Association Between Nonoptimal Blood Pressure and Cochlear Function

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Objectives: The association between hearing loss and risk factors for cardiovascular disease, including high blood pressure (BP), has been evaluated in numerous studies. However, data from population- and laboratory-based studies remain inconclusive. Furthermore, most prior work has focused on the effects of BP level on behavioral hearing sensitivity. In this study, we investigated cochlear integrity using distortion product otoacoustic emissions (DPOAEs) in persons with subtle elevation in BP levels (nonoptimal BP) hypothesizing that nonoptimal BP would be associated with poorer cochlear function.

Design: Sixty individuals [55% male, mean age = 31.82 (SD = 11.17) years] took part in the study. The authors measured pure-tone audiometric thresholds from 0.25 to 16 kHz and computed four pure-tone averages (PTAs) for the following frequency combinations (in kHz): $PTA_{0.25, 0.5, 0.75}$, $PTA_{1, 1.5, 2, 3}$, $PTA_{4, 6, 8}$, and $PTA_{10, 12.5, 16}$. DPOAEs at the frequency $2f_1$-f_2 were recorded for L_1/L_2 = 65/55 dB SPL using an f_2/f_1 ratio of 1.22. BP was measured, and subjects were categorized as having either optimal BP (systolic/diastolic <120 and <80 mm Hg) or nonoptimal BP (systolic ≥120 or diastolic ≥80 mm Hg or use of antihypertensives). Between-group differences in behavioral thresholds and DPOAE levels were evaluated using 95% confidence intervals. Pearson product-moment correlations were run to assess the relationships between: (1) thresholds (all four PTAs) and BP level and (2) DPOAE [at low ($f_2 \leq$ 2 kHz), mid ($f_2 >$ 2 kHz and ≤10 kHz), and high ($f_2 >$ 10 kHz) frequency bins] and BP level. Linear mixed-effects models were constructed to account for the effects of BP status, stimulus frequency, age and sex on thresholds, and DPOAE amplitudes.

Results: Significant positive correlations between diastolic BP and all four PTAs and systolic BP and $PTA_{0.25, 0.5, 0.75}$ and $PTA_{4, 6, 8}$ were observed. There was not a significant effect of BP status on hearing thresholds from 0.5 to 16 kHz after adjustment for age, sex, and frequency. Correlations between diastolic and systolic BP and DPOAE levels were statistically significant at the high frequencies and for the relationship between diastolic BP and DPOAE level at the mid frequencies. Averaged across frequency, the nonoptimal BP group had DPOAE levels 1.50 dB lower (poorer) than the optimal BP group and differences were statistically significant (p = 0.03).

Conclusions: Initial findings suggest significant correlations between diastolic BP and behavioral thresholds and diastolic BP and mid-frequency DPOAE levels. However, adjusted models indicate other factors are more important drivers of impaired auditory function. Contrary to our hypothesis, we found that subtle BP elevation was not associated with poorer hearing sensitivity or cochlear dysfunction. We consider explanations for the null results. Greater elevation in BP (i.e., hypertension itself) may be associated with more pronounced effects on cochlear function, warranting further investigation. This study suggests that OAEs may be a viable tool to characterize the relationship between cardiometabolic risk factors (and in particular, stage 2 hypertension) and hearing health.

Key words: Blood pressure, Distortion product otoacoustic emissions, Extended high-frequency audiometry.

(Ear & Hearing 2020;XX;00–00)

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INTRODUCTION

High blood pressure (BP) is a common chronic condition in the United States with an estimated prevalence of 31% of adults ≥18 years (or 68 million persons; Centers for Disease Control and Prevention 2011). In addition to a heightened risk of stroke and coronary heart disease (Arima et al. 2011), elevated BP may also increase risk of hearing loss. In fact, the two are common comorbid conditions. A connection between BP and hearing loss was first posited by Rosen et al. (1962) who studied audiometric thresholds and BP levels in Mabaans in remote Sudan. Their cross-sectional data showed that Mabaans demonstrated little variation in BP or hearing sensitivity across a wide age range (10 to 79 years). In contrast, deterioration in hearing sensitivity was observed as early as the 3rd decade of life in Americans, who also exhibited overall higher BP levels. Increase in BP (particularly systolic BP) with age is commonly observed in the United States (Franklin et al. 1997). As hearing loss remains a leading cause of noncommunicable years lived with disability (Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators 2016), identification of preventable or modifiable risk factors such as hypertension is of increasing public health interest.

Since the work of Rosen et al. (1962), numerous population-based studies have examined the association between BP and prevalent hearing loss, most using large datasets and pure-tone audiometric thresholds. For example, the National Health and Nutrition Examination Survey (NHANES) reported higher prevalence of hearing loss in subjects with hypertension [systolic BP >140, and/or diastolic BP >90 mm Hg (millimeters of mercury), and/or medication use] compared to subjects without hypertension (Agrawal et al. 2008). The Busselton Healthy Ageing Study identified a positive association between low-frequency hearing loss and hypertension (defined as in Agrawal et al., 2008) in a study of 5107 subjects (Tan et al. 2018). The Nurse's Health Study, with over 774,096 person-years of follow-up, reported a slightly increased risk of self-reported hearing loss in women with hypertension compared with women without hypertension (Lin et al. 2016). Other large-scale studies have identified significant associations between prevalent (Sun et al. 2015) or incident (Brant et al. 1996) hearing loss and hypertension. Laboratory data suggest an additional possibility. Early work in the spontaneously hypertensive rat demonstrated that young and older noise-exposed animals with hypertension had poorer hearing than normotensive noise-exposed rats (Borg 1982). More recently, a population-based study of >250,000 noise-exposed workers found that persons with hypertension had poorer hearing than noise-exposed normotensive individuals although effects were small (Wang et al. 2018). Noise exposure might exacerbate the effects of hypertension on the auditory system.

Smaller clinical studies also support a link between high BP and hearing loss. For example, Agarwal et al. (2013) compared hearing sensitivity from 0.25 to 8 kHz between 150 hypertensive

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<zdoi; 10.1097/AUD.0000000000000937>

cases and 124 controls and found a graded association between severity of hypertension and severity of hearing loss. Similarly, Tan et al. (2009) examined patients with comorbid hypertension and retinopathy and compared their audiometric thresholds to healthy age- and sex-matched controls. The group with hypertension had significantly poorer hearing from 2 to 8 kHz.

The effect of BP level on hearing has typically been evaluated via behavioral pure-tone audiometry although some studies have used otoacoustic emissions (OAEs) to noninvasively assay outer hair cell integrity. One such report compared distortion product otoacoustic emissions (DPOAEs) in 21 persons with diagnosed arterial hypertension to 21 individuals without hypertension. Ninety percent of the hypertensive group had unmeasurable DPOAEs from 4 to 8 kHz compared with only 52% of the normotensive group (Esparza et al. 2007). Soares et al. (2016) examined pure-tone thresholds up to 16 kHz and OAEs in 20 persons with systemic arterial hypertension and 20 persons without hypertension. Although behavioral thresholds did not differ significantly between groups, DPOAE amplitudes were significantly lower in the hypertensive group at 1.5, 2, and 3 kHz. Another study identified significantly reduced DPOAE amplitudes from 4 to 6 kHz in a group of 32 patients with diagnosed arterial hypertension compared with controls (Przewoźny et al. 2016).

In contrast, other investigators have not found evidence of auditory abnormalities in persons with hypertension. The Epidemiology of Hearing Loss Study did not observe a significant association between hypertension (or BP level) and prevalent hearing loss (Cruickshanks et al. 2015b). Other large-scale studies have failed to detect significant associations between hypertension and hearing loss using pure-tone audiometry as the auditory measure (Engdahl et al. 2015; Lee et al. 2016). In addition, Torre et al. (2005) did not find an association between cochlear impairment (assessed via DPOAEs) and hypertension in 1501 subjects from the Epidemiology of Hearing Loss Study. Thus, data on the relationship between BP and auditory function remain inconclusive.

