Time Series Analysis in Intensive Care Medicine

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Abstract

Objectives: Time series analysis techniques facilitate statistical analysis of variables in the course of time. Continuous monitoring of the critically ill in intensive care offers an especially wide range of applications. In an open clinical study time series analysis was applied to the monitoring of lab variables after liver surgery, and to support clinical decision making in the treatment of acute respiratory distress syndrome.

Patients and Results: For the analysis of lab variables (blood lactate) in 19 patients after liver resections ARIMA (Auto Regressive Integrated Moving Average) models were developed for an estimation period of at least 14 measurements. Prediction values from these models for the following data points were then compared to the actual lab values. With these models in all cases of hepatic complications pathological changes in the lab values could be differentiated from random variance.

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In 25 patients with ARDS the effect of therapeutic interventions on pulmonary target variables (PVR, Q_S/Q_T, $AaDO_2$) was estimated with interrupted ARIMA models. The time series before the therapeutic intervention was compared to changes under intervention using the same model including an intervention regressor. With all therapeutic interventions clinically relevant therapeutic effects could be statistically identified in all patients. Similarly, non-effective therapeutic maneuvers could be detected early, eventually changing therapeutic strategy.

Conclusions: Even on the basis of short time series of intensive care monitoring variables ARIMA models could be successfully employed for the analysis of lab variables and of therapeutic interventions. Nevertheless, due to high demands for manpower and to statistical methodological limitations the general use of this methodology in clinical practice apart from controlled clinical studies cannot be recommended today.

Key words

time series analysis- intervention analysis - decision support - intensive care - patient monitoring - laboratory tests

1 Introduction

1.1 Decision making in intensive care

Today most of our bedside decisions are based on subjective judgement and experience rather than on hard data and statistical analysis. Most of the time changes of a variable in time are more important than one pathological value at the time of observation.

Traditional statistical methods, such as the t-test or the analysis of variance, are aimed at the analysis of groups of measurements, i.e. groups of patients, at one or a limited number of points in time. None of these methods helps with repeated measurements in a single, individual subject. This is exactly the problem health care professionals face every day during their decision making process at the bedside.

The multitude of variables presented at the bedside precludes medical judgement. We can currently be confronted with more than 200 variables in the critically ill during a typical morning round [1], while an experienced physician may not be able to develop a systematic response to any problem involving more than seven variables [2]. Moreover, humans are limited in their ability to estimate the degree of relatedness between only two variables [3].

This problem is most pronounced in the evaluation of the measurable effect of a therapeutic intervention, where personal bias, experience, and a certain expectation of the respective intervention may distort an objective judgement [4].

Over the last two decades statistical methods have been developed that could help with these problems. Time series analysis techniques allow the assessments of single or multiple variables in the course of time. Moreover, interrupted time series can be used to evaluate the effect of interventions on a given variable of interest. Thus time series analysis techniques are statistical methods that may offer a potential for statistically analyzing physiologic measurements in the individual patient.

1.2 Time series analysis in intensive care

Methods of time series analysis in general, intervention analysis and ARIMA models in particular, first published in 1970 [5], are widely applied in psychology, psychometrics, sociology and epidemiology [6, 7, 8, 9, 10]. Conversely there have been few investigations into this methodology in the field of intensive care [11] or longitudinal physiological experiments [12]. This is surprising, as in intensive care large amounts of data are acquired, registered and stored at regular or irregular time intervals in one or multiple patients. Changes of single variables in the course of time due to pathophysiological disturbances or therapeutic interventions offer in principal a broad range of potential applications for time series analysis. Only with these statistical methods can so-called single case studies be done [13, 14].

ARIMA models appear to be very promising for intensive care time series analysis for a number of reasons:

- ARIMA modeling facilitates very flexible and differentiated model development, which should in theory well match and describe the complex underlying pathophysiology.
- ARIMA models assist forecasts with the use of confidence intervals.
- ARIMA models offer the statistical infrastructure for intervention analysis for the assessment of the clinical effect of therapeutic interventions.

Still, four major problems with the application of ARIMA models to intensive care time series can be anticipated:

- Missing observations are as frequent as variable time intervals between measurements. While regular time intervals can be accomplished by adaption of methods, missing values have to be bridged through interpolation or by the application of a *Kalman*-filter.
- Artifacts constitute a further, notorious problem especially with on-line measurements of vital signs, e.g. invasive blood pressure measurement or Holter ECG. Detected and identified artifacts can be handled like missing values.
- A limited number of data points can mean a serious restriction to the applicability of time series analysis in intensive care. The number of available measurements can be compromised both by the critical state of the respective patient and the thus limited time for measurement, and by methodological and organizational problems (e.g. laboratory). From a conservative point of view, more

than 50 observations are needed for a reliable estimation of an ARIMA-model [15]. But more recent simulation experiments show that a number of 20 data points can be sufficient [16]. In recent years different study groups could successfully develop ARIMA-models from time series of approx. 20 observations [6, 17].

- Although the calculation of ARIMA-models with intervention (interrupted time series) is regarded more critical concerning the series length [8], intervention analysis have been successfully described for time series with less than 20 observations on each side of the intervention [18].

The current study investigates two possible applications of time series analysis techniques in intensive care medicine.

1.3 ARIMA-models

1.3.1 General

ARIMA-models are flexible and applied to a wide spectrum of time series analysis. The abbreviation ARIMA stands for Auto Regressive Integrated Moving Average [19]. The general ARIMA-model combines three processes: Autoregression (AR), differentiation in order to eliminate integration (trend) of a time series (I), and moving average (MA). All three processes are based, generally speaking, on the principle of random disturbances or shocks.

The notation of a general ARIMA-model expresses the order of each process with whole numbers. An ARIMA-(p,d,q)-model, therefore, describes a time series with a p-th order autoregressive process, a d-th order differentiation, and a q-th order moving average process.

The present discussion can only provide a general outline of this complex methodology. For a complete description of these concepts, the comprehensive monographs by *Box* and *Jenkins* [19], and by *Schlittgen* and *Streitberg* [20] are recommended for further reading, as well as the program libraries from *SPSS Inc*. [23, 24, 25] for a complete description of the algorithms used in this paper.

1.3.1.1 Autoregressive (AR) Process

Definition [20]:

A stochastic process (X_t) is an autoregressive process of the order p, indicated by the notation AR(p), where

$$X_t = \alpha_1 X_{t-1} + \ldots + \alpha_p X_{t-p} + \varepsilon_t \,, \qquad t \in \aleph$$

ε_t is a white noise process.

This equation formally represents a multiple regression, although, in this instance the determining variable is not an independent variable, but the historic value of X_t itself.

Conceptually, an autoregressive process is one with a "memory", in the sense that each value is correlated with all preceding values. Following this interpretation, each value in an AR(p)-process is determined by p preceding values, where older values will have a fading effect. Low order processes, therefore, only have a "short memory". In an AR(1) process, also written as ARIMA (1,0,0), the current value is a function of the preceding value, which is a function of the one preceding it, and so on. Thus each shock or disturbance to the system has a diminishing effect on all subsequent time periods. Low order AR-processes can be typically found to describe physiological variables.

1.3.1.2 Moving Average (MA) Process

Definition [20]:

A stochastic process (X_t) is a moving average process of the order q, indicated by the notation MA(q) or ARIMA (0,0,q), where

$$X_t = \varepsilon_t - \beta_1 \varepsilon_{t-1} - \ldots - \beta_q \varepsilon_{t-q} , \qquad q \in \aleph$$

ε_t is a white noise process.

The difference between an autoregressive process and a moving average process is subtle but important. Each value in a moving-average series is a weighted average of the most recent random disturbances, while each value in an autoregression is a weighted average of the recent values of the series. Since these values in turn are weighted averages of the previous ones, the effect of a given disturbance in an autoregressive process dwindles as time passes. In a moving average process, a disturbance affects the system for a finite number of periods (the order of the moving average) and then abruptly ceases to affect it.

1.3.1.3 Differencing - Integration

A time series that reflects the cumulative effect of some process is called integrated. Such a time series has a trend and is instationary.

The stationarity of a series is necessary for the estimation of AR and MA processes. Therefore, time series that show a trend should be differenced, until stationarity is accomplished. In general first or second order differencing will be sufficient for series with a trend to assure stationarity.

1.3.2 Steps in Using ARIMA

The model-building procedure, described by *Box* and *Jenkins* [19], consists of three steps: identification, estimation, and diagnosis. These steps will be repeated until the model is satisfactory. This method requires the active interaction of the investigator. Since the three steps will have to be repeated and a number of repetitive steps are involved, this approach is also known as “iterative”.

A different approach is the application of a major number of models, where the order of the models is varied over a wide range (e.g. AR processes with p = 1 - 20).

The models are then compared by a pre-defined goodness-of-fit criterion, and the best model will be selected. This so-called (semi)automatic approach requires extensive computation times especially for higher order models. For economic reasons it is, therefore, most often restricted to scientific applications.

1.3.2.1 Identification

The identification of the model is the determination of the order of the respective processes of the ARIMA model.

It is necessary to difference the time series, until stationarity is accomplished. In addition, seasonal or cyclical variation has to be eliminated through an appropriate seasonal differencing.

Then p and q will be determined. It should be noted that values for p and q between 0 and 2 are sufficient to describe natural, observed time series.

The model identification will be derived from the analysis of the autocorrelation function and the partial autocorrelation function of the respective time series $\{x_t\}, t \in \{1, \ldots, N\}$ (N = number of observed time points). The plot of the autocorrelation coefficient $\rho_\tau = Corr(X_t, X_{t+\tau})$ as a function of the lag τ is called the autocorrelation function (ACF) of the process.

The estimated ACF is given by

$$\hat{\rho}_\tau = \frac{\frac{1}{N}\sum_{t=1}^{N}(x_t - \bar{x})(x_{t+\tau} - \bar{x})}{\frac{1}{N}\sum_{t=1}^{N}(x_t - \bar{x})^2}, \bar{x} = \frac{1}{N}\sum_{t=1}^{N} x_t$$

The ACF simply describes the autocorrelation between X_t and $X_{t+\tau}$ for $\tau \geq 1$, whereas the partial autocorrelation function is the partial correlation of X_t and $X_{t+\tau}$, for a constant process variable X_n, with $t < n < t + \tau$, between X_t and $X_{t+\tau}$ [20].

For practical purpose the calculation of the PACF is performed by use of the recursive formulas introduced by *Durbin* [21]:

$$\hat{\alpha}_{p+1,j} = \hat{\alpha}_{pj} - \hat{\alpha}_{p+1,p+1}\hat{\alpha}_{p,p-j+1}, j = 1, \ldots, p$$

$$\hat{\alpha}_{p+1,p+1} = \frac{\hat{\rho}_{p+1} - \sum_{j=1}^{p} \hat{\alpha}_{pj}\hat{\rho}_{p+1-j}}{1 - \sum_{j=1}^{p} \hat{\alpha}_{pj}\hat{\rho}_{j}}$$

AR(p) processes have exponentially declining values of the ACF, and have precisely p spikes in the first p values of the PACF.

