# Brainstem Auditory Evoked Potentials–A Review and Modified Studies in Healthy Subjects

*James L. Stone,*† Mateo Calderon-Arnulphi,* Karriem S. Watson,* Ketan Patel,† Navneet S. Mander,* Nichole Suss,‡ John Fino,† and John R. Hughes†*

**Summary:** The authors review the brainstem auditory evoked potential (BAEP), and present studies on 40 healthy subjects. In addition to the conventional click evoked BAEP, three modified BAEP examinations were performed. The modified BAEP tests include a 1,000 Hz tone-burst BAEP, and more rapid rate binaural click and 1,000 Hz tone-burst BAEPs–each of the last two studies performed at four diminishing moderate intensities. In addition to the usual parameters, the authors examined the Wave V to Vn interpeak latency, and stimulus intensity versus Wave V latency and amplitude functions in the rapid rate binaural studies. Studies were also repeated on healthy subjects in a dependant head position in an attempt to increase intracranial pressure. Discussion centers on the BAEP, its current utility in medicine, unique neurophysiology, and literature support that the above modifications could increase the practicality of the test in patients at risk with intracranial lesions and perhaps improve the feasibility for real-time continuous or frequent monitoring in the future.

**Key Words:** Brainstem auditory evoked potential, Auditory brainstem response, BAEP, BAER, ABR, Rapid stimulation rate, Latency intensity function, Intensive care monitoring.

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The brainstem auditory evoked potential (BAEP), brainstem auditory evoked response (BAER), and auditory brainstem response (ABR) has well-established utility in neurology, neurologic surgery, and otology since its introduction to clinical medicine in the 1970s (Davis, 1976; Hecox and Galambos, 1974; Jewett and Williston, 1971; Starr and Achor, 1975; Starr and Hamilton, 1976; Stockard and Rossiter, 1977). This far-field potential is presumed to reflect highly synchronous activation of the major auditory centers from cochlea to midbrain. The conventional BAEP elicited by click stimuli delivered to each ear separately is sensitive to brainstem lesions from tumors, trauma, hemorrhage, ischemia, demyelination, or metabolic insult (Burkard, 2007; Chiappa, 1997; Hood, 1998; Hughes, 1985; Legatt, 2005; Picton, 1990; Stone et al., 1988). Being largely resistant to the level of consciousness, sedative medications, and general anesthesia, the BAEP is also used as an intraoperative monitoring tool during brainstem, acoustic nerve or posterior fossa tumor surgery (Hall, 2007; Legatt, 2002; Moller, 2006), and the prognostication of coma (de Sousa et al., 2007; Young et al., 2006). Despite its sensitivity, the BAEP has found only limited use in the neurologic intensive care unit (NICU) as a continuous monitor for brainstem ischemia and transtentorial herniation in unconscious, sedated or pharmacologically paralyzed patients with intracranial mass lesions and increased intracranial pressure (ICP) (Garcia-Larrea et al., 1992; Hall and Harris, 1994; Hall, 2007; Luders and Terada, 2000; Smith et al., 2006; Stone et al., 1988).

In this article, we present an up to date review of the BAEP and relevant auditory physiology, emphasizing newer modified BAEP (MBP) methodology such as our use of pure tone stimuli and rapid rate auditory stimulation at diminishing intensities. Due to the lower stimulation intensities used and the desire to use the test in the presence of a unilateral hearing loss as in a head injured patient—we adopted both binaural (bilateral simultaneous) stimulation and a midfrontal to neck recording linkage to increase waveform amplitude. Although BAEP sensitivity to small or unilateral brainstem lesions may be compromised with binaural compared with unilateral stimulation, our major intention was to advance the development of a rapidly acquired NICU brainstem monitoring tool perhaps sensitive to ischemia, herniation, or increased ICP.

The conventional click generated BAEP is a robust response, producing five vertex recorded positive peaks (Waves I–V) usually within 6 to 7 milliseconds after very brief duration (0.1 milliseconds), moderately high intensity click stimulation, at rates of roughly 8 to 24/s. About 2,000 to 4,000 repetitions are averaged from each ear within a 10 to 15 milliseconds recording window representing one trial, and generally two superimposed trials are necessary from each ear. The sequence of vertex-frontal recorded BAEP waveforms - Waves I–V after click, only Wave V after less intense or rapid (>40/s) click stimuli or pure tone-burst stimuli–is the result of abrupt activation of auditory neurons from the cochlea to the inferior colliculus. The most prominent positive peak is Wave V with its characteristic following negativity (Vn or $SN_{10}$). (Burkard, 2007; Chiappa, 1997; Davis and Hirsh, 1979; Hall, 2007; Hood, 1998; Hughes, 1985; Jewett and Williston, 1971; Legatt, 2005; Moller, 2007; Picton, 1990).

Brainstem auditory evoked potential waveform origins in man span the auditory (8th) nerve, pons, and midbrain and are believed to be: ipsilateral (ipsi) distal 8th nerve- Wave I, ipsi proximal 8th nerve- Wave II, ipsi cochlear nucleus/superior olivary complex- Wave III, bilateral multiple brainstem origins- Wave IV, and contralateral distal lateral lemniscus/inferior colliculus- Wave V and Vn (Hall, 2007; Moller, 2007).

Routine BAEP interpretation consists of Waves I, III, and V absolute and interpeak interval (IPI) determinations, and comparison with normative data. In neurologic practice, the cornerstone of BAEP interpretation has been the IPIs representing central or brainstem conduction times, often obviating confounding middle ear conductive delay or hearing problems which usually cause a delayed Wave I. Waveform amplitudes perhaps more dependant on neuronal generators, are more variable between individuals, susceptible to background noise and less reliable than latency conductions, al-

From the Departments of *Neurosurgery, †Neurology Sections of Electroencephalography and Neurocritical Care, and ‡Otolaryngology/Audiology, University of Illinois Medical Center at Chicago, Chicago, Illinois.
Address correspondence and reprint requests to James L. Stone, M.D., Departments of Neurological Surgery and Neurology, University of Illinois Medical Center (M/C 799), 912 S. Wood St, 4th Floor, Chicago, IL 60612, U.S.A.; e-mail: jlstone4@aol.com.

