Following furosemide, a shift in the OHC transducer operating point causes cochlear amplification to recover more slowly than EP

Yi Wang[1], Elika Fallah[1] and Elizabeth S. Olson[1, 2]

[1]Department of Biomedical Engineering, and [2]Department of Otolaryngology-Head & Neck Surgery, Columbia University, New York

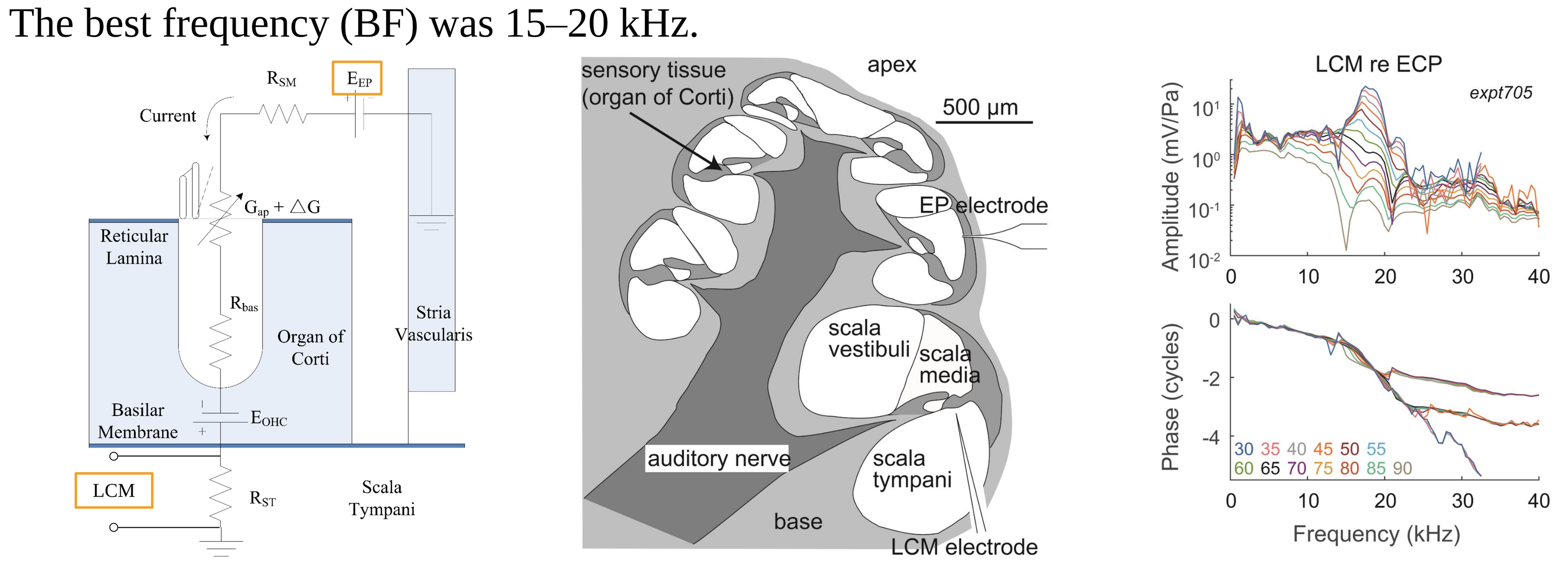
Introduction

Endocochlear potential (EP) provides the voltage drop needed to drive outer hair cell (OHC) transducer current, which leads to OHC electromechanical force and cochlear amplification. A previous study used furosemide to reversibly reduce EP. Their results suggested that cochlear amplification may be able to adjust to low EP. To probe this idea we measured the time course of recovery of cochlear amplification and EP following furosemide administration.

Methods

Adult gerbils with normal CAP response were used in the experiments. 100 mg/kg furosemide was injected intravenous (IV) to reversibly reduce EP. Sound stimulus was delivered in a closed system. Ear canal pressure (ECP) was measured with a Sokolich ultrasonic microphone.

