Audiological, Phonatory and Cardiac Correlates of Individuals Exposed to Low-Frequency Noise or at Risk of Vibroacoustic Disease

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Abstract

Introduction  Low-frequency noise (LFN) is hazardous to hearing. Long-term exposure to LFN may lead to vibroacoustic disease (VAD), which not only affects a specific organ but the physiological function of entire systems, such as the auditory, phonatory, respiratory, and cardiac systems. Moreover, VAD may lead to many psychological problems and hence affect the quality of life.

Objective  To investigate the adverse effects of LFN on hearing, acoustic and perceptual correlates of the voice, blood pressure, cardiac rate, and anxiety level.

Method  A total of 20 subjects exposed to LFN and 20 not exposed to LFN were included, and a detailed case history was recorded. The patients were submitted to pure tone audiometry, otoscopic examination, acoustic and perceptual analyses of the voice, maximum phonation time, and an assessment of the s/z ratio. We also assessed blood pressure, and the results of a voice-related quality of life questionnaire and of the Hamilton anxiety rating scale.

Results  The results indicate that LFN had an adverse impact on the high-frequency threshold. The present study found a significant difference in shimmer and harmonics-to-noise ratio (HNR) values. Few subjects had high blood pressure and showed the sign of anxiety on the Hamilton anxiety rating scale.

Conclusion  Low-frequency noise has adverse effects on entire systems of the body and causes many psychological issues, which, in turn negatively affect quality of life.

Keywords
► anxiety
► hoarseness
► hearing loss
► blood pressure

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Introduction

Noise is an unwanted sound that is detrimental to our auditory system. Low-frequency noise (LFN) ranging from 10 Hz to 500 Hz is hazardous to hearing and may cause permanent impairment. Long-term exposure to LFN may lead to vibroacoustic disease (VAD), which not only affects a specific organ but entire systems of the body, such as the auditory, phonatory, respiratory, and cardiac systems, as well as body metabolism and sleep disturbances. Many studies have reported that exposure to LFN mostly leads to high-frequency hearing loss and, if prolonged, may gradually reduce the auditory sensitivity in the ear, which affect the auditory system.

Prolonged exposure to LFN leads to many histological changes in the auditory system affecting cochlear function, increasing mitochondrial activity, and the production of free radicals. This increase in the levels of free radicals reduces the cochlear blood flow and lead to excitotoxic neural swelling, causing the death of necrotic and apoptotic cells in the organ of corti. The longer the exposure to LFN, the greater the severity of the VAD symptoms. Long-term exposure to LFN may also lead to the tinnitus and affect the vestibular system. A study reported that the prevalence of tinnitus is 24% higher among individuals exposed to noise than among the overall population. Many studies have provided evidence that exposure to LFN can give rise to vestibular deficiency, and one has reported that LFN may damage the sacculeocolic reflex pathway and damage the vestibular hair cells.

VAD and the Auditory System

Many studies have discussed the adverse effect of VAD on the human and mammalian auditory systems. Studies have reported that exposure to LFN mostly leads to high-frequency hearing loss and, if prolonged, it may gradually include the mid and low octave frequencies. In VAD, pressure in the eardrum increases due to LFN, resulting in unpleasant sensations in the ear, which affect the auditory system. Prolonged exposure to LFN leads to many histological changes in the auditory system affecting cochlear function, increasing mitochondrial activity, and the production of free radicals. This increase in the levels of free radicals reduces the cochlear blood flow and leads to excitotoxic neural swelling, causing the death of necrotic and apoptotic cells in the organ of corti. The longer the exposure to LFN, the greater the severity of the VAD symptoms.

Long-term exposure to LFN might thicken blood vessels and they are anchored to the actin cytoskeleton (CSK). With the increase in blood pressure, most commonly high blood pressure. Most studies have also revealed that LFN exposure may lead to the changes in blood pressure, most commonly high blood pressure. High levels of anxiety may be caused by different VAD symptoms. The anxiety related to LFN exposure may be due to disturbance in daily activities, sleep, thoughts. High anxiety may also result from negative emotional responses, such as irritation, distress, and a wish to escape from the noise.

Hypertension, Anxiety, and Psychological issues in VAD

There is evidence on the effect of prolonged exposure to LFN on blood pressure and anxiety. Many studies have suggested that prolonged exposure to causes many psychological issues, such as mood swings, increased stress, irritation, annoyance, sleep disorders, and changes in behavior. Studies have also revealed that LFN exposure may lead to the changes in blood pressure, most commonly high blood pressure. Most studies report that individuals exposed to LFN develop high levels of anxiety. High levels of anxiety may be caused by different VAD symptoms. The anxiety related to LFN exposure may be due to disturbance in daily activities, sleep, thoughts. High anxiety may also result from negative emotional responses, such as irritation, distress, and a wish to escape from the noise.

