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Intracranial Pressure Variation Associated with Changes in End-Tidal CO2

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Abstract— **Maintaining intracranial pressure (ICP) below 20-25mmHg is an important clinical goal in the treatment of patients with traumatic brain injury (TBI). It is well known that the partial pressure of arterial CO2 (PaCO2) can affect cerebral blood flow, cerebral blood volume, and therefore ICP. The end-tidal CO2 (ETCO2) is usually monitored by clinicians as a proxy for PaCO2. We show examples where subclinical fluctuations in ETCO2 are associated with clinically significant fluctuations in ICP. We estimated ICP from past and present values of ETCO2 with a linear estimator. The variance of the ICP residuals was 37 percent of the variance of the ICP signal at frequencies above 0.33mHz. We suggest that a large proportion of clinically significant ICP fluctuations could be eliminated or reduced if the patients ventilation and CO2 levels were more tightly regulated.**

I. Introduction

Traumatic brain injury (TBI) is an acquired injury to the brain caused by an external physical force. The most frequent causes of TBI are related to motor vehicle crashes, bicycle accidents, falls, sport-related accidents, and abuse/assault.

Secondary brain Injury occurs after the primary physical trauma and is usually a result of hypoxemia, hypotension, and/or cerebral edema (swelling). Increasing cerebral edema results in increased intracranial pressure (ICP) which can cause regional or global ischemia. This secondary injury may result in cell injury or cell death and lead to a worse clinical outcome. Therapeutic interventions aimed directly at controlling elevated ICP have resulted in improved survival and neurologic outcomes [1].

Most patients with severe TBI and elevated ICP require mechanical ventilation in order to ensure adequate oxygenation and ventilation. However, inadvertent changes in the partial pressure of carbon dioxide or oxygen in arterial blood may lead to hypoxemia, hypercarbia, or hypocarbia, all of which may adversely affect either cerebral blood flow, ICP, or both. Thus, careful regulation of $PaCO_2$ and PaO_2 is an essential component of patient care in severe TBI.

The cerebrovascular reactivity to changes in $PaCO_2$ (i.e. cerebral autoregulation) is often impaired in patients with severe TBI [2]. Controlled mild hyperventilation may reduce elevated ICP, and reactivity to changes in $PaCO_2$ may serve as a prognostic marker for outcome from TBI [5]–[7].

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Patients are typically ventilated to achieve a specified minute ventilation (respiratory rate $\times$ tidal volume). Ventilation is assessed through intermittent measurement of arterial $PaCO_2$ and continuously through $ETCO_2$ measurements from exhaled gases. Typically the $PaCO_2$ and $ETCO_2$ are maintained in the range 30–35 mmHg in cases of severe TBI [1].

In a pilot study of observational clinical data we found significant fluctuations in ICP that occurred synchronously with subclinical (< 5 mmHg) fluctuations in $ETCO_2$. In other words, the ICP values were above 20 mmHg but were not detected by the bedside monitoring system as they were too brief to result in a significant change in the mean signal value that is the basis for the clinical alarm. Taken cumulatively, these brief increases in ICP have potential for patient harm. Thus, there may be an opportunity to prevent clinically significant elevations in the ICP by better regulation of ventilation.

Our objective was to estimate the sensitivity of the ICP signal to small fluctuations in $ETCO_2$ and determine how much of the ICP variability might be eliminated by better regulation of ventilation.

II. Methodology

A. Data Acquisition

We studied 2 patients (one male/one female), who were managed according to published guidelines [8]. No changes in mechanical ventilation or oxygenation were being made either immediately before (within 2 minutes) or during the data epochs analyzed for this study.

ICP was monitored continuously using a fiber-optic ventricular catheter or parenchymal pressure transducer (Integra Neurocare, Integra LifeSciences, Plainsboro, NJ). The ICP monitor was connected to a Philips Merlin patient monitor (Philips, Best, Netherlands) that sampled the ICP signal at 0.9766 Hz. The $ETCO_2$ was monitored by sidestream capnometer attached to the endotracheal tube and sampled at the same rate. The resolution of the measurements was ± 0.5 mmHg. An HPUX workstation automatically acquired these signals through a serial data network and stored them on CD-ROM [9].