The majority of published reports on this topic have used pure-tone audiometric thresholds to assess auditory function in individuals with hypertension, although some work has incorporated OAE measurements with mixed results (Torre et al. 2005; Esparza et al. 2007; Soares et al. 2016). OAEs are a valuable tool for identification of subtle cochleopathology. Impaired microcirculation has been implicated in the pathophysiology of hearing loss related to disrupted cochlear blood flow as normal blood supply is critical for maintenance of the endocochlear potential (for review, see Shi, 2011). If the proposed theory is accurate, OAEs would be an apropos tool to study the relationship between BP level and auditory function. There have been few such studies published to date. Furthermore, past reports have measured emissions at frequencies up to 8 kHz. Advances in OAE technology permit the evaluation of high-frequency OAEs, up to the limit of human hearing (20 kHz; e.g., Lee et al. 2012; Dewey & Dhar, 2017).

The current study explores cochlear function in persons with adverse BP levels. We extend previous work by examining the effect of BP on auditory status using extended high-frequency audiometry and DPOAEs. In addition to evaluating the correlation between hearing and continuous levels of systolic and diastolic BP, we also use a binary classification scheme wherein BP is defined as either "optimal" (systolic/diastolic BP <120/<80 mm Hg) or "nonoptimal" (systolic ≥120 or diastolic ≥80 mm Hg or use of antihypertensives) to reflect the new American College of Cardiology/American Heart Association recommendations (Whelton et al. 2018). This strategy permits a more nuanced understanding of the effects of subtle BP elevation on auditory function.

Study Aims

In summary, the purpose of the current study was to characterize peripheral auditory function in persons with optimal and nonoptimal BP levels. The main objectives were as follows: (1) to examine the effects of BP level on behavioral pure-tone sensitivity in adults aged 18 to 55 years and (2) to evaluate cochlear function using DPOAEs in individuals with optimal and nonoptimal BP levels.

MATERIALS AND METHODS

Subjects

Sixty individuals [55% male, mean age = 31.82 (SD=11.17) years] were recruited from within and around the Boulder, Colorado community. Subjects underwent a prescreening and were excluded if they had one or more of the following: (1) severe to profound hearing loss, (2) conditions associated with hearing loss such as acoustic neuroma or active middle ear infection, (3) past or current cancer diagnosis, (4) excessive cerumen in the external auditory meatus, and/or (5) air-bone gaps >10 dB at 0.5, 1, or 2 kHz. Subjects underwent otoscopy and standard clinical 226 Hz tympanometry (GSI Tympstar; Grason-Stradler, Minnesota) to confirm normal middle ear function. Subjects were compensated for their time. This study was approved by and conducted in accordance with the Institutional Review Board at the University of Colorado Boulder.

Health Assessment

Subjects underwent a physical examination with a physician or nurse. Owing to the substantial time commitment for participation in this study, some individuals opted to separate the health and audiological assessments and undergo testing on separate days although the majority (57%) completed testing within the same week and 47% on the same day.

Height and weight were measured by a nurse during the physical examination. BP level was measured three times with two minutes of rest between measurements using an automated Mindray-Datascope, Accutorr instrument (Medaval). The average of all three measurements was used for analysis. A binary grouping scheme was used to compare BP levels as follows: (1) optimal BP (systolic <120 and diastolic <80 mm Hg) versus (2) nonoptimal BP (systolic ≥120 or diastolic ≥80 mm Hg or use of antihypertensives). Definitions for optimal and nonoptimal BP were based on the American College of Cardiology/American Heart Association guidelines (Whelton et al. 2018) and an established cardiovascular disease risk burden scheme used to predict sudden cardiac death (Bogle et al. 2016). Three subjects reported use of antihypertensives, placing them in the nonoptimal BP category.

Audiological Testing

Before testing, subjects completed a comprehensive questionnaire including items related to noise exposure (e.g., use of personal listening devices, occupational/recreational exposure, etc.). Audiological evaluations were performed in a

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double-walled sound-attenuating chamber with subjects seated comfortably. Air conduction behavioral hearing thresholds were obtained bilaterally from 0.25 to 16 kHz with a SHOEBOX audiometer and DD450 RadioEar circumaural headphones. Bone conduction thresholds were tested at 0.25, 1, 2, and 4 kHz using a RadioEar B-81 oscillator. A modified Hughson-Westlake procedure with 5-dB steps was used to obtain air and bone conduction thresholds. Based on air conduction thresholds, four pure-tone averages (PTAs) in dB HL were computed as follows: (1) $PTA_{0.25, 0.5, 0.75}$, average threshold at 0.25, 0.5, and 0.75 kHz; (2) $PTA_{1, 1.5, 2, 3}$, average threshold at 1, 1.5, 2, and 3 kHz; (3) $PTA_{4, 6, 8}$, average threshold at 4, 6, and 8 kHz; and (4) $PTA_{10, 12.5, 16}$ average threshold at 10, 12.5, and 16 kHz. In the case of nonresponse, threshold was recorded as 10 dB above the maximum output of the audiometer at that test frequency. Word recognition testing was performed using a randomly assigned list of 25 Northwestern University Auditory Test No. 6 words presented at 40 dB SL re: PTA. Word recognition scores (WRS) were recorded as percent correct words from the 25-word list.

One ear was selected at random for DPOAE testing. There were 37 right ears and 23 left ears. Custom MATLAB software (supplied by S. Goodman) running on a Macintosh computer was used for DPOAE experiments. Analog-to-digital and digital-to-analog conversion were achieved with an RME UCX Fireface sound card (96 kHz, 24 bit). An Etymotic Research 10X probe microphone and preamplifier (+20 dB gain) were used for signal generation and DPOAE recordings. Calibration was carried out according to procedures described previously (Goodman et al. 2009; Brumbach et al. 2019). DPOAEs at the frequency $2f_1$-f_2 were obtained using discrete primary tones presented at an f_2/f_1 ratio of 1.22 for L_1/L_2 = 65/55 dB SPL. Primary tones were presented from f_2 of 0.5 to 19.027 kHz in 1/8-octave steps (43 test frequencies). Owing to high noise floors at frequencies below 1000 Hz, we report emission levels for f_2 frequencies ≥1 kHz resulting in 35 total f_2 frequencies included in statistical analyses. Twenty-four stimulus repetitions (1 sec each) were presented per frequency. Subjects were seated comfortably during recordings and were instructed to inform the examiner in the event of probe slippage. In such cases, recordings were paused and the probe repositioned. In the event of a suddenly noisy recording, the session was paused, and the examiner waited for the subject to settle movement before continuation of testing.

Following digitization, DPOAE waveforms were stored for subsequent off-line analysis. For each f_2 frequency, 1-sec waveform recordings were transformed via a fast Fourier transform. The complex value corresponding to the $2f_1$-f_2 Hz bin was stored. The mean of these values was considered the DPOAE level and the SE of the mean, the noise floor. Estimates of DPOAE amplitude and noise floor were expressed in dB SPL. All datapoints were included in statistical models.

Statistical Analysis

We present case history data as mean (SD) for continuous variables and count (percent) for categorical variables. Independent samples *t* tests were used to compare continuous variables between the optimal and nonoptimal BP categories. For non-Gaussian distributions, Wilcoxon Rank-Sum tests were used, and data are reported as mean (range). Fisher's exact tests were used for categorical variables.

Using 95% confidence intervals, we compared behavioral hearing thresholds (from 0.25 to 16 kHz and the pooled difference for all 13 test frequencies) and DPOAE levels (from f_2 of 1.091 to 14.672 kHz) between the optimal and nonoptimal BP groups.

Pearson product-moment correlations were used to assess the relationship between all four PTAs and diastolic and systolic BP levels. Likewise, Pearson correlations were also used to evaluate the relationship between WRS and diastolic and systolic BP levels and finally, to examine the relationship between DPOAE levels and BP levels. Separate analyses were conducted for the two stimulus conditions. Threshold data were analyzed as four distinct bins based on PTA (i.e., $PTA_{0.25, 0.5, 0.75}$, $PTA_{1, 1.5, 2, 3}$, $PTA_{4, 6, 8}$, and $PTA_{10, 12.5, 16}$) and averaged within a given bin for correlation analyses. Likewise, DPOAE data were grouped into bins based on f_2 frequency: low [$f_2 \leq 2$ kHz (9 f_2 frequencies)], mid [$f_2 > 2$ kHz and ≤10 kHz (18 f_2 frequencies)], and high [$f_2 > 10$ kHz (8 f_2 frequencies)].

