Proceeding of the 2004 American Control Conference
Boston, Massachusetts June 30 - July 2, 2004

Controlling Respiratory Mechanical Impedance; An Analysis of Proportional Assist Ventilation

Michael A. Borrello, Senior Systems Engineer, Trex Enterprises, San Diego, CA
stablesystems@ieee.org

1.0 Introduction

Just over a decade ago, a new type of breath delivery was introduced to critical care life support called proportional assist ventilation (PAV) [11]. Compared to conventional breath delivery, PAV offers a revolutionary approach since it allows the patient full control over volume delivery and shape of the flow waveform. Instead of targeting a pressure or volume like conventional methods, PAV targets a desired respiratory impedance as seen by the patient's respiratory muscles. Since its conception, PAV has appeared on the market in a couple of ventilators sold outside the U.S., but has not yet been widely used, probably because of it's operational complexity relative to conventional breath types. To date, PAV has not received regulatory approval in the U.S. Although there are many publications regarding PAV, most, if not all, are written by medical professionals and are directly focused on clinical aspects. A very recent publication [7] summarizes current progress of PAV, and provides an excellent list of references. Although much attention has been paid to the clinical aspects, the literature has not thoroughly examined PAV from a systems engineering perspective. This paper attempts to investigate fundamental concepts of PAV using linear system modeling, analysis and simulation. Although the models are simple, at this level they clearly reveal issues that may help explain some of the reasons why the practical application of PAV has been so difficult.

2.0 Lung–Ventilator Models

Previous work by the author et al. [1]-[4] and [6] treats modeling of the lung for the purpose of ventilator control systems design and analysis. The simplest model of respiratory admittance, based on an analogy of an electrical linear RC circuit is shown in figure 1.

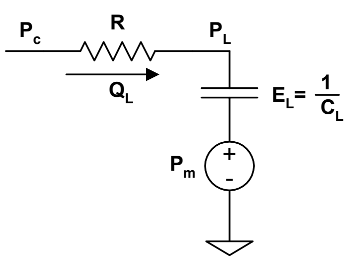

Figure 1 Linear 'RC' Model of the Unsupported Lung

For this analogy, pressures are voltages, flows are currents, flow resistance is electrical resistance, and compliance is capacitance. All pressures are assumed to be relative to atmospheric pressure. For either side of the analogy, Kirchoff's voltage laws apply. In the linear RC model P_c is the pressure at the airway inlet also referred to as circuit pressure, Q_L is the flow into the lung, R is the airway resistance, P_L is the pressure in the lung, E_L is the lung elastance (the reciprocal of lung compliance, C_L), and P_m is a variable pressure that models the effort applied by the respiratory muscles. To compare the effects that different support breath types have on how gas enters the lung, the RC model in figure 1 is applied and the linear dynamic respiratory admittance model as a function of the LaPlace operator *s* is (1).

$$Q_L = \frac{s}{Rs + E_L}\left(P_c - P_m\right) \tag{1}$$

To simplify notation, the operator *s* will not be included in specifying operationally dependent variables; i.e. $Q_L(s)$ shall be written as Q_L. P_m is a periodic, negative valued function so a positive Q_L is flow entering the lung. For P_c zero (atmospheric pressure), the unsupported lung admittance is (2)

$$\frac{Q_L}{P_m} = \frac{-s}{Rs + E_L} \tag{2}$$

For an unsupported, healthy lung, the admittance in (2) provides sufficient flow and volume for some sustained exertion by P_m. Figure 2 illustrates typical waveforms for P_m and Q_L in a normal healthy adult. In this example, the individual need only exert a peak 10 cm H_2O of pressure to inhale 0.5 liters of gas.

