Electrocochleography and Auditory Brainstem Responses in Persons with Non-Optimal Blood Pressure

Rachael R. Baiduc, PhD, MPH[1] Caitlin M. Berry, MA[2] Katherine Lemons, BA[1] Eric A. Vance, PhD, MS[2]

[1] Department of Speech, Language, and Hearing Sciences, University of Colorado Boulder, Boulder, Colorado
[2] Department of Applied Mathematics, University of Colorado Boulder, Boulder, Colorado

Address for correspondence Rachael R. Baiduc, PhD, MPH, Rachael.Baiduc@colorado.edu

J Am Acad Audiol 2021;32:576–587.

Abstract

Background Numerous cardiometabolic factors may underlie risk of hearing loss. Modifiable risk factors such as non-optimal blood pressure (BP) are of interest.

Purpose To investigate early auditory evoked potentials (AEPs) in persons with nonoptimal BP.

Research Design A cross-sectional nonexperimental study was performed.

Study Sample Fifty-two adults (18–55 years) served as subjects. Individuals were classified as having optimal (systolic [S] BP <120 and diastolic [D] BP <80 mm Hg, $n=25$) or non-optimal BP (SBP $\geq$=120 or DBP $\geq$=80 mm Hg or antihypertensive use, $n=27$). Thirteen subjects had hypertension (HTN) (SBP $\geq$130 or DBP $\geq$80 mm Hg or use of antihypertensives).

Data Collection and Analysis Behavioral thresholds from 0.25 to 16 kHz were collected. Threshold auditory brain stem responses (ABRs) were recorded using rarefaction clicks (17.7/second) from 80 dB nHL to wave V threshold. Electrocochleograms were obtained with 90 dB nHL 7.1/second alternating clicks and assessed for summating and compound action potentials (APs). Outcomes were compared via independent samples *t* tests. Linear mixed effects models for behavioral thresholds and ABR wave latencies were constructed to account for potential confounders.

Results Wave I and III latencies were comparable between optimal and non-optimal BP groups. Wave I was prolonged in hypertensive versus optimal BP subjects at stimulus level 70 dB nHL ($p=0.016$). ABR wave V latencies were prolonged in non-optimal BP at stimulus level 80 dB nHL ($p=0.048$) and in HTN at levels of 80, 50, and 30 dB nHL (all $p<0.050$). DBP was significantly correlated with wave V latency ($r=0.295$; $p=0.039$). No differences in ABR amplitudes were observed between optimal and non-optimal BP subjects. Electrocochleographic study showed statistically comparable action and summating potential amplitudes between optimal and non-optimal BP subjects. AP latencies were also similar between the groups. Analysis using a set baseline amplitude of 0 μV showed that hypertensive subjects had higher summating ($p=0.038$) and AP ($p=0.047$) amplitudes versus optimal BP subjects; AP latencies were comparable.

Keywords

- auditory brain stem response
- auditory evoked potentials
- blood pressure
- electrocochleography

received
February 2, 2021
accepted after revision
June 12, 2021

DOI https://doi.org/10.1055/s-0041-1733970.
ISSN 1050-0545.

Conclusion Elevated BP and more specifically, HTN was associated with subtle AEP abnormalities. This study provides preliminary evidence that nonoptimal BP, and more specifically HTN, may be related to auditory neural dysfunction; larger confirmatory studies are warranted.

Hypertension (HTN) affects ~46% of the U.S. adults[1] and has been linked to hearing loss in numerous reports. Early work by Rosen et al[2] showed that older persons from a nonindustrialized tribe in the Sudan maintained normal blood pressure (BP) and (near) normal hearing, even in advanced age. In contrast, both BP and hearing typically worsen with age in Americans. Since then, population-based studies on the relationship between hearing loss and HTN have shown contradictory results. A longitudinal report from the Baltimore Longitudinal Study of Aging indicated that high systolic BP (SBP) increased the risk of incident hearing loss in men.[3] A study of 13,475 Japanese workers found that those with HTN exhibited a higher prevalence of mild hearing loss compared with participants without HTN.[4] HTN was associated with bilateral hearing loss in the Hispanic/Latino population.[5] In contrast, other epidemiological studies have failed to find associations between HTN and hearing loss including the Epidemiology of Hearing Loss Study,[6] the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002,[7] and the Copenhagen Male Study.[8] Analysis of more recent NHANES data (2011–2012) found HTN to be associated with hearing loss only in adjusted models.[9]

Although numerous reports link HTN to reduced hearing sensitivity, little is known about the effect of elevated BP on central auditory function specifically. Tandon et al[10] found that although subjects (mean age 45 years) with HTN did not have significantly longer auditory brain stem response (ABR) wave latencies, there were moderate correlations between BP and wave I latency and between diastolic (D) BP and wave V latency. Goyal et al[11] identified significantly prolonged ABR wave V latencies and waves III to V interwave intervals (IWIs) in patients (40–60 years) with HTN compared with age- and sex-matched controls. Similarly, Gawali et al.[12] reported delayed ABR waves I and V latencies and prolonged IWIs in hypertensive patients compared with controls. However, the effect of slight BP elevation (i.e., prior to diagnosable HTN) on early auditory evoked potentials (AEPs) has not been studied. Work in hypertensive animals suggests possible cochlear or neural compromise. For example, increased compound action potential (AP) thresholds[13,14] and elevated endolymphatic and strial potassium concentrations[13] have been reported in the spontaneously hypertensive rat.

The motivation for the current study was to build upon previous AEP research and characterize ABR and electrocochleography (ECochG) responses in persons <55 years to determine if subtle BP elevation is associated with auditory neural dysfunction. Recently, the American College of Cardiology/American Heart Association (ACC/AHA) released updated guidelines defining normal BP as SBP/DBP < 120/< 80 mm Hg, elevated BP as SBP 120 to 129 and DBP < 80 mm Hg, stage 1 HTN as SBP 130 to 139 or DBP 80 to 89 mm Hg, and stage 2 HTN as SBP ≥140 or DBP ≥90 mm Hg.[1] To our knowledge, no studies have used these new guidelines in the context of evaluating early AEPs in persons with normal (or "optimal") BP and elevated BP or HTN (together "nonoptimal" BP). The present study aimed to characterize the influence of nonoptimal BP on: (1) ABR wave latencies and IWIs, (2) ABR amplitudes, (3) ECochG summating potential (SP) amplitudes, (4) ECochG AP latencies and amplitudes. We expand upon previous work by dichotomizing BP as "optimal" or "nonoptimal," allowing us to test the hypothesis that there may be a relationship between BP elevation and early AEPs.

Methods

Subjects

An extensive case history was taken to assess general and otologic health including items related to noise exposure. Exclusion criteria were as follows: (1) age >55 years, (2) abnormal otoscopic or tympanometric findings (e.g., compliance <0.30 mL), (3) excessive noise exposure history, (4) current/former use of ototoxic or illicit (e.g., methamphetamine) drugs, (5) current/former cancer diagnosis, and (6) known otologic pathology (e.g., acoustic neuroma).

BP was measured in triplicate with 2 minutes of rest between measurements using an automated Mindray DataScope, Accutorr instrument (Medaval). Measurements were averaged and subjects were classified as having normal or "optimal" (SBP < 120 *and* DBP < 80 mm Hg) or nonoptimal BP (SBP ≥120 *or* DBP ≥80 mm H) per updated ACC/AHA guidelines.[1] Subjects on antihypertensives ($n = 3$) were categorized as nonoptimal regardless of their treated BP. Twenty-five subjects with optimal BP (64% female; $\bar{x}_{age} = 29.7$ years [18–54]) and 27 with nonoptimal BP (26% female; $\bar{x}_{age} = 33.7$ years [19–55]) participated. Of the nonoptimal group, 12 subjects had elevated BP (SBP 120–129 *and* DBP < 80 mm Hg) and 15 had HTN (SBP ≥130–139 *or* DBP ≥80 mm Hg *or* use of antihypertensives). The study was approved by the University of Colorado Boulder Institutional Review Board (IRB).

