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Multivariable optimization of mechanical ventilation. A linear programming approach

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Abstract

The proposed method aims at improved ventilatory care with reduced morbidity. It combines two important aspects of mechanical ventilation: gas exchange and lung mechanics. A single criterion was selected as optimization index of lung trauma: peak respiratory power (PRP) defined as the maximum product of pressure times flow during inspiration. Arterial blood gases reflect gas exchange and constitute the constraints of the problem. The constraints as well as the optimization index are expressed as linear functions of the input variables (frequency of breathing, tidal volume, and positive end expiratory pressure). A linear programming approach can therefore be used to determine the values of input variables that minimize PRP and at the same time keep arterial blood gases within the prescribed limits. The coefficients of the constraints and the optimization index equation are found by manipulating input variables in order to obtain four different values of PaO_2, $PaCO_2$ and PRP (there are four coefficients in each equation). The coefficients can then be calculated and the optimization procedure run. In a pilot study 5 patients suffering from diseases of varying pulmonary pathology were investigated with this method. In 4 out of 5 the ventilator treatment improved in terms of blood gas values (mean increase in PaO_2 was 4.7%) and reduction of mechanical load on the lungs (mean PRP reduction was 20%). Lower PRP is accompanied by lower mean power and pressure values, which results in increased cardiac output. Presently, the main problem is the time it takes to determine the patient coefficients (approx one hour), a procedure that needs to be simplified.

1. Introduction

The primary goal of mechanical ventilation is to maintain arterial oxygen and carbon dioxide tensions at a physiological level. This goal can be achieved by a combination of different ventilator settings. However, it may be difficult to determine which combination optimally helps the patient. Several optimization indices have been proposed in the past [1–8]

- functional residual capacity FRC [1]
- compliance [2]
- shunt (Qs/Qt) [3]
- physiological dead space (VDphys)
- physiological dead space/tidal volume ratio (VDphys/TV) [3]
- alveolar efficiency CO_2 [4]
- peak inspiratory pressure (PIP) [5]
- peak respiratory power (PRP) [6]
- oxygen availability (O_2 content × Qt) [7]
- oxygen toxicity measured by inspired oxygen fraction (FIO_2) [8]

These indices can be divided into two groups reflecting two important aspects of mechanical ventilation: lung mechanics and gas exchange. We do not, however, believe that a formulation of the optimization problem that is based on only one of these aspects is complete, and we therefore here present a formulation, that takes into account both aspects at the same time.

Recently, an optimization concept based on multivariate value function [9] has been proposed: first the value of the individual attributes is determined, secondly, the values of the attributes are combined to produce a metric of the desirability of the decision option.

2. Methods

The primary objective of mechanical ventilation is to provide adequate oxygenation and CO_2 elimination with minimal risk of lung trauma. The index chosen to estimate the risk of lung trauma was peak respiratory power (PRP) which has been tested in a clinical study [6]. The superiority of PRP over PIP index in predicting lung trauma has been shown in an animal study [10]. The index is related to the amount of energy delivered to the lung and is the maximum product of pressure and flow during inspiration

$$\text{Power} = \text{pressure} \times \text{flow} \quad (1)$$
$$\text{PRP} = \max\ (\text{pressure} \times \text{flow}) \quad (2)$$

For the constant flow pattern of the ventilator the formula is:

$$\text{PRP} = Q(QR + TV/C + PEEP) \quad (3)$$

where Q – inspiratory flow
TV – tidal volume
PEEP – positive end-expiratory pressure
R – airway resistance
C – lung/chest compliance

Equation [3] shows that PRP, for a constant flow ventilator, is the product of flow and maximum pressure, the latter being the sum of pressure drop across airway resistance, pressure required to overcome the elastic recoil of the lungs when tidal volume (TV) is introduced, and positive end-expiratory pressure.

