Novel insights into the complexity of ischaemic heart disease derived from combined coronary pressure and flow velocity measurements
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Chapter 10

Basal stenosis resistance index derived from simultaneous pressure and flow velocity measurements


Submitted
Chapter 10

ABSTRACT

Background
Basal stenosis resistance index (BSR), a vasodilator-free stenosis severity index, compares favorably with fractional flow reserve (FFR) for the identification of ischemia-inducing stenoses. Nonetheless, hyperemic stenosis resistance index (HSR) was documented to be more accurate than both FFR and BSR, and basal condition variability was suggested to impair BSR accuracy compared with HSR. We evaluated the influence of basal hemodynamic condition variability, as encountered in routine clinical practice, on the accuracy of BSR versus HSR. Moreover, we determined the diagnostic performance of BSR, calculated from simultaneous pressure and flow velocity measurements, for HSR-defined significant stenoses, as compared to other contemporary indices.

Methods and results
We studied 131 stenoses by simultaneous coronary pressure and flow velocity measurements. The impact of basal hemodynamic conditions on BSR was evaluated by means of their relationship with the relative difference between BSR and HSR. Diagnostic performance of BSR, FFR, instantaneous wave-free ratio (iFR), and resting $P_d/P_a$ was assessed by comparing the area under the receiver-operating-characteristics curves (AUC), using HSR as the reference standard.

The relative difference between BSR and HSR was not associated with heart rate, aortic pressure or rate pressure product during basal conditions. Both among all stenoses, as well as within the 0.6-0.9 FFR-range, BSR AUC was significantly greater than resting $P_d/P_a$ and iFR AUC; all other AUCs were equivalent.

Conclusion
When pressure and flow velocity are obtained simultaneously, basal conditions do not systematically limit BSR accuracy compared with HSR. Consequently, diagnostic performance of BSR is equivalent to FFR, and closely approximates HSR.
INTRODUCTION

The hemodynamic consequences of a coronary stenosis are most adequately identified by the stenosis-specific relationship between the pressure drop across the stenosis and the flow (velocity) through it. In the catheterization laboratory, assessment of both coronary pressure and flow velocity allows the calculation of the hyperemic stenosis resistance index (HSR), defined as the pressure drop across the stenosis divided by distal coronary flow velocity under hyperemic conditions. Such an index of stenosis resistance, as a summary of the stenosis-specific pressure drop – flow velocity relationship, "normalizes" the pressure drop for the magnitude of flow at which it was obtained, and thereby provides a more objective and consistent evaluation of the hemodynamic consequences of the stenosis than a pressure-only evaluation (Figure 1). Consequently, HSR was found to provide a notably high discriminative value for inducible ischemia on myocardial perfusion imaging.

Since the pressure drop across a stenosis and distal flow velocity change in the same direction with altering coronary flow through the stenosis, the stenosis resistance index is relatively insensitive towards the magnitude of flow at which it is calculated. This suggests that stenosis resistance assessment during basal conditions may provide a measure of physiological stenosis severity. The concept of stenosis resistance calculated during basal conditions (basal stenosis resistance index (BSR)) recently demonstrated equivalent diagnostic accuracy for inducible myocardial ischemia compared with current clinical standards. Nonetheless, BSR did not match its hyperemic counterpart, HSR, perfectly in that study, which was attributed to the presumption that basal condition variability impairs the diagnostic accuracy of basal indices, and that hyperemic conditions are required to adequately reveal the flow-limiting potential of coronary stenoses.

For the ongoing development of BSR, the index should be validated in a contemporary data-set outside of that in which it was developed, using currently available pressure-flow wires, and the influence of hemodynamic variability during the resting state must be assessed to see if it accounts for an impairment in diagnostic efficiency of BSR compared to HSR. Accordingly, in the present study we sought to evaluate whether the variability in basal hemodynamic conditions encountered in routine practice may explain potential differences between BSR and HSR, and how the diagnostic performance of BSR compares with other indices of stenosis severity, including FFR as the current standard of care, when assessed, for the first time, in a contemporary cohort of simultaneous pressure and flow velocity measurements.
We included patients that were scheduled for coronary angiography or percutaneous coronary intervention at the Academic Medical Centre, Amsterdam, the Netherlands, and Imperial College, London, United Kingdom. The sample from Amsterdam included 56 lesions, collected between November 2001 and January 2012. The sample from Imperial College consisted of 75 stenoses, collected from 2010 to 2013. Exclusion criteria were restricted to significant valvular pathology, and prior coronary artery bypass graft surgery. The local ethical review boards approved the respective study protocols, and all subjects gave written informed consent.

