Coronary hemodynamics by Cardiac CT

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I love “Images”, But, I hate “Hemodynamics”!

The expression \( \text{FFR}_{\text{in}}^{\text{pre}} \) represents the improvement of \( \text{FFR}_{\text{in}} \) of the stenotic artery and is identical to what we called revascularization maximum flow ratio (MFR) in a previous study.\footnote{Equation 1 can also be derived directly from Figure 4.3 by the following:}

\[
\frac{Q_{\text{in}}^{\text{pre}}}{Q_{\text{in}}^{\text{post}}} = \left( \frac{P_{a}^{\text{pre}} - P_{s}^{\text{pre}}}{P_{s}^{\text{pre}} - P_{c}^{\text{pre}}} \right) \left( \frac{P_{s}^{\text{pre}} - P_{c}^{\text{post}}}{P_{c}^{\text{post}} - P_{v}^{\text{post}}} \right)\]

Theoretically, maximum flow through the stenotic artery can be compared before and after the intervention by:

\[
\frac{Q_{\text{in}}^{\text{pre}}}{Q_{\text{in}}^{\text{post}}} = \left( \frac{P_{a}^{\text{pre}} - P_{s}^{\text{pre}}}{P_{s}^{\text{pre}} - P_{c}^{\text{post}}} \right) \left( \frac{P_{s}^{\text{pre}} - P_{c}^{\text{post}}}{P_{c}^{\text{post}} - P_{v}^{\text{post}}} \right) = \frac{P_{\text{in}}^{\text{pre}} - P_{\text{in}}^{\text{post}}}{P_{\text{in}}^{\text{pre}} - P_{\text{in}}^{\text{post}}} \quad (66)
\]

or, if correction for pressure changes is made by:

\[
\frac{\text{FFR}_{\text{in}}^{\text{pre}}}{\text{FFR}_{\text{in}}^{\text{post}}} = \frac{P_{a}^{\text{pre}} - P_{s}^{\text{pre}}}{P_{s}^{\text{pre}} - P_{c}^{\text{post}}} \cdot \frac{P_{s}^{\text{pre}} - P_{c}^{\text{post}}}{P_{c}^{\text{post}} - P_{v}^{\text{post}}} = \frac{P_{\text{in}}^{\text{pre}} - P_{\text{in}}^{\text{post}}}{P_{\text{in}}^{\text{pre}} - P_{\text{in}}^{\text{post}}} \quad (66a)
\]

Note that the measurement of the functional improvement of a stenotic artery after PTCA, \( \text{FFR}_{\text{in}}^{\text{post}} \), theoretically is a better measure than \( Q_{\text{in}}^{\text{post}}/Q_{\text{in}}^{\text{pre}} \) because the first expression is independent of arterial pressure.
Evaluation of coronary artery disease

Is there a room for more?

- Clinical information: Symptom, risk factors, ….
- Functional study: SPECT, TMT, ….
- Coronary CT angiography
- Invasive coronary angiography
- Intravascular ultrasound
- Virtual histology
- Optical Coherance Tomography ….
Cardiology Is Flow

Yoram Richter, PhD; Elazer R. Edelman, MD, PhD

Panta rhei. (Everything flows).¹

Cardiology is about flow. The primary purpose of the
...is to quantify cardiac blood flow and assess its vital role in clini-
...rosis. Flow disturbances are therefore ubiquitous; they are a
...fundamental feature of the vascular system. An entire field of
...study arose correlating disease with its overlying flow pat-

• Quality of FLOW: wall shear stress, OSI.....
• Quantity of FLOW: flow velocity, pressure.....
Low or abnormal wall shear stress

→ Proliferative, pro-inflammatory, pro-thrombotic stimulus

Physiologic Arterial Shear Stress
($\tau_s > 15$ dyne/cm$^2$)

Low Arterial Shear Stress
($\tau_s \approx 0-4$ dyne/cm$^2$)

**Anticoagulant, Anti-thrombotic State**

**Monocyte Activation**

**Procoagulant, Pro-thrombotic State**

**High EC Antioxidant Activity**

**Paracrine Quiescent State**

- TGF-β
- PDGF-B
- NO/NOx/NOS
- ACE
- PGH$_2$/PGI$_2$ Synthase
- ET-1
- Adrenomedullin
- ECE
- CNP

**High EC Proliferative Activity**

- COX-1, 2
- Mn SOD
- Cu/Zn SOD

**Paracrine Proliferative State**

- ET-1
- NO/NOx/NOS
- ACE
- Adrenomedullin
- PDGF-B
- PGH$_2$/PGI$_2$ Synthase
- ECE
- TGF-β
- CNP

Malek AM, JAMA 1999
Anatomy & Hemodynamics

Why “the plaque” is there?