MA(q) processes have precisely q spikes in the first q values of the ACF, and exponentially declining values of the PACF.

For integrated processes ($d > 0$) the ACF declines very slowly. The processes first have to be differenced before identifying the model.

Mixed AR and MA processes have more complex ACF and PACF patterns. Identifying them often takes several cycles of identification - estimation - diagnosis. Beside the investigator’s experience and knowledge handbooks with typical ACF and PACF plots can be helpful [25]. A selection of typical ACF and PACF plots is depicted in diagram 1.

1.3.2.2 Estimation

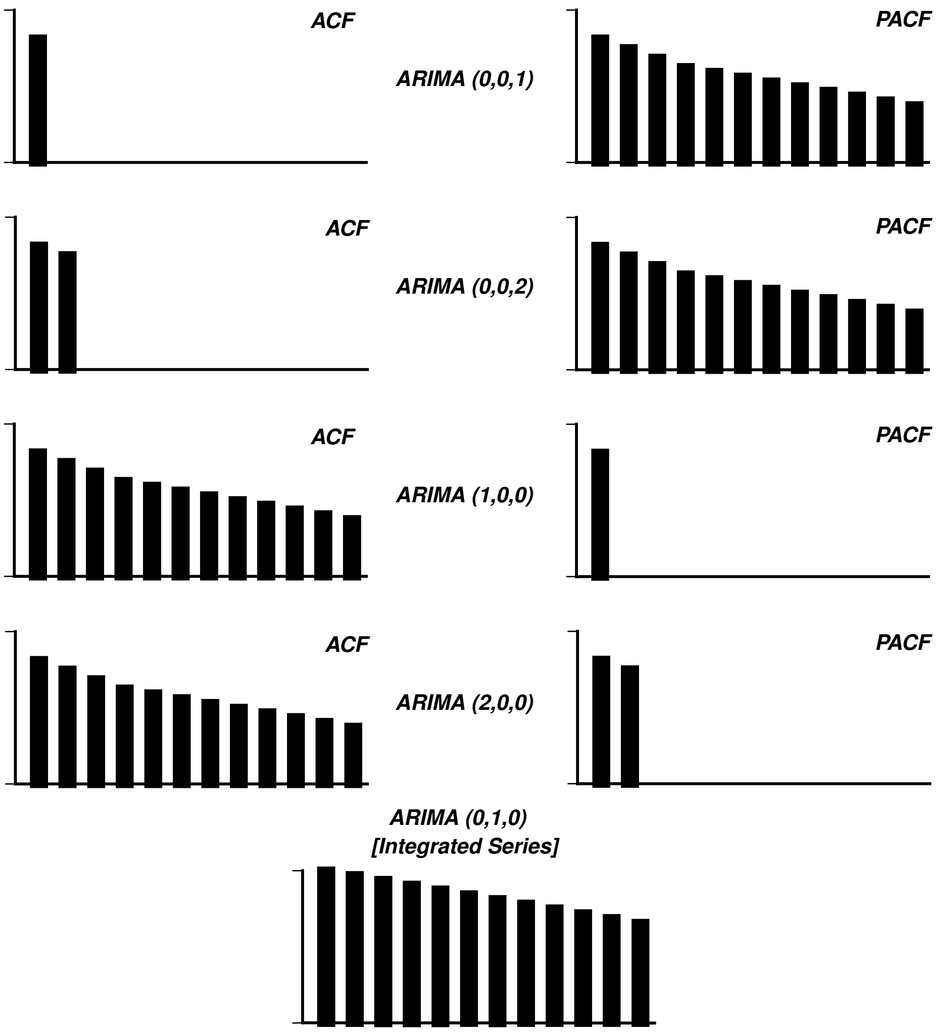
The next step is the estimation of the individual parameters of the identified model. The number of coefficients describing the model corresponds exactly to the order of the model. These coefficients are then calculated using adequate algorithms. The values for the modeled series, the residuals, i.e. the difference between the model and the actual series, the residual variance and the respective confidence intervals are computed by applying the final coefficients. Even for simple models the computational demands are remarkable and require adequate hardware and software resources.

A detailed description of the necessary algorithms and computational procedures can be found in the relevant literature.

1.3.2.3 Diagnosis

A number of different procedures can be employed to test whether the selected model is really a statistically sufficient description of the time series.

Diagram 1 Model identification: typical ACF and PACF plots for different ARIMA-Models. Details in text.



The diagnosis is based on the analysis of the residuals of the model. The ACF and PACF of the residual series should, especially with low order models, not be significantly different from zero.

After proper model identification and estimation residuals should constitute a white noise series. This can be tested with the *Box-Ljung* Q-statistics, a modified *Box-Pierce* statistics [26], although it is considered unreliable with short time series below 50 observations. The use of *Ansley* residuals can offer a better diagnostic estimation for short time series [27]. Unfortunately, this option is currently not available in any commercial statistical software package.

The *Durbin-Watson* statistics can be used as an additional test for stationarity. Test values around 2 imply a lack of correlation, values close to 0 indicate a positive and values close to 4 a negative correlation [28].

1.4 Clinical background

1.4.1 Blood lactate after liver resections

Elimination of peripheral lactate is a sensitive and reliable marker for hepatic function, as long as states of abnormally high lactate production (e.g. septic shock, intestinal ischemia) can be ruled out [29]. Recent clinical [30] and animal studies [31, 32] have demonstrated that blood lactate is a very sensitive variable for hepatic function. Moreover, serial patterns of blood lactate levels after liver resections appear to have prognostic value [33].

With very sensitive variables like blood lactate a marked variance can be observed even in healthy subjects. Major changes, however, point to the presence of a pathological process. Therefore, the problem is to differentiate between physiological variability and clinically important changes. Time series analysis may help to determine the limit, where random changes become too large to be attributed to physiological variability.

1.4.2 Acute respiratory distress syndrome

Acute respiratory distress syndrome is a serious complication after trauma or surgery. The broad range of etiological factors is contrasted by the rather uniform reaction of the lung [34, 35]:

- Pulmonary hypertension.
- Elevated intrapulmonary shunt, causing a decrease of p_aO_2, and
- Release of mediators leading to secondary organ dysfunction (kidney, liver, coagulation, cardio-vascular).

A release of arachidonic acid metabolites is characteristic of the early stages of ARDS [36, 37, 38]. In the course of the disease the intrapulmonary shunt (Q_S/Q_T) increases [39], which may be accompanied by mediator and mechanical destruction induced permeability edema of the lung induced by mediators and mechanical stress [40]. This pathophysiological sequence results in a rapid increase in the alveolar-arterial oxygen difference ($AaDO_2$), which can be regarded as one of the most important general parameters of pulmonary function [41, 42].

All ventilatory and medical support in ARDS is only a symptomatic treatment, which may also explain the great variety of therapeutic approaches, among which two basic therapeutic principles can be distinguished:

The increase of the functional residual capacity of the lung (FRC) is to recruit alveolar space and reduce intrapulmonary shunt (“open up the lung”, [43]). This can typically be done by positive end-expiratory pressure (PEEP) [44] as well as by inversed-ratio ventilation (IRV) [45, 46], or a combination of both. Both techniques can induce volo- and barotrauma of the lung [47, 48]. Further side effects are a cardio-vascular depression and renal impairment, as well as compensatory volume overload [34, 35, 38, 49]. Therefore, IRV and PEEP should be limited to the shortest possible time.

Reducing elevated pulmonary vascular pressures is also an important approach to ARDS. Animal experiments have shown an advantageous effect of nifedipine on thromboxane synthesis and thrombocyte aggregation with a consecutive reduction of pulmonary vascular resistance [50, 51, 52]. Early clinical studies in patients with ARDS and COLD had corresponding results [53, 54]. Studies in polytraumatized patients with ARDS showed a decrease of PVR and an improvement of pulmonary compliance during the infusion of nifedipine [34, 35].

With either concept effectiveness in the individual patient cannot be predicted. Pronounced negative effects on pulmonary function can be induced both by high airway pressures as well as by the vasodilating potency of nifedipine. Therefore, it is of major importance to make therapeutic decisions on the basis of statistical analysis of pulmonary variables in the individual patient.

1.5 Goal of the study

The use of ARIMA models for the analysis of intensive care data and for therapy control should be evaluated under actual clinical conditions. ARIMA models were tested in two different applications.

- How time series analysis can contribute to a better and more precise description of lab variables, and eventually support the clinical evaluation of the patient, compared to the physician's professional judgement alone.
- Intervention analysis was also applied as a tool for testing effectiveness of intensive care therapeutic interventions in the individual patient.

The primary goal of the present study is to evaluate the clinical applicability of time series analysis techniques to medical problems. The actual medical applications used in this study have been chosen at will from a large number of potential applications, and should serve as a vehicle to allow the use of ARIMA-models. This study is not intended to evaluate the efficacy or effectiveness of any of the therapeutic or pathophysiological principles presented in this paper.

2 Methods and materials

2.1 Patients

2.1.1 Blood lactate after liver resection

Nineteen patients (13 male, 6 female, mean age 52 years) were included in this study after liver resections of variable extent (5 right trisegmentectomies, 8 right hemihepatectomies, 1 left hemihepatectomy, 5 segmental resections).

Starting two hours after end of surgery blood lactate levels were measured in the arterial blood in addition to other standard lab variables (blood count, coagulation, blood chemistry) every 12 hours. All values were measured with automatic or semi-automatic standard methods [55].

In all patients elevated lactate levels (3.3 - 20.1 mmol/l) were rapidly eliminated during the first 24 to 36 postoperative hours. This period was excluded from model estimation.

2.1.2 Acute respiratory distress syndrome

In 25 cases (20 male, 5 female, mean age 58 years) of severe secondary ARDS after major gastrointestinal surgery an extended hemodynamic monitoring with Swan-Ganz catheter was performed.

All patients met the NHLBI criteria [56] for severe ARDS for more than 24 hours. All patients were ventilated in controlled ventilation (CMV) mode and with PEEP (PEEP = 8 -14 mbar), and received catecholamines (dopamine/dobutamine) and analgosedation with opiates and benzodiazepines.

After the onset of ARDS the following measurements were recorded every hour:

- arterial and mixed-venous blood gas analysis,
- heart rate, arterial and pulmonary arterial pressures, central venous pressure, cardiac output (thermodilution),
- ventilatory variables.