Linear mixed-effects models were used to evaluate the effect of BP level and other predictors (e.g., age and sex) on hearing thresholds and DPOAE level. For thresholds, models were constructed for $PTA_{0.25, 0.5, 0.75}$, $PTA_{1, 1.5, 2, 3}$, $PTA_{4, 6, 8}$, and $PTA_{10, 12.5, 16}$. The response variable was threshold (in dB HL) with fixed effects of BP group, frequency, age and sex, and random effects based on individual subject variation. Similarly, linear mixed-effects models were run for response variable DPOAE level (in dB SPL) with fixed effects of BP group, frequency (f_2), age and sex, and random effects based on individual subject variation. Models were created using the lmer function in the lme4 package in R (Bates et al. 2015).

Analysis was performed using R [R Core Team (2019) v. 3.6.1]. *P*-values of ≤0.05 were considered significant.

RESULTS

General Characterization of the Optimal and Nonoptimal Blood Pressure Groups

A summary of demographic (age and sex) and hearing outcomes (e.g., PTA) by BP group is presented in Table 1. Subjects in the nonoptimal BP group were more likely to be male ($p = 0.001$) and consequently, were taller and weighed more than the optimal BP group ($p = 0.005$ and <0.001, respectively). On average, persons with nonoptimal BP were only 1.5 years older than persons with optimal BP. Table 1 also presents audiological outcomes, showing that WRS and all four PTAs were comparable between groups. WRS was weakly negatively correlated with diastolic BP [$r(58) = –0.19$; $p = 0.144$] and uncorrelated with systolic BP [$r(58) = –0.09$; $p = 0.51$]. Neither correlation was statistically significant. Table 1 demonstrates that noise exposure history was comparable between groups based on common sources of noise. Given the similar noise exposure histories, noise variables were not included in the linear mixed-effects models described below.

Behavioral Hearing Sensitivity

Figure 1 displays mean [± standard error of the mean (SEM)] thresholds as a function of frequency for the optimal (black triangles) and nonoptimal (red circles) BP groups. Threshold data correspond to the randomly selected ear used for DPOAE testing. In the lower panel, we show the difference in means (filled circles) and Cohen's effect sizes by frequency. Differences were computed such that negative values indicate poorer thresholds in the nonoptimal BP group. Statistically, significant differences are determined by the separation of the confidence intervals

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TABLE 1. Characteristics of the study sample

	Optimal BP	Nonoptimal BP	*p*
Demographic characteristics			
Sex (female)	21 (66)	6 (27)	0.001*
Age (yrs)	31.06 (11.83)	32.68 (10.52)	0.578
Height (cm)	170.52 (12.53)	178.16 (7.08)	0.005*
Weight (lbs)	143.30 (27.72)	180.43 (31.81)	<0.001*
Systolic blood pressure level (mm Hg)	108.75 (7.02)	132.93 (12.39)	<0.001*
Diastolic blood pressure level (mm Hg)	65.66 (6.95)	77.75 (11.74)	<0.001*
Hearing-related outcomes			
$PTA_{0.25, 0.5, 0.75}$	4.48 (–3.33, 25)	6.49 (–5, 15)	0.097
$PTA_{1, 1.5, 2,3}$	4.02 (–3.75, 25)	5.0 (–3.75, 22.5)	0.337
$PTA_{4, 6, 8}$	8.44 (–3.33, 28.33)	11.07 (–1.67, 33.33)	0.083
$PTA_{10, 12.5, 16}$	14.02 (–6.67, 55)	18.86 (–6.67, 80)	0.224
WRS	97.75 (92, 100)	97.71 (76, 100)	0.510
Noise exposure history			
Use of PLDs (yes)	28 (88)	24 (86)	1.0
PLDs, hr/day	1.83 (2.05)	2.05 (2.29)	0.691
Occupational noise exposure (yes)	13 (41)	11 (39)	1.0
Recreational noise exposure (yes)	3 (9)	8 (29)	0.093
Current concert attendance (per year)	3.72 (0, 24)	2.3 (0, 20)	0.354

*Data are mean (SD) for continuous variables or count (percent of BP group) for categorical data. Continuous variables were compared between groups via independent samples t tests and categorical variables via Fisher's exact tests. PTAs, WRS, and current concert attendance were compared using Wilcoxon Rank-Sum tests. Mean (range) are reported for these data. The nonoptimal BP group had significantly more men and therefore, higher weight and height than the nonoptimal BP group. PTAs and WRS are specific to the randomly selected test ear (i.e., the ear used for DPOAE testing). N = 32 optimal and 28 nonoptimal. BP, blood pressure; DPOAE, distortion product otoacoustic emissions; WRS, word recognition scores; PLD, personal listening device; PTA, pure-tone average.*Indicates statistically significant at the p ≤0.05 level.*

from the zero-line. The difference in mean measurements is statistically significant at 0.25 kHz and for the overall, pooled frequency measurements.

To gain a more nuanced understanding of the effects of BP level on behavioral hearing sensitivity, the Pearson correlations between BP level and threshold were examined. Figure 2 displays correlation plots for all four PTAs as a function of diastolic (left) or systolic (right) BP level. Significant correlations were obtained for all four of the diastolic BP-PTA correlations {$PTA_{0.25, 0.5, 0.75}$ [$r(58) = 0.310$; $p = 0.016$]; $PTA_{1, 1.5, 2, 3}$ [$r(58) = 0.291$; $p = 0.024$;]; $PTA_{4, 6, 8}$ [$r(58) = 0.481$; $p = 0.0001$]; $PTA_{10, 12.5, 16}$ [$r(58) = 0.361$; $p = 0.005$]}. The correlation between systolic BP and $PTA_{0.25, 0.5, 0.75}$ was significant [$r(58) = 0.260$; $p = 0.044$] as was the correlation between systolic BP and $PTA_{4, 6, 8}$ [$r(58) = 0.340$; $p = 0.008$]. The remaining two correlations did not reach significance.

Linear mixed-effects models were constructed to further evaluate the effect of BP, accounting for the potential covariates of age and sex, on hearing thresholds (as binned in the four PTAs). For all models except $PTA_{0.25, 0.5, 0.75}$, we obtained a significant effect of age. BP group was not a significant predictor for any of the PTAs. Specific results from the models are reported in Table 2.

Cochlear Function: Distortion Product Otoacoustic Emissions Experiment

Figure 3 plots mean (± SEM) DPOAE level as a function of f_2 frequency. The right panel shows the differences in mean DPOAE amplitudes between groups (optimal BP–nonoptimal BP) such that values >0 indicate poorer responses in the nonoptimal BP group, which were observed primarily at f_2 frequencies > ~10 kHz. Effect sizes are indicated for each frequency in the right panel. Emission levels were significantly lower (worse) in the nonoptimal two BP group at 11.314 kHz and overall, with effect sizes of 0.578 and 0.096, respectively. According to two-sample *t* tests, the differences in means were not significant for the remaining comparisons. Averaged across frequency, the nonoptimal BP group had DPOAE levels 1.50 dB lower (poorer) than the optimal BP group ($p = 0.03$).

Recall that linear mixed-effects models were constructed for three frequency bins to evaluate the effect of BP category, stimulus frequency (f_2), sex, and age on DPOAE level. Model results are presented in Table 3. Results for the low-frequency model (f_2, 1 to ≤2 kHz) suggest a significant effect of age on DPOAE level such that increased age is associated with lower (poorer) DPOAE levels. For the mid (f_2 > 2 to ≤10 kHz) and high (f_2 > 10 kHz) frequency bins, f_2, age, and sex were significant predictors of DPOAE level. Additional linear mixed-effects models constructed to account for ear, tobacco smoking, and use of antihypertensives did not alter these findings (data not shown).

Figure 4 shows correlations between DPOAE level (at low, mid, and high f_2 frequencies, from bottom to top) and diastolic (left) or systolic (right) BP levels. Significant correlations were obtained for the relationship between diastolic BP and DPOAE level [$r(57) = –0.337$; $p = 0.009$] and systolic BP and DPOAE level [$r(57) = –0.277$; $p = 0.034$] at the high frequencies. The correlation between diastolic BP and DPOAE level neared significance for the mid frequencies ($p = 0.052$).