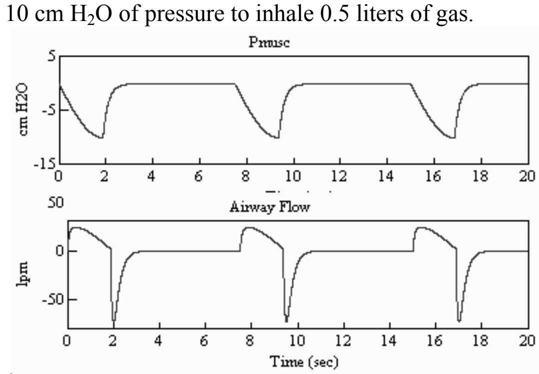

Figure 2 Unsupported Lung Waveforms

Disease or injury that can stiffen the lung increases E_L, and disease or injury that restricts airway flow increases R. Either or both impairments in lung mechanics decrease admittance so that P_m must increase to compensate for insufficient flow and volume. If the mechanical impairment becomes too great for too long, fatigue and failure of the respiratory muscles ensue. In this event the patient may have to be put on mechanical ventilation, which provides an external positive pressure ($P_c > 0$) to relieve the additional work imposed on P_m. The types of support considered in this paper are 'assisted', meaning that support is applied by the ventilator, but only after actively being initiated by the patient (using ventilator triggering methods).

With external support applied, dynamics of the patient circuit, conduits that connect the ventilator with the patient, need to be considered in the model. For adult and most pediatric patient circuits, where patient circuit resistance is low relative to the airway resistance, only the patient circuit elastance, E_T need be

0-7803-8335-4/04/$17.00 ©2004 AACC

considered. For infant patient circuits, which have a significantly smaller flow area, resistance may also need to be included. The linear RCC model, which includes only patient circuit elastance to model the patient circuit, is shown in figure 3.

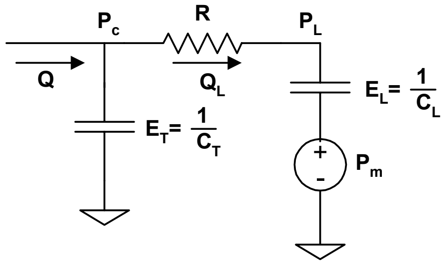

Figure 3 Linear 'RCC' Model of Patient Circuit and Lung

For the RCC model, Q may represent flow either entering or exiting the patient circuit on the ventilator side. The relation between Q and Q_L is (3)

$$\frac{Q_L}{Q} = \frac{\frac{E_T}{R}}{s + \frac{E_L + E_T}{R}} \tag{3}$$

Together, (2), (3) and some means to apply Q provide a model for the ventilator supported lung. Alternatively, (1) and a means for controlling P_c can also provide a ventilator supported model assuming stiff control of P_c that minimizes the influence of patient circuit dynamics.

3.0 Methods of Assisted Support

The RC model described in the last section will now be used to compare two of the most common breath types used in assisted ventilation with PAV. This comparison considers only the breath delivery (inspiration) phase of the breath. It is also assumed in each breath type that losses caused by the patient circuit have been fully compensated so that the RC model can be used directly to analyze the system admittance that relates Q_L and P_m. The bias pressure known as PEEP (Positive End Expiratory Pressure) is assumed zero since it does not (comparatively) affect dynamics.

3.1 Assist Control Ventilation

One of the simplest breath types used in conventional methods of assisted ventilation is Assist Control (AC). For AC the goal is to deliver a prescribed volume to the patient with a prescribed flow profile, F(s). In AC, other than initiation of the breath, flow and volume to the patient is entirely controlled by the ventilator. The commanded flow is therefore given as (4).

$$Q_L = F(s) \tag{4}$$

On most ventilators, the flow waveform, F(s) is selected as either a constant or descending ramp gated in time and sized in amplitude to meet volume requirements. For any F(s), the patient has neither control over the flow waveform shape nor the amount of volume inhaled. Figure 4 illustrates a typical application of AC using constant (square) flow waveform. In this example lung mechanics are compromised by excessive stiffness and resistance which requires over 50 cm H_2O peak pressure to deliver 0.5 liters into the lung.