Auditory Measures

Audiometry was conducted in a double-walled sound-attenuated chamber. Using a modified Hughson–Westlake procedure, air conduction thresholds at octave and interoctave frequencies from 0.25 to 16 kHz and bone conduction

thresholds from 0.5 to 4 kHz were established. A SHOEBOX audiometer (Ottawa, ON) and DD450 RadioEar circumaural headphones (air) or RadioEar B-81 bone oscillator (bone; New Eagle, PA) was used. Three puretone averages (PTAs) were computed: $PTA_{0.5,1,2}$, $PTA_{4,6,8}$, and $PTA_{10,12.5,16}$.

One randomly selected ear was used for electrophysiological testing, which took place in an electrically shielded chamber. Standard recording procedures were used; the experimental protocol has been described in depth elsewhere.[15] In brief, AEP testing was performed using a Biologic AEP Navigator Pro instrument (v.7.2.1; Pleasanton, CA) equipped with Bio-logic insert earphones. Fifty subjects underwent ABR testing; two had too many artifacts to analyze. Single-channel ABRs were acquired using a vertical montage and elicited with 100 microsecond rarefaction clicks (17.7/second). Two or more trials of 1,000 sweeps were collected for stimulus levels ranging from 80 dB nHL to wave V threshold in 10 dB steps (5 dB near threshold). The epoch was 10.66 milliseconds (1.29 milliseconds prestimulus period) and artifacts >23.80 μV were rejected. Response voltages were amplified (×100,000) and digitally filtered (30–1,500 Hz). The weighted average function was performed on 2(+) repeatable waveforms at each stimulus level. Two trained examiners visually inspected the averaged waveforms and identified waves I, III, and V absolute latencies and amplitudes.

Extratympanic ECochG was performed on 39 subjects. As cerumen removal is not part of our IRB-approved laboratory procedure, individuals who had cerumen buildup that prohibited TM electrode placement were excluded ($n = 4$). The remainder refused the test ($n = 2$) or were excluded for other reasons (e.g., too many artifacts). Single-channel recordings were made with a horizontal electrode montage. A Sanibel TM electrode was placed on or near the tympanic membrane. Precise physical placement decisions were driven in part by subject comfort; TM electrodes were placed near the TM for those who were uncomfortable with TM placement. Electrode placement was confirmed via impedance check prior to the initiation of the ECochG measurement. Average impedance for surface electrodes was <5 kΩ. For TM electrodes, average starting impedances were 24.8 kΩ (standard deviation [SD] = 10.9) for the nonoptimal BP group and 22.2 kΩ (SD = 12.9) for the optimal group ($p = 0.342$). In addition, if measurement anomalies arose during testing, the examiner rechecked impedances and adjusted electrode placement if necessary. The inverting electrode was affixed on the contralateral mastoid and the ground electrode on Fz. Responses were elicited using alternating polarity clicks (100 microseconds, 7.1/second) delivered to the test ear at 90 dB nHL. Epochs (10.66 milliseconds) consisted of 1,000 sweeps and measurements were repeated at least twice. A 1.79 milliseconds prestimulus period and 1.29 milliseconds blocking were used. Response filtering (10–1,500 Hz) and preamplification (× 50,000) was performed and artifacts >47.50 μV were rejected. Grand averaged waveforms were inspected and baseline (−0.01 milliseconds), SPs, and APs were identified. SP/AP ratios were computed. Two techniques for SP and AP amplitude measurements were used. The first method accounts for the possibility of a negative amplitude value at baseline. The second method employed a set baseline amplitude of 0 μV.

Statistical Analyses

Statistical analyses were performed using R (R Core Team [2019] v. 4.0.2). Due to the exploratory nature of the study, an a priori power analysis was not performed. Between-group (optimal BP vs. nonoptimal BP or optimal BP vs. hypertensive) comparisons (ABR wave latencies, amplitudes, and IWIs, and ECochG SP [amplitudes], AP [amplitudes and latencies], and SP/AP ratios) were made using *t*-tests for independent samples or Mann–Whitney *U* tests for data with non-Gaussian distributions. A two-way analysis of variance (ANOVA) was conducted to evaluate the effect of sex and BP status on wave V latency. Pearson's bivariate correlations between ABR wave latencies and BP level are reported. Cohen's *d* effect size estimates were derived using the computation $d_s = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1-1)SD_1^2 + (n_2-1)SD_2^2}{n_1+n_2-2}}}$. The *p*-values of <0.05 were considered significant.

To more thoroughly probe the effect of BP on ABR waves I, III, and V latency and behavioral thresholds, varying-intercept linear mixed effects models were developed. Models were created for response variables ABR waves (I, III, and V) latency and behavioral threshold (0.5–16 kHz) with differing combinations of fixed effects (stimulus level [ABR], $PTA_{1,2,3,4}$ [ABR], BP, frequency [behavioral threshold] test ear, recreational noise exposure [yes/no], and sex) and random effects based on subject variation. Models considered BP level as a continuous and dichotomous (optimal vs. nonoptimal) predictor and were generated using the lmer function in R.[16] Bayesian information criterion, calculated using the ANOVA function in R, was used to compare model fit to determine if including BP level in the models would improve said fit.

Results

Characteristics of the subjects are reported in ►**Table 1**. Owing to the higher number of males in the nonoptimal BP group, height and weight were significantly higher in the nonoptimal group. All three PTAs were significantly higher in the nonoptimal group (all $p < 0.05$). Subjects in the nonoptimal BP group reported similar occupational noise exposure but significantly higher recreational exposure as measured by a "yes" response to the prompt "Do you have any hobbies or are you engaged in activities which involve being in noisy environments or loud machinery?" ($p = 0.040$).

►**Fig. 1**] displays mean (±standard error of the mean [SEM]) thresholds. The nonoptimal BP group had significantly poorer thresholds at 0.25, 0.75, 2, 3, 4, 8, 12.5, and 16 kHz according to Mann–Whitney *U* tests (►**Fig. 1**, upper). Additionally, thresholds were poorer at all frequencies except 10 and 12.5 kHz in the hypertensive group ($n = 15$) versus the optimal BP group ($n = 25$; [►**Fig. 1**, lower]). The

Table 1 Demographic, medical, and audiologic characteristics of the study sample (*t*-test [Mann–Whitney *U*-test] or Fisher's exact test)

	Optimal BP SBP <120 and DBP <80 mm Hg	*N*	Nonoptimal BP SBP ≥120 or DBP ≥80 mm Hg or meds	*N*	*p*-Value
Demographic attributes (mean [SD or range] or *N* [%])					
Sex (female)	16 (64)	25	7 (25.9)	27	0.011[a]
Age (y)	29.7 (18–54)	25	33.7 (19–55)	27	0.133
Height (cm)	170.87 (13.07)	25	177.99 (7.49)	27	0.022[a]
Weight (lb)	142.23 (107–225)	25	182.77 (112–279)	27	<0.001[a]
SBP (mm Hg) SPSS file Average	108.27 (96–119)	25	133.09 (109–166)	27	<0.001[a]
DBP (mm Hg) Average	65.29 (6.43)	25	79.22 (11.90)	27	<0.001[a]
Use of antihypertensives (yes)	0 (0)	25	3 (11.5)	27	0.236
Diabetes (yes)	2 (8)	25	0 (0)	27	0.226
Tobacco smoking (yes)	2 (8)	25	6 (22)	27	0.252
Occupational noise exposure (yes)	10 (40)	25	10 (37)	27	1.0
Recreational noise exposure (yes)	2 (8)	25	9 (33)	27	0.040[a]
Puretone audiometric summary (mean [range])					
$PTA_{0.5,1,2}$	3.27 (−10 to 25)	25	7.10 (−10 to 25)	27	<0.001[a]
$PTA_{4,6,8}$	7.07 (−5 to 40)	25	12.03 (0–45)	27	<0.001[a]
$PTA_{10,12.5,16}$	10.93 (−10 to 65)	25	20.37 (−10 to 90)	27	0.004[a]

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; PTA, puretone average; SBP, systolic blood pressure; SD, standard deviation.
[a]$p < 0.05$.

hypertensive group was significantly older (35.5 [10] vs. 29.7 [11.2] years; $p = 0.028$) and contained more males (87 vs. 36%; $p = 0.003$) than the optimal BP group (data not shown).

