33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Plateau Waves and Baroreflex Sensitivity in Patients with Head Injury
A Case Study

S. Shahsavari, T. McKelvey, C. Eriksson Ritzén, and B. Rydenhag

Abstract— **The study aimed to investigate baroreceptor reflex sensitivity in a patient with head injury for whom plateau waves of intracranial pressure (ICP) were recorded. Baroreflex sensitivity index was separately estimated on top of plateau waves and during intermediate intervals between two consecutive waves. The EuroBaVar data set was utilized to verify and validate the results. A very high baroreflex sensitivity associated with dominant parasympathetic activity was observed spontaneous to the acute elevations of ICP. The high vagal afferent discharge was found to be suggestive for the high firing rate of carotid baroreceptors and probably an active Cushing reflex mechanism during plateau waves.**

I. INTRODUCTION

PLATEAU waves or Lundberg "A-waves" [1] often develop in patients with increased intracranial pressure (ICP) resulting from traumatic brain injury (TBI) or other types of damages to the brain. They are the most extreme form of ICP elevation, consisting of a sudden rise up to 50-100 mmHg. ICP normally remains at high levels for more than 5 minutes before the waves diminish spontaneously [2]. These acute elevations of ICP may lead to dramatic decreases of cerebral perfusion pressure (CPP) and can therefore contribute to ischemic secondary brain insult. Since the prime aim in neurointensive care of TBI patients is to prevent and treat secondary brain injury, plateau waves has become the center of attention in many ICP related studies. The majority of investigations, conducted within this area, have suggested plateau waves to be the result of an intact or mostly intact autoregulatory response to systematic circulatory events [3, 4]. The origin and clinical significance of the waves, however, are still debated and are of considerable interest to neurologists and neurosurgeons [4, 5].

The interconnection between the blood circulatory system, brain and autonomic markers from one side and dependency of plateau waves on the circulatory events from the other side, raise the question whether baroreflex sensitivity assessment, can provide more information about the plateau-wave phenomenon. Numerus studies have been carried out to bring physiological and pathophysiological complexities associated with plateau waves to light [2–5], nevertheless, to the best of our knowledge, baroreflex sensitivity is never addressed in this context. The aim of this study is to analyze the occurrence of plateau waves and its relation with baroreflex sensitivity in a patient with head injury, for whom the acute elevation of ICP has been recorded and recognized.

S. Shahsavari and T. McKelvey are with the Department of Signals and Systems, Signal Processing, Chalmers University of Technology, Sweden shahsava@chalmers.se

C. Eriksson Ritzén is with the Departments of Anesthesia and Intensive Care Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

B. Rydenhag is with the Department of Neuroscience and Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden

II. MATERIALS AND METHODS

A. Experimental Data

In the present study, two sets of data with the following descriptions were utilized:

1) TBI Data: Clinical data was acquired from a patient with TBI admitted to the Neurointensive Care Unit at Sahlgrenska University Hospital, Gothenburg, Sweden. ICP was monitored continuously using a parenchymal fiber optic pressure transducer (ICP express, Codman). Meanwhile, arterial blood pressure (ABP) was invasively measured by a pulmonary artery catheter inserted to the radial artery. A Datex-Ohmeda S/5 critical care monitor collected electrocardiogram (ECG) at the sampling rate of 300 Hz, while both ICP and ABP were measured at the sampling rate of 100 Hz. These signals were collected from an S/5 network, using S5-collecting software.

The patient did not have external ventricular drainage, nor decompressive craniectomy. Plateau waves of ICP were recorded and recognized within the last 18 hours of the recording (see Fig. 1). These part of the data which included premonitory drift phase [3] and following plateau waves, were selected and used within the present study.

A closer look to the ICP signal with plateau waves on its top and the associated ABP, CPP and heart rate (HR) is provided by Fig. 2. From the figure depressed heart rate can be clearly recognized during elevated episodes of ICP. The data, spontaneous to large fluctuations of ICP, were labeled with either "Plateau" or "floor". A threshold scheme was used in the classification. The former class was defined as the part of ICP exceeding 58 mmHg; while, the latter class was defined to be the interval limited to the end of one plateau wave and the start point of the consecutive one. From Fig. 1, 13 plateau waves can be recognized on top of the ICP signal, which results in 13 segments labeled as "Plateau" and 13 segments classified as "floor". However, since the data was initially segmented to 1 h intervals, the same plateau waves or floor segments could appear in two different intervals. This resulted in 16 "Plateau" and 18 "floor" segments. The ABP and ECG signals were segmented using the same time indices and later were used to estimate desired parameters.