Last, Figure 5 displays mean (± SEM) DPOAE levels as a function of f_2 frequency for subjects with and without hypertension as well as those on antihypertensive medications. Hypertension was defined as systolic BP ≥140 or diastolic BP ≥90 mm Hg or the use of antihypertensives ($n = 3$). Nine subjects (all men) met these criteria. The mean age of subjects with hypertension ($n = 9$) was similar to that of subjects without hypertension [$n = 51$; 34.78 years (SD = 9.51) vs. 31.29 years (SD = 11.44); $p = 0.345$]. The three individuals on medication had a mean age of 36.7 years. Emission levels were lower in subjects with untreated hypertension for f_2 frequencies from ~2

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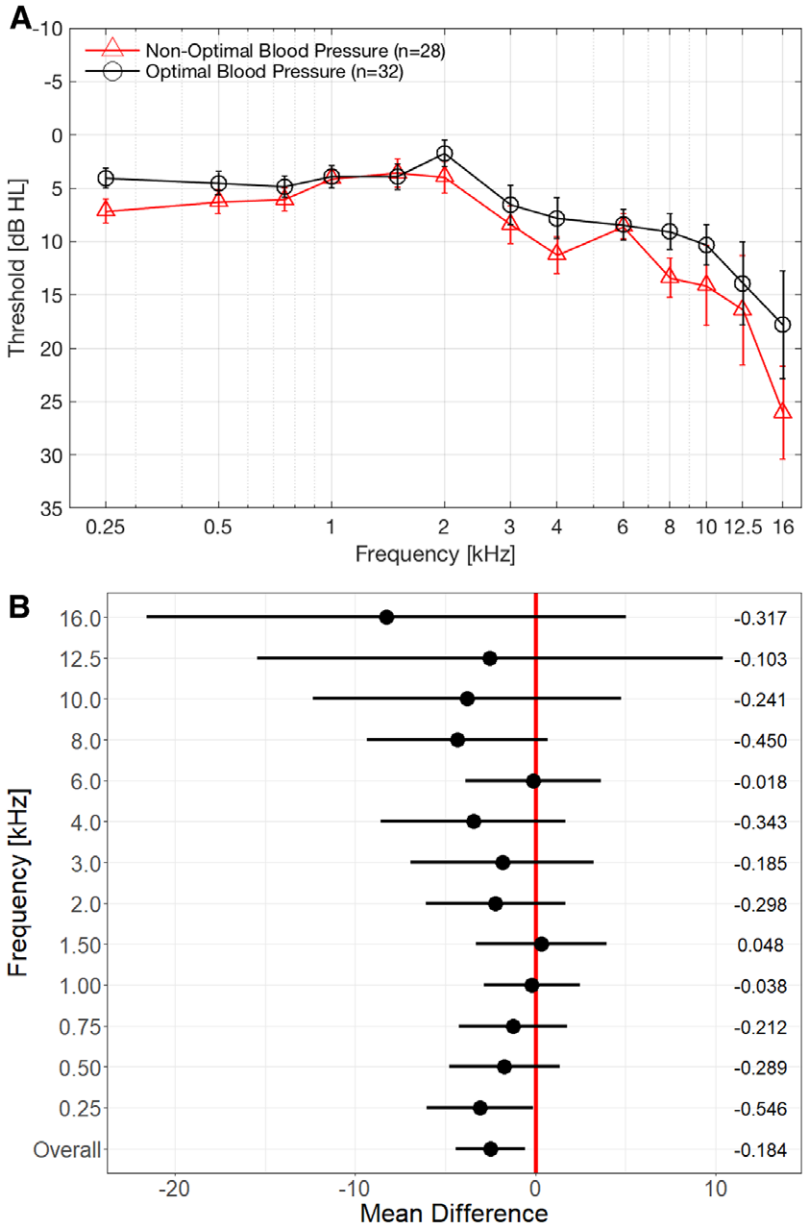

Fig. 1. Behavioral hearing thresholds in the optimal and nonoptimal BP groups. Upper: mean (± SEM) thresholds for test ears for the optimal and nonoptimal BP groups. Thresholds correspond to the randomly selected test ear used for DPOAE testing. Lower: mean (circles) and 95% confidence intervals for the difference in thresholds between groups by frequency. Difference in means computed as optimal BP- nonoptimal BP groups, by frequency. Negative values indicate poorer thresholds in the nonoptimal BP group. Confidence intervals generated using two-sample *t* test statistics. Cohen's *d* effect sizes for each frequency are displayed on the right. DPOAE, distortion product otoacoustic emissions.

to 6.2 kHz and >11.3 kHz. Subjects on antihypertensives had lower DPOAE responses compared to both groups at most frequencies. Owing to the unequal sample sizes, statistical analysis was not performed on these data. Visual inspection suggests that hypertension is associated with reduced cochlear function as evidenced by the reduction in DPOAE amplitudes.

DISCUSSION

Overview

With the estimated prevalence of hypertension at 43 to 48% in U.S. adults (using the new American College of Cardiology/American Heart Association recommendations; Whelton et al. 2018), it is becoming increasingly important to understand the role of adverse cardiometabolic condition plays in hearing health. Yet to date, results of published reports on the relationship between hypertension and hearing loss remain controversial. The current study aimed to investigate the association between BP level and auditory status using both objective and subjective measures of auditory function with a focus on cochlear health. This study is differentiated from earlier work in this area owing to our BP classification scheme (namely, optimal vs. nonoptimal) and the use of high-frequency emission measurements. Initial results indicate that pure-tone thresholds were significantly correlated with diastolic BP (i.e., higher diastolic BP was associated with poorer PTAs) although thresholds at discrete audiometric frequencies were not statistically distinct between the optimal and nonoptimal BP groups with the exception of

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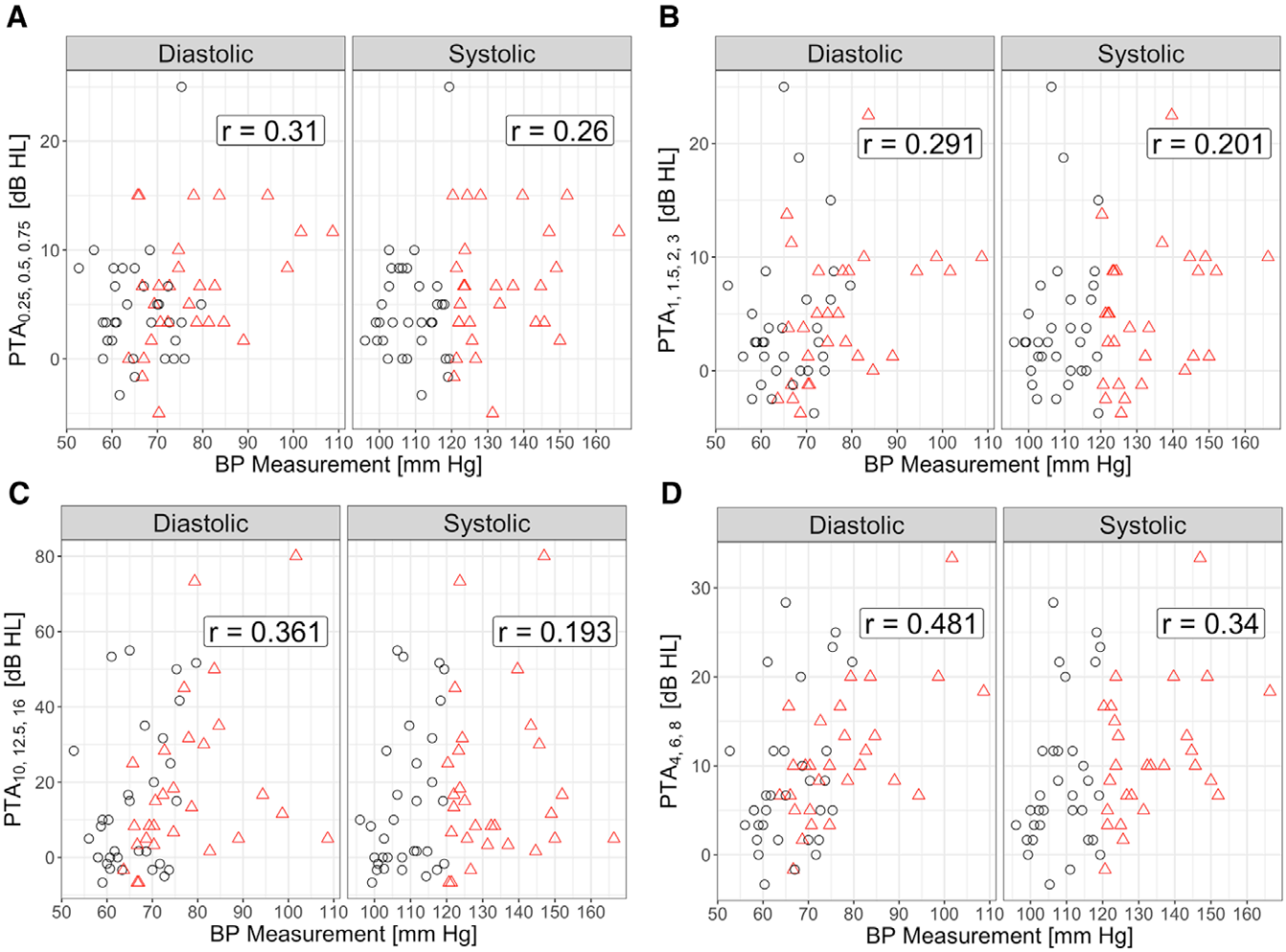

