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History and principles of closed-loop control applied to mechanical ventilation

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Summary. Patients in respiratory distress may be put on machines (ventilators) that fully or partly breathe for them. Adjusting such ventilators to the patient‘s needs is done by the physician, the respiratory therapist, or the nurse, depending on the hospital, country, culture, or reimbursement structure. Alternatively, it is theoretically possible to design ventilators that adjust themselves based on data obtained from the patient (closed-loop control). This review covers such automatic control mechanisms. While historically much effort was devoted to expired-CO_2 (end-tidal CO_2, $ETCO_2$) control mechanisms, no such machine is available today due to practical medical technical problems and fundamental physiologic limitations when using $ETCO_2$. However, other methods of closed loop control have found their way into clinical practice. Two examples are highlighted: Adaptive Support Ventilation (ASV) and Proportional Assist Ventilation (PAV). The review concludes with a conceptual frame that may be helpful in understanding the different methods of closed-loop controlled ventilation.

Introduction

Mechanical ventilators are high-tech life support devices. They fully replace or partially support the respiratory function of patients in three distinctly different yet sometimes overlapping areas [1]:

a) Ventilation: i.e., elimination of CO_2, achievement of a desired arterial pH level
b) Pump support: support of the respiratory muscles, short- or long-term
c) Oxygenation: oxygenation of arterial blood

No matter what the modes on a particular ventilator are called, they all have the goal of maintaining a preset alveolar ventilation, unloading the respiratory muscles to a certain degree, preventing end-expiratory alveolar collapse (by use of positive end-expiratory pressure, PEEP), providing a respiratory gas of preset oxygen content, or doing any combination of the above. The pertinent parameters like tidal volume (V_T), rate (f), inspiratory time, etc. must be set manually and such adjustment may be rather complex. A recent consensus conference on mechanical ventilation concluded that there is no recipe for adjusting the complex parameters of a ventilator [1]. In light of such a depressing conclusion one wonders how ventilator adjustment can be automated.

However, a few facts are well known and even trivial. One fact is that alveolar ventilation affects the partial pressure of arterial CO_2 ($PaCO_2$). When the first researchers thought about automation of ventilation, “alveolar ventilation” was an obvious choice as a parameter to control $PaCO_2$ (or arterial pH). And since arterial CO_2 is not readily or continuously available, its surrogate, end-tidal CO_2 ($ETCO_2$), was used first [2,3]. The control structures were simple, and only tidal volume or rate was adjusted to vary alveolar ventilation in order to achieve a preset $ETCO_2$ value. Since $ETCO_2$ control was extensively studied in the past, it is used in figure 1 to illustrate one method of closed loop control: negative feedback, breath-by-breath control. While breath-by-breath negative feedback control was widely used and became almost the synonym for closed-loop control, it is not the only possible method of automation.

Methods of closed-loop control

Apart from “negative feedback control” methods, there is also a “positive feedback control”. Besides breath-to-breath control (rather slow, inter-breath control) there is also intra-breath control (within breath, rather fast control). A negative feedback control circuit aims to reduce the difference between the target and the measured value to essentially zero, as illustrated in figure 1. For this purpose, the actual value is subtracted from the target value.

A positive feedback control circuit aims to create a difference between the target and the measured value. For this purpose, the actual value is added to the nominal target value. The ventilator control (for example the pressure) is manipulated to achieve the desired difference. Positive feedback control systems thus act as “amplifiers“ of the patient. They amplify the target depending on how the patient behaves. A good example is Proportional Assist Ventilation PAV [4]. PAV adjusts the instantaneous inspiratory pressure level (intra-breath control) based on instantaneous flow and volume entering the patient. Figure 2 shows the schematic diagram.

Negative feedback controlled systems do have clear advantages. One is that the output of a process can be controlled *very precisely*. In control theory terminology, the steady state error can be made zero. This means, for example, that the target can be achieved, within limits, even if the respiratory system mechanics change. A second advantage is that the transient response of a process can be dramatically improved, i.e., it can be accelerated. A third advantage is that external disturbances like physiotherapy, pain stimuli, and others are automatically compensated. A potential disadvantage is that control may be “rigid”, i.e. the preset value will be achieved at any cost.

Positive feedback control is inherently unstable. In the example of Figure 2, PAV augments patient activity as well as artifacts, since the method cannot distinguish between true patient activity and signal noise. PAV rests on the assumption that the patient’s respiratory activity is stable in nature. If the patient stops breathing or behaves unexpectedly in other ways, the positive feedback approach fails [5]. Furthermore, positive feedback modes like PAV potentially add complexity to the ventilator. Particularly, the patient-ventilator system may become unstable. For these reasons, special safety measures are needed for clinical application. If used under tight operator control, however, positive feedback control can be a very useful auxiliary muscle.