B. Remove Slow Trend in ICP and $ETCO_2$ Signals

Both $ETCO_2$ and ICP contain significant long-term trends that prevent analysis and modeling based on techniques that assume statistical stationarity. Based on preliminary analysis, we found that the fluctuations corresponded to so-called ICP B waves with a typical duration of < 30 min [4]. We

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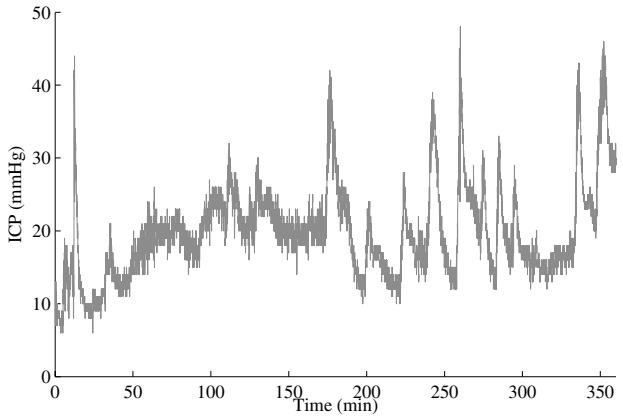
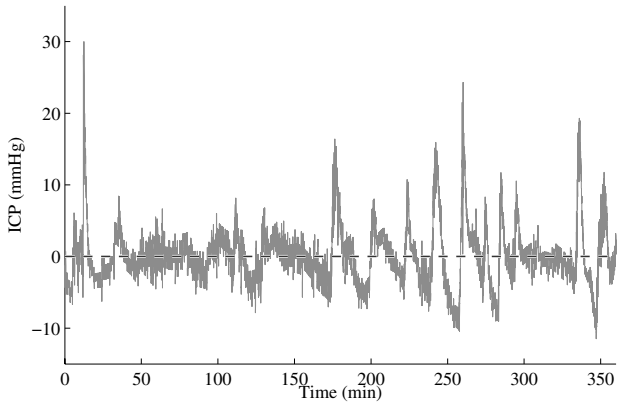


(a) Original ICP signal



(b) Detrended ICP signal

Fig. 1. Example of an ICP signal before (a) and after (b) detrending.

detrended the signals with a noncausal highpass filter with a cutoff frequency of $1/50$ cycles per minute (0.33 mHz). The filter had a stopband of 0–0.27 mHz with $\geq$ 40 dB of attenuation and a passband starting at 0.40 mHz with ≤ 0.50 dB of attenuation. Fig.1 shows a typical ICP signal before and after detrending.

C. Cohereogram

Coherence is a measure of correlation in the frequency domain. It can be used to identify the frequency range over which one signal is correlated with another signal. As with all physiologic signals, ICP and $ETCO_2$ are nonstationary so we used a moving window approach to estimate how the coherence changes with time. We call this time-frequency analysis of coherence a *cohereogram*. For each data window, the estimated coherence is given by

$$C_{xy}^2(\omega) \triangleq \frac{|R_{xy}(\mathrm{e}^{j\omega})|^2}{R_x(\mathrm{e}^{j\omega})R_y(\mathrm{e}^{j\omega})} \tag{1}$$

where $R_{xy}(\mathrm{e}^{j\omega})$ is the cross-power spectral density and $R_x(\mathrm{e}^{j\omega})$ and $R_y(\mathrm{e}^{j\omega})$ are the power spectral densities of $x(n)$ and $y(n)$, respectively. We used Welch's method of periodogram averaging to estimate the power spectral densities.

D. Linear Least Square Error Estimation of ICP from $ETCO_2$

To estimate the degree of variation in ICP that might be eliminated if $ETCO_2$ were better regulated, we created a linear estimator of ICP based on past and present values of $ETCO_2$. We denote the detrended ICP as $y(n)$ and represent a vector of past and present values of the detrended $ETCO_2$ as

$$\boldsymbol{x}(n) \triangleq \begin{bmatrix} x(n) & x(n-1) & \dots & x(n-M+1) \end{bmatrix}^{\mathrm{T}} \tag{2}$$

The detrended ICP estimated from the $ETCO_2$ signal is given by

$$\hat{y}(n) = \sum_{\ell=0}^{M-1} c_\ell x(n-\ell) = \boldsymbol{c}^{\mathrm{T}}\boldsymbol{x}(n) \tag{3}$$

where $\boldsymbol{c}$ is a vector of the linear estimator filter coefficients

$$\boldsymbol{c} \triangleq \begin{bmatrix} c_0 & c_1 & \dots & c_{M-1} \end{bmatrix}^{\mathrm{T}} \tag{4}$$

