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Functional relationship of arterial blood pressure, central venous pressure and intracranial pressure in the early phase after subarachnoid hemorrhage

Maissen, Gabriela ; Narula, Gagan ; Strässle, Christian ; Willms, Jan ; Muroi, Carl ; Keller, Emanuela

Abstract: **BACKGROUND:** Intracranial pressure (ICP) and arterial blood pressure (ABP) are related to each other through cerebral autoregulation. Central venous pressure (CVP) is often measured to estimate cardiac filling pressures as an approximate measure for the volume status of a patient. Prior modelling efforts have formalized the functional relationship between CVP, ICP and ABP. However, these models were used to explain short segments of data during controlled experiments and have not yet been used to explain the slowly evolving ICP increase that occurs typically in patients after aneurysmal subarachnoid hemorrhage (SAH). **OBJECTIVE:** To analyze the functional relationship between ICP, ABP and CVP recorded from SAH patients in the first five days after aneurysm. **METHODS:** Two methods were used to elucidate this relationship on the running average of the signals: First, using Spearman correlation coefficients calculated over 30 min segments Second, for each patient, linear state space models of ICP as the output and ABP and CVP as inputs were estimated. **RESULTS:** The mean and variance of the data and the correlation coefficients between ICP-ABP and ICP-CVP vary over time as the patient progresses through their stay in the ICU. On average, after an SAH event, the models show that a) ABP is the bigger driver of changes in ICP than CVP and that increasing ABP leads to reduction in ICP and (b) increasing CVP leads to an increase in ICP. **CONCLUSIONS:** Finding a) agrees with the hypothesis that patients with subarachnoid hemorrhage have defective autoregulation, and b) agrees with the positive correlation observed between central venous pressure and intracranial pressure in the literature.

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TITLE

Functional Relationship of Arterial Blood Pressure, Central Venous Pressure and Intracranial Pressure in the early phase after subarachnoid hemorrhage

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ABSTRACT

BACKGROUND: Intracranial pressure (ICP) and arterial blood pressure (ABP) are related to each other through cerebral autoregulation. Central venous pressure (CVP) is often measured to estimate cardiac filling pressures as an approximate measure for the volume status of a patient. Prior modelling efforts have formalized the functional relationship between CVP, ICP and ABP. However, these models were used to explain short segments of data during controlled experiments and have not yet been used to explain the slowly evolving ICP increase that occurs typically in patients after aneurysmal subarachnoid hemorrhage (SAH). **OBJECTIVE:** To analyze the functional relationship between ICP, ABP and CVP recorded from SAH patients in the first five days after aneurysm. **METHODS:** Two methods were used to elucidate this relationship on the running average of the signals: First, using Spearman correlation coefficients calculated over 30 min segments. Second, for each patient, linear state space models of ICP as the output and ABP and CVP as inputs were estimated. **RESULTS:** The mean and variance of the

data and the correlation coefficients between ICP-ABP and ICP-CVP vary over time as the patient progresses through their stay in the ICU. On average, after an SAH event, the models show that a) ABP is the bigger driver of changes in ICP than CVP and that increasing ABP leads to reduction in ICP and (b) increasing CVP leads to an increase in ICP. CONCLUSIONS: Finding a) agrees with the hypothesis that patients with subarachnoid hemorrhage have defective autoregulation, and b) agrees with the positive correlation observed between central venous pressure and intracranial pressure in the literature.

KEYWORDS

Intracranial pressure, arterial blood pressure, central venous pressure, relationship, correlation, state space models.

INTRODUCTION

The pioneering works of Monro, Kellie and Cushing (1,2) states that the sum of the volume of the brain, blood and cerebrospinal fluid compartments is constant in an intact, rigid skull (3,4). An increase in volume of one compartment has to cause a decrease in one or both of the remaining two compartments. Additionally, the concept of estimated cerebral perfusion pressure (CPP) emerged in the early 1970s (5). It is calculated from mean arterial pressure (MAP) and intracranial pressure (ICP), namely $CPP = MAP - ICP$. If CPP remains constant even under fluctuations of MAP, it indicates an intact autoregulatory capacity in the brain (6). However, the equation for CPP implies no venous involvement. Therefore, neurocritical care focused for years mostly on arterial and ICP regulation as in patients with intracranial hypertension. However, recent studies have questioned the classic static Monro-Kellie doctrine when considering the fact that the continuous arterial inflow and venous outflow contribute to a dynamic system

