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Changes in Resting Coronary Blood Flow During a Cardiac Catheterization Procedure - Implications for Use of Non-Hyperemic Pressure Ratios for Lesion Assessment☆

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The current standard of invasive coronary stenosis assessment is the hyperemic translesional pressure ratio, widely known as the fractional flow reserve (FFR). FFR is the ratio of distal post-stenotic pressure (Pd) to the aortic pressure (Pa) during pharmacologically-induced maximal flow stimulation usually with adenosine. In the last decade in order to simplify workflow and reduce the side effects of adenosine, clever investigators demonstrated that a resting diastolic sub-cycle pressure measurement, the instantaneous wave-free pressure ratio (iFR), is non-inferior to FFR in low risk coronary artery disease (CAD) patients [1,2] and that other non-hyperemic pressure ratios (NHPRs) are numerically and clinically equivalent to iFR for the limited outcome data available ([3,4] and Table 1).

Fundamental to the accuracy and reproducibility of the NHPRs is that the resting coronary blood flow during the signal acquisition be constant over the measurement period. Some critiques of the NHPR concept have raised concerns over the reliability and variance of the resting conditions. Thus, the question was posed and answered by Modi BN et al. [5] in this issue of CRM, "Is resting flow in the cath lab constant during the course of the procedure?"

To study resting coronary blood flow, Modi BN et al. [5] measured simultaneous intracoronary Pd and Doppler average peak flow velocity (APV) at rest and following a stimulus to the patient with a verbal warning that the patient will receive an intravenous adenosine infusion. Measurements were collected in 72 patients during elective angiography for stable CAD. The CAD severity was mild (FFR mean 0.86 ± 0.09). The average peak flow velocity (APV) increased from the flow state at rest and to the alert period by approximately 10% (18 cm/s vs. 20 cm/s, $p < 0.001$) with a small but significant parallel drop in microvascular resistance (6.3 $\text{mmHg}\cdot\text{cm}^{-1}\cdot\text{s}^{-1}$ vs. 5.8 $\text{mmHg}\cdot\text{cm}^{-1}\cdot\text{s}^{-1}$, $p < 0.001$) without alterations in blood pressure or heart rate. Importantly, there were no statistically or clinically significant changes in Pd/Pa and iFR (0.92 vs. 0.92, $p = 0.110$; and 0.90 vs. 0.89, $p = 0.073$).

These data should reassure operators that although there are small variations of resting coronary flow and microvascular resistance during a catheterization procedure, these changes likely have little or no clinical impact on the NHPR indices (specifically, Pd/Pa, and iFR). As with most first studies of its kind, it is natural that the authors would suggest that large cohorts are needed before definitive conclusions may be reached. We concur and would like to see this work repeated with different stimuli over longer periods of time and, most importantly appreciate the change in resting flow after PCI to insure the usefulness of the NPHRs in this setting.

1. Strengths and limitations of the study

The strengths of this study include that it was executed by highly experienced researchers in invasive coronary physiology, application of a strong data collection methodology, and acceptable (although small) patient groups. The findings represent an important initial observation for physiologic devotees of NHPRs in interventional cardiology.

The study is limited by the small single-center cohort of 72 patients that had only a mild burden of disease with a mean FFR of 0.86. Patients with more severe lesions, more co-morbidities, or a more potent stimulus (such as transient ischemia and chest pain), a full bladder, or discomfort on the cath lab table might have greater changes in resting flow. It was assumed that APV approximates the volumetric flow but this assumption requires knowledge of the vessel cross-sectional area at the Doppler sample volume site at the time of each measurement, something that is very challenging, if not impossible in some of our cath lab studies. Even quantitative coronary angiography may be unable to detect small changes in diameters which would influence the

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Table 1
Table of Non-hyperemic pressure ratios

NHPR	Name	Definition	Company
Pd/Pa	Resting whole cycle Pd/Pa	Average Pd/Pa during the entire cardiac cycle	Generic
iFR®	Instantaneous wave-free ratio	Average Pd/Pa during wave free period (WFP)	Proprietary – Philips
DPR	Diastolic pressure ratio	Average Pd/Pa during the entire diastole	Generic – Opsens, Acist (pending approval)
RFR™	Resting full-cycle ratio	Lowest Pd/Pa ratio during the entire cardiac cycle	Proprietary – Abbott/Coroventis
DFR™	Diastolic hyperemia-free ratio	Average Pd/Pa during the period between Pa < mean Pa ending at systole	Proprietary – Boston Scientific

Table of NHPRs. 5 non-hyperemic diastolic pressure ratios (Pd/Pa, iFR, DPR, DFR, RFR). Pd, distal pressure, Pa, aortic pressure. Mean Pd/Pa, whole cycle distal to aortic pressure ratio; RFR, resting full cycle ratio is the lowest absolute mean Pd/Pa; iFR instantaneous wave free pressure ratio. DPR, full diastolic pressure ratio. DFR, full diastolic cycle Pd/Pa. *Source: Tiren Technology 2018, Mona Tirén.*

calculation of coronary blood flow (APVx0.5x $\pi^* r^2$). Alternatively, simultaneous Doppler flow through an IVUS catheter has been used to assess volumetric flow in transplant patients but this is also an expensive and highly complicated methodology [6]. We should not forget that hyperemic blood flow with IV adenosine also shows large fluctuations during many infusions, a phenomenon which prompted the development of the 'smart minimum' point at which to choose the correct FFR [7]. Based on pressure ratios alone, variations of resting flow may go unnoticed for the most part.

Finally, the most challenging aspect of coronary blood flow studies is measuring Doppler flow velocity, a technique highly dependent on acquiring a clear and stable velocity envelope. In the best hands, Doppler flow signals are historically reproducible with no significant difference between repeated measurements [8,9]. A modern study on intracoronary Doppler signal reproducibility is still lacking, mostly due to the limited number of researchers and engineers still engaged in Doppler signal quality studies.

1.1. Implications for use of NHPRs

The small but significant changes in resting APV do not invalidate use of iFR (and other NHPRs) during a quiescent diagnostic catheterization procedure but could become clinically relevant with larger variations in resting flow that might occur with PCI. Although all the NHPRs seem to correlate strongly ($r > 0.95$) with iFR, there are only two large iFR outcome trials [1,2]. Controversy exists whether the NHPR indices with strong correlations with each other could be differentiated by comparative trials (see conversations in Cardiology – "Do we need trials of NHPRs?" [10]). A large outcome-based trial for each resting index will likely never be performed as the number of subjects needed to show a difference would be in excess of all patients having these measurements worldwide and would be exceedingly expensive and not likely to show differences among the NHPRs.

1.2. The bottom line

Use of NHPRs requires that resting flow during the diagnostic signal acquisition be constant. Modi BN [4] showed that for the most part, iFR and Pd/Pa remain unchanged even when the patient is alerted to a potentially uncomfortable stimuli coming soon. It remains unknown what other stimuli might not be so mild as to have only a 10% change in flow. At this time with the available data, to achieve optimal results, and get a true NHPR value, we should continue to make the patient comfortable, avoid alerts when unnecessary, administer plenty of sedation and analgesia, and maybe play relaxing music to minimize the unavoidable variations of the normally responsive resting coronary blood flow we all experience.

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