Development of $\text{FFR}_{\text{CT}}$

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Disclosures

- Founder, Shareholder and Employee of HeartFlow, Inc.
HeartFlow Company Overview

- Computational fluid dynamics applied to cardiac CT scans – Non-invasive assessment of hemodynamic significance of coronary artery lesions
- HeartFlow, Inc. founded in 2007 by Charles A. Taylor, Ph.D. and Christopher K. Zarins, M.D. based on technology developed in their labs at Stanford University
- HeartFlow team led by John H. Stevens, M.D., Chairman and CEO
- 103 patient, First-in-man DISCOVER-FLOW study published in JACC (Koo et al. 2011)
- 17 center, 285 patient prospective clinical trial (DeFACTO) will be completed imminently
HeartFlow is developing a technology platform that answers two key clinical questions, in detail.

Does my patient have CHD?  How do I treat it?

Cardiac CT Angiography  \( \text{FFR}_{CT} \)  \( \text{PCI Planner} \)  \( \text{CABG Planner} \)  Medical Therapy Planner
Fractional Flow Reserve (FFR) is the gold standard to identify lesions causing ischemia.

$$\text{FFR} = \frac{\text{Distal Coronary Pressure (Pd)}}{\text{Proximal Coronary Pressure (Pa)}} \quad \text{(During Maximum Hyperemia)}$$

33% reduction in the risk of death or major cardiac events and reduced cost\(^1,2\)

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Current non-invasive tests do not measure lesion-specific ischemia and do not compare well to FFR

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress ECHO</td>
<td>46%</td>
<td>77%</td>
</tr>
<tr>
<td>SPECT</td>
<td>48%</td>
<td>80%</td>
</tr>
<tr>
<td>CCTA</td>
<td>94%</td>
<td>48%</td>
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64 slice coronary CT angiography

- Coronary CTA has a high sensitivity and high negative predictive value for diagnosis of obstructive CAD
- However, coronary CTA cannot define the hemodynamic significance of coronary lesions

Both of these patients have obstructive CAD (>50% diameter stenosis), but only one of these patients has hemodynamically significant CAD. Which one is it?
Obstructive CAD identified by coronary CTA and Coronary Angiography correlates poorly with FFR

>50% of lesions with greater than 50% diameter stenosis by CCTA have FFR>0.81

65% of intermediate lesions are incorrectly identified for stent placement by Angiograms2

2. Tonino et al. JACC 2010;55:2816-21
Need for Noninvasive FFR

- Fractional Flow Reserve
  - is standard of care for determining need for PCI ...
  - but requires invasive cath
  - and, when performed, is negative in the majority of patients with obstructive CAD

- Coronary CTA alone is insufficient
  - has a high false positive rate when compared to FFR

There is a compelling need for a means to determine FFR prior to cardiac catheterization
$\text{FFR}_{\text{CT}}$: Non-invasive FFR based on CT data

FFR values are available at every point on the coronary tree.
HeartFlow Process for Obtaining FFR\textsubscript{CT}

Computational Model based on coronary CTA

3-D quantitative, anatomic model from coronary CTA

Physiologic models:
- Myocardial demand
- Morphometry-based boundary conditions
- Effect of adenosine on microcirculation

Blood Flow Solution

Blood flow equations solved on supercomputer

\begin{equation}
\rho \bar{v} \cdot \nabla \bar{v} = -\nabla p + \nabla \cdot \frac{1}{\rho} \vec{\tau}
\end{equation}

\nabla \cdot \bar{v} = 0

Calculate FFR\textsubscript{CT}

3D FFR\textsubscript{CT} map computed

\text{FFR}_{\text{CT}} = 0.72

(can select any point on model)
FFR\textsubscript{CT} is accessed via web-based service

Hospital Workflow

- Patients with positive or ambiguous CT results are referred for a HeartFlow study
- CT tech uploads CT data to HeartFlow servers through a web-interface
- HeartFlow processes case data and returns an interactive report
- Report could be viewed by multiple physicians from their computers
FFR_{CT} technology leverages centuries of research in fluid dynamics

- In 1738 Bernoulli derived basic energy balance relationships for fluids
- In 1755 Euler applied Newton’s laws of motion to a fluid to derive equations of motion for inviscid fluids
- In 1827 Navier and in 1845 Stokes generalized equations of motion of a fluid to viscous fluids
- In 1883 Reynolds described transition of laminar flow to turbulence

Osborne Reynolds and his experiment releasing dye in steady flow in circular tube.

