Imaging to Measure Cardiac Contractility: Current and Future

Safety Pharmacology Society
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Jon Heyen on behalf of Bob Coatney
Background / Context / Scope

Contractility = Force generated under very controlled conditions in single orientation (force generated at a constant length)

Myocardial Function / Mechanics under dynamic conditions (preload, afterload, neurologic input etc) in multiple planes and orientations

Imaging offers the evaluation of Myocardial Performance with “Context”
Objectives

- Overview of Non-clinical Cardiac Imaging - Current State
  - Echocardiography and Cardiac Magnetic Resonance Imaging (cMRI)
  - “Routine” Parameters of Cardiac Function (Systolic and Diastolic)
  - Parameters Associated with Cardiac Performance / “Contractility”

- Emerging Techniques to Evaluate Myocardial Mechanics – Future State
  - Strain and Strain Rate Imaging
  - 4 dimensional Imaging (Echocardiography)
  - Functional or Contractile Reserve (Pharmacologic “Stress Echo”)

- Challenges to Greater Application and Acceptance
  - Sensitivity / Capability to detect relevant change
  - Variability - Robust, Repeatable, and Reliable
  - Challenges of “Fitting into” typical safety study paradigms
  - Cost Effectiveness

- Where does Cardiac Imaging “Fit” in Non-clinical Safety Studies?
  - Integrate Cardiac Approach
  - Integration of Structure and Function in most Relevant Context
  - Translation
Echo and cMRI for Cardiac Structure & Function

- **Left Ventricular Structure and Function (Systolic and Diastolic)**
- **Right Ventricular Structure and Function (Systolic) – Largely MRI**
- **Atria and Valves**
  - Mitral Valve lesion
- **Left Ventricular Structure and Function (Systolic and Diastolic)**
Left Ventricular Structure

- Wall thickness
- Left Ventricular Mass
- Chamber dimensions & Volumes

Volumetric, planar and single point approaches

- SHR-SP
- Normal Diet
- Fat / Salt Diet 16 weeks
- FSD + Drug 16 weeks

Aortic Banding

Anterior LV Wall
LV Chamber Diameter
Posterior LV Wall

M-Mode

cMRI
Left Ventricular Function

- Left Ventricular Systolic Function
  - End Diastolic Volume
  - End Systolic Volume
  - Stroke Volume
  - Cardiac Output / Index
  - Ejection Fraction
  - Fraction Shortening
  - Fractional Area Change

- Volumetric Techniques
  - Fast cine MRI
  - 3 & 4 Dimension Echocardiography

- Geometric Techniques
  - Multi – slice or plane reconstructions

- Blood Flow
  - Outflow Doppler
  - Velocity encoding MRI

Myocardial Infarction (MI)
- Normal EF=75%
- MI EF=19%

Tsusaki et.al, J Med. Primatol. 2006
Left Ventricular Function

Left Ventricular Diastolic Function

- **Transmitral Doppler**
- **Myocardial Tissue Doppler**
- **Parameters**
  - Early Peak Velocity (E, E’)
  - Atrial Peak Velocity (A, A’)
  - Isovolumic Relaxation Time (IVRT, IVRT’)
  - E wave Deceleration Time
  - E/E’ ratio

MRI Techniques

- Phase contrast of Transmitral Flow
- Velocity Encoding TMF, AO and PVF

## Parameters of Myocardial Performance ("Contractility")

### Parameters of systolic function

<table>
<thead>
<tr>
<th></th>
<th>2 D Grey Scale / M-mode</th>
<th>Doppler</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td>Ejection Fraction</td>
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<td>IsoVolumic Contraction Time (transmitral and myocardial Doppler)</td>
<td>Velocity of Circumferential Fiber Shortening</td>
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<tr>
<td>Fractional Shortening</td>
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<td>LV Ejection Time (LVET)</td>
<td>LV Pre-Ejection Period (PEP)</td>
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<td>Fractional Area Change</td>
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<td>Tei index / MPI</td>
<td>LVPEP/LVET</td>
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<tr>
<td>Cardiac Output</td>
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<td>Cardiac Output</td>
<td></td>
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<tr>
<td>E Point to Septum Separation</td>
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<td>LV Ejection Time</td>
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*With So many possibilities – what to choose / use?*
Parameters of Myocardial Performance ("Contractility")

- **Ejection Fraction**
  - Translationally Relevant
  - Widely used
  - Sensitivity – Capable of detecting a 5% change
    - Concordant with similar change in dP/dt
    - Under controlled experimental design with skilled individuals
  - Is it a Good Biomarker of contractility???
  - Calculated parameter
    - \((\text{End diastolic volume} - \text{End systolic volume}) / \text{End diastolic volume}\)
    - EDV, & ESV are calculated parameters
  - Effected by preload (venous return, ventricular filling)
  - Effected by heart rate
  - Can have substantial changes in cardiac structure and function with no change in EF
  - Most useful in context of “complete” imaging structure and function evaluation
Dog Echo: Milrinone and Contractility