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though absence of waves after Wave I or II has prognostic significance (Burkard, 2007; Chiappa, 1997; Hood, 1998; Legatt, 2005; Picton, 1990; Young et al., 2006).

On-going or frequent BAEP monitoring as performed during an operative or angiographic procedure, or in the NICU requires recording the patient's own baseline waveform values, monitoring for later changes such as a 10% Wave V latency prolongation or 50% amplitude drop from baseline, and accounting for generalized effects such as lowered blood pressure, increased anesthetic effects and hypothermia (Hall, 2007; Legatt, 2002; Moller, 2006; Smith et al., 2006).

Disadvantages of the conventional BAEP include the slower stimulation rates (8–10/s) usually used in neurology to facilitate Waves I and III for IPI calculations, resulting in about 45 minutes total time to perform the procedure. In addition, BAEP is not related to cerebral hemispheric function and thus falls short of the somatosensory evoked potential in outcome prognostication related to hemispheric insults (Moulton, 1997). A final disadvantage is the necessity that a technologist or clinical neurophysiologist be present for conventional BAEP interpretation.

## Auditory Physiology as Applied to the Brainstem Auditory Evoked Potential

Sound pressure waves or acoustic energy in air is captured by the external ear and auditory canal, and concentrated upon the tympanic membrane. The middle ear ossicles impedance match and transmit this amplified energy through their bony medium to the stapes footplate where a piston-like motion occurs at the oval window of the cochlear base. Consequently, within the bony and membranous labyrinth of the inner ear a hydraulically initiated perilymphatic fluid traveling wave of acoustic energy, if of sufficient amplitude or loudness, and containing frequencies within the human range, will stimulate the basilar membrane epithelium sensory hair cell receptors (Organ of Corti). This perilymphatic wave, if containing higher frequency acoustic energy, stimulates the more basal cochlear sensory receptor hair cells, and if lower frequency energy is present, after a slight time delay, stimulates the more apically located, lower frequency hair cells. Stimulation and BAEP onset synchronization will occur more rapidly with a louder and higher frequency stimulus such as the click (maxima energy 2000–4000 Hz), which is broadband producing activation throughout much of the cochlea, especially the base (Burkard, 2007; Davis and Owen, 1985; Hood, 1998; Hughes, 1985; Picton, 1990; Stapells et al., 1994). In lower mammals and presumably man, increased cerebrospinal fluid pressure (increased ICP) is transmitted to the perilymph by the cochlear aqueduct (perilymphatic duct) resulting in fixation of the stapes footplate with stiffening of the ossicular chain and tympanic membrane (Reid et al., 1998).

The BAEP qualifies as a far-field or volume-conducted potential recorded some distance from its electrical sources in that movement of the active recording electrode does not dramatically alter or degrade the typically low voltage (<1 uV) waveform response. Factors which influence the BAEP include: the total number of activated auditory neurons and fiber tracts, the synchronization of a critical mass of onset-type neurons, the geometry of summated transmembrane electrical activity, and volume conductor impedance (Eggermont, 2007; Moller, 2007; Picton, 1990). The far-field BAEP is adequately recorded at Fz in addition to Cz, which is advantageous in neurosurgical patients with head-dressings or ICP monitoring devices, and Wave V amplitude may be augmented with a C2 (noncephalic) reference electrode (Hall et al., 1984; Hall, 2007; Hughes and Fino, 1985). However, Wave I of the BAEP, behaves as a negative near-field response whose amplitude markedly decreases as the recording electrode is moved away from the cochlea, and is not consistently identified without a mastoid or ear-lobe electrode (Hall, 2007; Hughes, 1985; Stone et al., 1986). Higher intensity, alternating stimulus polarity, and slower stimulation rates optimize Wave I visualization.

The BAEP in response to binaural clicks is about 25% greater in amplitude than the potential acquired with monaural stimulation and unlikely to be equivalent to simple addition of unilateral responses. The effects of binaural interaction on the resulting response are complex and the sensitivity to smaller unilateral brainstem lesions, as in multiple sclerosis, is believed to be diminished (Chiappa, 1997; Davis, 1976; Moller, 2007; Picton, 1990). Binaural stimulation is well adapted; however, to the less complex task of simply acquiring and determining the presence of a BAEP response at lower stimulus intensities, or in the case of diminished hearing. The use of interleaving (alternate left then right unilateral stimulation) allows separate left and right waveform responses (as used in intraoperative monitoring) but essentially doubles the time necessary to determine whether a response is present or has changed in latency or amplitude. Slower stimulation rates and lengthening of the recording window will also prolong the completion of any BAEP trial (Hall, 2007; Moller, 2006; Smith et al., 2006). Although interleaving is necessary during surgical procedure monitoring when the detection of a smaller or unilateral change is crucial, it may be counterproductive when monitoring for rapid detection of global or bilateral conditions such as ischemia, brain herniation, or increased ICP.

The BAEP achieves normal adult waveform configuration and latency values by age 18 months. Advancing age affects the BAEP, and Wave V is known to increase in latency about 30 to 40 usec/decade with arrival of the fifth decade. Perhaps due to smaller head size, females have a slightly decreased latency of the later waves (about 0.15 milliseconds) and greater amplitude than males (Burkard and Sims, 2001; Hall, 2007; Picton, 1990).

The appearance of Wave V generally follows by about 10 to 20 dB the threshold to hear the respective click or tone-burst stimuli, and increasing stimulus intensity shortens Wave V latency and increases Wave V and Vn amplitude. Waves I and III require at least moderate intensity to begin to appear, but also shorten their latency and increase in amplitude with higher stimulus intensity. This results in relative consistency of the I–III, III–V, and I–V IPIs as stimulus intensities are changed (Burkard, 2007; Chiappa, 1997; Hall, 2007; Picton, 1990; Thornton, 2007). With diminishing click or tone-burst intensity the increase in BAEP peak latency is mechanical in nature and due to increased latency of basilar membrane movement resulting in more apical lower frequency stimulation. Lower frequencies are likely emphasized as evidenced by BAEP latency prolongation. This is believed to be secondary to a reduction in higher frequency acoustic stimulus side-band splatter with diminishing intensities (Burkard, 2007; Hall, 2007; Picton, 1990).