We estimated the coefficients from a segment of ICP and $ETCO_2$ signals acquired from a single patient. Specifically, we formed a vector of detrended ICP signals, $\boldsymbol{y}$, and a data matrix of detrended $ETCO_2$ signals,

$$\boldsymbol{y} = \begin{bmatrix} y(M) \\ y(M+1) \\ \vdots \\ y(N-1) \end{bmatrix} \tag{5}$$

and

$$\boldsymbol{x} = \begin{bmatrix} x(M) & x(M-1) & \dots & x(1) \\ x(M+1) & x(M) & \dots & x(2) \\ \vdots & \vdots & \ddots & \vdots \\ x(N-1) & x(N-2) & \dots & x(N-M) \end{bmatrix} \tag{6}$$

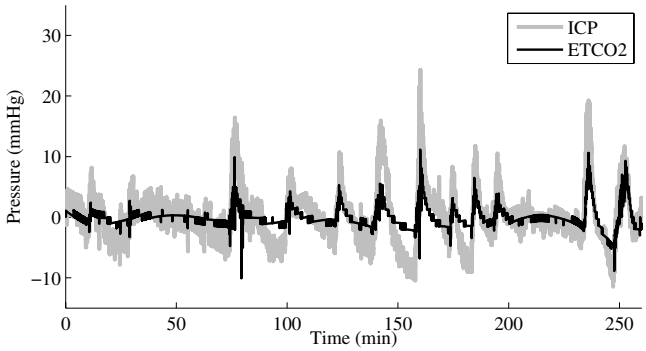
where N is the length of the segments of $y(n)$ and $x(n)$ used to estimate the coefficients $\boldsymbol{c}$.

The signals were recorded with a coarse resolution of ± 0.5 mmHg. When the $ETCO_2$ is stable, this can result in a sequence of input signal values that are constant. This can cause the data matrix $\boldsymbol{X}$ to have collinear columns and make the least squares estimate of $\boldsymbol{c}$ ill defined due to a poorly conditioned matrix inverse.

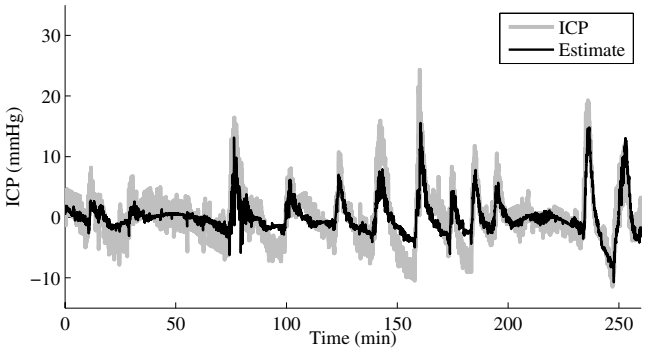
To limit the impact of collinearity we estimated the coefficients with principal component regression (PCR). This is based on a singular value decomposition of the data matrix,

$$\boldsymbol{X} = \boldsymbol{U}\boldsymbol{D}\boldsymbol{V}^{\mathrm{T}} \tag{7}$$

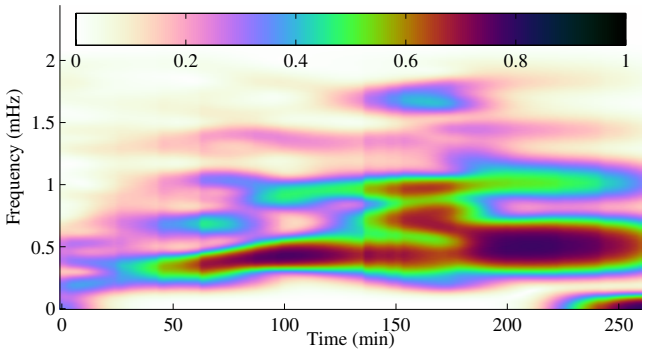
where $\boldsymbol{U} \in \mathbb{R}^{N-M\times N-M}$ is a unitary matrix, $\boldsymbol{D} \in \mathbb{R}^{N-M\times M}$ is a diagonal matrix containing the singular values, and $\boldsymbol{V} \in \mathbb{R}^{M\times M}$ is a unitary matrix. The diagonal elements d_i's of $\boldsymbol{D}$ are the singular values of $\boldsymbol{X}$ and are organized in decreasing order $d_i \geq d_{i+k}$ for any $k > 0$. Principal component regression projects $\boldsymbol{y}$ onto a subspace of the column space of the data matrix. The subspace is chosen such that it contains the most variation of the data. The dimension of the subspace is based on the relative size of the singular values. Singular values that are below a threshold