Fig. 2. Correlation plots for the four PTAs vs. diastolic (left) and systolic (right) BP. Open red triangles represent nonoptimal BP and open black circles, optimal BP. Significant correlations were obtained for the relationship between diastolic BP and all four PTAs ($PTA_{0.25, 0.5, 0.75}$, $p = 0.016$; $PTA_{1, 1.5, 2, 3}$, $p = 0.024$; $PTA_{4, 6, 8}$, $p = 0.0001$; $PTA_{10, 12.5, 16}$, $p = 0.005$) and systolic BP and $PTA_{0.25, 0.5, 0.75}$ ($p = 0.044$) and $PTA_{4, 6, 8}$ ($p = 0.008$). Other correlations were not statistically significant.

0.5 kHz. Correlations between systolic BP and thresholds were less consistent with significant correlations observed for $PTA_{0.25, 0.5, 0.75,}$ and $PTA_{4, 6, 8}$. The present study demonstrated that DPOAE amplitudes were correlated with BP level at the high frequencies (f_2 > 10 kHz) such that increasing BP level was correlated with lower (poorer) emission levels. However, after adjustment for confounders, there was not an independent relationship between BP level and behavioral thresholds or BP level and DPOAE amplitudes. Our preliminary data suggest that greater elevation in BP (i.e., stage 2 hypertension) might be associated with reduced cochlear function, which warrants further investigation. Here, we discuss audiological outcomes for individuals with optimal and nonoptimal BP.

On Consideration of Blood Pressure Categorization

BP measurement reveals information about the large arterial system. Specifically, systolic BP is the maximum pressure during cardiac muscle contraction, driving blood through the system, while diastolic BP is the lowest pressure within the large arteries during cardiac relaxation between heartbeats (Shahoud & Aeddula, 2019). Recently, the American College of Cardiology/American Heart Association released updated BP guidelines, lowering the cutpoint for defining hypertension (Whelton et al. 2018). Previously, hypertension was defined as BP ≥ 140/90 mm Hg. With the updated guidelines, BP <120/<80 mm Hg is considered normal and levels above that range are either elevated (systolic BP 120–129 and diastolic BP <80 mm Hg) or stage 1 hypertension (systolic BP 130–139 or diastolic BP 80–89 mm Hg). Higher levels are considered stage 2 hypertension (systolic BP ≥140 or diastolic BP ≥90 mm Hg) and above that, hypertensive crisis. With the new guidelines, age- and sex-adjusted prevalence estimates for hypertension in the U.S.-based on the NHANES data are 43% for women and 48% for men (Whelton et al. 2018). In light of these new recommendations, we were particularly interested in exploring the effects of elevated BP and stage 1 hypertension (as opposed to hypertension per se) on auditory function.

In this study, we dichotomized BP level using an "optimal" versus "nonoptimal" grouping scheme. This approach differs from that used in previous studies, which has primarily been to compare audiological outcomes in persons with hypertension (i.e., systolic BP ≥140 or diastolic BP ≥90 mm Hg or use of antihypertensives) to normotensive individuals (e.g., Agarwal et al.

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TABLE 2. Summary statistics for linear mixed-effects models for behavioral thresholds (in dB HL) for four PTAs

	Estimate	Standard Error	*p*
Model 1: Threshold ~ frequency + group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 1, $PTA_{0.25, 0.5, 0.75}$			
Intercept	3.28	2.29	0.157
Frequency	-1.67×10^{-4}	1.07×10^{-3}	0.876
BP category (optimal)	–1.22	1.50	0.421
Age	0.11	0.06	0.075
Sex (male)	–1.39	1.50	0.358
Model 2: Threshold ~ frequency + group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 1, $PTA_{1, 1.5, 2, 3}$			
Intercept	–6.35	2.41	0.008*
Frequency	1.73×10^{-3}	4.71×10^{-4}	<0.001*
BP category (optimal)	0.53	1.51	0.726
Age	0.27	0.06	<0.001*
Sex (male)	–2.43	1.51	0.114
Model 3: Threshold ~ frequency + group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 1, $PTA_{4, 6, 8}$			
Intercept	–5.10	3.03	0.096
Frequency	4.17×10^{-4}	2.65×10^{-4}	0.119
BP category (optimal)	–0.51	1.74	0.769
Age	0.44	0.07	<0.001*
Sex (male)	–3.19	1.74	0.071
Model 3: Threshold ~ frequency + group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 1, $PTA_{10, 12.5, 16}$			
Intercept	–48.90	6.99	<0.001*
Frequency	1.62×10^{-3}	3.57×10^{-4}	<0.001*
BP category (optimal)	–1.10	3.55	0.759
Age	1.46	0.14	<0.001*
Sex (male)	–3.18	3.55	0.375

*Statistics correspond to data in Figure 1.*Indicates statistically significant at the $p \leq 0.05$ level.BP, blood pressure; PTA, pure-tone average.*

2013). To our knowledge, the current study is the first to evaluate the effects of BP on auditory function using the new American College of Cardiology/American Heart Association guidelines.

Audiometric Findings

In the present study, we observed a significant graded association between diastolic BP and behavioral hearing sensitivity (as measured by four mutually exclusive PTAs), which would initially suggest that elevated BP, and more specifically, diastolic BP, is negatively associated with audiometric thresholds. However, additional analysis indicated potential confounders such as age and sex may underlie these relationships. Interestingly, in a longitudinal study that tracked variations in BP and hearing, systolic (but not diastolic) BP variability was associated with hearing loss in adjusted models (Bao et al. 2019). An elegant physiological explanation for the discrepant systolic and diastolic BP findings is not entirely clear. Systolic BP increases linearly from ages 30 to 84 years whereas diastolic BP peaks at ~50 years of age and falls thereafter, an observation most likely due to increased stiffening of large arteries (Franklin et al. 1997). Further investigation of the causal relationship between large artery stiffening and cochlear microcirculation might clarify this issue.

Our in-depth analysis using linear mixed-effects modeling demonstrated that the effect of age was more predictive of a threshold than BP category. Comparison to previous reports is limited as prior studies have typically explored the effects of hypertension as a binary predictor on hearing as we discuss in greater detail below. Multiple population-based studies have identified significant associations between high BP and hearing loss (e.g., Agrawal et al. 2008; Sun et al. 2015; Tan et al. 2018). The NHANES showed that among 3527 persons aged 20 to 69 years, those with hypertension (defined as BP ≥140/90 mm Hg) had significantly poorer audiometric thresholds than normotensive individuals, but only at 1 kHz (Agrawal et al. 2009). Sun et al. also evaluated the effects of elevated BP (defined as systolic BP ≥130 or diastolic ≥85 mm Hg) on hearing in 2100 subjects ≤65 years old using the NHANES dataset. They reported a significant association between low-frequency hearing loss and high BP in a fully adjusted model accounting for age, sex, smoking status, diabetes, and other potential confounders. Tan et al. (2018) evaluated the effects of multiple cardiovascular disease risk factors, including hypertension, on hearing in 5107 subjects from the Busselton Healthy Ageing Study. Hypertension (BP ≥ 140/90 mm Hg or medication use) was significantly associated with low frequency (0.25–1 kHz) hearing loss. Last, in a recent study of 13,475 Japanese individuals, Umesawa et al. (2019) found a significant association between prevalent hearing loss and hypertension (BP ≥140/90 mm Hg) even after adjustment for multiple confounders (e.g., age, sex, smoking, and diabetes). Hearing data were limited to 1 and 4 kHz and based on screening cutoffs and therefore thresholds were not reported. In their study, 2.7% of normotensive individuals had hearing loss vs. 5.2% of hypertension persons at 1 kHz. Similarly, the percentage of hypertensive persons with hearing loss was lower than the percentage of normotensive persons with hearing loss at 4 kHz (8.7% vs. 5.0%). Conversely, others have not observed significant associations between hypertension and hearing loss (Zhan et al. 2011; Cruickshanks et al. 2015a). Taken together, population-based studies remained mixed regarding this association perhaps owing to differing methodological and/or statistical approaches.