Inter-breath control refers to adjusting a given control parameter from breath to breath but keeping the parameter constant

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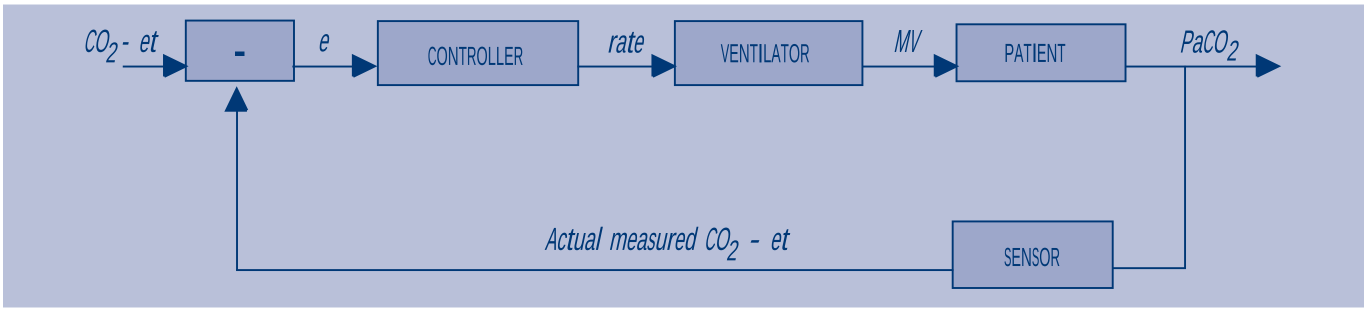

Figure 1. Basic diagram of end-tidal CO_2 (CO_2-et) closed-loop controller, feedback controller, or servo controller. A target value (CO_2-et) is compared with (added to or subtracted from] the controlled variable (actual measured end-tidal CO_2), and an error signal e is passed to the CONTROLLER. The CONTROLLER regulates the output variable or command signal (rate) to the VENTILATOR in order to change the total minute ventilation (MV). The resulting change in alveolar ventilation subsequently changes $PaCO_2$ and thus end-tidal CO_2, which is fed back and compared again to the target. As soon as the desired value of end-tidal CO_2 is achieved, the error becomes zero and the rate remains unchanged.

throughout a given breath. Such controllers need to adjust parameters within seconds since breaths can also be controlled within seconds. Intra-breath control refers to adjusting a given parameter within a given breath. Intra-breath control needs to be extremely fast, i.e. the parameters need to be adjusted within milliseconds.

Historical development of closed-loop ventilation

Published work on the subject can be analyzed based on the three main tasks of mechanical respiratory support: Ventilation, oxygenation, and pump support (see introductory chapter). table 1 provides an overview of selected papers.

Ventilation

The first report on a closed-loop controlled ventilator was published in 1953 [2]; it describes “an electro-mechanical substitute for the human respiratory center.“ The data was not published. The control method was based on $ETCO_2$ and regulation of the inspiratory pressure. The same idea was later put into practice by Frumin [3,26] who developed the famous “Autoanestheton,“ an anesthesia machine with integrated ventilation feedback-control. $ETCO_2$ was measured, compared to a target value, and the inspiratory pressure was subsequently adjusted to meet the set $ETCO_2$ target.

Many authors invented closed-loop controllers in the years after Frumin‘s landmark study. Most of them used $ETCO_2$ and, with the advent of the first intravascular sensors, either pHa or $PaCO_2$ in the feedback loop. The controller output was pressure, tidal volume, or respiratory rate. A Japanese group [6,9] was the first to adjust two variables at the same time (V_T and f) to control CO_2. They were also the first to introduce Work Of Breathing (WOB) as a parameter to select the breathing pattern. Finally, East *et al*. controlled not only ventilation (CO_2) but also end-expiratory lung expansion by means of PEEP adjustment [15].

Many authors used $ETCO_2$ as a substitute for arterial PCO_2. However, $ETCO_2$ might deviate significantly from expected values. The degree to which it deviates depends on lung disease and even heart disease [3,27]. For example, alveolar dead space and arteriovenous shunting increase the difference between end-tidal and arterial PCO_2 [28]. It may even be dangerous to use $ETCO_2$, since a lung embolus might cause ventilation to stop altogether in an automatically controlled ventilator, as was concluded from animal experiments [13].