Based on the review of the literature, we can see that VAD causes a plethora of symptoms and may affect the whole physiology of the body. In the recent literature, there are many studies on the effect of VAD on the hearing and cardiovascular systems, and on psychological issues. On the other hand, the previous literature consists only of a handful of studies on the effect on the voice of prolonged exposure to LFN. After going through the previous literature, we were motivated to look into the adverse effects of VAD on the various systems and its correlation with the duration of LFN exposure. In the present study, we investigate acoustic and perceptual correlates of the voice, since in the previous literature most of the inference was drawn from animal model studies, not studies in humans. Therefore, the goal of the current investigation is to investigate the adverse effects of LFN on hearing, acoustic and perceptual correlates of the voice, blood pressure, cardiac rate, and anxiety level.
Methodology

Before data collection, consent was taken from all of the participants. All of the instrument analyses were performed using non-invasive procedures. In the present study, non-invasive instrumental analysis were conducted.

Participants

A total of 20 male subjects with ages ranging from 18 to 54 years (mean: 36.5 ± 10.4 years) who worked in noisy environments and 20 male subjects with ages ranging from 21 to 50 years (mean: 38.2 ± 9.67 years) working in non-noisy environments participated in the present study. We included subjects with a minimum of two years of working experience. Subjects with psychological, behavioral, neurological and other health-related issues were excluded. All the participants were recruited from a textile factory and gave written informed consent. The mean working experience of the noisy group was of 13.75 ± 9.01 years. The demographic details of the subjects exposed to LFN are described in Table 1. The mean daily working hours of the subjects was of 10.45 ± 1.14 hours. A detailed interview with the whole sample revealed a common habit of drinking tea five to six times per day on average. Seven subjects used to smoke (that is, more than four bidi/cigarettes per day), and all subjects had a habit of chewing tobacco while working.

Tools and Instrumentation

Initially, we recorded the case history in detail, including the information regarding the duration of work, the daily exposure to noise, tinnitus, vertigo, and nausea, and we also asked questions that helped identify other health-related issues. To assess the hearing status, we performed pure tone audiometry (PTA) using the Elkon mini audiometer (Elkon Pvt. Ltd., Mumbai, Maharashtra, India). To assess the effect of LFN on voice, we performed an acoustic analysis using the Praat software (Paul Boersma and David Weenink, Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands), and a perceptual analysis using the Buffalo III voice screening profile.44 To assess the effect of voice impairment on quality of life, we used the Voice-related Quality of Life (VRQOL) questionnaire.45 The maximum phonation time (MPT) and the s/z ratio were assessed as an aerodynamic measure of the voice. Blood pressure and the cardiac rate were measured using the Omron HEM 7113 (Omron Corporation, Kyoto, Japan). In order to assess anxiety, we used the Hamilton Anxiety Rating Scale (HAM-A),46 which consists of 14 questions scored from 0 to 4 (0: not present; 4: severe).

Procedure

Before data collection, noise levels were analyzed using a portable sound level meter (B&K 2250-L, Brüel & Kjær, Nærum, Denmark) three times a day randomly in the participants’ workplace. The data were collected in two phases: first, the case history was recorded in detail, and it included health-related issues, changes in mood, the duration of work, daily exposure to noise, and the presence of tinnitus, vertigo, recruitment, and nausea. We further assessed the stress level (using the HAM-A), blood pressure, and cardiac rate. In the second phase, we conducted an outer-ear inspection using an otoscope, and PTA for the frequencies of 1 kHz, 2 kHz, 4 kHz and 8 kHz in a silent room with a minimal noise level. The silent room was located another building in the same campus due to the non-availability of a soundproof room/chamber. We made sure that the background noise was within permissible limits by measuring the noise level using sound level meter and applying the calibration factor as per the ANSI S3.1-1999 (R2018) standard issued by the American National Standard Institute47 for each participant. We could not include the frequencies of 500 Hz and 250 Hz in the PTA due to the higher calibration factor. The acoustic parameters of the voice were measured using the stimulus /a/. Along with these measurements, we further assessed the MPT, the s/z ratio, and the VRQOL.

