Xenon/CT in the Management of Traumatic Brain Injury

Andrew P. Carlson* and Howard Yonas*

Department of Neurosurgery, University of New Mexico, MSC10-5615, 1 University of New Mexico, Albuquerque, NM 87131-0001, USA

Abstract: Xenon/CT provides quantitative CBF data that has a proven record of being both safe and prognostic for decision making. The technique itself has been extensively validated. Modern equipment has allowed for integration of the data into immediate bedside decision-making with the use of a portable head CT scanner and improved data processing. The use of xenon/CT in decision making in traumatic brain injury may have a high utility in determining whether a specific treatment— whether it is hyperventilation, induced hypertension, or other intervention—is in fact helpful to the individual patient. This can allow for decision making based on an individual patient's physiology rather than generalized guidelines which may, in some cases, even be harmful.

Keywords: Computed tomography, cerebral blood flow, critical care, ICU monitoring.

INTRODUCTION

Xenon enhanced computed tomography (xenon/CT) is a powerful physiological imaging tool which provides a clinician with rapid access to quantitative cerebral blood flow (CBF) data, allowing measurement of the physiologic response to prescribed interventions, and provides prognostic data to guide patient management. This CBF information is uniquely useful because it is in a high resolution tomographic format with direct CT correlation. Though general guidelines for management of traumatic brain injury (TBI) exist, it is clear that not all patients may be benefitted but these guidelines. By measuring a patient's regional CBF and testing hypotheses of management, the physician can move from general principles of management of brain injury toward management based on an individual patient's physiological needs.

TECHNOLOGY

Background, Theory, and Physiology

CBF has been measured by a number of diffusible tracers that allow measurement of the delivery to and the arrival within the brain substance. Xenon133 was an ideal early tracer because xenon is highly lipid soluble and its 133 isotope could be readily tracked with external scintillation counters. Using xenon133, technology was developed that could measure hemispheric and then superficial regional flow in cc/100g/min. Although valuable work was achieved with this tracer, the need for radioisotope precautions and its lack of resolution within the depth of the brain left much to be desired for routine neuro-ICU application.

Soon after it was reported in the late 1970's that stable xenon was radiodense (similar to iodine, given their proximity in the periodic table) the first applications with CT imaging were reported [1]. This was followed shortly by the group at the University of Pittsburgh reporting the ability to tomographically image CBF [2]. Since that time, tens of thousands of Xenon/CT CBF studies have been reported in hundreds of articles from around the world. The first 15 years of studies were reported with 33% xenon inhalation, though the dose of xenon was reduced in 2000 because newer CT scanners had a lower noise level allowing reduction of xenon to 28% while maintaining an eight to one signal to noise ratio. This reduction of xenon helped further reduce the already low incidence of sensorial effects while also reducing the cost of studies.

The calculation of cerebral blood flow (CBF) relies on a modification of the Kety-Schmidt equation. The two variables required to solve the equation include the arterial concentration curve of the agent as well as the extent and time course of tissue arrival (which is dependent upon the blood flow and the blood-brain partition coefficient or lambda). The arterial concentration is measured indirectly from the end-tidal xenon concentration—which is an excellent approximation, given that it is a highly diffusible gas. In addition, the brain partition coefficient is calculated along with flow for each CT pixel by solving the Kety-Schmidt for both variables using an iterative mathematical approach (equation 1). This calculation is performed for each CT pixel, typically at four CT levels, however many more levels can be imaged with newer multi detector scanners, dependent only on the number of parallel detectors. This approach of calculating both the input functions in a continuous fashion makes xenon/CT uniquely accurate in terms of CBF measurement among other CBF technologies.

$$Cxe_{br}(t) = \lambda k \int_{o}^{t} Cxe_{Art}(u)\, e^{-k(t-u)}\, du \qquad (1)$$

(Cxe_{br} (t) is the time dependent brain xenon concentration, λ is the brain-blood partition coefficient, k is the brain uptake flow rate constant, $Cxe_{Art}(u)$ is the time dependent arterial xenon concentration).

While studies with xenon133 utilized the "wash out" curve of this tracer, work with stable xenon focuses upon the "wash in" curve, thereby minimizing any theoretical alteration of flow due to an activation of CBF from the xenon it-

*Address correspondence to these authors at the Department of Neurosurgery, University of New Mexico, MSC10-5615, 1 University of New Mexico, Albuquerque, NM 87131-0001, USA; Tel: 505-272-3401; Fax: 505-272-6091; E-mails: acarlson@salud.unm.edu; hyonas@salud.unm.edu

1876-5297/10

self. Practically, this has found to not be a concern, as the flow activation is minimal and occurs later than the period of measurement. The accuracy of the xenon/ CT method has undergone rigorous cross-correlation assessment with destructive (microspheres [3], iodoantipyrine [4]), and *in vivo* (xenon133 [5], PET [6], thermal dilution flow probes [7]) CBF technologies.

The CBF values are then represented pictorially with colors overlaying the tomographic slices. Each color is a standardized, quantitative CBF value for each pixel after the calculation is complete. One can then manipulate the data in multiple ways to aid visual display. In order to obtain useful regional values, the cortical mantel can automatically be divided into six or twenty 2cm deep regions of interest (ROI), and the average for each region displayed. Alternatively, any ROI of regular or irregular shape and size can be selected by the user on either the CT or the CBF image. Additional analysis can be performed to assess the validity and further manipulate the data.

In contrast to the half hour needed to calculate one level of flow in the 1980's, a four level study, which measures almost 100,000 flow values on four CT levels of study, now requires less than ten seconds. This almost instantaneous turnaround time allows for the integration of xenon/CT CBF derived flow information into prospective clinical decision making.

For mixed cortical sources, CBF in the range of 54 +/- 10 cc/100g/min is considered normal, and values less than 15-20cc/100g/min represent ischemia and correlate closely with neurologic deficit and infarction [2, 8-12]. Normal grey matter is 84cc/100g/min and white matter is 20cc/100g/min. The mixed cortical flow and grey matter flow decrease with age, but white matter flow remains constant [11]. Using xenon/CT, the metabolic state of the brain can also be assessed. Normal pressure autoregulation causes vessels to dilate in response to decreasing CPP as a compensatory mechanism to maintain CBF. If one performs a CBF study, then administers a vasodilatory challenge (such as tissue acidification with acetazolamide or increasing PCO_2), the second study should show increased CBF. If the CBF does not increase as expected or even decreases, this offers insight into the state of autoregulatory vasodilatation or cerebrovascular reserve (CVR), and is useful in detecting marginally perfused tissue [13-21].

