Derivation and Validation of a Novel Adenosine-Independent Index of Coronary Artery Stenosis Severity Resting Flow Reserve (RFR)

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Purpose:
To evaluate the accuracy and precision of a novel adenosine-independent index of coronary artery stenosis, the resting flow reserve, against the instantaneous wave-free ratio and fractional flow reserve.

Background:

Fractional flow reserve (FFR) measurement under hyperemic conditions is the invasive gold standard for determining the physiologic extent of cardiac ischemia (1).FFR has been validated in several clinical outcomes studies as a way of optimizing case selection for PCI.(1, 2) Recently two large-scale randomized controlled trials using a non-hyperemic resting measurement, the instantaneous wave free ratio (iFR), showed non-inferiority in major adverse cardiovascular events (MACE) comparing iFR to FFR for physiological assessment of moderate coronary stenosis (3,4). Moreover, these studies demonstrated a dramatic reduction in patient discomfort by avoidance of adenosine, suggesting that iFR may be superior to FFR as a diagnostic tool in clinical practice.

FFR is calculated as the ratio of the distal coronary pressure to the aortic pressure (Pd/Pa) during maximal microcirculatory relaxation, induced by pharmacological vasodilators (hyperemia). The iFR negates the time averaging and administration of vasodilators necessary for FFR by identifying from the resting pressure waveform a period when the native microcirculatory resistance is constant and minimized in diastole. Measurement of Pd/Pa during this time (iFR) is at a point of not only minimal resistance, but also high flow, thus allowing the resistance of an epicardial stenosis to be isolated from the microcirculation.

While iFR has been shown to be non-inferior to FFR, it has a number of inherent limitations. The computational algorithm requires ECG gating or automated landmarking of components of the pressure waveform, thus being limited in clinical scenarios where the ECG is suboptimal or the rhythm is disturbed. Furthermore, iFR assumes that the maximal flow and minimal resistance occurs during diastole, which while true for the left coronary artery, is not constant in the right coronary artery.

Here we aim to determine the accuracy, precision and clinical utility of an adenosine free resting measure of pressure during the point of absolute lowest Pd/Pa during the cardiac cycle, the resting flow reserve (RFR). The RFR represents the maximal relative pressure difference in the cardiac cycle, irrespective of systole or diastole and independent of the ECG, thus negating the limitations of iFR. This measurement thus represents a point of the cardiac cycle when the relative difference between native microcirculatory resistance and the flow is highest, allowing isolation of the resistance across the epicardial stenosis. Moreover, similar to iFR, as the RFR is measured each cardiac cycle it has the ability to display high sensitivity to small pressure changes enabling a pullback at rest separating the contribution of individual stenoses in a coronary vessel with multiple lesions.

By performing the investigations described below, we aim to clarify the validity of RFR, determine its ability to detect ischemia compared to iFR and FFR and place it in

clinical context with specific reference to moderate coronary stenoses of unclear physiological significance.

Resting Flow Reserve:

The RFR is the point at which the relative difference in the diastolic pressure and the aortic pressure is greatest during the cardiac cycle, thus representing the point at which the native microcirculatory resistance is the lowest and coronary flow is highest (Figure 1).