2) EuroBaVar Data Set: The EuroBaVar dataset [6] was used as the reference dataset: first, to evaluate the performance of the estimation methods and second, to compare the result of TBI data with. This data set provides two forms of data. The first category provides beat-to-beat systolic blood

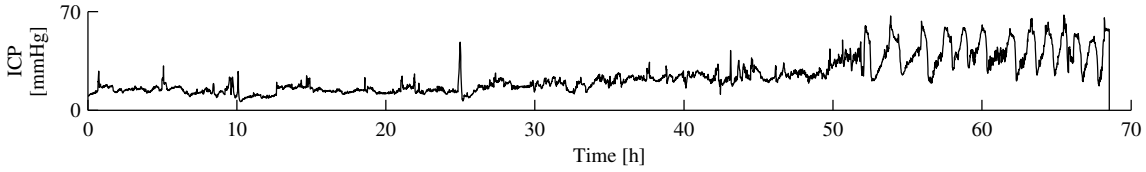

Fig. 1. Intracranial pressure collected from a TBI patient. Plateau waves can be observed in the last eighteen hours of the trend.

pressure and RR-intervals, while the second is a collection of recorded signals at the sampling rate of 500Hz. This data set consists of forty-six 10-12 min recordings obtained in 21 subjects in lying (L) and standing (S) positions. Subjects were monitored non-invasively with a Finapres 2300 (ohdema, Louisville, Colorado, USA) and a Cardiocap II (Datex Engstrom, Helsinki, Finland). The data is non-homogenous including two diabetic patients with and without cardiac neuropathy, one recently heart transplanted, eight normotensive outpatients, one untreated hypertensive, two treated hypertensive, two treated hypercholesterolemia, one pregnant woman, four healthy volunteers and replica records of two subjects [7]. No information regarding association of data and subjects was available at the time of this study.

B. Methods

Cardiovascular activity is regulated by intrinsic rhythmicity of the myocardium as well as various local, reflexive mechanisms. The baroreceptor reflex is a homeostatic mechanism in human body which maintains blood pressure through the central nervous system [8]. When systemic blood pressure increases, the baroreceptor reflex provides a negative feedback and reflexively decreases heart rate as well as blood pressure. The feedback is initiated on the level of stretch-sensitive baroreceptors, located on the carotid sinuses and aortic arch and is completed through the inhibition of the sympathetic and activation of the parasympathetic nervous system. Conversely, decrease in arterial blood pressure increase sympathetic neural activity and decrease the activity of the parasympathetic branch, resulting in increased heart rate, stroke volume and total peripheral resistance (TPR). By this arterial blood pressure will return to its normal level [8].

The sensitivity of the baroreceptor reflex can be evaluated from spontaneous changes in blood pressure and heart period. Baroreflex sensitivity (BRS) index is an estimation of the sensitivity using either time or frequency-domain methods. These approaches, however, do not represent identical estimates of BRS [9]. The current study utilized both approaches to investigate the behavior of the central nervous system (CNS) during plateau waves of ICP. The mentioned methods are briefly described in the following.

1) Time-Domain BRS Index: Time-domain analysis of BRS is performed over time series of systolic blood pressure (SBP) and RR-intervals of ECG, denoted by $\mathbf{x}_{SBP}(n)$ and $\mathbf{x}_{RR}(n)$ in order, where $n = 1,2,...,N_{max}$. To estimate RR-intrvals, R-peaks were automatically detected by applying a thresholding scheme to the normalized ECG signal [10]. The maximum pressure point of the ABP signal within each RR-interval was then found in order to create the SBP vector. Although a beat lag of $\tau = 1$ was found to be a common approach in BRS analysis, this study allowed a beat lag not exceeding 5 seconds. This was decided based on several studies which represented the latency of baroreflex response in human to vary between 1 to 5 seconds [7, 11]. The estimation process was performed in two steps: first the identification of baroreflex segments (segments which contain changes in SBP and reflexive variations of RR-intervals) and then BRS estimation from the slope between RR-intervals and SBP. While the former task was conducted through the event technique, the latter accomplished by using a global approach for slope estimation [12].