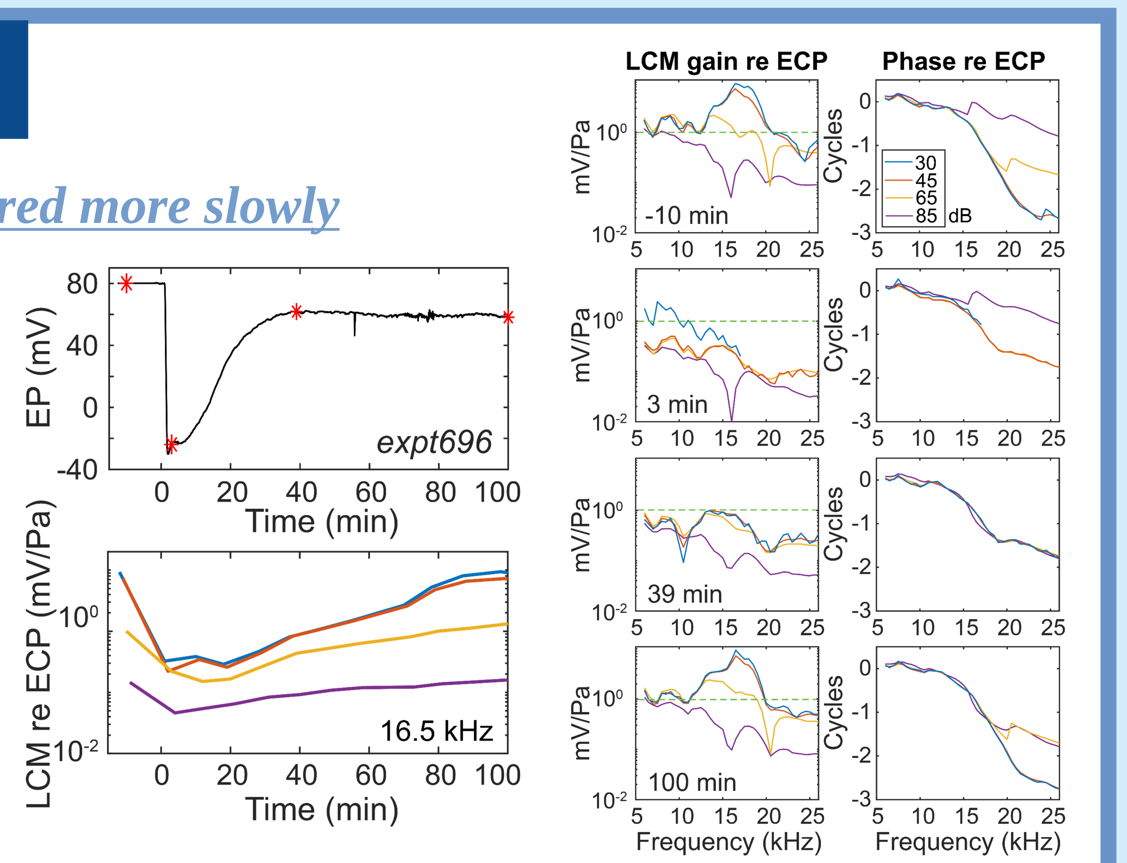
- Endocochlear potential (EP): measured via a ~10 µm diameter hole in the scala media (SM) of the second basal turn of the cochlea.
- Local cochlear microphonic (LCM): measured using a microelectrode with ~ 1 µm tip diameter (FHC Inc. Bowdoin, ME). The electrode was placed close to the basiler membrane (BM) via ~100 µm diameter hole, in the scala tympani (ST) of the basal turn of the cochlea. The best frequency (BF) was 15–20 kHz.



Results

Cochlear amplification recovered more slowly than EP

- The Local cochlear microphonic (LCM) fundamental amplitude variation does not follow EP exactly.
- A two-stage recovery of LCM response was observed: the overall amplitudes were increasing all the time, but nonlinear compression began to recover at 70 min.

