Audiometric Pattern as a Predictor of Cardiovascular Status: Development of a Model for Assessment of Risk

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Objectives/Hypothesis: This study hypothesizes that low-frequency hearing loss is associated with underlying cardiovascular disease. The objective of this study was to use a mathematical model of hearing thresholds to predict cardiovascular status.

Study Design: Logistic regression analyses of audiometric and cardiovascular data obtained through retrospective chart review. Application of a derived mathematical formula to a distinct prospectively enrolled cohort.

Methods: Cardiovascular status was determined for a cohort of 1,168 patients seen in the audiology division. Associations between audiogram pattern and cardiovascular variables were tested with the Mantel-Haenszel statistic controlling for age and gender. Logistic regression models were developed incorporating cardiovascular risk factors and audiogram pattern. The models were applied to a separate cohort of 90 subjects recruited from cardiology and geriatric medicine clinics in whom audiograms were performed.

Results: A significant association was found between low-frequency hearing loss and cardiovascular disease and risk factors. When controlling for age, hypertension, diabetes, smoking, and hyperlipidemia, low-frequency presbycusis was significantly associated with intracranial vascular pathology such as stroke and transient ischemic attacks. Significant associations were also seen with peripheral vascular disease, coronary artery disease, and a history of myocardial infarction. A mathematical formula using audiometric pattern and medical history to predict the probability of cardiovascular diseases and events was developed and tested.

Conclusions: Audiogram pattern correlates strongly with cerebrovascular and peripheral arterial disease and may represent a screening test for those at risk. Patients with low-frequency hearing loss should be regarded as at risk for cardiovascular events, and appropriate referrals should be considered.

Key Words: Cardiovascular, hearing loss, audiogram, stria vascularis, presbycusis.

INTRODUCTION

Cardiovascular disease, notably coronary heart disease and stroke, accounts for 30% of all deaths worldwide. Early intervention and treatment of these disorders and their risk factors are credited with recent declines in incidence, but further advances are needed. Ideally, a simple, reproducible, and sensitive marker for cardiovascular disease could improve detection and promote early intervention before the onset of significant organ compromise. Further, a sensitive marker of impending coronary vascular or cerebrovascular events can promote aggressive therapies to stave off these morbid attacks.

Recent guidelines place an emphasis on defining total cardiovascular risk in patients and cite the importance of identifying target organ damage as an indicator of vascular disease. Most important is the identification of subclinical organ damage, as organ damage places the patient at increased risk beyond that due to the simple presence of a risk factor. Hypertensive organ damage defined by current guidelines can occur in the heart, arteries, brain, kidneys, or eyes. Hearing thresholds, or any form of compromise in the auditory system, are not mentioned nor currently recognized as evidence of organ damage due to cardiovascular disease. This study evaluates the relationship between audiometric pattern and the presence of cardiovascular disease.

Presbycusis

Presbycusis, or presbyacusis, is the gradual loss of hearing that occurs with aging. It is typically a bilaterally symmetric phenomenon and is influenced by genetics,
environmental noise and exposures, and systemic disease. The classic characterization of presbycusis was developed by Schuknecht, who correlated audiometric patterns with cochlea histopathology. The Schuknecht classification, as a general template for age-related hearing loss, has been validated through further investigation. The presbycusis patterns include strial, cochlear conductive, sensory, and neural hearing losses.

Presbycusis is typically the result of degeneration within the cochlea, most commonly to outer hair cells but also to inner hair cells, spiral ganglion neurons, or the stria vascularis. According to Schuknecht, sensory presbycusis reflects loss of hair cells at the base of the cochlea. This causes a high-frequency sloping hearing loss with relatively preserved speech discrimination. Neural presbycusis shows a similar high-frequency down-sloping audiometric pattern, but is associated with poorer speech discrimination. This form of presbycusis involves the auditory nerve fibers and degeneration of spiral ganglion cells. Sensory presbycusis and neural presbycusis are often combined to denote age-related senosorineural hearing loss. This article refers to this pattern as high-sloping presbycusis. Cochlear conductive presbycusis shows a hearing loss that begins to encroach upon the middle frequencies with variable speech discrimination. Anatomic changes at the basilar membrane of the cochlea have been observed with this loss. This pattern is referred to herein as mid-sloping presbycusis.

Strial presbycusis is a distinct class of age-related hearing loss described by Schuknecht. The characteristic feature of strial presbycusis is the involvement of all frequencies, creating a flattened appearance on audiogram. This pattern is histologically correlated with degeneration within the stria vascularis, although reports are variable. As described below, strial hearing loss reflects a reduced endocochlear potential, but with an intact sensory system. As such, word discrimination is commonly better than expected for the threshold of hearing. Predisposition for the strial pattern appears to be related to cardiovascular disease and may also have a genetic and gender-specific predisposition.

This study investigates strial presbycusis as an early sign of underlying cardiovascular disease.