Osborne Reynolds’ sketches from his experiment showing laminar flow then transition to turbulence. (a) laminar flow, (b) transition to turbulence induced by increased flow through tube w/ stationary fluid in exterior tank.
Governing Equations of Blood Flow have been Known for more than 150 years

**Mass Conservation (1 equation):**

\[ \frac{\partial v_x}{\partial x} + \frac{\partial v_y}{\partial y} + \frac{\partial v_z}{\partial z} = 0 \]

**Momentum Balance (3 equations):**

\[ \rho \frac{\partial v_x}{\partial t} + \rho \left( v_x \frac{\partial v_x}{\partial x} + v_y \frac{\partial v_x}{\partial y} + v_z \frac{\partial v_x}{\partial z} \right) = - \frac{\partial p}{\partial x} + \mu \left( \frac{\partial^2 v_x}{\partial x^2} + \frac{\partial^2 v_y}{\partial y^2} + \frac{\partial^2 v_z}{\partial z^2} \right) \]

\[ \rho \frac{\partial v_y}{\partial t} + \rho \left( v_x \frac{\partial v_y}{\partial x} + v_y \frac{\partial v_y}{\partial y} + v_z \frac{\partial v_y}{\partial z} \right) = - \frac{\partial p}{\partial y} + \mu \left( \frac{\partial^2 v_x}{\partial x^2} + \frac{\partial^2 v_y}{\partial y^2} + \frac{\partial^2 v_z}{\partial z^2} \right) \]

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where \( \rho \) is the fluid density, and \( \mu \) is the fluid viscosity (both assumed known).

We solve these for \( v_x(x, y, z, t), v_y(x, y, z, t), v_z(x, y, z, t), p(x, y, z, t) \)

for every point in the 3D model and over whatever time interval we are interested in.

**However, the solution of these equations would have to await the development of the digital computer and numerical methods**

This law states that **blood is an incompressible fluid**

These equations come from the application of Newton’s 2\textsuperscript{nd} law, \( F=ma \) to a fluid
FFR\textsubscript{CT} technology leverages 50 years of Research in Computational Fluid Dynamics

**Computational fluid dynamics (CFD)** quantifies fluid pressure and velocity, based on physical laws of mass conservation and momentum balance and is widely used in the aerospace and automotive industries for design and testing.

*HeartFlow applies CFD to solve problems of human coronary blood flow*

Images courtesy of Prof. Charbel Farhat, Dept. of Aeronautics & Astronautics, Stanford University
FFR\textsubscript{CT} technology leverages 30 years of research on hemodynamics, vascular wall biology and atherosclerosis

- Plaque localization
- Artery wall adaptive responses
- Shear stress regulation of artery size
- Atherosclerotic plaque evolution

**COMPENSATORY ENLARGEMENT OF HUMAN ATHEROSCLEROTIC CORONARY ARTERIES**

Seymour Glagov, M.D., Elliot Weisenberg, B.A., Christopher K. Zarins, M.D., Regina Stankunavicius, M.P.H., and George J. Kolettis, B.A.


\textit{FFR}_{CT} technology incorporates proven scientific relationships between vascular form (anatomy) and function (physiology)
FFR\textsubscript{CT} technology based on 15 years of research on patient-specific 3D modeling of blood flow

- **1995**: First patient specific 3D blood flow analysis
  - Patient specific treatment planning introduced

- **2002**: Validation of patient specific blood flow analysis

- **2005**: Anisotropic, adaptive and boundary layer mesh generation for cardiovascular flow

- **2006**: Physiologically realistic outflow boundary conditions
  - Coupled blood flow and wall dynamics

- **2008**: Direct 3D image segmentation and geometric modeling

- **2009-10**: Development of methods for modeling coronary flow and autoregulatory mechanisms
Image-Based Modeling circa 1995


Predictive Medicine circa 1998

ASPIRE System

Live Demo at 1998 Society for Vascular Surgeons

Core Technology – Mid 2000’s

Image-based geometric modeling

Realistic Boundary Conditions

Anisotropic, adaptive and boundary layer mesh generation

Parallel, CFD solver
Overview of $\text{FFR}_{\text{CT}}$ Process

CT data reviewed

Major vessels and plaque segmented from CT data

Luminal surface identified and branches added

Model trimmed and outlet boundary conditions defined

Blood flow and pressure computed under conditions of maximum hyperemia; $\text{FFR}_{\text{CT}}$ reported
How is FFR computed from static coronary CT?