Left main

Left anterior descending coronary arter
Plaque location: accordant to abnormal flow
Anatomy & Hemodynamics

Can anatomy predict the functional significance?

LA: Lumen cross sectional area
Anatomy vs. Hemodynamics

Minimal lumen diameter: 1.8mm
Lumen area: 2.8mm²

CT angiography: significant
Angiography: significant
Intravascular ultrasound: significant

Pressure drop by LAD stenosis: 11%
Can CCTA provide hemodynamic information?

- Quality of FLOW: wall shear stress, OSI.....
- Quantity of FLOW: flow velocity, pressure.....
Relation between Stenosis, Flow speed, and Density

Poiseuille’s law:

\[
\text{Blood flow} = \pi \times \text{radius}^4 \times \frac{\text{difference in pressure}}{8} \times \text{viscosity} \times \text{length}
\]
CT time-density curve vs. Flow

Animal study

- Flow = 100%
- Flow = 43%
- Flow = 10%

Flowmeter
Silicone occluder at LAD

Courtesy of Jin-Ho Choi, MD, Samsung Medical Center
Transluminal Attenuation Gradient (TAG)

TAG = ΔHU / vessel axial length (mm)

Courtesy of Jin-Ho Choi, MD, Samsung Medical Center
Transluminal Attenuation Gradient (TAG)

TAG = $\Delta$HU / vessel axial length (mm)

<table>
<thead>
<tr>
<th>0-49%</th>
<th>50-69%</th>
<th>70-99%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>TAG (HU/10/mm)</td>
<td>-1.91±4.25</td>
<td>-3.54±4.43</td>
<td>-10.55±7.20</td>
</tr>
</tbody>
</table>

Courtesy of Jin-Ho Choi, MD, Samsung Medical Center
Pitfalls of Coronary Flow Velocity

Variation of “Resting Flow (Velocity)”

Variations in resting flow (velocity):

- 10 cm.s\(^{-1}\)
- 20 cm.s\(^{-1}\)
- 48 cm.s\(^{-1}\)
- 56 cm.s\(^{-1}\)

Coronary Flow Reserve (CFR):

- CFR = 4.8
- CFR = 2.8
Estimation of pressure changes from geometry

\[ \Delta P = \Delta P_{\text{convective}} + \Delta P_{\text{diffusive}} + \Delta P_{\text{expansion}} \]
Can CCTA provide hemodynamic information?

- Quality of FLOW: wall shear stress, OSI.....
- Quantity of FLOW: flow velocity, pressure.....
Computational Fluid Dynamics (CFD)

- Computational fluid dynamics (CFD) quantifies fluid pressure and velocity, based on physical laws of mass conservation and momentum balance.
- CFD is widely used in the aerospace and automotive industries for design and testing.
Application of CFD to coronary artery disease: Modeling

Courtesy of Gary Binyamin, TMI

Williams & Koo, J Appl Physiol 2010
Inflow waveforms and estimates of downstream coronary vascular resistance obtained from previous investigations


Systolic coronary impedance spectra

Velocity Profiles

Pre-Stent

Rest (cm/s)

Post-Stent

Worst

Exercise (cm/s)

Post-Kiss

Rest (cm/s)

Rest (cm/s)
**Stent cross over & Distal MB over-expansion**

**Time Averaged Wall Shear Stress**

Shear stress distribution

% area of low WSS (< 4dyne/cm²)

- **Post MB stenting**
- **Post SB angioplasty**

[Graph showing shear stress distribution and percentage area of low WSS] (Williams & Koo, J Appl Physiol 2010)
**Stent cross over & Distal MB over-expansion**

**Fractional flow reserve of Side branch**

Fractional flow reserve of Side branch

$$\text{FFR} = \frac{Q_{max}^S}{Q_{max}^N} = \frac{P_d}{P_a}$$

Post MB stenting

Post MB stenting & Post SB angioplasty

Williams & Koo, J Appl Physiol 2010
Clinical relevance of “abnormal flow”? 