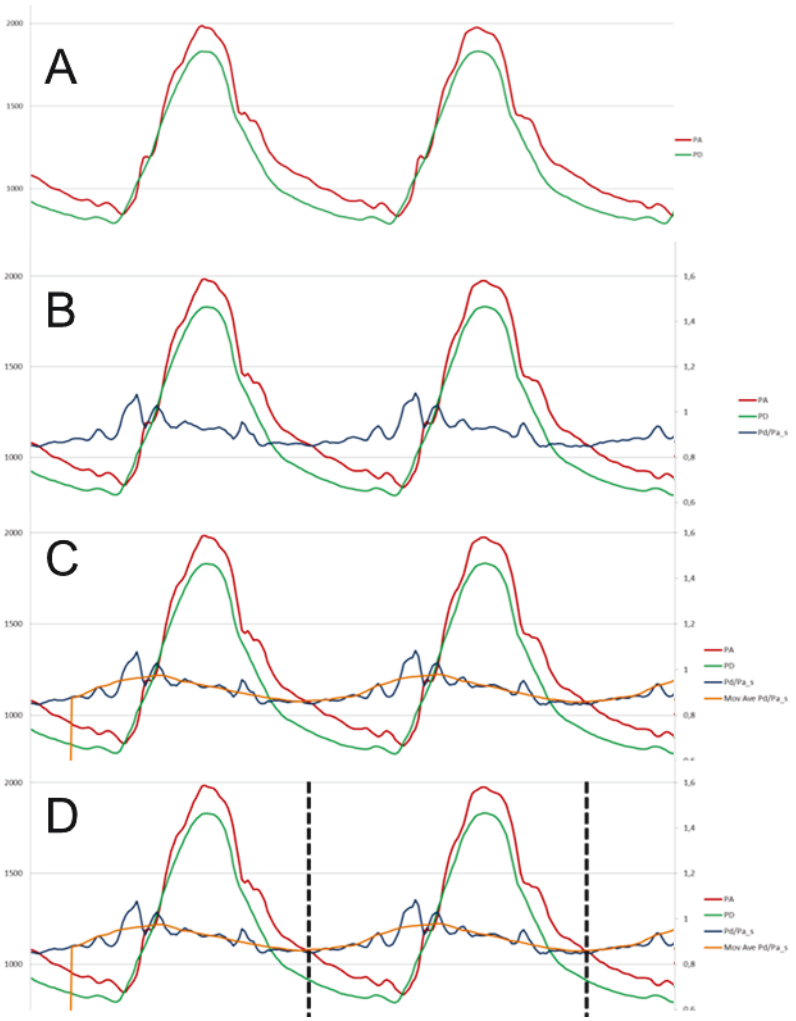

Figure 1. Resting Flow Ratio. A) Pa (red) and Pd (green) wave forms. B) The instantaneous Pd/Pa ratio (blue). C) A filter is applied to the instantaneous Pd/Pa ratio to reduce noise (orange). D) The RFR corresponds to the minimum Pd/Pa during the cardiac cycle (black dash), representing the point at which the native microcirculatory resistance is the lowest and coronary flow is highest.

Objectives:

3) Compare the agreement of RFR and iFR to detect ischemia in a clinical setting.

Endpoints:

Primary Endpoints:

- The agreement between RFR and iFR for detection of ischemia.

Secondary Endpoints:

- Lesion classification (≤/>0.80) by RFR and iFR
- Pressure drift of RFR and iFR
- Measurement reproducibility for RFR compared to iFR
- Ability to advance to the target lesion and measure RFR and iFR
-

Design:

Patients will have both RFR and iFR measured in the following sequence:

- A minimal 6F guiding catheter will be used
- Zero AO transducer and PC
- Flush and zero both wires.

- Deliver 100-200mcg of intracoronary nitroglycerine to maximize epicardial dilation (if clinically indicated)
- Advance the RFR wire to equalize position (guide disengaged)
- Equalize RFR wire
- Advance RFR wire across lesion with the sensor located at least 3 cm distal from the lesion
- Advance the iFR wire to equalize position (guide disengaged)
- Equalize iFR wire
- Advance iFR wire across lesion with the sensor located at least 3 cm distal from the lesion
- Disengage guiding catheter if necessary
  Record basal Pd/Pa
- Record RFR Pd/Pa (RFR value) and iFR Pd/Pa (iFR value)

If administration of adenosine is clinically indicated:

  - Administer intravenous adenosine at a rate of 140mcg/min to achieve maximal hyperemia
  - Measure hyperemic FFR using RFR and iFR wires
  - Stop adenosine
  - Wait 3 minutes
- Perform simultaneous resting flow pullback of RFR wire and iFR wire
- Stop recording on both systems

If PCI is indicated perform PCI per standard of care.

Devices:
SJM Medical Aeris FFR Pressure wire system for RFR
Volcano Verrata Pressure wire system for iFR

Study Population:
The study population will consist of patients who are referred for coronary angiography and require physiological assessment of intermediate lesions for clinical indications based on the local standard of care. A patient becomes a subject once he/she has been fully informed about the study, has agreed to participate, has signed & dated the consent, and has been determined to meet all the inclusion criteria and none of the exclusion criteria.

1. Inclusion Criteria Age ≥ 18 years.
2. Patient provides signed written informed consent before any study-specific procedure.
3. Undergoing coronary angiography, for silent ischemia, stable angina, acute coronary syndrome, or other acceptable indication per the local standard of care.
4. Angiographically 40%-90% stenosis present in at least one native coronary artery.
5. Undergoing physiological assessment for standard clinical or diagnostic indications

Exclusion Criteria

1. Aorto-ostial lesion location within 3 mm of the aorta junction (both right and left).
2. Left main stenosis
3. Vessel(s) and lesion(s) not amenable for PCI, for example diffuse disease.
4. Saphenous vein graft, chronic total occlusion
5. Haemodynamic instability at the time of intervention (heart rate<50 beats per minute, systolic blood pressure <90mmHg), balloon pump
6. Currently participating in another clinical study that interferes with study results.
7. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure.
8. Any other medical condition that in the opinion of the investigator will interfere with patient safety or study results.
9. High degree A-V block, sinus node disease.
10. Asthma/COPD with active wheeze
11. Known hypersensitivity to adenosine
12. STEMI within 48 hours.

Power:
The primary hypothesis is:
Null-

- mean RFR measurements = mean iFR measurements
- Δ ±0.05

A sample size of 92 patients will provide 90% power to detect a 95% agreement between RFR and iFR to detect ischemia

Data Collection:
Data will be collected at baseline/screening, during angiography, and at discharge.

Duration:
The total duration of the study is expected to be 1 year.

Flow Chart

	Baseline/ Procedure	Discharge
	Hospital	Hospital
Demographics	X	

	Baseline/ Procedure	Discharge
Pregnancy Test if female of child bearing age	X	
Medical History (incl. physical exam)	X	
Angiogram	X	
FFR (PW and PC)	X	
Investigator Treatment Decisions	X	
Adverse Events Assessment	X	X

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