Data Analysis

The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US) software, version 20.00. The means and

<table>
<thead>
<tr>
<th>Participants</th>
<th>Age (years)</th>
<th>Work experience in noisy situation (years)</th>
<th>Daily working hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant 1</td>
<td>54</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Participant 2</td>
<td>44</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Participant 3</td>
<td>49</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>Participant 4</td>
<td>18</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Participant 5</td>
<td>27</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Participant 6</td>
<td>28</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Participant 7</td>
<td>40</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Participant 8</td>
<td>30</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Participant 9</td>
<td>30</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Participant 10</td>
<td>42</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Participant 11</td>
<td>32</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Participant 12</td>
<td>26</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Participant 13</td>
<td>38</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Participant 14</td>
<td>50</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Participant 15</td>
<td>45</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Participant 16</td>
<td>51</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Participant 17</td>
<td>20</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Participant 18</td>
<td>37</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Participant 19</td>
<td>40</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Participant 20</td>
<td>29</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Mean ± standard deviation</td>
<td>36.5 ± 10.4</td>
<td>13.75 ± 9.01</td>
<td>10.45 ± 1.14</td>
</tr>
</tbody>
</table>
standard deviations were recorded, and the independent samples t-test was used to assess the mean differences regarding the parameters of the experimental and control groups. Multiple linear regression analysis was used to assess the effect of the years of working experience in environments with LFN and the amount of daily noise exposure on the hearing thresholds, acoustical voice parameters, anxiety level, and cardiac rate.

Results

In the present study, the factory’s mean noise level in the subjects’ working area was above 90 ± 5 dB(A) in three daily measurements made at different times. Descriptive analysis revealed that the subjects had a minimum of 3 years and a maximum of 37 years of experience working in noisy environments.

Effect of LFN on Hearing

An otoscopic examination revealed that the tympanic membrane was intact in all subjects. The hearing assessment revealed that all participants had poor threshold at high frequencies, and 3 of them had a dip at 4 kHz. The independent samples t-test revealed a significant difference between the right and left ear thresholds for all the frequencies between the experimental and control groups, as shown in Table 2 and Fig. 1.

The participants with longer exposure to LFN also reported the presence of high-frequency tinnitus and occasional vertigo. More than half of the population (that is, 16 subjects) reported tinnitus, but only 3 subjects reported bothersome tinnitus that caused them to have a disturbed sleep pattern. Eleven (55%) subjects reported intolerance to sounds which would be comfortable to a person not exposed to LFN. Multiple linear regression was calculated to predict the hearing loss based on the years of working in noisy environments and the daily hours of exposure. A significant regression equation was found for the frequency of 8 KHz in right and left ears, as shown in Table 3.

Effect of LFN on the Voice

The results revealed significant differences regarding shimmer (p = 0.004) and the harmonics-to-noise ratio (HNR; p = 0.002). Table 4 shows a mean difference in the jitter values of both groups, which was not statistically significant. The multiple linear regression analysis was used to explore the effect of the years of work experience in environments with LFN and the daily hours of noise exposure on the acoustical parameters of the voice. A significant regression equation was only found for the HNR, as shown in Table 5.

Fig. 2 shows that, regarding the voice, 55% (n = 11) of the sample had the normal quality, pitch, and intensity on the Buffalo III voice screening profile. However, the quality of the voice was mild in 20% (n = 4), moderate in 10% (n = 2), and severely hoarse in 5% (n = 1), whereas 10% had mildly breathy voice quality. Most participants (n = 9, 45%) had poor and limited pitch variation; however, only 6 (30%) had a limited intensity range. The analysis revealed a significant difference in the maximum phonation time (p = 0.000)

### Table 2

<table>
<thead>
<tr>
<th>Ear</th>
<th>Frequency</th>
<th>Group</th>
<th>Mean ± SD</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Right</td>
<td>1 kHz</td>
<td>Control</td>
<td>24 ± 4.47</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>39 ± 5.02</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1 kHz</td>
<td>Control</td>
<td>17 ± 2.51</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>38 ± 5.40</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>2 kHz</td>
<td>Control</td>
<td>24.75 ± 3.52</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>37.50 ± 5.05</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>2 kHz</td>
<td>Control</td>
<td>20 ± 2.80</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>38 ± 4.02</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>4 kHz</td>
<td>Control</td>
<td>25 ± 2.80</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>38.50 ± 4.38</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>4 kHz</td>
<td>Control</td>
<td>23 ± 2.82</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>39 ± 4.65</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 kHz</td>
<td>Control</td>
<td>26.25 ± 2.75</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>38.5 ± 5.22</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8 kHz</td>
<td>Control</td>
<td>26 ± 2.22</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental</td>
<td>40 ± 4.09</td>
<td></td>
</tr>
</tbody>
</table>

![Fig. 1](image_url) Mean values of both groups for each tested frequency.
between the individuals exposed to LFN (mean ± standard deviation [SD] = 13.65 ± 5.13 s) and not exposed to LFN (mean ± SD = 25 ± 7 s). Regarding the s/z ratio, it was higher than 1.40 in 9 (45%) participants, indicating laryngeal pathology.