On the other hand, CBF is altered by chemoregulation as well. Elevation of PCO_2 by 1mmHg should result in a 3% rise of CBF in normal tissue, however in pediatric patients, this CBF response may be 5 or even 10%, leading to tissue very sensitive to PCO_2 manipulation. Furthermore, if CBF does not fall with lowering of PCO_2 with forced hyperventilation, this is a sign of tissue death, where vascular channels remain open, but are unresponsive to normal chemoregulatory stimuli. This concept becomes important to understand, particularly in TBI, where autoregulation may be altered by tissue death or dysfunction, and lowering intracranial pressure (ICP) by hyperventilation may only be driving CBF down in normal tissue; potentially even to ischemic levels [22].

Equipment and Procedure

Xenon/CT CBF is dependent upon a number of components-- software that uses CT images to document the arrival of xenon within the brain, a computer required to handle the complex mathematical process, and hardware that monitors, maintains, and delivers fixed concentrations of xenon and oxygen. With the passage of two decades, CT scanners have evolved to not only provide more levels, more rapidly, but with less radiation and lower noise. During this interval, the computer upon which the technology is dependent has also evolved beyond what we could have conceived in 1970. As a result, more and better data is provided in a timely manner, compatible with integration into prospective decision making. In order to standardize CBF data between CT scanners, a "phantom" was developed for calibration. Xenon/CT is the only technology that provides the ability to know that a flow value has the same physiological implications despite even different CT manufacturers. With the integration of xenon/CT CBF within a modern portable CT scanner (CereTom-NeuroLogica: Danvers, MA), these blood flow studies have achieved an ideal configuration where the procedure can be done at the patient's bedside with simultaneous monitoring, measurement, and manipulation of critical care parameters (Fig. **1**).

Xenon itself is a safe, radio-opaque, noble gas. Historically it has been used at very high concentrations (80%) as a general anesthetic agent since the early 1900s, though more recently has regained popularity due to its favorable safety and anesthetic profile [23-25]. Even after hours of inhalation, it has not been associated with any physiological side effects and it is associated with a uniquely rapid awakening [26]. Recent studies have even provided evidence that xenon is neuro-protective due to its ability to block NMDA receptors [27]. Since there are physiological effects at high doses, the lowest concentration possible is used for imaging to avoid side effects. All the data prior to the early 2000's used 33% xenon, and even at this concentration, the side effects were typically mild, and typically consisted of self limited respiratory pauses (~3.6%) [28]. Now with improvements in CT imaging technology, the concentration has been lowered to 28% and detailed safety data has been prospectively collected, showing a rate of respiratory pause >20 seconds of 1.9% (unpublished data). These pauses are always self limited, and respond to gentle coaching. To date, no permanent sequelae or morbidity has ever been reported with use of xenon. Patients occasionally describe some anxiety or sense of loss of control with even 28% the xenon inhalation, while others perceive a mild euphoric feeling. All sensorial phenomena are cleared within a few minutes of study cessation. Vital signs are not typically affected. There are no possible allergies or toxicities associated with xenon inhalation unlike other CT or MRI contrast agents [29-32].

Xenon/CT CBF has a mixed history of accessibility due to expense and difficulty with access to xenon gas. Because of a FDA (food and drug administration) "grand-father" approval for the use of xenon as a contrast agent was held by Praxair (the company that was supplying medical grade xenon for imaging) this technology had wide application within the United States and elsewhere in the early 1990's. With the withdrawal of Praxair from the rare gas market due to busi-

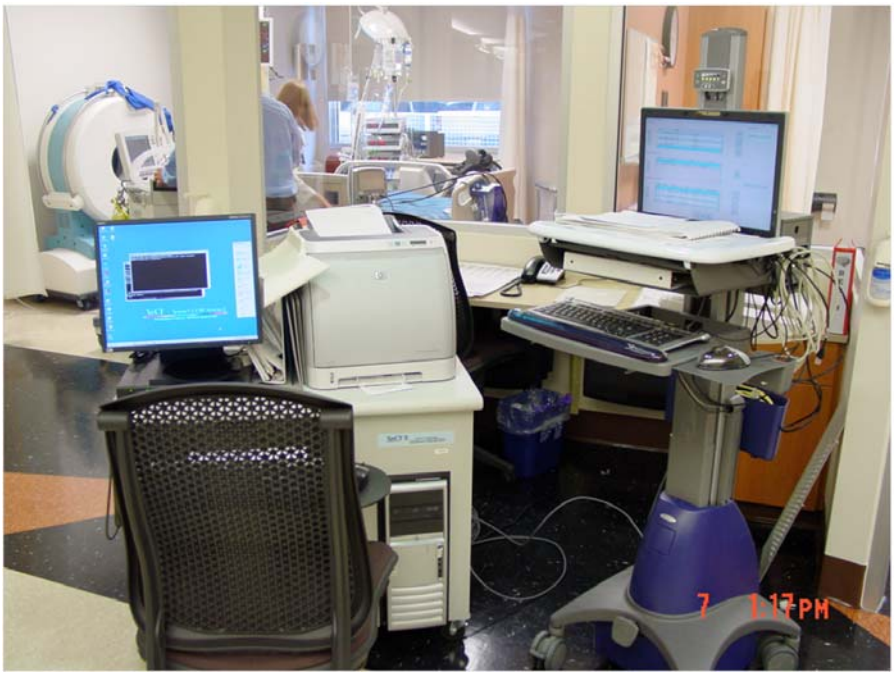

Fig. (1). The bedside set-up to perform a xenon/CT study in the intensive care unit. The portable CT scanner is seen in the upper left at the patient's bedside, and the control station for the scanner is the rolling stand on the right. The xenon administration and analysis unit is in the foreground to the left.

ness restructuring, xenon lost its wide accessibility. Currently the technology is available as part of an IND (investigational new drug) that is part of a reapplication to the FDA for a formal approval. Xenon/CT CBF has been available in Japan and elsewhere in the world for almost two decades. Though over 500 xenon units have been sold in Japan, there have been, to date, no reports of safety concerns presented to the Japanese manufacturer.