**Pathological Findings at Bifurcation Lesions**

The Impact of Flow Distribution on Atherosclerosis and Arterial Healing After Stent Implantation

Gaku Nakazawa, MD,* Saami K. Yazdani, PrinD,* Aloke V. Finn, MD,† Marc Vorpahl, MD,* Frank D. Kolodgie, PrinD,* Renu Virmani, MD*

*Gaithersburg, Maryland; and Atlanta, Georgia

**Limitations of current CFD analyses**

- Simple models, not patient-specific
- Not completely reflects human coronary circulation
- No established clinical relevance
Patient-specific modeling using CCTA

Computational Model based on CCTA
3-D anatomic model from CCTA

No additional imaging
No additional medications

Koo & LaDisa, 2010
Patient-specific non-invasive coronary hemodynamic assessment

**Computational Model based on CCTA**

- 3-D anatomic model from CCTA
- No additional imaging
- No additional medications

**Blood Flow Solution**

Blood flow equations solved on supercomputer

- Physiologic models
  - Myocardial demand
  - Morphometry-based boundary condition
  - Effect of adenosine on microcirculation
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…
Patient-specific CFD analysis
**Estimation of flow by pressure: Fractional flow reserve (FFR)**

\[
	ext{FFR} = \frac{Q^S_{\text{max}}}{Q^N_{\text{max}}} = \frac{(P_d - P_v)/R}{(P_a - P_v)/R} = \frac{\text{Distal Pr } (P_d)}{\text{Proximal Pr } (P_a)}
\]

Proximal Pressure \((P_a) = 100\text{mmHg}\)

- **Distal Pressure \((P_d) = 100\text{mmHg}\)**
  - \(\text{FFR} = 100/100 = 1.0\)
  - Not significant

- **Distal Pressure \((P_d) = 60\text{mmHg}\)**
  - \(\text{FFR} = 60/100 = 0.6\)
  - Significant stenosis

**FFR**

- \(1.0\)
- \(0.80\)
- \(0.75\)
- \(0\)
Patient with ≥ 2 vessel disease (N=1005)

Angiography-guided PCI (N=496)

FFR-guided PCI (N=509)

2 Year MACE-free Survival

FFR-Guided
Angio-Guided
730 days
Δ4.5%

2 Year Death/MI-free Survival

FFR-Guided
Angio-Guided
730 days
Δ4.3%

PCI: percutaneous coronary intervention

Tonino, et al. NEJM 2009; Pijls, et al. JACC 2010
FFR is good for the patients and (relatively) simple........

**Guidelines on myocardial revascularization**

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

<table>
<thead>
<tr>
<th>Class*</th>
<th>Level†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.</td>
<td>I</td>
</tr>
<tr>
<td>DES§ are recommended for reduction of restenosis/re-occlusion, if no contraindication to extended DAPT.</td>
<td>I</td>
</tr>
<tr>
<td>Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolization of debris and prevent MI.</td>
<td>I</td>
</tr>
</tbody>
</table>

But, requires invasive procedure and expensive...... cannot provide 3D anatomical information....
Patient-specific non-invasive FFR using CT & CFD

**Computational Model based on CCTA**

- 3-D anatomic model from CCTA
- No additional imaging
- No additional medications

**Blood Flow Solution**

- Blood flow equations solved on supercomputer
- Physiologic models:
  - Myocardial demand
  - Morphometry-based boundary condition
  - Effect of adenosine on microcirculation

**CT-derived computed FFR (FFR\textsubscript{CT})**

- $\text{FFR}_{\text{CT}} = 0.72$
- (can select any point on model)
Case Examples

CCTA
>50% diameter stenosis

FFR<sub>CT</sub>
FFR<sub>CT</sub> 0.74 → ischemia

Invasive angiography
>50% diameter stenosis

FFR
FFR 0.74 → ischemia

>50% diameter stenosis

FFR<sub>CT</sub> 0.85 → no ischemia

>50% diameter stenosis

FFR 0.84 → no ischemia
First-in-Human study: DISCOVER-FLOW

Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms

Results From the Prospective Multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) Study

