

# Diabetic foot ulcers: improved microcirculation after low-energy laser irradiation

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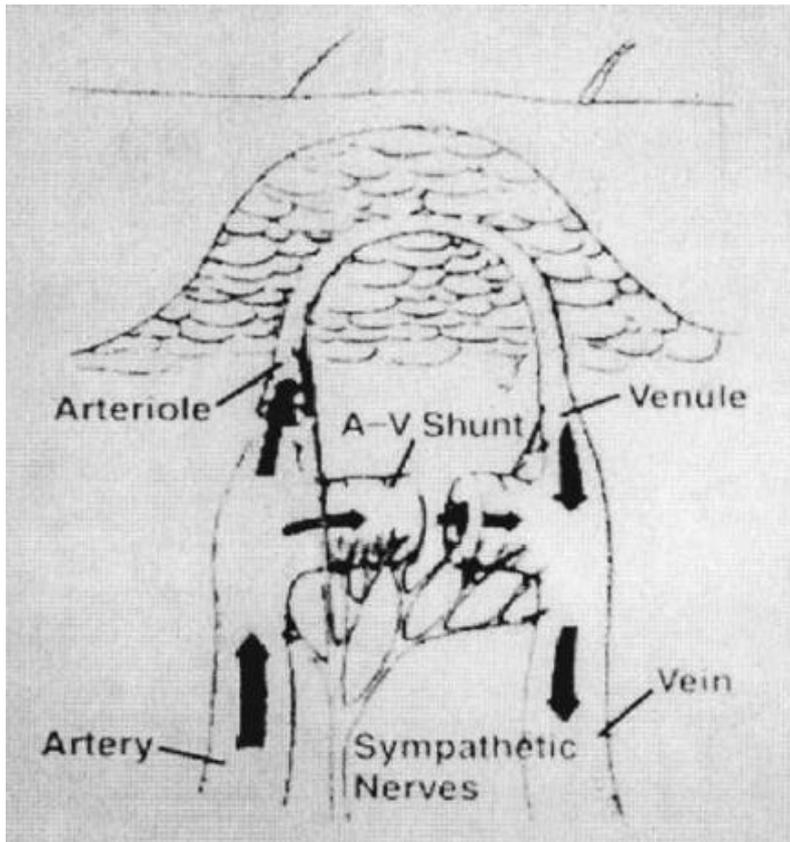
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# Background

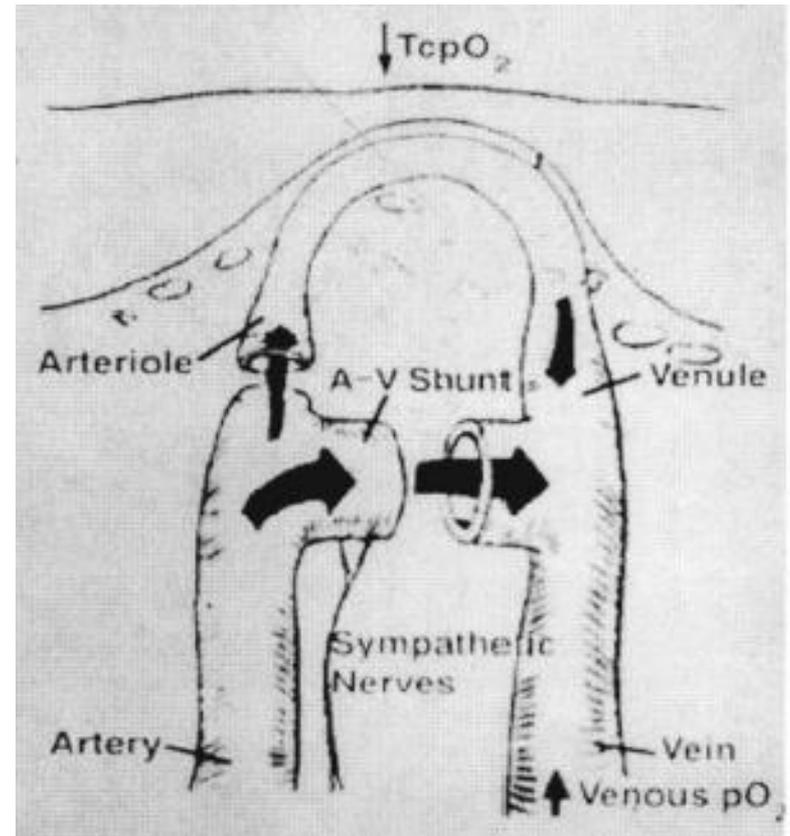
- Resting laser-doppler skin blood flow in diabetic patients is significantly higher than in non-diabetic individuals (high perfusion microangiopathy) due to increased flow through low-resistance arterio-venous anastomoses.
- Low amplitude of oscillations