In order to perform a scan, the patient is brought to the CT scanner, or a portable scanner is brought to the patient's bedside. The xenon technology can be used with most CT scanners with only minimal adaptation. The patient must either be cooperative, amenable to mild rapidly reversible sedation, or chemically paralyzed and ventilated as the head position must remain very stable during the 4.5 minutes of data acquisition. The xenon delivery system is attached to the patient's mask or to the ventilator circuit. The end tidal CO2 and end tidal xenon concentration are continuously monitored and displayed on the system monitor. The baseline CT levels selected for CBF examination are identified and imaged prior to starting xenon inhalation. The xenon inhalation is started and the scanner begins serial imaging at the same preset levels as the arterial xenon concentration increases. The first two minutes are the most critical phase of data acquisition because significant movement at this time will make the study quantitatively unreliable while movement later allows for salvage of the study by exclusion of later poor quality data. Movement during the acquisition of images degrades the study because the baseline images are subtracted from the subsequent images to get a measure of the change of Hounsfield units. The CT data is then transferred to the xenon work station which already contains the time linked air (arterial) curve data.

Once the CT data has been brought to the workstation, the computer uses the Hounsfield enhancement as well as the end tidal xenon data to solve the above integral equation for each pixel of the CT scan. The program also analyzes for the numerical reliability of the data which needs to be factored into the clinical analysis of the CBF data. The data can then be manipulated using the software in many ways. While the error of remeasurement of a single pixel is close to 100%, the error of measurement of a 10x10 voxel approximates 10%, which is comparable with any quantitative physiological study [33].

An important point to emphasize is that just as the xenon washes in very rapidly, it is also cleared very rapidly by exhalation once the gas is turned off. 99% of the agent is washed out of the body within 5 minutes. This is a key and unique characteristic, such that it is possible to repeat the study nearly immediately to assess the effect on CBF of manipulation of a physiologic parameter such as pCO2 or blood pressure. This allows for testing management hypotheses in critical patients at the bedside with ongoing monitoring of all the patients vital signs and other invasive or noninvasive monitors which cannot be transported.

Limitations

Simply due to the fact that this technique is CT based, there are inherent risks of radiation exposure, and though the study involves multiple serial slices, they should be directed above the orbit and lens (the most radiosensitive structure of the head). These risks are certainly not to be ignored, however are of very low concern in the setting of patients with life threatening critical illness. Additional training is needed for the nursing and other ICU staff with regards to radiation safety to perform portable studies in the ICU. Xenon itself is very safe as described above, especially when one considers

the severe effects that commonly used iodinated and gadolinium-based agents can have. As discussed above, the data is limited by motion artifact during scanning. The study takes longer than a standard CT scan to set up, and requires experienced personnel to operate the equipment. The technology and equipment is not widely available but its continued presence at a half dozen institutions in the US demonstrates the belief of those that have access to xenon/CT CBF that it is a vital clinical tool. Though the techniques have been proven to reliably and safely guide clinical practice as described below, it has not as of yet been approved by the FDA, making access somewhat challenging and typically requiring institutional human research committee approval.

Xenon/CT in Traumatic Brain Injury

The historical utility of xenon/CT has been in such modalities as predicting risk of infarction after carotid occlusion, evaluating hemodynamic reserve in states of carotid occlusion, and in fact, these remain some of the most powerful utilities of the technique [34, 35]. In addition, the versatility of the technique has led to its use in myriad fields. Xenon/ CT is commonly used where available to determine tissue at risk of infarction as well as testing management strategies in vasospasm [36]. In ischemic stroke, it can be used to determine the core infarct size [37]. Some of the first data using xenon/CT, however evaluated the effects of hyperventilation on CBF in TBI [22] and was used to describe a reduced CBF in traumatic central herniation syndrome, reversed by decompression [38]. More recently, the role of xenon/CT in managing TBI seems to be becoming even more prominent. As neuro-critical care strategies are placing more emphasis on individualizing therapy based on more sophisticated monitoring, xenon/CT fits very well into this paradigm. The coupling of detailed tomographic data with invasive monitors can allow a physician to have both intermittent, detailed CBF information with focal, continuous data from implanted probes. Xenon/CT allows the clinician to know where the most useful information may be gained prior to placing a monitor. In addition, xenon/CT can give insight into the autoregulatory status of the injured brain, can determine the local effect of traumatic contusions, and guide medical or surgical therapy for these lesions.

Management of traumatic brain injury (TBI) is still generally guided by cerebral perfusion pressure (CPP) based protocols [39, 40], though alternative physiologic strategies are emerging [41]. Underlying the theory of CPP based management is to ensure that the blood pressure is adequate to maintain CBF, even if intracranial pressure is elevated. In traumatic brain injury, the normal autoregulation may or may not be preserved, leading to markedly different types of physiology underlying different patients with ICP elevations. Controversy exists regarding the optimal level of CPP, and it is clear that when a patient's autoregulatory response is preserved, even CPPs in the range of 50mmHg provide adequate CBF [42]. This suggests that if one is considering placing a patient on vasopresor agents to maintain a certain CPP, it is important to know whether that patient even requires a potentially harmful drug. Furthermore, it has been shown, both in trauma [43] and in subarachnoid hemorrhage [44], that a paradoxical decrease in CBF can occur in some patients on vasoactive drugs, emphasizing the importance of measuring the individual tissue response to an intervention.

Patients with increased ICP are heterogeneous. Patients with severe brain injury may lose both pressure autoregulation and chemoregulation, becoming focally or globally unresponsive to CO2 manipulation. In this situation, there is essentially dysfunctional, dead tissue with open vascular channels showing hyperemic CBF [45]. When there is this dysfunctional, hyperemic CBF, the only tissue which may be responsive to decreasing pCO2 is the normal tissue. If pCO2 is lowered too aggressively, it may lead to ischemia in the normal tissue that one is trying to preserve [22]. Conversely, in some patients, the hyperemic response may be due to increased metabolic activity [46]. These patients will maintain CO2 chemoregulatory responsiveness, and will likely benefit from induced moderate hypocapnea. This is an example where a specific treatment (hyperventilation) may be harmful in some patients [47], but may specifically address the pathophysiological problem in others. This loss of autoregulation can be measured by a vasodilatory challenge with CO2 inhalation, and loss of the normal response has been associated with worse clinical outcomes [45], underscoring that the loss of responsiveness to CO2 manipulation likely defines dysfunctional or dead tissue.

