Catheter tip ultrasound mediated nanodroplet to microbubble conversion for intravascular therapeutic applications

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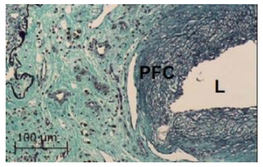
Introduction

Background

- **Vascular blockage diseases** including **thrombosis**, **chronic total occlusions (CTO)**, or **atherosclerosis** are a leading cause of disability and mortality
- **Therapeutic intravascular ultrasound** in combination with **microbubbles** is a promising therapy for treating these **blockages**
- We have previously reported the development of a novel **catheter-based transducer** using a radially polarized annular geometry which allows for the **introduction** and **stimulation** of cavitation agents adjacent to an occlusion



CTO Histology
(Jaffe et al JACC 2009)

- **Nanodroplets** have shown potential as alternative cavitation agents which can be **converted** to microbubbles directly at target sites, **reducing risks** of premature destruction during introduction and allowing potential **advantages** such as enhanced population control or improved agent extravasation into blockages

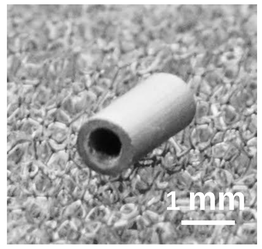
Objectives

- Demonstrate conversion of liquid phase nanodroplets to microbubbles using our catheter tip ultrasound transducer

Methods

Transducer

- The **forward-looking catheter-based** transducer is built from a **compact** (~1 mm diameter) **cylindrical** piezoelectric single element
- The **internal lumen** can accommodate a **guidewire** and permits **fluid injection** (e.g. nanodroplets, microbubbles, enzymes)
  - An internal thin-walled steel tube provides the electrical connection and physical protection
- By operating at different **resonant modes** we can produce both **high forward-directed pressures** (e.g. length modes) for the sonication of agents adjacent to blockages or **high internal pressures** within the lumen (e.g. radial or complex modes) for the activation of nanodroplets
  - **>3 MPa** PNP 0.5mm from surface at 1.6 MHz
  - Pressures produced within the lumen can be many times higher than external pressures



Representative active element

Transducer design

Hydrophone Measurements

- Fiber optic hydrophone scans characterize the spatial distribution of pressure at different frequencies through **pressure maps** and **on-axis frequency sweeps**

FEA Simulations

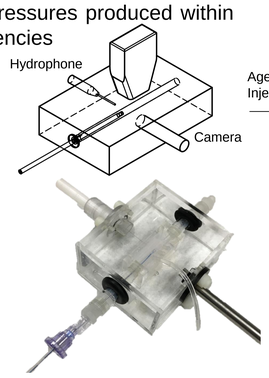
- **FEA simulations** in OnScale allow probing of pressures produced within the transducer lumen, particularly at higher frequencies

Nanodroplets

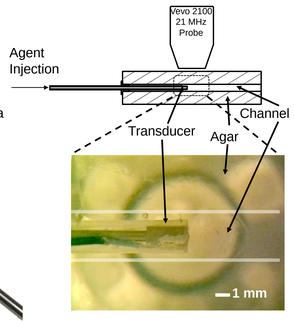
- Fluoropropane filled lipid shelled MBs formed via mechanical agitation
- Condensed using dry ice

Vessel Phantom

- Testing the conversion of nanodroplets to microbubbles using the catheter transducer was done in a vessel phantom
- Vessel channel cast in **agarose**
- **Syringe pump** controls flow
- Water bath held at 37 C
- High resolution high frame rate ultrasound imaging using Vevo 2100 system and **21 MHz probe**



