Ultrasound-mediated drug delivery for cardiovascular disease

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CVD Drug Delivery: Strategies

Conventional Drug Delivery Strategy:
*Perfuse entire vasculature with drug*
  - tissue specificity
  - systemic effects

Ultrasound-mediated drug delivery:
1. **Target** drug/bubbles to pathologic tissue
   - Antibody conjugation
   - Molecular image-guidance
2. **Trigger** release & penetration
   - Permeabilize barriers
   - Drive drug penetration
3. **Induce** bioeffects
   - Stabilize plaques
   - Inhibit cell proliferation
   - Expedite clot lysis

Sonothrombolysis

- Ischemic Stroke
- Cerebral Hemorrhage
- Myocardial Infarction
- Deep Vein Thrombosis
Acute Ischemic Stroke: sudden cerebrovascular stenosis
- Treatment: I.V. recombinant tissue-type plasminogen activator (rt-PA)
  - 20 – 40% reperfusion, 4-7% hemorrhage. treatment window

Progress: sonothrombolysis to expedite clot lysis

Roger et al., Circulation. 2011.
Sonothrombolysis: Drug Penetration = Lysis

Enzyme penetration: rt-PA

Datta et al. UMB. 2008
Implement an accurate transcranial propagation numerical model. Validate experimentally.

- 1 cycle, 120 kHz sinusoidal excitation
- Simulations compared with hydrophone measurements
- Degassed human skulls
- 15 – 33% pressure reduction (rel. FF)
- Shift in peak pressure position < 2.5 mm
- Homogenous acoustic pressure in MCA

Bouchoux et al. PMB. 2012.
Research Question: Does clot retraction affect extent of sonothrombolysis?

Sonothrombolysis: Ex vivo perfusion model

INFUSION PUMP
PRESSURE TRANSDUCER
FLOW CLAMP
EFFLUENT
120-kHz Therapy Transducer

AFTERLOAD RESERVOIR
PRELOAD RESERVOIR
MEMBRANE OXYGENATOR
PULSATILE PUMP
2.25-MHz PCD
Acoustic Absorber
Sonothrombolysis: Bioeffects

Ex Vivo Thrombosis System

- Plasma Alone
- rt-PA
- rt-PA, Definity + US

US: 120 kHz, 0.48 MPa_{PK-PK}, CW

Cardiovascular Drug Delivery:
US Contrast Agents
Drug Targeting & Image-Guidance: ELIP

Proposed schematic of an Echogenic Liposome (ELIP)

Raymond et al. UMB, (Submitted).
Drug Targeting & Image-Guidance: ELIP Targeting to Smooth Muscle

Neuroprotection

Atherosclerosis

Peripheral vascular disease

Cardiovascular Drug Delivery: Therapeutics
Sonothrombolysis: Ex vivo perfusion model
Bioeffects: Drug penetration

**Bevacizumab (Avastin)**

**Rx:** Anti-angiogenesis

**Size:** 149 kDa antibody

**Form:** BEV-ELIP

BEV-ELIP Sham

Control

BEV-ELIP + US

US: 1 MHz, 0.58 MPa_{PK-PK}, CW
Bioeffects: Bioactive gas delivery

**Nitric Oxide (NO)**
- **Size:** Soluble gas, 30 Da
- **Form:** NO Liposomes
- **Mechanism:**
  \[ \text{NO} + \text{SM} = \text{Vasodilation} + \text{Permeability} \]

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*Image of a device labeled with 'UCP' and a needle labeled '22G Blunt Hypo. Needle.'*
Bioeffects:
Nitric Oxide

Buffer
Nitric Oxide
Liposomes

Arterial Tension (%)

Time after Treatment (s)
Bioeffects: Nitric Oxide

Buffer
Nitric Oxide
Liposomes
Nitric Oxide
Liposomes + US

Arterial Tension (%)

Time after Treatment (s)

US: 1 MHz, 0.18 MPa, 30 cycles, 1% DC
Bioeffects: Nitric Oxide

US: 1 MHz, 0.18 MPa, 30 cycles, 1% DC

Arterial Tension (%)

Time after Treatment (s)
Goal of UC IgUTL:
Investigate possible role of ultrasound to treat cardiovascular disease
- circulatory stability of drug carriers
- ultrasound image guidance, molecular imaging
- tissue targeting
- promote bioeffects, understand mechanism

Current Work:
- Developing/assessing novel drug carrier & US contrast agent (ELIP)
- sonothrombolysis
- drug penetration into tissue & resulting bioeffect
  • fibrinolytic enzymes, bevacizumab, nitric oxide
Thank You

Questions, Comments?