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Perspective:

Blast-induced hearing loss

Kunio MIZUTARI
(*Department of Otolaryngology, Head and Neck Surgery, National Defense Medical College, Saitama, 359-8513, Japan*)
E-mail: tari@mbf.ocn.ne.jp

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The incidence of blast injury has increased recently. As the ear is the organ most sensitive to blast overpressure, the most frequent injuries seen after blast exposure are those affecting the ear. Blast overpressure affecting the ear results in sensorineural hearing loss, which is untreatable and often associated with a decline in the quality of life. Here, we review recent cases of blast-induced hearing dysfunction. The tympanic membrane is particularly sensitive to blast pressure waves, since such waves exert forces mainly at air–tissue interfaces within the body. However, treatment of tympanic membrane perforation caused by blast exposure is more difficult than that caused by other etiologies. Sensorineural hearing dysfunction after blast exposure is caused mainly by stereociliary bundle disruption on the outer hair cells. Also, a reduction in the numbers of synaptic ribbons in the inner hair cells and spiral ganglion cells is associated with hidden hearing loss, which is strongly associated with tinnitus or hyperacusis.

1 Blast injury and its correlation with ear injury

A blast injury refers to the trauma caused by a blast. After an explosive detonates, high-pressure gases expand away from the center of the explosion, compress the surrounding air, and finally produce blast overpressure waves. When the explosion occurs, a shock wave faster than the speed of sound is generated by the blast wind. Therefore, a blast wave contains both a blast wind and a shock wave. Either of these blast wave components can affect living tissue, but the shock wave, which is characterized by an extremely fast increase in pressure and a high peak pressure, is considered to be the most invasive (Cullis, 2001; Sato *et al.*, 2014).

The incidence of blast injuries has increased recently, due to the increased use of improvised explosive devices (IEDs) by terrorists in civilian situations, and the increased use of explosives by military forces, such as in the wars in Afghanistan and Iraq (Owens *et al.*, 2008; Wolf *et al.*, 2009). Blast injuries are categorized into four classes, from primary injury to quaternary injury (DePalma *et al.*, 2005; Wolf *et al.*, 2009). The most critical and pathognomonic injury is a primary blast injury. This is caused by barotrauma, which consists of overpressurization or underpressurization relative to atmospheric pressure. A blast pressure wave exerts forces mainly at air–tissue interfaces within the body, and therefore the auditory system is at high risk (DePalma *et al.*, 2005). Not only the tympanic membrane, but the whole auditory system, i.e., the cochlea and central auditory pathways, comprises the part of the body most commonly damaged by blast overpressure (Wolf *et al.*, 2009; Gallun *et al.*, 2012; Shah *et al.*, 2014). For example, in the Boston Marathon bombings of April 15, 2013, tympanic membrane perforation (TMP), temporary and permanent hearing losses, tinnitus, and hyperacusis were frequent consequences in those affected by exposure to the blasts (Remenschneider *et al.*, 2014). The most common outcome of blast exposure is sensorineural hearing loss (SNHL), which has a high incidence rate in blast-injured patients (Perez *et al.*, 2000; Persaud *et al.*, 2003).

Such permanent SNHL caused by blast exposure is untreatable and is often associated with a decline in the quality of life (Mrena *et al.*, 2004; Fausti *et al.*,

ORCID: Kunio MIZUTARI, http://orcid.org/0000-0002-0340-8293

2009). For example, 38% of the soldiers who served in the Iraq War have tinnitus, and this symptom correlates strongly with cognitive or depressive disorders (Halford and Anderson, 1991; Lew *et al.*, 2007; Langguth, 2011). Cases of suicide in patients with tinnitus associated with depression after blast exposure have also been reported (Turner *et al.*, 2006).

2 Conductive hearing loss after blast exposure

As described above, the tympanic membrane is the tissue in the human body that is most vulnerable to blast exposure. Therefore, the tympanic membrane represents an ideal site for detecting the primary effects of blasts (DePalma *et al.*, 2005). In a report of the 2004 train bombing in Madrid, TMPs occurred in 99 of 243 victims. Among 17 victims who were critically ill with pulmonary injuries caused by the blast, 13 (about 76%) had TMPs. This report also revealed that TMPs occurred in 18 of 27 critically injured victims, 17 of whom were bilaterally affected (Gutierrez de Ceballos *et al.*, 2005). If dynamic overpressures are sufficiently high, the ossicles of the middle ear may even become dislocated.