which can quickly lead to an acute ICP increase if venous drainage is impaired (2). As early as 1896, Leonard Hill (7) suggested that ICP would be more affected “from the venous side to a far greater degree than from the arterial side, because it is on the arterial side that the resistance lies”. Patients with severe aneurysmal subarachnoid hemorrhage (SAH) after aneurysm rupture suffer from space-occupying brain edema leading to intracranial hypertension and secondary brain injury in the early phase (8–10). Although literature is sparse, in daily clinical practice, it becomes evident that CVP can strongly influence ICP under certain conditions. Prior modelling efforts have formalized the functional relationship between CVP, ICP and ABP. However, these models were used to explain short segments of data during controlled experiments mostly in animals with traumatic brain injury and have not yet been used to explain the slowly evolving ICP dynamics that occurs typically in patients after aneurysm rupture and aneurysmal subarachnoid hemorrhage (SAH). The purpose of the present study was to investigate the functional relationship between CVP, ICP and ABP by analyzing long term pressure signal data from patients with SAH.

METHODS

1.1 Patients

High resolution pressure signal data from $N = 15$ patients was retrospectively analyzed during their stay at the Neurocritical Care Unit, University Hospital Zurich. All patients suffered from aneurysmal subarachnoid hemorrhage (SAH) with need for ICP monitoring due to occlusive hydrocephalus or brain edema. Signal recording typically began immediately after the external ventricular drain (EVD) had been inserted and recording continued up to day five after bleeding.

1.2 Data collection

ICP, CVP and ABP signals were recorded using Draeger Infinity (Draeger, Luebeck, Germany) or Phillips Intellivue (Philips Medical systems, Boeblingen, Germany) systems at 100 Hz (13 patients) and 125 Hz (two patients) respectively. ICP was measured either with EVD (Neuromedex, Hamburg, Germany) or brain tissue probes (Neurovent-PT, Raumedic, Helmbrechts, Germany). Due to the severity of disease, all patients were installed with arterial and central venous lines. Pressure transducers were used for ICP via EVD (Neuromedex, Hamburg, Germany), ABP and CVP (IBP Medical, Hannover, Germany). Typically, simultaneous data from all three signals was recorded continuously for a period of 1-5 days. A dedicated IT infrastructure called “ICU Cockpit” was built to buffer, export and save streaming data from these devices. Export to a secure server was done daily at midnight. Data from the Draeger and Phillips systems was ported through a CNS Data Collector (Moberg ICU Solutions, Ambler, Philadelphia, USA). Data collectors and monitoring devices are placed at each ICU bed at the Neurocritical Care Unit. The data exported for each signal contained both the signal values and UTC formatted timestamps. An IBM Infosphere system (IBM, Armonk, New York, USA) was used to buffer and collect data from the different beds in the ICU. This explanatory study, part of the project “ICU Cockpit”, was approved by the local ethics committee. Written consent was given by legal representatives, as all patients were incapable of judgment.

1.3 Artifact rejection and Time series preparation

Typically, the recorded signals were contaminated with different sources of noise. Noise from sensors or occurring during the sensitive data export process can lead to non-physiological pressure values, e.g. negative pressure values. Second, detachment of the sensor or switching off a device can lead to missing values and lags in consecutive data timestamps. Significant patient movement can also induce large fluctuations in pressure signals. Finally, maneuvers such as leg raising, getting up, changing the bed position and performing drainage of cerebrospinal fluid (CSF) through an EVD to lower ICP can induce rapid changes in the signals that should not be considered as part of the normal dynamics. Given these issues, our goal was to extract long, relatively artifact-free periods of recordings where all three signals

were available. 30-minute segments of artifact free data were extracted from each patient's recordings. Then, a set of rules was applied to filter out artifacts (see Appendix, Artifact rejection for more details). 1) Any implausible physiological values were set to "missing". 2) Any large deviations from the running average of the signal were smoothed using an exponential averaging method. 3) The data was segmented into short windows and variance was calculated in each window. Windows with variance below or above the tails of the distribution of variances were rejected as artifactual. Finally, in each accepted 30-min segment, the average value of the signals was computed in 30 second moving windows with 29 second overlap (1 sec shift). This was the final form of the analyzed time series. Note that the terms ICP, ABP and CVP denote the 30 sec window average (with 1 sec shift) time-series not the raw, high resolution signal measured from the sensors.

