Comparative Study With a 133Xenon Clearance Technique
J.F. Soustiel, MD; T.C. Glenn, PhD; P. Vespa, MD; B. Rinsky; C. Hanuscin; N.A. Martin, MD

Background and Purpose—We sought to evaluate a new, angle-independent ultrasonic device for assessment of blood flow volume (BFV) in the internal carotid artery (ICA).

Methods—Nineteen patients and 4 healthy volunteers were enrolled in a comparative study conducted in the Care Unit of the Division of Neurosurgery at UCLA Medical Center. All patients had been admitted because of severe brain injury: 15 patients with severe head trauma (Glasgow Coma Scale score ≤8) and 4 patients with subarachnoid hemorrhage due to aneurysm rupture. In all patients and subjects, cerebral blood flow (CBF) values obtained with the 133 xenon-clearance technique were compared with BFV measurements in the ipsilateral ICA.

Results—Hemispheric CBF values showed a close and linear correlation with BFV measurements (r=0.76, P<0.0001). Global CBF values showed a higher correlation with the total BFV value obtained from both ICAs (r=0.84, P<0.0001). With 37 mL·min⁻¹·100 g⁻¹ as a cutoff value for the ischemic range, a BFV value of 220 mL/min would yield a positive predictive value of 91.7% and a negative predictive value of 82.6% (sensitivity 73.3%, specificity 95%). Conversely, BFV sensitivity and specificity were 60% and 96%, respectively, for the hyperemic range defined by a CBF value >55 mL·min⁻¹·100 g⁻¹ (positive predictive value of 85.7% and negative prediction value of 85.7%).

Conclusions—BFV measurements with this new technology proved to accurately correlate with CBF values evaluated by the 133 xenon-clearance technique. These results support the implementation of this technique for bedside assessment of cerebral hemodynamics in critically ill neurosurgical patients. (Stroke. 2003;34:1876-1880.)

Key Words: cerebral blood flow ■ hemodynamics ■ ultrasonography, Doppler

During the past 2 decades, there has been a continuous trend of increasing efforts toward the refinement of neuromonitoring technologies. Because most of the pathologic processes that affect the acutely injured brain might eventually result in impairment of cerebral blood flow (CBF), early identification of ischemia or hyperemia might be critical to define the most appropriate therapeutic strategies. Not surprisingly, numerous modalities have been developed and applied to the evaluation of CBF in neurosurgical patients, although such modalities seldom fit the reality of neurointensive care patients.¹ Isotopic studies such as positron emission tomography, single-photon emission tomography, and imaging studies such as stable xenon computed tomography and magnetic resonance imaging–based technology have all proved to achieve reliable and accurate measurements of CBF. All of these techniques, however, are cumbersome and expensive and most important, imply the transfer of critically ill and often sedated and ventilated patients to the imaging or radionuclear facility. As such, these techniques cannot be repeated as clinically indicated and therefore, are of limited use in the clinical setting of intensive care. In an attempt to develop CBF measurement capabilities at the patient’s bedside, attention has been drawn to clearance techniques, such as the Kety-Schmidt² or the 133 xenon-clearance³ technique. These techniques, particularly the Kety-Schmidt technique, have proved to be reliable and accurate, especially when incomplete diffusion equilibrium for the inert gas tracer between the brain and its venous blood is taken into consideration and corrected.⁴ Nevertheless, both methods are limited by specific technical drawbacks. The Kety-Schmidt technique is invasive and provides a global CBF assessment that does not take into consideration possible asymmetry in the jugular veins. The 133 xenon-clearance technique, on the other hand, is limited by personal safety issues, such as repeated exposure of patients to radioactive tracers, as well as possible contamination by external carotid vessels.¹
Eventually, the urgent need for reliable data on cerebral hemodynamics status has led to the implementation of indirect methods of CBF approximation in the neuromonitoring armamentarium, such as transcranial Doppler, jugular bulb oxymetry, and near-infrared spectroscopy. Unfortunately, none of these has reached a level of accuracy that would allow critical therapeutic decisions to be made.

As a result, increasing attention has been drawn to the potential value of ultrasound Doppler technology for the measurement of blood flow volume (BFV) in the internal carotid artery (ICA) as a correlate for hemispheric CBF. A recent report has suggested the implementation of digital Doppler ultrasound and angle-independent dual-beam technology for improvement of accuracy in the assessment of hemispheric CBF. The aim of the present study was to evaluate this novel ultrasound device by means of the $^{133}$xenon-clearance technique.

