

## **Distortion Products Otoacoustic Emissions as Markers of Tinnitus Persistence after Acute Acoustic Trauma**

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### **SUMMARY**

*It is a common thought in the physicians military community that persistence of tinnitus after acute acoustic trauma (AAT) essentially depends on severity of hearing thresholds shifts. Nevertheless it has never been demonstrated scientifically. Here we have looked for predictive factors of tinnitus duration after AAT by using hearing thresholds and distortion product otoacoustic emissions (DPOAEs). DPOAEs are otoacoustic emissions that revealed the functional state of the active cochlear mechanical processes. Young military adults under 25 years old, without history of tinnitus and hospitalized for an AAT were followed-up for 15 days. Examination during which the tinnitus state was recorded were carried out at three periods of time :  $24 \pm 5$  hours, 72 hours and 15 days after the trauma. Two groups were defined according to their tinnitus duration after AAT (Group 1 < 72 hours and Group 2 > 72 hours). At 24 hours after AAT, hearing levels in the high frequency range did not differ significantly ( $p=0.250$ ) between the short-lasting tinnitus group (Group 1) and the long-lasting tinnitus group (Group 2). In contrast, 24 hours after AAT, groups differed for DPOAEs, significantly ( $p=0.016$ ). When statistical analyses took into account the severity of the acoustic trauma (Hearing levels held constant), DPOAEs were even more significantly different between the long and short-lasting groups ( $p=0.007$ ). This result is mainly in favour of an outer hair cell (OHC) dysfunction in persistent tinnitus. Here we show that even moderated acoustic trauma could generated persistent tinnitus and was associated with poorer hearing thresholds recovery 15 days after AAT. DPOAEs may be useful predictors at 24 hours after the trauma, but also certainly before any deleterious acoustic event. Prospective studies are in progress. They could be interesting markers for subsequent pharmacological studies.*

### **1.0 INTRODUCTION**

Tinnitus is a symptom associated with acute acoustic trauma (AAT). Literature is abundant (Temmel et al. 1999; Axelsson and Hamernik 1987; Axelsson and Barrenäs 1992; Man and Naggan 1981; etc.). It is usually the most disabling functional after effect. In the context of the study, AAT was defined as an ear trauma provoked by impulsive noise exposure with specific clinical signs (i. e., High-pitched whistling

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(tinnitus) and a notch on audiograms corresponding to hearing losses at frequencies between 3 and 6 kHz) typically described for noise-induced hearing loss (NIHL). Human investigation on AAT are not easy for statistical comparisons because acoustic sources (impulsive noise) that came into ears are very inhomogeneous (type of arms, distance, protections, etc.).

In the military environment, permanent tinnitus associated with marked NIHL is a subject of medical concern. In spite of this, there are only few studies measuring the fluctuations of hearing levels (HL) just after impulse noise (Dancer et al. 1991; Plinkert et al. 1995; Veillet et al. 2001). There is a lack of studies of the persistence of tinnitus over the hours and days after the AAT. In practice, subjects are usually far from hospitals and are sent to be examined by an otologist only when tinnitus persists for more than a week. Therefore, it is rarely possible to examine injured ears at an early stage. For the purpose of this preliminary study, we urged the officers of several military regiments to send any subjects complaining of tinnitus after target practice rounds to the regional hospital as soon as possible, for ear examination.

For assessment of hearing status and for identifying potential predictive factors of persistent tinnitus, we tested hearing levels and used measurements of distortion product otoacoustic emissions (DPOAEs). The relationship between NIHL and otoacoustic emissions is abundantly described in the literature showing the advantages of using OAEs as sensitive indicators of hearing loss (Bonfils et al. 1988; Bonfils and Uziel 1989; Collet et al. 1991; Kemp et al. 1990; Kim et al. 1992; Martin et al. 1990; Smurzynski et al. 1990; Wilson 1992), but it had never been proved sensitive indicators of persistence of tinnitus after AAT.