Figure 1 | Stenosis pressure drop – flow velocity relationship. The stenosis-specific pressure-drop flow velocity relationship implicates that the pressure drop across a stenosis increases with increasing flow through the stenosis. Hence, a given pressure drop across a stenosis, $X$, may represent a stenosis severity ranging from mild to severe, depending on the flow velocity at which it was obtained, 1 to 3. The stenosis resistance index, defined as the ratio of the pressure drop across the stenosis to distal coronary flow velocity, “normalizes” the pressure drop for the magnitude of flow at which it was obtained, providing a more objective assessment of hemodynamic stenosis severity, and allows the attribution of the measured pressure drop to stenosis severity 1, 2, or 3.

**METHODS**

**Data source**

We included patients that were scheduled for coronary angiography or percutaneous coronary intervention at the Academic Medical Centre, Amsterdam, the Netherlands, and Imperial College, London, United Kingdom. The sample from Amsterdam included 56 lesions, collected between November 2001 and January 2012. The sample from Imperial College consisted of 75 stenoses, collected from 2010 to 2013. Exclusion criteria were restricted to significant valvular pathology, and prior coronary artery bypass graft surgery. The local ethical review boards approved the respective study protocols, and all subjects gave written informed consent.

**Cardiac catheterization and hemodynamic measurements**

Cardiac catheterization was performed according to standard clinical practice, and angiographic images were recorded in a manner suitable for quantitative coronary angiography (QCA) analysis. After diagnostic angiography, a 0.014 inch dual sensor-equipped guide wire (ComboWire, Volcano Corporation, San Diego, CA) was used to obtain simultaneous...
recordings of distal coronary pressure and flow velocity. Measurements were performed during basal conditions, as well as during hyperemia induced by either intravenous infusion (140µg/kg/min), or intracoronary bolus injection (20-60µg) of adenosine.

### Hemodynamic data analysis

Data (EKG, coronary pressure and flow velocity) was extracted from a digital archive (ComboMap® or personal computer). Pressure drift was identified either by returning the pressure sensor to the catheter tip at the end of the procedure or by means of pressure drop-flow velocity curves, using the zero-flow pressure intercept as a measure of pressure drift. Hemodynamic data analysis was performed off-line using a custom software package written in MatLab (Mathworks Inc., Natick, Mass). The derived physiological indices were defined as depicted in Table 1.

<table>
<thead>
<tr>
<th>Parameter definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSR = (mean Paorta - mean Pdistal)/ APV (during basal conditions)</td>
</tr>
<tr>
<td>HSR = (mean Paorta - mean Pdistal)/ APV (during hyperemia)</td>
</tr>
<tr>
<td>Resting Pd/Pa = mean Pdistal/ mean Paorta (during basal conditions)</td>
</tr>
<tr>
<td>iFR = mean Pdistal/ mean Paorta (in wave-free period during basal conditions)</td>
</tr>
<tr>
<td>FFR = mean Pdistal /mean Paorta (during hyperemia)</td>
</tr>
</tbody>
</table>

BSR: baseline stenosis resistance index, Pdistal (Pd): distal coronary pressure, Paorta (Pa): aortic pressure, APV: average peak flow velocity distal to the coronary lesion, HSR: hyperemic stenosis resistance index, iFR: instantaneous wave-free ratio, FFR: fractional flow reserve

### Statistical analysis

First, the effect of aortic pressure, heart rate and rate pressure product during basal conditions on the difference between BSR and HSR was evaluated by testing their association with the relative difference between BSR and HSR. Second, receiver-operating-characteristics (ROC) curves were constructed for BSR, iFR, FFR, and resting Pd/Pa using HSR as the physiological reference standard, in which HSR > 0.80 mmHg/cm/s was considered physiologically significant.

ROC curves were compared by comparing the area under the ROC curves (AUC) using the method proposed by DeLong et al. Additional ROC-curves were constructed and comparison of AUCs was performed for stenoses within the clinically important 0.6 to 0.9 FFR-range. Within both cohorts, classification agreement of BSR, iFR, and FFR with the reference standard was evaluated at the respective predefined ischemic cut-off values of 0.66 mmHg/cm/s for BSR, 0.86 for iFR, and 0.75 for FFR, and was compared by means of McNemar’s test of symmetry.