**Stria Vascularis**

The stria vascularis, in the lateral wall of the cochlea, is critical for establishing the endocochlear potential necessary for the propagation of auditory signals to the central nervous system. The stria vascularis is a capillary-rich structure fed by radial branches of the spiral modiolar artery. Arteries feeding the stria vascularis are terminal vessels with no anastomoses to supplement flow or accommodate for spasm or occlusion. Additionally, the strial capillary network is relatively sparse at the apex when compared with the dense organization at the base. These anatomical features leave the apical cochlea exquisitely sensitive to ischemia. A reduction in endocochlear potential and clinically significant hearing loss occurs almost immediately after vascular occlusion or anoxia. The central hypothesis of this study is that the vascular anatomy of the stria at the cochlear apex (low frequencies) establishes this area as a sensitive marker for systemic cardiovascular disease.

**MATERIALS AND METHODS**

All chart reviews, data collection, and audiometric measures were approved by the institutional review board for the Medical College of Wisconsin and Froedtert Hospital. A model for the prediction of cardiovascular risk was developed by analyzing a cohort of 1,168 patients referred for audiological assessment whose medical charts were reviewed retrospectively (cohort 1). The model was secondarily applied to a separate cross-sectional cohort of 90 patients with well-defined cardiovascular histories upon whom audiometric testing was performed (cohort 2).

**Cohort 1: Analysis of Associations and Development of a Predictive Model**

**Audiogram definitions.** Audiograms performed over a 5-year period were reviewed for pattern of hearing loss. Asymmetric hearing losses (>15 dB normal hearing level [nHL] difference between ears over three consecutive frequencies) and conductive hearing losses were excluded. There were 1,168 audiograms included for which five distinct patterns were mathematically defined (Fig. 1). Normal hearing was defined as a hearing level of ≤25 dB nHL averaged across frequencies 500 Hz to 8 kHz. For the remaining subjects with hearing loss, levels of loss were determined for low frequencies (i.e., 500 Hz to 2 kHz), middle frequencies (i.e., 2 kHz to 4 kHz), and high frequencies (i.e., 4 kHz to 8 kHz). Further, the variability of the audiogram pattern within those ranges was determined. If the variability between lowest and highest frequency in the range was >15 dB, it was considered sloping. A variability of ≤15 dB was considered flat.

Four hearing loss categories were defined: 1) Strial: ≥25 dB hearing loss between 500 Hz and 2 kHz with ≤15 dB variability; 2) Low-sloping: ≥25 dB hearing loss between 500 Hz and 2 kHz with >15 dB variability; 3) Mid-sloping: ≥25 dB hearing loss between 2 kHz and 4 kHz with >15 dB variability and normal thresholds at lower frequencies; and 4) High-sloping: ≥25 dB hearing loss between 4 kHz and 8 kHz with >15 dB variability and normal thresholds at lower frequencies. The average audiometric patterns for all 1,168 subjects for left and right ears are depicted in Figure 2.

**Demographics and medical history.** Medical records were reviewed for all subjects, and demographic data were recorded for age and gender. Cardiovascular status was recorded and categorized into risk factors, events, and interventions (Fig. 3). These categories defined the variables of interest for statistical analyses. Risk factors included five binary variables: hypertension (variable = HTN), diabetes mellitus (DM), hyperlipidemia/cholesterolemia (LIPIDS), age ≥75 years (AGE≥75), and a history of smoking (SMOKING). Events included myocardial infarction (MI), diagnosis of coronary artery disease (CAD), stroke (CVA), transient ischemic attack (TIA), and claudication (CLAUDICATION). Interventions included coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), and peripheral artery bypass surgery. The latter intervention was dropped from analyses due to a small number of peripheral bypass surgeries among the 1,168 subjects. Umbrella categories were defined for coronary vascular disease, cerebrovascular disease, and peripheral vascular disease. Inclusion in any of these qualified a subject as having overall cardiovascular disease.

**Statistical analyses.** Data from cohort 1 were used to investigate an association between audiometric pattern and
cardiovascular status. The presence of an association between cardiovascular variables and audiometric patterns was tested with a chi-square test based on a $2 \times 5$ contingency table. In the presence of small cell counts (i.e., $<5$) the chi-square test was substituted by the Fisher exact test. Results were considered significant at $P < .05$. Odds ratios and confidence intervals were calculated for significant associations. Associations between the strial audiometric pattern and cardiovascular variables were further tested with the Mantel-Haenszel statistic controlling for age and, in a separate analysis, for gender. Adjusted odds ratios for age and gender were calculated.

After the above exploratory analyses, which lacked a focus on controlling for family-wide false discovery rates, attention was turned toward building a multipredictor model. Logistic regressions were performed incorporating risk factors of $\text{AGE}\geq75$, HTN, DM, LIPIDS, and SMOKING. The optimal cutoff of 75 years was found to define the highest (among other cutoff ages) likelihood in the logistic regression model. Audiogram pattern was defined as a variable AUDIOGRAM and forced into the logistic regression model. Thus, effects of different audiogram patterns on cardiovascular variables could be compared with the normal hearing pattern, and among themselves, controlling for age, hypertension, diabetes, hyperlipidemia, and smoking status.

A second logistic regression model was generated in which we looked solely at the contribution of low-frequency hearing loss (LFHL) to cardiovascular risk. Two analyses were performed in which a threshold of $>25$ dB nHL at frequencies 250 Hz to 1 kHz and 500 Hz to 2 kHz in either ear was considered a low-frequency loss. All other subjects, regardless of other hearing loss pattern, were placed in the null category. Variables of $\text{AGE}\geq75$, HTN, DM, LIPIDS, and SMOKING were included. Both regression models were applied to the cardiovascular categories of MI, CAD, CVA, TIA, CABG, PTCA, and PVD.