The observation time ranged from 28 to 225 hours with a mean of 61 hours. Pulmonary vascular resistance (PVR), intrapulmonary right-left shunt (Q_s/Q_t) and alveolar-arterial oxygen difference ($AaDO_2$) were calculated from the measured values with standard formulae.

Patients with an elevated intrapulmonary right-left shunt ($Q_S/Q_T > 15\%$) were ventilated with inverse-ratio ventilation (I:E > 1,5:1, max. 4:1) and increased PEEP (PEEP > 10 mbar, max 20 mbar).

13 patients with elevated PVR (PVR > 200 dyn•sec•cm^{-5}) received a continuous infusion of nifedipine at a dosage of 5 -10 µg/kg/h (20-30 mg/die). At the end of treatment the dose of nifedipine was reduced slowly over 48 hours. 9 patients with an elevated intrapulmonary right-left shunt (Q_S/Q_T > 15%) were ventilated with inverse-ratio ventilation (I:E > 1,5:1, max. 4:1) and/or with PEEP (PEEP > 10 mbar, max 20 mbar). 3 patients with both pathologies first received the continuous nifedipine infusion and than the described change of ventilation mode after the nifedipine infusion had been stopped.

2.2 Methods

For each patient after liver resection a time series analysis was done to differentiate significant changes in blood lactate levels from random fluctuations.

For each patient in ARDS an intervention analysis was performed to access therapeutic effects.

Starting with twelfth hour of measurement in ARDS or with the seventh day after liver resection ARIMA models were developed for the previous measurements. Where possible, 20 or more observations were used for estimation.

For model diagnosis a classical, iterative approach was preferred and only simple, low order models with AR[p] ≤ 2, MA[q] ≤ 2, I[d] ≤ 1 used.

The initial values for p, q, and d were derived from the autocorrelation function and partial autocorrelation function (ACF, PACF) of the original series, and after first order differentiation if necessary. The final parameters of the model were calculated using *Marquardt*'s algorithm. If more than one model appeared suitable for the series, all models were computed and the definite model selected by the goodness of fit [20].

The goodness of fit was estimated by the ACF and PACF of the residual series. In addition, the *Box-Ljung* statistics was applied [26], although it has only limited value with short time series [57]. Models were only accepted when the residual series did not surpass the 95% confidence interval of the ACF and the PACF.

The *Akaike* Information Criterion (AIC) and the *Schwartz Bayesian* Criterion (SBC) were also computed [58, 59]. These criteria were especially useful to choose between different models for one series.

For each coefficient the t-statistics were determined, derived from the quotient of the coefficients and the respective standard error, to test, whether the addition of the respective coefficient to the model was appropriate. Only models were selected, in which the coefficients were significant on an 0.05-level.

Finally, the root mean square error (RMS) and the *Durbin-Watson* statistics were computed, where test values between 1.5 and 2.5 for the *Durbin-Watson* statistics were accepted. The later statistics being used to detect violations of stationarity.

After liver resection patients typically show elevated blood lactate levels, which is due to the intraoperative vascular exclusion of the liver. These levels return to normal after the first 24 to 36 hours[33]. This period was excluded from model estimation. After the first week of observation the actual values for the last 24 hours were compared to the values predicted from the model for the previous measurements. In the case of a normal clinical course the new values for these 24 hours were then integrated into the model for the following 24 hours. Thus the estimation period was constantly enlarged and, therefore, the reliability of the model improved.

For the prediction period of 24 hours maximum the values predicted by the model (including the 95% confidence interval) were compared to the actual lab values. The clinical statement was reduced to the dichotomous question of whether or not the actual measurements surpassed the 95% confidence interval of the prediction period.

For patients suffering from ARDS in case of continuous compromised pulmonary function over the estimation period of the model, one of two therapeutic interventions was done depending on the actual physiological measurements.

For the period of infusion or the change of the ventilation mode, respectively, a dummy variable (“STEP”) was set from 0 to 1.

For a therapeutic period of at least 12 hours the same ARIMA model was applied as for the estimation phase. The dummy variable was integrated as an additional regressor to describe the therapeutic intervention.

The model equation for an AR(I)MA model with an integrated step function

$$S_t^{(T)} = \begin{cases} 0 & t < T \\ 1 & t \geq T \end{cases}$$

is given by

$$\begin{aligned} X_t = \alpha_1 X_{t-1} + \ldots + \alpha_p X_{t-p} + \varepsilon_t \; - \\ \beta_1 \varepsilon_{t-1} - \ldots - \beta_q \varepsilon_{t-q} \; - \omega S_t^{(T)}, \\ p, q \in \aleph \end{aligned}$$

The parameter ω represents the size of the intervention effect and has to be estimated. The addition of more step functions follows the same notation.

The analysis of the therapeutic effect was only done, when the model met the goodness-of-fit criteria mentioned above.

A significant therapeutic effect was assumed, if PVR or Q_S/Q_T were reduced by at least 20% and the t-statistics for the dummy variable showed a significance level of $p < 0.05$.

Over the whole observation period the cross-correlation function between PVR or Q_S/Q_T respectively with $AaDO_2$ was calculated. The values for PVR or Q_S/Q_T at the respective lags were introduced into a linear regression analysis with $AaDO_2$. Only if more than 50% of the variance of $AaDO_2$ could be statistically explained by the changes of PVR or Q_S/Q_T respectively, a positive treatment effect on pulmonary function was accepted.

All analyses were computed with SPSS-X™ Release 5 and SPSS-X TRENDS™ for Sun Solaris™ 2.x.

All investigations were done at a 16-bed surgical intensive care unit in a tertiary care center during routine operation.

3 Results

3.1 General Results

Simple models ($p, q \leq 2$) were sufficient for a good model description in all time series. Actually, all series could be described with first or second order autoregressive models. This appears plausible, because physiological measurements will typically exhibit a strong correlation to the most recent values of the same variable.

Also for short estimation periods a model could always be developed, that met the goodness-of-fit criteria. Twelve to sixteen observations appeared to be sufficient for a reliable model estimation under the condition of a relatively small overall variance.

In most cases the models could be directly identified from the analysis of the autocorrelation and partial autocorrelation functions. In only a limited number of cases was it necessary to develop more than one model and select the final model by the goodness-of-fit criteria.

3.1.1 Liver resections

For the analysis of blood lactate values the final model could be directly diagnosed in 11 cases, whereas in 8 cases two models each had to be develop, from which the final model was then selected.

For those cases where two models had to be calculated the estimation period was significantly shorter than for those where the model could be directly derived from the ACF and PACF (19.75 vs. 27.5 observations; $p < 0.02$, U-test).

In 12 cases a first order AR-model was used, in 5 cases a second order AR-model, in one case each an ARIMA-(1,1,0)-model and an ARIMA-(0,0,0)-model.

The demographic data, models, parameters and variables for each patient are listed in table 1.

Three out of 19 patients died from hepatic failure in the postoperative phase.

In case of an uncomplicated course lactate levels stayed stable around 2 mmol/l (in some cases up to 4 mmol/l, a value that is considered pathologic in healthy subjects), and did never surpass the 95% confidence interval of the individual ARIMA model.

With the onset of complications, e.g. portal venous thrombosis, fulminant hepatic failure, lactate levels rose sharply and rapidly left the 95% confidence interval of the respective ARIMA model. In all fatalities lactate levels left the 95% confidence interval at least 36 hours before death. Time series analysis of lactate levels allowed a differentiation between random fluctuations and clinically relevant changes.

Table 1 Liver resections. Demographic data, models, parameters, and diagnostic effect. Details in text. (Sheet 1 of 3)

ID	Age	Sex	Diagnosis	Surgery	Complication	Outcome	Estimation period[a]	Prediction period[a]	Calc models[b]	Final Model	AR1	p <	AR2	p <	const.	p <	Deviation from Model[c]	Time before death[a]
1	54	m	Metastasis, colo-rectal	right hemihep.	no	survive	3-28	29-33	1	(2,0,0)	1.4333	.001	-.6661	.001	1.3513	.001	no	n/a
2[d]	66	m	HCC	right trisegmentect.	portal thromb	died	3-26	27-34	1	(1,0,0)	.7442	.001			1.3757	.001	yes	7
3	30	f	FNH	resect. segment IV	no	survive	3-11	12-13	2	(0,0,0)					.8000	.001	no	n/a
4	50	m	Metastasis, colo-rectal	right hemihep.	no	survive	4-16	17-18	1	(1,1,0)	-.6844	.01			-.2819	.1	no	n/a
5	29	f	Metastasis, colo-rectal	right trisegmentect.	no	survive	3-28	29-32	1	(1,0,0)	.6160	.001			1.2280	.001	no	n/a
6	58	m	Cholangiolar Carcinoma	right hemihep.	liver failure	died	3-15	16-17	2	(1,0,0)	.5654	.001			4.6233	.001	yes	2

Table 1 Liver resections. Demographic data, models, parameters, and diagnostic effect. Details in text. (Sheet 2 of 3)

16	15	14	13	12	11	10	9	8	7[d]	**ID**
65	46	50	64	43	48	32	58	59	64	**Age**
f	m	m	m	m	m	w	m	m	m	**Sex**
Metastasis, colo-rectal	Metastasis, colo-rectal	HCC, Cirrhosis	Metastasis, colo-rectal	Metastasis, colo-rectal	Metastasis, colo-rectal	Cholangiolar Carcinoma	Metastasis, colo-rectal	Cholangiolar Carcinoma	HCC	**Diagnosis**
resect. segment IV	right trisegmentect.	left hemihep.	right hemihep.	right hemihep.	right hemihep.	right trisegmentect.	right hemihep.	resect. segment IV	right hemihep.	**Surgery**
no	no	no	no	no	no	no	no	liver failure	no	**Complication**
survive	survive	survive	survive	survive	survive	survive	survive	died	survive	**Outcome**
3-33	2-36	2-25	3-27	3-24	3-18	3-23	3-23	3-24	3-25	**Estimation period[a]**
34-37	37-40	26-28	28-30	24-28	19-20	24-26	24-26	25-29	26-33	**Prediction period[a]**
1	1	1	1	2	2	1	2	1	2	**Calc models[b]**
(1,0,0)	(1,0,0)	(2,0,0)	(2,0,0)	(2,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	**Final Model**
.6824	.6389	1.2712	1.0459	1.0213	.5474	.7877	.3365	.6059	.6314	**AR1**
.001	.001	.001	.001	.001	.05	.001	.05	.01	.001	**p <**
		-.6909	-.6091	-.5664						**AR2**
		.001	.01	.01						**p <**
2.0795	1.6887	1.7355	1.4738	1.8732	1.8332	.8718	1.0179	2.1453	1.1922	**const.**
.001	.001	.001	.001	.001	.001	.001	.001	.001	.001	**p <**
no	yes	no	no	no	no	no	no	yes	no	**Deviation from Model[c]**
n/a	3	n/a	n/a	n/a	n/a	n/a	n/a	4	n/a	**Time before death[a]**

Table 1 Liver resections. Demographic data, models, parameters, and diagnostic effect. Details in text. (Sheet 3 of 3)

ID	Age	Sex	Diagnosis	Surgery	Complication	Outcome	Estimation period[a]	Prediction period[a]	Calc models[b]	Final Model	AR1	p <	AR2	p <	const.	p <	Deviation from Model[c]	Time before death[a]
17	63	m	Metastasis, colo-rectal	right hemihep.	no	survive	3-20	21-24	2	(1,0,0)	.3099	.05			5.6824	.001	no	n/a
18	55	f	Metastasis, breast cancer	multiple segments	no	survive	3-19	20-22	2	(2,0,0)	1.1563	0.001	-.7380	.001	2.9789	0.001	no	n/a
19	64	f	Metastasis, colo-rectal	multiple segments	no	survive	3-37	38-41	1	(1,0,0)	.6814	0.001			1.9634	0.001	no	n/a

a) Number of measurements postop (= number of 12 hour intervals)
b) Number of different calculated models selected for diagnosis
c) Deviation of actual measurement from predicted 95% confidence interval
d) Detailed description of this case in "Casuistics"

3.1.2 Acute respiratory distress syndrome

In 16 patients with nifedipine therapy for 10 patients the model for PVR could be directly identified. In the other 6 cases the final model had to be selected from up to three initial models. In 5 out of 12 interventions with IRV (including 3 patients after nifedipine therapy) more than one model had to be developed to find the final estimate.

