

Decision support of inspired oxygen fraction using a model of oxygen transport

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Abstract: Setting inspired oxygen fraction (FiO_2) is a complicated balance between ensuring adequate oxygenation and minimizing the risk of lung damage. This paper presents a retrospective test of a model-based decision support system (INVENT) for advising on FiO_2 levels in intensive care patients. Clinically determined FiO_2 levels and the resulting blood oxygenation are compared with INVENT determined FiO_2 levels and model simulated blood oxygenation. The results indicate that INVENT can maintain an acceptable level of oxygenation using similar or more appropriate levels of FiO_2 compared to clinical practice.

1. INTRODUCTION

Choosing appropriate ventilator settings may be regarded as a balance between ensuring sufficient gas exchange whilst preventing ventilator induced lung injury (VILI). Achieving this balance can be difficult, partly due to changes in ventilator settings both improving gas exchange and at the same time increasing the risk of VILI. In the case of inspired oxygen fraction (FiO_2) increases can improve oxygenation but also increase risk of the effects of oxygen toxicity (Nash *et al.*, 1967, Altemeier and Sinclair, 2007), and absorption atelectasis (Dantzker *et al.*, 1975, Edmark *et al.*, 2003).

Several computer systems have been developed to aid in ventilator management, these including the setting of FiO_2 (Rutledge *et al.*, 1993, Shahsavar *et al.*, 1995, Raemer *et al.*, 1997, McKinley *et al.*, 2001, Kwok *et al.*, 2004, Tehrani *et al.*, 2004, Rees *et al.*, 2006). These systems can be divided into closed loop ventilator control systems (Raemer *et al.*, 1997, Tehrani *et al.*, 2004) and decision support systems (DSS) (Rutledge *et al.*, 1993, Shahsavar *et al.*, 1995, McKinley *et al.*, 2001, Kwok *et al.*, 2004, Rees *et al.*, 2006). Closed loop ventilator control systems may be valuable when targets for the ventilator therapy have been defined, but do not provide assistance in setting the appropriate target for the individual patient.

Recent advances in DSS have focused on applying a rule-based approach, implementing the heuristics of clinicians either by automating clinical protocols (McKinley *et al.*, 2001) or using fuzzy rule bases (Kwok *et al.*, 2004). While such systems may indeed support management of ventilator therapy, they do not support the clinician in understanding the pathophysiology of the individual patient.

A DSS based on physiological models and utility theory provides both advice on the appropriate target, and provides physiological understanding. When physiological models are tuned to fit data for a particular patient, the model parameters describe the state of the patient, and the model can be used to simulate the outcome of changes in ventilator settings. Utility theory (Keeney and Raiffa, 1993) can be used to quantify the expected utility of outcomes, and when combined with physiological models, the ventilator settings associated with maximal expected utility can be located and provided as advice to the clinician.

The INVENT system (Rees *et al.*, 2006) provides advice on setting FiO_2 and minute volume using physiological models of oxygen transport, carbon dioxide transport and lung mechanics combined with utility theory.

The purpose of this study was to retrospectively evaluate the advice provided by the INVENT system in intensive care patients. The physiological model of oxygen transport used to calculate advice on FiO_2 , is identifiable from clinically available measurements (Rees *et al.*, 2002), and has been shown capable of describing various patient types including intensive care patients (Kjærgaard *et al.*, 2003). The advice on minute volume is dependent on all the three aforementioned models in INVENT. The mathematical model of lung mechanics currently applied in INVENT assumes a linear static compliance of the respiratory system. However, this is not sufficient to simulate the effects of changes in minute volume in intensive care patients with acute respiratory problems, where the compliance has been shown to be nonlinear (Matamis *et al.*, 1984). As a first step, therefore, this article evaluates only the ability of INVENT to provide advice on setting FiO_2 .