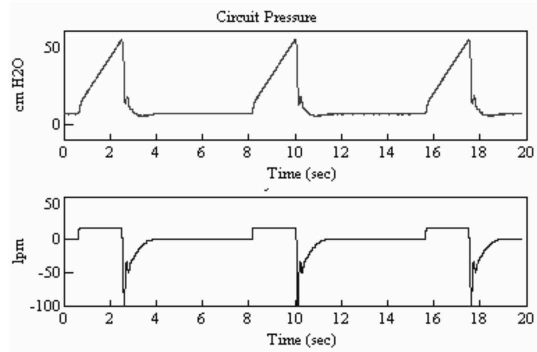

Figure 4 Typical Assist Control Waveforms

3.2 Pressure Support Ventilation

The other most common type of assisted breath is pressure support ventilation (PSV), which, unlike AC, does allow the patient some control over breath delivery. For PSV, the goal after initiation of the breath is to control the inlet airway pressure to a set 'plateau' level elevated above PEEP. Assuming that the ventilator provides instant rise and perfect control of pressure,

$$Pc = P_{PLATEAU} \tag{5}$$

Substituting (5) into (1), the admittance for a PSV supported lung is a function of the plateau pressure and patient effort and is represented by (6).

$$Q_L = \frac{s}{Rs + E_L} P_{PLATEAU} - \frac{s}{Rs + E_L} P_m \tag{6}$$

Assuming $P_{PLATEAU}$ is a step pressure, the first term of this equation introduces an initial burst of flow at the very start of the breath, independent of patient effort. This burst peaks at 1/R and decays exponentially to zero with a time constant R/E_L. The second term, identical to (2), allows the patient to control any further input of volume to the lung however with the original lung impedance, which if impaired either limits volume or requires the patient to work harder. Furthermore, if $P_{PLATEAU}$ is set too large, the first term may dominate the delivery of volume in excess of what the patient demands. Forcing excess volume or sudden flow can cause the patient to fight the ventilator, which can further lead to respiratory fatigue. Since PSV does provide the patient some ability to control inspired volume, it is a significant improvement over AC, but still does not address the underlying problem of impaired mechanics.

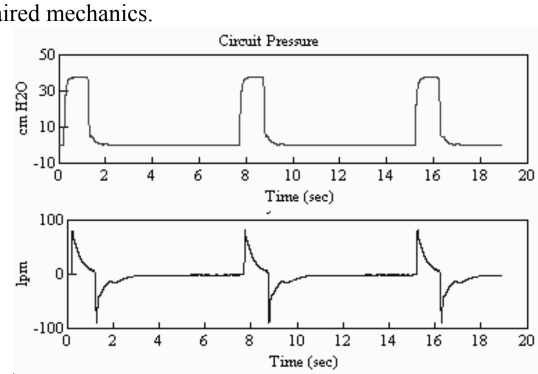

Figure 5 Typical Pressure Support Waveforms

Figure 5 above illustrates an example of the same patient from the example in figure 4, but with pressure support ventilation applied. In this example, the pressure support level was adjusted to deliver 0.5 liters to the lung. Note PSV requires less peak pressure than AC. Also the shape and size of the flow waveform differs substantially from the shape of the flow for the unsupported lung in figure 2 with obvious over-delivery at initiation of the breath.

3.3 Proportional Assist Ventilation

For PAV, support pressure is controlled as a function of the lung flow, filtered by a transfer function that matches the same structure as the RC lung model. Support pressure for the PAV controller consists of two components: one that is proportional to the patient's flow and one that is proportional to inhaled volume. The classical PAV controller is shown by (7).

$$P_C = \left(\frac{K_R s + K_E}{s}\right) Q_L \tag{7}$$

Here K_R and K_E are the resistive and elastic support factors respectively. A conceptual model that combines (7) and (1) and illustrates the PAV supported lung is shown in figure 6.

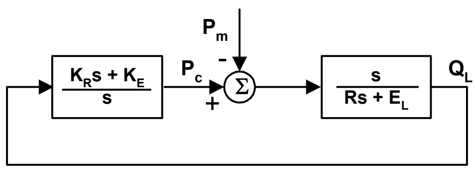

Figure 6 Conceptual Model of the PAV Supported Lung

The admittance for this system is given by (8)

$$\frac{Q_L}{P_m} = \frac{-s}{(R - K_R)s + E_L - K_E} \tag{8}$$

Note the PAV supported lung has the same structure as the unsupported lung, but with an effective impedance less than or equal to the unsupported lung impedance. The effective impedance is determined by the selection of K_R and K_E and is the actual load seen by P_m. By choosing appropriate values for K_R and K_E, impedance can be lowered and inspired volume increased for the same level of effort compared to the unsupported lung.