It has previously been shown in a clinical investigation [6] that the values of PRP during mechanical ventilation are of the order 1000–6000 milliwatts depending on the state of the lungs and the ventilator settings. In contrast, as reported by Engström & Norlander [11], values occurring during spontaneous breathing for an adult person, are about 200 milliwatts.

A more common index is peak inspiratory pressure (PIP). For the constant flow pattern of the ventilator the equation is

$$\text{PIP} = Q\ R + TV/C + PEEP \quad (4)$$

Here we use the PRP function as an optimization index, although the described optimization method can equally well be applied to the PIP function.

The PRP function depends on tidal volume and PEEP variables and also on the frequency of breathing.

Inspiratory flow is related to tidal volume by the equation (assuming a constant flow pattern)

$$TV = Q\ Ti \quad (5)$$

Table 1. The orthogonal experiment design.

No of measurement	f b/min	TV 1	PEEP kPa	PaO_2 kPa	$PaCO_2$ kPa	PRP mwatt
1	+ [a]	–	–	.	.	.
2	–	+	–	.	.	.
3	–	–	+	.	.	.
4	+	+	+	.	.	.

[a] '+' upper value of variable.
'–' lower value of variable in relation to the initial point (f)o, (TV)o, (PEEP)o.

The experiment design that appears is shown in Table 2.

The variable FIO_2 is not taken into consideration. It does not affect the chosen optimization index PRP. The value of FIO_2 is inherent in the value of a constant b_{10} in the PaO_2 equation.

The experiment performed in the described way supplies the values of PaO_2, $PaCO_2$ and PRP needed to calculate the patient model coefficient values.

Optimization

The optimization problem expressed by the set of equations (8) is a linear programming problem and can be solved by the simplex method. The method can best be explained by a simple two-dimensional example of the optimization problem:
minimize the peak respirator power depending linearily on the frequency of breathing (f) and positive end-expiratory pressure (PEEP) according to the equation

$$PRP = 200f + 800\ PEEP - 1200 \quad (9)$$

subject to constraints

$$10 <= f <= 20\ \text{(breaths/min)} \quad (10)$$
$$O <= PEEP <= 1\ \text{(kPa)}.$$

The constraints (10) mean that f values between 10 and 20 (breath/min) and PEEP values between 0 and 1 (kPa) are feasible. The solution space which is defined as the space enclosed by the constraints (10) is shown in Fig. 1. Each point within the boundaries of the rectangle (simplex) ABCD satisfies the constraints. The optimum point is the point within the ABCD boundaries which yields the minimum value of PRP. The minimum value of PRP always occurs at one of the corner (extreme) points A, B, C or D of the solution space. The search for the optimum point can therefore be limited to the corner points. The simplex method [13] is an algebraic procedure which is capable of identifying the optimum point starting from one of the corner points (A, B, C, D) and moving successively through a sequence of points in such a way that each new point (solution) improves the value of an optimization index (9). The search is continued until no better point is found.

The PRP values for each corner point in our example are given in Table 3. The possible sequence in the search for optimum setting could be CBA or DBA, but not DCA (Fig. 1). A is the optimum point.

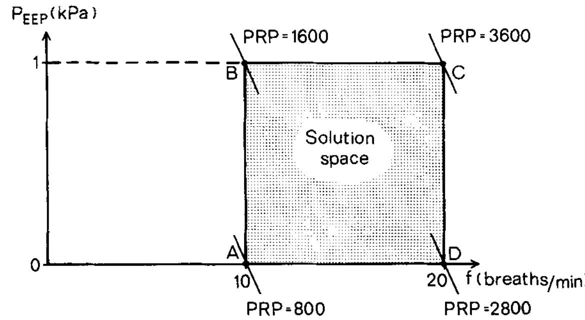

Fig. 1. The simplex method. The solution space (A B, C, D) for an example described in the text. A is the optimum point as shown by the minimum peak respiratory power value. See marked planes PRP = const.

Table 3. Peak respiratory power (PRP) values for each corner point.