On the VRQOL self-assessment questionnaire, most of the sample (n = 16, 80%) answered “No Problem in Voice.” However, 3 (15%) participants reported a small amount of problem, and 1 (5%) subject reported a moderate amount of problem, as shown in Fig. 3.

**Effect of LFN on Blood Pressure, Cardiac Rate, and Anxiety Level**

All participants had normal blood pressure (systolic: mean ± SD = 134.95 ± 12.20; diastolic: mean ± SD = 85.9 ± 8.45). However, blood pressure was elevated 4 (20%) subjects and 3 (15%) participants reported a small amount of problem, and 1 (5%) subject reported a moderate amount of problem, as shown in Fig. 3.
The subjects with elevated blood pressure more than 20 years of LFN exposure. The results also revealed that most participants had normal cardiac rate (mean ± SD = 75.55 ± 10.43), but it was high (> 100) in 2 (10%). Participants who had high cardiac rate had longer periods of exposure to noise. On the HAM-A, 55% (n = 11) of the sample was classified as having “no anxiety,” 35% had “mild anxiety,” and 10% had a “mild to moderate” level of anxiety, as shown in Fig. 4.

To identify the effect of daily noise exposure and working experience on the cardiac rate and anxiety level, we performed a multiple linear regression analysis, and we found a significant regression equation for both dependent variables, as shown in Table 6.

**Discussion**

The present study investigated the hearing, acoustical and perceptual parameters of the voice, cardiac rate, blood pressure, and anxiety level in individuals exposed to LFN, and the results revealed that prolonged exposure to LFN gradually affects systems of the body.

**Table 6** Multiple linear regression analysis showing the effect of daily noise exposure and years of work in environments with low-frequency noise on the Anxiety level cardiac rate

<table>
<thead>
<tr>
<th>Variables</th>
<th>Independent variables</th>
<th>Model coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily noise exposure</td>
<td>0.737 (0.859)</td>
</tr>
<tr>
<td>Anxiety level</td>
<td>Years of work in environments with low-frequency noise</td>
<td>0.382 (0.109)</td>
</tr>
<tr>
<td></td>
<td>Daily noise exposure</td>
<td>1.879 (2.188)</td>
</tr>
<tr>
<td>Cardiac rate</td>
<td>Years of work in environments with low-frequency noise</td>
<td>0.679 (0.278)</td>
</tr>
</tbody>
</table>

Note: *Significant at the level of 0.05.
VAD and the Audiological Profile

In the present study, we conducted PTA at the frequencies of 1KHz, 2KHz, 4KHz, and 8KHz, and the result revealed that exposure to LFN gradually affects the high frequencies and leads to high-frequency hearing loss as was also reported by Nair and Kashyap.\(^1\) They conducted a study with Indian Air Force personnel, and reported a high prevalence of high-frequency hearing loss among technicians (who are more exposed to LFN) compared with non-technicians. Similar results were reported by Senturia,\(^4\) who conducted a study on long-term exposure to aircraft noise which revealed that individuals exposed to aircraft noise developed high-frequency sensorineural hearing loss. Reduced hearing sensitivity at high frequencies results in deterioration in speech perception,\(^48\) which also worsen in the presence of noise.\(^49\) In the present study, individuals exposed to LFN also reported high-frequency tinnitus and recruitment, similar to what was reported by Castelo Branco,\(^9\) Nair and Kashyap,\(^1\) Shargorodsky et al.,\(^17\) and Mazurek et al.\(^18\) Previous studies have reported that LFN affects the histological structure of the cochlea\(^14–16\) and results in hearing deterioration, tinnitus, and recruitment, and that increases in the amount of LFN exposure affect the high frequency threshold\(^19–21\). The results of the present study are in lines with those of the studies conducted by Senturia,\(^4\) Castelo Branco et al.,\(^3\) Ribeiro and Câmara,\(^2\) and Nair and Kashyap,\(^1\) who reported that the longer the exposure to LFN, the greater the severity of the VAD symptoms. The results of previous studies have also pointed that exposure to LFN could affect the vestibular system; however, in the present study we were not able to assess the vestibular system.