**Methods**

**Patients**

Nineteen patients and 4 healthy volunteers were enrolled in this study. All were studied in the Neurointensive Care Unit of the Division of Neurosurgery at UCLA Medical Center. Informed consent was obtained, in compliance with guidelines of the UCLA Medical Institutional Review Board. All patients were admitted to UCLA Medical Center because of severe brain injury: 15 with severe head trauma (Glasgow Coma Scale score ≤8) and 4 with subarachnoid hemorrhage due to aneurysm rupture. There were 16 men and 7 women, ranging in age between 20 and 75 years (age, 38.9 ± 16.1 years).

**Management Protocol**

After initial evaluation in the emergency department and surgery as clinically indicated, patients were admitted to the intensive care unit. According to their clinical condition, patients received routine management, including ventilation and sedation as indicated. Intracranial pressure was managed by intravenous administration of mannitol and barbiturates. Fluids and vasopressors were administered to maintain cerebral perfusion pressure above the ischemic threshold. Routine monitoring included intracranial pressure, central venous pressure, systemic arterial pressure, and electroencephalogram as clinically indicated.

**Cerebral Hemodynamic Monitoring**

The Brain Injury Research Center protocol included daily evaluation of blood flow velocities in all basal arteries of the brain, jugular bulb oxymetry, and CBF measurement by means of the $^{133}$xenon-clearance technique. Initial evaluation was obtained as soon as possible after each patient's admission to the intensive care unit.

**CBF Measurements**

CBF measurements were performed according to a technique described previously. In brief, 20 to 30 mCi of gaseous $^{133}$xenon dissolved in normal saline was injected. Thereafter, the cerebral clearance curves were recorded for 11 minutes at the patient's bedside from the area over the estimated scalp projection of the middle cerebral artery supply territory by 8 NaI detectors connected to a portable unit (Cerebrograph Cortexplorer 16, Ceretronix). The data obtained were then extrapolated to 15 minutes, after referencing the cerebral clearance curve of $^{133}$xenon to the clearance curve of exhaled end-tidal $^{133}$xenon, which was used as an estimate of arterial concentration. As previously described, a 2-compartment, modified height-over-area method was then used to calculate the hemispheric CBF (derived from 8 ipsilateral detectors) and global CBF (from all detectors). CBF represents the mean flow of fast- and slow-clearing compartments, because it is more stable than a single-compartment method in pathologic situations, especially in trauma. Ancillary parameters necessary for further calculations of cerebral hemodynamics and metabolism indexes such as hematocrit, hemoglobin, and arterial and jugular venous blood gases were simultaneously recorded.

**BFV Measurements**

According to a recently described technique, ICA BFV measurements were acquired with the use of an angle-independent dual-beam Doppler ultrasound device (FlowGuard, Cardiosonix Inc). Both beams are pulse-wave range-gated with sample volumes <200 μm in length. Hundreds of sample volumes are simultaneously analyzed by digital Doppler along each ultrasound beam. Full fast Fourier transform analysis for each sample volume and application of an original algorithm allow real-time detection of flow velocity in the set of successive gates, followed by determination of the chord segments that each beam traverses within the blood vessel (Figure 1). Because the angle between the 2 beams is known, the insonation angle for each ultrasound beam can be drawn from simple calculation based on trigonometric and Doppler considerations. Further processing of the large number of small sample volumes allows determination of the pulsatile velocity profile and vascular diameter.

Determination of the insonation angles allows, in turn, calculation of absolute BFVs, so that BFV can be directly obtained through integration of the velocity profile across the vascular cross-sectional area.

Insonation of the ICA was performed slightly below the jaw near the mandibular angle with the patient in a supine position with slight rotation of the head. BFV measurements were made in all patients immediately before CBF measurements by an operator blinded to the results of CBF measurements.

**Statistical Analysis**

Comparison between BFV and CBF values was performed by linear correlation analysis with commercially available software (NCSS 2000, Number Cruncher Statistical Systems).

**Results**

**Overview**

A total of 42 hemispheric CBF measurements were made in 19 patients and 4 volunteers, ranging from 1 to 6 measurements in a single subject. In 2 patients, CBF could not be obtained from 1 hemisphere, so that 82 hemispheric CBF values were eventually recorded. These hemispheric CBF
values could be compared with only 77 BFV measurements, because BFV could not be obtained on 1 side in 5 patients (failure rate of 6%). Failure was related to an unacceptable difference in either vessel diameter or BFVs, as measured by the 2 ultrasound channels of the dual probe.