Corner point	f (b/min)	PEEP (kPa)	PRP (mwatt)
A	10	0	800
B	10	1	1600
C	20	1	3600
D	20	0	2800

Table 4. Patients included in the study.

Patient No	Sex	Age	Pathology
1	M	80	LVF[a]
2	F	65	Neuromuscular disease, COPD[b]
3	F	52	COPD
4	F	39	Pneumonia
5	F	33	Pneumonia, COPD

[a] LVF - left ventricular failure.
[b] COPD - chronic obstructive pulmonary disease.

Assuming a constant Ti/T ratio (as with a Siemens Servoventilator) flow equals

$$Q = \frac{TV}{Ti} = \frac{TV \cdot f}{Const} \qquad (6)$$

and is a product of tidal volume and the frequency of breathing divided by a constant. The dependence of PRP on the frequency of breathing thus becomes clear.

Problem formulation

The mathematical formulation of the optimization problem is:

Minimize PRP (f, TV, PEEP)

subject to the constraints:

$$\begin{aligned} &\min PaO_2 <= PaO_2 <= \max PaO_2 \qquad (7)\\ &\min PaCO_2 <= PaCO_2 <= \max PaCO_2 \end{aligned}$$

The constraints (7) mean that the PaO_2 and $PaCO_2$ values are to be found within a range determined by a minimum and maximum limit. Let us make the assumption of a linear dependence of the arterial gas tensions PaO_2, $PaCO_2$ and PRP on ventilator settings around the equilibration point $(PaO_2)o$, $(PaCO_2)o$ and (PRP)o.
This allows for the following mathematical description:

$$\begin{aligned} PaO_2 &= b_{11}\, f + b_{12}\, TV + b_{13}\, PEEP + b_{10}\\ PaCO_2 &= b_{21}\, f + b_{22}\, TV + b_{23}\, PEEP + b_{20} \qquad (8)\\ PRP &= b_{31}\, f + b_{32}\, TV + b_{33}\, PEEP + b_{30} \end{aligned}$$

where the first two equations play the role of constraints and the third is the optimization index (b_{10}. . .b_{33} - constant coefficients).

In the set of equations (8) each dependent variable (PaO_2, $PaCO_2$, PRP) is a linear function of the ventilator settings (f, TV, PEEP).

It is worth noticing that the first and third equations of (8) can be interchanged. This is the equivalent of demanding that PaO_2 be maximal at the constraints imposed on peak respiratory power.

Patient model identification

In order to obtain the values of the coefficients in a patient model (8), measurements should be performed during mechanical ventilation. The smallest number of measurements is four, as there are four coefficients in each equation. The traditional way of experimentation would be to change the value of a single variable at one time and then make readings of PaO_2, $PaCO_2$ and PRP values. This does not, however, result in coefficient values calculated with minimum variance. Coefficients can be calculated with minimum variance only if several input variables are changed at the same time. What is refered to as an orthogonal design [12] can be proposed with the diagonal design matrix, where covariances of the coefficients are equal to zero. The design of an experiment fulfilling the orthogonality condition is illustrated with Table 1.

Let us use an example to elucidate the problem. The initial point is $f_0 = 18$ (breaths/min), $TV_0 = 0.5$ (1) and $PEEP_0 = 0.6$ (kPa). Let the increments of ventilator settings be f = 0.5 breath/min, TV = 0.1 (1) and PEEP = 0.2 (kPa).

Table 2. Example of the orthogonal experiment design.

No of measurement	f b/min	TV 1	PEEP kPa	PaO_2 kPa	$PaCO_2$ kPa	PRP mwatt
1	18.5	0.4	0.4	·	·	·
2	17.5	0.6	0.4	·	·	·
3	17.5	0.4	0.8	·	·	·
4	18.5	0.6	0.8	·	·	·

Table 5. Coefficients of the patient model equations.