When stimulation intensity is held constant, increasing the stimulation rate results in an increased latency to Wave V, believed due to neural adaptation or fatigue possibly related to synaptic and/or conduction inefficiency (Don et al., 1977; Thornton and Coleman, 1975; Thornton, 2007). Wave V prominence may be somewhat improved at stimulus rates above 50/s due to an increase in signal-to-noise ratio, but Waves I–IV are generally less apparent with the faster rates of stimulation (>40/s) and the usual IPIs cannot be calculated (Chiappa, 1997; Hood, 1998; Picton, 1990; Thornton, 2007). In adults, stimulus rate associated Wave V latency changes are essentially constant over changes in intensity (Hall, 2007). However, infants and older subjects show greater prolongation of Wave V absolute latency with increasing click stimulus rate than younger adults (Burkard and Sims, 2001; Chiappa, 1997). It is believed that most of the BAEP latency prolongation at rapid stimulation rates involves the I–V IPI as opposed to Wave I latency

prolongation (Burkard, 2007; Hall, 2007; Picton, 1990; Thornton, 2007). Because IPI prolongation usually implies slowed brainstem conduction, this raises the possibility that faster rates of stimulation could increase the sensitivity of BAEP in asymptomatic or minimally symptomatic patients to detect structural, ischemic, or metabolic brainstem abnormalities. In multiple sclerosis for example, only some investigators found an increased sensitivity with BAEP performed at more rapid rates, however, most agree that abnormalities detected by conventional BAEP were accentuated by rapid rate BAEP (Chiappa, 1997; Davis and Owen, 1985).

Surprisingly, the largest BAEP potential, Wave Vn, has received little attention in neurology (Hughes and Fino, 1985). A slow negativity (Vn or $SN_{10}$) at about 10 milliseconds was described in early attempts at BAEP audiometry in response to increasing 500 and 1,000 Hz tone-burst stimuli (Davis and Hirsh, 1979). This broader waveform, believed to originate within the complex gray mater of inferior colliculis, appears less like the smaller positive peaked synchronized responses and more like a graded or postsynaptic dendritic potential (Davis, 1976; Hall, 2007; Hashimoto, 1986; Moller, 2007).

As a relatively recent innovation to conventional BAEP stimulation evoked by click, a narrower frequency more cochlear specific "tone evoked BAEP" may be obtained in response to electronically smoothed pure tone-burst stimuli delivered at rates comparable with the click BAEP (Gorga et al., 1988, 1992; Picton, 1990; Stapells et al., 1994; Stapells, 2000; Thornton, 2007). The resulting BAEP waveform, especially in response to lower frequency tone-bursts (i.e., 500 Hz, 1,000 Hz), lacks the sharp definition and multiple waveforms of the higher frequency click evoked BAEP, but with a moderately intense stimulus and adequate recording parameters a clear but delayed Wave V and Vn is seen (Fig. 1). When a low frequency BAEP tone-burst stimulus intensity (i.e., 1,000 Hz) diminishes nearer to threshold, the BAEP response is then believed to derive better cochlear place-specificity to that particular frequency (i.e., the more apical 1,000 Hz) receptor region with resultant Wave V and Vn latency delay (Burkard, 2007; Picton, 1990; Stapells et al., 1994; Thornton, 2007). The earlier BAEP, produced in the more basal cochlear by louder high frequency splatter no longer dominates, and allows the delayed more apical 1,000 Hz BAEP to be recorded (Burkard, 2007; Hall, 2007; Picton, 1990). Alternatively, a tone BAEP may be derived from the click BAEP recorded in the presence of high-pass masking noise, by a process of subtracting a series of frequency specific cutoff bands with a time base correction for cochlear delay (Don and Eggermont, 1978; Don et al., 1997; Parker and Thornton, 1978; Telian and Kileny, 1989).

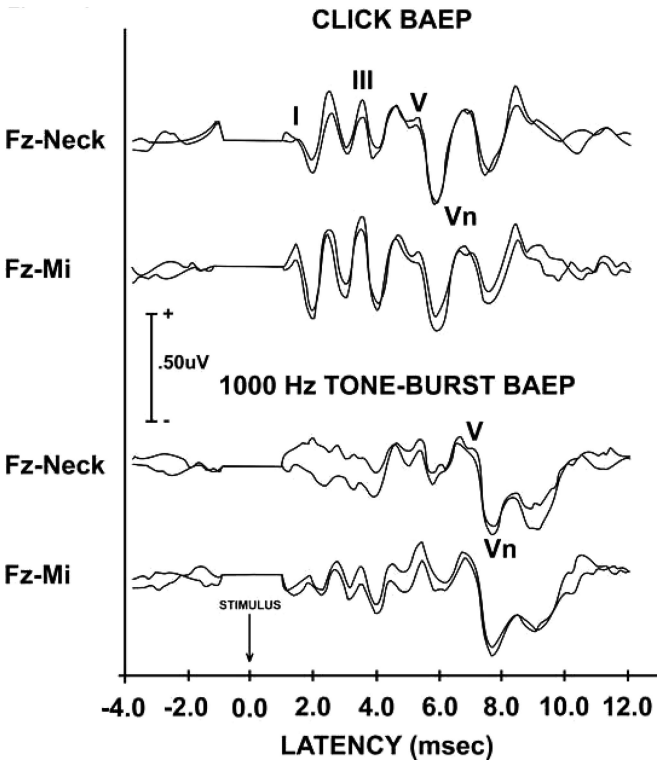


**FIGURE 1.** Conventional Click BAEP & 1,000 Hz tone-burst BAEP.

Tonal BAEPs, beyond their audiological value in detecting relative frequency specific cochlear hearing losses in otherwise untestable infants or children (Gorga et al., 1992; Hall, 2007; Hyde et al., 1998; Sininger, 2007; Stapells, 2000), have also been shown to improve detection of acoustic nerve tumors (Don et al., 1997; Don et al., 2005; Tanaka et al., 1996). A "tonal BAEP" by stimulating a narrower zone of the cochlea and centrally projecting auditory pathways could have additional central diagnostic sensitivity.