**An everyday example:** Flow over an airplane wing

**Input data:**
- **Geometry** – obtained from design specifications
- **Boundary conditions** – velocity of incoming air relative to wing, atmospheric pressure
- **Fluid properties** – viscosity and density of air

**Calculated data:**
- **Velocity and pressure** of air in front of, around, behind wing
- Lift and drag
How is FFR computed from static coronary CT?

**A novel example:** Flow through the coronary arteries

**Input data:**
- **Geometry** – extracted from CCTA anatomic data
- **Boundary conditions**
  - resting coronary blood flow (calculated from myocardial mass)
  - mean blood pressure (estimated from brachial artery pressure)
  - coronary microcirculatory resistance (derived from morphometry data)
- **Fluid properties** – viscosity and density of blood

**Calculated data:**
- **Velocity and pressure** of blood in coronary arteries
- FFR, CFR, etc…
Scientific Principle #1

Resting coronary blood flow proportional to myocardial mass

1. Allometric scaling laws can be applied to estimate physiologic parameters, e.g. coronary flow, under baseline conditions given organ mass

\[ Q_{c}^{\text{rest}} \propto M_{\text{myo}}^{\beta} \]
Scientific Principle #2

*Resistance of microcirculatory vascular bed at rest is inversely proportional to size of feeding vessel*

1. Healthy and diseased blood vessels adapt to amount of flow they carry
2. Power law relationships of form $Q \propto d^k$ apply to different vascular beds – including coronary arteries
3. Since mean pressure ($P$) is essentially constant down the length of the coronary arteries at rest

AND \quad P = QR

AND \quad Q \propto d^k

THUS \quad R \propto d^{-k}

*Small coronary artery branches have a higher resistance to flow than larger branches*
Scientific Principle #3

*Microcirculation has a predictable response to adenosine*

1. When the heart lacks O₂, breakdown of ATP results in release of Adenosine → vasodilation

2. Exogenous administration of Adenosine elicits the maximum hyperemic response by forcing complete smooth muscle cell relaxation

3. Led to standard of care for induction of hyperemia in non-invasive tests and the cath lab

*Adenosine relays smooth muscle cells lining arterioles resulting in vasodilation*

*Intravenous administration of adenosine elicits remarkably consistent vasodilatory response at sufficient doses*
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**Calculate $\text{FFR}_{\text{CT}}$**

3D $\text{FFR}_{\text{CT}}$ map computed

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Case examples from DISCOVER–FLOW

*Coronary CTA*

>50% diameter stenosis → FFR\(_{CT}\) 0.74 → ischemia

*Invasive angiography*

>50% diameter stenosis → FFR 0.74 → ischemia

*Source:* Koo et al. J Am Coll Cardiol 2011
DISCOVER–FLOW – Reclassification of CCTA data

Reduction of false positives: 70%

Source: Koo et al. J Am Coll Cardiol 2011
Frequently Asked Questions

1. How could FFR<sub>CT</sub> provide better results than coronary CTA alone since it uses the same anatomic data?

   FFR<sub>CT</sub> technology incorporates a more complete anatomic model and also leverages physical laws of blood flow and established principles of coronary physiology.

2. Are the coronary CTA scans performed with Adenosine?

   No, standard coronary CTA scans are used to build Heartflow models. Hyperemia is simulated using known vasodilatory response of Adenosine.

3. Does microcirculatory disease or scar tissue affect FFR<sub>CT</sub>?

   It may, but this is factored into the model since the feeding epicardial coronary arteries remodel in response to elevated microcirculatory resistance and reduced flow.
Frequently Asked Questions

4. Can low dose coronary CTA scans be used for FFR$_{CT}$ analysis?
   Yes, any coronary CTA protocol that results in good quality coronary artery images is fine.

5. Can FFR$_{CT}$ analysis be performed in patients with calcified arteries?
   Yes, provided that the coronary lumen boundary is quantifiable from coronary CTA data.

6. Is the FFR$_{CT}$ service currently available?
   Yes, on a limited basis in Europe. It is not yet approved for use outside of Europe.
Summary

• FFR is the gold-standard for identifying lesion-specific ischemia
• All of the currently available non-invasive tests fall short in identifying lesion-specific ischemia
• FFR_{CT} provides the clinician with valuable information to help him/her make better decisions for patient care