Data is presented as mean (± standard deviation) or median (1st and 3rd quartiles (Q1, Q3)). Comparison was performed by Student’s T-test, or the Chi square test, as appropriate. A p-value below the two-sided α-level of 0.05 was considered statistically significant.
RESULTS

Patients
Within 118 patients, a total of 131 coronary stenoses were evaluated by means of simultaneous coronary pressure and flow velocity measurements. Demographics and angiographic stenosis characteristics are summarized in Table 2. Stenosis severity distribution by FFR is depicted in Figure 2, showing a preponderance of stenoses (57.3%) that fell within the 0.6-0.9 FFR range. Hyperemia was induced by means of intravenous adenosine (IV) in 57% of stenoses, while an intracoronary bolus injection (IC) of adenosine was used in the remaining 43% of stenoses.

The ranges of basal hemodynamics in this study population are depicted in Table 3. Across all stenoses, BSR was linearly related to HSR (R=0.95 (R²=0.90), P<0.001; Figure 3).

Table 2 | Baseline characteristics

<table>
<thead>
<tr>
<th>Number of stenoses (patients)</th>
<th>131 (118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62±10</td>
</tr>
<tr>
<td>Male %</td>
<td>79</td>
</tr>
<tr>
<td>Co-morbidities, %</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>53</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>80</td>
</tr>
<tr>
<td>Smoking history</td>
<td>51</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>3</td>
</tr>
<tr>
<td>Severe LV dysfunction (EF&lt;30%)</td>
<td>2</td>
</tr>
<tr>
<td>Clinical presentation, %</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>97</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3</td>
</tr>
<tr>
<td>Coronary anatomy, %</td>
<td></td>
</tr>
<tr>
<td>Single vessel CAD</td>
<td>56</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>44</td>
</tr>
<tr>
<td>LAD</td>
<td>58</td>
</tr>
<tr>
<td>LCx</td>
<td>21</td>
</tr>
<tr>
<td>RCA</td>
<td>18</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Diameter stenosis, % ± SD</td>
<td>56 ± 16</td>
</tr>
<tr>
<td>Adenosine route, %</td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>57</td>
</tr>
<tr>
<td>Intracoronary</td>
<td>43</td>
</tr>
</tbody>
</table>

LV: left ventricle, CAD: coronary artery disease, LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery, RCA: right coronary artery
The relative difference of BSR compared with HSR (BSR – HSR/HSR) was not associated with heart rate ($R^2=0.003$, $P=0.546$), mean aortic pressure ($R^2=0.000$, $P=0.894$) or rate pressure product ($R^2=0.009$, $P=0.288$) during basal conditions.

**Diagnostic performance against HSR**

ROC-curve analysis for HSR-identified physiologically significant coronary stenoses yielded an excellent AUC for BSR, iFR and FFR (Figure 4A, Table 4). The numerically higher AUC for BSR compared with FFR did not reach statistical significance ($P=0.155$). Notably, the AUC of BSR was significantly higher than the AUC of resting $P_d/P_a$ and also significantly higher than the AUC of iFR ($P=0.015$, and $P=0.022$, respectively), while the numerical difference in AUC between FFR and resting $P_d/P_a$ or iFR did not reach statistical significance ($P=0.38$, and $P=0.35$, respectively).

Of all coronary stenoses, 57.3% fell in the 0.6 – 0.9 FFR range. Within this clinically important range, the AUC of BSR was significantly greater than that of iFR and resting $P_d/P_a$ (Figure 4B, Table 5), and was numerically greater than the AUC of FFR, with a trend towards statistical significance ($P=0.054$; Figure 4B, Table 5). The AUC of FFR was equivalent to that of iFR, and resting $P_d/P_a$ ($P=0.67$, and $P=0.70$, respectively).