Smaller clinical studies further elucidate the BP-hearing loss relationship. Agarwal et al. (2013) evaluated behavioral thresholds from 0.25 to 8 kHz in a case-control study of persons aged 45 to 64 years. Their results suggested that as hypertension severity increased, pure-tone thresholds increased (worsened). However, their study did not statistically account for the effects of sex or age. Another study examined 32 hypertensive patients and 32 age- and sex-matched controls and found significantly poorer hearing thresholds in the hypertensive group at almost all frequencies from 0.125 to 12.5 kHz (Przewoźny et al. 2016). Differences were most striking at high frequencies. In the current study, we also observed greater between-group disparities (i.e., larger effect sizes) in behavioral thresholds at higher frequencies (namely ≥8 kHz) although the differences were not statistically significant. We observed an average pooled threshold difference (for frequencies from 0.25 to 16 kHz) of <5 dB. In contrast, the difference in Przewoźny et al.'s study was ~12 dB (for frequencies from 0.125 to 12.5 kHz). A comparison of the two studies reveals that our subjects have slightly lower (better) BP. Average systolic BPs were similar (±1 mm Hg) although the subjects in our study had lower diastolic BP by

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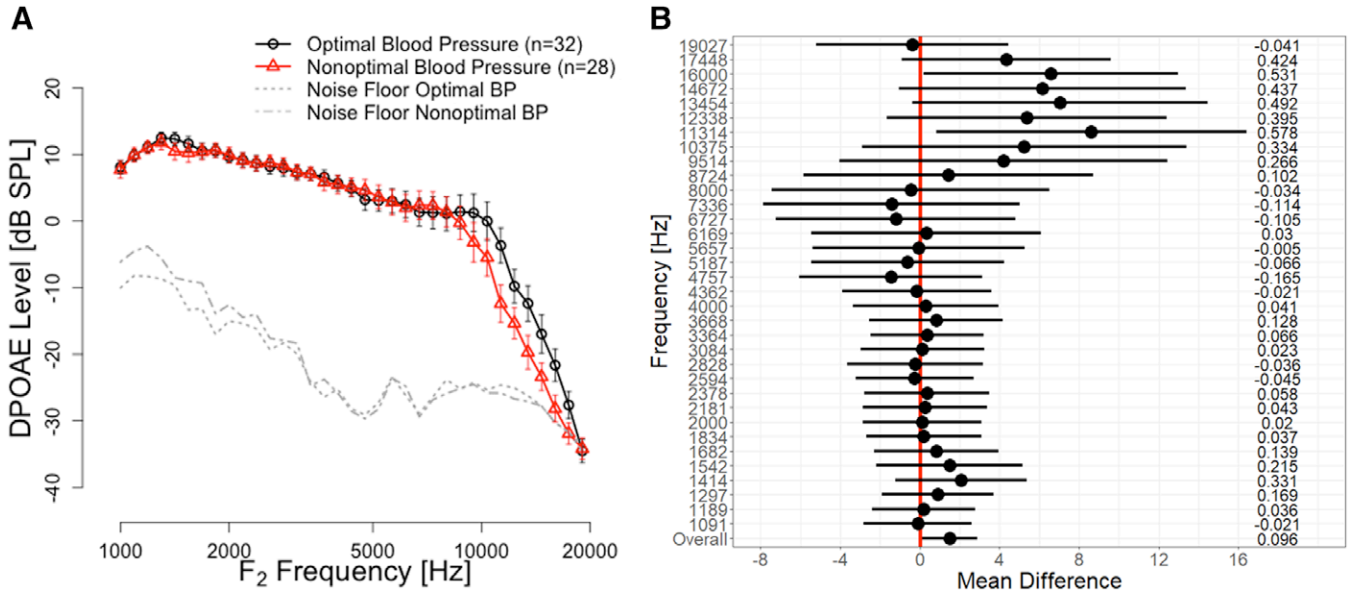

Fig. 3. DPOAE responses in optimal and nonoptimal BP groups. Stimulus levels are L_1/L_2 = 65/55 dB SPL. Left: mean (± SEM) DPOAE level vs. f_2 for optimal (black circles) and nonoptimal BP (red triangles) groups. Right: mean (circles) and 95% confidence intervals for the difference in DPOAE levels between groups by frequency. Cohen's *d* effect sizes indicated at right. Differences in means computed as optimal BP – nonoptimal BP; positive values indicate poorer responses in the nonoptimal group. At the highest f_2 frequencies (>14.6 kHz), there was an insufficient number of observations (after accounting for noisiness in the dataset) to accurately compute effect sizes. Noise floors indicated by gray dashed lines. DPOAE, distortion product otoacoustic emissions.

TABLE 3. Summary statistics for linear mixed effects models for DPOAE level (in dB SPL) for three frequency bins

	Estimate	Standard Error	*p*
Model 1: DPOAE level ~ f_2 + group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 3, low frequencies (f_2 1–2 kHz)			
Intercept	16.33	2.15	<0.001*
F_2 frequency	-9.57×10^{-4}	5.24×10^{-4}	0.069
BP category (optimal)	–0.63	1.36	0.644
Age	–0.15	0.05	0.009*
Sex (female)	2.16	1.36	0.119
Model 2: DPOAE level ~ f_2 + Group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 3, mid frequencies (f_2 > 2 to 10 kHz)			
Intercept	23.60	2.44	<0.001*
F_2 frequency	-1.34×10^{-3}	8.42×10^{-5}	<0.001*
BP category (optimal)	–2.81	1.64	0.092
Age	–0.41	0.07	<0.001*
Sex (female)	5.05	1.64	0.003*
Model 3: DPOAE level ~ f_2 + group (optimal vs. nonoptimal BP) + age + sex + (1 | subject)			
Figure 3, high frequencies (f_2 hearing 10 kHz)			
Intercept	45.56	4.26	<0.001*
F_2 frequency	-3.59×10^{-3}	1.28×10^{-4}	<0.001*
BP category (optimal)	1.58	2.62	0.548
Age	–0.52	0.10	<0.001*
Sex (female)	6.56	2.62	0.015*

*Stimulus levels were L_1/L_2 = 65/55 dB SPL. Statistics correspond to data in Figure 3.*Indicates statistically significant at the p ≤ 0.05 level.BP, blood pressure; DPOAE, distortion product otoacoustic emissions.*

6.55 mm Hg. A difference in subject age, which was ~20 years, might explain the discrepancy between our study and Przewoźny et al.'s report.

One possible explanation for the somewhat conflicting findings between previous reports and our study is the differing definitions of high BP. For example, Przewoźny et al., (2016) used the European Society of Hypertension/European Society of Cardiology guidelines (Mancia et al., 2013) and Agarwal et al. (2013), the World Health Organization classification, both of which establish BP cutpoints higher than what we used to define nonoptimal BP here. Moreover, both Przewoźny et al. (2016) and Agarwal et al. (2013) studied older subjects (mean age ~53 years and range of 45–64 years, respectively) and therefore, duration of hypertension for a given subject was likely longer in those studies compared to ours, as our average subject age was closer to 30 years. It is possible that BP has a negligible influence on hearing for younger persons but plays a larger role with increased age.

Overall, in terms of behavioral hearing sensitivity, our work primarily supports past reports that have not identified a significant effect of BP on hearing sensitivity (Zhan et al. 2011; Cruickshanks et al. 2015a). The possibility remains that greater elevation in BP (i.e., stage 2 hypertension) would have a more pronounced effect on hearing sensitivity, making this an area for future investigation.