# Diminished flow through nutritive blood vessels → neuropathic foot ulceration



Normal plantar vasculature



Severe (stage III) diabetic neuropathy

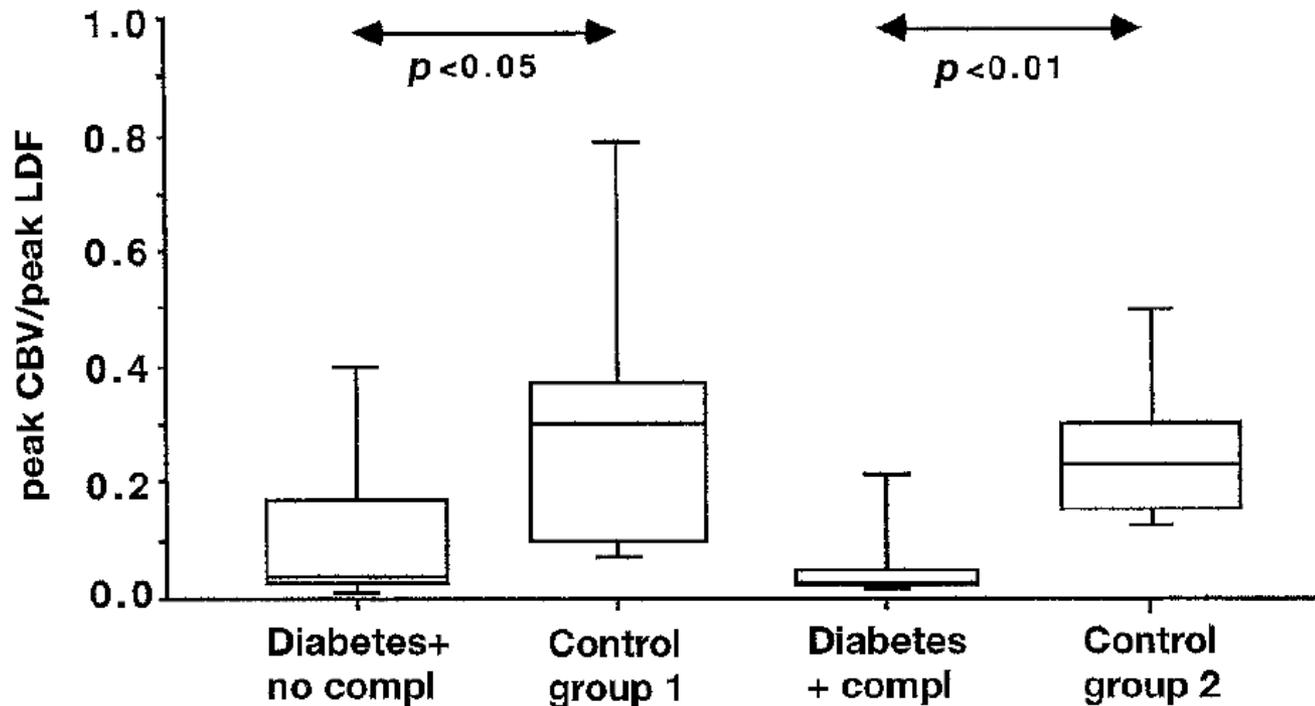
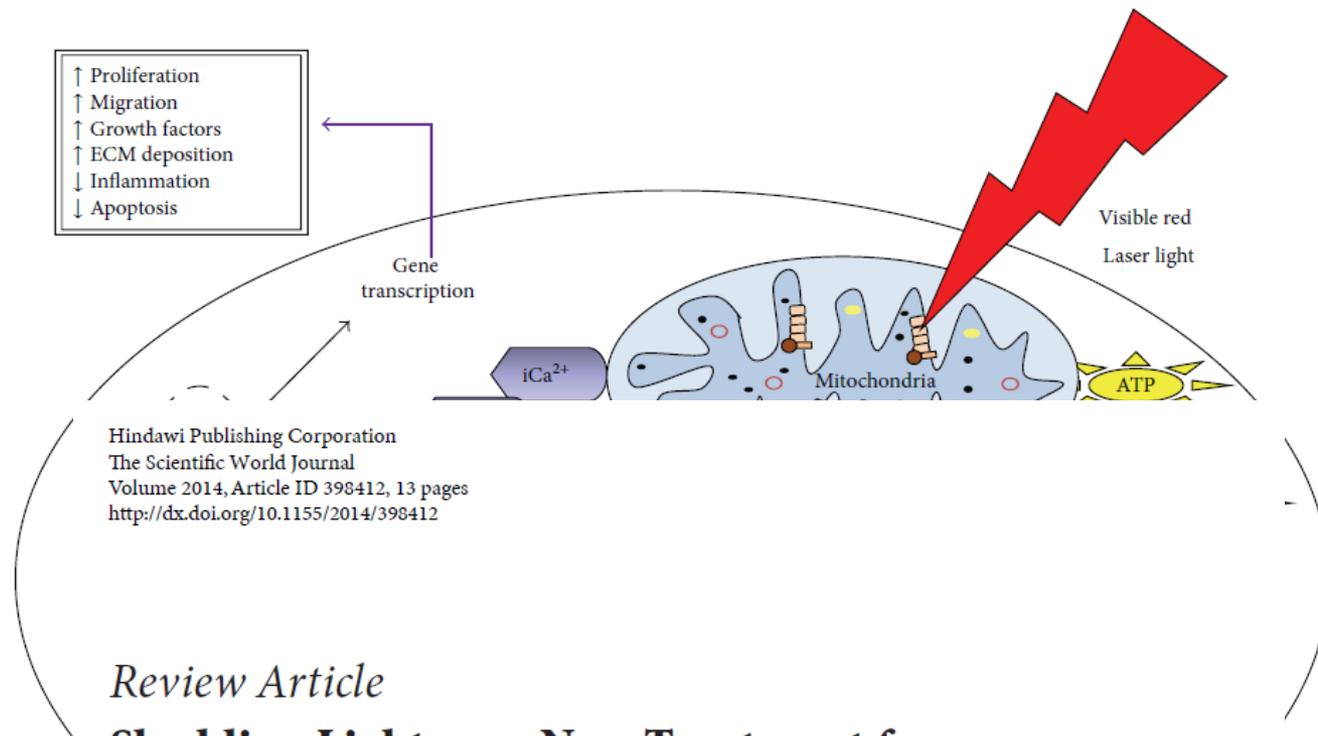


Fig.2. Ratio between peak blood flow in nutritional (CBV) and non-nutritional (LDF) microvascular compartments in diabetic patients with (+ Compl) and without (No compl) complications and their respective control subjects.

# LLLT & impaired circulation

- Low-energy laser beam irradiation has been demonstrated to augment wound healing in conditions of reduced microcirculation (Schindl et al, 1998; Schindl et al, 2002).
- Athermic laser irradiation on one foot in people with diabetes with angiopathy causes a significant increase in skin circulation in both feet and points to the possibility of systemic effects.



*Review Article*

## **Shedding Light on a New Treatment for Diabetic Wound Healing: A Review on Phototherapy**

**Nicolette N. Houreld**

Laser light is absorbed by chromophores in the cell, mitochondria in the case of visible red light. This leads to an increase in adenosine triphosphate (ATP), reactive oxygen species (ROS), nitric oxide (NO), and intracellular calcium (iCa<sup>2+</sup>). There is an activation of transcription factors which get translocated to the nucleus and activate gene transcription. This leads to increased cell survival and wound healing.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3913345/figure/fig2/>

# Possible mechanisms

- Promotion of proliferation and migration of human epidermal stem cells (Hourelid NN, Scientific World Journal; 2014)
- Enhanced angiogenesis (Dungel P et al, Lasers Surg Med; 2014)
- Reduction of TNF- $\alpha$  concentration and enhancement of cell proliferation (Góralczyk K et al. Lasers Med Sci; 2016 )
- Increased skin blood perfusion (Saied et al, Lasers Med Sci; 2011)

# Evidence-based recommendations

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Working Group on the Diabetic  
Foot (IWGDF)

DIABETES/METABOLISM RESEARCH AND REVIEWS

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SUPPLEMENT ARTICLE

## **IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes**

8. Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care. (strong; low)

# Aim of the study

We sought to investigate the influence of low-energy laser beam irradiation on microvascular blood flow.

# Study subjects

- 12 diabetic patients with chronic foot ulceration (D):
  - 3 F, 9 M
  - Average age  $62,3 \pm 10,21$  years
  - HbA1c  $8.97 \pm 1.11$  %
  - ankle/brachial index  $1.18 \pm 0.25$
  - Foot ulcer size  $4,01 \pm 4,93$  cm<sup>2</sup>
- 9 healthy controls (C):
  - 3 F, 6 M
  - Average age  $49,0 \pm 11,2$  years

# Low-level laser therapy

- portable BTL – 2000 laser therapy device, power 100 mW, wavelength 830 nm
- frequency 4 Hz
- power density 4 J/cm<sup>2</sup>



# Protocol

- 5 sessions of pulsatile low-level laser irradiation at two-day intervals.
- Laser-Doppler flowmetry on the sole of the ulcerated foot for 30 minutes at baseline, after the first session of LLLT, before and after the final session of LLLT
- Spectral analysis of the laser-Doppler blood flow signal by wavelet transform

# Spectral analysis

- The dynamics of biologic signals (blood flow, heartbeat) consists of several periodic oscillations whose characteristic frequencies are not constant but rather vary with time.
- With time-frequency analysis, spectral properties of biologic signals can be observed.
- Wavelet transform is a non-linear method of spectral analysis which provides excellent frequency resolution for the low frequency components.