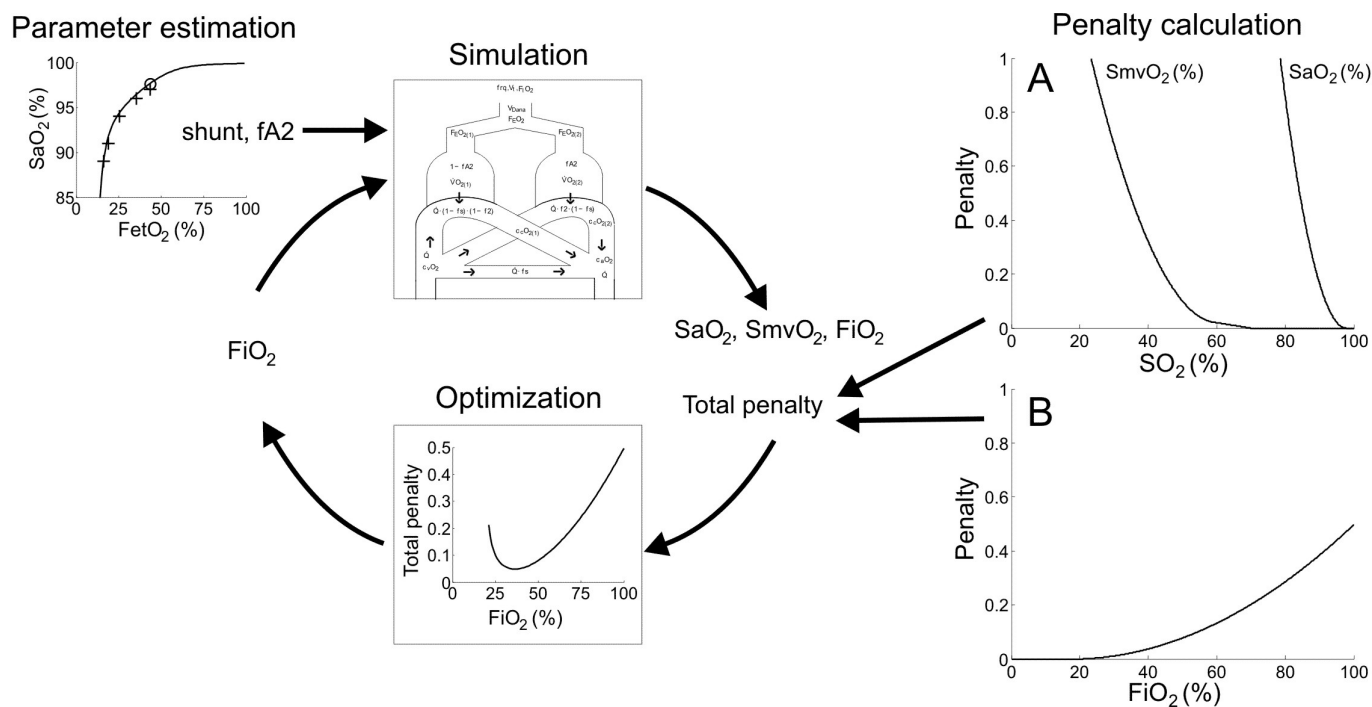


Fig. 1. Components of INVENT: INVENT FiO_2 advice is calculated in a feedback loop initiated with newly identified model parameters. The optimization component changes FiO_2 and the model simulates resulting oxygenation (arterial: SaO_2 , mixed venous: $SmvO_2$). A total penalty is calculated from FiO_2 , SaO_2 and $SmvO_2$ and fed back to the optimization component. The optimal FiO_2 is that resulting in minimal total penalty.

2. METHODS

2.1 The INVENT system

Figure 1 illustrates the components of INVENT for providing advice on FiO_2 . The physiological model of oxygen transport is identified using a previously published parameter estimation method (Rees *et al.*, 2002), fitting data describing arterial oxygen saturation (SaO_2) and end tidal oxygen fraction ($F_{et}O_2$). This method yields two model parameters describing the patient's pulmonary gas exchange status; shunt quantifies the amount of blood flowing through the lungs without reaching ventilated alveoli, and $fA2$ quantifies the degree of ventilation/perfusion mismatch in the lungs. When identified for a patient, the model can simulate the resulting oxygenation for a particular patient at any FiO_2 .