Surprisingly, the spontaneous healing rate of TMPs was reported to be only 38% six months after the Boston Marathon bombing (Remenschneider *et al.*, 2014). This percentage is much lower than that of spontaneous TMP closure reported for other pathologies. In a review of 210 blast-induced TMPs that occurred in military situations, Kronenberg *et al.* (1993) reported a spontaneous healing rate of 74%. Moreover, reports of non-blast-mediated traumatic TMPs revealed that the spontaneous tympanic membrane closure rate was 89% (Lou *et al.*, 2012). Some possible reasons for the low rate of spontaneous closure of TMPs in patients after blast exposure in a non-military situation have been suggested. The biggest difference between blast and traumatic TMPs is that implanted shrapnel or keratin debris is often present after blast injury (Chandler and Edmond, 1997; Sridhara *et al.*, 2013). Therefore, during tympanoplasty in patients with blast-induced TMPs, careful removal of implanted shrapnel or keratin debris is necessary and the use of endoscopy during tympanoplasty is recommended (Remenschneider *et al.*, 2014).

3 Sensorineural hearing dysfunction after blast exposure

Sensorineural hearing dysfunction, such as hearing loss, tinnitus, or hyperacusis, is a common symptom after blast exposure. For example, about 80% of victims of the Boston Marathon bombings had some forms of sensorineural hearing impairment (Remenschneider *et al.*, 2014). If the hearing impairment persisted until the sub-acute phase, this SNHL caused by blast exposure was permanent, untreatable, and often associated with a decline in the quality of life (Fausti *et al.*, 2009), whereas conductive hearing loss can often be treated by surgery or other treatment. If the damage suffered by the inner ear is relatively minor, the inner ear dysfunction tends to be temporary. Thirty-two percent of patients with significant hearing loss after blast exposure reported spontaneous hearing recovery within minutes (Remenschneider *et al.*, 2014). This type of temporary hearing impairment is also observed in other types of inner ear dysfunction, such as noise-induced hearing loss.

In addition to being used to study noise-induced hearing loss, animal models are useful for investigating blast-induced inner ear dysfunction. Several blast-induced hearing loss models are available. Recent studies have used a permanent hearing loss mouse model created by a tube chamber that reproduces a blast wave (Mao *et al.*, 2012; Cho *et al.*, 2013). After exposure to the blast, sensorineural hearing dysfunction, measured using auditory brainstem responses (ABRs) and distortion-product otoacoustic emission thresholds, was observed to be dependent on blast intensity (Cho *et al.*, 2013). In general, these reports showed that inner ear pathology after blast exposure was similar to that seen after acoustic trauma.

The most obvious damage in the cochleae was loss of outer hair cells, which was seen mainly at higher frequencies (Cho *et al.*, 2013). Moreover, loss of spiral ganglion cells, presynaptic vesicles, and synaptic ribbons at the inner and outer hair cells, and invasion of macrophages into the modiolus of the cochleae were observed, all of which are also seen in noise-exposed cochleae (Wang Y. *et al.*, 2002; Wang H. *et al.*, 2011).

Previous papers concerning blast-induced hearing loss research using blast tubes have reported

detailed results from histological examinations of cochleae after blast exposure (Mao *et al*., 2012; Cho *et al*., 2013). However, determining the physiological function of cochleae after blast exposure is difficult, because blast-exposed animals always have TMPs, leading to conductive hearing loss. To examine the precise cochlear function, laser-induced shock waves (LISWs) have been used to replicate blast injury (Satoh *et al.*, 2010). A shock wave induced by irradiation of solid material with a high-power laser pulse is called a photomechanical wave or an LISW. Previous studies have described animal models of inner ear injury using LISWs (Kurioka *et al.*, 2014; Niwa *et al.*, 2016). The biggest advantage of LISWs for blast-related research is their site-specificity for the injured organ, as LISWs do not leak out beyond the targeted site in exposed animals. The wave propagation and kinetics of LISWs are different from those of a blast wave, because an LISW complies with the theory of propagation and kinetics of a solid phase rather than that of a fluid phase. However, the histological changes in the regions damaged by LISWs have characteristics similar to those of regions damaged by a real blast (Satoh *et al.*, 2010). Therefore, using this technique, it is possible to avoid TMP in the blast-induced hearing dysfunction model; LISW can reproduce the SNHL component alone after blast injury.