For nonzero K_R, K_E, and as long as $R > K_R$ and $E_L > K_E$, the PAV supported lung is stable, and impedance to move gas into the lung is decreased. Still further constraints need to be considered such that the targeted impedance remains within a reasonable range compared to 'normal' lung impedance. For a normal, healthy average size adult, R is 1.75 cm H_2O/l/s and E_L is 10 cm H_2O/l. With K_E and K_R adjusted such that the effective resistance and elastance are near zero but still positive, the system may be stable, but this state of almost complete unloading of the lung can cause flow rates and inhaled volumes to become dangerously high for the patient. For either $K_R > R$ or $K_E >$ E, the system is unstable. Unstable operation of PAV is often referred to in clinical literature as 'runaway'. An interesting result of the idealized system is that if *both* $K_R > R$ and $K_E > E_L$, the system is stable in the strict sense however it ceases to behave in a causal manner. This absurdity would result in gas exiting the lung as the respiratory muscles attempt to inhale.

It is important to note that the PAV controller is based on the RC (unsupported lung) model and that it requires lung flow as an input to determine the desired support pressure. The transfer function in (3) clearly shows that the lung flow, Q_L, and flow commanded by the ventilator, Q are dynamically different. This difference occurs by considering the patient circuit elastance, which describes more accurately a practical model for the supported lung. Figure 7 illustrates an example of the same patient used in the examples for AC and PSV supported by PAV.

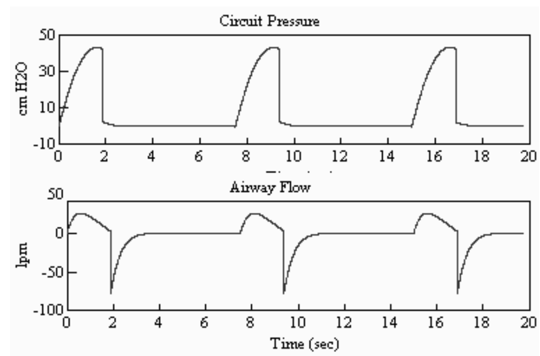

Figure 7 Typical PAV Waveforms

For this example, K_R and K_E were adjusted to allow the patient to draw 0.5 liters of gas using the same effort applied in the AC and PSV examples. For PAV, the peak pressure is about the same as in PSV however the flow waveform appears nearly identical to the waveform of the normal healthy adult in figure 2.

4.0 Practical Control of PAV

For the conceptual PAV system shown in figure 6, the controller measures lung flow and commands support pressure. For practical systems, flow, not pressure, is the actuating variable since valves or blowers are the mechanisms by which control is applied. Furthermore, as pointed out in the last section, lung flow, not ventilator applied flow is the input to the PAV controller. Therefore to properly implement classical PAV, as described by Younes [11], requires a pressure control loop to interface between the PAV controller and the flow actuating device or system and some means must be available to either measure or estimate lung flow. The pressure control loop is required to perform such that patient circuit pressure will track the pressure commanded by the PAV controller. The pressure controller, if not sufficiently responsive, can result in inaccuracy or worse lead to instability in the PAV supported system. Figure 8 shows how PAV, as described by Younes, is realized with a pressure tracking system.