OAEs are known to represent the cochlear mechanical activity of outer hair cells (OHC) and some studies suggest that one source of tinnitus may be related to dysfunctions in cochlear mechanical activity (Ceranic et al. 1998; Chery-Croze et al. 1994; Kemp 1981; Lind 1996; Shiomi et al. 1997; Zenner and Ernst 1993). In three studies, for example, chronic tinnitus from different etiologies associated or not with hearing loss was found to be associated with low level DPOAEs (Shiomi et al. 1997)

Here, the main test was to determine if tinnitus duration after an acute acoustic trauma (AAT) due to firearm discharge was associated with hearing levels or/and DPOAEs). Thus the purpose was to approach or localize tinnitus duration mechanisms.

## **2.0 MATERIELS & METHODS**

### **2.1 Subjects**

Subjects were soldiers who were sent to the hospital when they complained of tinnitus after target practice rounds during regular training. Subjects were  $22 \pm 2.3$  years old, free from pre-existing AAT or tinnitus or significant hearing loss, as assessed by hearing control at the time of enlistment in the army.

On admission to the otology department of the hospital, subjects underwent a cortico-steroid therapy (5-d, methylprednisolone: Solumedrol IV<sup>®</sup>, 2 mg/kg/day, as usually prescribed for acoustic traumas in French military hospitals). This therapy had been shown to slightly enhance the recovery in animal models (Lamm and Arnold 1998; Gervais d'Aldin et al. 1999) and in human (Suc and Asperge 1988; Suc et al. 1994). Afterwards they were subjected to OAE measurements and a pure tone audiometry.

### **2.2 Instrumentations**

Pure tone audiometry (Midimate 622 Madsen) was performed at 1, 2, 3, 4, 6, and 8 kHz using a 5 dB-steps method in a sound proof room of the hospital otolaryngology unit. Hearing loss were expressed in dB re ISO 389 (ISO, 1975, 1983) with reference to a standard normal ear.

DPOAEs were recorded (ILO 92, Otodynamic Analyser, Otodynamic Ltd) in the sound-proof room, with subjects sitting in a comfortable chair and instructed to remain as quiet as possible. The three port probe (one microphone and two transducers) was positioned in the subject's outer ear canal using a foam ear tip.

2f<sub>1</sub>-f<sub>2</sub> DPOAE levels were measured using the DP-gram procedure, in response to pure tones of moderate level (L<sub>1</sub>=65 dB SPL, L<sub>2</sub>=55 dB SPL), and plotted with respect to the f<sub>2</sub> primary tones, ranging from 1 to 6 kHz, (8 points/octave). The f<sub>2</sub>/f<sub>1</sub> frequency ratio was set at 1.22.

For each subject, the mean responses in dB SPL at frequencies centered around 1 kHz (from 875 to 1437 Hz), 2 kHz (from 1437 to 2875 Hz) and 4 kHz (from 2875 to 6025 Hz) were calculated. Average noise floor was  $-14 \pm 5$  dB SPL across subjects and frequencies.

### 2.3 Procedures

We used a standardized questionnaire that is completed in French military hospitals following an AAT. This questionnaire included data concerning the date and time of the accident, the damaged ear(s), tinnitus characteristics (low or high frequency, continuous or intermittent), the wearing of ear protectors, the type of ear protectors, the type of deleterious acoustic source and the distance from the patient.

According to the questionnaire, the deleterious acoustic source was less than 1 m from the ear and was due essentially to gunfire from a French manufactured automatic machine gun called FAMAS. Spectrum data of FAMAS involved frequencies from 0.06 to 16 kHz. The average sound pressure level (10 ms) was 120-125 dB SPL and the peak pressure was 158 dB SPL at the onset (0.5 ms) of the shot (DTAT 1983, Parmentier 1996).

Data collection (n=37) revealed a large variability in the time delay between AAT and the first examination at the hospital (i.e., from 2 hours to 5 days). In order to insure a homogenous delay group, we restricted the study to subjects with delays between 16 h and 32 h. This selection yielded a group of 24 young military subjects, examined at three time points after the AAT: (1) at  $24 \pm 5$  hours (from 16 h to 32 h), (2) at 72 hours, (3) at 15 days.

Over the 15 days period, patients stay for one week in quiet at the hospital and for one week on sick leave at home with strict recommendations of no noise exposure.

During training wearing earplugs is compulsory. 54 % had no earplug at the time of the accident (accidental fall). The remaining subjects suspected a non correct insertion of their foam earplugs.