To further investigate the contribution of BP in these significant differences, linear mixed effect models were created to model behavioral thresholds using differing combinations of frequency, sex, age, noise exposure, and BP (both as a binary and continuous variable) as well as a random effect for individual subject variation. Models were created for both optimal versus nonoptimal and optimal versus hypertensive classifications, and best fit was chosen based on the Bayesian information criterion. The best model to fit the optimal versus nonoptimal classification was that which modeled behavioral thresholds with frequency and age. For the optimal versus HTN classification, the best model was that which used frequency, sex, and age. Overall, including BP (as a binary or continuous variable) did not improve model fit.

Auditory Brain Stem Responses

Fifty subjects underwent ABR testing. We first present grand-averaged (±SEM) ABR waveforms. Exemplar results are presented for the 80 dB nHL stimulus condition (►**Fig. 2**). Overall, the waveforms appear morphologically similar.

Given that sex has a reported influence on ABR wave latencies,[17] we investigated the interaction effects of sex and BP status on ABR wave V latency using a two-way ANOVA. ►**Supplementary Table S1** shows that mean wave latencies did not differ significantly between males and females in the optimal and nonoptimal BP groups or between the optimal BP and hypertensive groups at any stimulus level. Remaining analyses were therefore not separated by sex.

Bivariate correlations were used to explore relationships between BP (systolic and diastolic) level and ABR wave (I, III, V) latencies. Weak correlations were generally observed, with the strongest correlation between DBP and wave V latencies ($r = 0.295$; $p = 0.039$; ►**Fig. 3**). No other correlations were statistically significant. With the exception of SBP and wave III amplitude ($r = -0.384$; $p = 0.007$), correlations between BP level and ABR wave amplitudes were weak (<0.26) and insignificant (data not shown).

The next analysis conducted was a comparison of ABR wave latencies and IWIs between the two BP groups via *t*-tests for independent samples (or Mann–Whitney *U* tests as warranted). The results are shown in ►**Table 2**. Although ABR wave latencies were slightly longer in the nonoptimal BP group at most stimulus levels, the difference was only significant for wave V at 80 dB nHL ($W = 201.5$; $p = 0.048$). IWI_{III-V} was also significantly longer in the nonoptimal BP group at 80 dB nHL ($W = 201.5$; $p = 0.006$]. Wave V thresholds and the remaining IWIs were statistically comparable. The results in ►**Supplementary Table S2** indicate that ABR wave I, III, and V amplitudes were similar.

Next, we conducted linear mixed effects models to examine ABR wave latencies accounting for the following factors:

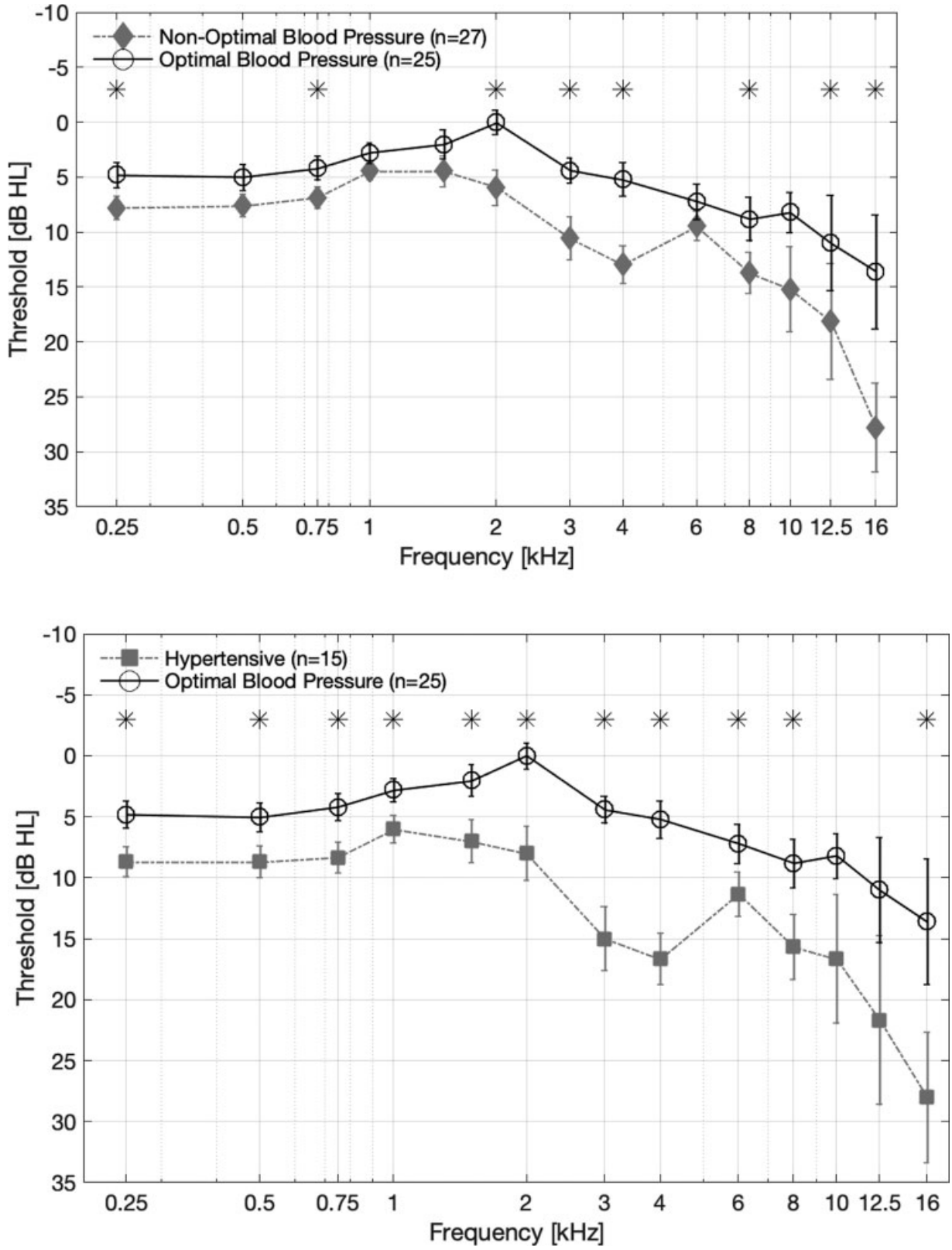

Fig. 1 Mean (standard error of the mean) behavioral hearing thresholds. $^{*}p < 0.05$ for the difference between optimal versus nonoptimal (upper) or optimal versus hypertension (lower).

stimulus level, sex, age, BP, $PTA_{1,2,3,4}$, and recreational noise exposure. All models included a random effect for individual subject variation. The Bayesian information criterion was used for model selection and the best fit models for each wave are reported in ►**Table 3**. The best model to fit the wave V latency data was that which predicted latency using stimulus level, sex, and age. Addition of BP level (as a continuous or binary variable), recreational noise exposure,