The optimization component varies FiO_2 to evaluate the utility associated with possible FiO_2 levels. For each FiO_2 value, the model simulates the corresponding arterial oxygen saturation (SaO_2) and mixed venous oxygen saturation ($SmvO_2$). SaO_2 and $SmvO_2$ are used to calculate the penalty associated with risk of ischemia. This penalty is calculated as the sum of penalty associated with risk of local ischemia and general ischemia calculated from SaO_2 and $SmvO_2$, respectively (see A, Fig. 1). FiO_2 is used to calculate the penalty associated with risk of the effects of oxygen toxicity and with absorption atelectasis (see B, Fig. 1). The total penalty for a given FiO_2 is the sum of the penalty due to ischemia risk and the penalty due to risk of the effects of oxygen toxicity and absorption atelectasis. The FiO_2 value

resulting in minimal total penalty is provided as advice to the clinician.

2.2 Data Collection

Eighteen patients with acute lung injury (ALI) were included in the study, 14 male and 4 female. Median age was 64.5 years (range 27-85) and weight 80 kg (range 70-140). The study was performed at the department of intensive care at Rigshospitalet (Copenhagen, Denmark). Patients were ventilated using a Servo 300 or a Servo (Maquet A/B, Solna, Sweden). Nine patients were ventilated using controlled ventilation modes, either pressure regulated volume control or pressure control modes. Seven patients were ventilated using pressure support mode. Informed consent was obtained from nearest relative or legal guardian. The study was approved by the Ethical Committee of North Jutland and Viborg Counties and the Ethical Committee of Copenhagen.

After inclusion in the study the patient was connected to a Servo ventilator dedicated for the study. FiO_2 and $F_{et}O_2$ were measured side-stream by a paramagnetic oxygen analyser (Oxigraf, Mountain View CA, USA). Pulse oximetry oxygen saturation (SpO_2), anatomical dead space and end tidal carbon dioxide fraction were measured using a stand alone respiratory monitor (CO₂SMO Plus, Novamatrix Medical Systems, Wallingford CT, USA). For each patient FiO_2 was modified in 4-6 steps to achieve oxygen saturations ranging from 88 % - 100 %, as previously described (Rees *et al.*, 2002). When steady state was reached for each FiO_2 level, measurements were taken of ventilation volumes, SpO_2 , oxygen consumption, end tidal carbon dioxide fraction,

FiO₂, and FetO₂. In addition, an arterial blood sample was drawn at each FiO₂ level and analyzed to obtain blood gases, acid-base status, and concentrations of haemoglobins (pH, SaO₂, PaO₂, PaCO₂, Base excess, Hb, HbMet and HbCO) (Radiometer ABL 700, Copenhagen, Denmark).

Two patients were excluded from the study due to malfunction of the data collection software. For the remaining 16 patients data from the experiments could be used for analysis. In 11 patients measurements of pulmonary gas exchange were performed at 2 different settings of PEEP. Therefore a total of 27 patient cases were used in the study.

2.3 Retrospective evaluation of INVENT

Several steps were taken to evaluate the value of FiO₂ suggested by INVENT:

The oxygen model was fitted to measurements of respiration and arterial oxygenation as described above. Measurements of arterial oxygenation at different FiO₂ levels were taken from a pulse oximeter (SpO₂), and supplemented by a single measurement of SaO₂ taken from blood. These conditions reflect the amount of data normally available in intensive care and are realistic when considering clinical application of INVENT. SpO₂ and SaO₂ were given different values of error (SD_{SpO₂} = 1 %, SD_{SaO₂} = 0.5 %) in the least squares fitting algorithm to reflect the different measurement precision.