Bar-Kwon Koo, MD, PhD;* Andreja Erglis, MD, PhD;‡ Joong-Hyung Doh, MD, PhD;§ David V. Danis, MD;§ Sandra Jegers, MD;§ Hyo-Soo Kim, MD, PhD;* Allison Dunning, MD,§ Tony DeFranco, MD & Alexandra Lasley, MD,* Jonathan Lepicic, BSc, MD,‡‡ James K. Min, MD‡‡ Seoul and Gangwon, South Korea; Riga, Latvia; Palo Alto, San Francisco, and Los Angeles, California; New York, New York; New Haven, Connecticut; and Vancouver, British Columbia, Canada

Objectives
The aim of this study was to determine the diagnostic performance of a new method for quantifying fractional flow reserve (FFR) with computational fluid dynamics (CFD) applied to coronary computed tomographic angiography (CCTA) data in patients with suspected or known coronary artery disease (CAD).

Background
Measurement of FFR during invasive coronary angiography is the gold standard for identifying coronary artery lesions that cause ischemia and improves clinical decision-making for percutaneous coronary intervention. Computation of FFR from CCTA data (FFR$_{CCTA}$) provides a noninvasive method for identifying ischemia-causing stenoses. However, the diagnostic performance of this new method is unknown.

Methods
Calculation of FFR from CCTA data was performed on 118 vessels in 108 patients undergoing CCTA, invasive coronary angiography, and FFR. Independent core laboratories determined FFR$_{CCTA}$ and CAD stenosis severity by CCTA. FFR was defined as an FFR$_{CCTA}$ with a standard deviation (SD) of 0.25. Diagnostic performance of FFR$_{CCTA}$ and CCTA stenoses was assessed with invasive FFR as the reference standard.

Results
Fifty percent of patients had 2.1 vessels with FFR < 0.80. On a per-vessel basis, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 84.2%, 80.2%, 82.2%, 67.9%, and 92.2%, respectively. For FFR$_{CCTA}$, these values were 58.8%, 39.9%, 88.9%, 88.9%, and 71.2%, respectively. The area under the receiver operating characteristic curve was 0.96 for FFR$_{CCTA}$ and 0.70 for CCTA (p = 0.001). The FFR$_{CCTA}$ and FFR were well correlated (r = 0.71, p < 0.001) with a slight underestimation by FFR$_{CCTA}$ (2.03% ± 3.53, 0.001).

Conclusions
Noninvasive FFR$_{CCTA}$ derived from CCTA is a novel method with high diagnostic performance for the evaluation and extraction of coronary lesions that cause ischemia. (The Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional FLOW Reserve. NEJM118821) © Am Coll Cardiol 2011; 189:1-7 | © 2011 by the American College of Cardiology Foundation
Patients and lesions

- 159 vessels in 103 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63 ± 9 yrs</td>
</tr>
<tr>
<td>Male</td>
<td>72 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 %</td>
</tr>
<tr>
<td>Current smoker</td>
<td>36 %</td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 4</td>
</tr>
<tr>
<td>Prior MI</td>
<td>17 %</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>16 %</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>62 ± 6 %</td>
</tr>
</tbody>
</table>

Invasive FFR vs. Non-invasive $\text{FFR}_{\text{CT}}$

$R = 0.72$, $p<0.001$

<table>
<thead>
<tr>
<th></th>
<th>FFR</th>
<th>$\text{FFR}_{\text{CT}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.82 ± 0.13</td>
<td>0.80 ± 0.14</td>
</tr>
<tr>
<td>Delta</td>
<td>0.02 ± 0.12</td>
<td></td>
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</tbody>
</table>

FFR vs. CT and FFR$_{CT}$

Reduction of false positives: 70%

CCTA

<table>
<thead>
<tr>
<th></th>
<th>True -</th>
<th>False +</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT&lt;50% (N=45)</td>
<td>40 (25%)</td>
<td>61 (38%)</td>
</tr>
<tr>
<td>CT ≥50% (N=114, 71%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>False -</th>
<th>True +</th>
</tr>
</thead>
<tbody>
<tr>
<td>False - 5 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True + 53 (33%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FFR$_{CT}$