Fig. 1. Algorithm for mathematically defining five distinct patterns of audiogram based on thresholds in the low, middle, and high frequencies. These five reproducible patterns were termed strial, low-sloping, mid-sloping, high-sloping, and normal.

Fig. 2. The average audiometric pattern for the five categories defined in cohort 1. Left and right ears are depicted along with standard deviations for each frequency and threshold.

Fig. 3. The cardiovascular variables used in data analysis of cohort 1. These variables were used in the regression model correlating audiometric pattern with cardiovascular disease.
The logistic regression models were internally validated using the bootstrap method. We performed 500 iterations and calculated area under the receiver operating characteristic (ROC) curve with associated standard deviation. Bootstrap bias and bootstrap standard deviation were considered as measures of internal validity for the area under the ROC curve calculated on the whole cohort 1 dataset of 1,168 patients.

Cohort 2: Application of the Logistic Regression Model

Recruitment and demographics. Cohort 2 consisted of subjects in whom a cardiovascular history was obtained who were subsequently prospectively audiometrically tested. Cohort 2 subjects were recruited from cardiology, geriatric, and internist was also excluded. Questionnaires regarding cardiovascular history and status were completed by subjects. These surveys specifically asked for the presence or history of all cardiovascular variables assessed in cohort 1. Responses to history questions were secondarily validated by review of the medical record.

Audiological testing. Audiograms were performed on 90 subjects who completed the cardiovascular questionnaire. Audiograms were performed in a double-walled soundproof booth meeting American National Standards Institute specifications (ANSI S3.6-2004). Current American Speech-Language-Hearing Association guidelines for Pure-Tone Threshold Audiometry were employed to test subjects for this study. Signals were generated by the ANSI-compliant Aurical AudioDiagnostic Fitting System audiometer manufactured by Madsen, GN Otometrics (Copenhagen, Denmark). For air-conduction testing, the electrical signal generated by the audiometer was coupled with E-A-R® TONE 5A Insert Earphones (E-A-R Auditory Systems, Indianapolis, IN). For bone conduction testing, the audiometer was coupled to a Radiseer B-71 bone-conduction vibrator (New Eagle, PA).

For the audiometric test procedures, the subject was seated in the examination room of the sound booth in a chair at an angle so as not to infer any cues from the tester. Insert earphones were placed in the ear canals for air-conduction threshold testing, and the bone-conduction vibrator was placed on the subject's mastoid bone for bone conduction threshold testing. Octave frequency and interoctave frequencies were tested (250, 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz). For a given frequency, pulsed pure tone signals were presented at decreasing intensity levels until threshold was determined. A threshold measurement was recorded when two responses of three presentations were noted at a single level. Statistical analyses. All audiogram thresholds were mathematically filtered through Excel spreadsheet macros to identify one of the five patterns defined in cohort 1. Audiograms not fitting any pattern by objective mathematical modeling were classified as "other." These six categories (i.e., strial, low-sloping, mid-sloping, high-sloping, normal, and other) were assessed for association with cardiovascular status, including MI, CAD, CVA, TIA, CABG, PTCA, and CLAUDICATION. In addition, audiograms were filtered for low-frequency hearing loss in either ear at frequencies from 250 Hz to 1 kHz. The logistic regression models developed for AUDIOMETER and LFHL were applied to this cohort. Probabilities for the presence of each cardiovascular variable were calculated using the logistic regression function and descriptively analyzed with respect to the actual cardiovascular status of the subject.

RESULTS

Demographics: Cohort 1

There were 1,168 subjects with complete medical histories and audiogram patterns meeting the inclusion criterion. The average subject age was 67.5 years (standard deviation ± 12.7; range, 34-98). There were 499 men and 669 women. Hearing loss patterns were defined as "presbycusis" rather than simply hearing loss to reflect the average age of the cohort and the absence of significant otologic histories. There were 251 patients with a strial pattern, 205 with low-sloping presbycusis, 358 with mid-sloping presbycusis, 168 with high-sloping presbycusis, and 186 normal audiograms (Fig. 1). Consistent with previous findings, the ratio of female subjects to male subjects was higher with the strial pattern than in the overall cohort. This was also true for high-sloping losses and those with normal hearing. The distribution of audiogram patterns for this cohort, however, is not reflective of the general population, as a large enough sample size in each group was intentionally chosen to allow for statistically significant analyses.

Cardiovascular status was determined from a retrospective chart review. There were 316 patients with overall cardiovascular disease. Coronary vascular disease was present in 237, with 230 having CAD, 98 having had an MI, 78 having had a CABG, and 76 having had PTCA. There were also 137 patients with cerebrovascular disease, of whom 111 had a history of CVA and 43 a history of TIA. Peripheral vascular disease was present in 42 subjects, of whom 38 reported CLAUDICATION and 12 had peripheral arterial bypass surgery. Frequently subjects had more than one of these events and diagnoses.