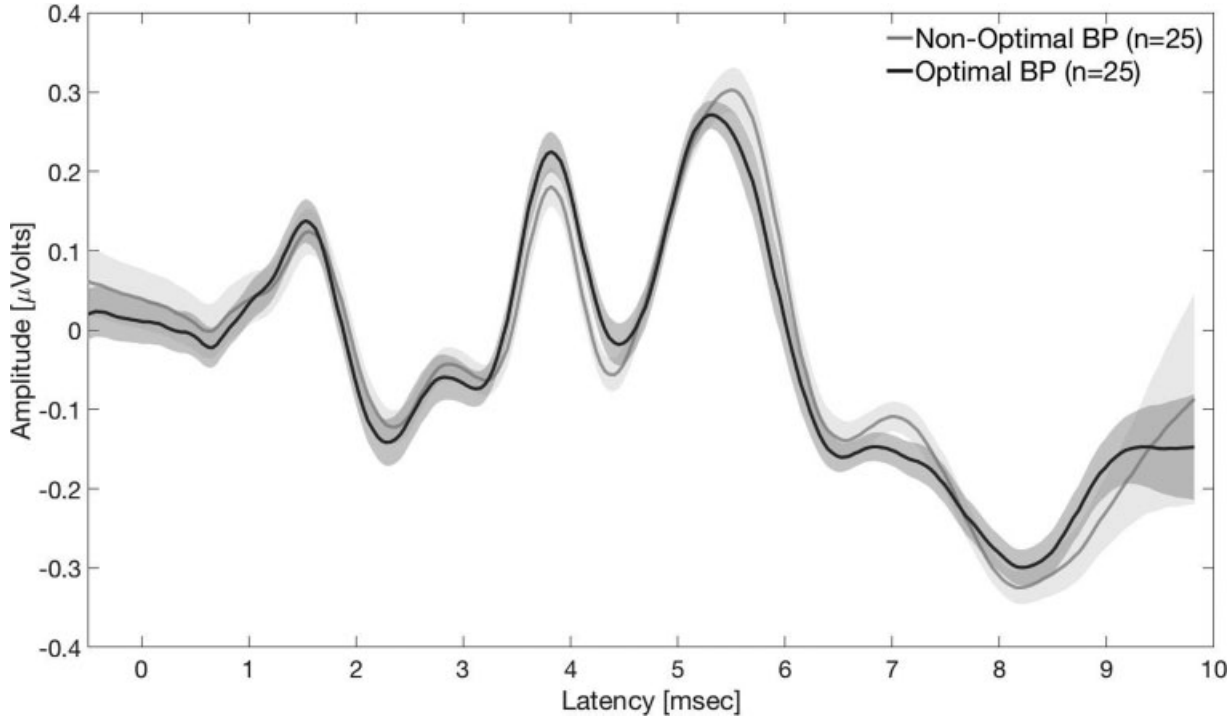

Fig. 2 Grand averaged auditory brain stem response waveforms (mean [standard error of the mean]) for the 80 dB nHL stimulus condition.

$PTA_{1,2,3,4}$, or test ear did not improve model fit. Wave III latency data were best fit by the model that included stimulus level and sex. Finally, ABR wave I data were best fit by the model that included sex, age, and recreational noise exposure.

Finally, we compared ABR wave latency-intensity functions between subjects with optimal BP ($n = 25$) to those with HTN (SBP $\geq$130 or DBP $\geq$80 mm Hg or use of antihypertensives; $n = 13$) via independent samples *t*-tests or Mann–Whitney *U* tests as appropriate. ►**Fig. 4** presents latency-intensity functions for all three BP groups (optimal, nonoptimal, and HTN); optimal versus nonoptimal numerical comparisons are reported in ►**Table 2** and were discussed earlier. Wave I latencies were significantly longer in the hypertensive group than the optimal BP group for stimulus level 70 dB nHL ($W = 73$; $p = 0.016$) with a large effect size of −0.95. There were no significant differences in wave III latencies. Wave V latencies were prolonged in the hypertensive group for stimulus levels of 80 ($t_{(df)} = -2.26_{(26.2)}$; $p = 0.033$), 50 ($t_{(df)} = -2.17_{(31.8)}$; $p = 0.038$), and 30 dB nHL ($t_{(df)} = -2.16_{(24.9)}$; $p = 0.040$). Medium effect sizes were observed, ranging from −0.47 to −0.76 (at 60 and 80 dB nHL, respectively). The remaining comparisons did not reach significance.

Electrocochleography

ECochG was performed on 39 subjects (22 optimal and 17 nonoptimal BP). ►**Fig. 5** shows an exemplar ECochG waveform with two peak picking strategies where (1) corresponds to correction for negative baseline amplitude if applicable and (2) corresponds to a predetermined baseline amplitude of 0 μV. In one nonoptimal BP case, there was no identifiable SP and thus, no resulting SP/AP ratio. ►**Fig. 6**, left shows mean (±SEM) electrocochleograms for the two BP groups and ►**Fig. 6**, right is a violin plot displaying mirrored densities and 50% quantiles. In ►**Fig. 6**, data correspond to the second peak picking method (0 μV baseline). Consistent with the ABR wave I latency results, ECochG AP latencies were slightly longer in the nonoptimal BP group versus the optimal BP group (1.50 milliseconds [SD, 0.11] vs. 1.46 milliseconds [SD, 0.12], respectively); however, this between-group difference was not statistically significant ($p = 0.226$; data not shown).

Results of the two ECochG peak picking strategies are shown in ►**Supplementary Table S3**. The first method accounted for the possibility of a negative baseline amplitude. Using this strategy, the nonoptimal BP group had slightly higher AP amplitudes, but there were no significant differences between BP groups in terms of SP or AP amplitude. The second method set baseline at 0 μV for all subjects. As with the first strategy, there were no significant between-group differences in SP or AP amplitude. Given the analogous nature of ECochG AP and ABR wave I, a comparison of these outcomes is of interest. ABR wave I amplitude was 0.02 μV higher in the optimal BP group versus the nonoptimal BP group, but this difference was not statistically significant (►**Supplementary Table S2**). That is, the ABR amplitude and ECochG AP results are in alignment regardless of ECochG peak picking strategy. Average SP/AP ratios did not differ significantly between groups for either peak picking method. According to Grasel et al,[18] average normal SP/AP ratios are <0.356. The average ratios in both groups were within this range.

Additional analysis was performed to compare ECochG outcomes between optimal BP ($n = 22$) and hypertensive ($n = 9$) subjects and revealed marginally prolonged AP latency in the hypertensive group versus the optimal BP group (1.50 milliseconds [SD, 0.11] vs. 1.46 milliseconds [SD, 0.12]); this difference was not statistically significant