Linear Regression of $\frac{dp}{dt^+}$ vs Ejection Fraction

- Study by Terri S and Laura R
- Echo parameters can provide contractility data in acute tox studies
- Positive vs Negative inotrope
- Rat similar results: 1200 mmHg/s = ~5% EF

$r^2=0.887 \ P=0.005$
Emerging and Advanced Techniques / Applications
Strain & Strain Rate Imaging

- **Strain** = Deformation
- **Strain Rate** = Time course of Deformation
- **Directionality**
  - Longitudinal shortening
  - Circumferential shortening
  - Radial Thickening
  - Torsional / Rotational
  - Twist = Basal Rotation – Apical Rotation
- **Global vs Regional**
  - **Echocardiography**
    - Tissue Doppler
    - 2 & 3 D grey scale speckle tracking
  - **MRI**
    - Tissue Tagging (pulse phase)
    - Deformation Tracking
    - DENSE – Displacement Encoding

Wu, et al. JACC: Cardiovascular Imaging, 2009
Strain and Strain Rate Echocardiography

- Peak systolic strain rate has been positively correlated with dP/dt max
  - Index of myocardial contractility
- Global Systolic strain has been positively correlated with Ejection Fraction
  - Index of global myocardial function
- Strain Rate is minimally affected by preload and afterload
- Strain can be affected by load
  - Increased preload increases strain
  - Increased afterload decreases longitudinal strain & increases Rotation / Torsion

Gaining popularity and utility in human cardiology

- Often combined with Pharmacologic stress testing
- Strain / Strain Rate imaging used clinical to detect and monitor chemotherapeutic cardiotoxicity
  - TDI reveals early Epirubicin –induced strain rate decrease…
    - Mercuro, et.al The Oncologist, 12:1124, 2007
  - Detection and monitoring cardiotoxicity – what does modern cardiology offer?
  - Early detection of pegylated-doxorubicin toxicity in elderly patients.
Regional Strain and Strain Rate Echocardiography

2D Tissue Tracking Strain and Strain Rate Imaging

Radial and Circumferential Strain increase during dobutamine infusion (10ug/kg/min)
Pushing the Envelope – Early Detection

- **Global Strain and Strain Rate Echocardiography**
  - Increasing application clinically to detect and monitor chemotherapeutic cardiotoxicity

- **Functional (Contractile) Reserve**
  - The heart is an adaptable demand pump influenced by numerous inputs
    - So why do we routinely study its function at rest condition / state?
  - Clinical Cardiology focuses on function above baseline / rest
    - Stress Echocardiography
      - Physiologic (Exercise)
      - Pharmacologic (Dobutamine, Adenosine, Dipyridamole, milrinone, levosomendan)
Low Dose Doxorubicin – Early Detection

**Left Ventricular Fractional Shortening**

- **Con-Rest**
- **Con-Dob**
- **Dox-Rest**
- **Dox-Dob**

No change in Baseline FS
Dobutamine increased FS
No Change in dobutamine induced increase in FS

**Dobutamine increased Radial Strain**
Dobutamine induced increase in Radial Strain decreased (day21)
Trend to decrease baseline Radial strain at day 42

Detected decrease in functional reserve after 3 doses of 2.0mg/kg of doxorubicin (~1.8mg)
Emerging and Advanced Techniques / Applications
3 & 4 Dimensional Echocardiography

• Capability available for larger animals
  • not yet for rodents
• Potential to reduce operator variability
• Potential to increase precision / accuracy
• Translation- increasing use in Clinical Medicine

Tsusaki et.al, J Med. Primatol. 2006
Challenges to Greater Application and Acceptance

- **Sensitivity**
  - Numerous examples in the literature demonstrating sensitivity to detect ~5% change in both measured and calculated parameters in experimental studies
  - Strongly related to experience and capability of site / sonographer

- **Specificity**
  - Most parameters are not “specific” for contractility per se
  - No one parameter “stands alone” in interpretation
    - Structural and functional parameters are interpreted together in context
    - Concordance with other parameters (dP/dt, QA, etc) not well understood
      - HESI Integrated CV strategy Combined telemetry and echo studies

- **Variability – the larger challenge**
  - Understanding the potential source / cause
  - Methods / Efforts to reduce
  - Efforts to Measure and Understand and Improve
    - HESI Multisite Study
Variability/Repeatability