1.5 Correlation measure

Spearman rank correlation coefficients (11) were computed between ICP-ABP and ICP-CVP. Spearman rank correlation coefficient is valid for continuous variables that may share a monotonic but non-linear relationship, while Pearson correlation is only valid for continuous variables that share a linear relationship. Spearman rank correlation is the Pearson correlation coefficient between the rank of values between two random variables X and Y. If n pairs of values (X_i, Y_i) are recorded, they are rank ordered to get the ranks (r_X, r_Y) and the correlation coefficient is computed as:

$$r_s = \frac{cov(r_X, r_Y)}{\sigma_{r_X} \sigma_{r_Y}}$$

Here, cov is the covariance function of the ranks $cov(r_X, r_Y) = E[r_X r_Y] - E[r_X]E[r_Y]$, E stands for expected value. $\sigma_{r_X}, \sigma_{r_Y}$ are the standard deviations of the ranks. Expected value was replaced with the empirical average over data points for computing the correlation coefficient.

1.6 Linear state space models

A linear state space approach was taken to learn a functional relationship between the three signals. The modelled systems have two inputs, namely CVP and ABP, and as log(ICP) as output. The log was used to allow a Gaussian distributed noise to describe the output error of the model. Formally, the measured values of an output signal $y_t = \log \text{ICP}(t)$ are generated by the linear combination of input signals u_t (here a vector of length 2, namely $[\text{ABP}(t), \text{CVP}(t)]$) and the unobserved state variable $x_t \in \mathbb{R}^p$ ('p' is the order of the model) which has the following dynamics:

$$x_t = Ax_{t-1} + Bu_t + Ke_t$$

$$y_t = Cx_t + e_t$$

Here, e_t represents the error terms in the output estimation i.e. $e_t = y_t - \hat{y}_t$. The parameters of the model are the matrices $\{A, B, C \text{ and } K\}$. The size of each matrix depends on the order of the model (p) and the number of control inputs (u_t) and the number of outputs (1 in this case). For example, for a $p = 3$ order model with two inputs and one output signal, $A \in \mathbb{R}^{3 \times 3}$ $B \in \mathbb{R}^{3 \times 2}$ $C \in \mathbb{R}^{1 \times 3}$ $K \in \mathbb{R}^{3 \times 1}$. Individual models were estimated for each patient, pooling in all except the last ten of the 30-minute segments obtained over all recording days for the patient and treating them as separate, independent experiments. The parameters of the state space models were estimated using stochastic gradient descent over a squared error loss between recorded data and estimated ICP values from the model. Akaike Information Criteria (12) was used to estimate the model order. To validate the models, mean absolute prediction error estimates were computed for ten "test" segments of data from each patient. These segments were not used for parameter estimation. For further details on the model and parameter estimation see Appendix, Linear state space models.

1.7 Step response and response strength

The state space model step response was computed by setting the value of one input variable (either ABP or CVP) = 1. That is, for ABP step response, the value of $u = [1, 0]$ and for CVP step response $u = [0, 1]$. Thus, starting at an initial state $x_{t=0} = 0$, for each time step $t = 1$ to 5000, the state of the system

was propagated as $x_t = Ax_{t-1} + Bu$, and the output log(ICP) was $y_t = Cx_t$. The strength of the step response was then $R = \exp(y_{t=5000})$. Total response strength R_{TOT} was the Euclidean norm of the two-dimensional vector $g = [R_{ABP}, R_{CVP}]$, $R_{TOT} = \sqrt{R_{ABP}^2 + R_{CVP}^2}$.

1.8 Simulation of ICP using learned state space models

To simulate ICP for each patient, 20 segments of 30-min were randomly selected and the initial state of the system in each segment was estimated using the MATLAB function *findstates*. Then, the value of CVP and ABP was varied from their initial measured value, linearly over a period of 100 s to a final chosen value, after which they were held constant for another 100 s. This was done to avoid having sharp transients in the dynamics because of large jumps in CVP or ABP. A small amount of Gaussian white noise (standard deviation = 0.5) was added to CVP and ABP to make the simulation more realistic.

Results

Patient characteristics

Median age of our cohort of 15 patients was 58 (min 39, max 76) years, 56.25% percent of the patients were female. All patients suffered from aneurysmal SAH. The median World Federation of Neurological Societies (WFNS) grade was 4 (min 2, max 5), median Fisher grade was 4 (min 3, max 4). The median number of days spent in the ICU was 25 (min 4, max 87, mean 29, SD 19). Ruptured aneurysms were treated within 48 hours either with coiling (10 patients) or clipping (5 patients). There were four patients with severe vasospasm, treated with intraarterial nimodipine spasmolysis and eight who needed to receive a ventriculo-peritoneal shunt because they developed a hydrocephalus. Acute occlusive hydrocephalus developed in seven patients, while malresorptive hydrocephalus occurred in four patients. ICP was measured with EVD in all 15 patients. All patients were artificially ventilated but for varying number of days (median days of artificial ventilation = 22, min 1, max 39, mean 17.5, SD 15).