Thus in a total 28 therapeutic intervention analyses 11 cases required the comparative calculation of more than one model. Also these 11 cases had a shorter estimation period (19.6 vs 24.8 observations), although this difference is not significant ($p < 0.1$, U-test).

The majority of time series (22 cases) could be described with first order AR-models. One case required a second order AR-model, and in five cases a linear model was used.

The therapeutic effect could always be assessed after 12 to 24 hours. In most of those cases that showed a significant effect of the dummy variable on the time series of PVR or Q_S/Q_T a significant decrease of $AaDO_2$ could also be observed after a time lag of 1 to 48 hours. Moreover, between 50% and 96% percent of the overall variance of $AaDO_2$ could be explained by the lagged values of PVR or Q_S/Q_T, derived from the cross-correlation function. These observations were also well reflected in the clinical course.

In those cases where no significant therapeutic effect could be detected the therapeutic intervention was reduced to initial values. A number of patients received an alternate therapy (e.g. IRV/PEEP after futile nifedipine treatment). This new intervention was than controlled by time series analysis again.

Intervention analysis supported a more differentiated approach to therapeutic selection. It helped to limit aggressive therapy to short time periods and to decide, whether a therapeutic intervention resulted in a detectable effect.

Ten of sixteen patients showed a significant drop in PVR in the time series model. In the other 6 cases the therapeutic intervention (i.e. nifedipine) was, according to the statistical analysis, phased out. From these, 3 patients were subjected to IRV in the later course.

These 3 (patients 2, 9, and 11) and another 9 patients were treated with IRV and PEEP. Again in 8 subjects a instantaneous effect on Q_S/Q_T could be observed. Two patients (patients 18 and 25) showed no significant changes and were consequently returned to the initial ventilation pattern. In two other patients (patients 19 and 24) the initial significant improvement displayed in the intervention analysis could not be maintained in the later course. All four patients were then placed in prone position.

Fourteen of twenty-five patients deceased. In 13 cases the cause of death was an irreversible multi organ failure. One patient suffered from an acute myocardial infarction during weaning, which could not be seen as a direct consequence of ARDS.

With the exception of the latter case all patients displayed a good correlation between the clinical results and the findings of time series analysis.

The demographic data, models, parameters and variables for each patient are listed in tables 2 and 3.

Table 2 ARDS. Treatment with nifedipine. Demographic data, models, parameters, interventions. Details in text. (Sheet 1 of 3)

ID	**Age**	**Sex**	**Diagnosis**	**Outcome**	**Estim period[a]**	**Intv period 1[a]**	**Series length**	**Calc model[b]**	**Final model**	**AR1**	**p <**	**STEP1**	**p <**	**init PVR[c]**	**PVR step[d,e]**	**init $AaDO_2$**	**$AaDO_2$ step[d,e]**	**Lag[a]**	**r^2**	**Scd Ther[f]**
1	69	m	Esophageal Carcinoma	survive	32	32	129	1	(1,0,0)	.97	.001	-159.47	.001	249.49	159.84	231.25	219.93	44	.27	no
2	65	m	Esophageal Carcinoma	survive	16	16	127	1	(1,0,0)	.72	.001	-32.57	.1	185.32	195.25	149.42	156.97	28	.40	yes
3	63	m	Esophageal Carcinoma	died	16	16	47	3	(1,0,0)	.91	.001	-15.19	n.s.	167.23	164.57	227.24	259.36	9	.03	no

Table 2 ARDS. Treatment with nifedipine. Demographic data, models, parameters, interventions. Details in text. (Sheet 2 of 3)

ID	Age	Sex	Diagnosis	Outcome	Estim period[a]	Intv period 1[a]	Series length	Calc model[b]	Final model	AR1	p <	STEP1	p <	init PVR[c]	PVR step[d,e]	init $AaDO_2$	$AaDO_2$ step[d,e]	Lag[a]	r^2	Scd Ther[f]
4[g]	73	f	Hepatic Tumor	survive	16	16	42	3	(1,0,0)	.62	.001	-77.15	.001	252.50	128.58	287.00	161.50	8	.81	no
5	59	m	GI-Bleeding	died	18	18	65	2	(1,0,0)	.52	.001	-73.59	.001	643.44	533.32	262.55	160.90	1	.42	no
6	64	m	Peritonitis	survive	24	24	119	1	(0,0,0)			-116.23	.001	267.05	143.94	266.96	154.04	44	.55	no
7	59	m	Peritonitis	died	18	17	35	1	(1,0,0)	.97	.001	-9.07	n.s.	147.97	177.79	210.03	200.96	4	.21	no
8	58	m	Esophageal Carcinoma	died	14	14	36	2	(1,0,0)	.99	.001	-69.10	.05	348.70	256.33	109.08	149.47	2	.43	no
9[g]	58	f	Abdom. gunshot	died	12	12	87	1	(0,0,0)	.	.	59.72	.002	250.00	333.39	377.00	360.00		.01	yes
10	67	m	GI-Bleeding	survive	32	32	117	1	(1,0,0)	.99	.001	-163.48	.001	236.92	159.15	232.27	208.07	57	.59	no
11	65	m	Peritonitis	died	16	16	143	1	(1,0,0)	.53	.002	-15.15	n.s.	188.08	194.09	206.20	215.84	26	.18	yes
12	63	m	Esophageal Carcinoma	died	16	16	54	3	(1,0,0)	.47	.006	-21.09	n.s.	163.37	147.78	298.55	326.21	4	.06	no
13	69	m	Gastric Carcinoma	died	16	16	45	2	(1,0,0)	.40	.02	-78.47	.001	205.36	126.93	374.89	219.46	8	.69	no
14	57	m	Hepatic Tumor	survive	18	18	70	1	(0,0,0)			-88.01	.001	637.38	526.97	352.03	212.29	3	.29	no

Table 2 ARDS. Treatment with nifedipine. Demographic data, models, parameters, interventions. Details in text. (Sheet 3 of 3)

ID	**Age**	**Sex**	**Diagnosis**	**Outcome**	**Estim period[a]**	**Intv period 1[a]**	**Series length**	**Calc model[b]**	**Final model**	**AR1**	**p <**	**STEP1**	**p <**	**init PVR[c]**	**PVR step[d,e]**	**init $AaDO_2$**	**$AaDO_2$ step[d,e]**	**Lag[a]**	**r^2**	**Scd Ther[f]**
15	64	m	Peritonitis	survive	24	24	107	1	(0,0,0)			-109.26	.001	267.40	<u>144.62</u>	345.98	<u>207.12</u>	47	.62	no
16	59	m	Esophageal Carcinoma	died	18	18	40	1	(1,0,0)	.26	n.s.[h]	18.47	.05	150.81	177.32	293.59	262.10	10	.28	no

a) Estimation period, intervention period and lag period in hours
b) Number of different calculated models selected for diagnosis
c) Mean value during estimation period
d) Mean value during intervention period
e) Underlined values denote significant changes of the parameter
f) Secondary therapy after nifedipine treatment. For secondary therapy see same patients in table 3.
g) Detailed description of this case in "Casuistics"
h) Model selected, because parameters were significant ($p < 0.05$) for estimation period

Table 3 ARDS. Treatment with PEEP and IRV. Demographic data, models, parameters, interventions. Details in text. (Sheet 1 of 2)

ID	**Age**	**Sex**	**Diagnosis**	**Outcome**	**Intv 1[a]**	**Intv 2[a]**	**Estim per[b]**	**Intv per1[b]**	**Intv per2[b]**	**Series length[b]**	**Calc model[c]**	**Final model**	**AR1**	**p <**	**AR2**	**p <**	**STEP1**	**p <**	**STEP2**	**p <**	**init**	**Q_s/Q_t step[e,f]**	**init $AaDO_2$[d]**	**$AaDO_2$ step[e,f]**	**Lag[b]**	**r^2**
17	54	m	GI-Bleeding	survive	PEEP	IRV	17	9	17	64	1	(2,0,0)	-.1255	n.s.[g]	.0776	n.s.[g]	-7.9	.001	-10.3	.001	38.2	<u>16.2</u>	602	<u>177</u>	0	.88
18	53	m	Peritonitis	died	PEEP+IRV		29	29		81	1	(1,0,0)	.3052	.05			-2.8	n.s			29.5	28.7	489	475	0	.45
19	59	m	Esophageal Carcinoma	survive	PEEP+IRV		20	20		83	2	(1,0,0)	.3038	.05			-8.6	.001			20.9	<u>10.9</u>	221	<u>131</u>	1	.56
20	60	f	Peritonitis	died	PEEP	IRV	25	3	25	56	1	(0,0,0)					-10.1	.001	-15.5	.001	35.3	<u>9.8</u>	383	<u>96</u>	0	.94

Table 3 ARDS. Treatment with PEEP and IRV. Demographic data, models, parameters, interventions. Details in text. (Sheet 2 of 2)