At the first examination, all patients had a continuous high frequency tone (whistling) in their ear, fluctuating in pitch and intensity. Eight subjects had persistent tinnitus less than 72 h after AAT, 16 subjects had persistent tinnitus superior to 72 hours, among them, 5 subjects still had persistent tinnitus at 15 days after the AAT. When tinnitus was bilateral (one subject), data concerning the more severely affected ear (notch on audiogram) was used for analysis.

To test for OAEs and hearing levels differences between subjects with various tinnitus duration, two classes were defined : Group 1 (n= 8) represented subjects with short-lasting tinnitus (< 72 hours) and Group 2 (n= 16) represented subjects with long-lasting tinnitus (> 72 hours). In addition, in order to contrast strongly short-lasting tinnitus with long-lasting tinnitus, we compared group 1 with a subgroup of group 2 : the five subjects with still persistent tinnitus at 15 days (group 3). Non parametric Mann-Whitney tests to compare these two groups were performed in this particular case for a better statistical robustness.

Otherwise, statistical analyses were carried out by using analysis of variance ANOVA with a between-subject factor "tinnitus duration groups" and a within-subject factor "frequencies" for comparing hearing levels and DPOAEs levels. Equality of variance were checked (Levene's test) for DPOAEs and HL.

A significant inter dependence between hearing levels and otoacoustic emissions after impulse noise exposure was previously demonstrated (Wagner and Plinkert 1999). For this reason it seemed important (in order to extract the role played by tinnitus duration itself) to analyse the relationship between HL, DPOAEs and tinnitus duration by covariance analysis COVAR, (Mc Pherson 1990) using the 24h-high frequency worse hearing level (notch) as an indicator of AAT severity (covariate).

This specific analysis was interesting because the adjustment took into account the various severity of AAT and thus allowed us to test differences between tinnitus duration groups all audiogram notches equal. The present study was approved by a national public institutional ethics committee on the use of human subjects in biomedical research (CCPRB LYON-B/06/07/2000). Written, informed consent was obtained from each subject.

### **3.0 RESULTS**

#### **3.1 Hearing levels and DPOAEs features**

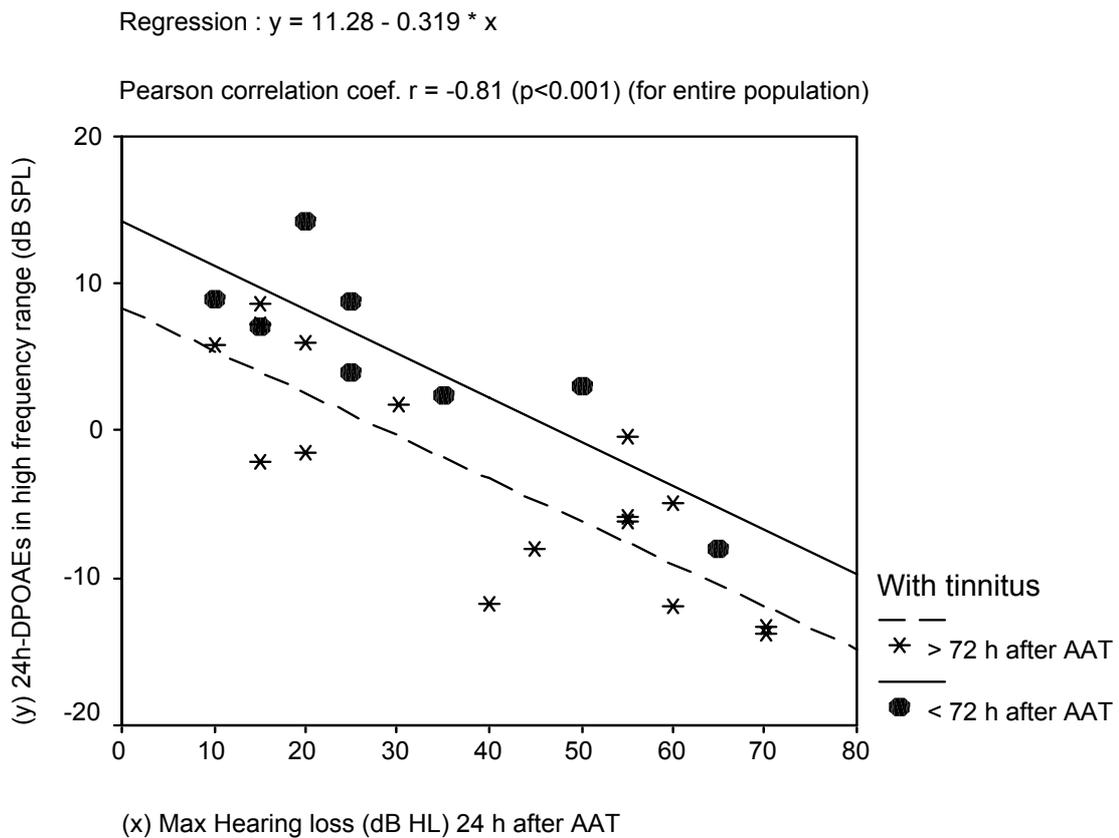
In this population, right and left ears were affected in equal proportion (Table 1). AAT was characterized by a hearing loss at high-frequency showing a notch on audiograms with a maxima focused at 4 kHz (38% of cases), 3 kHz (33%), 6 kHz (21%) or 5 kHz (8%) with a various severity comprised between 10 to 70 dB HL (Table 1).