For stenoses between FFR 0.70 – 0.80, 23 stenoses in this dataset, HSR was normal in 15 (65%), and abnormal in 8 (35%). The findings for BSR were similar; BSR was normal in 17 (74%), and abnormal in 6 (26%) of these stenoses. For stenoses between FFR 0.81 – 0.85, 31 stenoses in this dataset, HSR was normal in 27 (87%), and abnormal in 4 (13%). Findings for BSR were equal, with normal BSR in 27 (87%), and abnormal BSR in 4 (13%) of cases.
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Table 3 | Range of basal hemodynamics within the full study cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± Standard deviation</th>
<th>Median (Q1, Q3)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal heart rate, BPM</td>
<td>82±23</td>
<td>75 (67, 93)</td>
<td>51</td>
<td>153</td>
</tr>
<tr>
<td>Basal aortic pressure, mmHg</td>
<td>101±15</td>
<td>99 (90-109)</td>
<td>67</td>
<td>149</td>
</tr>
<tr>
<td>Basal rate pressure product</td>
<td>8948±2844</td>
<td>8203 (6935, 10098)</td>
<td>4602</td>
<td>17854</td>
</tr>
</tbody>
</table>

BPM: beats per minute

Classification agreement with the reference standard was higher for BSR than for FFR or iFR, both in the full cohort (92.4% for BSR versus 87.0% for iFR, and 90.8% for FFR; Table 6, Left panel), as well as within the 0.6-0.9 FFR range (89.3% for BSR, versus 78.7% for iFR, and 84.0% and FFR; Table 6, Right panel). However, these numerical differences did not reach statistical significance (p>0.05 for all), although the difference in classification agreement between BSR and iFR within the 0.6 – 0.9 FFR range showed a trend towards statistical significance (P=0.057).

Discordance in stenosis classification between BSR and HSR occurred in 7.6% of stenoses (10 out of 131). In the 8 cases where BSR was ≤0.66 mmHg/cm/s while HSR was >0.80 mmHg/cm/s, BSR and HSR agreed with coronary flow velocity reserve (CFVR) in 50% of cases. Moreover, in the 2 cases where BSR was >0.66 mmHg/cm/s while HSR was ≤0.80 mmHg/cm/s, BSR agreed with CFVR in both cases.
Figure 4 | Receiver-operating-characteristics curves against the hyperemic stenosis resistance index as the reference standard within A) the full study cohort, and B) the 0.6 – 0.9 FFR range.

Table 4 | Area under the receiver-operating-characteristics curve within the full cohort (N=131)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>95% Confidence Interval</th>
<th>P-value versus</th>
<th>P-value versus</th>
<th>P-value versus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BSR</td>
<td>Pd/Pa</td>
<td>FFR</td>
</tr>
<tr>
<td>BSR</td>
<td>0.99</td>
<td>0.97 - 1.00</td>
<td>-</td>
<td>0.015</td>
<td>0.16</td>
</tr>
<tr>
<td>Resting Pd/Pa</td>
<td>0.95</td>
<td>0.92 - 0.99</td>
<td>0.015</td>
<td>-</td>
<td>0.38</td>
</tr>
<tr>
<td>iFR</td>
<td>0.95</td>
<td>0.92 - 0.99</td>
<td>0.022</td>
<td>0.92</td>
<td>0.35</td>
</tr>
<tr>
<td>FFR</td>
<td>0.96</td>
<td>0.94 - 0.99</td>
<td>0.16</td>
<td>0.38</td>
<td>-</td>
</tr>
</tbody>
</table>

BSR: basal stenosis resistance, Pd/Pa: distal coronary to aortic pressure ratio, iFR: instantaneous wave-free ratio, FFR: fractional flow reserve
We observed that variations in basal hemodynamic conditions as encountered in routine clinical practice do not systematically lead to differences between BSR and its hyperemic counterpart, HSR, and that, when derived from simultaneous coronary pressure and flow velocity measurements, BSR agrees very closely with HSR both in terms of a linear relationship between the two parameters, and in terms of stenosis classification. Moreover,
the discriminative power of BSR is at least equivalent to that of FFR across the complete range of coronary stenosis severities, and BSR yields a numerically greater discriminative power compared with FFR within the 0.6-0.9 FFR range, showing a trend towards statistical significance. Finally, the simultaneous assessment of both pressure and flow during basal conditions provides a significant increment in discriminative value compared with basal pressure-only evaluation.