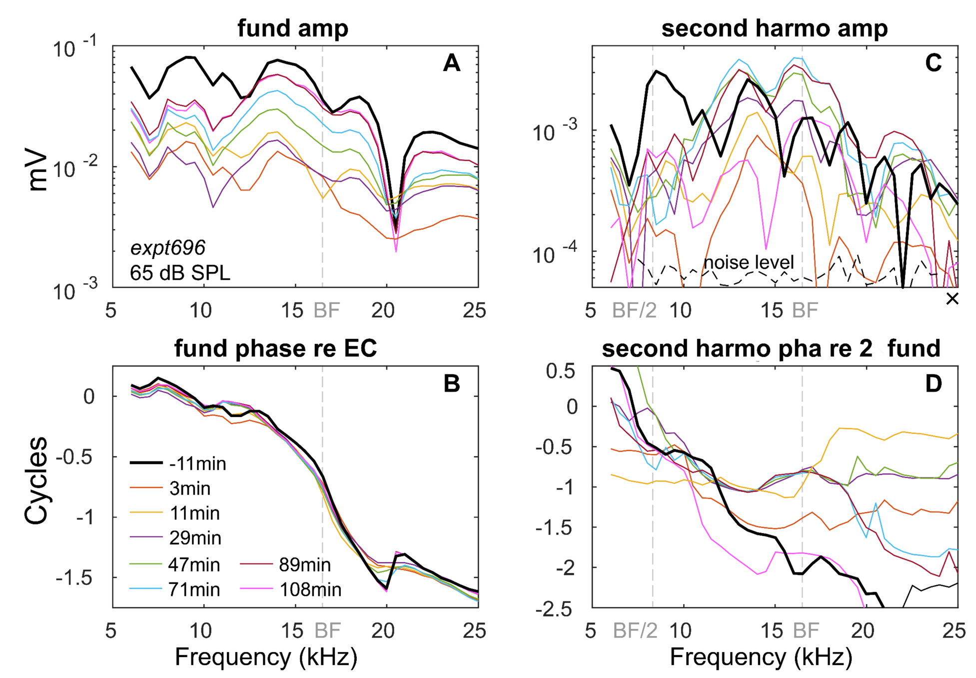


Conclusion

- The cochlear amplification observed in LCM attained nearly full or even full recovery with 20 mV reduced EP. The cochlea has an ability to adjust to diminished operating condition.
- The cochlear amplifier just started to recover after the EP was nearly fully recovered and stabilized. Using a Boltzmann model and the harmonic of the LCM to estimate the transducer OP, we showed that this non-simultaneous recovery of cochlear amplification resulted from a shift in the OP. The re-centering process was linked with cochlear amplification recovery in time.

Results

Second harmonic overshoot



- At frequencies below the plateau frequency (~ 20 kHz), the 2nd harmonic phase was generally half or full cycle relative to the fundamental.

Fundamental (A, B), 2nd harmonics (C, D), and 3rd harmonics (E, F) of LCM frequency responses (un-normalized) (expt696).

- At the BF, 2nd harmonic overshoot in the period of 47–89 min and decreased by 109 min. Fundamental and 3rd harmonic decreased and substantially recovered.

Second harmonic and fundamental variation indicate MET channel operating point (OP) shifts

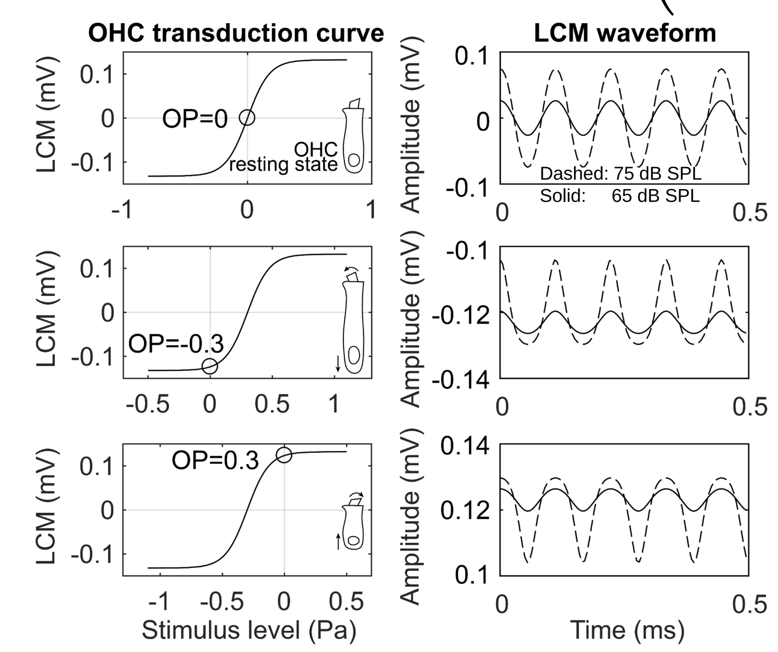
LCM variations (normalized) are shown at two frequencies (expt705).