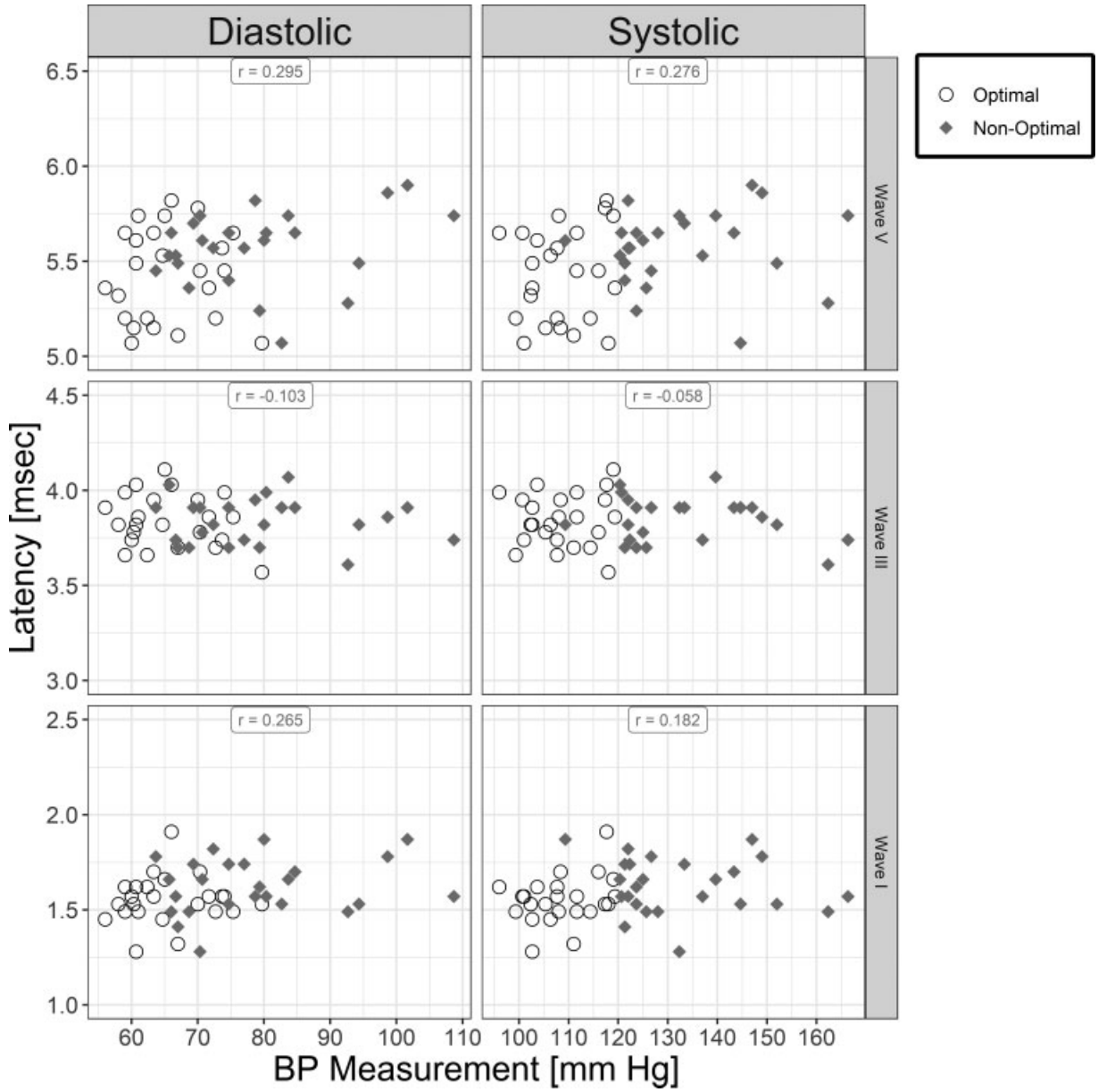

Fig. 3 Pearson's correlations between auditory brain stem response waves I, III, V latency and diastolic (left) and systolic (right) BP.

($p = 0.345$; data not shown). Using the first peak picking method, which accounted for possible negative amplitude at baseline, SP and AP amplitudes were statistically comparable between HTN and optimal BP subjects. With the second peak picking method (i.e., 0 µV amplitude at baseline), both SP and AP amplitudes were significantly higher in the hypertensive group (SP: optimal BP, 0.12 [0.13] vs. hypertensive, 0.25 [0.14] µV, $p = 0.038$; AP: optimal, 0.48 [0.22] vs. hypertensive, 0.71 [0.30] µV, $p = 0.047$ [►**Supplementary Table S3**]).

Discussion

Mounting evidence suggests that modifiable determinants of health including high BP may contribute to development of hearing loss. Most studies have focused on behavioral hearing sensitivity and few have explored AEPs in this population. The electrophysiological profile of persons with nonnormal BP therefore remains equivocal. This preliminary study aimed to characterize early AEPs in adults with normal and elevated BP using standard clinical measures and recent guidelines to define BP elevation. We identified several alterations in early AEPs of persons with elevated BP and HTN.

In this study, hearing sensitivity was poorer in persons with nonoptimal BP compared with those with optimal BP. Threshold differences were most striking between optimal and hypertensive subjects, although, on average, all three groups presented with clinically normal hearing up to 12.5 kHz. Linear mixed effects modeling suggests that age and/or sex might explain much of the between-group difference, that is, the influence of BP on hearing sensitivity may be overshadowed by these more powerful contributors. Past reports are mixed regarding this relationship; some have identified significant associations,[4,19,20] though others have not.[6,8] Our definition of

Table 2 Mean (SD) ABR wave I, III, and V latencies, interpeak latencies (ms), and wave V threshold (dB nHL)

Stimulus intensity (dB nHL)	ABR latency (ms)	Optimal BP	*n*	Nonoptimal BP	*n*	Effect size (*d*)	*p*-Value
80	I	1.55 (0.13)	24	1.63 (0.15)	25	−0.54	0.063
	III	3.84 (0.14)	24	3.84 (0.12)	24	0.05	0.876
	V	5.43 (0.25)	24	5.57 (0.20)	25	−0.64	0.048[a]
	I–III	2.29 (0.14)	24	2.21 (0.17)	24	0.54	0.067
	III–V	1.59 (0.17)	24	1.73 (0.18)	24	−0.81	0.006[a,b]
	I–V	3.88 (0.24)	24	3.95 (0.22)	25	−0.30	0.306
70	I	1.67 (0.11)	24	1.73 (0.14)	22	−0.52	0.088
	III	3.88 (0.16)	24	3.91 (0.12)	24	−0.22	0.443
	V	5.57 (0.28)	24	5.71 (0.24)	25	−0.54	0.066
	I–III	2.21 (0.17)	24	2.16 (0.13)	21	0.38	0.207
	III–V	1.69 (0.21)	24	1.79 (0.20)	24	−0.48	0.102
	I–V	3.90 (0.24)	24	3.95 (0.23)	22	−0.22	0.464
60	I	1.86 (0.21)	13	1.86 (0.15)	15	0.02	0.926[b]
	III	4.11 (0.28)	21	4.10 (0.19)	19	0.03	0.849[b]
	V	5.92 (0.31)	25	6.01 (0.21)	25	−0.34	0.289
	I–III	2.24 (0.19)	12	2.23 (0.20)	15	0.05	0.807[b]
	III–V	1.81 (0.24)	21	1.86 (0.16)	19	−0.21	0.497
	I–V	4.07 (0.25)	13	4.09 (0.17)	15	−0.11	0.775
50	I	—	—	—	—	—	—
	III	4.37 (0.29)	10	4.47 (0.27)	9	−0.34	0.486[b]
	V	6.24 (0.32)	24	6.37 (0.24)	25	−0.49	0.097
	I–III	—	—	—	—	—	—
	III–V	1.75 (0.23)	10	1.78 (0.15)	9	−0.18	0.702
	I–V	—	—	—	—	—	—
40	I	—	—	—	—	—	—
	III	4.80 (0.25)	8	5.06 (0.32)	5	−0.93	0.170
	V	6.65 (0.41)	25	6.80 (0.32)	25	−0.39	0.177
	I–III	—	—	—	—	—	—
	III–V	1.65 (0.27)	8	1.62 (0.13)	5	0.15	0.758
	I–V	—	—	—	—	—	—
30	I	—	—	—	—	—	—
	III	5.18 (0.28)	7	5.36 (0.34)	3	−0.62	0.465
	V	7.20 (0.46)	25	7.38 (0.43)	25	−0.40	0.160
	I–III	—	—	—	—	—	—
	III–V	1.60 (0.18)	7	1.78 (0.19)	3	−1.01	0.227
	I–V	—	—	—	—	—	—
20	I	—	—	—	—	—	—
	III	—	—	—	—	—	—
	V	7.77 (0.54)	24	7.92 (0.40)	22	−0.33	0.266
	I–III	—	—	—	—	—	—
	III–V	—	—	—	—	—	—
	I–V	—	—	—	—	—	—
Wave V threshold (dB nHL)		14.2 (5.72)	25	17.0 (6.12)	25	−0.47	0.091[b]

Abbreviations: ABR, auditory brain stem response; BP, blood pressure; SD, standard deviation.
Note: Em dashes indicate data not available (no recordable responses).
[a]$p < 0.05$.
[b]Comparison via Mann–Whitney *U* test.