More recent innovations in computer technology have emphasized decreasing the BAEP recording time by very rapid stimulation rates (i.e., 66.7/s for a 15 milliseconds window), and enhancement of response quality and objectivity by improved signal-to-noise ratio averaging methods (Cebulla et al., 2000; Hall and Rupp, 1997; Picton et al., 1992). Related developments have aided world-wide application of automated Wave V peak detection, template matching, and automated interpretation for neonatal BAEP hearing screening. These advances could lead to more practical NICU monitoring in the future (Bertrand et al., 1987; Hall and Harris, 1994; Hall, 2007; Hilz et al., 1991; Sgro et al., 1997; Sininger, 2007).

In recognition of the clear potential of BAEP methodology to monitor brainstem integrity in patients with ischemic conditions and intracranial mass lesions which could be altered by progressively increased ICP and brain herniations–we have modified the BAEP. This article describes a test battery consisting of BAEPs that were conventional, and those evoked from a 1,000 Hz pure tone-burst, and more rapid rate binaural click (click MBP) and 1,000 Hz (1,000 Hz MBP) stimuli on a group of 40 normal hearing and neurologically intact adults. Approval was obtained from the University of Illinois at Chicago Institutional Review Board in accordance with Federal and State guidelines. Our sponsor is Bio-logic System Corp, Mundelein, IL (Natus-Biologic, San Carlos, CA). The study design was patterned after NIH SBIR 1R43NS055613-01.

## METHODS

Forty volunteer subjects with normal hearing participated in this study. The ages ranged from 19 to 71 years with mean age of 40 years. Fifteen volunteers were age 50 years or greater, and four 60 years or greater. There were 18 females and 22 males, including multiracial minorities in accordance with IRB specifications. All subjects denied any known hearing problem, neurologic condition, or any history of head injury which could have resulted in skull fracture. Each subject while seated in a recliner had normal hearing as tested with a pure tone screening audiogram in each ear at 500, 1,000, 2,000, and 4,000 Hz (Eckstein Tetra-Tone Audiometer, Model 46, Los Angeles, CA). The BAEP battery of tests described below was administered to each healthy subjects positioned comfortably on a recliner with 30 degrees of head elevation, and advised to rest or sleep during the 60 to 70 minutes of set up and testing.

A Navigator Pro (Bio-logic Systems Corp, Mundelein, IL) 2 channel auditory evoked potential unit was used in this study to

 

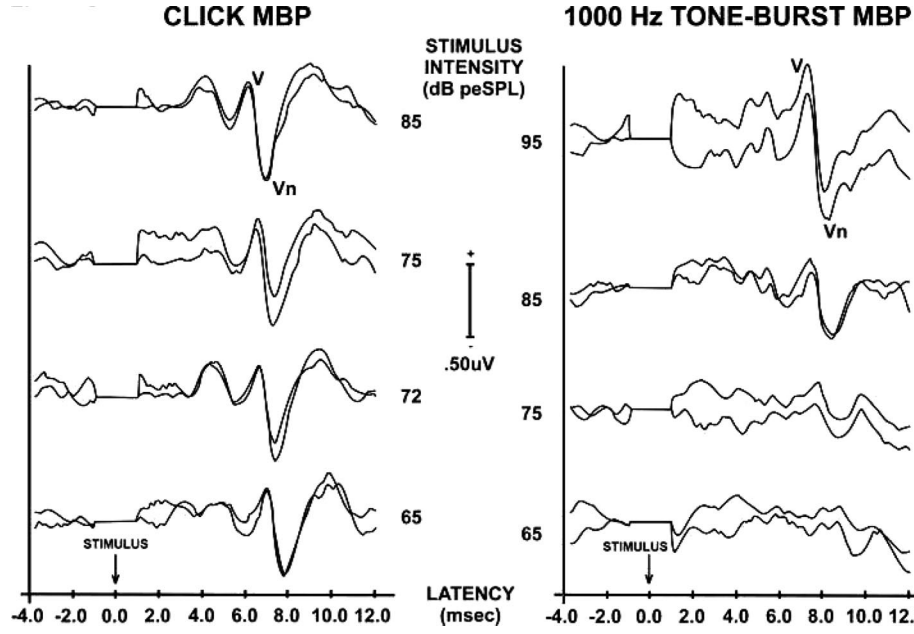


**FIGURE 2.** Click MBP, Fz to C2 neck linkage & 1,000 Hz tone-burst MBP, Fz to C2 neck linkage.

stimulate, record, display and visually analyze the responses. Amplifier specifications included a gain of ×100 to ×300,000, filter slope 12 dB/octave, input impedance >100 megaohms, and common mode rejection ratio >110 dB at 50/60 Hz. Data acquisition used 16 bit A/D resolution and 256/512 points per trace. Standard Bio-logic ER-3A insert earphones were used to deliver the sound stimuli (click or 1,000 Hz tone-burst with Blackman envelope, 2 milliseconds rise and fall time, 2-0-2), and all intensity levels used in the evoked response battery were checked and calibrated using a Bruel and Kjaer 2235 Precision sound level meter (Denmark).

Routine gold-disc surface EEG electrodes were placed at the nasion (ground), Fz (frontal hairline), M1 and M2 (mastoids), and C2 neck, with impedances <5 Kohms.

The BAEP test battery consisted of: (1) A conventional click generated study performed in each ear (Fig. 1), (2) A pure tone-burst 1,000 Hz study in each ear (Fig. 1), (3) A binaural, click MBP at 4 moderate diminishing sound intensities (Fig. 2), and (4) A binaural, 1,000 Hz MBP study at four moderate diminishing sound intensities (Fig. 2). All click and 1,000 Hz tone-burst stimuli were generated by a 0.1 milliseconds rectangular electrical pulse and of rarefaction polarity. Filter settings (notch in) were 300 Hz- 3 kHz and 150 Hz- 3 kHz for click BAEP and click MBP; and 100 Hz- 3 kHz for 1,000 Hz tone-burst BAEP/MBP. For the click and 1,000 Hz BAEP 2 channels were recorded–Fz (frontal hairline) to ipsilateral mastoid (Mi), and Fz to C2 neck, and for all MBP studies only Fz to C2 neck. Ground electrode was at the nasion. At least 2 trials of 4,000 repetitions were recorded for each waveform.