The resulting model parameters were used to calculate the INVENT FiO₂ advice (FiO₂^{sugg}) and to simulate the resulting SaO₂ (SaO₂^{sugg}) using the INVENT suggested FiO₂ level.

Values of INVENT suggestions FiO₂^{sugg} and SaO₂^{sugg} were then compared with those set and measured clinically (FiO₂^{clin}, SaO₂^{clin}).

In the experiments performed here, in contrast to clinical practice, values of SaO₂ were measured in arterial blood at each FiO₂ level. By fitting the model to these arterial SaO₂ values it was possible to calculate the optimal model description of the patient's pulmonary gas exchange status. The resulting model parameters from this fit allowed obtaining information as to the 'true' variation in SaO₂ on changing FiO₂ and therefore simulate the 'true' resulting SaO₂ for the INVENT FiO₂ advice, i.e. SaO₂^{true}. Values of SaO₂^{true} were then compared against those obtained in clinical practice (SaO₂^{clin}).

Differences in INVENT calculated SaO₂ values and clinical values were skewed and therefore all comparisons were performed graphically using scatter plots and statistically using Wilcoxon matched pairs test (Bland, 2000).

A Bland-Altman plot (Bland and Altman, 1986) was applied to assess the agreement between values of SaO₂ measured using pulse oximetry and arterial blood gas analysis.

3. RESULTS

Fig. 2 and table 1 compare clinical values of FiO₂ and SaO₂ (FiO₂^{clin}, SaO₂^{clin} (o)), with those suggested by INVENT

(FiO₂^{sugg}, SaO₂^{sugg} (x)). The range of values of FiO₂ and SaO₂ suggested by INVENT are narrower than those used in clinical practise. INVENT suggested values of FiO₂ significantly different from clinical practice (p < 0.01), with INVENT limiting FiO₂ to values lower than 64 %, which is in contrast to clinical practice where 6 patients were ventilated with FiO₂ levels between 65 % and 83 %. SaO₂ suggested by INVENT were significantly different from clinical values (p < 0.01) values but remained above 90 % for both clinical practice and INVENT advice in all patient cases.

Fig. 3 and table 1 compare clinical values of FiO₂ and SaO₂ (FiO₂^{clin}, SaO₂^{clin} (o)), with INVENT suggested FiO₂ and the 'true' SaO₂ (FiO₂^{sugg}, SaO₂^{true} (x)). The range of SaO₂^{true} is wider than that of SaO₂^{sugg} as shown in fig. 2, and values of these were significantly different (p < 0.05). Values of SaO₂^{true} are however within clinically acceptable limits, i.e. SaO₂^{true} remains above 90 % in all patient cases except one where SaO₂^{true} is 89 %.

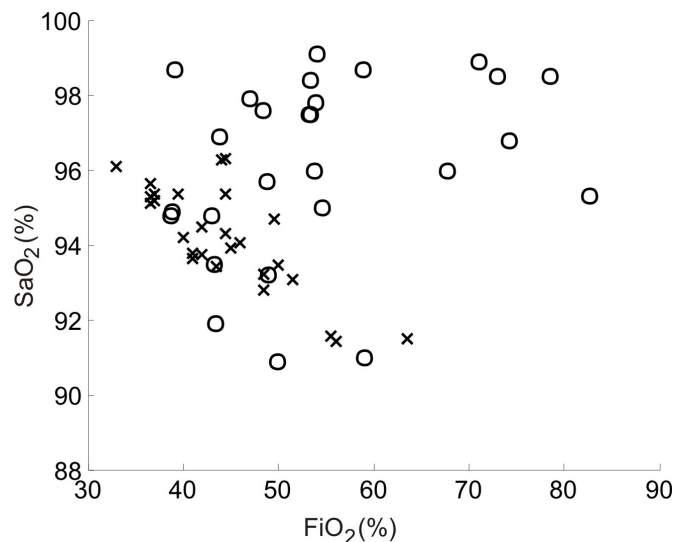


Fig. 2. Scatter plot of FiO₂^{clin} versus SaO₂^{clin} (o) and FiO₂^{sugg} versus SaO₂^{sugg} (x).