Pat No	Equation	Coefficient				FIO_2
		f(b/min)	TV (1)	PEEP (kPa)	const	
1	PaO_2[a]	0.1512	7.4333	−1.9205	2.3953	
	$PaCO_2$	−0.0209	−2.4062	0.6343	5.9011	0.35
	PRP	609.4	15574.3	−2136.0	−15927.7	
2	PaO_2	−0.4191	−19.0394	−1.7973	31.3546	
	$PaCO_2$	−0.0184	−6.4790	0.0008	7.9267	0.4
	PRP	269.2	7762.8	907.8	−6592.6	
3	PaO_2	0.4265	26.2254	4.0828	−12.2534	
	$PaCO_2$	−0.1104	−6.6652	−1.5810	12.3677	0.3
	PRP	287.5	10616.9	1065.0	−8814.3	
4	PaO_2	−0.0444	6.1877	0.1671	2.9035	
	$PaCO_2$	−0.1721	−9.5417	−0.1111	14.6904	0.5
	PRP	584.0	22235.6	475.0	−21860.4	
5	PaO_2	−0.3195	−2.1901	2.7933	17.2627	
	$PaCO_2$	−0.1466	−8.2372	0.2407	12.0281	0.3
	PRP	84.7	10275.1	1635.8	−4934.9	

[a] PaO_2, $PaCO_2$ kPa PRP milliWatts.

3. Patients and procedures

Five patients with acute respiratory failure were included in the optimization study. All patients are listed in Table 4. The majority of the patients were in a stable cardio-respiratory state. The patients were ventilated with a Siemens Elema Servoventilator S 900 B.

Data collection and sampling of arterial blood (radial artery catheter) were carried out simultaneously. Blood gas analysis was performed with Radiometer ABL II, Copenhagen. A minimum equilibration time of 10 minutes passed between the introduction of new settings and blood gas measurements. Sedatives and muscle relaxants were administered as needed.

The increments of the settings were introduced according to the design presented in Table 1. Mean values of increments (the mean difference between the initial values f_0, TV_0 and $PEEP_0$, and the values of the new setting) were f = 1.86 breaths/min, TV = 0.0745 1 and PEEP = 0,275 kPa. The mean value of initial minute volume was 11.52 1/min. The minute volume was not corrected for compressed volume.

The limits set for PaO_2 in the optimization pro-

Table 6. Coefficients of an 'average' patient model.

Equation	Coefficient ± Standard deviation			
	f (b/min)	TV	PEEP (1)	Const (kPa)
PaO_2[a]	−0.0411	3.7216	0.6651	8.3325
	±0.345	±16.4267	±2.702	±16.5701
$PaCO_2$	−0.0937	−6.6586	−0.1633	10.5848
	±0.0711	±2.6888	±0.8425	±3.5759
PRP	366.95	13293.0	389.49	−11626.0
	±224.41	±5745.14	±1471.70	±7093.31

[a] PaO_2, $PaCO_2$, kPa, PRP milliWatts.

gram were within a 7.5–9 kPa range for lower and a 11–16 kPa range for upper limits dependent on the actual patient PaO_2.

The limits set for $PaCO_2$ were 4–6 kPa except for patient no 3 (4.5–5.5 kPa). The study was approved by the Local Ethical Committee.

4. Results

4.1. Patient model identification

The coefficients of the set of equations (8) were calculated individually for each patient on the basis of the measurements and are presented in Table 5. The mean values of the coefficients for 5 patients and their standard deviations are given in Table 6. The coefficients in Table 6 correspond to an 'average' patient model. The results of a qualitative analysis of the patient models restricted to coefficient signs are shown in Table 7. The sign pattern of the 'average' patient model (Table 6) is given in Table 8. The '–' sign in the f column and PaO_2 row means that the frequency increase reduces PaO_2 while other variables remain constant.

Table 7. Coefficient sign patterns for each patient.