1. The conventional left and right BAEP was elicited by a click rate of 11.4/s and intensity of 95 dB pe SPL. Contralateral white masking noise was presented at 60 dB pe SPL. A 16.0 milliseconds recording window was used to include a 4 milliseconds prestimulation baseline.
2. Pure tone-burst 1,000 Hz BAEP was elicited at a rate of 22.8/s and intensity of 95 dB pe SPL. Contralateral white noise was presented at 60 dB pe SPL. A 16.0 milliseconds recording window was used to include a 3 milliseconds prestimulation baseline.
3. Binaural, click MBP was elicited in each ear simultaneously at a stimulation rate of 59/s and intensity of 85, 75, 72, and 65 dB pe SPL. A 16.0 milliseconds recording window was used to include a 4 milliseconds prestimulation baseline.
4. Binaural, pure tone-burst 1000 Hz MBP was elicited at a rate of 44.4/s and intensity of 95, 85, 75, and 65 dB pe SPL. A 20.0 milliseconds recording window was used to include a 3 milliseconds prestimulation baseline.

Because only absolute (dB pe SPL) auditory stimuli were given to all the healthy subjects, we performed threshold testing of delivered sound stimuli on four of the normal study volunteers. We approximate that for our conventional BAEP a 60 dB nHL stimulus was given; a 65 dB nHL stimulus for pure tone-burst 1000 Hz BAEP; 65, 55, 50, and 45 dB nHL for binaural click MBP; and 70, 60, 50, and 40 dB nHL for the binaural 1,000 Hz pure tone-burst MBP.

Seventeen healthy subjects (mean age 28 years) additionally underwent an abbreviated study battery with the head lowered on the recliner approximately 10 to 15 degrees below the horizontal to evaluate the effects of increasing ICP by postural dependence. This abbreviated study battery excluded the more prolonged conventional slower rate BAEP which takes about 24 minutes to perform (two replications of 4,000 stimuli from each ear). They were instructed to swallow at the onset of the recordings and anytime thereafter.

The senior neurophysiologist (JF) and lead author (JLS) agreed upon each waveform designation. For MBP, the Wave V peak was taken as the highest positive peak before the distinctive following negativity defining the proximal arm of Wave Vn, and the replicated waveform with the greatest Wave V to Vn peak-to-peak amplitude was selected. Absolute and IPI (I–III, III–V, I–V, V–Vn) data, as well as absolute and peak-to-peak Wave V amplitude data were secondarily recorded onto a computerized spread-sheet for computations and statistical analyses. Representative waveforms from one volunteer are illustrated in Figures 1 to 2 and the means, and standard deviations (SD) of the major BAEP peaks are presented in Table 1. For MBP the Wave V latency-intensity function and Wave V amplitude-intensity function curves for the binaural, rapid rate click and 1,000 Hz MBP studies are depicted including 2 and 2.5 SD limits in Table 2 and Figures 3 to 6, respectively. The influence of advancing age upon the BAEP modalities of latency and amplitude are examined in Tables 3 and 4.

**TABLE 1.** Latencies and Amplitudes With Standard Deviations of Click and 1,000 Hz. Tone-Burst BAEP (40 Healthy Subjects)

| | Absolute Latency (msec)/Amplitude (uV) | | | | Interpeak Interval (msec)/Amplitude (uV) | | | |
|---|---|---|---|---|---|---|---|---|
| **PEAK/IPL** | **I** | **III** | **V** | **Vn** | **I–III** | **III–V** | **I–V** | **V–Vn** |
| | | | | Click BAEP | | | | |
| Latency/S.D. | 1.66/0.14 | 3.73/0.22 | 5.65/0.31 | 6.28/0.32 | 2.07/0.17 | 1.93/.24 | 4.00/0.28 | .62/0.11 |
| Amplitude/S.D. | 0.06/0.05 | 0.11/0.06 | 0.08/0.06 | −0.21/0.06 | | | | 0.29/ 0.12 |
| | | | | 1,000 Hz. Tone-burst BAEP | | | | |
| Latency/S.D. | | 5.66/0.55 | 7.27/0.45 | 8.30/0.54 | | | | 1.03/ 0.22 |
| Amplitude/S.D. | | 0.15/0.14 | 0.16/0.15 | −0.25/0.08 | | | 0.41/0.20 | |

**TABLE 2.** Latencies and Amplitudes With Standard Deviations of Click and 1,000 Hz. Tone-Burst MBP (40 Healthy Subjects)

| | | Absolute Latency (msec) Absolute Amplitude (uV) | | Interpeak Interval (msec) Interpeak Amplitude (uV) |
|---|---|---|---|---|
| **Peak/IP** | **Stimulus Intensity (dB peSPL)** | **V** | **Vn** | **V–Vn** |
| | | | Click MBP | |
| Latency/S.D. | 85 | 6.58/0.57 | 7.52/0.57 | .94/0.20 |
| | 75 | 7.03/0.63 | 8.01/0.70 | 0.98/0.24 |
| | 72 | 7.22/0.60 | 8.18/0.67 | 0.95/0.21 |
| | 65 | 7.60/0.65 | 8.57/0.74 | 0.97/0.22 |
| Amplitude/S.D. | 85 | 0.08/0.07 | −0.29/0.12 | 0.37/0.15 |
| | 75 | 0.08/0.08 | −0.29/0.11 | 0.37/0.16 |
| | 72 | 0.08/0.06 | −0.29/0.10 | 0.37/0.14 |
| | 65 | 0.08/0.06 | −0.26/0.09 | 0.34/0.13 |
| | | | 1,000 Hz. Tone-burst MBP | |
| Latency/S.D. | 95 | 7.58/0.35 | 8.64/0.46 | 1.06/0.24 |
| | 85 | 7.87/0.45 | 9.06/0.56 | 1.18/0.30 |
| | 75 | 8.34/0.64 | 9.64/0.77 | 1.31/0.42 |
| | 65 | 9.42/0.87 | 10.78/0.88 | 1.36/0.45 |
| Amplitude/S.D. | 95 | 0.21/0.11 | −0.41/0.14 | 0.62/0.20 |
| | 85 | 0.13/0.07 | −0.29/0.11 | 0.43/0.15 |
| | 75 | 0.08/0.06 | −0.18/0.08 | 0.27/0.12 |
| | 65 | 0.05/0.06 | −0.14/0.05 | 0.19/0.08 |

The recent American Clinical Neurophysiology Society Guidelines to neurologists for conventional click BAEP (Epstein et al., 2006) suggest two channel recording to include not only Cz to ipsilateral earlobe or Mi, but also Cz to contralateral earlobe (Mc)–to improve Wave IV/V differentiation. In our experience, the Fz to C2 neck linkage used in this study similarly improves differentiation and amplitude of Wave V (Hughes et al., 1981; Hughes, 1985).