The event technique is a newly defined criterion for the segmentation of SBP and RR-intervals. This technique consists of identification of segments which exhibit high positive correlation between two series. Each segment needs to meet the required length of beats ($N_{min} = 3$) and correlation coefficient ($r_{min} = 0.8$) to be identified as an event segment. There is no limit on minimum changes in SBP within one RR-interval, though. This means SBP or RR-intervals may not be consecutively increasing or decreasing on a beat-to-beat basis as in the sequence technique [13]. The k^{th} identified event segment, represented by BE_k, $k = 1,2,...,K$, was characterized by N_k pairs of values $(\mathbf{x}^k_{SBP}, \mathbf{x}^k_{RR})$ beginning at index n_k and the beat lag of D_k. The pair of (N_k, D_k) was chosen to maximize $\beta(\mathbf{x}^k_{RR}, \mathbf{x}^k_{SBP})$, the slope between the two series, that is

$$\begin{aligned} (N_k, D_k) &= \underset{N,D}{\operatorname{argmax}}\, \beta(\mathbf{x}^k_{RR}, \mathbf{x}^k_{SBP}) \\ \text{subject to} \quad & N \in [3, 256] \\ & D \in [1, D^k_{max} | T(D^k_{max}) < 5s] \end{aligned} \tag{1}$$

where D^k_{max} refers to the maximum permitted beat lags for the k^{th} identified event segment. Here $T(D^k_{max})$ stands for the related time lag and

$$\begin{aligned} \mathbf{x}^k_{RR} &= [x_{RR}(n_k)\, x_{RR}(n_k+1) \ldots x_{RR}(n_k+N-1)] \\ \mathbf{x}^k_{SBP} &= [x_{SBP}(n_k-D)\, x_{SBP}(n_k-D+1) \ldots \\ & \quad x_{RR}(n_k+N-D-1)] \end{aligned} \tag{2}$$

Identifying all event segments, the global approach suggested by [12] was then employed and the BRS index denoted by β_{GT} was estimated as the slope between all available pairs of SBP and RR-interval within these segments.

2) Frequency-Domain BRS Index: Spontaneous BRS assessment in frequency domain, the so-called α-index was

calculated using the following equation [14]:

$$\alpha = \sqrt{\frac{RR_{power}}{SBP_{power}}} \tag{3}$$

and accepted as valid only where the cross-spectral coherence between RR-interval and SBP was > 0.5. In the previous equation RR_{power} and SBP_{power} represent the spectral power density of the RR-interval and SBP fluctuations within a given frequency range. A distinction made between the α-index calculated at the low-frequency (LF) range (0.04-0.15 Hz) from the one calculated at the high-frequency (HF) range (0.15-0.4 Hz).

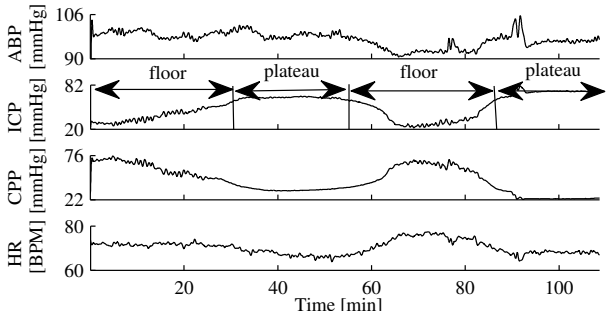

Fig. 2. Heart rate declines when ICP elevates to its extreme levels. ABP: arterial blood pressure, ICP: intracranial pressure, CPP: cerebral perfusion pressure, HR: heart rate.

III. Results

To determine if results will be affected by either the low sampling rate of ECG in TBI data or the employed detection algorithms, a comparative study was performed by handling the both classes of the EuroBaVar data set. First, the 500Hz continuous signals from this data set were re-sampled at the rate of 300Hz to simulate the similar condition of the TBI data. After locating R-peaks, the estimated series of SBP and RR-intervals along with the beat-to-beat series provided by the EuroBaVar data set were used to evaluate the time-domain BRS index (β_{GT}), the mean time lag and the mean length of event segments. The box plot of the achieved results for both categories are shown in Fig. 3. Each box has lines at the lower quartile, median, and upper quartile values. The lines extending from each end of the box are whiskers to show the extent of the rest of the data. As can be seen, no major difference is found between the outcomes obtained by handling the beat-to-beat series (denoted by LB and SB) and those resulted from processing the continues signals (denoted by LC and SC). These observations ensure us that the result we get by treating the TBI data with the same methodology are affected by neither the detection algorithms nor low sampling frequency.