Our observations support the fundamental proposition that basal conditions allow accurate assessment of functional stenosis severity, and that BSR can equal hyperemic indices in terms of diagnostic performance. Moreover, our results suggest that simultaneous assessment of pressure and flow velocity may provide important diagnostic advantages when stenosis discrimination is most challenging, when physiological stenosis severity is within the FFR grey zone or clusters around the cut-off, even in the absence of a hyperemic state.

**Physiological variations in basal versus hyperemic hemodynamics**

It has been argued that basal conditions do not allow functional stenosis severity assessment for two main reasons: 1) because it was assumed that hemodynamic variability is more extensive in basal conditions compared with hyperemic conditions, impairing the diagnostic accuracy of basal indices, and 2) because flow velocity at rest is assumed to be insufficient to allow discrimination of functionally significant from functionally non-significant coronary stenoses, particularly in coronary stenoses of intermediate physiological severity, e.g. within the 0.6-0.9 FFR range.

In our study population, we observed that there was a strong correlation between absolute BSR and HSR values, and that the relative difference between BSR and HSR was not associated with heart rate, aortic pressure or rate pressure product during basal conditions. This implies that variations in basal hemodynamic conditions as encountered in routine clinical practice do not systematically lead to differences between BSR and its hyperemic counterpart, HSR, and, analogous to the report by Berry et al., indicates that BSR is not susceptible to variations in heart rate and blood pressure during resting conditions.

Our results further confirm that resting flow does allow accurate discrimination of functionally significant from functionally non-significant coronary stenoses. BSR yielded a notably high discriminative power against HSR, with an AUC closely approximating 1.0, and this equivalence was maintained within the intermediate 0.6-0.9 FFR range. Moreover, dichotomous agreement of BSR with HSR was excellent, even in stenoses within the FFR grey zone, and in those close to the FFR cut-off value. Hence, our data add to the accumulating evidence suggesting that resting conditions allow adequate stenosis discrimination, even within the challenging intermediate 0.6-0.9 FFR range, if combined
pressure and flow assessment is utilized to maximize the discriminative power provided by resting conditions.

The pertinence of simultaneous pressure and flow velocity measurements for the assessment of BSR

In the BSR validation study, HSR was found to yield significantly higher discriminative value for inducible myocardial ischemia compared with BSR.\(^5\) It is important to acknowledge that, in that study, BSR was determined from intracoronary hemodynamic data obtained by means of two separate sensor-equipped guide wires: coronary flow was measured subsequent to coronary pressure. This methodology by definition limits the fundamental advantages of combining pressure and flow velocity in a single index, as it partly dissipates the intrinsic relationship between the pressure drop across a stenosis and flow velocity. Because physiological variation is not optimally accounted for when pressure and flow are not simultaneously obtained, and such variation is by definition most pertinent in basal low-flow, low-pressure drop conditions, this methodological limitation most likely affects the diagnostic accuracy of BSR more than that of HSR. Therefore, the difference in discriminative power between BSR and HSR identified previously may particularly be explained by the absence of simultaneously obtained intracoronary pressure and flow velocity data. Consequently, we observed that, when measured with a dual sensor-equipped guide wire, allowing simultaneous assessment of coronary pressure and flow velocity,\(^12\) BSR yields an excellent discriminative value for HSR-identified physiological coronary stenosis severity.

Discriminative power of combined pressure and flow, compared with pressure-only

Despite the fact that the discriminative power of BSR, and FFR for HSR-identified physiologically significant stenoses was high across the full range of stenosis severities, a pertinent drop in discriminative power was noted for FFR within the equivocal 0.6-0.9 FFR range. It is especially this range of FFR-values that is considered most challenging in terms of stenosis discrimination.\(^7\) Within the equivocal 0.6 to 0.9 FFR range, excluding lesions in which agreement between all parameters may be expected \textit{a priori},\(^13,14\) there was a trend towards a superior discriminative power of BSR over FFR (BSR AUC: 0.97 vs. FFR AUC: 0.87, \(p=0.054\)). Moreover, 65% and 74% of stenoses in the FFR grey zone would be reclassified by HSR or BSR, respectively, and 13% of stenoses with a negative FFR close to the cut-off value would be reclassified by either HSR or BSR. These observations may explain the incremental discriminative power previously documented for HSR over FFR for identification of stenosis-related inducible myocardial ischemia,\(^4,5\) despite a high concurrence across the full range of stenosis severities. This diagnostic advantage likely derives from the fact that BSR and HSR directly measure flow instead of estimating
it from coronary pressure. This advantage seems important considering the fundamental importance of coronary flow in myocardial function and ischemia,\textsuperscript{15} recent observational data suggesting that measurement of flow significantly enriches the diagnostic and prognostic information derived from coronary pressure measurements,\textsuperscript{16,17} and the documented incremental prognostic value of HSR over FFR in stenoses of equivocal physiological severity.\textsuperscript{18}