Data analysis

In total, $n = 921$ segments, each of 30 min duration were obtained from the 15 patients after artifact rejection. The variance and the average value of each signal changed as time in critical care progresses. This is an indication of *non-stationarity* in the data. Thus, ICP timeseries within each 30-min segment were correlated to the CVP and ABP timeseries in a pairwise manner, i.e. ICP-CVP and ICP-ABP.

On the local level, the non-stationarity in the data produced fluctuating correlation coefficients. Fig. 1a and b shows two example patients where both the sign and magnitude of correlation changes as time progresses. This high variability in correlation sign and strength was observed in all patients, and overall, the correlation coefficients were Gaussian distributed, Fig. 1c. The correlation coefficient for CVP was on average positive ($r = 0.1$, average of 921 30-min segments from 15 patients) and greater than for ABP ($r = 0.03$). This was also reflected in the relative frequency of correlation coefficients that were negative/positive. 46.2% of the ICP-ABP correlation coefficients were negative while 39.7% of the ICP-CVP correlation coefficients were negative. The average (SD) of the standard deviation of correlation coefficients between ICP and CVP was 0.39 (0.07, $n = 16$) and between ICP and ABP was 0.34 (0.05), Fig 2d. Table 1 shows the average (SD, computed over 30 min segments) of correlation coefficients for each patient.

Pairwise correlation between ICP and CVP and separately between ICP and ABP does not uncover the possible interaction between CVP and ABP in influencing ICP, nor do correlation coefficients capture the dynamical nature of these signals. The paradigm of linear state space models allows direct quantification of interdependence. Individual models for each patient's data were estimated using all but the last ten 30 min segments. The last ten segments were chosen as test segments to report model prediction error. The three signals were treated as a linear system with output as ICP and the inputs as ABP and CVP, Fig. 2a. The system consists of a possibly high dimensional "state" variable that is not directly observed but inferred from data. The dynamics of the state, the influence of the input signals on the state and the transformation that generates the output signal (log ICP) from the state are all linear transforms defined

by a set of parameters (see Methods section 1.5 and Appendix linear state space model, section 2). Parameters were estimated by fitting the models to the observed data using gradient descent optimization (13). ICP was modelled as the output of the system because we are interested in the effects of changes in CVP and ABP on ICP.

After estimating the model parameters, starting at a value of 0, the model's output was measured as a response to a unit step increase in ABP or CVP for a duration of 5000 sec. A long duration was chosen to allow the response to reach its asymptotic value. Fig. 2b shows the response of the model from one of the patients. Note that the response starts at 1 because the models were trained to predict $\log(\text{ICP})$ and thus, the output is exponentiated to display in the original units (mm Hg). Here, the ICP initially decreases as ABP is stepped up, then rises and settles at a higher asymptotic value. When CVP is stepped up, ICP rises gently to a slightly higher value. The strength (and sign) of the response as the change (from $t = 0$) in the value of simulated ICP after 5000 sec of applying the step input is shown in Fig 2c (see Methods section 1.7). Different patients showed varying degrees of strength and varying direction of change (increase or decrease) with respect to ABP and CVP, Fig 2c. In 11 patients, the response strength for ABP was greater than for CVP, in two it was equal and in two patients the response strength for CVP was greater than for ABP. On average, the response to change in CVP was positive but weaker (mean $\pm$ SD = 0.01 ± 0.014 , $N = 15$) than the response to change in ABP (mean $\pm$ SD = 0.02 ± 0.01 , $N = 15$). A single "Total" response strength (R_{TOT}) was constructed by taking the Euclidean norm of the 2-dimensional vector of [ABP response, CVP response], Fig 2d (see Methods section 1.7).

Clearly, the variability of R_{TOT} shows that in some patients the dependence between the input and output was higher than in others. However, the step response of the system does not mimic a common observation in critical care, that physiological signals often change on a much slower time scale, slowly drifting away from a stationary average value (see for example, Fig. 1b ABP or Fig. 1a ICP).