Fig. 4 illustrates the results achieved by handling "floor" and "plateau" segments of TBI data along with the driven results from the continuous EuroBaVar signals. As can be found from Fig. 4(a) the baroreceptor reflex shows its extreme sensitivity when plateau waves are created by sudden

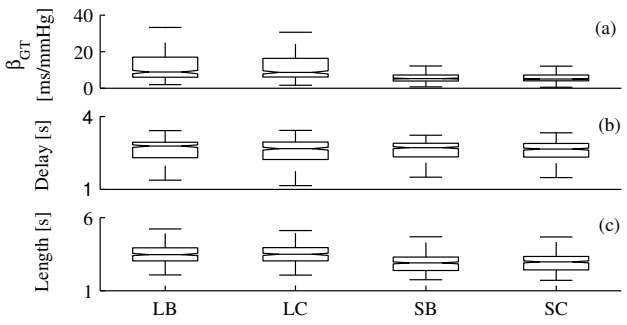

Fig. 3. L: supine position, S: standing position, B : beat-to-beat series, C: continuous signals. The top plot represents boxplots of baroreflex sensitivity index in ms/mmHg, while the middle plot shows boxplots of estimated delays between correlated variations in SBP and RR-intervals. Finally the last figure is dedicated to the length of correlated intervals of systolic blood pressure and RR-intervals.

elevations of ICP. This is while the BRS index associated to the floor segments is in the same range of supine position in the EuroBaVar data set. In order to identify the frequency source of the sensitivity, this observation was compared to the results from the frequency-domain assessment of BRS, shown in plots (b) and (c). Suggesting by the provided box plots, a significant contribution of HF component is responsible for the large β_{GT} spontaneous to the plateau waves of ICP.

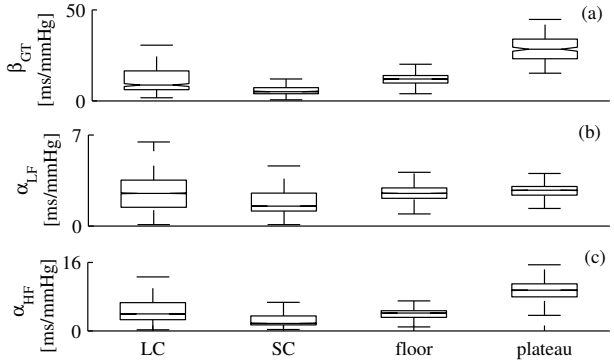

Fig. 4. LC: EuroBavar continuous signals supine position, SC: EuroBavar continuous signals standing position, floor: data limited to the ending and starting points of each two consecutive plateau waves, plateau: data spontaneous to plateau waves. The tree plots from top to bottom represent boxplots of baroreflex sensitivity indices estimated in time domian and low and high frequency bands.

IV. Discussion and Conclusions

This study indicates that plateau waves of ICP to be spontaneous to a significant increment in BRS associated with dominant HF component. This matter is apparent from Fig. 4(a) and (c). Since the vagal afferents discharge counts as a major contributor to the HF component of heart rate variability and hence BRS in high frequency range (α_{HF}), a high parasympathetic nervous activity can be concluded to occur during plateau waves of ICP. From Fig. 4(b) no big difference in LF component of BRS can be found between "floor" and "plateau" segments. Therefore the parasympathetic branch of

the autonomic nervous system may be regarded as the only factor affecting BRS as well as HR during plateau waves.

The high BRS and decreased HR may be indicative of an increased SBP during the plateau waves of ICP which is sensed by baroreceptors and responded by the activation of the parasympathetic branch of the autonomic system. Nevertheless, the high ICP acting on the brainstem may also contribute to an augmentation of parasympathetic outflow to the heart and a fall in HR [15]. If the former is accepted to be the major source of the high parasympathetic activity, then baroreceptors in carotid sinuses can be counted responsible for the high BRS. This conclusion is based on the fact that ABP, measured in radial artery, does not show a significant increase (see fig. 2). By this a global increase in blood pressure and resultant high firing rate of baroreceptors in aotic arch is rejected.