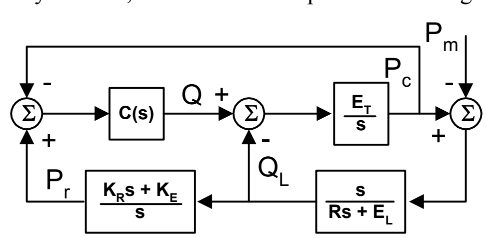

Figure 8 Classical PAV Control

The upper feedback loop of figure 8 clearly shows the pressure controller where C(s) is the loop compensator, designed such that P_c tracks P_r. From this figure, the closed loop admittance is determined as (9).

$$\frac{Q_L}{P_m} = \frac{-s(s+E_T C(s))}{Rs^2 + [E_T C(s)(R-K_R)+E_T+E_L]s + E_T C(s)(E_L-K_E)} \quad (9)$$

For C(s) large, the effects of E_T become small and the admittance in (9) approaches the admittance of the PAV supported lung (8). Before continuing to examine other system aspects that affect practical control of PAV, an interesting theoretical result is briefly noted. By considering an 'inverse' PAV controller expressed by a lung admittance model rather than impedance model, pressure becomes the measured variable and flow the controlled variable. The admittance-based controller would eliminate any need for a pressure tracking control loop since the controller output provides a direct flow command. Although this approach might seem inviting, it is impractical since the ventilator applied flow must be determined from Q_L , presumably by an accurate estimator based on (3) using estimates of R and E_L. The combined controller is improper, highly sensitive to noise, and places a lower bound on the bandwidth of flow actuation to at least achieve stability. Tighter bandwidth constraints are needed to achieve fidelity with respect to (8).

4.1 System Leaks

Although an effort is made to seal all connections between the ventilator and the patient, in practice leaks are inevitable. For AC, leaks will obviously have an affect on delivered volume accuracy. For PSV, leaks will cause a loss of gas, but if the leak is small or even moderate, plateau pressure can still be achieved. For either of these two common breath types in the presence of leaks, stability of the control is usually not an issue. For PAV however this may not be the case. The effects leaks have on the dynamics of a PAV supported lung can be analyzed assuming leaks as linear flow restrictions between system compartments and atmosphere, and that they exist in either of two places as illustrated by the model in figure 9.

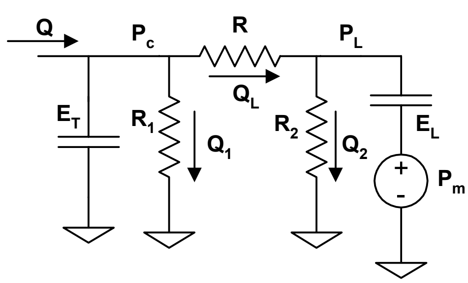

Figure 9 RCC Model Considering Leaks

Leaks that occur in the patient circuit are cumulatively lumped into the single leak flow, Q_1. These leaks typically occur from loose fittings in the patient circuit. Leaks that occur at or beyond the distal end of the ETT are cumulatively represented by Q_2. These leaks can occur from a lack of or leaky ETT cuff, chest tubes or an opening in the airway or lung caused by injury. For the analysis that follows, the model in figure 9 is used together with (7) and it is assumed that estimated lung flow is the flow, Q_L that crosses the airway resistance.

With Q_L assumed to be accurately measured or estimated, any leaks at R_1 can be dismissed if it is further assumed that the pressure controller accurately tracks the command and provides good disturbance rejection. Leaks that occur at R_2 however influence the dynamics more adversely. By using the model in figure 9 with P_c determined by (7), and assuming zero leak at R_1, the admittance for the PAV supported lung with leaks is expressed as (10).

$$\frac{Q_L}{P_m} = \frac{-s^2}{(R-K_R)s^2 + \left(\frac{E_L(R-K_R)}{R_2} + E_L - K_E\right)s - \frac{K_E E_L}{R_2}} \quad (10)$$

Since R > K_R and $E_L > K_E$, leaks of any size at R_2 result in an unstable system. The rate of this instability is determined by the leak size. If R_2 is large enough, the rate could certainly have negligible affect during the course of a single breath period. A smaller size of R_2 however raises more significant concern.