**CBF and BFV Correlations**

Hemispheric CBF values showed a close and linear correlation with BFV measurements (Figure 2). The correlation factor was 0.76, with a value of $P<0.0001$. Global CBF values showed a higher correlation with the total BFV obtained from both ICAs (Figure 3; $r=0.84$, $P<0.0001$). With the slope and intercept values obtained from the linear correlation analysis between CBF and BFV, global CBF could be derived from BFV from the equation global CBF=(average BFV×0.108)+10.5. Differences between calculated global CBF and measured global CBF ranged between 1.2% and 32.4%, with a mean difference of 14.5%.

**Ischemia and Hyperemia Prediction**

With 37 mL·min$^{-1}$·100 g$^{-1}$ used as the cutoff value for the ischemic range, a BFV value of 220 mL/min would yield a positive predictive value of 91.7% and a negative predictive value of 82.6% (sensitivity 73.3%, specificity 95%). With 30 mL·min$^{-1}$·100 g$^{-1}$ used as a threshold value for the definition of ischemia, a BFV of 180 mL/min would be indicative of ischemia in 4 of 5 patients (sensitivity 66.7%, specificity 96.6%; positive predictive value of 80%; negative predictive value of 93.3%). Conversely, BFV sensitivity and specificity were 60% and 96%, respectively, for the diagnosis of hyperemia, as defined by a CBF $>55$ mL·min$^{-1}$·100 g$^{-1}$ (positive predictive value of 85.7% and negative predictive value of 85.7%).

**Discussion**

Several authors have suggested the implementation of Doppler ultrasound technology for the assessment of BFV in the ICA as a correlate for CBF in the corresponding cerebral hemisphere.$^{11-14}$ Most studies have been based on the use of spectral Doppler imaging and have mostly reported on BFV in healthy subjects.$^{11-14}$ However, the accuracy of spectral Doppler imaging has been repeatedly challenged, and well-documented errors in the assessment of BFV have been reported in the literature.$^{15-17}$ Recently, Ho et al$^{18}$ have emphasized the poor correlation obtained between BFV, as measured by spectral Doppler imaging, and magnetic resonance phase-contrast flow quantification and have further supported a previous statement made by Licht et al$^{17}$ concerning the inaccuracy of spectral Doppler imaging, which prevents clinicians from drawing therapeutic conclusions by relying on this technique only. The reasons for the relative inaccuracy of spectral Doppler imaging are well known and inherent to the technology itself, based on data acquired from a single frame. As such, it will most likely generate significant errors in measurements of both velocity and diameter used for flow calculation. Flow velocity is currently assessed by Doppler shift, which implies an accurate knowledge of the insonation angle.$^{15,16}$ Although sonographic imaging modalities provide for calculation of this angle, errors in its determination have been reported. Moreover, significant variations in flow velocity are not taken into consideration in flow calculation. Even though spatial variations in flow velocity within the vessel lumen are supposed to be integrated by a sample volume that encompasses the entire cross section of the vessel, this integration does not take into consideration the imperfect uniformity of insonation,$^{19}$ nor the substantial variations in velocity profile during the cardiac cycle.$^{20}$ Most important, variations in vessel diameter as large as 10% occur during the cardiac cycle$^{21}$ and are obviously overlooked by the use of a single frame. This might result in a 20% error in flow calculations under physiologic conditions$^{22}$ and an even larger error in clinical situations associated with increased pulsatility of the ICA, such as increased peripheral cerebral vascular resistance. To cope with these shortcomings of spectral Doppler imaging, color-velocity imaging has been applied to BFV measurements, because this technology allows integration of temporal variations of flow velocity and vessel diameter.$^{23}$ This technique, however, does compute the velocity profile and its variations during the cardiac cycle, which might lead to inaccuracy in BFV measurements. In a comparative study with magnetic resonance phase contrast, spectral Doppler, and color-velocity imaging, Ho et al$^{18}$
showed improved accuracy in BFV evaluations by color-velocity imaging, although these investigators admitted that there was poor agreement between magnetic resonance phase contrast and any other ultrasound technique.