The Guidelines also suggest filter settings of 10 to 30 Hz to 2.5–3 kHz, but the low-frequency cutoff may be raised to 100 to 200 Hz in the presence of irreducible artifact (Epstein et al., 2006). Our use of a low-frequency (high pass) analog filter cutoff value of 300 Hz diminishes latencies and amplitudes of the waveforms (Chiappa, 1997; Picton, 1990), but may improve the signal-to-noise ratio in the noisy NICU environment where we plan to examine patients. Suggested Guideline click stimulation rates for conventional neurologic BAEP are 8 to 10/s; as a minimal standard <25/s; but for rapid screening identification of Wave V in neonates and adults, rates of 50 to 70/s may be used (Epstein et al., 2006). Brief Guideline suggestions are also given for the Wave V latency-intensity function (Epstein et al., 2006).

## RESULTS

Our conventional BAEP Wave V absolute latency SDs are greater than those usually reported for several likely reasons including the age range of our healthy subjects (Table 1). Of note is that the stimulus intensity levels exclusively used in these studies were maximum or peak sound pressure level values (dB pe SPL). For conventional BAEP, stimulation levels higher than our estimated 60 dB nHL are often used (Chiappa, 1997; Hall, 2007; Hood, 1998; Hughes, 1985; Picton, 1990). We have relied upon dB pe SPL levels in this normative study as we plan to perform these studies on NICU patients with intracranial lesions, because most will not be able to perform threshold testing.

For our 40 healthy subjects, regression analysis showed age was a significant factor affecting the click BAEP and MBP, and somewhat the 1,000 Hz tone-burst MBP (Tables 3 and 4). Regarding the click BAEP, age very significantly correlated with increased absolute latencies of Waves I, III, V, and Vn implying a conductive delay or more likely high frequency hearing loss missed by the screening audiogram. The respective IPIs (I–III, III–V, I–V, and

 

