm$ 0.87**
30 cc/kg, 7.5 cc/sec	11.9 $\pm$ 1.2	7.52 $\pm$ 0.19	1.82 $\pm$ 0.38	6.32 $\pm$ 0.89*
40 cc/kg, 2.5 cc/sec	15.3 $\pm$ 2.1	2.58 $\pm$ 0.12	17.67 $\pm$ 5.49	1.36 $\pm$ 0.77**
40 cc/kg, 5.0 cc/sec	13.23 $\pm$ 1.3	5.18 $\pm$ 0.24	8.03 $\pm$ 1.56	4.46 $\pm$ 0.32**
40 cc/kg, 7.5 cc/sec	15.27 $\pm$ 1.8	7.51 $\pm$ 0.29	1.86 $\pm$ 0.34	4.93 $\pm$ 1.23*

Values are reported as mean  $\pm$  SD,  $n = 9$  for each group. Comparisons of plateau vs. measured flow at pressure  $-60$  mm Hg for each EILV/ $\dot{V}_e$  group are marked with \* for  $P < 0.01$  and \*\* for  $P < 0.001$  (two tailed  $t$ -test).



**Figure 5.**  $P_c$  vs EILV for  $\dot{V}_s = 2.5$  cc/sec (diamonds), 5.0 cc/sec (squares) and 7.5 cc/sec (triangles).  $n = 9$  for each group. \* $p < 0.01$  when comparing EILV = 40 ml/kg vs 20 ml/kg; # $p < 0.05$  when comparing EILV = 30 ml/kg vs 20 ml/kg.

ness are at their lowest values. The relationship between EILV,  $\dot{V}_e$ , and  $\dot{V}_c$  would suggest that  $\dot{V}_e$  could be enhanced by tapering  $\dot{V}_s$  as lung volumes are reduced during expiration.  $\dot{V}_s$  at the start of expiration would be elevated, taking advantage of the relatively large lung volumes and  $\dot{V}_c$  values. As expiration proceeds,  $\dot{V}_s$  would be tapered to correspond to a decreasing  $\dot{V}_c$ . The  $\dot{V}_s$  at the end of expiration would be similar to that currently used during square wave ventilation. However, by virtue of the higher  $\dot{V}_e$  applied earlier in expiration, an equivalent volume of fluid could be expired in less time with tapered rather than fixed flow. This might allow either an increase in respiratory rate and minute ventilation at the same FRC or an equivalent minute ventilation at a lower FRC with an accompanying decrease in anatomic dead space and cardiovascular effects. Alternatively, the time gained because of enhanced expiratory efficiency could be applied toward an inspiratory dwell period that would allow more time for  $\text{CO}_2$  transport as suggested by theoretical work that includes both convection and diffusion (V. Suresh and J.B. Grotberg, unpublished data, 2004).

During inspiration, the alveolar surface area available for  $\text{CO}_2$  transport from the alveolar blood is increased compared with other times in the breathing cycle. Thus both gas exchange and cardiovascular function may be enhanced during TLV.

Since the onset of flow limitation has been shown to be dependent upon both EILV and  $\dot{V}_e$ ,  $\dot{V}_s$  could be empirically tapered based upon the known EILV and the predicted development of flow limitation at expiratory lung volumes and flow rates. However, these parameters may vary based upon the pulmonary mechanics of each subject, making flow profiles too aggressive in some cases and too conservative in others. The most efficient application of tapered expiratory flow requires the identification of a continuously measurable parameter that is associated with the onset of expiratory flow limitation in the airways and signals the need for reduction in  $\dot{V}_s$ . This experiment has demonstrated that  $P_c$ , which marks the onset of flow limitation during expiration of perfluorocarbon, exists within a narrow range as EILV and  $\dot{V}_s$  are widely varied. Note that the effect of animal weight and other factors on  $P_c$

was not investigated here. As  $P_c$  is both measurable and consistent, it represents an attractive signal for regulating the tapering of expiratory flow during TLV. Critical airway pressure values ranged from  $-6.02 \pm 1.83$  mm Hg to  $-9.01 \pm 3.2$  mm Hg in this study. To safely avoid the flow limited state, the pressure signal for flow tapering might be just above (less negative than) this range. The rate of expiratory flow could then be controlled by a microprocessor directed pump based upon dynamic pressure data obtained from a catheter placed at the tip of the endotracheal tube. Alternatively, proper tapering of  $\dot{V}_s$  might be determined by performing "test breaths" at the beginning of and during TLV to determine a range of  $P_c$  values for each individual. These  $P_c$  values could then be used to identify the most appropriate pressure signal for tapering of  $\dot{V}_s$ , which could be adjusted as a more or less aggressive approach was desired.

Whereas the possibility of servoregulation is suggested by the results of this study, the practicality of this technique remains unproven. The efficiency of servoregulation on a single pressure that lies just above the onset of flow limitation depends upon the biologic response time of the airways to a reduction in flow rate. The time required for airway pressure equilibration will determine the reserve in dynamic airway pressure that is required to prevent the development of flow limitation despite flow rate reduction. Further studies are necessary to delineate the benefits and limitations of this concept.

We were concerned that postmortem changes might present a confounding variable for these studies. However, the complexities associated with evaluating a wide range of  $\dot{V}_s$  and EILV while maintaining gas exchange and physiologic stability required performance of these studies in freshly killed animals. We previously examined the potential for confounding effects of a killed animal upon the development of choked flow over 3 hours after animal killing.<sup>16</sup> The volume remaining in the lungs at the point of development of choked flow ( $V_{ch}$ ) remained fairly constant, especially within the first 40 minutes after animal killing. Other studies have demonstrated that  $V_{ch}$  remains unaffected by animal sacrifice: Meinhardt *et al.*<sup>17</sup> demonstrated that mean  $V_{exp}$  was unchanged for 1 hour before and 1 hour after sacrifice in rabbits at  $\dot{V}_s = 2$  to 20 ml/sec. By completing our experimental protocol within 30 minutes of death, we minimized any postmortem confounding effects.