In a recent report, angle-independent dual-beam technology combined with digital Doppler proved to achieve highly accurate flow volume measurements made in a phantom model and reproducible and reliable BFV evaluations in healthy subjects. These combined technologies allow the integration of spatial and temporal variations in both vessel diameter and BFV, resulting in improved accuracy. In the present study, BFV evaluations made in the extracranial segment of the ICA demonstrated a close correlation with CBF measurements made by a “gold standard” technique, the 133Xe-clearance technique. When global CBF was considered for analysis, an even closer correlation was found with the summed BFV values from both ICAs (r=0.84). This closer correlation might be explained in part by the fact that assessment of CBF by means of BFV does not take into consideration extracerebral blood flow supplied by ICA-dependent vessels, such as the ophthalmic arteries and intracavernous branches of the ICA. More important, intracranial redistribution of blood flow from the ICA through the anterior and posterior communicating arteries cannot be evaluated extracranially and might represent an inherent source of error. Consequently, assessment of global CBF by means of bilateral ICA BFV is likely to be more accurate than hemispheric CBF. In addition to these considerations, when analyzing correlations between BFV with any gold standard of CBF measurement, one should keep in mind the difficulty that exists in accurately measuring CBF and the subsequent wide spectrum of values in the literature for normal CBF, ranging from 39 to 69 mL · min⁻¹ · 100 g⁻¹.24–27 These disparities are not limited to those yielded by comparing different type of modalities but do actually exist between different studies based on the same technology. As with other modalities of CBF measurement, the accuracy of the 133Xe-clearance technique is limited by several technical shortcomings that might have an influence, especially under ischemic conditions.28 Among these, various methodological shortcuts that correct for dispersed arterial input function and contamination from extracerebral tissue might account for the relatively wide range of reported results. In addition, cross-contamination from the opposite hemisphere might result and reduce side-to-side differences, which might partly account for the larger differences noted between hemispheric CBF and unilateral BFV values when compared with the global results in this study.

Nevertheless, the results of the present study show that ICA BFV can be reliably measured and monitored in critically ill patients, with a close correlation with CBF values. In this series, a BFV <220 mL/min was found to be indicative of an ischemic trend in 11 of 12 instances (positive predictive value of 91.7%, specificity 95%) and of mild or severe ischemia in 4 of 5 patients with a BFV <180 mL/min (positive predictive value of 80%, specificity 96.7%), whereas a total BFV value >460 mL/min accurately ruled out ischemia in 19 of 24 cases (negative predictive value of 82.6%). However, it should be kept in mind that despite the demonstrated correlation between reduced BFV in the ICA and impaired CBF in the corresponding cerebral hemisphere, no firm conclusion should be drawn regarding tissue outcome prediction without complementary data, such as cerebral blood volume (CBV).29,30 Magnetic resonance imaging studies have indeed suggested that CBV is more predictive of tissue outcome than is CBF in cerebral occlusive disease,29 as ischemic regions with reduced CBV were shown to be at higher risk of infarction.30 CBV, however, cannot be estimated by relying on CBF data alone, because the correlation between CBF and CBV is variable in ischemia.30 Nevertheless, these findings suggest that in patients with unstable cerebral hemodynamics, BFV measurements might be of clinical value as a bedside noninvasive tool that can be repeatedly performed as clinically indicated with a reasonable margin of error. Special care, however, should be given to elderly patients and those carrying a high risk of cerebral vascular occlusive disease. Although several authors have reported on the clinical value of BFV assessment in extracranial ICA stenosis by color-velocity imaging Doppler,31,32 the accuracy of those measurements is likely to decrease in such instances. A localized stenosis, if overlooked by the ultrasound beams, might result in miscalculation of the diameter, with an overestimation of the BFV. Although repeated measures with the use of different angles, along with an insonation target located as high as possible above the carotid bifurcation, might help reduce the probability of such an error, duplex assessment of the ICA before monitoring seems to be indicated in patients at high risk of extracranial vascular disease. Intracranial carotid stenosis, though less common, might represent another possible source of error in CBF estimation, as part of the flow to the corresponding cerebral hemisphere might be supplied by the opposite ICA or even the posterior circulation, in some instances. In such situations, discrepancy between BFV and CBF values should be expected on the same side. Accumulating experience, leading to improved skills and expertise with this new technology, should help improve the accuracy of BFV estimations and further define the place of this modality within the spectrum of neuromonitoring.

References
J.F. Soustiel, T.C. Glenn, P. Vespa, B. Rinsky, C. Hanuscin and N.A. Martin

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