The CBF patterns around traumatic intracerebral hemorrhage or contusions may be of use in determining when a patient might benefit from surgical evacuation or certain medical therapy. Xenon/CT data shows that the pericontusional tissue around hematomas may have marginal perfusion, but are usually not truly ischemic, arguing that decompression of the ischemic hematoma with attention to preservation of surrounding tissue is the most rational approach to these lesions when surgery is indicated [43, 48-50]. The most appropriate medical therapy (particularly blood pressure/CPP) to ensure adequate CBF to the pericontusional tissue may also be assessed in this manner [43, 50]. On the other hand, some data shows that this tissue may have an abnormally high degree of CO2 vasoreactivity, underscoring the importance of tight control of pCO2 to avoid edema formation and secondary injury [51]. The characteristics of traumatic lesions can also be clarified using xenon/CT, particularly in the case of non-hemorrhagic contusions, which may appear a hypodensity on CT. It may be useful to understand whether this represents an area of ischemic flow and stroke versus contusion with normal CBF [52].

The predictive and prognostic nature of quantitative CBF underscores the importance of this data in clinical decision making. In patients with global CBF by xenon/CT less than 18cc/100g/m there has been shown to be a 90% 6 month mortality after severe TBI compared to 19% mortality if the CBF is greater than 18cc/100g/m [53]. This lower flow is also closely correlated with increased ICP. Ischemic CBF measured very early in the hospital course has also been linked to early mortality [54]. Brainstem CBF measured at the level of the superior colliculus less than 40cc/100g/min has also been highly correlated with poor outcome [55]. A recent study showed that in patients with TBI who have evacuation of an acute subdural hematoma, that there is a persistent hyperemia under the area of evacuation, likely due to the metabolic disturbances described above, and furthermore, that this situation is associated with worse outcomes [56].

The need for quantitative CBF data is no different than the now understood needs for other physiologic variables such as intracranial pressure and brain tissue oxygenation in for the care of critically ill patients. Episodic, tomographic, high resolution, quantitative data at the bedside has proven to be very useful for understanding common clinical disorders such as an elevation of intracranial pressure [57-59]. When this is coupled with data such as CBF probe or brain tissue oxygenation [60], that data can be placed in perspective. For example a brain tissue oxygenation probe which reads low values found to be in a region of stroke or ischemic CBF would necessitate different management than if that probe were found to be in an area of what appears to be "normal" brain possibly with mildly decreased flow. Probe acquired data of tissue oxygen or CBF records a very small volume of the brain, though the advantage is that it is continuous. While the later type of measurement is increasingly available in neuro ICUs, its interpretation is limited due to its local nature [61]. It appears to us that the combination of episodic tomographic physiological data is needed for understanding whether focal data are relevant to other brain regions, and it should be very useful for choosing where to place focal probes. The interpretation of this data is also greatly increased by performing a challenge study in addition to the baseline xenon/CT in the region of the probe. This is key to determine if the focal data acquired from the probe can be generalized to elsewhere in the brain and may offer insight into whether, for example, a low CBF number is due to low metabolic demand versus compromised supply.

ILLUSTRATIVE CASE STUDIES

Case 1

This patient with a severe TBI was having ICPs maintained in the range of 24mmHg with maximal medical management including hyperventilation to pCO2 of 30mmHg. The routine CT showed a developing area of contusion or infarction in the left hemisphere. A xenon/CT CBF study was done (Fig. **2**) which showed that there was high blood flow to the area of infarct in the left hemisphere (red arrows) with ischemic levels of flow in other territories (blue arrows). The study was then repeated at a pCO2 of 38mmHg (Fig. **3**). This caused the ICP to increase from 24mmHg to 30mmHg, which would normally be considered detrimental, however, with the higher pCO2, the CBF was dramatically increased in the normal tissue. The mixed cortical CBF values are shown in Fig. (**3**) before (a) and after (b) the increase in pCO2. Hyperventilation in this case was decreasing the CBF in the normal reactive brain but not in the injured left hemisphere. Allowing the pCO2 to elevate was able to restore normal CBF to the remainder of the brain. Prolonged hyperventilation to maintain "normal" CPP and ICP in this case would likely have been harmful to the uninjured tissue.

Case 2

This 12 year old child with severe TBI showed diffuse injury on the standard CT scan with effacement of the basilar cisterns consistent with edema. The patient had maximal medical management including moderate hyperventilation to pCO2 of 36mmHg, but ICP remained 35mmHg. A xenon study was performed which showed hyperemic flow bilaterally (Fig. **4**, middle line of scans). The study was then repeated with hyperventilation all the way to 24, which allowed the ICP to fall to the range of the mid 20s. The xenon study at this pCO2 showed return to normal CBF without evidence of ischemia. This was clearly a case where hyperemic CBF was the principal contributor to increased ICP, and proved to be very sensitive to CO2 manipulation. Other interventions such as hypertension or hypertonic saline would likely have worsened the ICP problem by further increasing CBF.