Pat No	Equation	Coefficient sign		
		f	TV	PEEP
1	PaO_2	+	+	–
	$PaCO_2$	–	–	+
	PRP	+	+	–
2	PaO_2	–	–	–
	$PaCO_2$	–	–	+
	PRP	+	+	+
3	PaO_2	+	+	+
	$PaCO_2$	–	–	–
	PRP	+	+	+
4	PaO_2	–	+	+
	$PaCO_2$	–	–	–
	PRP	+	+	+
5	$PaCO_2$	–	–	+
	$PaCO_2$	–	–	+
	PRP	+	+	+

4.2. Optimization

The optimization results for the patients under investigation in the study are shown in Table 9. In that table there are three vertical columns marked I (initial values), C (optimum calculated by the program) and M (measured optimum values). The I column is a baseline to which the optimum values obtained from the patient (M column) are compared. Each patient serves therefore as its own control.

After the determination of patient model coefficients the optimal settings, blood gas values and PRP are calculated by the program (C column). Then the calculated settings are introduced and real values measured (column M). The comparison of M column values with I column (baseline) brings the optimization result. The percentage differences are given (Table 9) for PaO_2, $PaCO_2$ and PRP. The mean reduction of PRP in all patients was 20%. The risk of lung trauma due to mechanical ventilation may be considered to be reduced. The mean increase in PaO_2 was 4.7%.

5. Discussion

In four patients out of five in whom the optimum settings were introduced, an improvement of ventilator treatment was obtained in terms of blood gas values and peak respiratory power value. (Table 9). In our opinion it reflects the potential of optimization procedure in application to mechanical ventilation even if the number of investigated patients was small.

The separete issue is the identification procedure needed to establish patient model coefficients.

Table 8. Coefficient sign pattern for an 'average' patient model.

Equation	Coefficient sign		
	f	TV	PEEP
PaO_2	–	+	+
$PaCO_2$	–	–	–
PRP	+	+	+

Now they are not a priori known and the identification as performed in this study is necessary.

It is expected that in the future the coefficients will be a priori known on the basis of statistical analysis of large amount of collected data. The identification can then be simplified or totally avoided.

The large variation of patient model coefficients, characterized by high standard deviations (Table 6), was found. It suggests that the coefficients do not converge to certain values or, in other words, the patients cannot be classified into one class (and model) but into several classes.

This may be explained by different lung pathologies and patient status but may also be explained by the different initial settings of the ventilator. Less variation of the coefficients is to be expected if the initial settings are similar. The highest standard deviations in the 'average' patient model were obtained for the PaO_2 equation and then for the $PaCO_2$ and PRP equations.

In the situation of high variability of the coefficients we concentrated on the qualitative aspects of the models expressed by coefficient sign patterns (Table 7). These patterns may be treated as typical for future classes of the patients.

The typical sign pattern of coefficients in the PRP equation is '+, +, +', which means that increases of f, TV and PEEP cause an increase of PRP. The only exception is the '−' PEEP coefficient sign in patient no. 1, which could be explained by the compliance increase caused by PEEP.

The '−, −' coefficients pattern for f and TV is typical for the $PaCO_2$ equation. It means that increasing values of these two settings lower $PaCO_2$. This finding is in agreement with clinical experience.

Various sign patterns were observed for f and TV in the PaO_2 equation. The prevailing sign for the f coefficient was '−' which means that PaO_2 decreases at higher frequencies of breathing (if TV is kept constant), possibly due to poorer ventilation of lung regions characterized by longer time constants and also of dependent, well perfused regions (ventilation/perfusion (V/Q) mismatch) [14].