4.2 Estimation of Parameters

Unlike AC and PSV, the successful operation of PAV depends on an impedance model that closely matches true impedance and accurate estimation of model parameters. The original concept of PAV introduced by Younes [11] assumes the simple RC model of the lung (1). Since the lung is actually much more complex than the RC model, the first question is: how close can a linear RC model approximate this complex system of branching airways and compartments? Secondly, what affect do modeling errors have on the stability and accuracy of the closed loop PAV control? Neither of these questions are easy to answer, and are beyond the scope of this paper. Rather than attempt a detailed analysis, the two approaches considered to date for parameter estimation and based on the RC model are briefly discussed. These two methods of estimating and setting PAV controller parameters will be referred to as either automatic or manual.

For the manual method, a clinician determines, a priori, what the patient's respiratory mechanics are using standard clinical methods. Once mechanics are estimated, the clinician sets the K_R and K_E "gains" on the ventilator to target desired virtual impedance. The automatic method involves some automatic means provided by the ventilator to estimate respiratory mechanics and set the parameters in the PAV controller. Each method has advantages and disadvantages. With a clinician in the loop, expert knowledge may be able to provide a safer application however since respiratory mechanics can suddenly and often change, the clinician may be called upon too often for practical application. Results from clinical studies of PAV using manual methods strongly suggest that determining parameters for PAV be completely automatic and noninvasive [5], [8].

One of the major problems with the automatic method is that P_m has a disturbing affect on accurate estimates of E_L and R. One approach that has been suggested using the automatic method is to periodically force a mandatory breath when P_m is relatively inactive. This approach either requires patient participation or complicated algorithms that detect windows of opportunity within the breath cycle. For high airway resistance the time constant, RC_L ,becomes large requiring measurement intervals that greatly exceed any window in the breath cycle P_m could permit except maybe during an extended exhalation. So it is questionable whether this approach would be practical for all cases.

An open area of research considers using alternative PAV controllers in place of the RC model. These include higher order linear controllers, nonlinear components, and may provide a means to cancel the influence of the disturbance, P_m . Additional benefits these models might have to offer include improvement of the Q_L estimate, improved stability by better model matching, and as a possible side benefit, improved diagnostics.

5.0 Other Approaches to PAV Control

The obvious approach in controlling PAV supported breaths is to provide a pressure tracking loop, and by (9) it was clear that the more accurate and responsive pressure tracking controls are, the closer one approaches the ideal PAV supported lung of (8). For pressure-based ventilation, the PI or PID controller has been the traditional approach mainly because of simplicity and limited processor resources. Although classical, fixed gain controllers might be able to control PSV within some safe, acceptable performance bounds, they do not necessarily provide accurate tracking, and in some cases do not even provide close tracking. Now that high performance processors are affordable, there should be no technical constraints in considering more advanced methods of control to achieve the higher tracking accuracy PAV requires. The following sections describe two such methods.

5.1 Adaptive Pressure Tracking

In [1] the author describes an indirect adaptive controller for pressure based ventilation. Since PAV is categorized as pressure based ventilation, this method of adaptive control could certainly be applied to PAV. The adaptive control of pressure uses a partial inverse controller based on the RCC model in figure 3. The parameters for this controller are continuously adjusted using recursive least squares estimates of R, E_L and E_T. At first it would seem this indirect approach of adaptive control would be ideal for PAV since E_L and R are readily available from the parameter estimation. Although the adaptive controller provides a very small tracking error between P_r and P_c in the presence of P_m , P_m unfortunately leads to inaccurate estimates of R and E_L. Therefore the parameter estimation in the adaptive controller should not be used to determine gains for the PAV controller. Instead estimates of mechanics should be obtained by other independent means that are unbiased and provide a tolerance to the disturbance P_m.

5.2 FRCPAP based PAV

Another approach that has actually been applied in clinical studies of PAV is the flow regulated continuous positive airway pressure (FRCPAP) based system, as described in [4]. This method, as an alternative to conventional CPAP methods, was first proposed by Sakanaka et al. [9] and later applied as the basis to a prototype PAV ventilator called 'Harmony' [10]. A block diagram representing the linearized FRCPAP system to control PAV is shown in figure 10.