One shortcoming of the techniques described above was that the initial breath pattern had to be preset by the clinician. This handicap clearly limited the practical use of the controllers. Laubscher *et al*. were the first to address this problem [22,29] . They published an algorithm that needs no input from the operator and automatically selects a breath pattern adequate for an initial period of ventilation.

Respiratory Pump Support

Another shortcoming of the control algorithms described above is that the mechanism worked only when spontaneous breathing was absent. A French group was the first to take spontaneous activity into account by switching between Controlled Mechanical Ventilation and Pressure Support Ventilation based on $ETCO_2$ [17]. Laubscher *et al*. carried the idea further and made the transition from passive to active ventilation an integral part of their Adaptive Lung Ventilation (ALV) and its first commercial implementation Adaptive Support Ventilation (ASV) [23, 30, 31]. Both approaches make “negative-feedback“ the core of the control, i.e., if the patient breaths more, the ventilator provides less support.

“Positive-feedback” has been introduced more recently and is called Proportional Assist Ventilation PAV [4]. With positive-feedback, the ventilator provides increasing pressure support as the patient’s respiratory activity increases. The ventilator thus acts as an “auxiliary respiratory muscle“ and works similarly to power steering in an automobile. In other words, the ventilator amplifies the breathing activity of a patient.

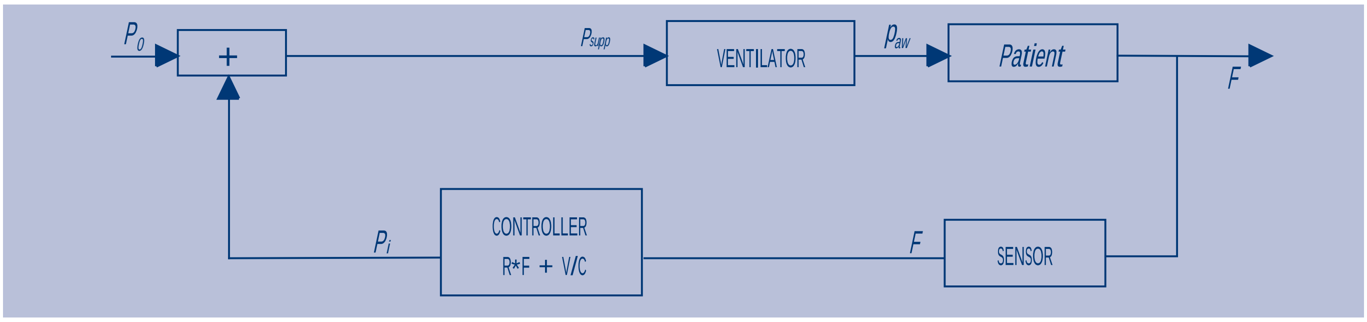

Figure 2: Principle diagram of Proportional Assist ventilation PAV. A SENSOR measures instantaneous flow F (and volume V as function of time, i.e., several hundred times per second). A CONTROLLER in the feedback loop calculates the pressure Pi that needs to be added to the baseline pressure P_0. The sum of the two is forwarded to the VENTILATOR (Psupp), which applies the instantaneous pressure to the patient’s airways. This pressure results in a new flow F, which is again fed back for a new adjustment of Psupp.

Table 1. Selected papers on closed-loop controlled ventilation.

Author Year [ref]	Target variable	Controller output	Remarks	vent	oxy	rp
Saxton 1953 [2]	End-tidal CO2	Pinsp	No patients	+	-	-
Frumin 1957 [3]	End-tidal CO2	Pinsp	64 patients	+	-	-
Mitamura 1971 [6]	Mixed exhaled CO2	VT, f	Takes dead space and WOB into account	+	-	-
Coles 1973 [7]	End-tidal CO2	VT	One sheep	+	-	-
Schulz 1974 [8]	Arterial pCO2	V'I (VT)	Uses indwelling catheter	+	-	-
Mitamura 1975 [9]	Mixed exhaled CO2 and SpO2	VT, f FiO2	Takes dead space and WOB into account	+	+	-
Hewlett 1977 [10]	Minute ventilation	fSIMV	MMV	+	-	+
Coon 1978 [11]	Arterial pH	VT	30 dogs	+	-	-
East 1982 [12]	Arterial PCO2	f	Differential lung ventilation	+	-	-
Ohlson 1982 [13]	End-tidal CO2	VT	Points out the pitfalls of using end-tidal CO2	+	-	-
Chapman 1985 [14]	End-tidal CO2	Minute ventilation	Uses a fixed normogram to select partitioning of MV into VT and f	+	-	-
East 1986 [15]	End-tidal CO2 FRC	f PEEP	Study of 6 animals	+	+	-
Yu 1987 [16]	SpO2	FiO2	Study of 8 dogs	-	+	-
Chopin 1989 [17]	End-tidal CO2	Mode (SIMV or SPONT)	On-Off controller	+	-	+
East 1991 [18]	Arterial pO2	PEEP FiO2	Uses a computerized protocol derived from ECMO studies	-	+	-
Rudowski 1991 [19]	End-tidal CO2	VT f	Uses a barotrauma index to optimize the choice of VT and f	+	-	-
Strickland 1991 [20]	f Min Vol exhaled SpO2	fSIMV PSV level	Applied during weaning phase	+	+	+
Dojat 1992 [21]	"Zone of comfort"	PSV level	"Zone of comfort" defined by f, VT, end-tidal CO2	+	-	+
Laubscher 1994 [22]	None	Pinsp fSIMV Te	Automatic start-up algorithm; no operator input needed	+	-	+
Laubscher 1994 [23]	Alveolar ventilation	Pinsp fSIMV Te	Works in paralyzed and spontaneously breathing subjects	+	-	+
Waisel 1995 [24]	SpO2	FiO2 PEEP	-	-	+	-
Iotti 1996 [25]	P0.1 alveolar volume	PSV level	-	-	-	+

