In vivo non invasive quantitative assessment of passive diastolic stiffness of infarcted myocardium using Shear Wave Imaging

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I have nothing to disclose.
Heart Failure and Stiffness

• **Global Myocardial Stiffness:**
  - Diastolic dysfunction stem from abnormalities in LV relaxation and LV stiffness
  - Myocardial Stiffness and Fibrosis prognosis parameter in cardiomyopathy (Hypertrophic and Dilated Cardiomyopathy)
    - Constrictive vs. restrictive pattern

• **Regional Myocardial Stiffness**
  - Ischemia: (Stunned vs. Infarcted myocardium)
Heart Failure
Myocardial Stiffness:
Major determinant of Diastolic Heart Failure

- **Definition of Diastole by physiologist**: « When Left ventricular relaxation ends, Diastolic phase rely on the passive property of LV wall described by the compliance: \( \frac{dV}{Dp} \) and by the stiffness \( E = \frac{\sigma}{\varepsilon} \).

Diastolic phase load and contractility independant:
- Slow filling phase and atrial systole
Phenotypic and pathophysiological heterogeneity in heart failure with preserved ejection fraction

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Figure 1 Model of progressive abnormalities in left ventricular (LV) diastolic and systolic function underlying heart failure across the LV ejection fraction (EF) spectrum. Early myocardial dysfunction, triggered by conditions such as hypertension and diabetes, may be associated with coupled impairments in both diastolic function and LV longitudinal deformation. Concomitant augmentation of circumferential deformation can lead to preservation of gross LVEF. Progression is characterized by worsening impairment in diastolic function and longitudinal deformation. Decline in circumferential deformation ultimately results in falling LVEF. The clinical syndrome of heart failure can occur at any point along this continuum, with varying contributions of diastolic and systolic dysfunction. HFP EF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Ultrasound Strain Imaging of Altered Myocardial Stiffness: Stunned Versus Infarcted Reperfused Myocardium
Cristina Pislaru, Charles J. Bruce, Peter C. Anagnostopoulos, Jill L. Allen, James B. Seward, Patricia A. Pellikka, Erik L. Ritman and James F. Greenleaf

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http://circ.ahajournals.org/content/109/23/2905
Typical example of data at reperfusion from an animal with stunning and an animal with transmural myocardial infarction

Reperfused transmurally infarcted myocardium has markedly reduced diastolic deformation (and rates of deformation) due to increased myocardial stiffness.

Stunned myocardium has nearly normal passive diastolic deformation (and rates of diastolic deformation), consistent with preserved tissue compliance.
« Invasive Myocardial stiffness evaluation allows to discriminate between: Stunned myocardium and infarcted myocardium »
Can this be done non invasively?
Non invasive quantification of myocardial stiffness remains a challenge.
Imaging cardiac mechanic with ultrasound

- The stress field is not completely known,
- therefore it is not possible to derive
- Stiffness = Stress/strain

Goal: Shear wave elastography
to measure locally the myocardial elasticity
at the different stages of a single heart cycle
Shear Wave Imaging

SWI
Back To History …

E.S.P.C.I.

Mathias Fink
Director of LOA (PR. ESPCI)

Pierre Curie

Theory of Piezo-electricity

Paul Langevin - 1914

First Sonar Experiment
Precursor of Modern Medical Echography

Langevin Radiation Force

Conference : Salle 352 AB
Renversement du temps, onde et médecine
What is Palpation for a physicist?

A Great Property of the Human Body !!

\( \lambda >> \mu \)

( \( \lambda = 2.5 \text{ GPa}, \ \mu = 25 \text{ kPa} \) )

\[
E = \mu \frac{3\lambda + 2\mu}{\lambda + \mu} \approx 3 \mu
\]

\( \lambda \) and \( \mu \) Lamé coefficients

\[
\rho \approx \frac{\lambda}{\rho} \approx 1500 \text{ m.s}^{-1}
\]

\[
\rho \approx \frac{\mu}{\rho} \approx 1-10 \text{ m.s}^{-1}
\]