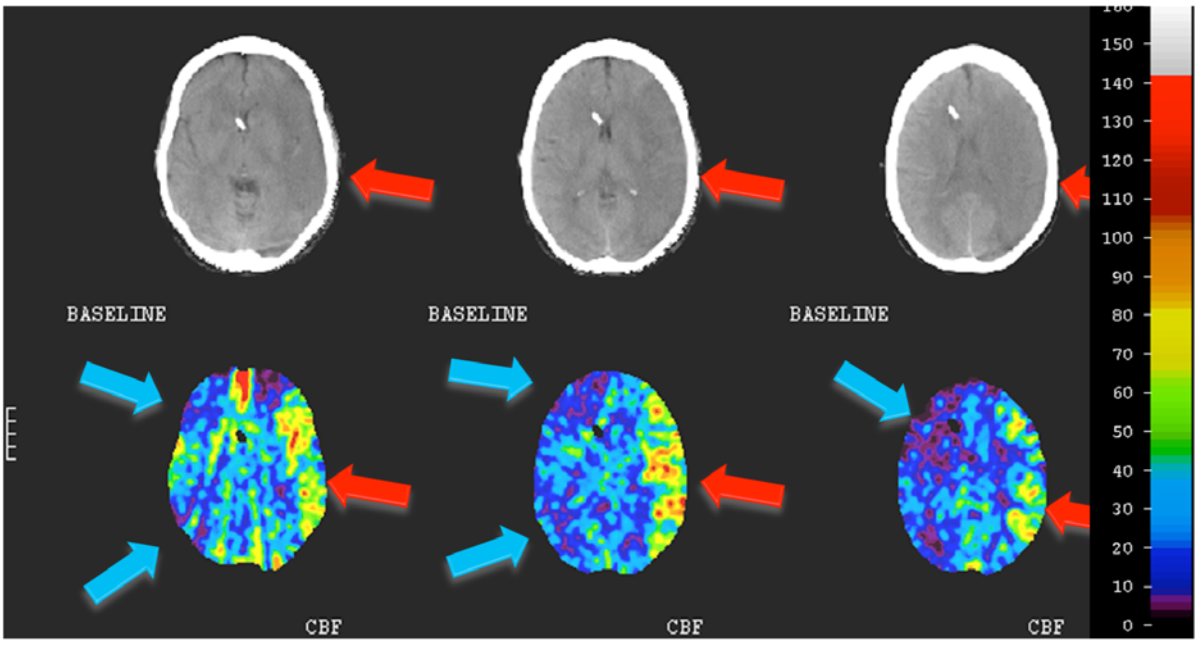

Fig. (2). Three level xenon/CT CBF study from case 1. The baseline standard CT levels are in the top row and the corresponding CBF maps are below. The scale on the right is a quantitative scale where each color corresponds to that CBF value in cc/100g/min. The red arrows point to the territory with stroke and hyperemia while the blue arrows point out the tissue becoming ischemic (CBF < 20cc/100g/min) with hyperventilation.

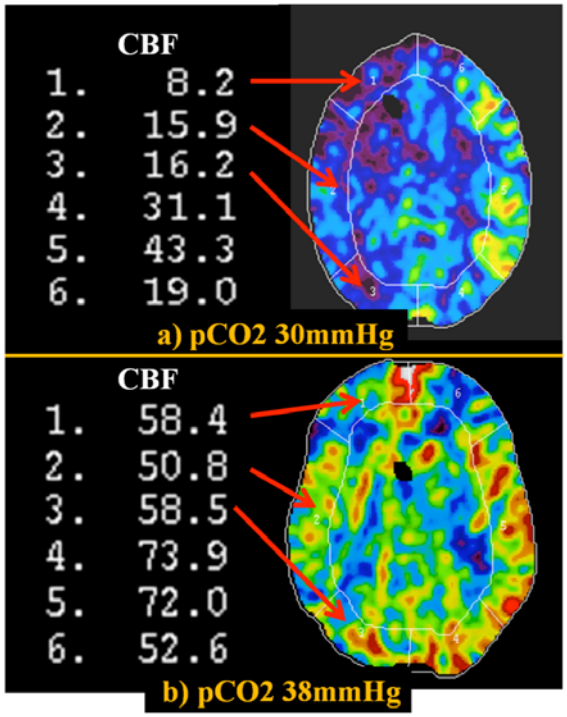

Fig. (3). Comparison between the study done with hyperventilation (top) and with normoventilation (bottom). The absolute averaged mixed cortical CBF values for the territories are shown for each study, clearly demonstrating the ischemic values with hyperventilation and return to normal with increased pCO2.

Case 3

This patient with severe TBI and right temporal contusions had ICPs in the 30s despite maximal medical management. He was started on pressors to increase his blood pressure to maintain a CPP of > 60. The patient was not tolerating the dopamine due to cardiac failure, and so a xenon/CT was done to determine the efficacy of this intervention (Fig. **5**). The baseline study is shown in the top row with ventricular catheter and parenchymal monitors in place. Even with pressors maintaining the blood pressure in the range of 180/100mmHg, there was generalized decreased CBF with focal decreased CBF in the region of the contusion. When the pressor was stopped and the blood pressure returned to the range of 130/80, the CBF did not change significantly, in fact, it increased slightly in several territories (Fig. **6**). In this case, the use of pressors was clearly detrimental to the patient systemically, and did not show any improvement in CBF. This information can only be determined by measuring CBF in the individual patient.

CONCLUSION

Xenon/ CT is a safe technique to reliably obtain tomographic CBF data with the ability to test management interventions. This technology is a very good match to the field of traumatic brain injury, especially with current trends toward more monitoring to guide intervention. Xenon/CT has a proven record of providing prognostic data for tissue at risk for stroke in a variety of clinical scenarios. The marriage of this technique with portable CT offers an ideal situation where physiology can be measured and treatments adjusted accordingly at the patient's bedside. Further experience with this technique will likely identify that patients with TBI are a heterogeneous group, some requiring traditional ICP lowering strategies and some requiring other interventions, such as CO2 or blood pressure manipulation. Multimodality monitoring including tomographic quantitative CBF data will