ID	11	9[h]	2	25	24	23	22	21
Age	65	58	65	31	30	52	59	59
Sex	m	f	m	m	m	f	m	f
Diagnosis	Peritonitis	Abdom. gunshot	Esophageal Carcinoma	Peritonitis	Abdom. gunshot	Peritonitis	Esophageal Carcinoma	Peritonitis
Outcome	died	died	survive	survive	died	died	survive	died
Intv 1[a]	PEEP+IRV	IRV	PEEP	PEEP+IRV	PEEP	PEEP+IRV	PEEP	PEEP
Intv 2[a]		PEEP			IRV			
Estim per[b]	24	36	20	37	42	33	28	20
Intv per1[b]	22	18	20	30	23	33	28	20
Intv per2[b]		30			30			
Series length[b]	46	129	42	67	95	73	57	57
Calc model[c]	2	2	2	1	1	1	1	4
Final model	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)	(1,0,0)
AR1	.2080	.7582	.0350	.6209	.6713	-.1161	.1242	.0450
p <	n.s.[h]	.001	n.s.[g]	.001	.001	n.s.[g]	n.s.[g]	n.s.[g]
AR2								
p <								
STEP1	-14.6	-9.2	-18.7	+9.7	-3.80	-17.1	-12.1	-17.8
p <	.001	.001	.001	.001	.001	.001	.001	.001
STEP2		-5.1			-5.9			
p <		.001			.001			
init	26.7	25.4	30.8	21.9	22.6	26.0	28.1	32.9
Q_s/Q_t step[e,f]	11.8	7.90	12.0	31.5	11.8	8.6	15.8	13.8
init $AaDO_2$[d]	601	390	372	300	310	580	347	351
$AaDO_2$ step[e,f]	276	126	132	462	159	108	160	120
Lag[b]	0	0	0	0	0	0	0	0
r^2	.94	.68	.88	.90	.86	.77	.69	.81

a) First and second ventilatory intervention
b) Estimation period, intervention periods (first and second intervention), total series length and lag period in hours
c) Number of different calculated models selected for diagnosis
d) Mean value during estimation period
e) Mean value during intervention period (one or two interventions)
f) Underlined values denote significant changes of the parameter
g) Model selected, because parameters were significant ($p < 0.05$) for estimation period
h) Detailed description of this case in “Casuistics”

3.2 Casuistics

The following casuistics exemplify the practical application of ARIMA-models to clinical problems. Two cases after liver resections and two cases of ARDS are chosen to show in detail the process of development of the time series model, its diagnosis, and finally the clinical relevance of these findings.

3.2.1 Liver resection

3.2.1.1 Patient 7: K.A., 64 years, male

This patient underwent a right hemihepatectomy for a hepatocellulary cancer. The postoperative course was without complication and the patient was discharged from hospital on the 17th day after surgery.

For the estimation period from 36 to 300 hours postop a first order AR model could be developed from the analysis of the ACF and PACF. The final parameters with the corresponding t-statistics were:

AR1 = 0.63	S.E. = 0.14	t = 4.42	$p < 0.001$
const. = 1.19	S.E. = 0.14	t = 8.63	$p < 0.001$

The residual series never left the 95% confidence interval of the ACF and PACF. The *Box-Ljung* statistics showed no significant deviations.

Goodness-of-fit criteria:

AIC = 14.8 SBC = 17.2

root mean square error = 0.31

Durbin-Watson = 1.92

The actual lactate values did not surpass the predicted 95% confidence interval of the ARIMA model for the time from the 312th hours postop until discharge (diag. 2).

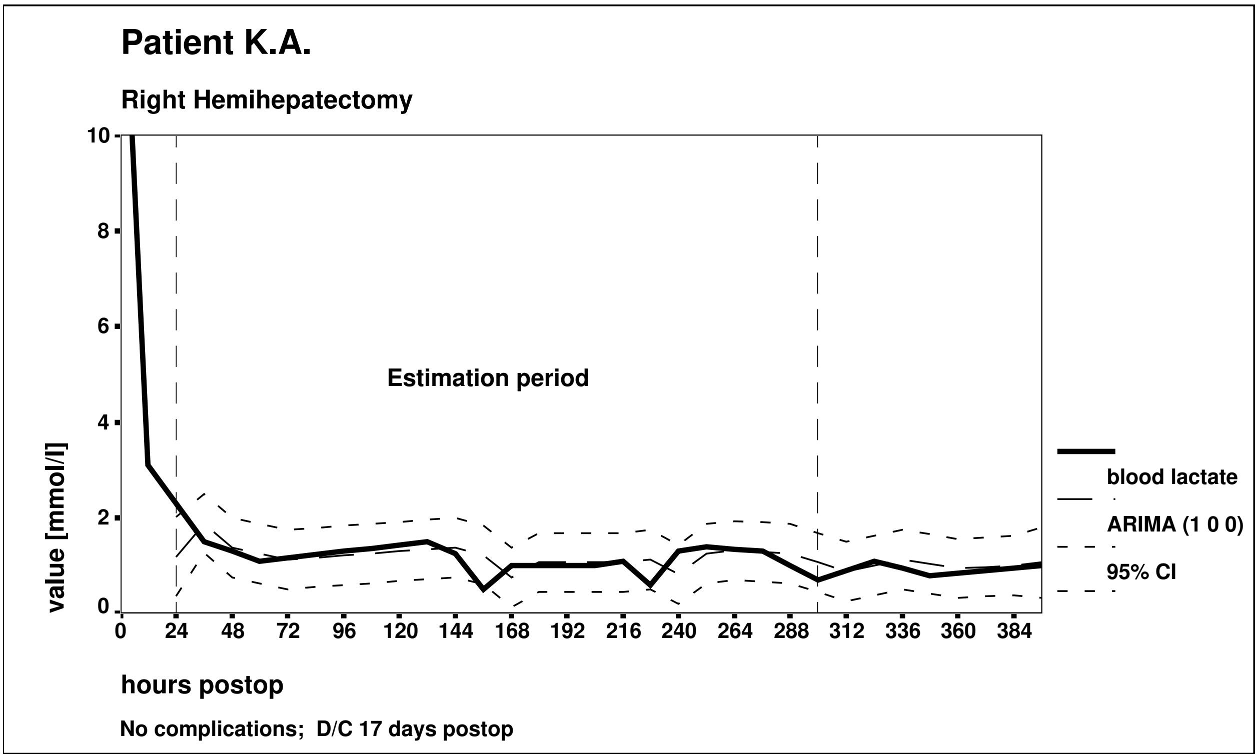
3.2.1.2 Patient 2: J.K., 66 years, male

In this patient a right trisegmentectomy was done for a hepatocellulary carcinoma. A portal venous thrombosis occurred 312 hour postop. The patient died on the 17th day after surgery.

The estimation period from 24 to 312 hours postop a first-order AR-model could be developed from the ACF and PACF:

AR1 = 0.74	S.E. = 0.14	t = 5.33	$p < 0.001$
const. = 1.38	S.E. = 0.18	t = 7.77	$p < 0.001$

Diagram 2 Patient K.A., 64 years, male. Hepatocellulary carcinoma. Right hemihepatectomy. Postoperative time series of lactate levels and ARIMA (1,0,0) model. Details in text.



Again, the residual series never left the 95% confidence interval of the ACF and PACF. The *Box-Ljung* statistics showed no significant deviations.

Goodness-of-fit criteria:

AIC =5.4 SBC = 7.8

root mean square error = 0.25

Durbin-Watson = 1.70

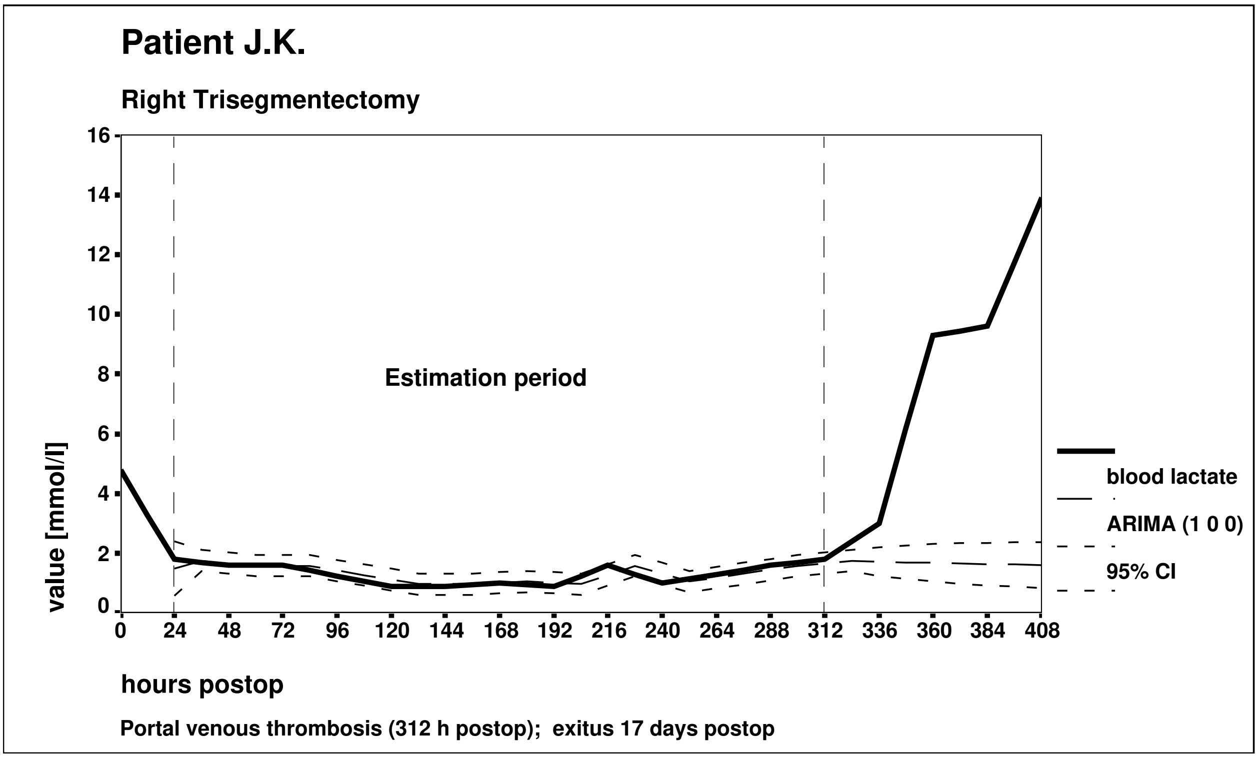
Starting at 324 hours postop lactate values deviated from the predicted model, immediately left the 95% confidence interval, and showed a steady increase until death of the patient (diag. 3).