To better understand these scenarios, the learned models were simulated forward in time under different input conditions and initial states. That is, given an initial value of ICP and using only the subsequent values of CVP and ABP, it was possible to approximately estimate the value of ICP without using the

actual ICP measurements. For all 30-min segments from each patient, the initial state of the system was estimated, and then the system dynamics were propagated up to 1 min into the future, using the measured the ABP and CVP values. Prediction accuracy degraded with longer time horizons (greater than 2 min). Predictions on two example test segments (not used for learning) from two example patients are show in Fig 3a. Overall, predictions with good accuracy were obtained in most models. The average (SD) of the mean absolute prediction error between 1 min ahead predicted ICP values and recorded data for all test segments across all patients was 0.46 mm Hg (SD = 0.17, N = 150, 15 patients x 10 test segments per patient). Next, the response of the learned systems to slow changes in ABP and CVP was analyzed. This can be important in clinical maneuvers that decrease intra-thoracic or abdominal pressure to alleviate intracranial hypertension respectively (14). The value of CVP was varied from 4 to 40 mm Hg, and the value of ABP from 70 (normotension) to 150 (hypertension) in 50 steps (step size of 0.72 for CVP and 1.6 for ABP). As an example, for the patient depicted in Fig 3b starting at a high ICP of ~ 20 mm Hg, the ICP reduces to a lower value as time progresses for three levels of CVP (namely 5, 20 and 40 mm Hg) though the reduction in ICP is larger for lower values of CVP, Fig. 3b. Note, CVP was changed linearly over a period of 100 s from its initial to its final value to avoid sharp transition artifacts and mimic a more realistic clinical maneuver, Fig. 3b middle. ABP was held constant around its initial value of 94.5 mm Hg, Fig. 3b bottom. The value of ICP after 200 s was obtained from simulations for each input pair of average ABP and average CVP values, Fig. 3c. In this patient, CVP and ABP have a pronounced effect on ICP. Secondly, increasing ABP leads to reductions in ICP while increasing CVP leads to a slight increase, Fig 3c.

To quantify these relationships for all patients, twenty 30-min segments were randomly selected in each patient, the initial state of the system was estimated from the segments, and the initial values of ABP and CVP were extracted (see Methods section 1.8). As before, the value of ABP and CVP was linearly varied over 100 s and then kept constant for another 100 s. The difference between the initial and final (after 200 s) value of ICP was computed for different values of ABP averaged over all CVP values (example Fig 3d), and different values of CVP averaged over all ABP values (example Fig 3e). When the difference value (initial – final ICP) is positive, it indicates a reduction in ICP and vice versa when the difference is negative. The average CVP and average ABP values effect the amount and direction of change in ICP.

Thus, the absolute value and sign of the slope of the curves in Fig 3d and e is an important indicator of the strength of the relationship between ICP and ABP and CVP. Note that, the response strength to step inputs of ABP or CVP, as shown in Fig 3c are different compared to these slope values because in this case the value of each signal is slowly altered to model a more natural clinical setting.

In most patients ($N = 12/15$), increasing ABP had the counteracting effect of decreasing ICP. The average (SD) ABP slope (for each patient, average the slopes derived from simulating with 20 initial values sampled from data) was 0.04 (0.01). A positive slope means a greater reduction in ICP from its high initial value to its final value as ABP is increased. On the other hand, the relationship between ICP and CVP was more variable. In 9 patients, increasing CVP increased ICP and in 6 patients, increasing CVP led to a greater decrease in ICP. The average (SD) CVP slope was smaller and negative (-0.01, SD = 0.006).

Discussion

Long term recordings of ICP, ABP and CVP (in total ~ 460 hours of data) in patients suffering from aneurysmal SAH were analyzed to better understand the dynamic functional relationship between them. In a first step, correlation coefficients between ICP-ABP and ICP-CVP in 30 minute segments were statistically significant in several cases though not relatively high in strength. Positive and negative correlations were found across all patients and for both ICP-ABP and ICP-CVP comparisons. However, almost half of all correlation coefficients for ICP-ABP were positive and half negative, reflecting defective and intact cerebral autoregulation mechanisms respectively. Defective autoregulation is known to occur in up to half of patients with severe SAH (15,16). However, the local correlation coefficients were not stationary, and showed high variance across recording time. As a clinical consequence, this means that autoregulation capacity is not static, can change quickly over time and must be assessed at short intervals. On average, a greater average positive correlation was observed between ICP-CVP compared to ICP-ABP. This might be explained by the hypothesis that increasing the CVP results in an increase of ICP only when compensatory mechanism are exhausted, i.e. compliance is reduced (10,17).