<table>
<thead>
<tr>
<th></th>
<th>True -</th>
<th>False +</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR$_{CT}&gt;0.80$ (N=90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR$_{CT}≤0.80$ (N=69, 43%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>False -</th>
<th>True +</th>
</tr>
</thead>
<tbody>
<tr>
<td>False - 7 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True + 51 (32%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Diagnostic performance of $\text{FFR}_{\text{CT}}$ and CCTA

Per-vessel analysis (n=159)

<table>
<thead>
<tr>
<th>Metric</th>
<th>FFRCT $\leq 0.80$</th>
<th>CCTA $\geq 50%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

PPV: positive predictive value, NPV: negative predictive value

Diagnostic performance of CCTA and FFR_{CT}

ROC curve analysis

Per-Vessel

- FFR-CT
- CT alone

Area Under the Curve

- FFR_{CT} = 0.90
- CCTA = 0.75

P = 0.001

Per-Patient

- FFR-CT
- CT alone

Area Under the Curve

- FFR_{CT} = 0.92
- CCTA = 0.70

P = 0.0001

FFR vs. TAG and $\text{FFR}_{CT}$

Overall vessels (N = 82)

Area under the curve

- $\text{FFR}_{CT}$: 0.94 (95% CI: 0.86-0.98)
- TAG: 0.63 (95% CI: 0.52-0.74)

P < 0.001

Yoon YY, Choi JH, Koo BK, ACC 2012
FFR vs. TAG and FFR$_{CT}$

**TAG**

- False - 20 (24.4%)
- FFR $\leq 0.8$ (n=32)
- FFR $> 0.8$ (n=50)

- False + 6 (7.3%)

**FFR$_{CT}$**

- False - 6 (7.3%)
- FFR $\leq 0.8$ (n=32)
- FFR $> 0.8$ (n=50)

- False + 3 (3.7%)

Yoon YY, Choi JH, Koo BK, ACC 2012
Treatment planning prior to invasive procedures

Virtual PCI and post-PCI FFR_{CT}
What is the best treatment option for the patient?

Which lesions are flow limiting?

How many stents are needed?

What will be the effect of a stent on the flow to other lesions?

Koo BK, EuroPCR 2011
Treatment planning prior to invasive procedures

Virtual PCI and post-PCI $\text{FFR}_{\text{CT}}$

**After LAD os PCI**

- **Post stent**
  - FFR $< 0.80$

**After Left main and LAD os PCI**

- **Post stent**
  - FFR $> 0.80$

Koo BK, EuroPCR 2011
Treatment planning prior to invasive procedures
- Virtual PCI and post-PCI flow rates-

Original

- LCX: 107.1 ml/min
- RI: 47.3 ml/min
- LAD: 84.5 ml/min

After Left main PCI

- LCX: 116.7 ml/min
- RI: 48.0 ml/min
- LAD: 92.1 ml/min

After LAD os PCI

- LCX: 107.2 ml/min
- RI: 48.0 ml/min
- LAD: 87.5 ml/min

After all PCI

- LCX: 121.6 ml/min
- RI: 49.4 ml/min
- LAD: 99.5 ml/min
FFR vs. $\text{FFR}_{CT}$ after Stenting

CT-derived computed FFR ($\text{FFR}_{CT}$)

Before Stenting

Angiography

Invasive FFR

After Stenting
Invasive FFR vs FFR_{CT}

**Pre-PCI**
- FFR: 0.68 ± 0.13
- FFR_{CT}: 0.69 ± 0.13
- 0.01 ± 0.12

**Post-PCI**
- FFR: 0.88 ± 0.05
- FFR_{CT}: 0.86 ± 0.05
- 0.02 ± 0.12

Invasive FFR vs FFR\textsubscript{CT} after stenting

Diagnostic performance of FFR\textsubscript{CT}

- Diagnostic accuracy 95%
- Sensitivity 100%
- Specificity 94%

CABG Planner
CABG before the surgery, with your computer

FFRCT after LIMA + 2SVGs
Conclusion

• Assessment of coronary hemodynamic parameters using CCTA is feasible with various novel technologies.

• Application of computational fluid dynamics to static CT images can provide quantitative and qualitative flow information.

• FFR\textsubscript{CT} can predict the functional significance of stenoses and can be helpful in planning the treatment strategy before the invasive procedures.

• Further studies are needed to evaluate the efficacy and to overcome the pitfalls of novel technologies.
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**Marquette university, USA**: John LaDisa Jr., PhD

Thanks for your attention...