- **Sources of variability**
  - Biological
  - Image Acquisition
    - Slice registration / alignment
    - Image quality
  - Image Analysis
  - Observer / Operator
  - Methodology
    - Mathematical reconstructions
    - Imaging Protocol
  - Other “systems or variables”
    - Anesthesia
    - Acclimation of subjects

- **Measures to Control Variability**
  - Sonographer Certification / Qualification
  - Single Sonographer per study
  - Optimize and validate methods
“Fitting In” on Typical Safety Studies

**Challenges**

- Imaging studies commonly require larger numbers of animals
  - due to variability
- Requires anesthesia for rodents and nonhuman primates
- **Timing / Potential interruption of measurement of other parameters – telemetry**
- Single dose or multiple dose paradigm – timing of effects to be monitored
- Acoustic window for echo may be altered by surgical implantation (thoracotomy)

**Approaches to “Fit in” better**

- Use the fewest, most robust parameters (reduce variability)
- Pooling of gender groups for statistics – statistical strategies
- Adapt advanced imaging platforms – 3 & 4 D Echo
Can Imaging Be Cost Effective?

- **Echocardiography Equipment is relatively inexpensive**
  - Very capable systems / portable units - $20,000 - $40,000
  - Capable for rats to larger species

- **Hidden Cost is in obtaining / gain / maintaining expertise**

- **With appropriate dedication and diligence can be a very valuable tool in the hands of the cardiology expert**

- **MRI Equipment still expensive**
  - Smaller “bench top” units available and improving

- **Commonly requires both “infrastructure” and technical expertise**
Where Does Imaging “Fit” into Safety Studies

- Evaluate Structure and Function simultaneously

- Serial assessment of structural and functional parameters

- Translation Opportunities – human to mouse to human

- Emerging Techniques / Platforms have the potential to increase utility in safety studies

- Best in an “Integrated Cardiac Biology” Evaluation
  - integration of structure, and function including pressure and biomarkers
Closing

- Echo and cMRI have great potential as informative, valuable, translational research tools

- It’s up to us to optimize the impact and application

- Integrative Cardiac Assessment
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Back Ups
Parameters of Myocardial Performance ("Contractility")

- **Fractional Shortening, Fractional Area Change**
  - Translationally Relevant
  - Sensitivity – Capable of detecting a 5% change
    - Concordant with similar change in dP/dt (in many situations)
    - Under controlled experimental design with skilled individuals
  - \( FS = \frac{(LV \text{ Diameter end diastole} - LV \text{ diameter end systole})}{LV \text{ Diameter end diastole}} \)
  - \( FAC = \frac{LV \text{ Area end diastole} - LV \text{ Area end systole}}{LV \text{ Area end diastole}} \)
  - Directly Measured Parameters
    - Potentially less variability than Ejection Fraction
    - Effected by preload (venous return, ventricular filling)
    - Effected by heart rate
    - Can have substantial changes in cardiac structure and function with no change
    - Most useful in context of “complete” imaging structure and function evaluation
Regional Strain, and Strain Rate Imaging

Early Detection of regional dysfunction

Rat Ischemia / reperfusion model
• 20 minute ischemia
• Early Detection of diastolic and systolic

Application in Safety Studies?
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✓ Emerging Techniques to Evaluate Myocardial Mechanics – Future State
  – Strain and Strain Rate Imaging
  – Functional or Contractile Reserve (Pharmacologic “Stress Echo”)
  – 4 dimensional Imaging (Echocardiography)

▪ Challenges to Greater Application and Acceptance
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▪ Where does Cardiac Imaging “Fit” in Non-clinical Safety Studies?
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Contractility Rat: EF and dp/dt

- Linear relationship for milrinone in rat
- Echo parameters can provide contractility data in acute tox studies
- 1500 mmHg/s ~ 5% EF
Parameters of Myocardial Performance ("Contractility")

- **Pre-Ejection Period (PEP)**
  - Requires ECG and Transmitral Doppler tracings on same image
  - Measured from start of Q wave to upstroke of outflow velocity (opening of aortic valves)
  - Similar to QA Analysis???
    - But no formal comparison??
  - Infrequently used
  - Effected by heart rate
    - Normalization using LV ejection time (PEP/LVET)
Demonstrating Capability, Addressing Variability

**HESI Preclinical Imaging Technical Committee**
- Understanding and Addressing these issues

**A Multi-Center and Multi-Modality Non-clinical Imaging Study for the Characterization of Drug-Induced Changes in Cardiac Structure and Function**

Purpose: Determine the ability of Echocardiography and Magnetic Resonance Imaging to repeatedly quantify drug-induced changes in cardiac structure and function in repeat dose studies performed at multiple different sites.