- At 58 – 60 min (gray shaded area), the active nonlinearity at 30–60 dB SPL recovered significantly at the BF. There was no noticeable EP change in this period, but the 2nd harmonic amplitude response decreased at both BF and subBF.
- This indicated the recovery of cochlear amplification was not due to a recovery in driving voltage, but instead likely resulted from a shift in the MET OP.

Nonlinear behavior simulated with sigmoidal OHC MET channel

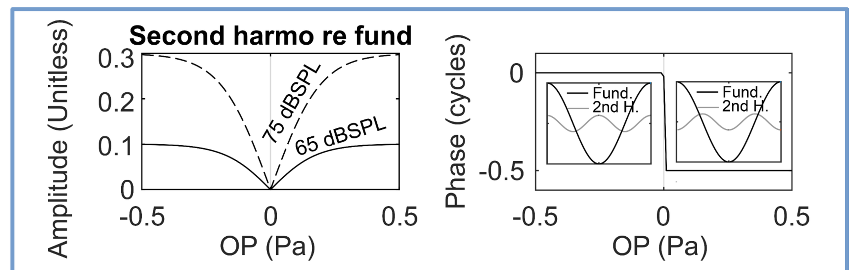
The LCM can be assumed to be proportional to the local mechanoelectrical transduction (MET) channel receptor current, and its relationship with the input stimulus follow a 2-state Boltzmann function:

$$\mathrm{CM} = V_{off} - V_{sat} + \left(\frac{2V_{sat}}{1 + \exp\left(2 \cdot S \cdot V_{sat} \cdot (\mathrm{input} + \mathrm{OP})\right)} \right)$$