To better explain the functional relationship between ICP, ABP and CVP, linear state space models were estimated by treating ICP as the output of a system with ABP and CVP as inputs to the system. Linear state space models can be directly mapped to linear transfer function models which have previously been used to understand cerebral autoregulation (18,19) and cerebrovascular resistance (20,21). In the estimated models a detectable relationship was observed between ICP and ABP, as well as between ICP and CVP although the strength of this relationship was variable across patients. Predictions of the ICP values up to 1 minute into the future in test segments agreed well with measured data. On average, increasing ABP led to increasing reductions in ICP, which is a sign of defective autoregulation. Furthermore, on average increasing CVP led to increase in ICP, which is reported previously in the literature as occurring after a loss of compliance (22,23). Nonlinear models of ICP dynamics have previously been proposed which specifically model the logarithmic relationship between intracranial volume and pressure (24,25) and also incorporate the effect of cerebral autoregulation through linear transfer functions (26–30). However, parameter estimation in nonlinear systems is much more involved than estimating linear system parameters because of the nonconvexity of the loss function. Furthermore, estimating linear model parameters can be done online, in a recursive manner (13). This flexibility can allow for modelling the evolving state of the patient's injury, at the very least, on the time scale of minutes. However, we envisage that even more powerful nonlinear models such as deep recurrent neural networks could be used to predict ICP at longer time scales. Simulations of ICP for a short duration of time (200 s) allowed to estimate the change in ICP starting at different initial values for varying average values of ABP and CVP. This may be of a clinical relevance because when a patient's model is learned and shows a strong dependence of the ICP on the input signals, a potentially beneficial effect of increasing ABP or decreasing CVP on ICP can be better understood and may even be predicted. Different maneuvers and treatments exist to lower CVP as raising the head position, reducing the intraabdominal pressure by laxatives or diuretics (2,14,31,32). In today's clinical practice, these treatments are mostly applied tentatively on a "trial and error" base. If an individual patient's model shows a strong dependence of the ICP on the CVP a stronger case can be made for the potential benefit of lowering CVP.

To our knowledge, this is the first attempt at analyzing the functional relationship between these three important signals in critically ill SAH patients, without performing a controlled interventional experiment as usually performed in traumatic brain injury animal experiments. An advantage of not performing a controlled interventional experiment is that in most clinically relevant scenarios not all of the physiological variables at play can be strictly controlled. Subsequently, one of the limitations of our work is that, even though more than 400 hours of patient recordings were analyzed in this work, treatments and clinical maneuvers performed on the patients to alleviate their cerebrovascular issues were not taken into account. Factors influencing CVP, such as head position, positive end expiratory pressure with artificial ventilation and intraabdominal pressure were also not considered. Furthermore, cerebral compliance was not measured regularly. This missing information could potentially at least partly explain the non-stationarity observed in the data, specifically the variance in the correlation coefficients and the fact that prediction horizons beyond one minute led to greater prediction error. However, the advantage of the linear state space approach is that one can easily combine treatment information (e.g. pharmacological interventions) or detected artefacts by combining these models with discrete states that change the underlying system parameters (33,34). This is an avenue for future research.

DECLARATIONS

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTIONS

G.M and J.W. collected patient data. G.N performed data analysis. G.N., G.M, E.K and C.M prepared the manuscript. C.S. provided software support. E.K, C.M and G.N devised the aim and scope of the study.

ETHICS APPROVAL

This explanatory study, part of the project "ICU Cockpit", was approved by the local ethics committee.

CONSENT TO PARTICIPATE

All patients provided general consent for the use of their clinical data for research.

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TABLES

Table 1. Average spearman correlation coefficients for each of 15 patients. SD = standard deviation, n = number of 30 min segments.