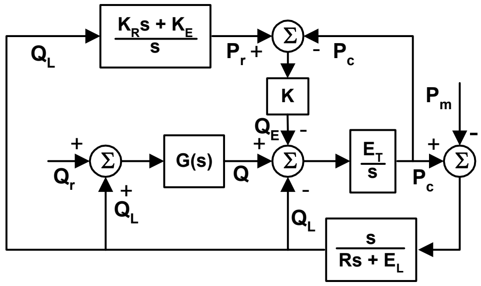

Figure 10 PAV using FRCPAP based controls

For this approach, the measured or estimated Q_L is used to close a positive feedback flow demand loop with Q_r , a constant bias flow. The demand loop is stable, provided a vented flow ($Q_E \cong Q_r$) through the exhalation valve exists. To apply FRCPAP to PAV, the support pressure command from the PAV controller modulates circuit pressure using the exhalation valve rather than using the flow delivery system, G(s). For G(s) unity and K large, the FRCPAP controlled PAV system also reduces to the admittance equation in (8). The main advantage offered by FRCPAP is that the flow source output impedance is reduced, providing a more sensitive response to patient flow demand. With patient demand solely managed by the flow loop, the pressure loop is only left with the task of tracking support pressure. Another distinct advantage using FRCPAP is that PAV, which is normally operated only during inspiration, can be seamlessly extended into exhalation as well since the exhalation valve is used to control pressure in both phases of the breath. The main problem in the FRCPAP approach is achieving stable and accurate control of pressure using the exhalation valve, which has long been proven to be a very challenging problem.

Although the FRCPAP approach to PAV control is based on the same impedance model used by Younes [10], the FRCPAP based system can be considered as an entirely different approach to PAV since it manages patient flow demand with one control loop (as a pressure control disturbance) and provides separate pressure tracking with another control loop.

[10] reported results on the Harmony ventilator from 42 patients and healthy adults at Aichi Medical University Hospital in Japan. These results indicate that the patients received sufficient ventilation in terms of their volume needs however that runaway (instability) and leaks were observed. The Harmony ventilator used the manual method to set the PAV controller gains, and so runaway might be expected. A mechanism that monitored delivered volume and stopped the breath at a set limit was used in Harmony to safeguard the patient in the event of runaway.

6.0 Automatic Tube Compensation

Automatic Tube Compensation (ATC) is an assisted breath type based on the concept of PAV but only affecting resistance to flow imposed by the endotracheal tube (ETT). Unlike PAV, ATC does not attempt to compensate for airway resistance other than the ETT nor does it compensate for stiffness of the lung. Presently, ATC requires the clinician to manually enter the diameter and length of the ETT into the ventilator before patient application. ATC was only introduced in the last few years and is offered in at least two ventilators marketed in the US. A recent bench study [12] compares the work of breathing of ATC with PSV

7.0 Conclusions

The comparison of AC and PSV with PAV using conceptual linear system models show that PAV provides a distinct approach to ventilation by (1) allowing the patient to entirely control the breath, (2) preserving the natural structure of the unsupported lung admittance, and (3) controlling effective impedance to target healthy mechanics from the perspective of P_m. Further investigation of the PAV supported lung identified particular issues encountered in the practical application of PAV and their affect on stability and accuracy. These issues include patient circuit dynamics, leaks, and methods of parameter estimation.

Although the issues mentioned above all need to be addressed in practical application, the single factor affecting progress in the development of PAV on the manufacturer's part is the lack of an adequate understanding of the underlying dynamics in both ventilator and patient. This has led to ineffective control systems that either provide poor performance or limit the range of use. One ventilator manufacturer states that use with an ETT less than 4.5 mm in ATC is not recommended because of potential instability. This limitation is presumably due to difficulties either in estimating lung flow or accurately tracking pressure with the smaller ETT diameters where nonlinearity is more pronounced. ETT diameters below 4.5 mm are where one would assume ATC may be most needed.

With regards to the three features outlined above it might seem that PAV has an advantage over conventional breath types. Such a conclusion certainly requires more rigorous support than the analyses provided here. Regardless of modeling fidelity, analyses alone can never serve as a means to argue improved patient outcome by any medical or scientific standards. Such conclusions can only be determined by controlled clinical studies that directly measure and compare patient outcome. Speculation by some is that PAV will have no measurable improvement over conventional methods based on results of earlier studies that compared PSV and AC. These studies were unable to clearly demonstrate significant difference in outcome. Still others argue, based on personal clinical experience using PAV that it provides far more comfort for the patient and reduces the chance of undesired patient-ventilator reactions. Although subjective, these arguments and the belief that patient relaxation and comfort promotes healing are what have promoted continued interest in PAV.