We calculated an overall high-frequency hearing level with mean hearing losses at high frequencies

Maximal high-frequency HL at 24 hours were strongly negatively correlated with 24 h-DPOAEs (Pearson correlation coefficient,  $r = -0.81$ ,  $p < 0.001$ ) (Figure 1). DPOAEs decreased as hearing thresholds increased.

<b>Subject</b>	<b>EAR</b>	<b>Loss max (dB) at 24 h</b>	<b>Most affected Frequency. in kHz</b>	<b>Tinnitus Duration</b>
N°2	L	10	5	< 72 h
N°5	L	15	4	< 72 h
N°8	R	20	4	< 72 h
N°10	R	25	3	< 72 h
N°11	L	25	4	< 72 h
N°13	L	35	3	< 72 h
N°16	L	50	3	< 72 h
N°22	R	65	3	< 72 h
N°1	L	10	6	> 72 h
N°3	R	15	6	> 72 h
N°4	R	15	6	>72 h (*)
N°6	L	15	4	> 72 h
N°7	L	20	4	>72 h (*)
N°9	R	20	3	> 72 h
N°12	L	30	4	> 72 h (*)
N°14	L	40	3	> 72 h
N°15	L	45	3	> 72 h
N°17	R	55	5	> 72 h
N°18	R	55	3	> 72 h (*)
N°19	R	55	6	> 72 h
N°20	R	60	4	>72 h
N°21	L	60	4	> 72 h
N°23	R	70	6	> 72 h
N°24	L	70	4	> 72 h (*)

**Table 1: Clinical data of 24 military subjects hospitalized 24 hours after an acute acoustic trauma (AAT) due to gunfire. R: Right, L: Left. (\*) Tinnitus persistent at 15 days.**



**Figure 1 : Scatter plot of the association between 24 h-high-frequency-DPOAEs and 24 h-maximum hearing loss. Comparison between tinnitus duration groups. Regression slope was lower with long-lasting tinnitus.**

### 3.2 Hearing levels and tinnitus duration after AAT

Analysis of variance with repeated measures in Table 2 showed that hearing levels were not significantly different between Group 1 and Group 2 in the 1, 2 and 3-6 kHz range at all periods of time after AAT. The same result was found with Mann-Whitney tests between Group 1 and Group 3 in Table 3.