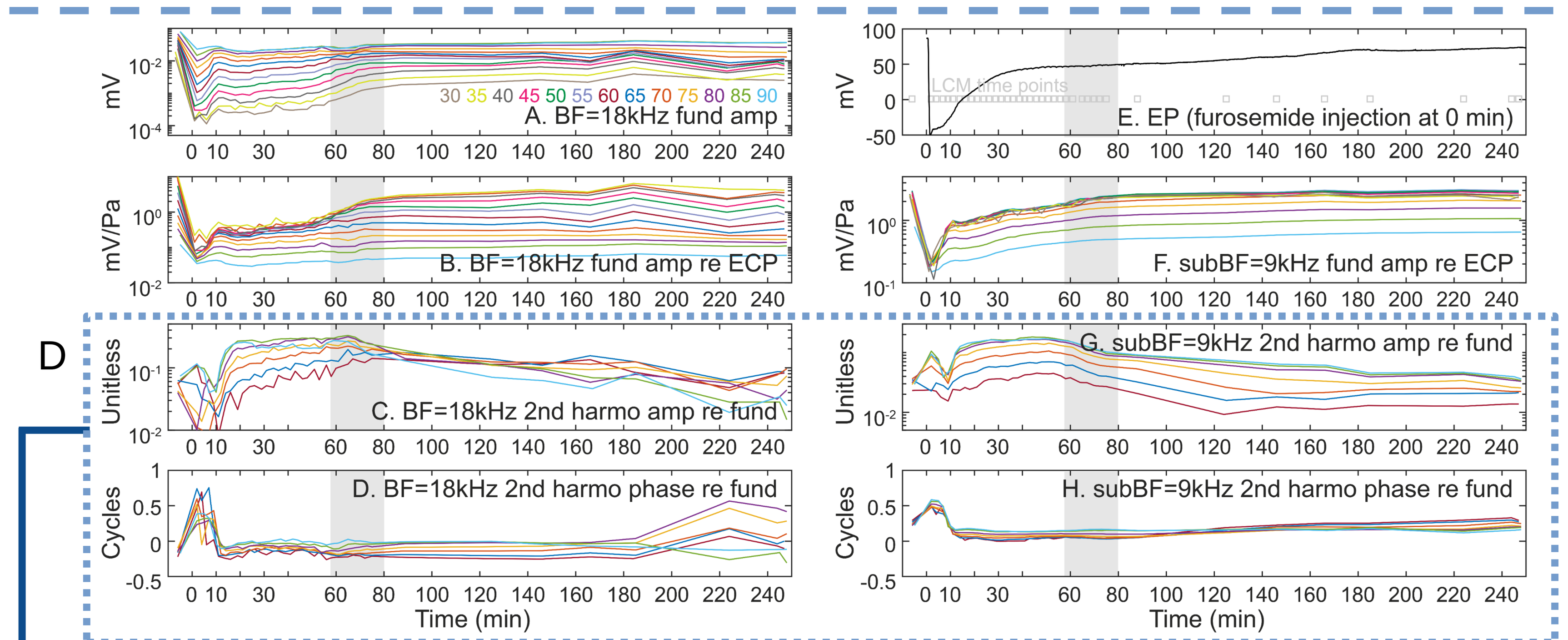


OP is the operating point of this OHC transduction curve.

If the OP is shifted, the waveform will become asymmetrically distorted.

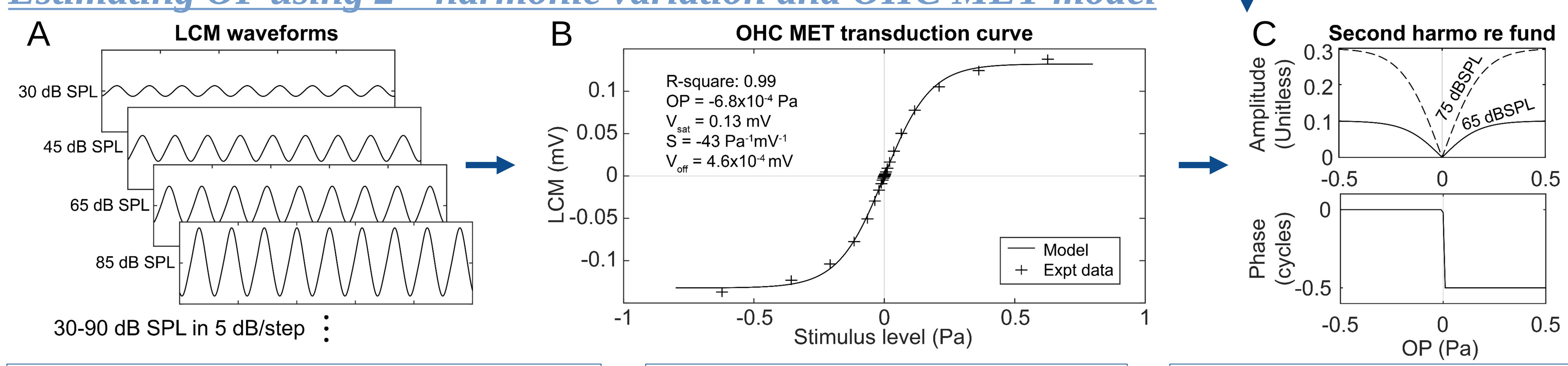


The normalized 2nd harmonic amplitude plotted vs. OP is V-shaped.