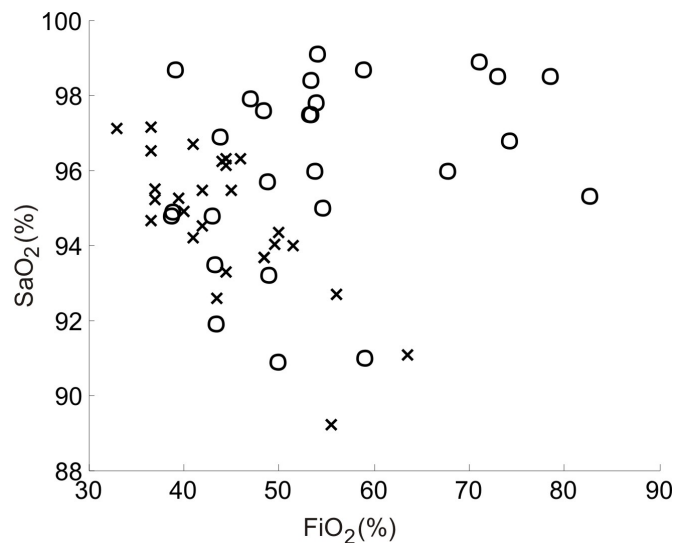


Fig. 3. Scatter plot of FiO₂^{clin} versus SaO₂^{clin} (o) and FiO₂^{sugg} versus SaO₂^{true} (x).

Table 1. Median and range of clinical and INVENT values.

	Median	Min	Max
FiO ₂ ^{clin} (%)	53.3	38.6	82.6
FiO ₂ ^{sugg} (%)	44.0	33.0	63.5
SaO ₂ ^{clin} (%)	96.8	90.9	99.1
SaO ₂ ^{sugg} (%)	94.2	91.4	96.3
SaO ₂ ^{true} (%)	94.9	89.2	97.1

Median and range (Min. and Max.) of: FiO₂^{clin}; FiO₂^{sugg}; SaO₂^{clin}; SaO₂^{sugg} and SaO₂^{true}.

Fig. 4 illustrates a Bland Altman plot of the difference between arterial oxygen saturation measured using arterial blood gas analysis and pulse oximetry (SpO₂ - SaO₂). The difference is plotted versus the mean measured arterial oxygen saturation ((SpO₂ + SaO₂)/2). The mean difference between SaO₂ and SpO₂ was -1.08 % ± 1.96 % (mean ± SD).

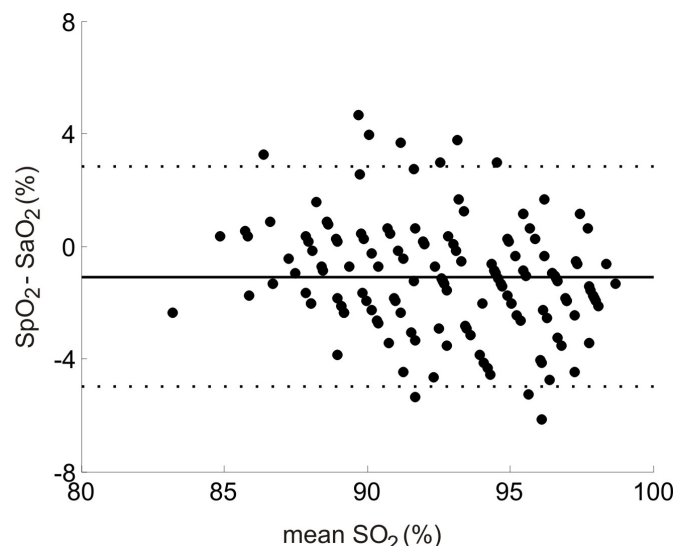


Fig. 4. Bland Altman plot of difference between arterial oxygen saturation measured using arterial blood gas analysis (SaO₂) and pulse oximetry (SpO₂). The solid line indicates mean difference (SpO₂ - SaO₂), the dotted lines show mean difference ±2 SD.