3.2.2 Acute respiratory distress syndrome

3.2.2.1 Patient 4: A.P., 73 years, female

This patient was treated for a hepatocellulary carcinoma with a right hemihepatectomy. An ARDS of unclear etiology developed immediately after surgery. During the first 16 hours the patient had a pulmonary hypertension with a mean PVR of 250 dyn·sec·cm^{-5}. The initial $AaDO_2$ with a mean of 287

Diagram 3 Patient J.K., 66 years, male. Hepatocellulary carcinoma. Right trisegmentectomy. Postoperative time series of lactate levels and ARIMA (1,0,0) model. Details in text.



mmHg reflected seriously damaged pulmonary function. For this initial period three different ARIMA models were diagnosed from the ACF and PACF. The goodness-of-fit criteria identified a first order AR-model as the final model:

AR1 = 0.40	S.E. = 0.24	t = 1.65	$p < 0.15$
const. = 201.79	S.E. = 7.33	t = 27.55	$p < 0.001$

The residual series met the goodness-of-fit criteria:

AIC = 140.7 SBC = 142.3

root mean square error = 17.3

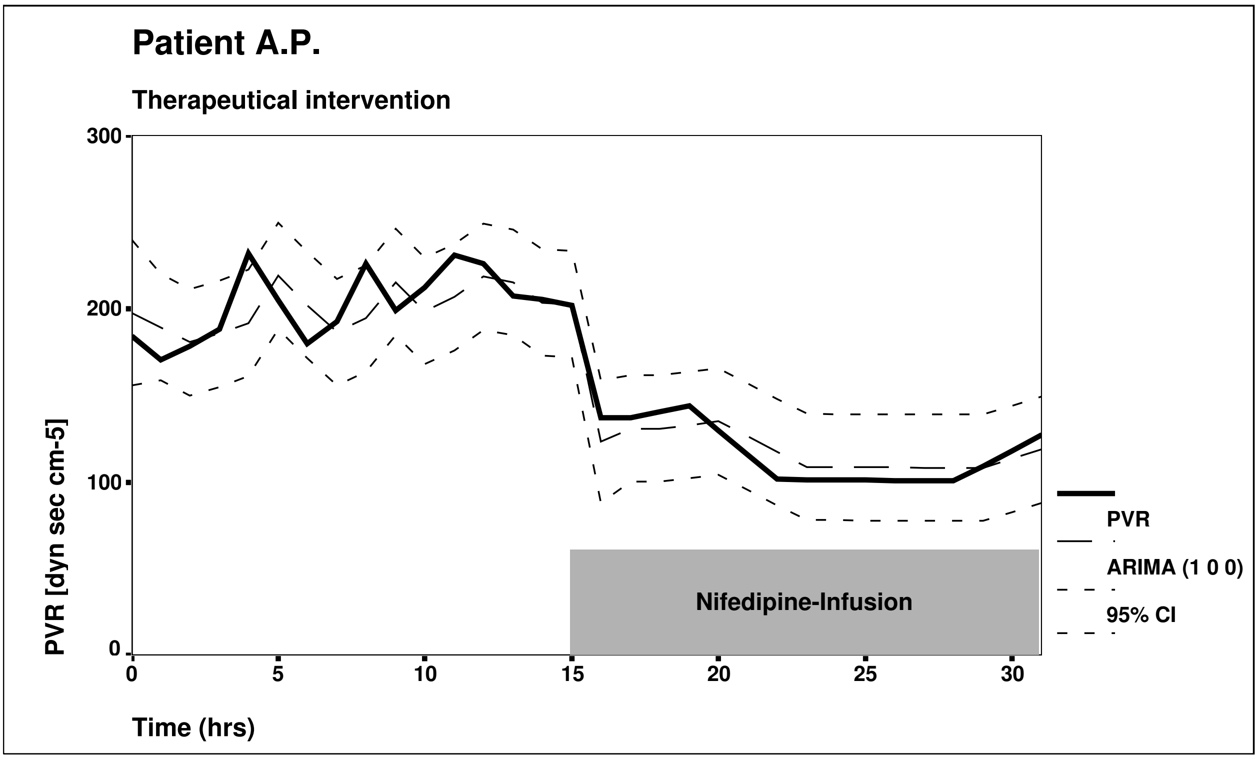
Durbin-Watson = 1.71

At the 17th hour a continuous nifedipine infusion was started at a rate of 0.8 mg/h. For the period of infusion the intervention regressor "STEP" was set from 0 to 1.

For the following 16 hours the same ARIMA model was applied to the series with "STEP" as an additional regressor (diag 4). The analysis showed a significant decrease of PVR by approx. one third during nifedipine treatment:

AR1 = 0.62	S.E. = 0.14	t = 4.54	$p < 0.001$
const. = 197.81	S.E. = 8.45	t = 23.42	$p < 0.001$

Diagram 4 Patient A.P., 73 years, female. ARDS of cryptogenic origin after right hemihepatectomy. Pulmonary hypertension. Therapeutic intervention (nifedipine-infusion). PVR and ARIMA (1,0,0) model with 95% confidence interval. Details in text.



STEP = -77.15 S.E. = 10.69 t = -7.21 p < 0.001

The residual series did not violate the goodness-of-fit criteria. Neither the ACF and PACF nor the *Box-Ljung* statistics showed significant deviations.

Goodness-of-fit criteria:

AIC = 266.1 SBC = 270.5

root mean square error = 14.0

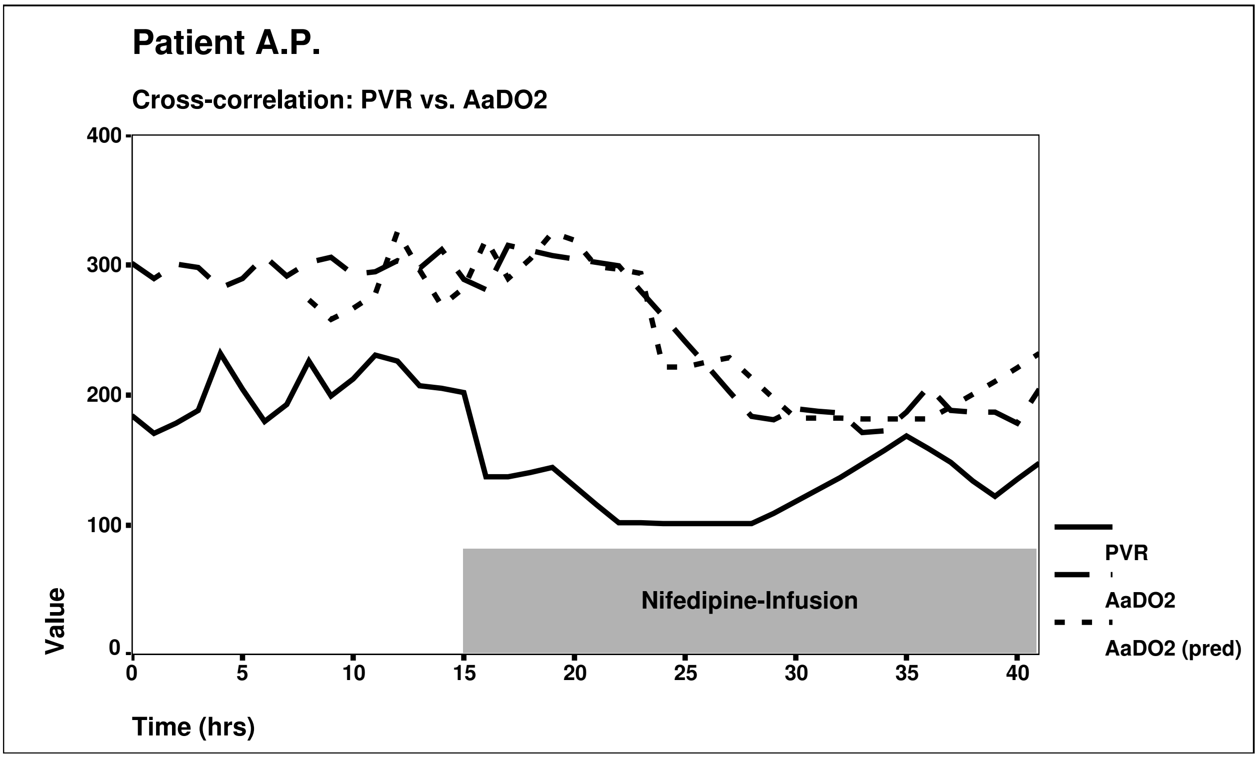
Durbin-Watson = 1.73

The cross-correlation function showed a maximum at lag 8. The linear regression between PVR at lag8 and $AaDO_2$ revealed a significant correlation ($r^2 = 0.81$; diag 5).

3.2.2.2 Patient 9: G.H., 58 years, female

This patient was shot in the thoracic and abdominal cavities at the site of a robbery. A central hepatic laceration led to a severe hemorrhagic shock. During emergency surgery the patient developed a severe ARDS. During the first estimation period of 12 hours both PVR and $AaDO_2$ were significantly

Diagram 5 Patient A.P., 73 years, female. PVR, $AaDO_2$ and predicted values for $AaDO_2$ based on a linear correlation between PVR at lag 8 and $AaDO_2$. Details in text.



elevated to a mean of 250 dyn·sec·cm^{-5} and 377 mmHg respectively. For this period a linear model could be identified:

const. = 249.73 S.E. = 6.97 t = 35.82 $p < 0.001$

Goodness-of-fit criteria:

AIC = 111.5 SBC = 112.0

root mean square error = 23.1

Durbin-Watson = 2.01

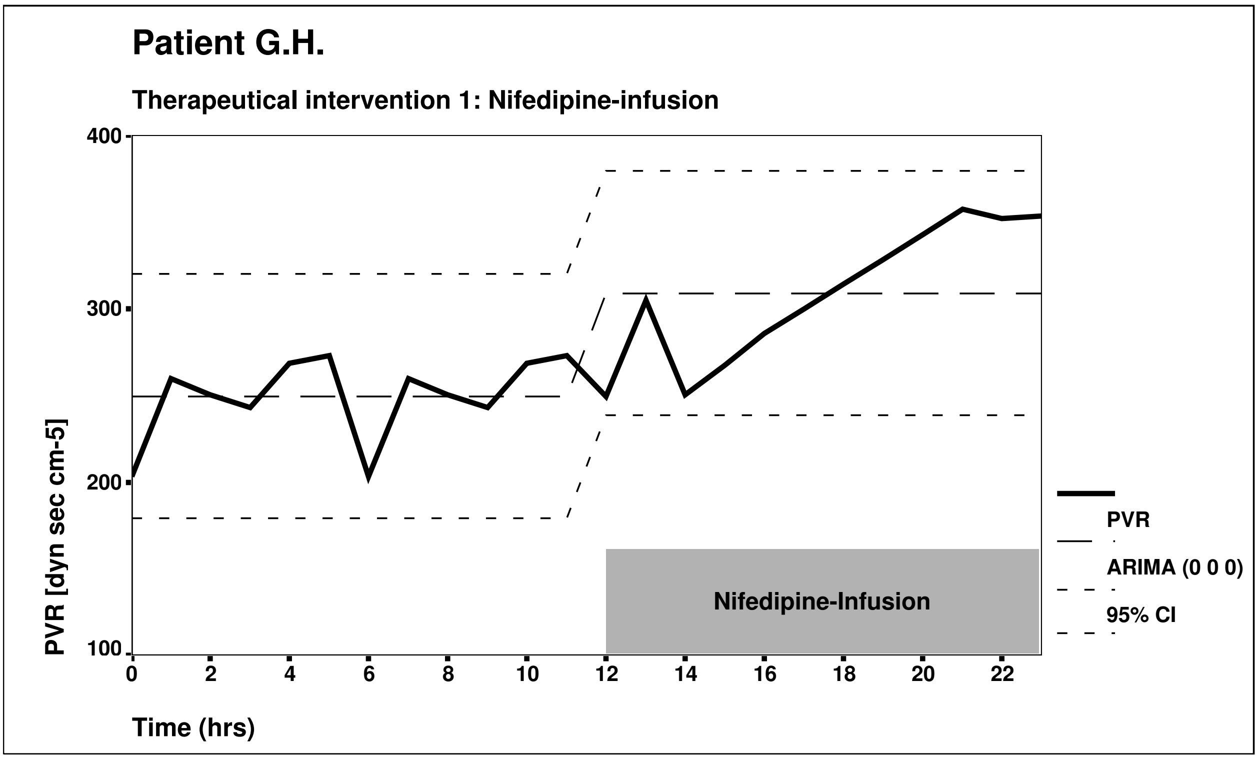
From the 13th hour on nifedipine was continuously infused at a rate of 1.2 mg/h. For the period of infusion the intervention regressor "STEP" was set from 0 to 1. For the following 16 hours the same ARIMA model was applied to the series with "STEP" as an additional regressor (diag. 6). The time series analysis revealed no significant reduction of PVR but did reveal a slight but significant increase:

const. = 249.73 S.E. = 9.42 t = 26.49 $p < 0.001$

STEP = 59.72 S.E. = 13.34 t = 4.45 $p < 0.002$

Goodness-of-fit criteria:

Diagram 6 Patient G.H., 58 years, female. Thoracic and abdominal gunshot. ARDS. Therapeutic intervention 1 (nifedipine-infusion). PVR and ARIMA (0,0,0) model with 95% confidence interval. Details in text.



AIC = 237.5 SBC = 239.8

root mean square error = 31.3

Durbin-Watson = 1.17

Thus the intervention analysis suggested a phase out of the nifedipine infusion was in order. Later it was determined, that the patient had a long history of fixed pulmonary hypertension. Still, no satisfactory explanation for the paradoxical increase of PVR under nifedipine infusion could be found.

During the following hours no improvement occurred and Q_S/Q_T remained high (between 25% and 30%) Thus IRV was applied.

For the 36 hours prior to the change of ventilation mode a first order autoregressive model was developed from the ACF and PACF for the series of Q_S/Q_T:

AR1 = 0.65	S.E. = 0.12	t = 5.32	$p < 0.001$
const. = 25.08	S.E. = 1.03	t = 24.30	$p < 0.001$

Goodness-of-fit criteria:

AIC = 168.4 SBC = 171.6

root mean square error = 2.3

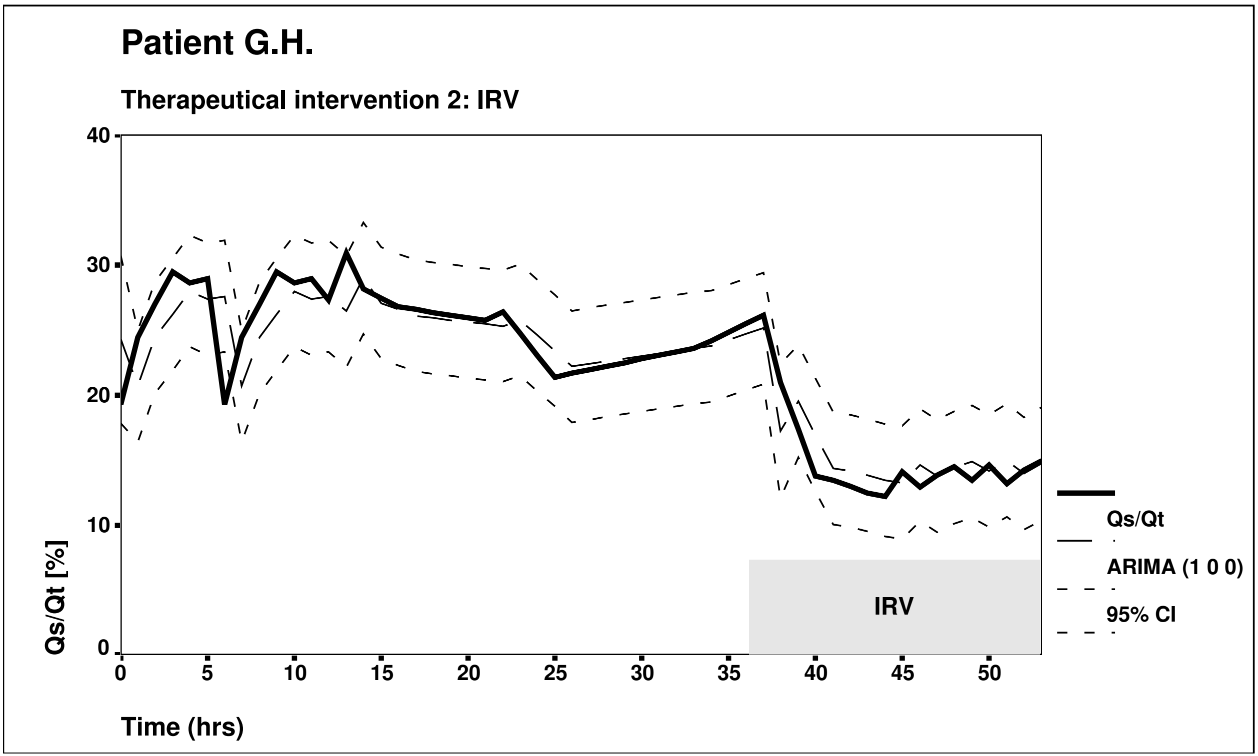
Durbin-Watson = 1.99

Neither the ACF and PACF nor the *Box-Ljung* statistics showed significant deviations of the residual series.

The effect of this therapeutic intervention was analyzed for the period from hour 37 to 54. The inversion of I:E-ratio was assigned the intervention regressor "STEP1".

A significant decrease of Q_S/Q_T was detected, where the model met the goodness-of-fit criteria (diag. 7):

Diagram 7 Patient G.H. 58 years, female. Thoracic and abdominal gunshot. ARDS. Therapeutic intervention 2 (IRV). Q_s/Q_t and ARIMA (1,0,0) model with 95% confidence interval. Details in text.



AR1 = 0.73	S.E. = 0.08	t = 8.81	p < 0.001
const. = 24.19	S.E. = 1.14	t = 21.25	p < 0.001
STEP1 = -8.20	S.E. = 1.63	t = -5.03	p < 0.001

Goodness-of-fit criteria:

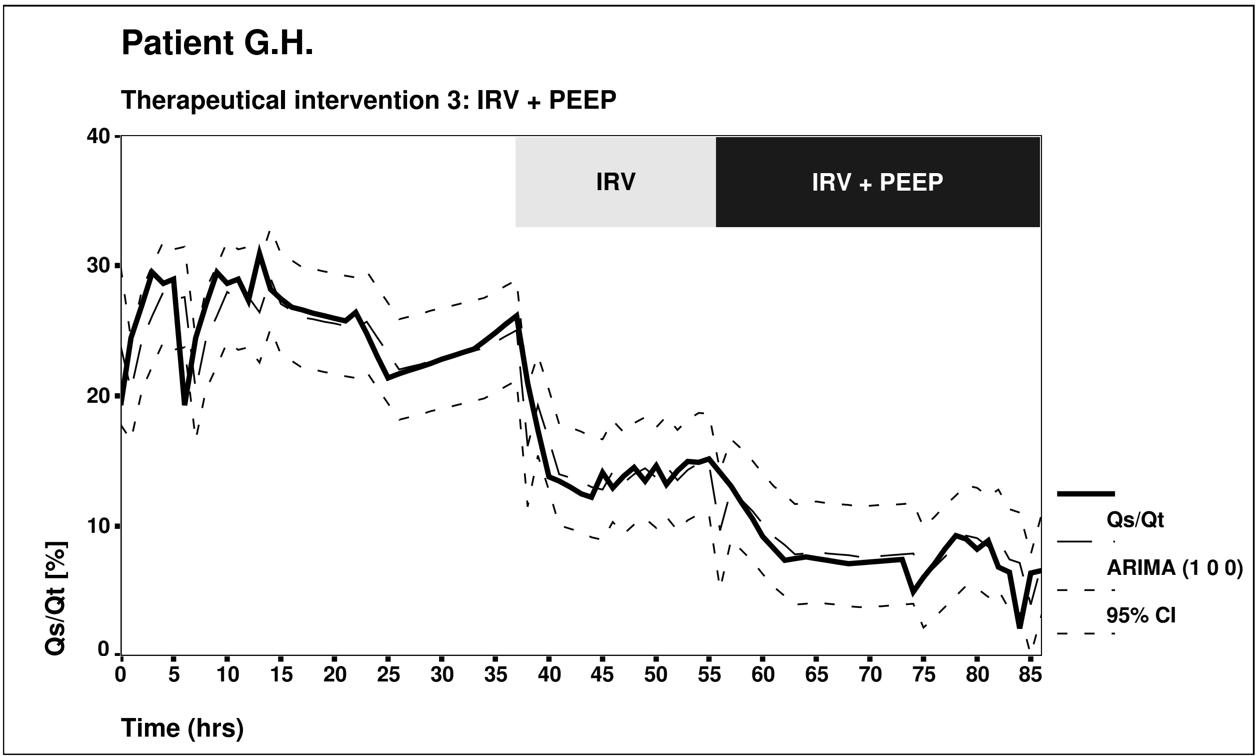
AIC = 236.7 SBC = 242.7

root mean square error = 2.1

Durbin-Watson = 1.99

As the intrapulmonary right-left shunt was still elevated, PEEP was increased from 14 to 20 mbar as a second therapeutic intervention. This intervention was assigned the intervention regressor “STEP2”. For a total of 87 hours the same first order autoregressive model was applied with the two intervention regressors (STEP1 = 1 from hour 37, STEP2 = 1 from hour 55). Both regressors had a significant effect, and reduction of Q_s/Q_t by more than half could be observed (diag. 8):

Diagram 8 Patient G.H. 58 years, female. Thoracic and abdominal gunshot. ARDS. Therapeutic intervention 3 (IRV + PEEP increase). Q_s/Q_t and ARIMA (1,0,0) model with 95% confidence interval. Details in text.