Risk factors were present in 975 of the 1,168 subjects. There was an average of 1.72 ± 1.16 risk factors per patient, with 193 having no risk factors, 345 having 1 risk factor, 310 having 2 risk factors, 242 having 3 risk factors, and 78 having all 4 risk factors. The most prevalent risk factor was hypertension in 706 subjects, followed by smoking in 562 patients, hyperlipidemia in 522 patients, and diabetes in 215 patients.

Association Between Audiometric Pattern and Cardiovascular Status

An association between cardiovascular status and audiometric pattern was identified (Fig. 4). This association was significant at P < .0001 for every variable studied except peripheral arterial bypass, which was significant at P = .0032. Normal hearing was present in 16% of all reviewed audiograms, yet those with any form of cardiovascular disease overwhelmingly had some pattern of hearing loss. Only 4.2% of those with coronary vascular disease, 2.2% of those with cerebrovascular disease, and 2.4% of those with peripheral vascular disease had normal hearing.

Strial hearing loss represented 21.5% of all reviewed audiograms, yet showed a highly significant association with cardiovascular disease and events. Audiograms for those with coronary vascular disease showed a strial pattern 50.6% of the time. For those
with cerebrovascular and peripheral vascular disease it was higher at 62.8% and 71.4% of subjects, respectively. A high association of the strial pattern and intracranial events was found: 63.1% of those with a history of CVA and 65.1% of those with a history of TIA.

Risk factors also showed a statistically significant association with audiometric pattern ($P < .0001$). The strial pattern was the most prevalent in those with hypertension, diabetes, and hyperlipidemia. Smokers were most likely to have a mid-sloping loss, followed by the strial pattern. Among nonsmokers the mid-sloping pattern was also most prevalent, but the strial pattern dropped to fourth most common. These analyses were not controlled for other risk factors or cardiovascular variables.

**Association Between Hearing Loss and Cardiovascular Status**

A bivariate analysis was performed comparing each audiometric hearing loss pattern to normal-hearing subjects for the presence of cardiovascular diseases and risk factors. Only the strial pattern showed a statistically significant association as compared with normal subjects for every cardiovascular variable examined ($P < .0001$ for all). Low-sloping presbycusis was significantly associated with most cardiovascular variables, but failed to reach significance for angioplasty, peripheral vascular disease, diabetes, and hyperlipidemia. Those subjects with classic high-sloping presbycusis showed no significant association with any cardiovascular condition as compared with normal subjects. Only the risk factor of smoking showed an association with each hearing loss pattern when compared with normal hearing subjects.

**Association Between Strial Presbycusis and Cardiovascular Status**

The strial pattern of hearing loss was specifically compared with other audiogram patterns while controlling for either age or gender (Table I). The strial pattern was statistically significantly associated with each cardiovascular variable studied when compared with low-sloping, mid-sloping, high-sloping, or normal audiograms. Odds ratios remained significantly high for CVA, TIA, MI, CAD, and the presence of risk factors when adjusting for gender or age. Age had some effect on the associations, but the correlation between the strial pattern and all cardiovascular variables as compared with other audiometric patterns remained significant. Gender showed no significant effect on odds ratios when comparing strial loss to normal hearing except for the association with smoking. There was also an interaction noted between gender, strial loss, and mid-sloping loss for cerebrovascular disease.

The strength of the association between cardiovascular status and audiogram pattern was most pronounced for the strial subjects and showed a distinct tendency to be associated with hearing loss in the low frequencies. That is, the association between the strial pattern and cardiovascular status was strongest when comparing patterns with the least low-frequency loss. Thus, for almost all variables studied, the association when comparing strial to normal was stronger than that for strial vs. high-sloping, which was stronger than that for strial vs. mid-sloping, which was stronger than that for strial vs. low-sloping. This
**TABLE I.** Association of Audiometric Pattern and Cardiovascular Status.

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>Coronary Vascular Disease</th>
<th>CAD</th>
<th>MI</th>
<th>Cardiac Interventions</th>
<th>CABG</th>
<th>PTCA</th>
<th>Cerebrovascular Disease</th>
<th>CVA</th>
<th>TIA</th>
<th>Claudication</th>
<th>Risk Factors Present</th>
<th>HTN</th>
<th>DM</th>
<th>Lipids</th>
<th>Smoking</th>
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<td>Hearing loss vs. normal</td>
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<tr>
<td>Strial vs. normal</td>
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<td>16.12</td>
<td>16.37</td>
<td>12.77</td>
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<td>8.12</td>
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<td>4.91</td>
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<td>13.74</td>
<td>8.47</td>
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</table>

Note: Bivariate analyses showed a highly significant association between all audiometric patterns and cardiovascular diseases and risk factors. Odds ratios were calculated for patterns of hearing loss in association with differing cardiovascular variables. Only statistically significant odds ratios are shown. The strial pattern was compared to other audiometric patterns while controlling for age and gender.
trend had some sporadic exceptions, which appeared to be influenced by age, and less so by gender.

**Model Construction**

To control for multiple variables simultaneously, a multiple logistic regression model for predicting cardiovascular status was developed. The initial model used known cardiovascular risk factors to determine probabilities for the presence of each cardiovascular variable. The second model added-in audiogram patterns and examined the effect of low-frequency hearing loss on the probability of cardiovascular diseases and events.