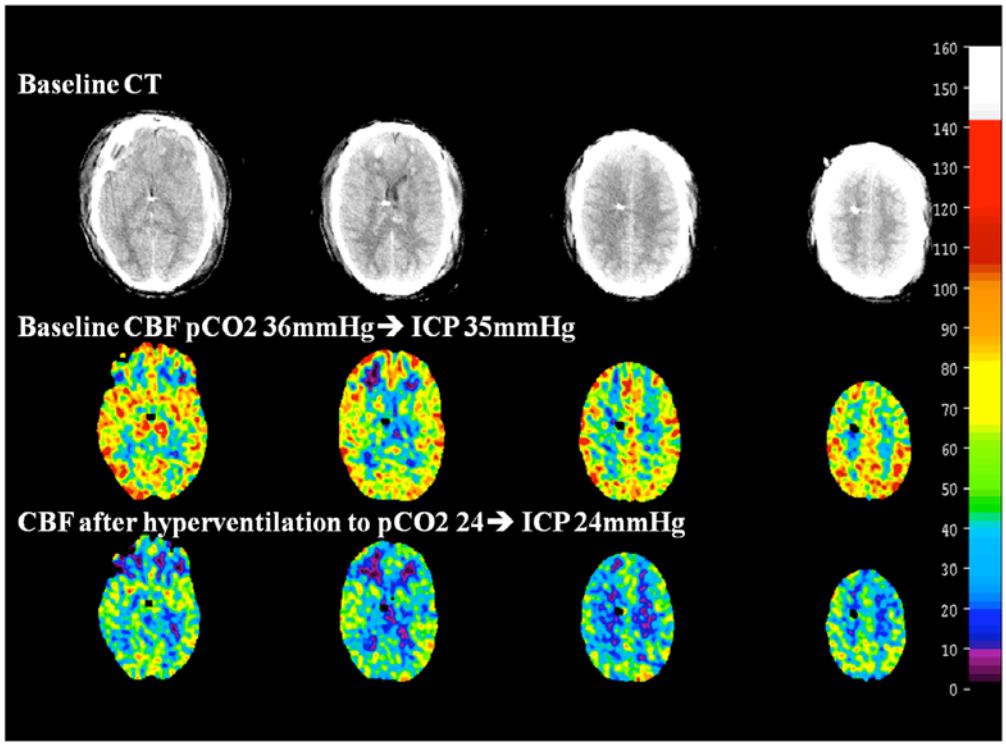

Fig. (4). Four level xenon/CT CBF study from case 2. Note that with significant hyperventilation, the CBF decreases, but not to ischemic levels in the mixed cortical territories.

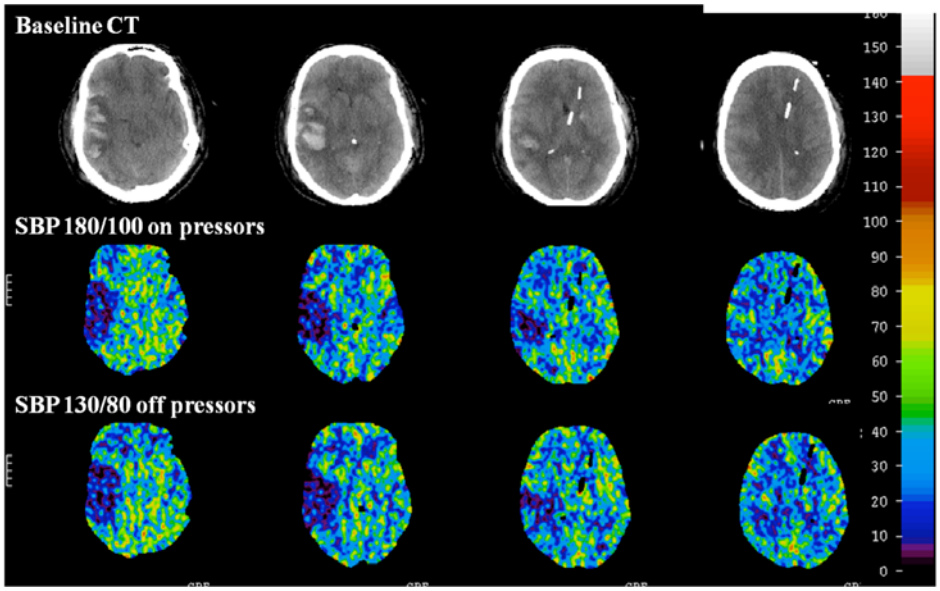

Fig. (5). Four level xenon/CT CBF study from case 3. Note that despite manipulation of blood pressure with pressors, CBF remains essentially unchanged.

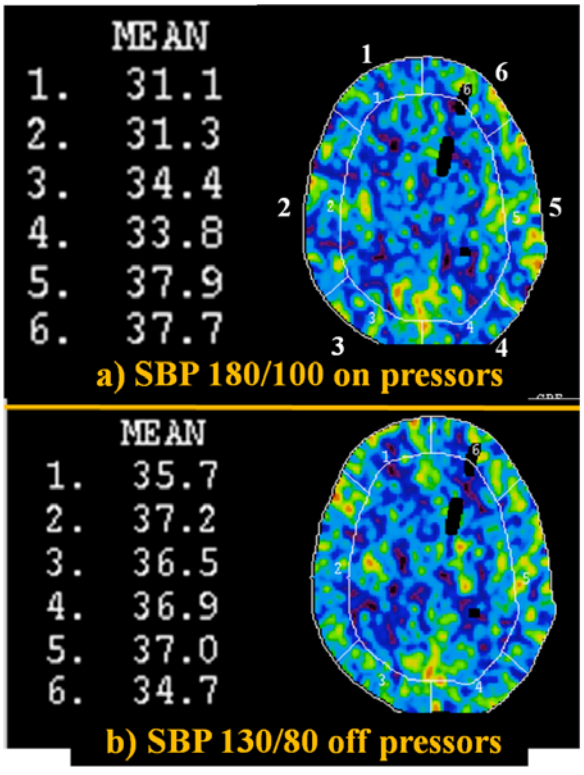

Fig. (6). Single level from case 3 with averaged mixed cortical CBF values for the given territories. Note that with lower blood pressure, CBF values actually increased slightly in most territories.

likely prove to be key in tailoring complex and varied therapies to individual patients needs.

CONFLICT OF INTEREST DISCLOSURE

No financial support was provided to either author related to the preparation of this manuscript. Dr Carlson has no financial relationships to disclose. Dr Yonas owns a small stock option in Neurologica- manufacturer of the CereTom portable head CT machine.

REFERENCES

[1] Drayer BP, Gur D, Yonas H, Wolfson SK, Jr., Cook EE. Abnormality of the xenon brain: blood partition coefficient and blood flow in cerebral infarction: an *in vivo* assessment using transmission computed tomography. Radiology 1980; 135(2): 349-54.

[2] Gur D, Good WF, Wolfson SK, Jr., Yonas H, Shabason L. *In vivo* mapping of local cerebral blood flow by xenon-enhanced computed tomography. Science 1982; 215(4537): 1267-8.