# Wavelet transform

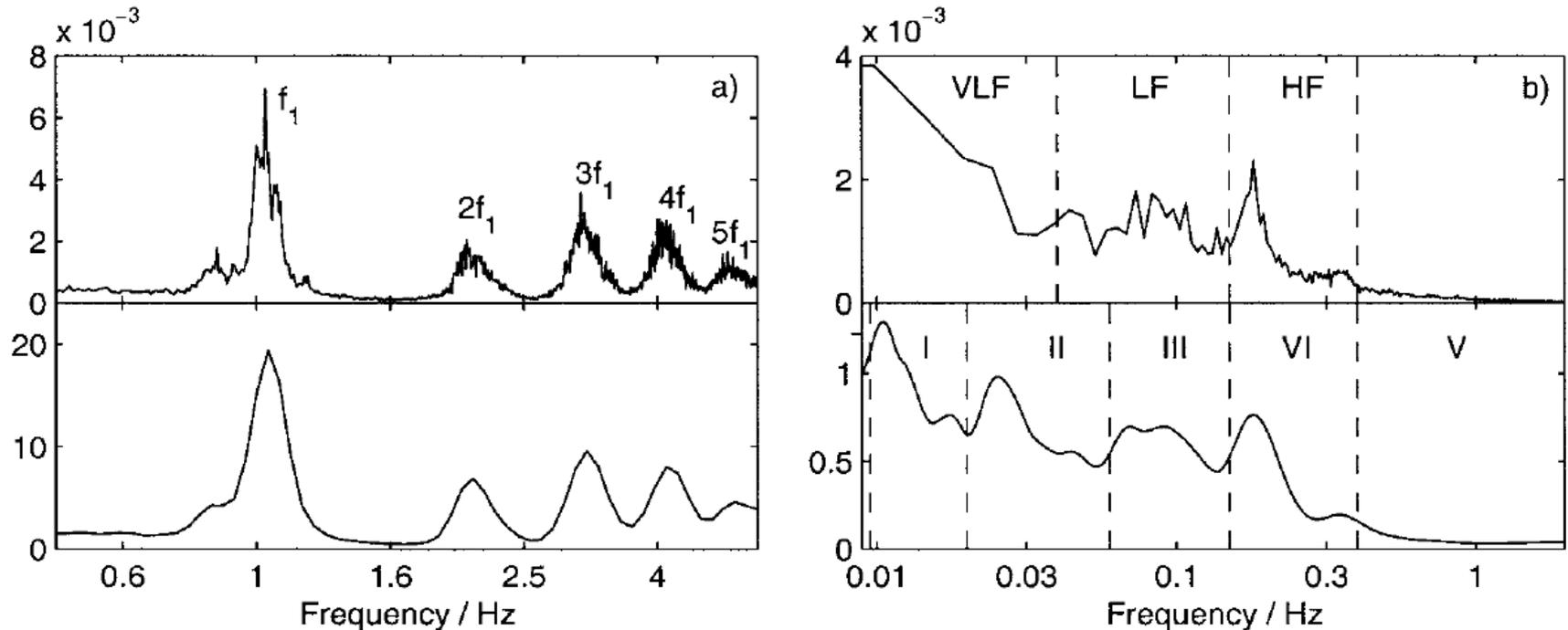


Figure 6. Fourier (top) and wavelet (bottom) transforms of (a) the ECG and (b) HRV signals. The Fourier spectra are obtained as an average of spectra calculated for 200 s time segments, shifted along the signal for 100 s. The wavelet transform is also averaged in time, obtained with (a)  $f_0 = 3$  and (b)  $f_0 = 1$ .

# Spectral analysis of LDF signal

by wavelet transform:

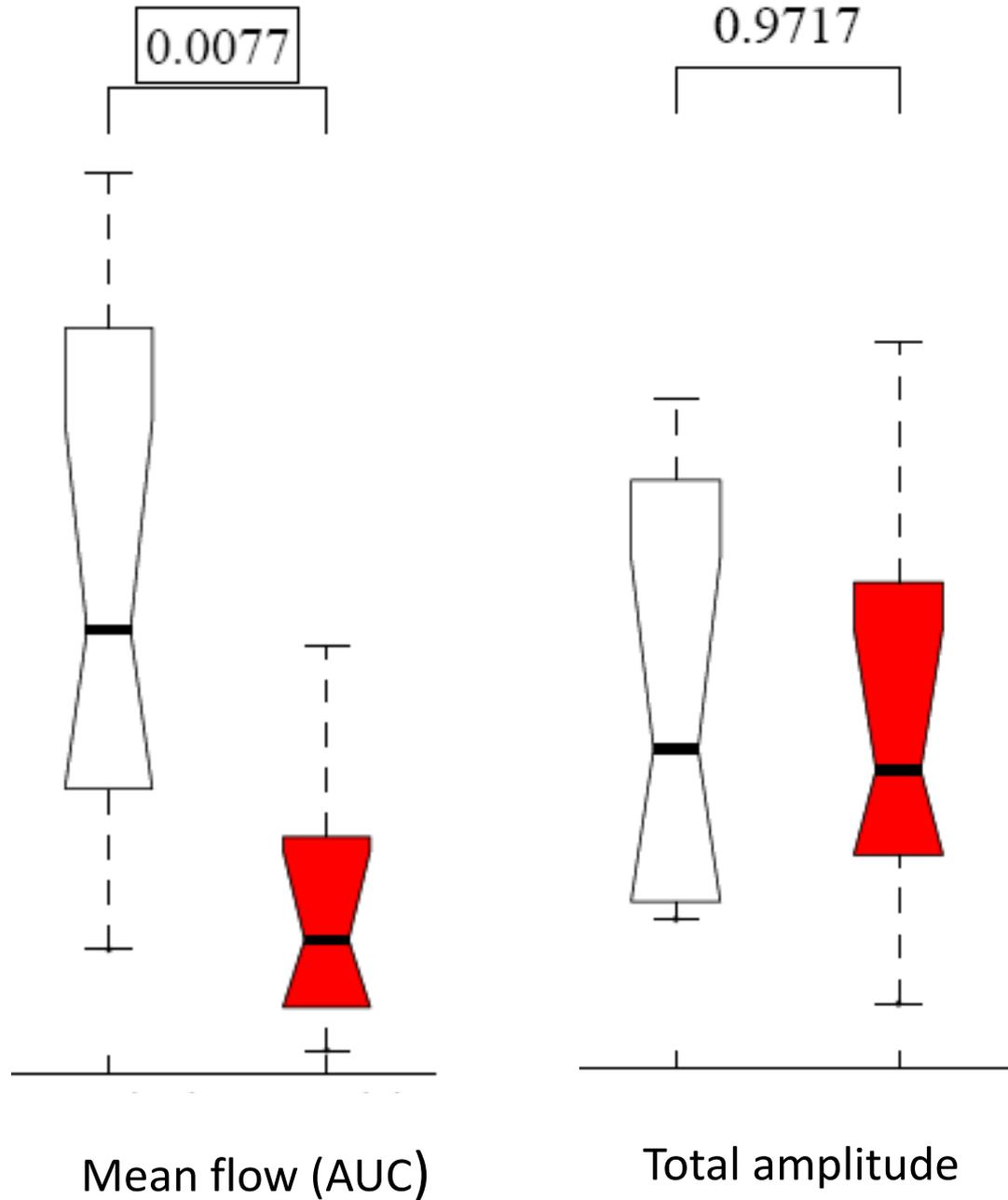
6 characteristic frequency peaks

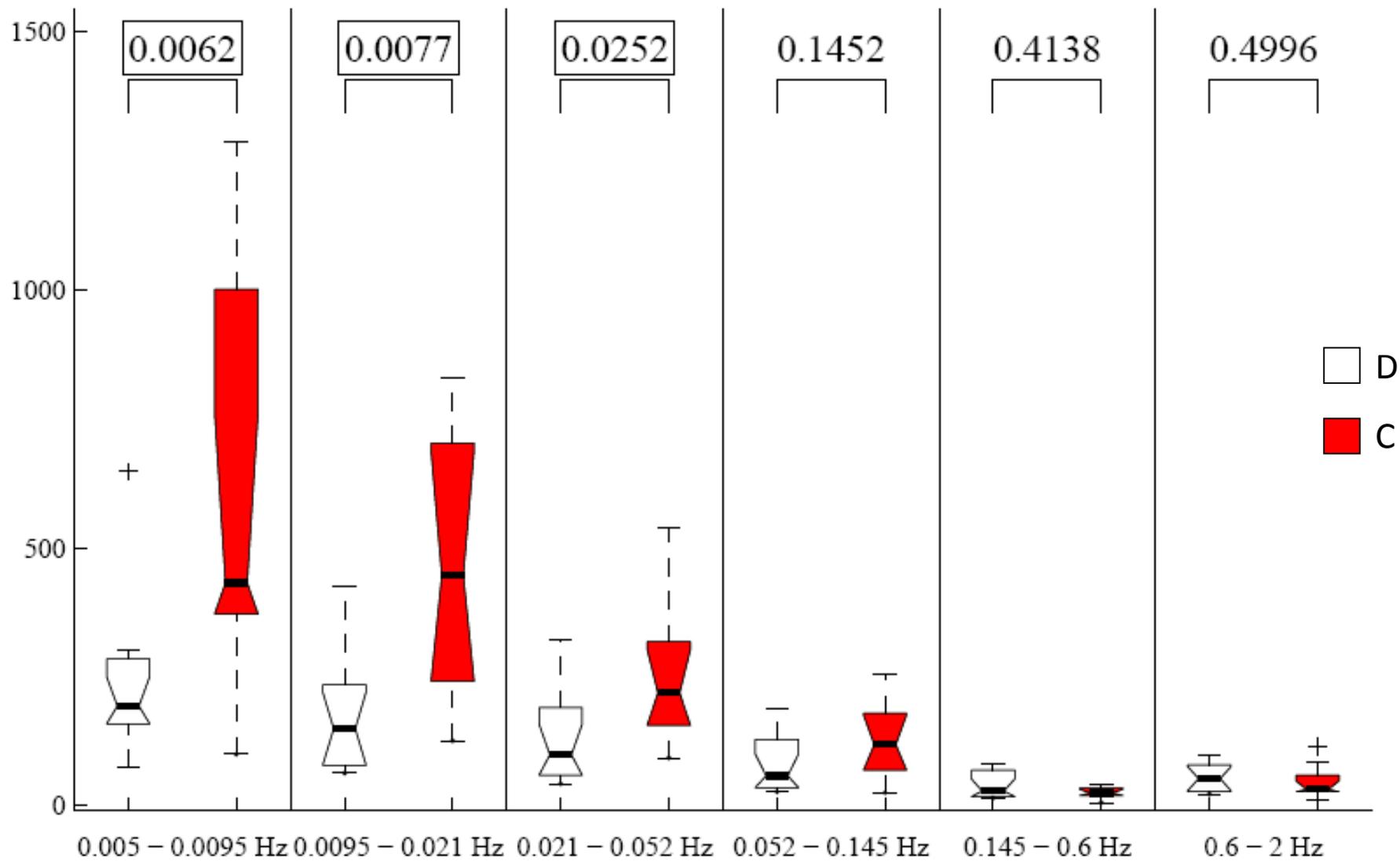
- 0.005-0.0095Hz (endothelial activity)
- 0.0095–0.021Hz (endothelial activity)
- 0.021–0.052Hz (sympathetic nerve activity)
- 0.052–0.145Hz (myogenic activity)
- 0.145–0.6Hz (synchronous with respiration)
- 0.6–1.6Hz (synchronous with heart rate)

# Results

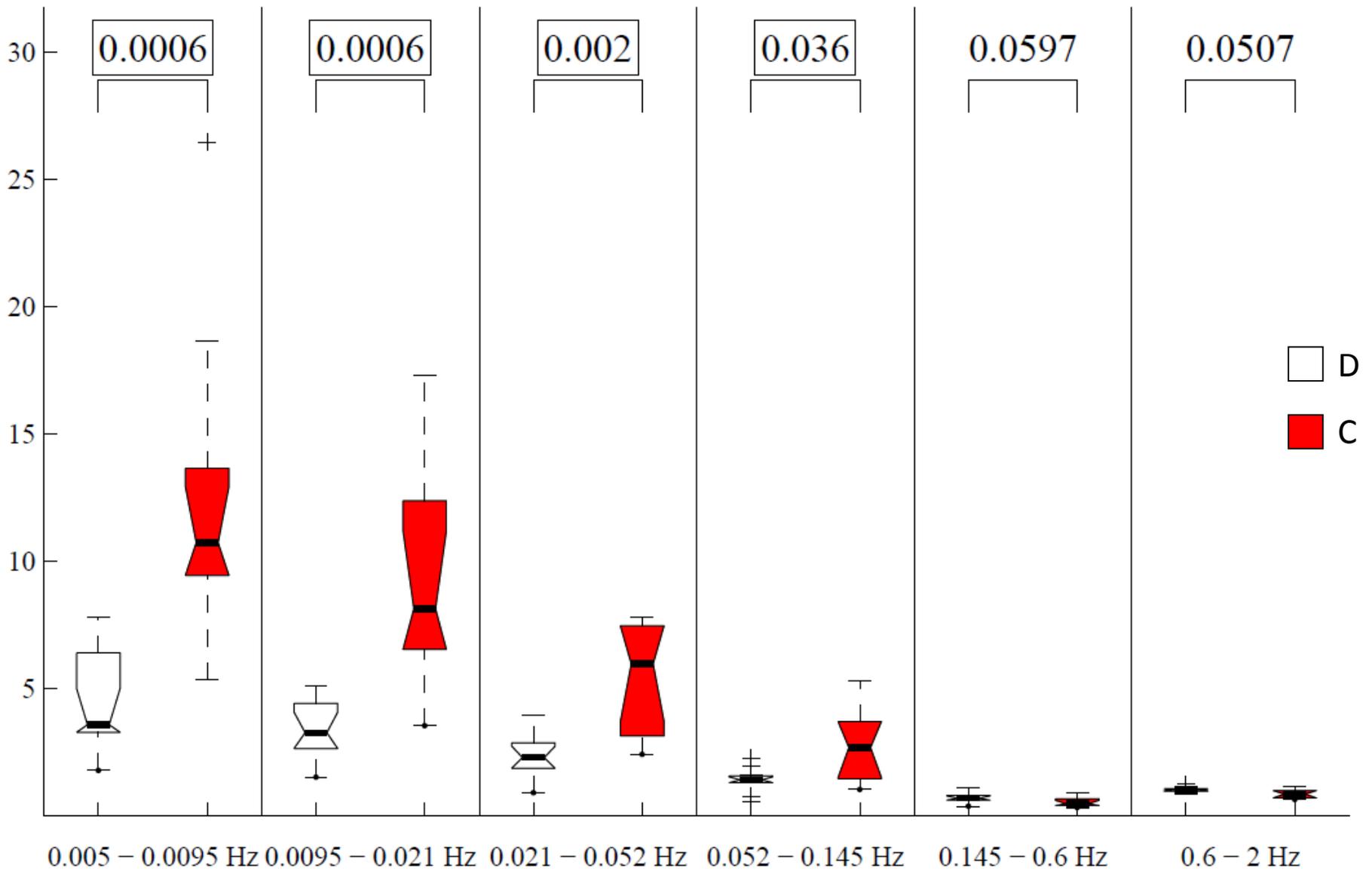
# Baseline

- Diabetic patients (D)
- Healthy controls (C)