**Risk Factors.** The base model for determining the probability ($p$) of the presence of a cardiovascular variable used the logit function of logistic regression. Using the variable $MI$ as an example, the function is represented by:

$$\text{logit}(MI) = \log\left(\frac{p(MI)}{1 - p(MI)}\right)$$

The solution for the probability of $MI$ is based upon the logistic regression:

$$p(MI) = \frac{\exp(\beta^T x)}{1 + \exp(\beta^T x)}$$

where:

$$\beta_x = \beta_0 + (\beta_1 \cdot \text{var}_1) + (\beta_2 \cdot \text{var}_2) + \cdots (\beta_k \cdot \text{var}_x)$$

and:

$$\beta_0 = \text{intercept}$$

$$\beta_x = \text{coefficient for variable } x$$

$$\text{var}_x = 1 \text{ if present; and } 0 \text{ if not present}$$

In this model the predictors, or variables, used were:

- $\text{var}_1 = \text{age greater than } 75$
- $\text{var}_2 = \text{history of smoking}$
- $\text{var}_3 = \text{hyperlipidemia}$
- $\text{var}_4 = \text{diabetes mellitus}$
- $\text{var}_5 = \text{hypertension}$

Using cohort 1, in which there were 1,163 subjects with complete data for all variables, this logistic regression for modeling $MI$ had an adjusted $r^2 = 0.22$ with an area under the ROC curve = 0.81. All risk factor variables, when controlling for the others, showed statistically significant associations with $MI$: $\text{AGE} > 75$ ($P = .0018$; odds ratio [OR] = 2.1), $\text{SMOKING}$ ($P = .0001$; OR = 2.6), $\text{LIPIDS}$ ($P < .0001$; OR = 3.6), $\text{DM}$ ($P = .0001$; OR = 2.5), and $\text{HTN}$ ($P = .0007$; OR = 3.1).

Similar models were developed for $\text{CVA}$, $\text{TIA}$, $\text{CAD}$, history of $\text{CABG}$ or angioplasty (PTCA), and $\text{CLAUDICATION}$. Not all risk factors remained significantly correlated for each outcome when controlling for the others. HTN was not independently significantly correlated with $\text{CABG}$, PTCA, or $\text{TIA}$. $\text{AGE} > 75$ was not correlated with PTCA. SMOKING was not significantly correlated with $\text{TIA}$. DM was not correlated with $\text{TIA}$ or $\text{CLAUDICATION}$. LIPIDS, however, remained significantly associated with all outcomes measured.

**Audiometric Pattern.** Audiometric pattern was added to the logistic regression model and was represented by four additional categories:

- $\text{var}_6 = \text{strial}$
- $\text{var}_7 = \text{mid-sloping}$
- $\text{var}_8 = \text{low-sloping}$
- $\text{var}_9 = \text{high-sloping}$

This overall variable was termed AUDIOMGRAM, and the null condition (i.e., none present) was the normal audiometric pattern. The association of the overall variable AUDIOMGRAM with each outcome measure was statistically significant: for $\text{MI}$ ($P = .007$), for $\text{CAD}$ ($P < .00001$), for $\text{CABG}$ ($P = .006$), for $\text{CVA}$ ($P < .00001$), for $\text{TIA}$ ($P = .003$), and for $\text{CLAUDICATION}$ ($P = .012$). The AUDIOMGRAM variable was not statistically significantly associated with PTCA.

The addition of audiogram pattern to the base regression model improved the ability to explain variability ($r^2$), as well the sensitivity and specificity of the model (i.e., area under the ROC curve). Specifically, $r^2$ improved from 0.19 to 0.27 for $\text{CVA}$, from 0.33 to 0.39 for $\text{CAD}$, from 0.22 to 0.25 for $\text{MI}$, from 0.13 to 0.21 for $\text{TIA}$, from 0.23 to 0.24 for $\text{PTCA}$, from 0.19 to 0.25 for $\text{CLAUDICATION}$, and from 0.22 to 0.25 for $\text{CABG}$. Likewise, area under the ROC curve improved from 0.79 to 0.84 for $\text{CVA}$, from 0.83 to 0.86 for $\text{CAD}$, from 0.81 to 0.82 for $\text{MI}$, from 0.78 to 0.85 for $\text{TIA}$, from 0.83 to 0.86 for $\text{PTCA}$, from 0.83 to 0.86 for $\text{CLAUDICATION}$, and from 0.82 to 0.85 for $\text{CABG}$.

Using the regression model, strial and low-sloping patterns were combined and compared with those with normal hearing or higher frequency losses. The prevalence of each hearing loss pattern was adjusted for their distribution within the cohort, as they were not evenly distributed. The presence of low-frequency hearing loss in both ears in this well-controlled regression model was significantly correlated with each outcome measure except PTCA. Specifically, there was a high correlation with $\text{CVA}$ ($P < .00001$; OR, 4.6; 95% confidence interval [CI], 2.5–8.5), $\text{CAD}$ ($P < .00001$; OR, 3.7; 95% CI, 2.4–5.6), $\text{MI}$ ($P = .007$; OR, 2.6; 95% CI, 1.8–5.2), $\text{TIA}$ ($P =
Low-Frequency Hearing Loss. A separate regression model was generated to look at the presence of low-frequency hearing loss in any ear and the association with cardiovascular status. This variable was termed LFHL and pertained to thresholds greater than 25 dB nHL between 250 Hz to 1 kHz and 500 Hz to 2 kHz. Only the former showed statistically significant association and was used for further analyses. Similar to AUDIOGRAM, LFHL improved the area under the curve for the regression analyses for the variables MI, CAD, CABG, PTCA, CVA, TIA, and CLAUDICATION. In each case, however, the improvement over the base model was not as strong as that seen using discrete audiometric patterns.