"vent": focus on removal of CO2; "oxy": focus on oxygenation of arterial blood; "rp": focus on respiratory pump support. ECMO: extracorporal membrane oxygenation. Pinsp: inspiratory pressure level; PSV: pressure support ventilation; VT : tidal volume; f: rate; PEEP: positive end-expiratory pressure

Iotti *et al*. attempted to combine the two feedback principles and have two measured variables drive the inspiratory pressure level: alveolar volume tidal volume minus dead space) and $P_{0.1}$ (a non-specific measure of the patient's respiratory activity)[25]. They showed that it is possible to combine positive and negative feedback control.

Oxygenation

Very few authors have addressed automation of arterial oxygenation (PEEP and FiO_2). This seems far more challenging than automation of ventilation because of the strong interaction with the cardiovascular system. Dugdale *et al*. automated the administration of FiO_2 in neonates [32]. Technically, the controller was rather simple, yet its combination with an umbilical catheter was an interesting feature. Strickland *et al*. attempted to automate the weaning process on the basis of multiple parameters, including oxygen [20]. They had the computer adjust the mandatory rate and the pressure support level in SIMV. Probably the most elaborate control procedures employ multidimensional control structures and simultaneous adjustment of PEEP and FiO_2 [18,24]. However, no patient data was published until today; thus, clinical feasibility remains to be shown.

Commercially available closed-loop controlled modes

Mandatory Minute Ventilation, proposed by Hewlett [10], has been available for some years in multiple forms, as an automatic mechanism to maintain minute ventilation at a preset level. The clinician presets timing, tidal volume, and rate (or minute volume), and the ventilator adjust respiratory rate and/or inspiratory pressure to achieve the preset values. Different vendors have implemented different versions of MMV. A selection is given in table 2; a more comprehensive review can be found elsewhere [33]. In all available MMV implementations except ASV, the clinician tightly controls tidal volume, inspiratory time, and respiratory rate. By contrast, ASV chooses the breath pattern automatically with the goal of the lowest possible work of breathing. It is based on continuously measured pulmonary mechanics, and it essentially follows the Adaptive Lung Ventilation controller scheme [23]. ASV constitutes the first commercially available MMV algorithm to base its decision on actual patient data and not solely on clinician input. As such, it is conceptually capable of following the disease process automatically and with a ventilatory pattern adapted to the respiratory system mechanics [34]. This capability is unique among all MMV methods currently available.

Conclusions

Respiratory management of intubated patients is a complex problem, even if airway management, sedation, nutrition, and infection control are excluded and only the very limited problem of "how to set a ventilator" is considered. In engineering terms, closed-loop control of ventilation may be viewed as a multidimensional problem with four dimensions: time, physiologic task, primary lung disease, and general therapeutic approach (see figure 3). Start-up, maintenance, and weaning are the principal dimensions in time. In each phase, three distinctly different dimensions must be addressed. The first dimension is the ventilator settings to treat problems like ventilation, oxygenation, and respiratory muscle (pump) support, as discussed above (note that any combination of these problems may occur at any time). The second dimension is the type of lung disease. For illustration purposes, we shall call them "normal" (like post-operative), ARDS (stiff lungs), and COPD (high airway resistance) in figure 3. The third dimension describes the level of risk a clinician is willing to accept for the treatment of a patient. This dimension is illustrated by three levels of therapeutic approach: "aggressive," "balanced," and "conservative."