VAD & the Voice Profile

During literature review, we found only a handful of studies\(^60–62\) on the effect of LFN on the phonatory system, and this motivated us to explore this subject. In the present study, we used acoustical and perceptual assessment methods to explore the effect of LFN on the phonatory system. We also used subjective assessment methods, such as the MPT and the s/z ratio. In the literature, the usefulness of the s/z ratio assessment method is the topic of debate; however, many previous studies\(^50–56\) have used this method to assess the vocal status in different pathologies, and it may be helpful in screening the laryngeal pathology due to the acoustic properties of the sounds used.\(^57–59\) In the present study, we found a significant difference in the shimmer and HNR values between the two groups. A difference was also found in jitter values, but it was not statistically significant. These could be due to the use of louder voice in the presence of LFN for the auditory feedback and to that fact that the frequent vocal abuse affects the physiology of the vocal folds, leading to changes in voice quality.\(^23\) Similar results were reported by Ribeiro and Câmara.\(^2\) On the other hand, Mendes et al.\(^5\) found no evident changes in acoustic parameters in a population exposed to LFN, but F0 parameter increased significantly with the number of years of professional activity. Mendes et al.\(^5\) did report changes in other acoustic parameters, but they were not statistically significant. These differences in results among different studies may be due to the different subject groups. In the present study, the subjects were recruited from a factory, and they did not wear any ear-protection devices, whereas Mendes et al.\(^5\) recruited airline pilots, who wear such devices. The present study further revealed that subjects exposed to LFN had decreased MPT and increased s/z ratio (higher than 1.40). The studies conducted by Mendes et al.\(^50–62\) and Alves-Pereira et al.\(^63\) also reported these results. The current study also revealed that hoarse voice quality may be due vocal abuse and unhealthy dietary habits, which is in line with the study by Castelo Branco.\(^9\) In the present study, we also found that the HNR decreases as the of the exposure to noise exposure increases with time. This indicates that, as the noise exposure increases, the probability of developing vocal pathology also increases due to the continuous vocal abuse, which cause changes in the histological morphology of the vocal folds.\(^24\)

Effect of LFN on Cardiac Rate, Blood Pressure and Anxiety Level

In the current study, we assessed the cardiac rate, blood pressure and anxiety level along with changes in the auditory and phonatory systems in individuals at risk of developing VAD. The study showed that subjects exposed to LFN are at a higher risk of having increased cardiac rate, which could disturb the cardiac cycle. Similar findings were reported by Marciniak et al.,\(^8\) Castelo Branco et al.,\(^7\) and Araujo Alves et al.\(^38\) Increased cardiac rate may lead to an episode of sudden tachycardia.\(^9\) The current study also showed that an increase in the exposure to noise has direct effects on the cardiac rate, that is prolonged exposure of LFN hampers and disturbs the functioning of the cardiac system, which is in line with the reports by Albuquerque e Sousa et al.,\(^35\) Carmo et al.,\(^36\) Marciniak et al.,\(^8\) and Araujo Alves et al.\(^37\) In the present study, we also found that individuals with a longer exposure to noise showed increased anxiety levels. Similar results were discussed in the health statement of the County of San Diego,\(^11\) the Department of Health of the Commonwealth of Australia,\(^10\) and Beutel et al.\(^13\) Our results also indicate that the anxiety level is affected by the increased level and duration of the exposure to noise. Increased anxiety levels may lead to changes in blood pressure or increased heart rate. Abbasi et al.\(^40\) reported that high levels of anxiety may lead to hypertension and vice versa. The current study also revealed that most of the experimental group had hypertension, which is in line with the studies by Leon Bluhm et al.\(^39\) and Araujo Alves et al.\(^38\)

Conclusion

Based on the current study, we can conclude that LFN has adverse effects on the whole body. Prolonged exposure to LFN not only affects different systems, but also leads to psychological issues. In the present study we tried to assess the effect of LFN on the different human systems using various methods. We predominantly aimed to explore the effect LFN exposure on the phonatory system using
acoustical and perceptual methods. From the results of the present study, we can infer that VAD affects different body systems as well as quality of life. The present is a preliminary study, and future studies will require extensive research in this field.

Conflict of Interests
The authors have no conflict of interests to declare.

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