There was no regular sign pattern for the PEEP variable in the PaO_2 and $PaCO_2$ equations. The expected pattern is '+' in the PaO_2 equation and '−' in the $PaCO_2$ equation (increasing PEEP causes an increase of PaO_2 and a decrease of $PaCO_2$ while other variables kept constant). However, for patients no. 1 and 2 the opposite pattern was noted. Analysis of the data of 20 mechanically ventilated patients [15] revealed that a non-typical PEEP pattern frequently occured in COPD patients suggesting that PEEP in these patients should not be applied as it deteriorates the blood gases. This finding is in agreement with Rossi et al. [16]. PEEP reduces shunt and abolishes areas of low V/Q ratio. This, however, takes place at the cost of increasing mal-

Table 9. The optimization results.

Patient No	1			2			3			4			5		
Settings; blood gas values, PRP	I[a]	C[b]	M[c]	I	C	M	I	C	M	I	C	M	I	C	M
f (b/min)	20.1	17.1	17.0	17.3	14.1	14.9	20.3	16.0	16.3	18.9	14.6	14.6	25.1	21.1	22.3
TV (l)	0.65	0.67	0.68	0.47	0.48	0.42	0.51	0.53	0.53	0.76	0.82	0.84	0.46	0.38	0.42
PEEP (kPa)	0.56	0.50	0.51	0.15	0.12	0.23	0.49	1.00	1.37	0.44	0.90	0.93	0.44	0.29	0.43
MV (l/min)	13.1	11.5	11.6	8.2	6.8	6.2	10.5	8.5	8.6	14.3	12.0	12.3	11.6	7.9	9.4
PaO_2 (kPa)	7.79	9.00	8.43	18.04	16.00	17.99	12.53	12.51	10.63	6.58	7.50	7.13	8.6	10.56	10.59
ΔPaO_2 (%)[d]		+8.22			−0.3			−15.2			+8.36			+22.3	
$PaCO_2$ (kPa)	4.36	4.25	4.41	4.90	4.53	5.30	5.11	5.5	6.47[e]	4.94	4.24	4.85	4.[illegible]2	6.00	5.58
$\Delta PaCO_2$ (%)[d]		+1.15			+8.16			+26.6			−1.82			+20.8	
PRP (mWatt)	5169	3842	4289	1805	1077	1236	2983	2460	2602	4790	5392	4544	2409	1106	1543
ΔPRP (%)[d]		−17.02			−31.11			−12.75			−5.22			−36.09	

[a] I - initial values; [b] C - optimum calculated by the program; [c] M - measured optimum; [d] ((I-M)/I · 100 (%); [e] $PaCO_2$ limit overrun

distribution created by the presence of high V/Q and increasing dead space with resultant reduction of alveolar ventilation. The net result may be CO_2 retention [17].

The advice given by the programme on ventilator settings can be summarized as follows. In several patients a minute volume (MV) decrease was advised. It was introduced having $PaCO_2$ at almost the same level or within the prescribed limits (patients no 1, 2, 4). The explanation may be that if MV keeps increasing, the ventilation is distributed to areas with abnormally high V/Q ratios [17]. This indicates the possibility of ventilating the patients at lower MV and consequently lower PRP. Lower MV was usually achieved by lowering the frequency of breathing.

In the majority of the patients a lower frequency of breathing than the initial one was advised by the programme as being the optimum setting. It was suggested that the initial frequency for the patient undergoing mechanical ventilation is around 16 (breaths/min).

The following advice for PEEP adjustment was given: increase (patient no 2, 3, 4) or slightly decrease (patient no 1, 5). The differences between calculated and measured ventilator settings (Table 9) can be explained by the difficulty in setting the exact values on a ventilator.

The optimum settings were also calculated for a more popular optimization index - PIP. It was found that in patients no 3, 4, 5 the optimum settings were exactly the same as for the PRP index. In the remaining patients no. 1 and 2 the optimum settings were different.

The disadvantage of the method presented in this study is the measurement procedure necessary to determine the patient model coefficients. It is both laborious and time consuming (about one hour for each patient). Further research should therefore be done into the statistical models so as eventually to avoid the measurements completely or at least to reduce their number significantly. More patient data should be collected for this purpose. However, the preliminary results are promising as far as optimization itself is concerned.

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