Compressional Waves propagate at

Shear Waves propagate at

Two Kinds of vibrations propagating at completely different wavespeeds !!
Example: Invasive Ductal Carcinoma (Zoom)

substraction

elasticity [kPa]
De la Transient Elastography en mode 1D au mode SuperSonic Shear Imaging

Recherche menée au LOA depuis 1994
Prototype sur site Aixplorer® (Inserm U765)
Ultrafast Imaging

Conventional Imaging

Ultrafast Imaging

Parallel Processing

RAM

25 - 50 Hz

2500 – 5000 Hz
Elastography Principles

- Acoustic radiation force (short burst (300μs) of focused ultrasound) induced micrometric displacement in a small zone of myocardium generating a shear wave in the low kHz frequency range and propagate at 1 to 10 m/s.

- Ultrafast imaging (12000 images/s) can image the shear wave propagation within 5 ms.

Probleme inverse:

\[ c = \sqrt{\frac{\mu}{\rho}} \]
Measuring temporal variation of myocardial elasticity in a single cardiac cycle acquisition

Langendorff perfused isolated adult rat heart
Real-Time Assessment of Myocardial Contractility Using Shear Wave Imaging

Mathieu Pernot, PhD,‡ Mathieu Couade, MSc,∗‡ Philippe Mateo, PhD,§ Bertrand Crozatier, MD, PhD,§ Rodolphe Fischmeister, PhD,§ Mickaël Tanter, PhD†

Paris, Aix-en-Provence, and Châtenay-Malabry, France
Figure 2  Myocardial Stiffness Dynamics

(A) An example of a myocardial stiffness map obtained in a rat heart in the region reached by the shear wave. The probing locations are shown by red dots. The region of interest where the shear wave velocity was calculated is shown by a white box. (B) Myocardial stiffness variation within a cardiac cycle for a control heart (mean ± SD of 5 different cardiac cycles). The mean left ventricular (LV) pressure (continuous line) ± SD (dotted lines) is plotted below.
Figure 7    Stiffness Correlation With Systolic Pressure

A strong correlation ($r^2 = 0.97$, $p < 0.0001$) was found between systolic stiffness and systolic pressure, used here as a left ventricular contractility index for one rat heart during the transitory response to isoproterenol stimulation.
Goal of Our study

• To investigate the potential of Shear Wave Imaging to quantify non invasively the change of Passive diastolic myocardial stiffness in an ovine model of ischemic heart failure.
Experimental Setup

- Anesthetized sheep (10 animals) with a lateral thoracotomy to enable the use of a high frequency linear probe (8 MHz)
- Elasticity acquisition rate: 15 acquisitions per cardiac cycle
- The elasticity acquisition is registered with ECG
Basic principle of Shear Wave Imaging

Step 1
Shear wave generation by focusing an ultrasound beam

Step 2
Ultrafast imaging

Ultrasonic probe

Shear wave propagation

Plane wave insonification at 10,000 Hz

M. Fink, M Tanter, J. Bercoff
Real-time acquisition of the time-varying myocardial stiffness

- Myocardial stiffness acquisition rate: 15 acquisitions per cardiac cycle

Systolic stiffness: active properties (contractility, pressure)

Diastolic stiffness: passive properties
Data acquisition

Ultrafast acquisition: 10000 frames/sec
Reperfused acute myocardial infarction model

Validation with Invasive Pressure-Segment length measurements
→ Ventricular pressure LVP (pressure catheter)
→ Segment and Volume (sono-micrometers)

• 5 sheep with ischemia (15 min) – Reperfusion (30 min) → **Stunned myocardium**
• 5 sheep with Ischemia (2H) – Reperfusion (30 min) → **Infarct**

Piezoelectric crystal implanted in the myocardium

Ligation of one diagonal coronary artery
Invasive Stiffness estimation

- End-diastolic stress-strain relationship during caval occlusion is fitted to an exponential function:

\[ \sigma = \alpha e^{\beta \varepsilon} + \gamma \]

- The Young’s modulus is the local slope of the stress-strain curve:

\[ E = \frac{d\sigma}{d\varepsilon} \sim \frac{dP}{d\varepsilon} \]
RESULTS
SWI Myocardial stiffness change during Reversible ischemia (stunned)/Irreversible ischemia (infarction)