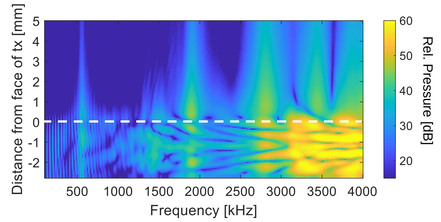
Vessel phantom apparatus



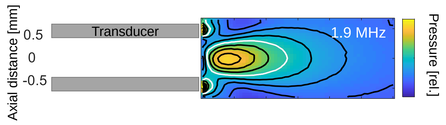
Cross-sectional view

Results

Hydrophone Measurements

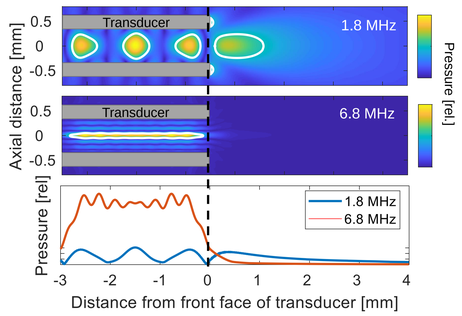


On-axis position and frequency hydrophone sweeps for a 2.5 mm transducer show resonant frequencies at the length mode (0.6 kHz), 3rd harmonic (1.9 MHz), and 5th harmonic (2.9 MHz) which project pressure **away from the transducer face** (above white dashed line) at potentially **therapeutically relevant frequencies**, while complex resonant modes at **higher frequencies** (>3 MHz) show high pressures within the transducer lumen which could be exploited for **nanodroplet activation.**



Representative pressure map of a 2.5 mm transducer operating at 1.9 MHz demonstrates **projection of pressure** outwards from transducer face for potential therapeutic application.

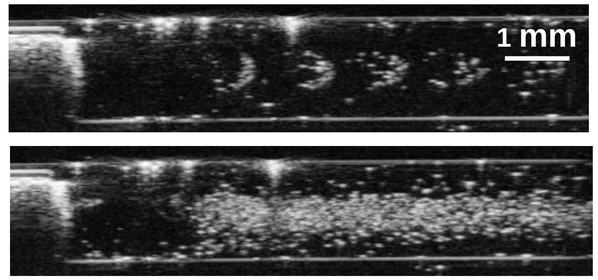
FEA Simulations



FEA simulations of a 3 mm transducer showing pressure maps for (top) a 1.8 MHz 3rd harmonic **length mode** that results in substantial **forward projected** ultrasound and (middle) a higher frequency 6.8 MHz **radial resonant mode** resulting in prominent **internal standing waves** and (bottom) pressure measurements along the central axis for both of these cases highlighting the high pressures localized within the transducer lumen with the high frequency mode while the lower frequency mode projects pressure further outwards from the face of the transducer.

Vessel Phantom Experiments

See "Videos" section on virtual poster



Ultrasound images of vessel phantom with transducer tip visible at left side. These demonstrate the successful conversion of nanodroplets to microbubbles as the droplets flow through the catheter and experience high pressures within the transducer lumen before the activated microbubbles flow out of the catheter tip. Sonication parameters for both scenarios are 5.75 MHz, 7 cycles, 60 V_{pk-pk} and injection flow rate of 75 mL/hr. A PRF of 1 s gives (top) showing activated droplets forming a banding structure, while a faster PRF of 10 ms gives (bottom) showing activated droplets filling entire chamber.

The degree of conversion of the nanodroplets depended on

- **Agent dilution level**
  - 1:50 to 1:1000
- **Injection flow rate**
  - 10 to 100 mL/hr
  - A slow flow rate relative to activation pulse interval ensures droplets are still within the lumen during a pulse, however it should be sufficiently high so the converted microbubbles can exit the lumen shortly after activation so that they do not get destroyed by subsequent pulses
- **Pulse length**
  - 4 to 20 cycles
  - Generally conversion was seen starting around 4 cycles and peaked around 12 cycles, and decreased beyond that
- **Pulse repetition frequency**
  - 1 millisecond to 1 second
- **Sonication frequency**
  - 0.5 to 8 MHz
  - Generally found increased conversion with high frequencies
- **Sonication pressure**
  - Must be sufficient to activate but not too high as to destroy converted microbubbles

Conclusions

- The **conversion** of **nanodroplets** to **microbubbles** at the tip of our catheter based transducer was demonstrated in a vessel phantom
- **Parameters** can be adjusted to achieve the desired droplet **spatial distribution**, such as continuous formation to fill the vessel or intermittent activation to create bands, and initial results suggest higher frequency complex modes result in increased activation
- These **structures** and **pulsing schemes** can have relevance for **optimizing treatment** of intravascular conditions
- We note that **in-situ production** of microbubbles using microfluidic approaches has previously shown **notable benefits** for thrombolysis and other intravascular conditions arising from greater control over microbubble populations
- The approach presented here produces MBs at the catheter tip by using droplets and altering the resonant mode employed and as such may be readily integrated into a relatively simple catheter package

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