Table 3 Results of linear mixed effects models for ABR wave latencies

	BIC	Fixed effects	Estimate	*t*-statistic	*p*-Value[a]
Wave V					
Wave V latency ~ stimulus level + sex + age + random effect (subject)	205.87	Stimulus level	−0.04	−67.03	<0.001
		Sex	−0.39	−6.77	<0.001
		Age	−0.01	3.89	<0.001
Wave III					
Wave III latency ~ stimulus level + sex + random effect (subject)	−22.18	Stimulus level	−0.03	−24.12	<0.001
		Sex	−0.16	−3.60	<0.001
Wave I					
Wave I latency ~ stimulus level + sex + age + noise exposure + random effect (subject)	−194.56	Stimulus level	−0.014	−17.62	<0.001
		Sex	−0.015	−3.79	<0.001
		Age	0.005	3.16	0.003
		Noise exposure	−0.015	−3.17	0.003

Abbreviations: ABR, auditory brain stem response; BIC, Bayesian information criterion.
[a]all $p < 0.05$.

nonoptimal BP, based on recent ACC/AHA guidelines,[1] was more stringent than past reports supporting the HTN–hearing loss relationship.[4,19,20] One population-based study defined high BP more closely to the present report (SBP ≥130 or DBP ≥85 mm Hg) and identified low-frequency hearing loss in elevated BP.[19] In a previous study, we found that age, but not BP, was a significant driver of reduced hearing sensitivity up to 16 kHz in persons with nonoptimal BP.[21] The present study is in agreement with those findings.

Compound AP threshold elevation has been reported in spontaneously hypertensive rats[13] suggesting possible eighth cranial nerve compromise in HTN. Clinically, such involvement is assessable using ABR (wave I) or ECochG (AP) measures. In this study, we did not observe significant wave I latency delays in ABRs of nonoptimal BP subjects compared with ABRs of normotensive. However, specific examination of hypertensive ABRs showed prolongation of wave I at some stimulus levels. Wave I latency delays in HTN have been recognized in previous studies.[10–12] Goyal et al[11] identified

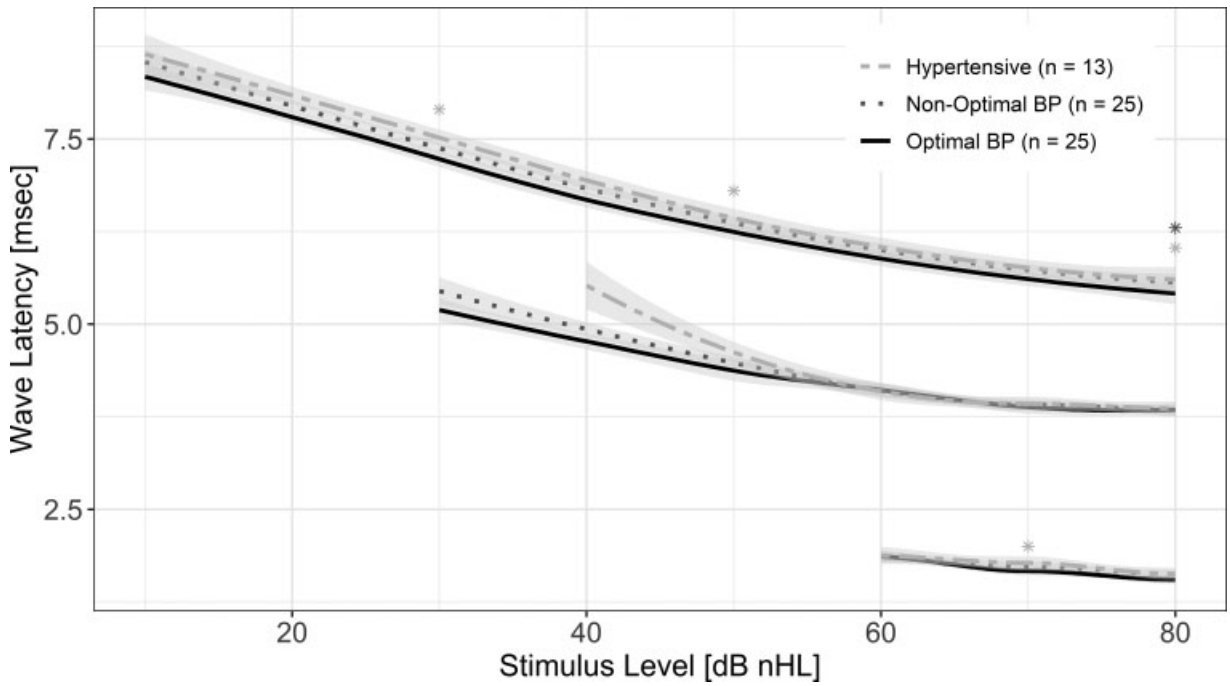

Fig. 4 Mean (95% confidence interval) auditory brain stem response wave latencies for optimal blood pressure (BP) (systolic blood pressure [SBP]/diastolic blood pressure [DBP] <120/<80 mm Hg), elevated BP (SBP ≥120 or DBP ≥80 mm Hg or antihypertensive use), and hypertension (SBP ≥130 or DBP ≥80 mm Hg or medication use) groups. Gray* $p < 0.05$ optimal BP versus hypertension; black* $p < 0.05$ optimal BP versus nonoptimal BP.

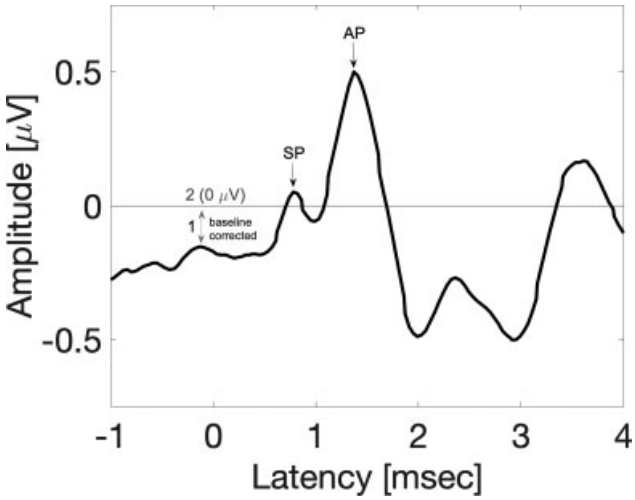

Fig. 5 Exemplar electrocochleography waveform showing two peak picking methods: (1) correction for negative baseline amplitude if applicable and (2) predetermined baseline amplitude of 0 μV.

significant ABR wave I latency delay (~0.16 milliseconds) in hypertensives versus controls but only for subjects with the severest HTN. Similarly, Tandon et al[10] found wave I latency prolongation only in Stage 3 HTN. Our analysis highlights the importance of age in these auditory outcomes. Subjects in our study were younger (~30 years) and had lower BP compared with those in prior reports, which might explain the somewhat discrepant findings.

We observed a correlation between DBP and ABR wave V latency. Tandon et al[10] also reported this correlation and others have demonstrated ABR wave V latency delays in hypertensives.[11,12] There is a clear visual pattern in ►**Fig. 4** that would suggest the HTN group has higher wave V latencies than those of the optimal group. However, this relationship was statistically significant only for some stimulus levels, which may reflect wave fragility or be related to the relatively low number of HTN subjects. Moreover, though we did initially identify significant between-group differences in wave V latencies at certain stimulus levels and in behavioral thresholds at most frequencies, linear mixed effects modeling suggests that inclusion of BP level did not improve model fits.