[3] Gur D, Yonas H, Jackson DL, *et al.* Simultaneous measurements of cerebral blood flow by the xenon/CT method and the microsphere method. A comparison. Invest Radiol 1985; 20(7): 672-7.

[4] Wolfson SK, Jr., Clark J, Greenberg JH, *et al.* Xenon-enhanced computed tomography compared with [14C]iodoantipyrine for normal and low cerebral blood flow states in baboons. Stroke 1990; 21(5): 751-7.

[5] Matsuda M, Lee H, Kuribayashi K, Yoshimura M, Honda T, Handa J. Comparative study of regional cerebral blood flow values measured by Xe CT and Xe SPECT. Acta Neurol Scand Suppl 1996; 166: 13-6.

[6] Nariai T. Comparison of measurement between Xe/CT CBF and PET in cerebrovascular disease and brain tumor. Acta Neurol Scand Suppl 1996; 166: 10-2.

[7] Valadka AB, Hlatky R, Furuya Y, Robertson CS. Brain tissue PO2: correlation with cerebral blood flow. Acta Neurochir Suppl 2002; 81: 299-301.

[8] Gur D, Yonas H, Good WF. Local cerebral blood flow by xenon-enhanced CT: current status, potential improvements, and future directions. Cerebrovasc Brain Metab Rev 1989; 1(1): 68-86.

[9] Johnson DW, Stringer WA, Marks MP, Yonas H, Good WF, Gur D. Stable xenon CT cerebral blood flow imaging: rationale for and role in clinical decision making. Am J Neuroradiol 1991; 12(2): 201-13.

[10] Yonas H. Cerebral blood measurements in vasospasm. Neurosurg Clin N Am 1990; 1(2): 307-18.

[11] Yonas H, Darby JM, Marks EC, Durham SR, Maxwell C. CBF measured by Xe-CT: approach to analysis and normal values. J Cereb Blood Flow Metab 1991; 11(5): 716-25.

[12] Yonas H, Sekhar L, Johnson DW, Gur D. Determination of irreversible ischemia by xenon-enhanced computed tomographic monitoring of cerebral blood flow in patients with symptomatic vasospasm. Neurosurgery 1989; 24(3): 368-72.

[13] Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive factor of stroke in asymptomatic patients? Stroke 1996; 27(12): 2188-90.

[14] Horowitz M, Yonas H, Albright AL. Evaluation of cerebral blood flow and hemodynamic reserve in symptomatic moyamoya disease using stable Xenon-CT blood flow. Surg Neurol 1995; 44(3): 251-61; discussion 62.

[15] Nemoto EM, Yonas H, Kuwabara H, *et al*. Identification of hemodynamic compromise by cerebrovascular reserve and oxygen extraction fraction in occlusive vascular disease. J Cereb Blood Flow Metab 2004; 24(10): 1081-9.

[16] Pindzola RR, Sashin D, Nemoto EM, Kuwabara H, Wilson JW, Yonas H. Identifying regions of compromised hemodynamics in symptomatic carotid occlusion by cerebrovascular reactivity and oxygen extraction fraction. Neurol Res 2006; 28(2): 149-54.

[17] Tarr RW, Johnson DW, Rutigliano M, *et al*. Use of acetazolamide-challenge xenon CT in the assessment of cerebral blood flow dynamics in patients with arteriovenous malformations. Am J Neuroradiol 1990; 11(3): 441-8.

[18] Webster MW, Makaroun MS, Steed DL, Smith HA, Johnson DW, Yonas H. Compromised cerebral blood flow reactivity is a predictor of stroke in patients with symptomatic carotid artery occlusive disease. J Vasc Surg 1995; 21(2): 338-44; discussion 44-5.

[19] Witt JP, Yonas H, Jungreis C. Cerebral blood flow response pattern during balloon test occlusion of the internal carotid artery. Am J Neuroradiol 1994; 15(5): 847-56.

[20] Yonas H, Kromer H, Jungreis C. Compromised vascular reserves does predict subgroups with carotid occlusion and an increased stroke risk. J Stroke Cerebrovasc Dis 1997; 6: 458.

[21] Yonas H, Smith HA, Durham SR, Pentheny SL, Johnson DW. Increased stroke risk predicted by compromised cerebral blood flow reactivity. J Neurosurg 1993; 79(4): 483-9.

[22] Latchaw RE, Yonas H, Darby JM, Gur D, Pentheny SL. Xenon/CT cerebral blood flow determination following cranial trauma. Acta Radiol Suppl 1986; 369: 370-3.

[23] Lachmann B, Armbruster S, Schairer W, *et al*. Safety and efficacy of xenon in routine use as an inhalational anaesthetic. Lancet 1990; 335(8703): 1413-5.

[24] Rossaint R, Reyle-Hahn M, Schulte Am Esch J, *et al*. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. Anesthesiology 2003; 98(1): 6-13.

[25] Sanders RD, Ma D, Maze M. Xenon: elemental anaesthesia in clinical practice. Br Med Bull 2004; 71: 115-35.

[26] Hecker K, Baumert JH, Horn N, Rossaint R. Xenon, a modern anaesthesia gas. Minerva Anestesiol 2004; 70(5): 255-60.

[27] Dickinson R, Peterson BK, Banks P, *et al*. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor by the anesthetics xenon and isoflurane: evidence from molecular modeling and electrophysiology. Anesthesiology 2007; 107(5): 756-67.

[28] Latchaw RE, Yonas H, Pentheny SL, Gur D. Adverse reactions to xenon-enhanced CT cerebral blood flow determination. Radiology 1987; 163(1): 251-4.

[29] Krol AL, Dzialowski I, Roy J, *et al*. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. Stroke 2007; 38(8): 2364-6.

[30] Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. Am J Roentgenol 2008; 191(2): 409-15.

[31] Bellin MF, Van Der Molen AJ. Extracellular gadolinium-based contrast media: an overview. Eur J Radiol 2008; 66(2): 160-7.

[32] Shellock FG, Spinazzi A. MRI safety update 2008: part 1, MRI contrast agents and nephrogenic systemic fibrosis. Am J Roentgenol 2008; 191(4): 1129-39.