AR1 = 0.76	S.E. = 0.06	t = 12.43	$p < 0.001$
const. = 23.59	S.E. = 1.12	t = 20.99	$p < 0.001$
STEP1 = -9.20	S.E. = 1.46	t = -6.31	$p < 0.001$
STEP2 = -5.05	S.E. = 1.49	t = -3.40	$p < 0.001$

Goodness-of-fit criteria:

AIC = 363.7 SBC = 373.6

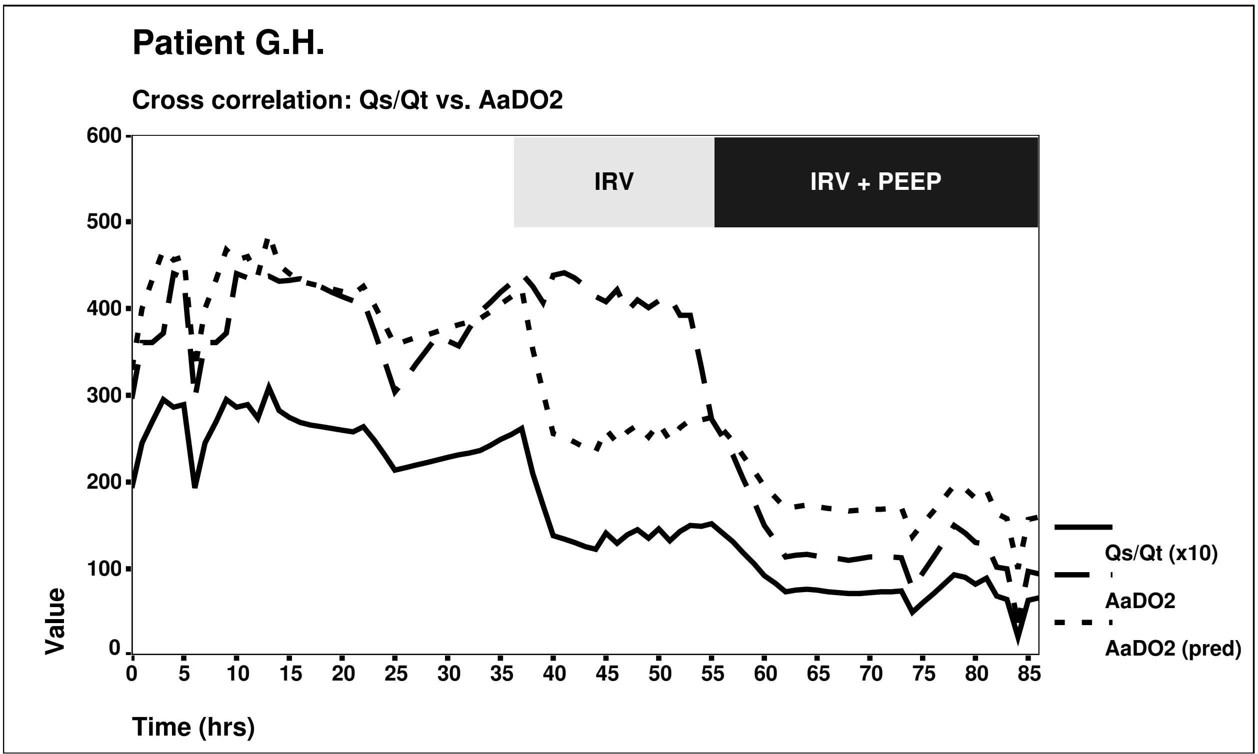
root mean square error = 1.9

Durbin-Watson = 2.04

The residual series did not violate the goodness-of-fit criteria. Neither the ACF and PACF nor did the *Box-Ljung* statistics show significant deviations.

The cross-correlation function showed a maximum at lag 0. The linear regression between Q_s/Q_t at lag 0 and $AaDO_2$ revealed a significant correlation ($r^2 = 0.68$; diag. 9).

Diagram 9 Patient G.H. 58 years, female. Thoracic and abdominal gunshot. ARDS. Q_S/Q_T, $AaDO_2$ and predicted values for $AaDO_2$ based on a linear correlation between Q_S/Q_T at lag 8 and $AaDO_2$. Details in text.



In both situations with ARDS intervention analysis helped choose the appropriate of two different therapeutic modalities. The decision could be based on significant statistics for each individual patient. The results of time series analysis related well to the clinical course.

4 Discussion

In this study intervention analysis could be successfully applied to all cases. Also from short time series with 20 or less observations significant and interpretable models could be developed, if the analysis was restricted to simple, low order models. This assertion is supported by other recent studies on short time series [6, 17]. Thus time series analysis for short series with approximately 20 data points, as described by *Zinkgraf* and *Wilson* [16], appears to be a valuable method for studies in intensive care medicine.

A combination of an iterative, or classical [19] and a so-called semi-automatic approach comparing different models for one series [20] yields advantageous results especially for short time series.

Short series and missing values present an important problem to the application of time series analysis in intensive care medicine. Series with 12 to 16 observations appear sufficient for a successful model estimation if the series has a moderate variance [11]. Such short series should not have missing values.

Missing values in series of more than 20 data points should be no obstacle for a reliable model estimation. In these series missing values can be eliminated through linear interpolation or a *Kalman* filter.

In the majority of cases in this study where estimation periods of less than 20 observations were obtained more than one model had to be developed, and that the final model could then be found by the comparison of these different models. Although this approach proved to be clinically useful, it shows a general limitation of ARIMA-models with very short time series.

The limitation to dichotomous questions, e.g. whether or not an observation lies within the confidence interval of a time series model, can produce clinically significant statements even with short series.

Reliable intervention analysis with about 20 data point prior to and after the intervention were done in several earlier studies [18]. Moreover, it has become obvious that symmetrical distribution of observations on both sides of the intervention is not required [60, 61]. Both results are of major importance for the application of interrupted time series analysis to intensive care problems.

The individual model identification and individual statistical evaluation of a single patient constitutes an important and successful methodology in intensive care monitoring. *Gordon* [13] showed positive results from the application of a multi-state Kalman filter to follow-up after kidney transplantation. Moreover, several other authors propose so-called single-case studies with the help of time series analysis [14, 62]. With these methods therapeutic effects can be reliably detected in a intra-individual cross-over, so that the course of the individual patient can be statistically analyzed [63, 64].

In socio-economics intervention analysis techniques have seen a broad recognition. With these methods the effect of a single event on a target variable can be easily and reliably estimated [8, 18, 60, 61].

In the assessment of changes in time of lab variables time series analyses can help to differentiate between random fluctuations and clinically relevant, pathological changes with high precision. As shown in this study, changes can be quickly and reliably detected with further diagnostic and therapeutic measures initiated at an early stage. Other work groups have succeeded in the application of this statistical approach to the lab monitoring of the chronically ill [65].

In the field of intensive care monitoring intervention analysis helps to detect and evaluate the effects of therapeutic interventions in the individual patient. Our study shows, that the effects of therapeutic measures in ARDS can be precisely analyzed. For the individual patient statistically relevant conclusions can be derived. This offers the opportunity to decide whether a specific therapy should be continued.

Therefore, time series analysis supports a differentiated statistical approach to intensive care monitoring and to the clinical assessment of the effectiveness of therapeutic interventions.

Despite the great potential value time series analysis methods in general and ARIMA models in particular may exhibit in intensive care medicine, a number of serious practical problems became obvious in our investigation:

- Due to the interactive model development a profound personal understanding of the statistical methodology is indispensable.
- The determination of the correct span of the confidence intervals still needs clinical validation.
- ARIMA models are relatively vulnerable to violations of model assumptions (stationarity, normal distribution of the disturbances), which cannot be ruled out in intensive care databases. ARIMA models are especially sensitive to the presence of outliers. The application of robust methods seems to be necessary for further research.
- The models used in this study represent univariate analyses. More complex relationships in the course of time can only to a limited extent, if at all, be described.

Therefore, the development of medical time series analysis should aim at the analysis of complex relationships and at an improvement of robustness of the statistical models. Moreover, it is desirable that methods that offer an automatic model diagnosis and estimation for use in clinical routine at the bedside will be developed.

5 Speculations

Time series analysis techniques hold a great potential for clinical applications.

In the research field they allow to quantify and test changes in time in the individual subject, which can help e.g. in phase 1 and 2 pharmacological studies. Currently univariate single case studies with and without intervention are feasible. Future developments are directed at algorithms for multiversity time series analysis.

In clinical practice time series analysis support a more analytical and reproducible approach toward the evaluation of pathological changes and therapeutic effects in the individual patient. Present research aims at the development of automatic methods for time series analysis, that would allow an instantaneous statistical analysis at the bedside. This would offer an option to the health care professional for a more reliable evaluation of the individual treatment.

Some time series analysis methods, e.g. the Kalman-filter, could also be used for on-line analysis of physiologic monitoring data. The generation of time series models including confidence intervals could dramatically enhance trend analysis, not only could the slope of a trend be calculated but also outliers, which could represent clinically significant changes. Moreover, in the long run these techniques could be employed to generate smart alarms, that may be more reliable and less error prone than currently used simple limit alarms.

Therefore, it appears that it may be rewarding to invest further efforts into the development of medical time series analysis techniques.

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7 List of abbreviations

7.1 Abbreviations in text

$AaDO_2$	alveolar-arterial oxygen tension gradient
ACF	autocorrelation function
AR	autoregression
ARIMA	autoregression integration moving average
HR	heart rate
IRV	inverse ratio ventilation
lag	number of time intervals between observations (measurements)
MA	moving average
PACF	partial autocorrelation function
PEEP	positive end-expiratory pressure
PVR	pulmonary vascular resistance
Q_s/Q_t	intrapulmonary shunt
S_pO_2	pulse oximetry

7.2 Abbreviations and symbols in formulas

X_t	process variable at time t
x_t	observed value (measurement) at time t
N	number of observed values (= number of measurements in time series
ρ_τ	autocorrelation between X_t and $X_{t+\tau}$
$\hat{\rho}_\tau$	estimate of ρ_τ
$\bar{x}$	process mean (estimated)
p	order of an AR-process
q	order of an MA-process

j	running index
α_j	coefficient in AR-model
$\hat{\alpha}_j$	estimate of α_j
$\hat{\alpha}_{p,j}$	estimate of the j-th coefficient in an AR(p)-model
β_j	coefficient in AR-model
$\hat{\beta}_j$	estimate of β_j
$\hat{\beta}_{q,j}$	estimate of the j-th coefficient in an MA(q)-model
τ	time lag
ε_t	white noise process at time t
ω	size of the intervention effect