In this study, subjects with nonoptimal BP demonstrated IWI_{I-III} 0.08 milliseconds shorter than optimal BP subjects for the 80 dB nHL stimulus condition. To a lesser extent, this trend was observed at 70 and 60 dB nHL as well. However, none of the IWI between-group differences were statistically significant. Goyal et al[11] reported shorter IWI_{I-III} in hypertensives and although the magnitude of difference was larger in their study compared with ours (0.22 vs. 0.08 milliseconds), it too was not statistically significant. Tandon et al[10] also failed to find significant differences in IWIs between hypertensives and controls. In contrast, Gawali et al[12] reported significantly shorter IWI_{I-III} in hypertensives than controls. In our study, the only significant difference in IWIs between optimal and nonoptimal BP subjects was IWI_{III-V} at the highest stimulus level, which was 0.14 milliseconds longer in the nonoptimal BP group. Prolonged IWI_{III-V} has been identified in some,[11,12] but not all[10] other related ABR studies in HTN. To evaluate the potential contribution of hearing sensitivity to absolute wave latencies and IWIs, we included $PTA_{1,2,3,4}$ as a covariate in the linear mixed effects model. The results suggest that behavioral hearing sensitivity (specifically, $PTA_{1,2,3,4}$, which is the frequency range evaluated by the click stimulus) did not play a significant role in the between-group ABR wave latencies or IWI_{III-V} reported here.

Collectively, these data demonstrate unfavorable BP levels may be associated with alterations in auditory neural function in a dose-dependent manner. We speculate severity and/or duration of BP elevation (collectively "exposure dose") was not extensive enough in our subjects to influence auditory neural function to a statistically measurable extent once accounting for potential confounders. Larger scale studies of young- and middle-aged persons with elevated BP (prior to clinical HTN) may provide further elucidation. However, given the low prevalence of HTN in younger persons compared with those aged 55 years and older[1] such a study could pose practical challenges. Also relevant is how BP control may relate to early AEPs. Specifically, though not examined here, treatment and duration of nonoptimal BP may play a role in these relationships. Another consideration is the potential role of other cardiometabolic risk factors. In the current study, two optimal BP subjects had diabetes, two reported using cholesterol-lowering medication (one from each BP group), and eight

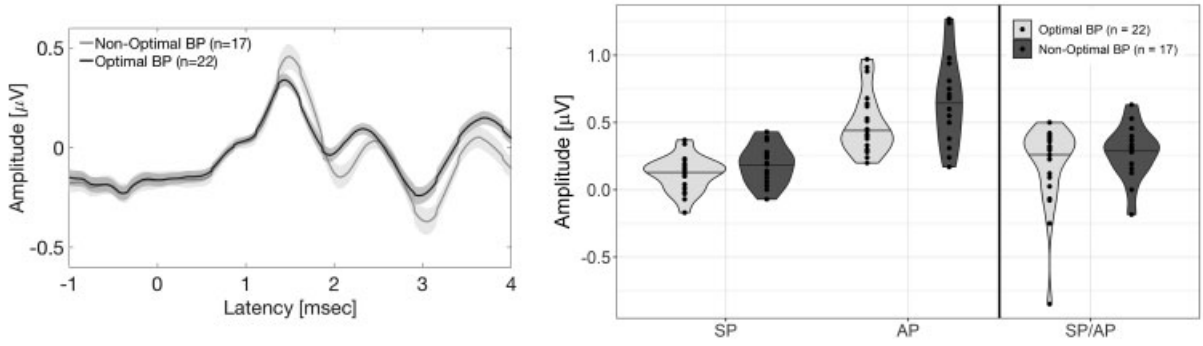

Fig. 6 (Left) Mean (standard error of the mean) electrocochleograms. (Right) Violin plot showing data distribution and quantiles. One subject in the nonoptimal BP group did not have a measurable summating potential (SP) or resulting SP/action potential ratio. Data for method 2 shown in ►**Fig. 5**.

($n = 6$ nonoptimal BP) were current tobacco smokers. Given evidence associating hearing loss with diabetes and tobacco smoking,[22–24] these comorbidities may play a small role in the AEP results reported herein. Due to the low prevalence of these health conditions in our study subjects, we were unable to address this possibility statistically. Potential interaction between elevated BP and other cardiometabolic risk factors may be considered in future AEP investigations. Finally, cross-sectional studies including ours only provide a "snapshot" of BP status. Longitudinal studies are necessary to understand the temporal relationship between BP fluctuation, duration of nonoptimal BP, and auditory neural function. Such studies may also help answer questions regarding the role of BP control.

To our knowledge, this is the first ECochG report in elevated BP. We utilized two peak picking strategies which yielded somewhat discrepant results. Using the approach that accounted for potential negative amplitude at baseline, we did not observe any significant between-group differences in ECochG outcomes for the optimal versus nonoptimal BP or optimal BP versus HTN comparisons. Similarly, when baseline was held constant at 0 μV for all subjects, the optimal and nonoptimal BP groups were statistically indistinguishable. However, when restricted to HTN, we observed significant elevation of both SP and AP amplitudes versus normotensives using the second method. Although the two peak picking strategies did not produce the same results in terms of statistical significance, the general trend (i.e., higher amplitude in nonoptimal BP vs. optimal BP) was consistent between the methods. Similar trends would be expected for ABR wave I as it also reflects auditory nerve activity. In this study, while ECochG AP amplitude was higher in nonoptimal BP subjects compared with optimal BP subjects, ABR wave I amplitudes were 0.02 μV *lower* in the nonoptimal BP group for the highest stimulus level of 80 dB nHL (►**Supplementary Table S2**). Importantly, though, these findings lacked statistical significance. The subtle differences between ECochG AP and ABR wave I amplitudes may be attributable in part to methodological dissimilarities between the tests (e.g., electrode placement, montage, stimulus level, etc.). In addition, we used a higher stimulus level to obtain ECochG than ABR. As a complement to threshold ABR, future studies might therefore evaluate ECochG amplitude growth functions. Tympanic ECochG AP amplitudes are typically higher than ABR wave I amplitudes given closer proximity to the generator site, but variability can be expected based on electrode placement, impedance, tissue conductivity, and other factors. Finally, we did not identify significant between-group differences in electrode impedances making impedance differences an unlikely explanation.

Although SP/AP amplitude ratios were statistically similar between the two groups, the average SP/AP ratio was higher in HTN (0.35 vs. 0.20) and closely approaches the normative cutoff of 0.356 proposed by Grasel et al.[18] Using the peak picking method that accounted for baseline amplitude, the SP/AP ratio in subjects with HTN was even higher at 0.38. With this method, SP/AP ratio in optimal BP was also higher (0.32). Some HTN subjects may be in the early stages of or will eventually develop endolymphatic hydrops; none reported being diagnosed with the condition.

ECochG AP latencies were statistically comparable between the BP groups, although the nonoptimal BP group had slightly longer latency than the optimal BP group. Similarly, ECochG AP latency was longer in the hypertensive group versus the optimal BP group but again, this difference did not reach statistical significance. This is curious given the significant ABR wave I latency delay observed in HTN. Sample size was lower for ECochG than ABR evaluation, therefore reducing statistical power to detect between-group differences. Nonetheless, this inconsistency underscores the need for cautious interpretation and further study using a larger group of HTN subjects.