[33] Gur D, Shabason L, Wolfson SK, Jr., Yonas H, Good WF. Measurement of local cerebral blood flow by xenon-enhanced computerized tomography imaging: a critique of an error assessment. J Cereb Blood Flow Metab 1983; 3(1): 133-5.

[34] Carlson A, Yonas H. Monitoring Carotid Interventions with xenon CT. In: Gillard J, Graves M, Hatsukami T, Yuan C, Eds. Carotid Disease: The Role of Imaging in Diagnosis and Management. Cambridge: Cambridge Universiy Press 2007; pp. 396-417.

[35] Carlson A, Yonas H. Xenon techniques in predicting patients at risk for stroke after balloon test occlusion. Neurosurgery 2009; 64(6): E1206.

[36] Carlson AP, Yonas H. Radiographic assessment of vasospasm after aneurysmal subarachnoid hemorrhage: the physiological perspective. Neurol Res 2009; 31(6): 593-604.

[37] Jovin TG, Yonas H, Gebel JM, *et al*. The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion. Stroke 2003; 34(10): 2426-33.

[38] Wozney P, Yonas H, Latchaw RE, Gur D, Good W. Central herniation revealed by focal decrease in blood flow without elevation of intracranial pressure: a case report. Neurosurgery 1985; 17(4): 641-4.

[39] The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Initial management. J Neurotrauma 2000; 17(6-7): 463-9.

[40] Adelson PD, Bratton SL, Carney NA, *et al*. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 1: Introduction. Pediatr Crit Care Med 2003; 4(3 Suppl): S2-4.

[41] Asgeirsson B, Grande PO, Nordstrom CH. A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. Intensive Care Med 1994; 20(4): 260-7.

[42] Chieregato A, Tanfani A, Compagnone C, *et al*. Global cerebral blood flow and CPP after severe head injury: a xenon-CT study. Intensive Care Med 2007; 33(5): 856-62.

[43] Chieregato A, Tanfani A, Compagnone C, Pascarella R, Targa L, Fainardi E. Cerebral blood flow in traumatic contusions is predominantly reduced after an induced acute elevation of cerebral perfusion pressure. Neurosurgery 2007; 60(1): 115-2; discussion 23.

[44] Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM. Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. J Neurosurg 1994; 80(5): 857-64.

[45] Kushi H, Moriya T, Saito T, Kinoshita K, Shibuya T, Hayashi N. Importance of metabolic monitoring systems as an early prognostic indicator in severe head injured patients. Acta Neurochir Suppl 1999; 75: 67-8.

[46] Kelly DF, Kordestani RK, Martin NA, *et al*. Hyperemia following traumatic brain injury: relationship to intracranial hypertension and outcome. J Neurosurg 1996; 85(5): 762-71.

[47] Stringer WA, Hasso AN, Thompson JR, Hinshaw DB, Jordan KG. Hyperventilation-induced cerebral ischemia in patients with acute brain lesions: demonstration by xenon-enhanced CT. AJNR Am J Neuroradiol 1993; 14(2): 475-84.

[48] Chieregato A, Fainardi E, Servadei F, *et al*. Centrifugal distribution of regional cerebral blood flow and its time course in traumatic intracerebral hematomas. J Neurotrauma 2004; 21(6): 655-66.

[49] von Oettingen G, Bergholt B, Gyldensted C, Astrup J. Blood flow and ischemia within traumatic cerebral contusions. Neurosurgery 2002; 50(4): 781-8; discussion 8-90.

[50] Chieregato A, Fainardi E, Tanfani A, *et al*. Induced acute arterial hypertension and regional cerebral flow in intracontusional low density area. Acta Neurochir Suppl 2003; 86: 361-5.

[51] McLaughlin MR, Marion DW. Cerebral blood flow and vasoresponsivity within and around cerebral contusions. J Neurosurg 1996; 85(5): 871-6.

[52] Furuya Y, Hlatky R, Valadka AB, Diaz P, Robertson CS. Comparison of cerebral blood flow in computed tomographic hypodense areas of the brain in head-injured patients. Neurosurgery 2003; 52(2): 340-5; discussion 5-6.

[53] Hlatky R, Contant CF, Diaz-Marchan P, Valadka AB, Robertson CS. Significance of a reduced cerebral blood flow during the first 12 hours after traumatic brain injury. Neurocrit Care 2004; 1(1): 69-83.

[54] Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg 1992; 77(3): 360-8.

[55] Ritter AM, Muizelaar JP, Barnes T, *et al*. Brain stem blood flow, pupillary response, and outcome in patients with severe head injuries. Neurosurgery 1999; 44(5): 941-8.

[56] Chieregato A, Noto A, Tanfani A, Bini G, Martino C, Fainardi E. Hyperemia beneath evacuated acute subdural hematoma is frequent and prolonged in patients with an unfavorable outcome: a xe-computed tomographic study. Neurosurgery 2009; 64(4): 705-17; discussion 17-8.

[57] Gunnarsson T, Theodorsson A, Karlsson P, *et al*. Mobile computerized tomography scanning in the neurosurgery intensive care unit:

increase in patient safety and reduction of staff workload. J Neurosurg 2000; 93(3): 432-6.

[58] Hillman J, Sturnegk P, Yonas H, *et al*. Bedside monitoring of CBF with xenon-CT and a mobile scanner: a novel method in neurointensive care. Br J Neurosurg 2005; 19(5): 395-401.

[59] Sturnegk P, Mellergard P, Yonas H, Theodorsson A, Hillman J. Potential use of quantitative bedside CBF monitoring (Xe-CT) for decision making in neurosurgical intensive care. Br J Neurosurg 2007; 21(4): 332-9.

[60] Menzel M, Doppenberg EM, Zauner A, *et al*. Cerebral oxygenation in patients after severe head injury: monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism and intracranial pressure. J Neurosurg Anesthesiol 1999; 11(4): 240-51.

[61] Schroder ML, Muizelaar JP. Monitoring of regional cerebral blood flow (CBF) in acute head injury by thermal diffusion. Acta Neurochir Suppl (Wien) 1993; 59: 47-9.

Received: March 08, 2010 Revised: March 08, 2010 Accepted: March 29, 2010