The Relationship Between Cochlear Function and Hypertension

The current study contributes to the limited body of literature concerning cochlear function and BP status. To our knowledge, there is only one population-based study that has explored this association using OAEs. In a study of 1501 subjects from the Epidemiology of Hearing Loss Study, hypertension was not associated with cochlear function as measured by DPOAEs from

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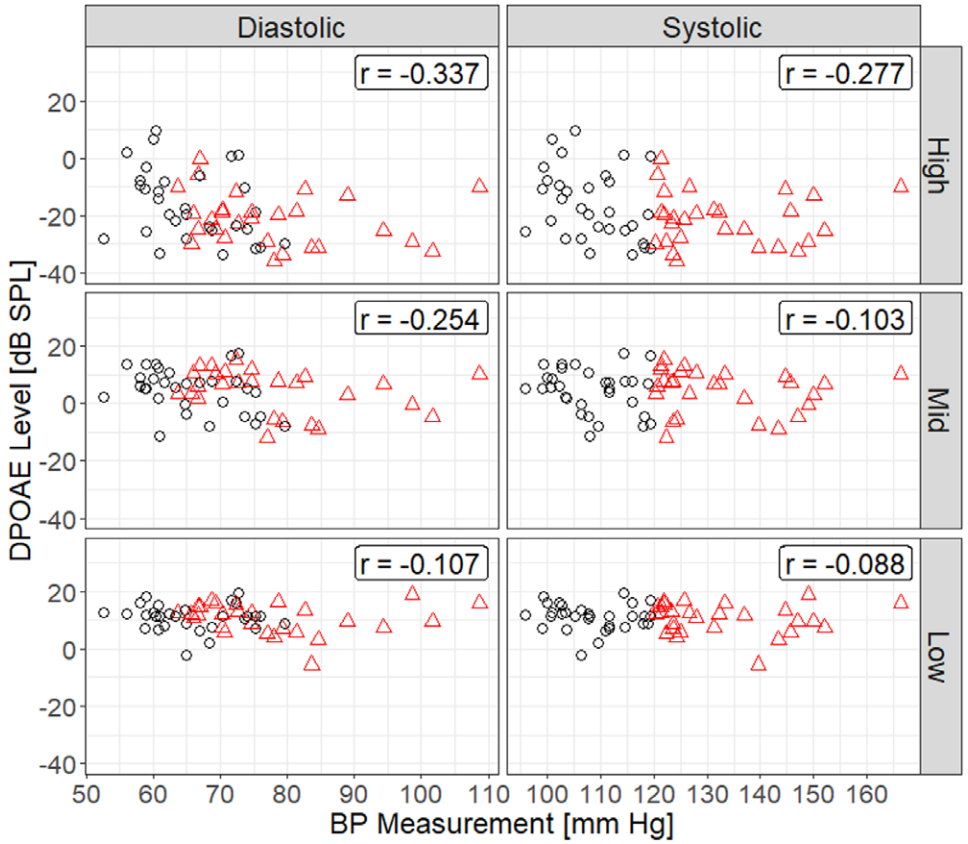

Fig. 4. Correlations between DPOAE and BP levels. The left panels represent diastolic BP and the right, systolic BP levels. DPOAE data were averaged within a bin for three f_2 frequency ranges: low (≤2 kHz), mid (>2 and ≤10 kHz), and high (>10 kHz). Negative correlation coefficients indicate lower (poorer) DPOAE levels as systolic or diastolic BP increases (worsens). Significant correlations were obtained for the relationship between diastolic BP and DPOAE level (p = 0.009) and systolic BP and DPOAE level (p = 0.034) at the high frequencies. Black circles represent optimal BP and red triangles represent nonoptimal BP. DPOAE, distortion product otoacoustic emissions.

1 to 8 kHz (Torre et al. 2005). However, emission measurements were limited to f_2 of 8 kHz. In the present study, the most apparent difference in DPOAE amplitudes between the optimal and nonoptimal BP groups emerged in the high frequencies (i.e., >10 kHz).

Przewoźny et al. (2016) evaluated DPOAEs (0.75–8 kHz) finding maximum between-group differences at 4 and 6 kHz. Although they excluded individuals with excessive occupational noise exposure, statistical analyses did not account for other sources of noise. Here, in contrast to Przewoźny et al., we observed the greatest difference in DPOAE amplitudes above 10 kHz and differences between 4 and 6 kHz were negligible. Soares et al. (2016) conducted a smaller clinical study using similar tests of auditory function as the current study including pure-tone audiometry from 0.25 kHz to 16 kHz and OAEs (both transient evoked and DPOAEs). Audiological data were collected from 40 individuals, including 20 patients with arterial hypertension. Behavioral thresholds were similar between hypertensive and normotensive groups. However, significantly lower (poorer) DPOAE amplitudes were observed at ~1.5, 2, and 3 kHz in the hypertensive group. Our comparison of emission levels between individuals with and without hypertension (i.e., systolic BP ≥140 or diastolic BP ≥ 90 mm Hg or use of antihypertensives) revealed visibly reduced emission amplitudes in hypertensive subjects, particularly for individuals on medication (Fig. 5). Pyykkö et al. (1989) identified a positive correlation between hearing loss and use of antihypertensives suggesting the possibility that some antihypertensives are ototoxic and/or that patients on medication have reached a more severe hypertensive state and thus, experience more negative auditory outcomes. Taken together, our preliminary data support the possibility that outer hair cell function, as assayed by DPOAEs, might be negatively affected by adverse BP levels, particularly once a state of hypertension is reached. Our data also suggest that DPOAEs are a valuable tool for future investigations. Additional human studies are warranted to better understand this association.

A detailed mechanistic explanation linking hypertension to sensorineural hearing loss is lacking. Blood flow to the inner ear is chiefly supplied by the labyrinthine artery (Makino & Morimitsu 1994). Hypertension occurs when pressure exerted against the arteries is elevated. It follows that blood vessels are vasoconstricted and blood flow to the cochlea reduced. Some have postulated that hypertension can lead to hearing loss due to this reduction in cochlear blood flow (for review, see Przewoźny et al. 2015). The inner ear depends on oxidative metabolism; consequently, when oxygen supply to the cochlea is compromised, auditory function may be compromised as well (Nakashima et al. 2003). Interestingly, previous reports suggest that hypotension (i.e., low BP) might also be associated with cochlear dysfunction (Balatsouras et al. 2003) as well as sudden sensorineural hearing loss (Pirodda et al. 1997; 2001) although there are few studies on the topic. An important caveat lies in

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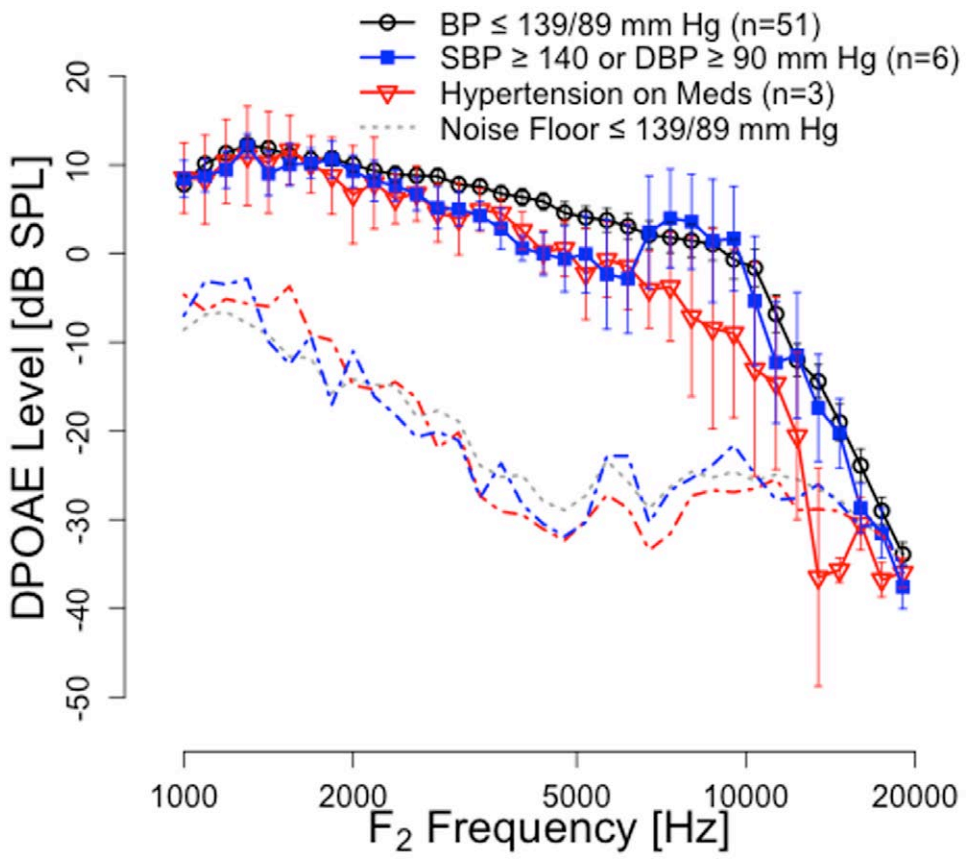