4. DISCUSSION

This study has retrospectively evaluated the advice on FiO₂ selection provided by INVENT for intensive care patients. FiO₂ values and corresponding arterial oxygenation measured as part of routine clinical practice has been compared with the FiO₂ suggested and SaO₂ calculated using INVENT. It has been shown that INVENT has potential to reduce FiO₂ in these patients, whilst maintaining an arterial oxygen saturation at or above 90%, thus limiting the potentially harmful effects of hyperoxia.

INVENT advice has been calculated using an oxygen transport model. The model has been identified using a

clinically applicable parameter estimation method. Application of INVENT in clinical practice therefore requires no extra measurements of arterial blood, and only a small procedure varying inspired oxygen fraction which takes approximately 10-15 min (Rees *et al.*, 2002) and may be computer controlled (Murley *et al.*, 2005).

The oxygenation results for INVENT advice using the ‘true’ model fits ((x) in Fig. 3), are significantly different ($p < 0.05$) to those obtained using the clinically realistic model fit ((x) in Fig. 2). The range of SaO₂ values is broader, however, all SaO₂ remain higher than 89 %. These are above the 88% suggested as being within a clinically acceptable range for patients with ALI and acute respiratory distress syndrome (The Acute Respiratory Distress Syndrome (ARDS) Network, 2000). All INVENT FiO₂ remained below 60 % except one (at 64 %). 60 % has been reported as the FiO₂ limit beyond which oxygen toxicity effects and absorption atelectasis may occur (Nash *et al.*, 1967, Dantzker *et al.*, 1975, Edmark *et al.*, 2003). In comparison, in clinical practise 6 of these patients received FiO₂ in the range 60-85 %. According to the INVENT simulation results, these patients could have been given safe levels of FiO₂ whilst maintaining an acceptable oxygenation.

The SD of the difference between SaO₂ and SpO₂ of 1.96 % (see Fig. 4) is comparable to an earlier study in intensive care patients (Van de Louw *et al.*, 2001) reporting a SD of 2.1 %. However, Van de Louw *et al.* reported a mean bias of -0.02 %, which is significantly lower than 1 % as found in this study. This bias means that the result of the ‘true’ model fit shows a higher median SaO₂ than SaO₂^{sugg}, as shown in Table 1. The specific case of a SaO₂ of 89 % for the ‘true’ model fit (see Fig. 3) is an example of the worst case of SaO₂ and SpO₂ difference, where SpO₂ is higher than SaO₂. Despite these quite large discrepancies the values of SaO₂^{true} remains above 88%, illustrating that the advice provided by INVENT is robust.

The penalty functions used in INVENT are based on a single intensive care physician’s preferences. The penalty functions may not comply with the preferences of all clinicians or all disease types encountered in the intensive care unit. The functions, however, could serve as a tool for reaching consensus on setting FiO₂.

This study has been performed retrospectively on existing data. The SaO₂ resulting from INVENT advice has therefore been simulated. As such the results reported here may only serve as an indication of the applicability of the INVENT system in intensive care patients. To further evaluate the system it is necessary to perform a prospective study evaluating the use of INVENT in an intensive care unit.

Setting FiO₂ may per se not be regarded as the most complex problem in ventilator management. However, the results of this study indicate the feasibility of using a DSS based on physiological models combined with utility theory to provide advice in ventilator management.