15 min Ischemia + 30 minutes reperfusion

2 hours Ischemia + 30 min reperfusion
Stunned myocardium (implanted crystals)

Baseline

Reperfused

<table>
<thead>
<tr>
<th></th>
<th>Peak cumulative strain systolic</th>
<th>Peak diastolic strain rate</th>
<th>Diastolic Segmental stiffness constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-13.97%±0.64%</td>
<td>1.74±0.22</td>
<td>2.9</td>
</tr>
<tr>
<td>After 30 min reperfusion</td>
<td>-8.92%±0.79%</td>
<td>1.19±0.10</td>
<td>3.4</td>
</tr>
</tbody>
</table>
## Infarction (2 hours) (implanted crystals)

### Pressure-Circumferential Strain Relationships

- **Baseline**
- **Reperfused after 2 hours of infarction**

### Table

<table>
<thead>
<tr>
<th></th>
<th>EDP (kPa)</th>
<th>ESP (kPa)</th>
<th>Maximum systolic circumferential strain</th>
<th>Diastolic Segmental stiffness constant (implanted crystals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.47±0.08</td>
<td>9.14±0.05</td>
<td>-17.41%±0.93%</td>
<td>3.65</td>
</tr>
<tr>
<td>Reperfused</td>
<td>1.90±0.15</td>
<td>6.71±0.12</td>
<td>-7.33%±0.18%</td>
<td>11.81</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>Infarct (n=5)</th>
<th></th>
<th>Stunning or Reversible ischemia (n=5)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 2H Ischemia</td>
<td>After 30 min of Reperfusion</td>
<td>After 15min Ischemia</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>124±29</td>
<td>113±37</td>
<td>110±26</td>
<td>ns</td>
</tr>
<tr>
<td>EDP(mmHg)</td>
<td>13.1±2.2</td>
<td>13.5±5.9</td>
<td>14.7±3.5</td>
<td>ns</td>
</tr>
<tr>
<td>ESP(mmHg)</td>
<td>79.0±8.2</td>
<td>54.0±14.2</td>
<td>55.9±14.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Sonomicrometers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES circumferential strain</td>
<td>15.4±1.2</td>
<td>1.3±1.6</td>
<td>1.3±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stiffness constant</td>
<td>5.8±2.5</td>
<td>not evaluated</td>
<td>20.8±11.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>SWE</strong></td>
<td></td>
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</tr>
<tr>
<td>Diastolic myocardial stiffness (kPa)</td>
<td>1.8±0.4</td>
<td>5.8±2.3</td>
<td>12.8±5.0</td>
<td>&lt;0.002</td>
</tr>
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</table>

**Non invasive SWE Diastolic myocardial stiffness can discriminate between Infarct and reversible ischemia which is not the case of ES circumferential strain**
Results

Stiffness constant (estimated from sonomicrometers)

\[ p < 0.0001 \]

Myocardial stiffness (from SWI)

\[ p < 0.0001 \]  \[ p < 0.0001 \]  \[ ns \]  \[ ns \]
Results: comparaison of the relative stiffness increase measured with SWI and sonomicrometers

![Graph showing the comparison between stiffness increase measured with SWI and sonomicrometers]

\[ R^2 = 0.8649 \]
Conclusions

• SWI was validated *in vivo* with an independent invasive technique (Pressure-Segment length) for the assessment of diastolic myocardial stiffness.

• Infarcted-reperfused myocardium showed strong alteration of myocardial stiffness which was detected by SWI.

• A strong increase of diastolic myocardial stiffness was found in all infarcted animals (~ x10) whereas no significant change in control animals was found (stunned myocardium with reversible ischemia)
Perspectives

• Implementation of SWI on transthoracic imaging for ischemia testing to discriminate between reversible ischemia and infarcted region.

• New tools for Diastolic heart failure diagnosis

• Non invasive measurement of true myocardial contractility
Acknowledgment

- Agence Nationale de la Recherche (ANR)
- French Society of Cardiology (SFC)
- Julie Piquet and all the staff of Fondation Carpentier PARCC