Fig. 5. DPOAE responses in subjects with untreated hypertension (red), on antihypertensives ("on Meds", blue), and without hypertension (black). Compared with those without hypertension, subjects with untreated hypertension had lower (poorer) DPOAE amplitudes from ~2 to 6.2 kHz and above 11.3 kHz. Subjects on antihypertensives had lower DPOAE responses compared with both groups at most frequencies. Axes as in as Figure 3. Statistical analysis not performed. DPOAE, distortion product otoacoustic emissions; DBP, diastolic blood pressure; SBP, systolic blood pressure.

the definition of hypotension. Pirodda et al. defined hypotension as systolic BP <105 and/or diastolic BP <60 mm Hg, a conservative estimate compared to the systolic BP <90 and/or diastolic BP <60 mm Hg criteria frequently applied in clinical practice (Sharma et al. 2020). According to the latter criteria, no subject in our study met the systolic BP cutoff although 12% would be classified as having diastolic hypotension. Nevertheless, it should be noted that the symptomology of orthostatic hypotension, the most common form of hypotension, is often vague and clinical criteria are not widely agreed upon (as discussed in Tzur et al. 2019). Furthermore, the present study was not designed to identify orthostatic hypotension (which requires BP measurements upon postural change) or to explore associations between hypotension and auditory function. Other reports suggest this may be a fruitful avenue for future study particularly in regard to "idiopathic" sudden sensorineural hearing loss.

Generation of the spontaneously hypertensive rat model (Okamoto 1969) has improved our understanding of potential pathophysiology. Electromicroscopic studies have shown that cochlear structures particularly vulnerable to reduced blood flow include the stria vascularis and organ of Corti (Tachibana et al. 1984). This work also revealed that cochlear function decreased to a greater extent in aged spontaneously hypertensive rats compared to aged control (normotensive) animals. In contrast to normotensive animals, rats with chronic hypertension have significant endocochlear potential reduction (Mosnier et al. 2001), which should theoretically result in DPOAE amplitude reduction. Last, hypertension may increase noise susceptibility, as suggested by Borg's (1982) experiment in which spontaneously hypertensive rats exposed to 100 dB L_{eq} noise for 10 hr/day had significantly greater hair cell loss compared to normotensive noise-exposed animals. The interaction between hypertension and noise exposure might be evaluated in future studies.

Limitations and Future Directions

This study has a number of strengths including audiometric and DPOAE measurements at extended high frequencies. Moreover, the critical evaluation of auditory status in persons with nonoptimal BP is timely in light of the American College of Cardiology/American Heart Association new BP guidelines. Some limitations must also be discussed. One limitation is that some potential confounders were not statistically accounted for (e.g., obesity and exercise). However, there was not a significant difference in the number of smokers in the optimal and nonoptimal BP group ($n = 3$ and 6, respectively, $p = 0.281$) and supplemental DPOAE analysis including smoking in a linear mixed-effects model did not alter our conclusions, making tobacco smoking an unlikely explanation for the present findings. Furthermore, this study is cross-sectional in design, and therefore, a cause-effect relationship can neither be determined nor inferred. Prospective studies offer insight into potential causality. One prospective study of ~3500 subjects found that hypertension was not associated with

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incident hearing loss in men (Shargorodsky et al. 2010). In contrast, a longitudinal study of 54,721 women from the Nurses' Health Study found a modest, but significantly increased risk of hearing loss in women with hypertension with an incidence rate of 25 cases per 1000 person-years (Lin et al. 2016). The Rotterdam Study demonstrated the 4-year progression of hearing loss was not affected by systolic BP level in 675 older adults (mean age ~71 years; Rigters et al. 2018). Further investigation of the association between hypertension and hearing loss in older adults (>55 years) is warranted. To date, there are no published longitudinal reports of cochlear function in persons with hypertension. Such future studies might incorporate DPOAE measurements and evaluate the effect of hypertension treatment on emission levels and incident hearing loss. Future studies might extend our findings by comparing OAEs in persons with optimal BP to those with hypertension, which is where we observed the greatest differences in emission amplitudes (Fig. 5). Last, study of other emission types could add valuable contributions to the literature regarding cochlear function in persons with hypertension. Early investigation of spontaneous OAEs (SOAEs) suggests a possible correlation between BP variation and change in SOAE frequency (Bell 1992). Reports have also linked objective pulsatile tinnitus to benign intracranial hypertension (Sismanis et al. 1990) although the presence of SOAEs was not probed in their study. Tinnitus in persons with hypertension could be related to the use of antihypertensive drugs, some of which (e.g., ethacrynic acid or furosemide) can be ototoxic (Bisht & Bist, 2011). The transient effect of drugs, including anesthetics, on cochlear micromechanics, has been an area of recent focus. One recent study demonstrated that beta-1 receptor blocker esmolol transiently reduced DPOAE levels during surgery (Gökahmetoğlu et al. 2020). Similarly, dexmedetomidine (a highly selective α2-adrenergic receptor) reduced DPOAE amplitudes postoperatively (Şahin et al. 2019). The implications for acute or long-term cochlear micromechanical dysfunction in medicated patients are unclear as esmolol is short-acting and not used for hypertension treatment outside of hypertensive crisis (Pevtsov et al. 2020). More work is needed to explore the potential consequences of standard hypertensive treatment on cochlear integrity.

CONCLUSIONS

Despite the high prevalence of hypertension in the U.S.—it remains a leading chronic condition (Collins 1997)—our understanding of its effects on auditory function remains incomplete. By considering behavioral and physiological measures of auditory status, we took a more holistic approach to exploring this connection than previous reports. Our deliberate inclusion of subjects with elevated BP who were not yet hypertensive permitted exploration of the effects of subtle BP elevation on cochlear integrity. Our data suggest that nonoptimal BP, and more specifically hypertension itself, may be associated with adverse cochlear health even though behavioral hearing sensitivity was not significantly different between the BP groups. Additional research is needed to illuminate the complex relationship between BP and cochlear function, particularly in older adults, and to explore differential effects of systolic BP and diastolic BP elevation on auditory function. Given the frequent comorbid presentation of hearing loss and hypertension and studies demonstrating cochlear pathology in hypertensive animals, the association between high BP and cochlear integrity should be further evaluated. We believe that DPOAEs may be a viable and clinically available tool for such future work.

ACKNOWLEDGMENTS

The authors wish to acknowledge Dr. Shawn Goodman for providing the software (ARLas) used to collect and analyze the DPOAE data. Gratitude is also owed to Mr. Shashidhar Prabhu for assistance with DPOAE calibration and MATLAB code and to Ms. Kailey Durkin, Ms. Jennifer Masters, and Mrs. Sarah Mullervy for collecting data for these experiments. The authors would also like to thank the participants for graciously donating their time to this study.

This study was funded by an Emerging Research Grant (Hearing Health Foundation) to R.R.B. Medical data (including blood pressure measurements) were collected by the Colorado Clinical and Translational Research Center, which is supported in part by Colorado CTSA Grant UL1 TR002535 from NIH/NCATS.

These data were presented, in part, at the American Auditory Society Meeting in Scottsdale, Arizona (February 2019).

The authors have no conflicts of interest to disclose.

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Received February 14, 2020; accepted June 26, 2020.

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