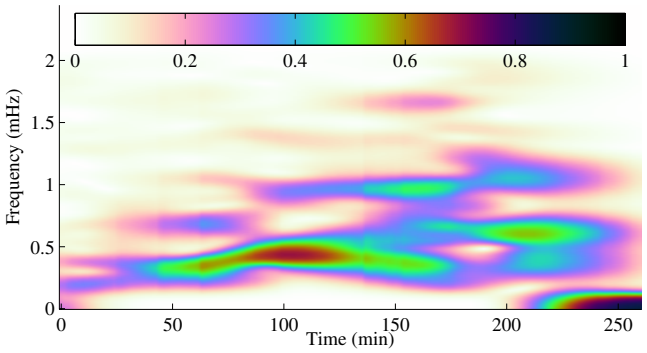
(a) Detrended CO_2 and ICP



(b) Detrended ICP and its estimate from detrended $ETCO_2$

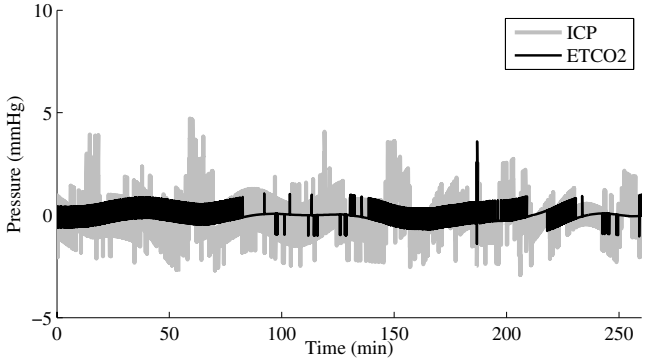


(c) Cohereogram of detrended $ETCO_2$ and ICP

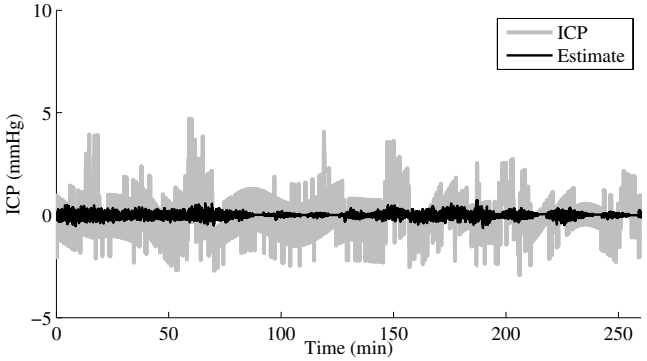


(d) Cohereogram of detrended $ETCO_2$ and residuals of ICP estimation

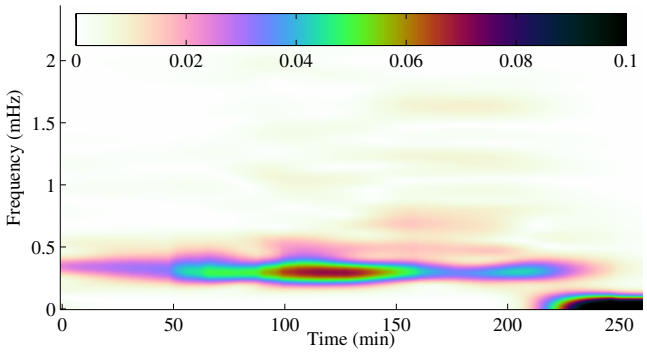
Fig. 2. A case in which small fluctuations in $ETCO_2$ caused significant fluctuations in ICP