Patient #	Average ICP-ABP correlation coefficient (SD, n)	Average ICP-CVP correlation coefficient (SD, n)
1	0.15 (0.29, 30)	0.125 (0.4, 30)
2	0.04 (0.35, 62)	0.165 (0.5, 62)
3	-0.01 (0.33, 99)	0.01 (0.35, 99)
4	0.015 (0.49, 24)	0.07 (0.5, 24)
5	0.03 (0.36, 37)	0.1 (0.53, 37)
6	0.04 (0.34, 107)	0.32 (0.29, 107)
7	-0.025 (0.37, 87)	0.17 (0.34, 87)
8	0.085 (0.35, 49)	0.18 (0.41, 49)
9	0.04 (0.3, 84)	0.06 (0.33, 84)
10	-0.11 (0.28, 62)	0.045 (0.38, 62)
11	-0.01 (0.34, 50)	-0.01 (0.38, 50)
12	0.06 (0.37, 63)	0.1 (0.41, 63)
13	0.040 (0.37, 17)	0.01 (0.33, 17)
14	0.06 (0.37, 67)	-0.02 (0.43, 67)
15	0.065 (0.26, 83)	-0.065 (0.29, 83)

FIGURE CAPTIONS

Fig. 1 Spearman correlation between ICP and ABP, and ICP and CVP (a and b) Local correlation coefficients within each 30-min segment for two example patients. Blue: ICP-CVP correlation coefficient, red: ICP-ABP correlation coefficient. Blue and red stars (*) indicate statistically significant coefficients ($p < 0.001$). x-axis denotes the 30-min segment number in chronological order for this patient. **(c)** Histogram of correlation coefficient values for ICP-CVP (blue bars) and ICP-ABP (red bars) for all patients ($N = 15$). **(d)** Standard deviation of correlation coefficients for ICP-CVP (blue bars) and ICP-ABP (red bars) across all 30-min segments for each patient separately.

Fig. 2 State space modelling of ICP, ABP and CVP timeseries (a) Scheme of the model: Inputs to the linear system (with state x that evolves with time t) are $ABP(t)$ and $CVP(t)$ and the output of the system is $ICP(t)$. The system parameters are estimated using the acquired data and gradient descent optimization. **(b)** Example response of the system to step increases (i.e. +1 unit) in ABP (red) and CVP (blue), starting at an initial value of 0. x-axis is time in seconds. **(c)** Response strength (ICP at $t=5000 - ICP$ at $t = 0$) for each of the 15 patients' learned models, for ABP (red) and CVP (blue). **(d)** Total response strength for each patient. Total response strength is the Euclidean norm of the 2D vector [ABP response, CVP response].

Fig. 3 Simulated ICP response of patient's model system to alteration in ABP and CVP (a) Measured (black, solid) and simulated (blue, dashed) value of ICP for two patients on a held-out test segment (30 min duration). Simulated values of ICP are obtained by numerically simulating the learned system model using the measured values of CVP and ABP as input, and an estimated initial state of the system in 1 min horizons. **(b – e)** Model simulations for patient show in Fig. 3(a) left. **(b)** Simulated ICP when starting at a high value (20 different values of CVP and constant ABP. Middle: the CVP value was changed from its initial value linearly in time to avoid transients. After 100 s, the average value of CVP was held constant at either 5 (blue), 20 (red) or 40 (yellow). The average value of ABP was fixed at its

initial value (here 94.5 mm Hg). **(c)** 3D plot of the value of ICP (vertical axis) after 200 secs as a function of different average values of CVP (4 to 40 mm Hg) and ABP (70 to 150 mm Hg) starting at an initial high ICP (~ 20 mm Hg). The color varies from high (yellow) to low (purple) ICP. **(d)** Initial ICP – Final ICP (after 200 s) as a function of different ABP values. Each point on the x-axis is an average over the different CVP values. Twenty different curves are obtained by performing the simulation with starting values of ICP from 20 segments randomly sampled from the data. An increasing curve shows that increasing ABP would lead to a greater decline in ICP from its initial value. **(e)** Initial ICP – final ICP (after 200 s) as a function of different CVP values. Each point on the x-axis is an average over the different ABP values. The slope of the ICP change curve as a function of CVP, for different initial ICP values. A decreasing curve shows that increasing CVP would lead to a greater increase in ICP from its initial value.

FIGURES

Figure 1.

Figure 2.

Figure 3.

APPENDIX

1. Artifact Rejection

The following rule-based filtering method was used to eliminate artifacts:

1. Set all values ≤ 0 or > 200 to a missing value indicator: “NaN”. These upper and lower thresholds define the range of physiologically plausible values for pressure signals.
2. Based on the first and last timestamp of a signal recording on a given day, detected missing time points by looking for consecutive timestamps with a significant time “jump” (> 2 sampling times) between them. “NaN” values and corresponding timestamps were inserted to lengthen the recording to the appropriate length.
3. Find the shortest period of recording time that overlaps for all three signals and extract those portions of signal.
4. For each signal, the data was smoothed with an exponential running average filter. If the *absolute difference in value between consecutive samples* was greater than a user defined threshold, the value of the current data point was made almost equal to the previous value. The following formula was used to change the value of the current data point:

$$\text{if } |y(i) - y(i - 1)| > \theta \rightarrow y(i) = \alpha y(i - 1) + (1 - \alpha)y(i)$$

Where $\alpha = 0.98$ and θ = threshold for the particular signal. The following thresholds were applied on the difference signal: ICP = 5, CVP = 5, ABP = 15.