Analysis

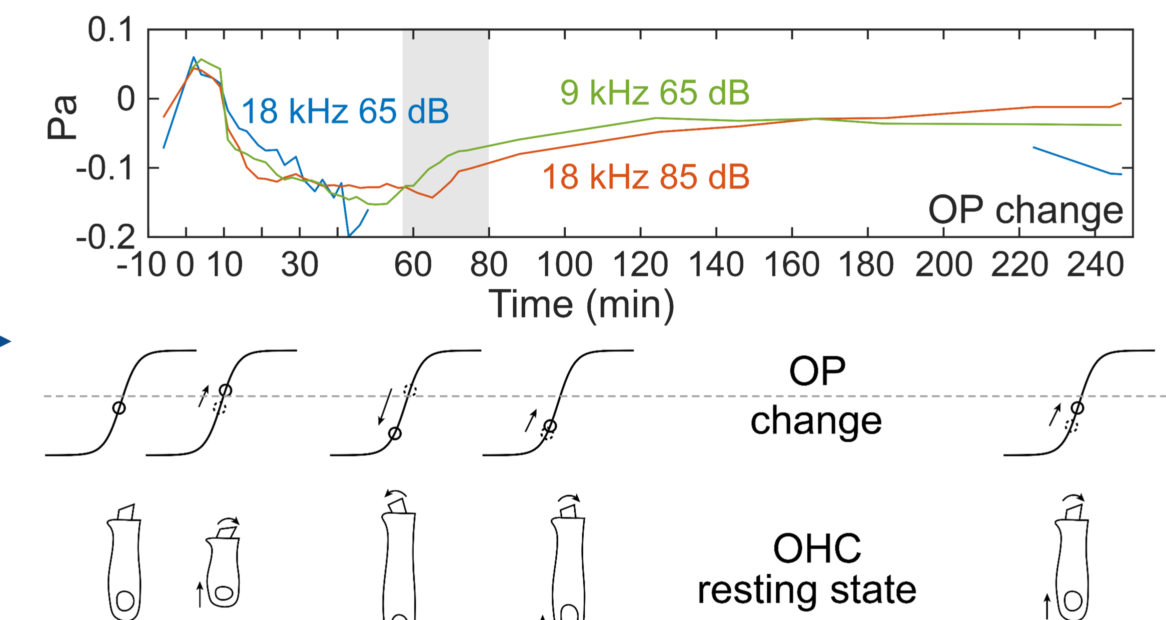
Estimating OP using 2nd harmonic variation and OHC MET model



1. The LCM waveforms were reconstructed using the fundamental, 2nd and 3rd harmonics. The response at 8 min was used to generate the model, because at the time: the cochlear amplification was ~ inactive; and the transduction curve was most symmetric.

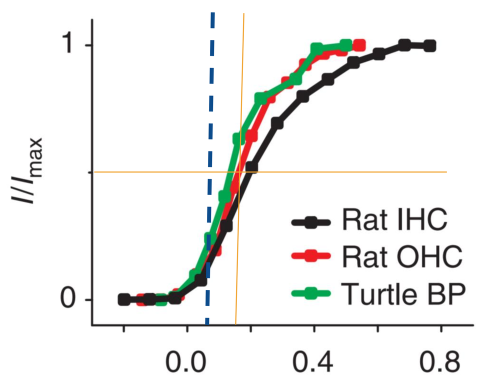
2. The maximum and minimum value of the waveforms were found, and plotted versus their stimulus levels. The transduction curve was then determined by a Boltzmann model fitting the experimental data.

3. The relationship of OP and 2nd harmonic was simulated using the model. Knowing the experimental LCM second harmonic response (normalized by the fundamental) shown in D, the OP change can be estimated.



Cochlear amplification recovered simultaneously with operating point re-centering

- At 58 – 80 min (shaded area), the OP was re-centered. This recovery was simultaneous with cochlear amplification recovery, evinced by the recovery of nonlinearity in the LCM at low SPL.
- This OP change was possibly induced by the decreased driving voltage hyperpolarizing the OHC soma, causing the OHC to lengthen and shift the position of the stereocilia.



The minimum OP change was ~ -0.15 Pa, which is ~ 20% of the extent of the Boltzmann curve. This corresponding to ~ 10 nm of stereocilia tip displacement (or a BM position shift of this magnitude). (from Peng and Ricci 2011, Fig.2)

We thank the NIDCD (R01DC015362) and the Emil Capita Foundation for supporting this research.