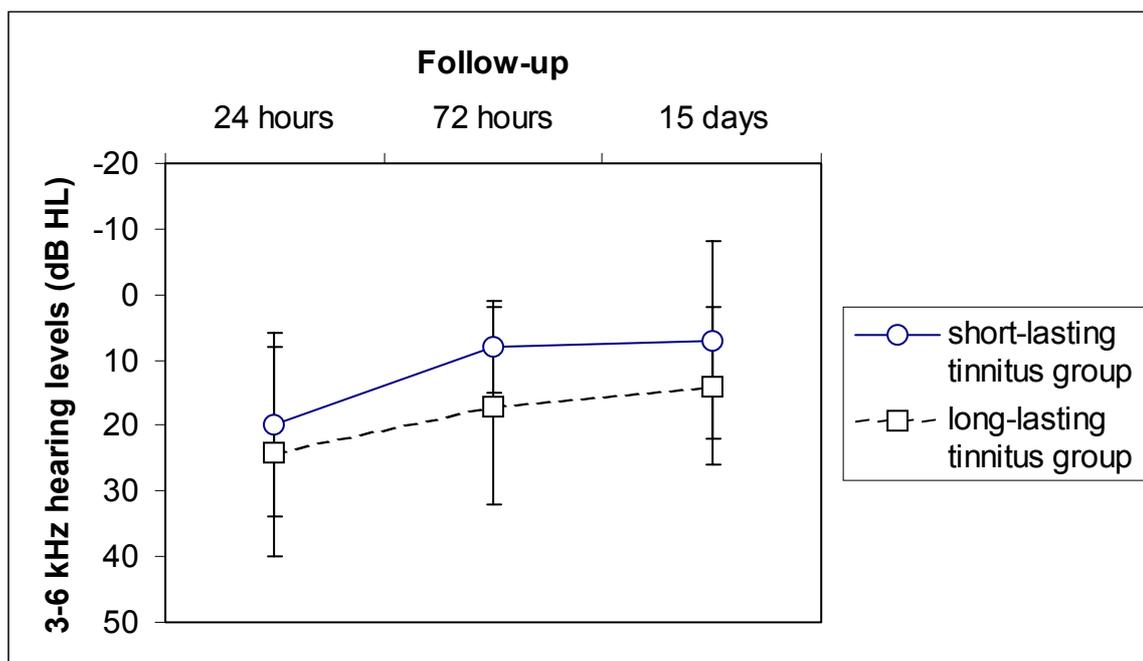
Mean hearing levels (HL) were presented in Figure 2 Differences between groups were not significant at 24h after AAT. At 72 hours and 15 days recovery to normal threshold was poorer in the long-lasting tinnitus groups but were not statistically significant.

Between tinnitus duration groups	TIME	HL p value	DPOAE p value
<b><i>At 3-6 kHz</i></b>			
ANOVA	24 h	0.250	<b>0.016</b>
	72 h	0.125	<b>0.018</b>
	15 d	0.113	0.112
COVAR (covariate= HL)	24 h		<b>0.007</b>
	72 h		<b>0.030</b>
	15 d		0.206
<b><i>At 2 kHz</i></b>			
ANOVA	24 h	0.345	0.677
	72 h	0.930	0.193
	15 d	0.250	0.174
COVAR (covariate= HL)	24 h		0.429
	72 h		0.160
	15 d		0.118
<b><i>At 1 kHz</i></b>			
ANOVA	24 h	0.461	0.704
	72 h	0.663	0.160
	15 d	0.314	0.217
COVAR (covariate= HL)	24 h		0.531
	72 h		0.095
	15 d		0.138

**Table 2 : Synopsis of ANOVA and Covariance analysis comparing hearing levels and DPOAEs of two tinnitus duration groups (long and short-lasting tinnitus).**

FREQUENCY BANDS	TIME	HL p value	DPOAE p value
3-6 kHz	24 h	0.724	<b>0.019</b>
	72 h	0.435	<b>0.030</b>
	15 d	0.065	<b>0.045</b>
2 kHz	24 h	0.093	0.943
	72 h	0.622	0.354
	15 d	0.524	0.171
1 kHz	24 h	0.435	0.435
	72 h	0.943	<b>0.045</b>
	15 d	0.171	0.093

**Table 3 : Non parametric tests comparing more contrasted tinnitus duration groups after AAT: group 1 (tinnitus <72 h) and group 3 ( tinnitus present at 15 days).**



**Figure 2 : Mean 3-6 kHz hearing thresholds at different periods of time in the short-lasting tinnitus group and long lasting-tinnitus group**

### **3.3 DPOAEs and tinnitus duration after AAT**

In Figure 1, the DPOAEs regression slope of the long-lasting tinnitus group was lower than the regression slope of the short-lasting tinnitus group following a marked parallelism.