Internal Validation. Both the AUDIOGRAM and LFHL models were subjected to bootstrap analyses for internal validation. The area under the curve with >500 iterations was well within the standard deviation and 95% confidence intervals for each cardiovascular variable (Table II).

Equations for Prediction of Cardiovascular Status. These regression analyses were used to build equations calculating a probability for each cardiovascular outcome. As an example, the formula for CVA probability is represented by:

\[
p(CVA) = \frac{\exp(\beta_{CVA}^T)}{1 + \exp(\beta_{CVA}^T)}
\]

where:

\[
\beta_{CVA}^T = -5.20 + .75(AGE > 75) + .59(SMOKING) + .67(LIPIDS) + .74(DM) + .17(HTN) + 2.5(strial) + .59(mid-sloping) + 1.72(low-sloping) + .86(high-sloping)
\]

The coefficients were generated from the regression model. The variables are equal to 0 if the risk factor is not present, or to 1 if the factor is present. For a patient having every risk factor plus a strial pattern, \(\beta_{CVA}^T = 0.22\) and \(p(stroke) = 0.55\). If the same subject with all risk factors alternatively had normal hearing, the probability of stroke decreases to \(p(stroke) = 0.09\). Similar formulas were generated for the other cardiovascular diseases and events, and the coefficients are presented in Table III. Coefficients that were independently significantly associated with each cardiovascular disease are marked with asterisks.
TABLE III. Regression Coefficients.

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>MI</th>
<th>CAD</th>
<th>CVA</th>
<th>TIA</th>
<th>CABG</th>
<th>PTCA</th>
<th>CLAUD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUDIOGRAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−4.89*</td>
<td>−4.42*</td>
<td>−5.20*</td>
<td>−5.58*</td>
<td>−5.78*</td>
<td>−5.48*</td>
<td>−6.55*</td>
</tr>
<tr>
<td>AGE &gt; 75</td>
<td>0.58*</td>
<td>0.60*</td>
<td>0.75*</td>
<td>0.91*</td>
<td>0.78*</td>
<td>0.30</td>
<td>0.58</td>
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<tr>
<td>Smoking</td>
<td>0.91*</td>
<td>0.82*</td>
<td>0.59*</td>
<td>0.27</td>
<td>0.92*</td>
<td>0.79*</td>
<td>1.34*</td>
</tr>
<tr>
<td>Lipids</td>
<td>1.11*</td>
<td>1.83*</td>
<td>0.67*</td>
<td>0.56</td>
<td>1.98*</td>
<td>2.07*</td>
<td>1.31*</td>
</tr>
<tr>
<td>DM</td>
<td>0.80*</td>
<td>0.63*</td>
<td>0.74*</td>
<td>−0.16</td>
<td>0.59*</td>
<td>0.74*</td>
<td>0.21</td>
</tr>
<tr>
<td>HTN</td>
<td>0.65</td>
<td>0.78*</td>
<td>0.17</td>
<td>0.54</td>
<td>0.62</td>
<td>0.63</td>
<td>0.61</td>
</tr>
<tr>
<td>Strial</td>
<td>0.89</td>
<td>1.04*</td>
<td>2.50*</td>
<td>1.89</td>
<td>0.26</td>
<td>0.42</td>
<td>1.44</td>
</tr>
<tr>
<td>Mid-sloping</td>
<td>−0.11</td>
<td>−0.23</td>
<td>0.59</td>
<td>−0.84</td>
<td>−0.19</td>
<td>−0.02</td>
<td>−0.68</td>
</tr>
<tr>
<td>Low-sloping</td>
<td>0.43</td>
<td>1.18*</td>
<td>1.72*</td>
<td>1.39</td>
<td>1.12</td>
<td>0.20</td>
<td>0.65</td>
</tr>
<tr>
<td>High-sloping</td>
<td>−0.88</td>
<td>−0.24</td>
<td>0.86</td>
<td>−0.03</td>
<td>−0.60</td>
<td>−0.82</td>
<td>−0.25</td>
</tr>
<tr>
<td>LFHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−5.22*</td>
<td>−4.28*</td>
<td>−4.77*</td>
<td>−5.62*</td>
<td>−5.48*</td>
<td>−5.74*</td>
<td>−6.95*</td>
</tr>
<tr>
<td>AGE &gt; 75</td>
<td>0.60*</td>
<td>0.81*</td>
<td>0.76*</td>
<td>1.08*</td>
<td>1.05*</td>
<td>0.31</td>
<td>0.61</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.92*</td>
<td>0.82*</td>
<td>0.63*</td>
<td>0.31</td>
<td>0.92*</td>
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</tr>
<tr>
<td>Lipids</td>
<td>1.20*</td>
<td>1.84*</td>
<td>0.81*</td>
<td>0.74*</td>
<td>1.92*</td>
<td>2.13*</td>
<td>1.50*</td>
</tr>
<tr>
<td>DM</td>
<td>0.88*</td>
<td>0.70*</td>
<td>0.87*</td>
<td>−0.01</td>
<td>0.57*</td>
<td>0.77*</td>
<td>0.35</td>
</tr>
<tr>
<td>HTN</td>
<td>0.91*</td>
<td>0.57*</td>
<td>0.34</td>
<td>0.42</td>
<td>0.32</td>
<td>0.89*</td>
<td>0.73</td>
</tr>
<tr>
<td>LFHL</td>
<td>0.66*</td>
<td>0.76*</td>
<td>1.42*</td>
<td>1.43*</td>
<td>0.24</td>
<td>0.26</td>
<td>1.18*</td>
</tr>
</tbody>
</table>