As a consequence of the Bernoulli effect, end-tap airway pressure measurements may have been underestimated at higher set flow rates. Although the  $P_c$  values obtained from these measurements may also have been underestimated, our aim was to identify an easily measurable parameter by which to signal the tapering of  $\dot{V}_s$ . As end-tap measurements are easily obtained with currently available endotracheal tubes, this parameter would be easily transferred to the clinical setting. The fact that  $P_c$  values varied little, despite a threefold variation in flow rate, suggests that liquid expiration could be effectively tapered based upon a single, end-tap measured  $P_c$ .

$\dot{V}_s$  values were confirmed by measurement of flow through the ventilator tubing and appropriate plateau  $\dot{V}_s$  values were achieved in all cases. While the piston was programmed to discontinue flow at  $T_{-60}$ , flow, although diminished, continued at this time point likely secondary to continued flow past

the flow probe because of compliance in the system and the inertial effects of the draining perfluorocarbon.

### Conclusion

Expiratory flow during TLV is limited by the relatively low  $\dot{V}_C$  of perfluorocarbons in an elastic respiratory tree and results in the development of high negative intratracheal pressures and reduction in  $\dot{V}_e$  when  $\dot{V}_C$  is exceeded by  $\dot{V}_S$ . As demonstrated in this study, the onset of the flow limited state is marked by a narrow range of dynamic intratracheal airway pressures, which are independent of  $\dot{V}_e$  and EILV. This critical range of pressures may be used as a signal for the servoregulation of expiratory flow in an attempt to maximize the efficiency of expiration during total liquid ventilation. Further experiments are needed to match these pressures with the biologic response of the airways, to determine the *in vivo* benefits and limitations of this servoregulatory technique, and to relate these findings to other animal/injury models.

### Acknowledgment

This study was supported in part by NIH R01 HL64373.

### References

- Shaffer TH, Lowe CA, Bhutani VK, Douglas PR: Liquid ventilation: Effects on pulmonary function in distressed meconium-stained lambs. *Pediatr Res* 18: 47–52, 1984.
- Shaffer T, Douglas P, Lowe C, *et al*: The effects of liquid ventilation on cardiopulmonary function in preterm lambs. *Pediatr Res* 17: 303–306, 1983.
- Hirschl RB, Parent A, Tooley R, *et al*: Liquid ventilation improves pulmonary function, gas exchange, and lung injury in a model of respiratory failure. *Ann Surg* 221: 79–88, 1995.
- Hirschl RB, Tooley R, Parent A, Johnson K, Bartlett RH: Evaluation of gas exchange, pulmonary compliance, and lung injury during total and partial liquid ventilation in the acute respiratory distress syndrome. *Critical Care Medicine* 24: 1001–1008, 1996.
- Clark LC Jr, Gollan F: Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. *Science* 152: 1755–1756, 1966.
- Clark L: Introduction to federation proceedings. *Fed Proc* 29: 698, 1970.
- Moscowitz G, Shaffer T, Dubin S: Liquid breathing trials and animal studies with a demand regulated breathing system. *Med Instrum* 9: 28–33, 1973.
- Shaffer TH, Moskowitz G: Demand-controlled liquid ventilation of the lungs. *J Appl Physiol* 36: 208–213, 1974.
- Schoenfisch WH, Kylstra JA: Maximum expiratory flow and estimated CO<sub>2</sub> elimination in liquid-ventilated dogs' lungs. *J Appl Physiol* 35: 117–121, 1973.
- Dawson SV, Elliott EA: Use of the choke point in the prediction of flow limitation in elastic tubes. *Federation Proc* 39: 2765–2770, 1980.
- Dawson S, Elliott E: Test of the wave-speed theory of flow limitation in elastic tubes. *J Appl Physiol* 43: 516–522, 1977.
- Dawson SV, Elliott EA: Wave-speed limitation on expiratory flow: A unifying concept. *J Appl Physiol* 43: 498–515, 1977.
- Shapiro AH: Steady flow in collapsible tubes. *J Biomech Eng Trans ASME* 99: 126–147, 1977.
- Koen PA, Wolfson MR, Shaffer TH: Fluorocarbon ventilation: Maximal expiratory flows and CO<sub>2</sub> elimination. *Pediatr Res* 24: 291–296, 1988.
- Meinhardt J, Sawada S, Quintel M, *et al*: Comparison of static airway pressures during total liquid ventilation while applying different expiratory modes and time patterns. *ASAIO J* 50: 68–75, 2004.
- Baba Y, Brant D, Brah S, Grotberg J, Bartlett R, Hirschl R: Assessment of the development of choked flow during total liquid ventilation. *Crit Care Med* 32: 201–208, 2004.
- Meinhardt JP, Ashton BA, Annich GM, Hirschl RB: The dependency of expiratory airway closure on pump system and flow rate in total liquid ventilation rabbits. *Eur J Med Res* 8: 212–220, 2003.
- Lowe C, Tuma RF, Sivieri EM, Shaffer TH: Liquid ventilation: Cardiovascular adjustments with secondary hyperlactatemia and acidosis. *J Appl Physiol* 47: 1051–1057, 1979.
- Lowe C, Shaffer T: Pulmonary vascular resistance in the fluorocarbon-filled lung. *J Appl Physiol* 60: 154–159, 1986.