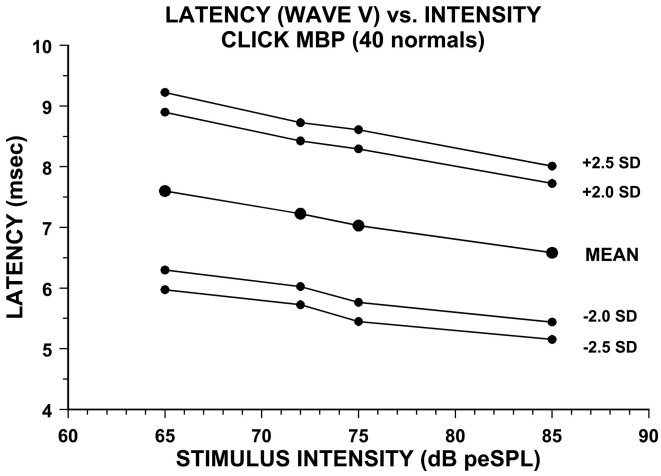


**FIGURE 3.** Click MBP, Wave V latency versus intensity, and standard deviations.

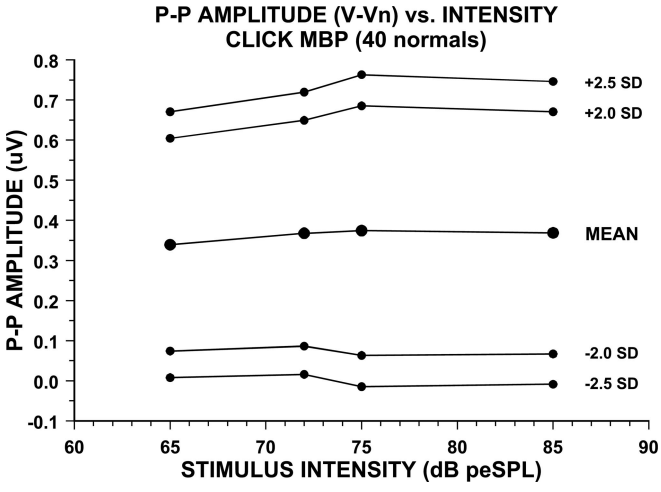


**FIGURE 4.** Click MBP, Wave V to Vn amplitude versus intensity, and standard deviations.

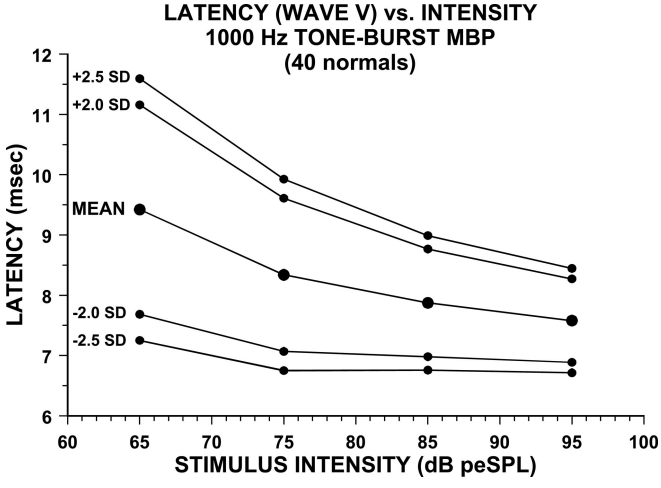


**FIGURE 5.** Tone-burst (1,000 Hz) MBP, Wave V latency versus intensity, and standard deviations.

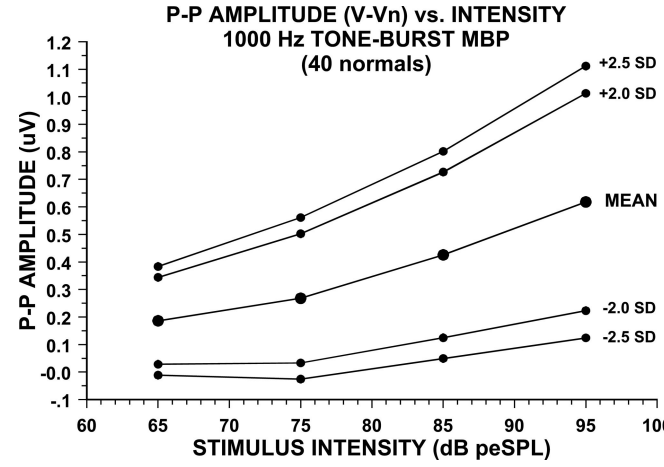


**FIGURE 6.** Tone-burst (1,000 Hz) MBP, Wave V to Vn amplitude versus intensity, and standard deviations.

V–Vn) were unaffected by age, confirming the likely peripheral origin of absolute latency delay. At the highest intensity click MBP (85 dB)–absolute latency of Wave V was unaffected, but all other click MBP latency values (V ,Vn, and V-Vn IPI) were significantly delayed especially for the lower intensities (Table 3). In older subjects, the click MBP absolute and V-Vn IPI latency increase, and isolated 85 dB 1,000 Hz tone-burst MBP Vn and V-Vn IPI latency increase could also have been secondary to the rapid stimulus rates known to show prolonged latency with advancing age (Table 3). Significant correlation of diminished amplitude with age was noted for multiple click MBP parameters (mostly Vn absolute and V-Vn peak-to-peak amplitude), and some 1,000 Hz tone-burst MBP (mostly V absolute amplitude) (Table 4). Click BAEP absolute and peak-to-peak amplitudes were unaffected by age (Table 4). The 1,000 Hz tone-burst BAEP was immune to significant Wave V and Vn latency and amplitude changes related to age (Tables 3 and 4).

As expected, the binaural 1,000 Hz tone-burst MBP latency-intensity function curve shows a more pronounced steepness of slope (exaggerated latency increase) compared with the click MBP, especially at the lower two stimulus intensities (Fig. 2). The V-Vn IPI is relatively consistent across intensity changes for click MBP, but demonstrates more prolongation with diminished stimulus intensity for the 1,000 Hz tone-burst MBP (Table 2). Likewise V-Vn peak-to-peak amplitude is consistent across intensity changes for click MBP, but decreases sharply with diminished intensity for the 1,000 Hz tone-burst MBP (Fig. 2, Table 2).

We performed a paired *t* test on the data for the 17 healthy subjects who were studied a second time with their head lowered 10 to 15 degrees below the horizontal compared with their earlier 30 degree head up study. Significant changes ($P < 0.05$) were found in the three tested modalities. For the 1,000 Hz BAEP diminished Wave Vn absolute and peak-to-peak amplitudes were noted ($P = 0.014$ and 0.010), and increased Wave V latency ($P = 0.026$). The 1,000 Hz MBP disclosed an increased V-Vn IPI at 75 dB ($P = 0.026$) and 95 dB ($P = 0.036$, similar trend at 85 and 65 dB), increased Wave Vn latency at 65 dB ($P = 0.025$), and decreased Wave V absolute amplitude at 75 dB ($P = 0.026$). The click MBP in the downward tilted volunteers disclosed an increased Wave V latency at 65 dB ($P = 0.01$), and at 75 dB increased Wave Vn latency ($P = 0.032$), and decreased Wave Vn absolute amplitude ($P = 0.023$). In summary, excluding the conventional BAEP which was not tested due to time constraints, the tilted volunteers tended to

**TABLE 3.** Correlation Coefficients and (*P*-Values) for Latency vs. Age (40 Healthy Subjects) ($P < 0.05$, 2 Tails)*

| | Absolute Latencies | | | | Interpeak Intervals | | | |
|---|---|---|---|---|---|---|---|---|
| **Peak/IP** | **I** | **III** | **V** | **Vn** | **I–III** | **III–V** | **I–V** | **V–Vn** |
| Stimulus intensity (dB peSPL) | | | | Click BAEP | | | | |
| 95 | 0.620 (<0.0001)* | 0.627 (<0.0001)* | 0.526 (<0.001)* | 0.597 (<0.0001)* | 0.270 (0.092) | 0.108 (0.253) | 0.264 (0.100) | 0.281 (0.079) |
| | | | | 1,000 Hz. Tone-burst BAEP | | | | |
| | | III/IV | | | | | | |
| 95 | 0.206 (0.202) | 0.121 (0.457) | 0.257 (0.109) | 0.228 (0.157) | | | 0.211 (0.191) | 0.044 (0.787) |
| | | | | Click MBP | | | | |
| 85 | | | 0.211 (0.191) | 0.334 (0.035)* | | | | 0.340 (0.032)* |
| 75 | | | 0.324 (0.041)* | 0.428 (0.006)* | | | | 0.397 (0.011)* |
| 72 | | | 0.475 (0.002)* | 0.569 (<0.001)* | | | | 0.454 (0.003)* |
| 65 | | | 0.543 (<0.001)* | 0.590 (<0.0001)* | | | | 0.379 (0.016)* |
| | | | | 1,000 Hz. Tone-burst MBP | | | | |
| 95 | | | 0.107 (0.511) | 0.231 (0.152) | | | | 0.291 (0.152) |
| 85 | | | 0.202 (0.216) | 0.357 (0.024)* | | | | 0.363 (0.021)* |
| 75 | | | 0.081 (0.624) | 0.058 (0.713) | | | | 0.017 (0.903) |
| 65 | | | 0.101 (0.539) | 0.167 (0.294) | | | | 0.134 (0.424) |