Niwa *et al.* (2016) reported that an elevated threshold in the ABR after blast exposure was caused mainly by outer hair cell dysfunction induced by disruption of the stereociliary bundle (Fig. 1). Interestingly, the pattern of bundle disruption was unique, with most of the disturbed stereocilia observed only in the outermost row, whereas the inner and middle row stereocilia were mostly intact. In addition, they observed a reduction of the ABR wave I amplitude, without elevation of the ABR threshold, in the lower energy exposure group. This phenomenon was caused by loss of the synaptic ribbon (Kujawa and Liberman, 2009). This type of hearing dysfunction, recently described as hidden hearing loss, is frequently observed in humans, and is caused by cochlear neuropathy, without an increase in the hearing threshold (Schaette and McAlpine, 2011; Plack *et al.*, 2014). It has been revealed that the pathology of hidden hearing loss is closely related to the pathogenesis of tinnitus (Schaette and McAlpine, 2011; Schaette *et al.*, 2012) and hyperacusis (Hickox and Liberman, 2014). Therefore, this model is also valuable for analyzing the etiologies of tinnitus and hyperacusis, which are among the most frequent symptoms after blast injury (Mrena *et al.*, 2004; Dougherty *et al.*, 2013; Saunders *et al.*, 2015).

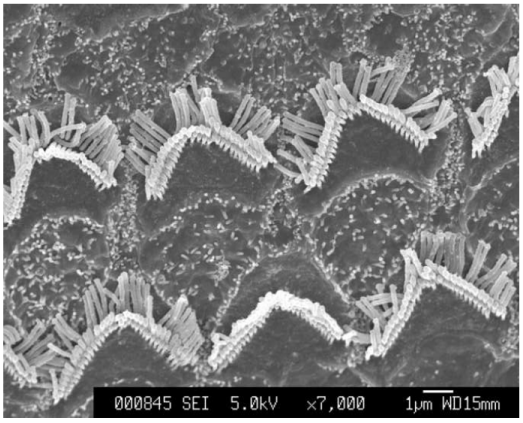

Fig. 1 Scanning electron microscopic image of outer hair cells showing disruption of the outermost layer of the stereociliary bundles, broken from the root

4 Conclusions

In this perspective, we have outlined the pathologies of blast-induced hearing loss, and the recent progress in research on blast-related hearing dysfunction. However, the detailed mechanisms underlying blast-induced hearing loss remain unknown. Further research is needed to establish new treatments for blast-induced hearing dysfunction.

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Compliance with ethics guidelines

Kunio MIZUTARI declares that he has no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the author.

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中文概要

题　目：爆震性听力损失

概　要：近年来爆震性损伤的发生率逐渐上升。由于耳朵是对爆炸压力最敏感的器官，因此它在爆震性损伤中最易受累。爆炸压力造成的耳朵损害主要是不可逆的感音神经性耳聋，进而导致生活质量的下降。我们在本文回顾了近年来爆震性听力损失的一些病例。鼓膜对爆炸压力波特别敏感，因为在体内这种压力波主要在空气-组织交界面释放能量。然而，由爆炸引起的鼓膜穿孔比其他原因引起的更难以治疗。爆炸压力能破坏内耳外毛细胞上的纤毛束，从而引起感音神经性耳聋。同时，内毛细胞的神经突触和螺旋节细胞的减少会引起隐性听力损失，从而引起耳鸣和听觉过敏。

关键词：爆震性损害；隐性听力损失；感音神经性耳聋；纤毛；鼓膜穿孔