Compared with optimal BP, recreational noise exposure was more common among nonoptimal subjects; none reported excessive exposure based on extensive questionnaire. The slight audiometric dip at 4 kHz in the nonoptimal group poses the possibility of noise-induced hearing loss. If so, the ABR wave I and ECochG findings could reflect possible synaptopathy. It was recently shown that young noise-exposed adults have higher SP amplitudes and lower AP amplitudes compared with individuals with little exposure.[25] Indeed, the finding that both SP and AP amplitudes were enhanced in nonoptimal BP and HTN subjects is curious and warrants further investigation.

The mechanisms underlying the HTN–hearing loss relationship are incompletely understood. As reviewed by Przewoźny et al,[26] HTN may damage the stria vascularis and alter strial potassium pump function. Acetylcholine (a cochlear efferent neurotransmitter) secretion abnormalities have also been identified in HTN rats.[27] Research in the spontaneously HTN rat has revealed greater inner and outer hair cell loss in HTN noise-exposed rats versus normotensive noise-exposed animals.[28] HTN may increase susceptibility of noise-induced hearing loss. Thus, in our study, the ABR results and subclinical behavioral threshold elevation in HTN subjects may be related to apical hair cell damage.

Conclusion

Overall, the present study is in agreement with previous reports, although abnormalities in ABRs were less striking. Differences in the definition of HTN, subject demographics, and/or statistical methodology might explain the above-mentioned discrepancies. This is the first study to explore early AEPs in the context of elevated BP prior to clinical HTN. The results suggest BP level and ABR wave latencies are related in possibly a dose-dependent manner. Given the preliminary nature of this study, larger confirmatory studies are needed to support this conclusion. Ultimately, identification of modifiable determinants health is important for mitigating risk of auditory dysfunction.

Note
Portions of this work were presented at the American Auditory Society conference, Scottsdale, AZ, February 2019.

Funding
This work was supported by an Emerging Research Grant from the Hearing Health Foundation (PI: Baiduc).

Conflict of Interest
None declared.

Acknowledgments
The authors wish to thank Ms. Kailey Durkin, Ms. Jennifer Masters, and Ms. Amy Sanders for assistance with data collection. We also appreciate the efforts of Dr. Kristin Sommerfeldt in reviewing the electrophysiological data and Mr. Shashidhar Prabhu for MATLAB programming assistance. We express our gratitude to the subjects for their time and dedication to this study. This study was supported by an Emerging Research Grant from the Hearing Health Foundation (Principal Investigator: Rachael R. Baiduc). Medical data were collected by the Colorado Clinical and Translational Research Center, which is supported in part by Colorado CTSA Grant UL1 TR002535 from NIH/NCATS.

References

1 Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71(19):2199–2269
2 Rosen S, Bergman M, Plester D, et al. Presbycusis study of a relatively noise-free population in the Sudan. Trans Am Otol Soc 1962;50:135–152
3 Brant LJ, Gordon-Salant S, Pearson JD, et al. Risk factors related to age-associated hearing loss in the speech frequencies. J Am Acad Audiol 1996;7(03):152–160
4 Umesawa M, Sairenchi T, Haruyama Y, Nagao M, Kobashi G. Association between hypertension and hearing impairment in health check-ups among Japanese workers: a cross-sectional study. BMJ Open 2019;9(04):e028392
5 Cruickshanks KJ, Dhar S, Dinces E, et al. Hearing impairment prevalence and associated risk factors in the Hispanic Community Health Study/Study of Latinos. JAMA Otolaryngol Head Neck Surg 2015;141(07):641–648
6 Zhan W, Cruickshanks KJ, Klein BE, et al. Modifiable determinants of hearing impairment in adults. Prev Med 2011;53(4-5):338–342
7 Agrawal Y, Platz EA, Niparko JK. Risk factors for hearing loss in US adults: data from the National Health and Nutrition Examination Survey, 1999 to 2002. Otol Neurotol 2009;30(02):139–145
8 Parving A, Hein HO, Suadicani P, Ostri B, Gyntelberg F. Epidemiology of hearing disorders. Some factors affecting hearing. The Copenhagen Male Study. Scand Audiol 1993;22(02): 101–107
9 Hoffman HJ, Dobie RA, Losonczy KG, Themann CL, Flamme GA. Declining prevalence of hearing loss in US adults aged 20 to 69 years. JAMA Otolaryngol Head Neck Surg 2017;143(03):274–285
10 Tandon OP, Ram D, Awasthi R. Brainstem auditory evoked responses in primary hypertension. Indian J Med Res 1996;104:311–315
11 Goyal GL, Mittal A, Chaudhary C, et al. The impact of severity of hypertension on auditory brainstem responses. Int J Community Med Public Health 2014;4:218
12 Gawali S, Suryavanshi S, Badkur M, et al. Study of brainstem auditory evoked potentials in early (grade I) essential hypertensive patients. Int J Res Med Sci 2018;6:3747–3751
13 Rarey KE, Ma YL, Gerhardt KJ, Fregly MJ, Garg LC, Rybak LP. Correlative evidence of hypertension and altered cochlear microhomeostasis: electrophysiological changes in the spontaneously hypertensive rat. Hear Res 1996;102(1-2):63–69
14 Tachibana M, Yamamichi I, Nakae S, Hirasugi Y, Machino M, Mizukoshi O. The site of involvement of hypertension within the cochlea. A comparative study of normotensive and spontaneously hypertensive rats. Acta Otolaryngol 1984;97(3-4):257–265
15 Baiduc RR, Mullervy S, Berry CM, Brumbach S, Prabhu S, Vance EA. An exploratory study of early auditory evoked potentials in cannabis smokers. Am J Audiol 2020a;29(03):303–317
16 Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67:1–48
17 Dehan CP, Jerger J. Analysis of gender differences in the auditory brainstem response. Laryngoscope 1990;100(01):18–24
18 Grasel SS, Beck RMO, Loureiro RSC, Rossi AC, de Almeida ER, Ferraro J. Normative data for TM electrocochleography measures. J Otol 2017;12(02):68–73
19 Sun Y-S, Fang W-H, Kao T-W, et al. Components of metabolic syndrome as risk factors for hearing threshold shifts. PLoS One 2015;10(08):e0134388
20 Tan HE, Lan NSR, Knuiman MW, et al. Associations between cardiovascular disease and its risk factors with hearing loss-a cross-sectional analysis. Clin Otolaryngol 2018;43(01): 172–181
21 Baiduc RR, Ramsey M, Sanders A, Vance EA. Association between nonoptimal blood pressure and cochlear function. Ear Hear 2020; 42(02):393–404
22 Akinpelu OV, Mujica-Mota M, Daniel SJ. Is type 2 diabetes mellitus associated with alterations in hearing? A systematic review and meta-analysis. Laryngoscope 2014;124(03):767–776
23 Gupta S, Eavey RD, Wang M, Curhan SG, Curhan GC. Type 2 diabetes and the risk of incident hearing loss. Diabetologia 2019;62(02):281–285
24 Hu H, Sasaki N, Ogasawara T, et al; Japan Epidemiology Collaboration on Occupational Health Study Group. Smoking, smoking cessation, and the risk of hearing loss: Japan Epidemiology Collaboration on Occupational Health Study. Nicotine Tob Res 2019;21(04):481–488
25 Liberman MC, Epstein MJ, Cleveland SS, Wang H, Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. PLoS One 2016;11(09):e0162726
26 Przewoźny T, Gójska-Grymajło A, Kwarciany M, Gąsecki D, Narkiewicz K. Hypertension and cochlear hearing loss. Blood Press 2015;24(04):199–205
27 Li S, Gong S, Yang Y, Yu Q. Effect of hypertension on hearing function, LDH and ChE of the cochlea in older rats. J Huazhong Univ Sci Technolog Med Sci 2003;23(03):306–309
28 Borg E. Noise-induced hearing loss in normotensive and spontaneously hypertensive rats. Hear Res 1982;8(02):117–130