**TABLE 4.** Correlation Coefficients and Corresponding (*P*-values) for Amplitude vs. Age (40 Healthy Subjects) ($P < 0.05$, 2 tails)

| | Absolute Amplitudes | | | | Interpeak Amplitudes |
|---|---|---|---|---|---|
| **PEAK/IP** | **I** | **III** | **V** | **Vn** | **V–Vn** |
| Stimulus intensity (dB peSPL) | | | Click BAEP | | |
| 95 | 0.063 (0.699) | −0.372 (0.018) | −0.189 (0.242) | 0.215 (0.183) | 0.232 (0.150) |
| | | | 1000 Hz. Tone-Burst BAEP | | |
| 95 | −0.012 (0.941) | −0.197 (0.223) | −0.181 (0.264) | 0.095 (0.560) | −0.174 (0.283) |
| | | | Click MBP | | |
| 85 | | | −0.070 (0.668) | 0.496 (0.001)* | −0.436 (0.005)* |
| 75 | | | −0.142 (0.382) | 0.436 (0.005)* | −0.373 (0.018)* |
| 72 | | | −0.382 (0.015)* | 0.386 (0.014)* | −0.450 (0.004)* |
| 65 | | | −0.106 (0.515) | 0.446 (0.004)* | −0.358 (0.023)* |
| | | | 1000 Hz. tone-burst MBP | | |
| 95 | | | −0.408 (0.009)* | 0.248 (0.123) | −0.399 (0.011)* |
| 85 | | | −0.359 (0.023)* | 0.113 (0.488) | −0.251 (0.118) |
| 75 | | | −0.191 (0.240) | −0.136 (0.389) | 0.011 (0.951) |
| 65 | | | 0.328 (0.038)* | −0.087 (0.581) | 0.310 (0.052) |

show significant increases in Wave V and Vn absolute latencies and V-Vn IPIs, and a decrease in their respective amplitudes. The V-Vn IPI prolongations were more apparent with the 1,000 Hz MBP, and the Wave V and Vn latency increase with the lower intensity click MBP but also found with the 1,000 Hz BAEP and MBP.

## DISCUSSION

Because the BAEP gives no information as to cerebral hemispheric function, its use as a prognostic indicator for the quality of outcome is limited, and the somatosensory evoked potential may be superior in this regard. Additionally, since the presence of a normal conventional BAEP does not insure a good outcome, some authors maintain that the BAEP shows clinical changes only in end-stage disease, and is of little or no benefit in the early detection and prevention of major morbidity (Moulton, 1997). Yet, it is established that conventional BAEP may be abnormal in patients with symptomatic hydrocephalus and increased ICP secondary to space-taking intracranial lesions, especially if early transtentorial herniation or midbrain compression is present (Benna et al., 1982; Chiappa, 1997; Garcia-Larrea et al., 1992; Hall, 2007; Handa et al., 1990; Krieger et al., 1995; Nagao et al., 1987; Stone et al., 1988). There is evidence that faster stimulation rates, and/or lower stimulation intensities which apparently desynchronize the BAEP yet preserve Wave V (and Vn), may capture otherwise undetectable peripheral or central auditory changes (Burkard, 2007; Legatt, 2005; Pratt et al., 1981; Schwartz et al., 1994; Sgro et al., 1997; Thornton and Coleman, 1975; Thornton, 2007). Such BAEP modifications were found to be more sensitive than the standard BAEP to possible

 

brainstem ischemia (Ben-David et al., 1986; Fradis et al., 1989; Karamitsos et al., 1996), minor head injury (Gerling and Finitzo-Hieber, 1983; Podoshin et al., 1990), acoustic nerve tumor detection (Legatt et al., 1988; Tanaka et al., 1996), hydrocephalus and intracranial space-taking lesions producing increased ICP (Ghaly et al., 1988; Stone et al., 1987; Stone et al., 1988; Yagi and Kaga, 1979). In the past our group evaluated the input/output functions of a rapid rate, binaural click MBP compared with the conventional BAEP, and found the MBP more sensitive to abnormalities in patients with space-taking intracranial lesions and increased ICP (Ghaly et al., 1988; Stone et al., 1987). In that study, although Wave Vn of the click MBP was noted to have significantly different latency values across the four intensity levels compared with Wave V, we failed to examine Vn in the patient population.

We are not aware of reports that 1,000 Hz tone-burst BAEP and MBP have been previously examined in neurologic patients and those with intracranial lesions. These modalities could hold promise for practical brainstem monitoring even though only waves V and Vn are recorded, and significant age related changes occur especially for the click MBP. In particular we believe that analysis of Wave Vn absolute latency, and both V-Vn IPI and amplitude measures may have diagnostic importance in neurologic disorders.

The present results in the downward tilted healthy subjects are of extreme interest. Although a dependant head position does not establish sensitivity to capture increased ICP in the clinically important ranges, the significantly prolonged Wave V, Vn, V-Vn IPI, and diminished amplitude findings are noteworthy. Current audiological methods utilizing tympanometry and otoacoustic emissions also capture postural adjustments and have shown limited success as a noninvasive monitor of ICP (Manwaring et al., 2005; Samuel et al., 1998; Voss et al., 2006). Brainstem auditory evoked potential technology being additionally sensitive to transtentorial brain herniation and midbrain compression may prove more valuable than other auditory related methods in patients with space-occupying intracranial lesions.

Modified BAEP recordings with automated Wave V detection protocols would appear attractive to NICU monitoring since most latency prolongation at rapid click stimulus rates involves I-V IPI (brainstem) delay as opposed to Wave I latency prolongation, in addition to the relative consistency of IPIs across changes in click stimulation intensity. The robust V-Vn IPI may also have diagnostic importance. Currently, nurse friendly automated BAEP Wave V detection methodology is routinely used world-wide in neonatal auditory screening (Hall, 2007; Hyde et al., 1998; Sininger, 2007) and perhaps similar methodology could be applied to the NICU patient population.

Comatose head injured and intubated patients can sustain or later develop inner and middle ear damage, eustachian tube dysfunction, or harbor preexisting hearing disorders which could cause false positive MBP results if BAEP Wave I latency was not monitored as well (Hall, 2007; Picton, 1990). Otologic examination and middle ear function tests, such as immittance audiometry and bone conduction BAEP, may occasionally be required to adequately interpret BAEP findings in the NICU (Hall and Harris, 1994; Hall, 1988; Hall, 2007). Future innovative methodology can likely identify these confounding factors in the majority of cases.

## CONCLUSION

We have presented evidence that the above MBP techniques employing both tonal and click stimuli in addition to relatively rapid rate have the potential to optimize the diagnostic utility of BAEP in patients with space-taking intracranial lesions demonstrating midline shift, other signs of mass effect and increased ICP. In addition these modifications may facilitate real-time monitoring in the NICU, which has not been adequately pursued to date, largely due to practical constraints. Our plan is to perform this test battery on patients with structural intracranial mass lesions and increased ICP. If the results are favorable, then computer controlled automatic evoked response instrumentation utilizing Wave V and Vn peak recognition, latency and amplitude changes, monitoring of input/output functions, and automated interpretation must be developed and implemented to improve monitoring of these critical patients.

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