Mi = myocardial infarction; CAD = coronary artery disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; CLAUD. = claudication; AGE > 75 = age > 75 years; DM = diabetes mellitus; HTN = hypertension; LFHL = low-frequency hearing loss.

Regression coefficients for the two models using individual audiometric patterns (AUDIOGRAM) or LFHL in either ear.

*Independently statistically significantly associated with the cardiovascular variable while controlling for all other factors.

External Application of Regression Equations

Ninety subjects recruited from cardiology and general medicine clinics underwent audiometric testing. The average age was 69 years (range, 44–92), and there were 48 women and 42 men. Raw audiometric data were mathematically filtered, as in Figure 1, and identified 9 patients with the strial pattern, 28 with low-sloping loss, 6 with mid-sloping loss, 4 with high-sloping loss, 6 with overlapping hearing loss patterns.

Correlation between audiogram pattern and cardiovascular status showed that eight of the nine subjects with the strial pattern had HTN, and 17 of 22 subjects with LFHL had HTN. Similarly, six of nine strial subjects were hyperlipidemic, as were 17 of 22 LFHL subjects. Interestingly, DM showed little correlation, as most subjects with strial or LFHL patterns were not diabetic. For those suffering CVA, 6 of 8 had a strial or low-sloping pattern. There were only 4 with TIA, of whom half had low-frequency losses.

The regression models (i.e., AUDIOGRAM and LFHL) were applied to the 90 subjects for each cardiovascular condition. These were solved for the probability of each condition and compared with the actual presence of disease (Figs. 5 and 6). There was a trend for those subjects with higher probabilities of having a disease or event to have that condition (i.e., spikes in the right-hand side of the graph). This was particularly notable for CVA, TIA, and CLAUDICATION, although there were overall few such events. The outlier in the former plots represented a patient with a patent foramen ovale who had a history of both CVA and TIA, despite having a low calculated probability. No significant difference was noted between applying the AUDIOGRAM and LFHL models. This likely reflects the strong component in both models of known cardiovascular risk factors as well as overlapping hearing loss patterns.

Specifically for CVA there was a notable improvement over the base model when adding in audiogram pattern or low-frequency hearing loss. This was quantifiable by the increase in the area under the ROC curve for both AUDIOGRAM and LFHL compared with the base (i.e., 0.789 [base], 0.837 [AUDIOGRAM], 0.810 [LFHL]). Graphically this was noted by a shift to the right when comparing the calculated probability of CVA versus the presence of CVA using each model (Fig. 7). Although the threshold above which CVA was seen (approximately 0.11) was similar in all models, the number of subjects reaching that threshold when adding in audiometric pattern was less. The net result was a greater proportion of subjects with a probability value above a given threshold having a history of stroke (i.e., greater specificity).
DISCUSSION

A relationship among cardiovascular disease, the stria vascularis, and hearing loss in various combinations has been reported for many years. The seminal clinical investigation relating these entities was performed by Gates and colleagues. A strong relationship was found between low-frequency hearing thresholds and cardiovascular events. In both men and women, there was a statistically significant correlation between low-frequency hearing loss and coronary heart disease and stroke. In men a correlation was also found for the occurrence of myocardial infarction, and in women a correlation was found with claudication. Risk factors of hypertension, diabetes mellitus, smoking, lipid levels, and weight were sporadically correlated with audiogram pattern, and when a
relationship was found it was typically with the low frequencies.

Additional studies have shown associations between cardiovascular disease, risk factors, and hearing loss. There have been correlations noted with hypertension, hyperlipidemia, diabetes mellitus, age, and smoking. For example, a correlation was noted between high systolic pressures and low- to mid-frequency hearing loss in older women.\(^{25}\) Also, low levels of high-density lipoprotein cholesterol (i.e., good cholesterol) were significantly associated with hearing loss at 2–4 kHz.\(^{26}\) The association with diabetes is inconclusive, as some studies show a relationship and others do not.\(^\text{27,28}\) Smoking has been shown to be associated with sensorineural hearing loss, particularly as an exacerbating factor of noise.\(^\text{29–31}\) Many of these studies note low-frequency hearing loss and raise the question of an association of these factors with stria vascularis compromise.\(^\text{32}\)