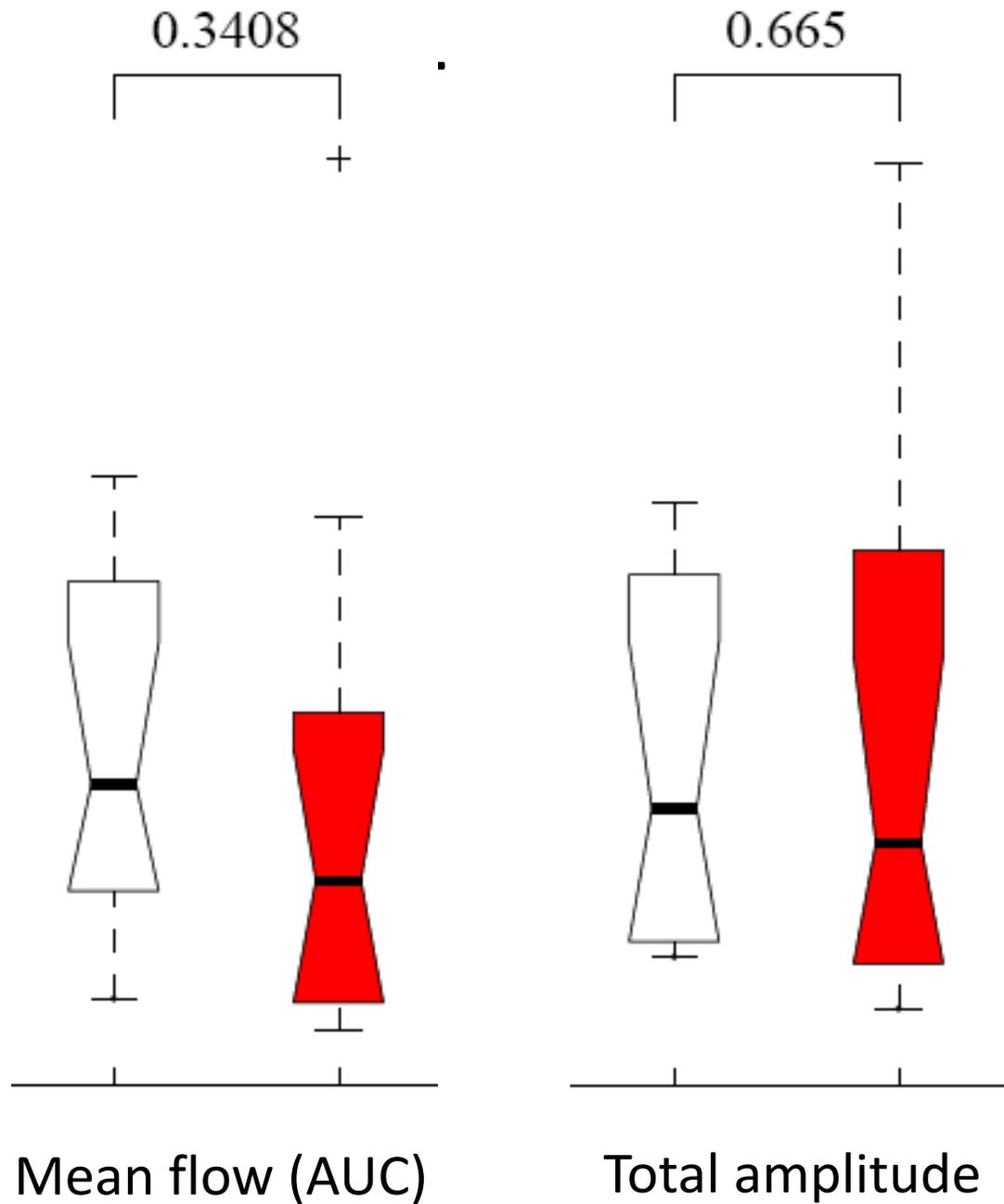


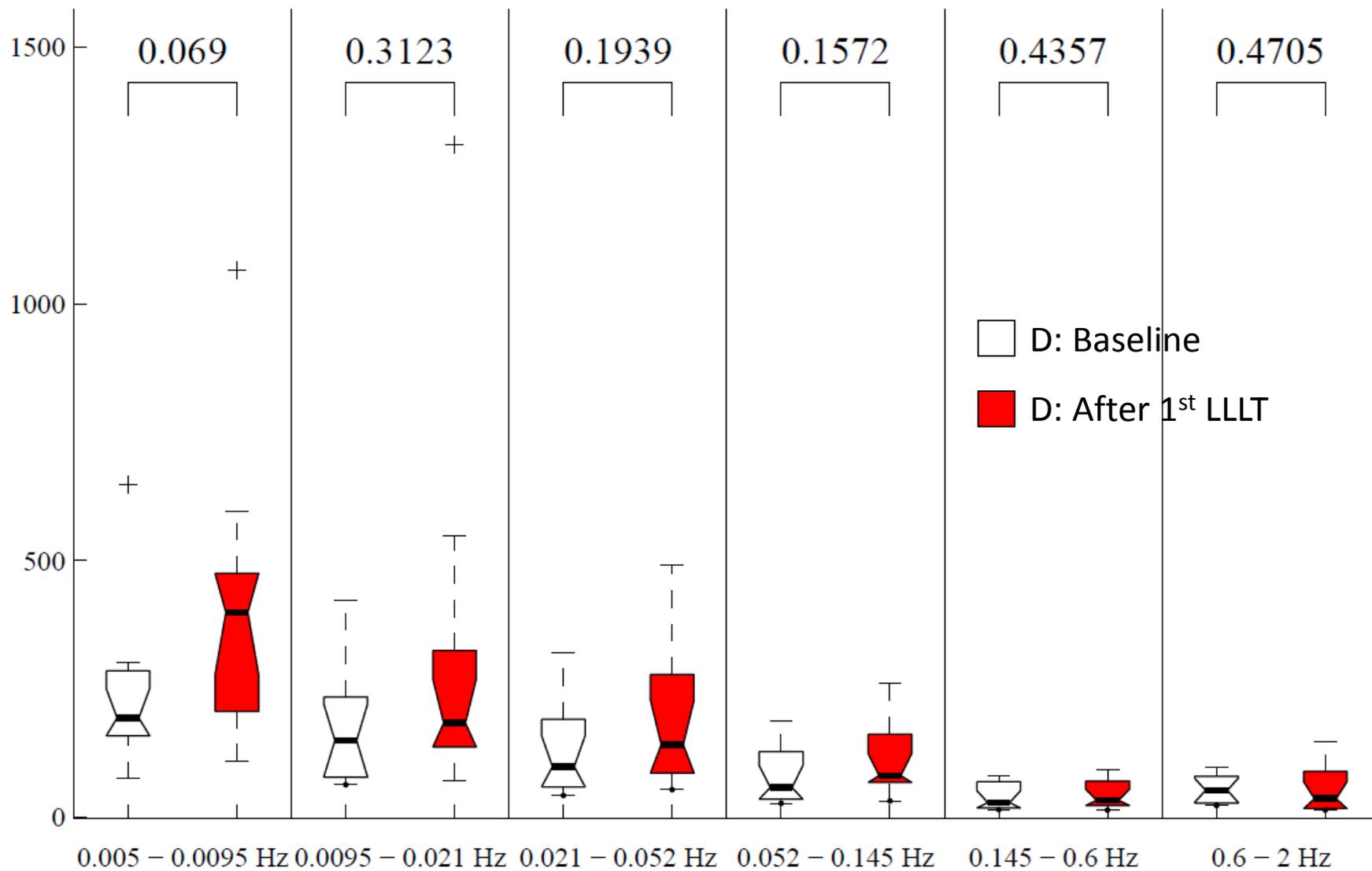
Absolute amplitudes, baseline



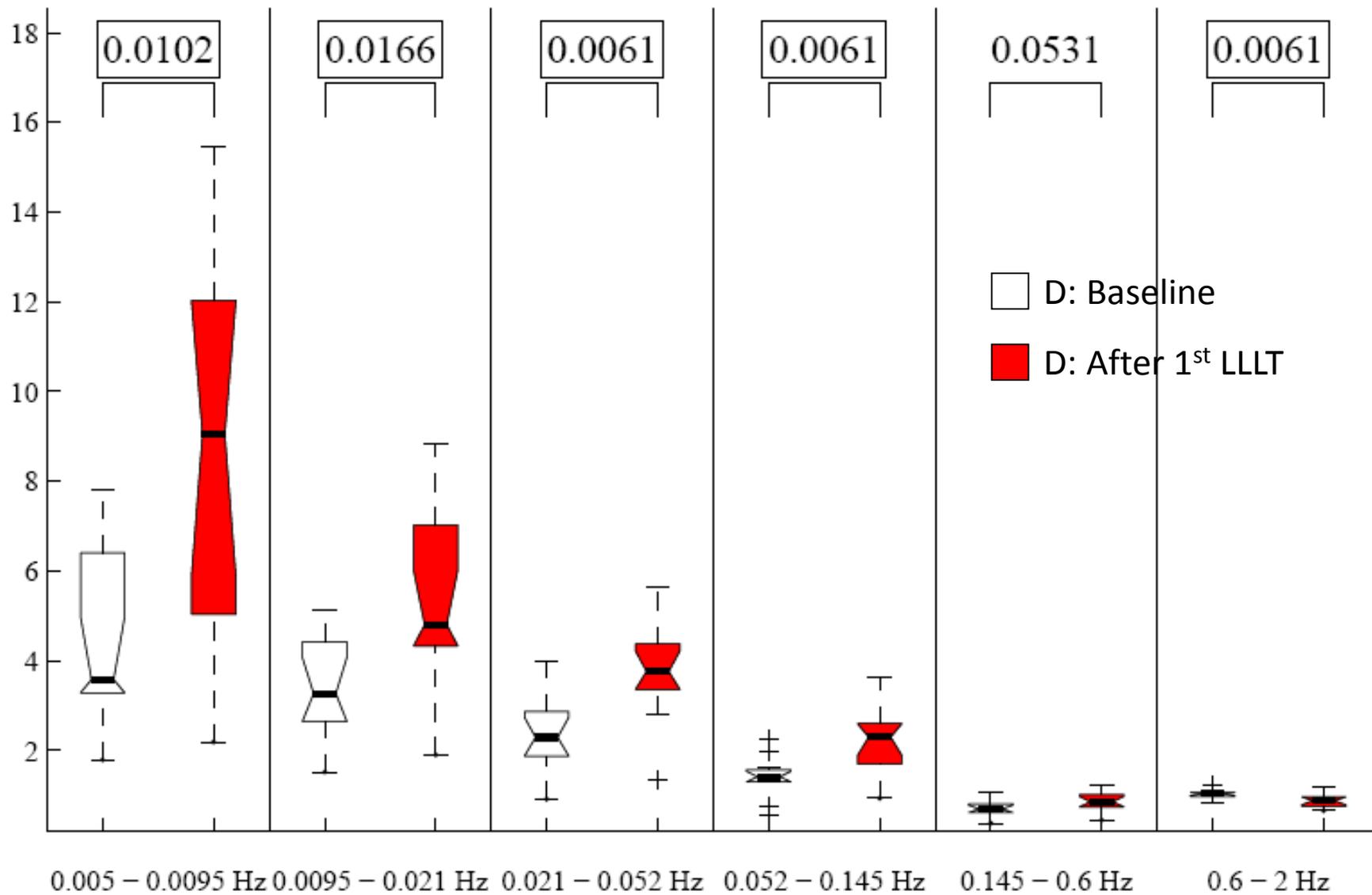
Normalized amplitudes, baseline