Clinical leaders experienced in using PAV often comment on the great potential PAV has to offer, but for the average practitioner, PAV is just too complicated. In the summary of [7], Mancebo states "Experts and manufacturers now have to make a last effort to render practical and simple this extremely useful (but still too complex) ventilatory tool".

From this engineer's perspective, although the concept of PAV is simple, the practical application must consider essential details neglected in the basic concept, which makes implementation difficult. Engineering these details requires considerable investment from the manufacturer. The rising expense of healthcare and demands from regulatory bodies for tighter controls in design and manufacturing has put intense pressure on medical equipment manufacturers often resulting in reduced R&D spending. Considering such pressures and the tumult of clinical and technical issues PAV presently faces, advancement, unfortunately, may not be possible in the near term.

The author wishes to express sincere gratitude and thanks to Kiyohiko Sakanaka for his assistance in reviewing this paper, and the contributions he and the doctors at Aichi Ika Daigaku have made towards the advancement and understanding of PAV.

References

[1] Borrello M.A., "Adaptive inverse model control of pressure based ventilation", Proceedings of the American Control Conference, Arlington, VA, (2001) pp.1286-1291.

[2] Borrello MA, "Biomedical Systems: Modeling and Simulation of Lung Mechanics and Ventilator Controls Design" (1997) http://www.vissim.com/APPS/tutorials.html#tutform

[3] Borrello MA, "Modeling and simulation of pressure regulated control systems for ventilation of the lung", 13th Annual International Conference IEEE EMBS, Vol 13, No. 5, (1991) pp. 2178-2179.

[4] Borrello MA," Stabilized positive feedback reduces ventilator imposed work of breathing for critical care patients", Proceedings of the American Control Conference, Anchorage, AK, (2002) pp. 4050-4055.

[5] Grasso S., Ranieri V.M., "Proportional Assist ventilation", Respir Care Clin N. Am., 7(3) (2001) pp. 465-473

[6] Guillaume D.W., Borrello M.A, "Simulating gas flow through the exhalation leg of a respirator's patient circuit", Journal of Biomedical Engineering, 13, (1991) pp. 77-82.

[7] Mancebo J., Net A., Brochard L., Eds. Mechanical Ventilation and Weaning (Update in Intensive Care medicine) Springer Verlag, (2003) pp. 193-198.

[8] Ranieri V.M., Grasso S., Mascia L., Martino S., Fiore T., Brienza A., Giuliani R., "Effects of proportional assist ventilation on inspiratory muscle effort in patients with chronic obstructive pulmonary disease and acute respiratory failure", Anesthesiology , 86(1), Jan (1997) pp. 79-91.

[9] Sakanaka K., Akashi M., Horiba K., Noguchi H., Takumi Y., " A ventilator to create a ventilatory pattern which harmonizes with the patient " Computing and monitoring in anesthesia and intensive care-recent technological advances, Springer Verlag , Tokyo (1992).

[10] Sakanaka K., Akashi M., Noguchi H., "Study of the Effectiveness of an Impedance Assistance Type Ventilation Method Developed at Aichi Medical University" Proceedings of Japan Society of Respiratory Care Medicine, Akita, Japan July 1-2, (1994), [Translated from Japanese].

[11] Younes M. "Proportional Assist Ventilation, a new approach to ventilatory support: Theory", Am Rev Respir Dis 145 (1992), pp. 114-120.

[12] Yuji Fujino MD, Akinori Uchiyama MD, Takashi Mashimo MD, and Masaji Nishimura MD, "Spontaneously Breathing Lung Model Comparison of Work of Breathing Between Automatic Tube Compensation and Pressure Support" Resp Care, 48:1, (2003), pp. 38-45.