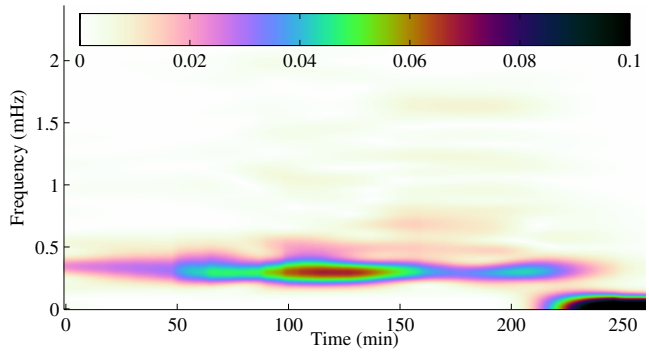
(a) Detrended CO_2 and ICP



(b) Detrended ICP and its estimate from Detrended $ETCO_2$



(c) Cohereogram of Detrended $ETCO_2$ and ICP



(d) Cohereogram of Detrended $ETCO_2$ and residuals of ICP estimation

Fig. 3. A case in which $ETCO_2$ was well regulated and no significant fluctuation in ICP was found

TABLE I

VALUES FOR USER-SPECIFIED PARAMETERS.

Symbol	Name	Value	Unit
f_c	Highpass filter cutoff frequency	0.33	mHz
τ	PCR threshold coefficient	0.001	
N	Segment length for $\boldsymbol{c}$ estimation	100	min
M	Length of estimator	5	min
S_c	Coherence data window length	200	min
W_c	Coherence segment length	100	min
SNR	Coherence signal to noise ratio	30	
V_c	Coherence segment overlap	95	%

are eliminated. The threshold is set to $d_1\tau$, where d_1 is the largest singular value and τ is a user-specified threshold coefficient. The linear estimator filter coefficients are then calculated by

$$\boldsymbol{c} = \sum_{i=1} \rho \frac{\boldsymbol{u}_i^{\mathrm{T}} \boldsymbol{y}}{d_i} \boldsymbol{v}_i \tag{8}$$

where ρ is the number of singular values that are above the threshold and $\boldsymbol{u}_i$ and $\boldsymbol{v}_i$ are the i^{th} column vectors of $\boldsymbol{U}$ and $\boldsymbol{V}$, respectively.

E. User-Specified Parameters

Table I lists the user-specified parameters and the values that we chose for this study.

III. RESULTS

Figs. 2(a) and 3(a) show examples of detrended ICP and $ETCO_2$ recordings. Fig. 2(a) shows acute increases in ICP that are strongly correlated with fluctuations in $ETCO_2$. Fig. 3(a) shows an example where both signals are stable and lack a significant correlation. Figs. 2(b) and 3(b) show the same ICP signals and the estimated ICP signals from the $ETCO_2$ signals. The coefficients were estimated using the first 100 min of these recordings. In the first example, the estimated ICP is able to estimate the actual ICP fluctuations very accurately. In fact, the variance of the residuals was 37% (7.1 $mmHg^2$) of the variance of the ICP signal. In the second case, the small fluctuations in ICP are not predictable by the $ETCO_2$. Both of these examples are consistent with the hypothesis that the ICP fluctuations could be significantly reduced if ventilation was better regulated.

Figs. 2(c) and 3(c) show the coherence between the ICP and $ETCO_2$ signals. In the first case large fluctuations are present, and the coherence shows a significant correlation in the 0.5–2.5 mHz frequency range. This is consistent with the large amplitude fluctuations seen in Fig. 2(a) which have a fundamental frequency of approximately 1.0 mHz. In the second case there is almost no coherence in the 0–5 mHz frequency range. Figs. 2(d) and 3(d) show the coherence between the ICP and the residuals between the ICP signal and its estimate, $y(n) - \hat{y}(n)$. The first case shows that most of the coherence is eliminated, which demonstrates that the estimator is able to track most of these fluctuations. The second case shows a nearly unchanged coherence, which shows that the ICP and $ETCO_2$ are largely uncorrelated.

IV. CONCLUSION AND DISCUSSION

It is clear from this data that routine but subclinical fluctuations in ETCO2 occur frequently in patients who are mechanically ventilated when no changes are being made to either the respiratory rate or tidal volume. Additionally, these subclinical fluctuations may result in clinically significant increases in ICP although they are brief. We suggest that fluctuations in ICP could be significantly reduced by tighter regulation of $ETCO_2$ levels.

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