□ D: Baseline  
■ D: After 1<sup>st</sup> LLLT





Absolute amplitude



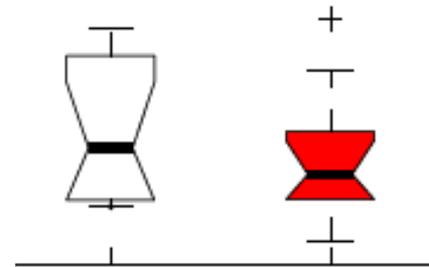
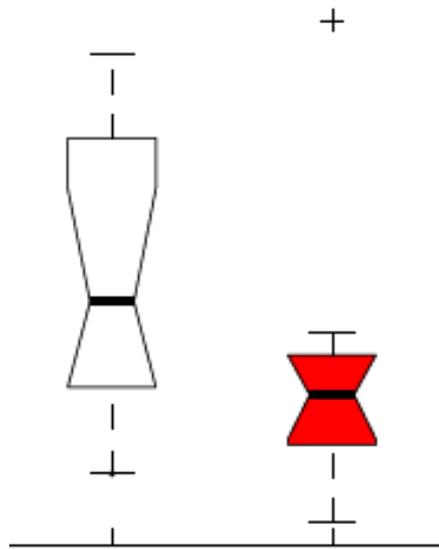
Normalised amplitude

