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

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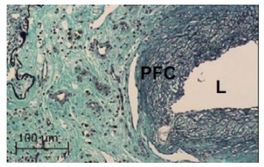
Introduction

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

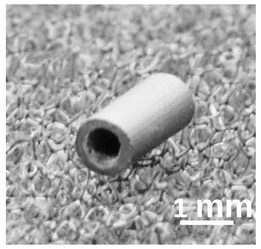
Objectives

- 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
- It can produce **high forward directed pressures** and can operate at different **resonant modes**
  - **>3 MPa** PNP 0.5mm from surface at 1.6 MHz
- Internal **lumen c**an accommodate **guidewire** and **permits fluid injection (e.g. nandroplets, microbubbles, enzymes)**
  - Internal thin-walled steel tube for electrical connection and physical protection
- Radially poled (reduce impedance)
- Higher frequency modes generate large intra-lumen pressures for conversion of nanoddroplets to microbubbles
- Resonant Modes
  - Length (Extensional)
  - Radial
  - Complex modes



Representative active element

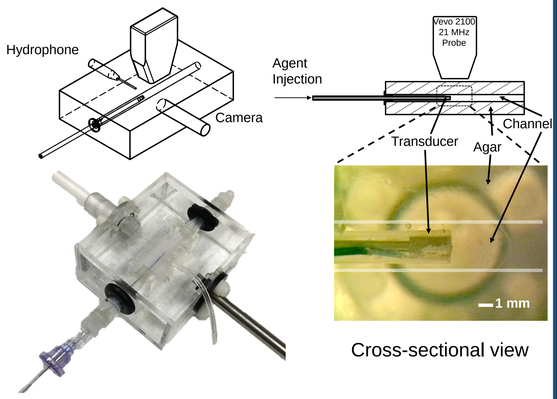
Transducer design

Nanodroplets

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

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**

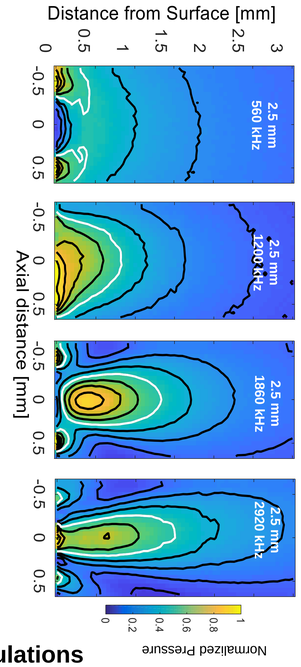


Vessel phantom apparatus

Cross-sectional view

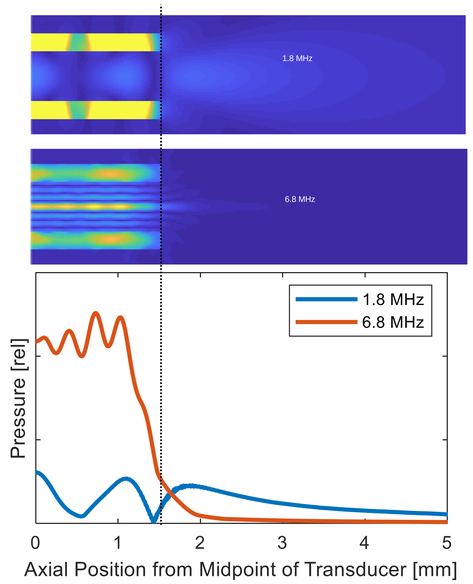
Results

Experimental

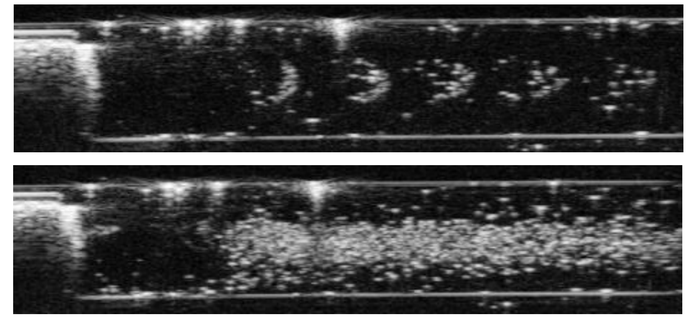


Experimental pressure maps showing the difference in spatial distribution of pressure for a 2.5 mm transducer operated at different resonant modes. Generally higher frequencies will create narrower beams which propagate further, however this is dependant on the particular vibrational mode. Probing pressures internal to the cylinder poses experimental challenges.

Simulations



FEA simulations of a 3 mm length transducer showing pressure maps for (a) a 1.8 MHz resonant mode that results in substantial forward projected ultrasound and (b) a 6.8 MHz radial resonant mode resulting in prominent internal standing waves and (c) pressure measurements along the central axis show internal and external pressure differences between modes.



Ultrasound images of vessel phantom with transducer tip visible at left edge. Sonication parameters are 5.75 MHz, 7 cycles, 60 $V_{pk\text{-}pk}$ and injection flow rate is 75 mL/hr. A PRF of 1 s gives (d) showing activated droplets forming a banding structure while a faster PRF of 10 ms gives (e) showing activated droplets filling entire chamber.

The degree of conversion of the nanodroplets depended on

- **Agent dilution level**
  - 1:50 to 1:1000
  - More droplets increases amount of activation
- **Injection flow rate**
  - 10 to 100 mL/hr
  - Slow flow rate relative to activation pulse interval ensures droplets are within the lumen for conversion, however should be fast enough so that they exit the lumen and do not get destroyed by subsequent pulses
- **Pulse length**
  - 4 to 20 cycles
  - Generally conversion started around 4 cycles and peaked around 12 cycles, then 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 microbubbles

Conclusions

- **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
- 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 benefit**s 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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