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REFERENCES

- Altemeier, W.A. and S.E. Sinclair (2007). Hyperoxia in the intensive care unit: why more is not always better. *Curr Opin Crit Care*, **13**, 73-78.
- Bland, J.M. and D.G. Altman (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, **1**, 307-10.
- Bland, M. (2000). *An Introduction to Medical Statistics*. Oxford University Press, New York.
- Dantzker, D.R., P.D. Wagner and J.B. West (1975). Instability of lung units with low V/Q ratios during O₂ breathing. *J Appl Physiol*, **5**, 886-895.
- Edmark, L., K. Kostova-Aherdan, M. Enlund and G. Hedenstierna (2003). Optimal oxygen concentration during induction of general anesthesia. *Anesthesiology*, **98**, 28-33.
- Keeney, R.L. and H. Raiffa (1993). *Decisions with multiple objectives*. Cambridge University Press, Cambridge.
- Kjærgaard, S., S. Rees, J. Malczynski, J.A. Nielsen, P. Thorgaard, E. Toft and S. Andreassen (2003). Non-invasive estimation of shunt and ventilation-perfusion mismatch. *Intensive Care Med*, **29**, 727-734.
- Kwok, H.F., D.A. Linkens, M. Mahfouf and G.H. Mills (2004). SIVA: A hybrid knowledge-and-model-based advisory system for intensive care ventilators. *IEE Trans Inf Technol Biomed*, **8**, 161-172.
- Matamis, D., F. Lemaire, A. Harf, C. Brun-Buisson and G. Atlan (1984). Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest*, **86**, 58-66.
- McKinley, B.A., F.A. Moore, R.M. Sailors, C.S. Cocanour, A. Marquez, R.K. Wright, A.S. Tonnesen, C.J. Wallace, A.H. Morris and T.D. East (2001). Computerized decision support for mechanical ventilation of trauma induced ARDS: Results of a randomized clinical trial. *J Trauma*, **50**, 415-425.
- Murley, D., S. Rees, B. Rasmussen and S. Andreassen (2005). Decision support of inspired oxygen selection based on Bayesian learning of pulmonary gas exchange parameters. *Artif Intell Med*, **34**, 53-63.
- Nash, G., J.B. Blennerhassett and H. Pontoppidan (1967). Pulmonary lesions associated with oxygen therapy and artificial ventilation. *N Engl J Med*, **276**, 368-374.
- Raemer, D.B., X. Ji, and G.P. Topulos (1997). F_{IX} controller: An instrument to automatically adjust inspired oxygen fraction using feedback control from a pulse oximeter. *J Clin Monit Comput*, **13**, 91-101.
- Rees, S.E., C. Allerød, D. Murley, Y. Zhao, B.W. Smith, S. Kjærgaard, P. Thorgaard and S. Andreassen (2006). Using physiological models and decision theory for selecting appropriate ventilator settings. *J Clin Monit Comput*, **35**, 421-429.
- Rees, S.E., S. Kjærgaard, P. Thorgaard, J. Malczynski, E. Toft and S. Andreassen (2002). The automatic lung parameter estimator (ALPE) system: Non-invasive estimation of pulmonary gas exchange parameters in 10-15 minutes. *J Clin Monit Comput*, **17**, 43-52.
- Rutledge, G.W., G.E. Thomsen, B.R. Farr, M.A. Tovar, J.Z. Polaschek, I.A. Beinlich, L.B. Sheiner and L.M. Fagan (1993). The design and implementation of a ventilator-management advisor. *Artif Intell Med*, **5**, 67-82.
- Shahsavari, N., U. Ludwigs, H. Blomqvist, H. Gill, O. Wigertz and G. Matell (1995). Evaluation of a knowledge-based decision-support system for ventilator therapy management. *Artif Intell Med*, **7**, 37-52.
- Tehrani, F., M. Rogers, T. Lo, T. Malinowski, S. Afuwape, M. Lum, B. Grundl, and M. Terry (2004). A dual closed-loop control system for mechanical ventilation. *J Clin Monit Comput*, **18**, 111-129.
- The Acute Respiratory Distress Syndrome (ARDS) Network (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*, **342**, 1301-1308.
- Van de Louw, A., C. Cracco, C. Cerf, A. Harf, P. Duvaldestin, F. Lemaire, and L. Brochard (2001). Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Med*, **27**, 1606-1613.