0.0806

0.4887

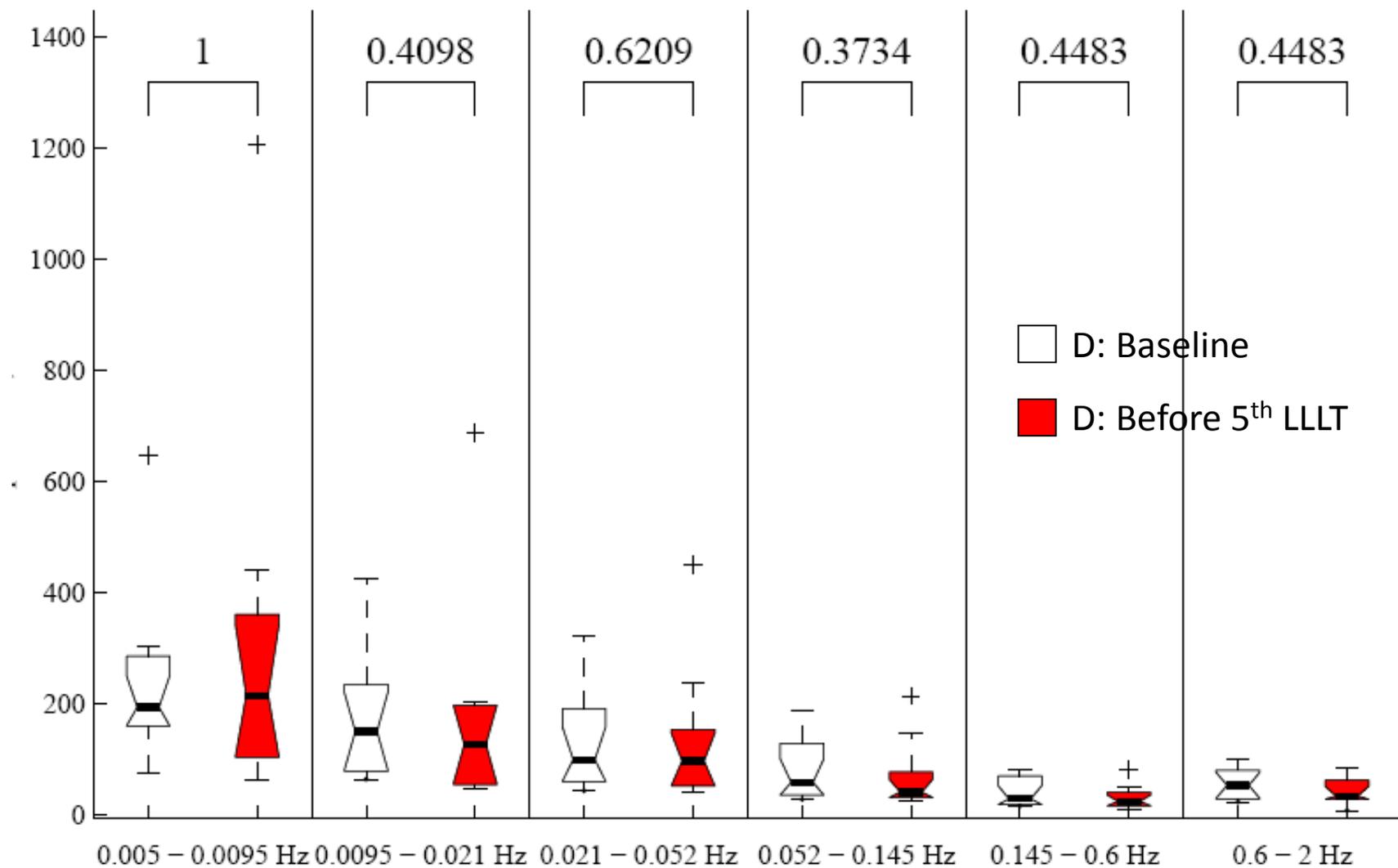
□ D: Baseline

■ D: Before 5<sup>th</sup> LLLT

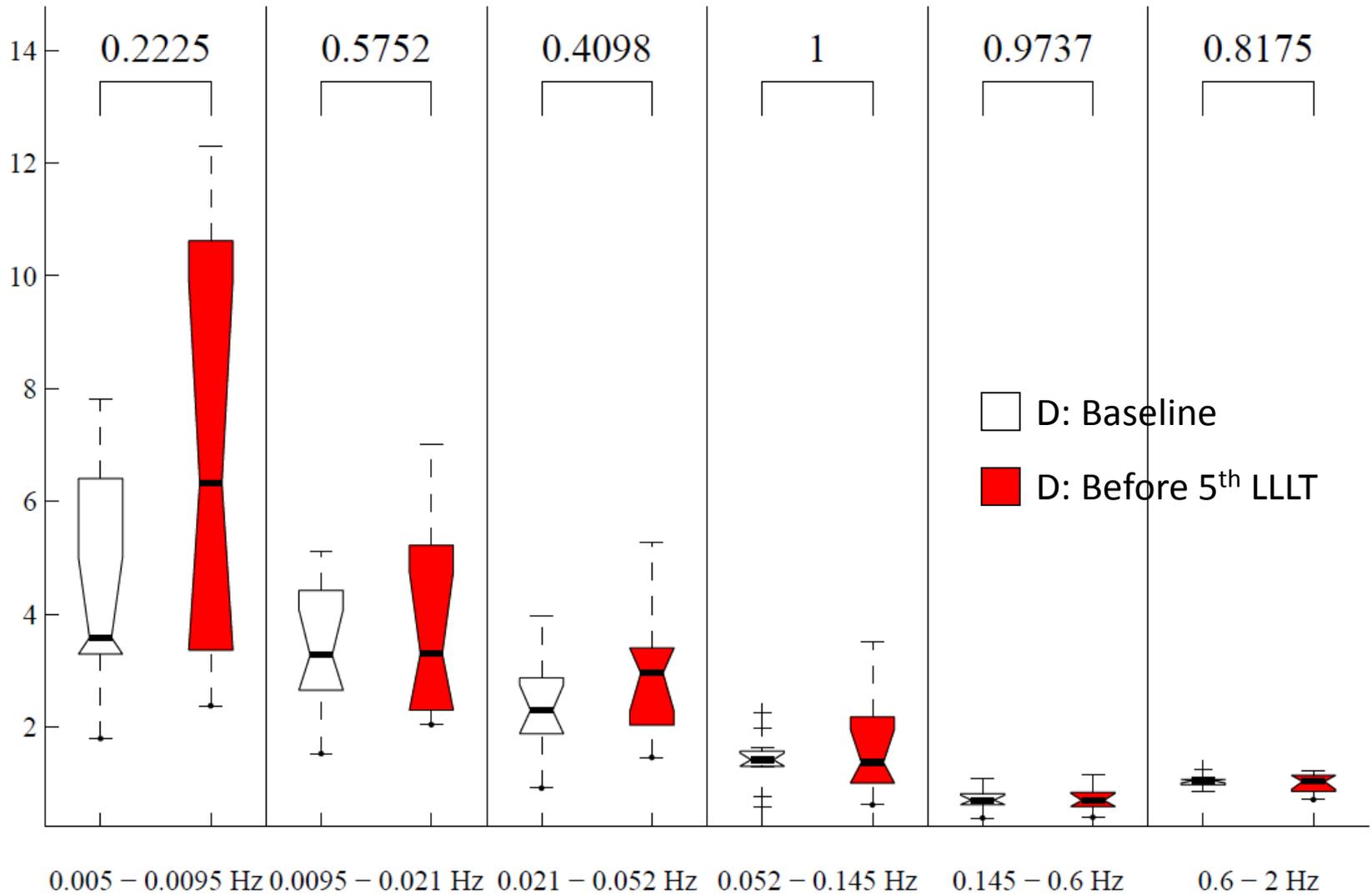


Mean flow (AUC)