5. The variance of each signal was computed in moving windows of 500 samples (~ 4 or 5 sec windows depending on the sampling rate), excluding any missing values. Windows with *variance* $< 5\text{th percentile}$ or $> 95\text{th percentile}$ of the entire distribution of variances on the same day were set entirely to “NaN”. This step was intended to remove “flat” windows with constant values and windows with large fluctuations. However, this assumes that the variance distribution for a whole day of recording was roughly unimodal, symmetric and peaked at a non-zero value.

6. Finally, the algorithm searched for 30 minute segments of data where the number of “NaN” values in each signal in the 30-min segment was less than 10%. These 30-min segments were accepted as part of the analyzed dataset. The remaining 10% “NaN” values were imputed with the median for the 30 minutes.

2. Linear state space models

Linear state space models are linear models of an observed timeseries that assume there is an underlying *unobserved* dynamical system that generates the observations. Further, the unobserved “state” can be influenced or controlled by exogenous control inputs. The view taken in a linear state space model is that the observed signal of interest (ICP) is the output of a system that has ABP and CVP as input influencing stochastic and possibly high dimensional internal state dynamics of first order.

Formally, the measured values of an output signal $y_t = \log \text{ICP}(t)$ are generated by the linear combination of input signals u_t (here a vector of length 2, namely [ABP(t), CVP(t)]) and the unobserved state variable $x_t \in \mathbb{R}^p$ ('p' is the order of the model) which has the following dynamics:

$$x_t = Ax_{t-1} + Bu_t + Ke_t$$

$$y_t = Cx_t + e_t$$

Here, e_t represents the error terms in the output estimation i.e. $e_t = y_t - \hat{y}_t$. The parameters of the model are the matrices {A, B, C and K}. The size of each matrix depends on the order of the model (p) and the number of control inputs (u_t) and the number of outputs (1 in this case). For example, for a p = 3 order model with two inputs and one output signal, $A \in \mathbb{R}^{3 \times 3}$ $B \in \mathbb{R}^{3 \times 2}$ $C \in \mathbb{R}^{1 \times 3}$ $K \in \mathbb{R}^{3 \times 1}$. For each patient, one model was estimated from all except the last ten of the 30-minute segments obtained after artifact removal. Parameter estimation was performed by gradient descent on a least square's loss function, i.e.

$\theta^* = \underset{\theta}{\operatorname{argmin}} \sum_{i=1}^n \sum_{t=1}^T \|y_t^i - \hat{y}_t^i(\theta)\|_2^2$. Here, $\hat{y}_t^i(\theta)$ represents the model's best estimate of the current value of the output signal (ICP) given the current estimate of the parameters (θ). 'i' is the index for the

segment number and 't' indexes time within each segment. Each time step was of 1 sec. The MATLAB System Identification Toolbox package *ssest* was used to estimate the parameters. The algorithm decided how to initialize the parameters and which gradient-based optimization procedure use ('auto' setting). Maximum number of iterations for gradient descent were set to 400 and regularization penalty for the parameters was varied between [1., 5., 10.]. Models of different orders (from 2 to 11, stepped by 1) were estimated with the three different regularization strengths, with/without enforcing stable dynamics and with a focus on simulation. For each patient, the best model was the one with the least Akaike Information Criteria (12). The median model order was 9 (min 6, max 10). This ensures that the least complex model that nonetheless fitted the data well was selected. For the chosen models, the mean absolute prediction error of the model was computed when predicting the value of ICP 1 min into the future, averaging over the timesteps within each 30-min segment and across all ten test 30-min segments for each patient separately.

Mean absolute error (MAE) for the i^{th} patient was given by:

$$MAE(i) = \frac{1}{10 * T} \sum_{k=1}^{10} \sum_{t=1}^T |y_t^k - \widehat{y}_t^k|$$

Here, y_t^k is the measured and predicted ICP at time step t in segment k for patient i . MAE is divided by ten to average over the ten test segments. The average and standard deviation of the MAE over all 15 patients is reported in the main text.