This result means that independently of severity of trauma tinnitus persistence was associated with an other parameter not depending of severity of notches.

We showed that DPOAEs were significantly lower in Group 2 in the 3-6 kHz range at 24 hours and 72 hours after AAT (Table 2). When the analysis was adjusted with the covariate 24h-high frequency worse HL, significance was higher ( $p=0.007$ ). This result clearly suggests that hearing loss after AAT was a confounding factor slightly masking the phenomenon of tinnitus persistence.

In Table 3, Mann-Whitney comparisons between the most contrasted groups (1 and 3) confirmed the previous results. Differences were also present at 1 kHz. DPOAEs were lower at 72h and 15d after trauma in the long-lasting tinnitus group.

## **4.0 DISCUSSION**

In moderate AAT, the association between hearing levels and tinnitus duration is weak. The results of the study, clearly showed that hearing levels (at least up to 70 dB HL) are not early markers to explain tinnitus persistence after an AAT compare to DPOAEs.

Tinnitus persistence after AAT is the most disabling after effect, it generates many problems at psycho-social and operational levels.

This study shows that even in AAT, tinnitus persistence mainly depends on cochlear outer hair cells (OHC) dysfunctions rather than cochlear inner hair cells (IHC) dysfunctions.

In general, tinnitus is nearly always present at AAT onset, which is the 'normal' response to an acoustic over stimulation. Persistence of tinnitus 15 days after AAT seemed clearly to belong to an abnormal phenomenon at recovery that had never been fully explained. This study provided some new information.

Later after trauma, at 72 hours and 15 days, tinnitus was stopped in one group, we found significant differences between groups at the edge of the trauma frequencies in particular at 1 kHz.

As Avan and coll. (Avan et al. 1991) had already observed, amplitudes of OAEs seemed not only the reflection of the stimulated zone but the state of the whole cochlear partition, and thus after an AAT, several peripheral and central factors might influence cochlear response.

As soon as no reference DPOAEs or audiograms could be provided for the traumatized subjects, we might suspected latent non frequency specific sub clinical OHC dysfunctions and alterations.

First, it could possibly partly come from history of infectious disease (otitis media) or head trauma that are known to potentiate the risk of chronic tinnitus and acoustic trauma when normal hearing subjects were exposed to noise (Job et al. 1999; Job and Nottet 2002; Ceranic et al. 1998).

Second, abnormality might also be present at the retrocochlear level and in central auditory activity as suspected before some authors (Attias et al. 1993 ; Komiya and Eggermont 2000). Furthermore individual susceptibilities at emotional level were probably involved. Tinnitus has been shown to activate the limbic system which controls emotional processing (Gardner et al. 2002; Lockwood et al. 1998; Mirz et al. 2000). A dysfunction in the centrally-controlled regulation at the synaptic level of OHC via the medial olivocochlear system (MOC) possibly occurred in response to the stress provoked by the impulsive noise and acoustic trauma (Horner et al. 2001). A recent retrospective study on tinnitus persistence induced by AAT tended to strengthen the hypothesis of an involvement of psychological factors (Mrena et al., 2002).

Recently, an experimental study on clinical normal hearing subjects (Job et al., 2004) showed that tense-anxious subjects were more susceptible to develop transient tinnitus after moderate impulse noise exposure to gunfire and related to slight alterations in cochlear DPOAEs at 3 kHz. Among young subjects ( $22 \pm 2$  years old) reporting transient tinnitus we found at 2 and 1 kHz an edge effect between subjects having no history of tinnitus and subjects with previous history of tinnitus. A significant association was found between tension-anxiety and history of tinnitus.

Thus other networks besides specific sensory one may be involved in tinnitus persistence after AAT. These networks had to be elicited and taken into account. DPOAEs were sensitive to the duration of tinnitus independently of severity of audiogram notches indicating the involvement of OHC and its regulation mechanism.

Further human experimental or prospective studies on DPOAEs at larger scale should be carried out, in order to detect earlier susceptibility to tinnitus persistence in subsequent acoustic over exposure, highly probable in a military environment.

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