Total amplitude

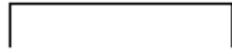


Absolute amplitude

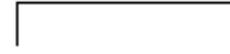


Normalized amplitude

0.9048



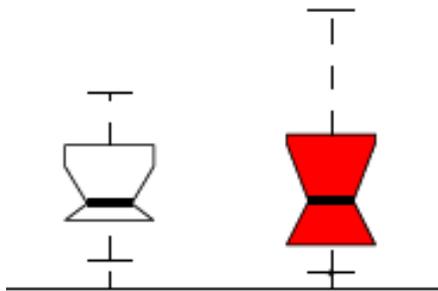
0.1564



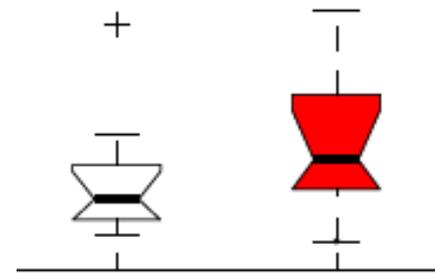
□ D: After 5<sup>th</sup> LLLT

■ C: Baseline

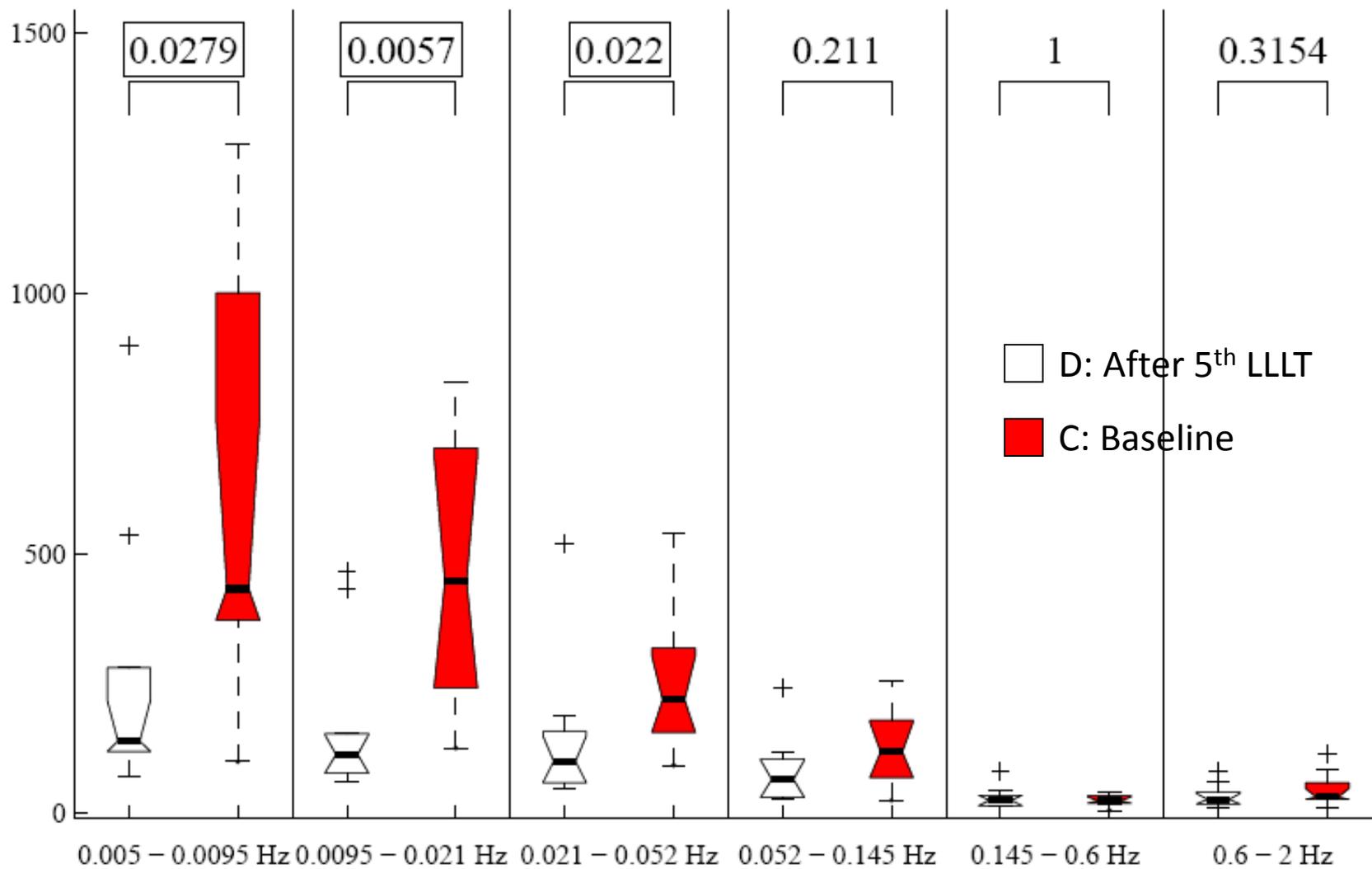
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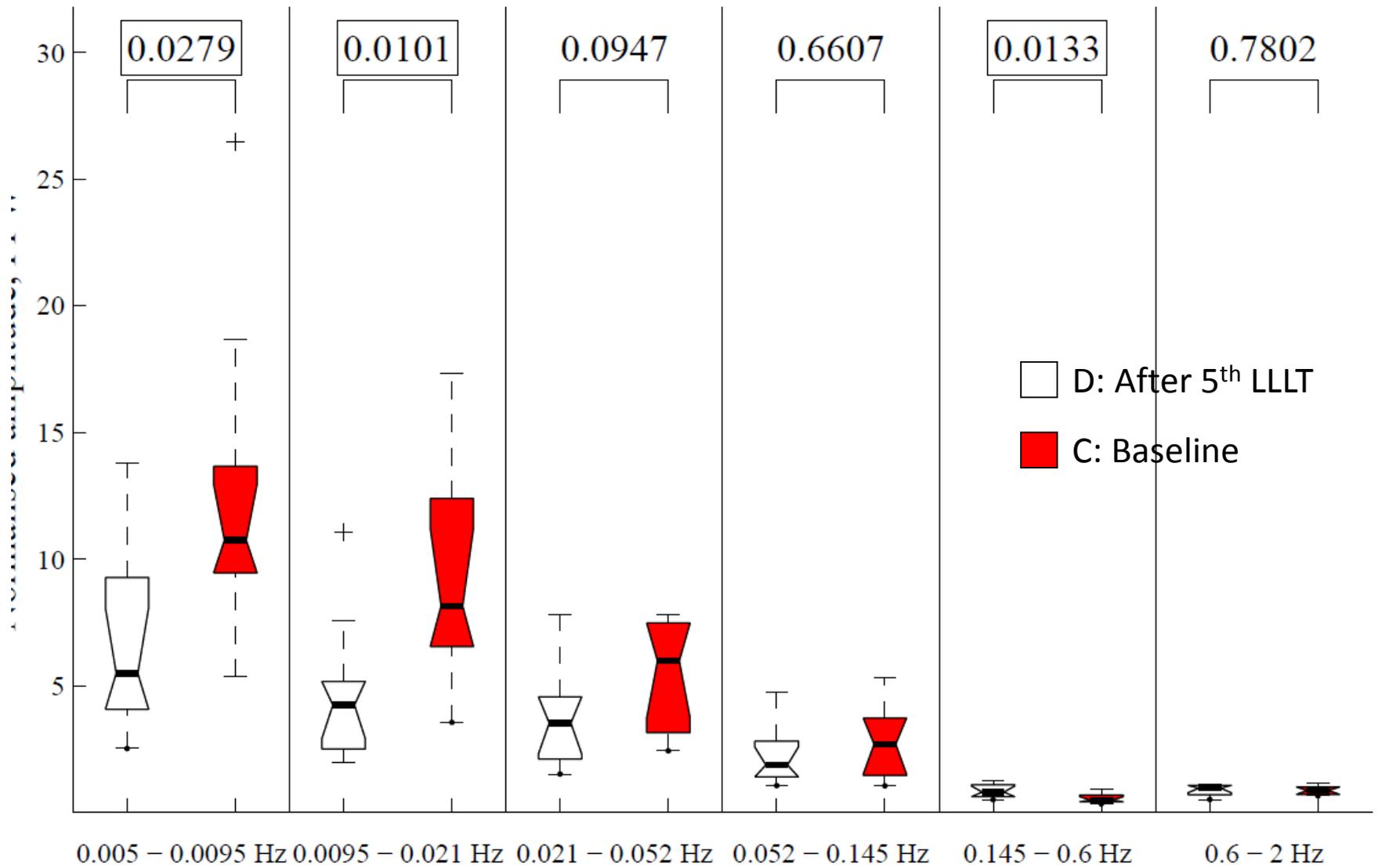
Mean flow (AUC)



Total amplitude



Absolute amplitude



Normalized amplitude

# Conclusion

Low level laser irradiation enhances wound healing through a favourable influence on microvascular flow dynamics:

- Decreased mean laser-doppler skin blood flow
- Increased amplitude of the low-frequency oscillations (endothelial and sympathetic nerve activity)

but...

- Short term / long term effect?