Fig. 6. Calculated probabilities for cardiovascular status compared with the actual cardiovascular status of the patient. If the disease is present, the value equals 1 and is represented by a spike in the histogram. Each tick on the x-axis represents an individual subject and is in rank order of increasing calculated probability. Numbers within the graph clarify the calculated probability at each spike. This figure applies the low-frequency hearing loss model built on cohort 1 to the patients from cohort 2. CAD = coronary artery disease; CABG = coronary artery bypass grafting; MI = myocardial infarction.
Animal models provide additional evidence of the effect of cardiovascular factors on the stria vascularis and low-frequency hearing loss. The spontaneously hypertensive rat is a well-established model for studying vascular disease. These rats begin to show elevations in systolic blood pressure at 3 months of age, associated with degeneration in the stria vascularis and elevation in auditory thresholds. Similar studies have demonstrated age-related hearing loss in the hypertensive rat beyond that seen in normotensive controls.

Hyperlipidemia or an atherogenic diet, and the association with hearing loss, has been well studied in animal models. Satar and colleagues noted hearing loss and stria vascularis pathology in guinea pigs fed a high-cholesterol diet. Similarly, chinchillas on a high-lipid diet had pathological changes in the stria and outer hair cells. A rabbit study showed that hypertension and high cholesterol had additive effects on hearing although, interestingly, low-frequency hearing improved, whereas high-frequency hearing declined. Pillsbury, in his American Otological, Rhinological, and Laryngological Society thesis, showed that noise needed to be present to effectuate a hearing decline in hypertensive rats on a high-lipid diet. Noise history was not obtained in this study, but the mathematical filtering of audiogram patterns would have excluded many typical notched and asymmetric audiograms often seen in noise exposure.

In some human temporal bone and animal studies, morphological changes in the stria vascularis have not been observed in the presence of cardiovascular diseases. One potential explanation is that changes were subcellular; at the molecular level. Indeed, molecular studies have shown a shift in expression of Na-K-ATPase isoforms with age in the spontaneously hypertensive rat and an increase in endolymph K+ concentration with ischemia. The shift in K+ concentration alters the endocochlear potential and results in elevated auditory thresholds. Thus, hearing loss may be an early marker of vascular compromise by showing initial molecular deficits before the onset of morphological damage.

Based upon the current study, we propose an alternative perspective to the relationship between hearing loss and cardiovascular disease from that initially raised by Gates and colleagues. Namely, we propose that low-frequency hearing loss is a marker for cardiovascular disease rather than the other way around. Low-frequency hearing loss would thus represent a potential predictor of impending cardiovascular events or underlying disease. We suggest that clinicians may use the audiogram as a sensitive and reproducible screen for cardiovascular compromise.

A limitation of the current study is that it is unable to define the temporal relationship between auditory compromise and the onset of altered cardiovascular status. The temporal association between hearing loss and cardiovascular disease has been proposed, however, in several prior studies. Sidman and colleagues found greater damage in the cochlea than in the heart in hypertensive and atherogenic-diet fed rats. They interpreted these results as suggesting that inner ear pathology precedes that associated with coronary artery disease. Similarly, Susmano and Rosenbush, despite limited objective audiometric data, found that hearing loss was strongly correlated with, and preceded, ischemic heart disease. Cohort 2 in this study will be followed to identify whether those subjects with high calculated probabilities of cardiovascular disease ultimately develop such conditions.

Among the strongest associations noted in this study was that between cerebrovascular disease (i.e., CVA and TIA) and low-frequency hearing loss. This may reflect either a common vascular pathology within the...
vertebrobasilar system or a generalized vascular compromise. We favor the latter explanation for several reasons. First, there was also a strong association between peripheral vascular disease and low-frequency hearing loss, suggesting a systemic, rather than local, vasculopathy. Second, the high metabolic demand of the inner ear and brain may render these regions more sensitive to systemic vascular disease than other organ systems. Third, the sensitivity of the audiogram as a measure of inner ear function, and magnetic resonance imaging as an indicator of cerebral local circulatory issues. Third, the sensitivity of the audiogram to aid in predicting impending vascular compromise. This may be strongest for the prediction of cerebrovascular disease and peripheral vascular disease based on our results. At present, we recommend that those patients presenting with a strial or low-sloping presbycusis pattern, and no history of vascular compromise, be further evaluated and monitored for cardiovascular diseases and risk factors.

CONCLUSION
This study provides further evidence of the association between low-frequency hearing loss and cardiovascular compromise. Additionally, this study provides a mathematical model for determining the probability of cardiovascular disease given a medical history and audiogram. Future studies will apply this formula to a prospective cohort of subjects and assess the ability of the audiogram to aid in predicting impending vascular compromise. This may be strongest for the prediction of cerebrovascular disease and peripheral vascular disease based on our results. At present, we recommend that those patients presenting with a strial or low-sloping presbycusis pattern, and no history of vascular compromise, be further evaluated and monitored for cardiovascular diseases and risk factors.

Acknowledgments
The authors would like to thank Jamie Jensen, AuD for audiometric testing and study coordination. They also appreciate the helpful comments while preparing this manuscript from Dr. George Gates, Dr. Maureen Hannley, and Dr. Christina Runge-Samuelson. The primary author wishes to acknowledge his thesis proposers Dr. Robert J. Toohill and Dr. P. Ashley Wackym for their continued support.

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