Despite some studies, emphasizing on the intactness of the autoregulatory mechanism during the generation of plateau waves [16], in a recent study plateau waves were suggested to be generated as a consequence of depressed cerebral autoregulation and due to the activation of the Cushing reflex [17]. This was found in agreement with the previous studies that reported the efferent discharge of sympathetic and parasympathetic nerve fibers during increased ICP and emphasized on Cushing reflex of the brain [15, 18, 19]. The Cushing reflex is commonly believed to be a protective response of nervous system to a raised ICP which attempts to maintain cerebral perfusion. The reflex is generally accompanied by arterial hypertension, increased TPR and bradycardia arisen from high activity in parasympathetic nerve fibers [20–22]. Fig. 2 which represents bradycardia spontaneous to the increased ICP and decreased CPP, is in a complete agreement with the general description of the Cushing reflex. Although some investigations point on mechanical effects of increased ICP upon the brainstem [15], some others suggest an independent reflexive mechanism to be responsible for the stimulation of sympathetic and vagal nerves during Cushing reflex [23]. The latter group, counts on the baroreceptor reflex to be the mechanism lying behind the bradycardia.

The estimation of baroreflex sensitivity in this study, in fact, reveals another perspective on the plateau-wave phenomenon. Comparing the short time scale baroreceptor reflex indices with the macro scale observation of Fig. 2, we can conclude that the baroreceptor reflex mechanism is active along with the Cushing reflex where plateau waves occur and induces the observed cardiac bradycardia. When the Cushing reflex mechanism is activated, the consequence increase in TPR guides more flow through the carotid arteries toward the brain, thus, induces a high pressure on the walls and strongly stretches the carotid baroreceptors. Cushing reflex can, therefore, motivate the high firing rate of carotid baroreceptors leading to a very high BRS during plateau waves of ICP. The aforementioned scenario may suggest the contribution of the Cushing reflex in the generation of plateau waves as reported by [17] and lead to a better understanding of cerebral hemodynamics. However, to confirm this a model-based framework and further assessment with a larger population of patients seems inevitable.

REFERENCES

[1] N. Lundberg, "Continuous recording and control of ventricular fluid pressure in neurosurgical practice," *Acta Psychiatr Neurol Scand Suppl*, vol. 36, no. 149, pp. 1–193, 1960.

[2] D. Kim, M. Kasprowicz, E. Carrera, G. Castellani, C. Zweifel, A. Lavinio, P. Smielewski, M. Sutcliffe, J. Pickard, and M. Czosnyka, "The monitoring of relative changes in compartmental compliances of brain," *Physiol. Meas.*, vol. 30, pp. 647–59, 2009.

[3] M. Rosner and D. Becker, "Origin and evolution of plateau waves. experimental observations and a theoretical model," *J Neurosurg*, vol. 60, no. 2, pp. 312–24, 1984.

[4] G. Castellani, C. Zweifel, D. Kim, E. Carrera, D. Radolovich, P. Smielewski, P. Hutchinson, J. Pickard, and M. Czosnyka, "Plateau waves in head injured patients requiring neurocritical care," *Neurocrit Care*, vol. 11, pp. 143–50, 2009.

[5] T. Lescot, L. Naccache, M. Bonnet, L. Abdennour, P. Coriat, and L. Puybasset, "The relationship of intracranial pressure lundberg waves to electrocephalograph fluctuations in patients with severe head trauma," *Acta Neurochir*, vol. 147, pp. 125–9, 2005.

[6] D. Laude, J. Elghozi, A. Girard, E. Bellard, M. Bouhaddi, P. Castiglioni, C. Cerutti, A. Cividjian, M. D. Rienzo, J. Fortrat, B. Janssen, J. Karemaker, G. Lefthériotis, G. Parati, P. Persson, A. Porta, L. Quintin, J. Regnard, H. Rüdiger, and H. Stauss, "Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study)," *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, vol. 286, no. 1, pp. R226–R231, 2004.