In figure 3 only three categories per dimension are allowed. This might seem like a simplistic approach. However, the combinations of the dimensions add the required

Table 2. Selected examples of MMV implementations

Name	Preset variables	Ventilator controlled variables	Device
Original MMV	f, VT	f	None
MMV	MV, VT	f	CPU-1 (Ohmeda)
MMV	MV, VT	f, Pinsp	Evita 4 (Dräger)
MMV	MV	Pinsp	VEOLAR (Hamilton Medical)
AutoMode	VT, f	Pinsp, Psupp, Mode (PRVC or VS)	Servo 300A (Siemens)
ASV	%MV	Pinsp, Psupp, f, Ti	GALILEO (Hamilton Medical)

f: rate; VT: tidal volume; MV: minute volume; Pinsp: inspiratory pressure level, Psupp; pressure support level, Ti: inspiratory time, PRVC: pressure-regulated volume control, VS: volume support, ASV: Adaptive Support Ventilation complexity. A simple calculation tells us that, overall, 27 (3 x 3 x 3) different isolated cases can be produced with the simple representation in Figure 3. For example, a patient with COPD in the start-up phase needs a ventilator to aid in ventilation and respiratory muscle support. The treatment depends on the level of risk the clinician is willing to take, i.e., on the patient's age, for example. When allowing for multiple diseases (like acute-on-chronic) and multiple problems (like ventilation and respiratory pump support problem), one ends up with 84 (4 x 7 x 3) different combinations per phase in time. When these 84 combinations are multiplied by the number of phases (3), 252 different clinical problems that can be described by Figure 3 are obtained. Each of these sub-problems may be solved by a dedicated automatic ventilator. However, it is clear that a ventilator with 252 modes of ventilation is a useless device. Thus, closed-loop control methods must address much more than isolated problems to be clinically useful. A few promising ideas were shown above. However, it remains a challenge to put all the particular and isolated solutions "under one hat" for the benefit of the patient and the team of care providers.

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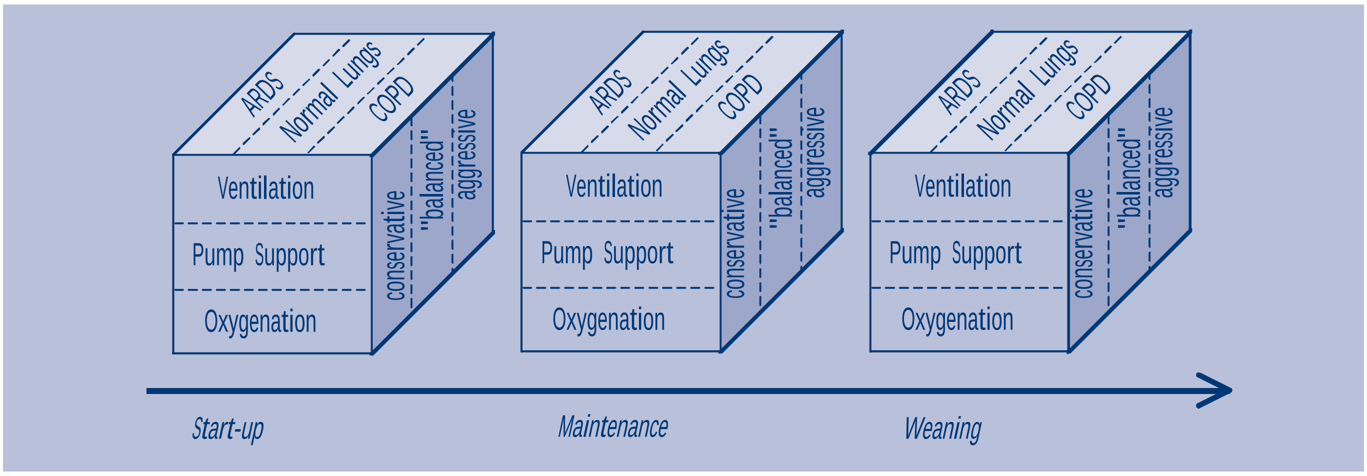

Figure 3: Closed-loop control of ventilation. Start-up, maintenance, and weaning are the principal phases. In each phase, three distinctly different issues need to be addressed: The first issue concerns one or more principal deficiencies that may be grouped in ventilation, oxygenation, respiratory muscle (pump) support or any combination of these. The second issue is the type of lung disease: normal (like post-operative), ARDS (stiff lungs), and COPD (high airway resistance). The third issue is the strategic dimension of risk management. This is illustrated by three levels of therapeutic approaches: aggressive, "balanced," and conservative.

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