[7] B. Westerhof, J. Gisolf, W. Stok, K. Wesseling, and J. Karemaker, "Time-domain cross-correlation baroreflex sensitivity: performance on the eurobavar data set," *Journal of Hypertension*, vol. 22, no. 7, pp. 1371–80, 2004.

[8] T. Rooke and H. Sparks, *Medical Physiology*, ch. 18, pp. 290–308. Lippincott Williams & Wilkins, 2nd ed., March 2003.

[9] P. Persson, M. DiRienzo, P. Castiglioni, C. Cerutti, M. Pagani, N. Honzikova, S. Akselrod, and G. Parati, "Time versus frequency domain techniques for assessing baroreflex sensitivity," *J Hypertens*, vol. 19, no. 10, pp. 1699–705, 2001.

[10] S. Shahsavari and T. McKelvey, "Harmonics tracking of intracranial and arterial blood pressure," in *Proc. 30th Annu. Int. Conf. IEEE*, pp. 2644–7, Eng. Med. Biol. Soc., 2008.

[11] T. Wu, C. Chen, and T. Kao, "Baroreflex sensitivity evaluation by volterra wiener model and the laguerre expansion technique," *Computers in cardiology*, pp. 741–4, 2008.

[12] S. Gouveia, A. Rocha, P. Laguna, and P. Lago, "Time domain baroreflex sensitivity assessment by joint analysis of spontaneous sbp and rr series," *Biomedical Signal Processing and Control*, vol. 4, no. 3, pp. 254–61, 2009.

[13] M. D. Rienzo, P. Castiglioni, G. Mancia, A. Pedotti, and G. Parati, "Advancements in estimating baroreflex function exploring different aspects of autonomic control of the heart through the sequence technique," *IEEE Eng. Med. Biol.Mag.*, vol. 20, pp. 25–32, 2001.

[14] Y. Tzeng, P. Sin, S. Lucas, and P. Ainslie, "Respiratory modulation of cardiovagal baroreflex sensitivity," *J Appl Physiol*, vol. 107, pp. 718–24, 2009.

[15] S. Matsuura, H. Sakamoto, Y. Hayashida, and M. Kuno, "Efferent discharges of sympathetic and parasympathetic nerve fibers during increased intracranial pressure in anesthetized cats in the absence and presence of pressore respone," *Brain Research*, vol. 305, pp. 291–301, 1984.

[16] M. Ursino and C. Lodi, "A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics," *Journal of Applied Physiology*, vol. 82, no. 4, pp. 1256–69, 1997.

[17] M. Ursino, M. Giannessi, M. Frapparelli, and E. Masosso, "Effect of cushing response on systemic arterial pressure," *IEEE Eng Med and Biol Mag*, vol. 28, no. 6, pp. 63–71, 2009.

[18] H. Cushing, "Concerning a definite regulatory mechanism of the vaso-motor center which controls blood pressure during cerebral compression," *Johns Hopkins Hosp. Bull.*, vol. 126, pp. 290–2, 1901.

[19] C. Su, Y. Yang, M. Lee, and H. Chen, "A severe vicious cycle in uncontrolled subarachnoid hemorrhage: The effects on cerebral bloosd flow and hemodynamic responses upon intracranial hypertension," *J. Physiol.*, vol. 49, no. 1, pp. 56–63, 2006.

[20] C. Su, C. Hu, and H. Chen, "Effects of intracranial hypertension on steady and pulsatile haemodynamics in dogs," *Clin. Exp. Pharmacol. Physiol.*, vol. 26, no. 11, pp. 898–902, 1999.

[21] H. Chen and D. Wang, "Systemic and pulmonary hemodynamic responses to intracranial hypertension," *Amer. J. Physiol.*, vol. 247, no. 5, pp. H715–H721, 1984.

[22] T. Ducker and R. Simmons, "Increased intracranial pressure and pulmonary edema. part 2. the hemodynamic response of dogs an monkeys to increased intracranial pressure," *J. Neurosurg.*, vol. 28, no. 2, pp. 118–123, 1968.

[23] J. McGillicuddy, G. Kindt, J. Raisis, and C. Miller, "The relation of cerebral ischemia, hypoxia, and hypercarbia to the cushing response," *Journal of Neurosurgery*, vol. 48, no. 5, pp. 730–40, 1978.