The observations in the present study suggest that simultaneous measurement of coronary pressure and flow velocity may provide the most efficient discrimination of physiologically significant from physiologically non-significant coronary stenoses, even in the absence of a hyperemic state. Nonetheless, although conceivable, it remains to be elucidated whether these differences translate into pertinent differences in clinical outcomes.

**Pressure-only versus combined assessment of pressure and flow velocity: clinical practice**

Despite the fact that our results point in the direction of an improved diagnostic efficiency by measuring both intracoronary pressure and flow velocity, even in the absence of a hyperemic state, there is an important practical consideration currently favouring pressure-only physiological assessment of coronary stenosis severity in clinical practice. Doppler flow velocity measurements are relatively difficult to obtain when compared with pressure measurements, and reliable assessment of Doppler signals currently depends on operator experience with this specific tool. Therefore, technical advancements with respect to dual sensor-equipped guide wires will play a critical role in the clinical potential provided by indices of stenosis resistance.

Considering the rigorously documented feasibility and clinical potential of coronary pressure measurements in daily practice, it is important to note that both across the full range of FFR-values, as well as within the 0.6-0.9 FFR range, iFR was equivalent to FFR in terms of discriminative power, as well as classification agreement with the reference standard. Thereby, our study confirms the findings in smaller studies that the diagnostic efficiency of iFR for identification of physiologically significant coronary stenoses equals that of FFR across the whole range of lesion severities, as well as within the equivocal 0.6 - 0.9 FFR range.\textsuperscript{19,20} This data further supports the clinical applicability of iFR as a vasodilator-free alternative for FFR, while awaiting further technical improvements of combined pressure/flow measurements to support the clinical feasibility of derived parameters, such as BSR.

**Limitations**

Considering the retrospective nature of the data, this study should be considered proof of concept, and should be interpreted in the light of several limitations. Assessment of
intracoronary flow velocity is sensitive to technical failures, and its accurate measurement depends on operator experience, which limits the practical applicability of currently available Doppler flow systems. All measurements in this study were performed by operators with ample experience in intracoronary flow velocity measurements. It must be noted that no gold standard for stenosis-specific inducible myocardial ischemia is available to date. With this limitation borne in mind, we used HSR as the physiological reference standard in the present study, an approach governed by the well-documented value of the stenosis-specific relationship between coronary pressure and flow velocity, as well as the understanding that HSR is least susceptible to variability in hyperemic conditions and has a high specificity for inducible myocardial ischemia.\textsuperscript{4,18,21-23}

Our current observations indicate that hemodynamic variability during basal conditions as encountered in routine clinical practice does not systematically lead to differences between BSR and its hyperemic counterpart, HSR. However, in contrast to other studies, no pharmacological perturbation of hemodynamics was performed in the present study. Nonetheless, since pharmacological perturbation of hemodynamics is not routinely performed in the assessment of physiological stenosis severity, our findings on the influence of hemodynamic variability in the magnitude encountered in clinical practice support the conclusion that basal conditions allow the assessment of physiological stenosis severity by means of BSR.

Different adenosine routes (both intravenous and intracoronary) and doses were used to induce hyperaemia. Although this might be seen as a potential limitation, it better reflects the real-world utilisation of FFR. Although larger doses of intracoronary adenosine can be used, the dose used in this study (20-60mcg) adheres to the doses used in the clinical validation of FFR, and achieves FFR values equivalent to 140 mcg/kg/min of intravenous adenosine infusion, as was recently discussed in detail.\textsuperscript{24} Moreover, FFR determined with low-dose intracoronary bolus administration of adenosine has been shown to provide similar clinical benefits compared with FFR determined with intravenous infusion of adenosine.\textsuperscript{25}

**CONCLUSION**

We documented that the discriminative power of BSR was substantially equivalent to that of FFR when simultaneous pressure and flow assessment is performed to maximize the discriminative power provided by resting conditions. Nonetheless, due to practical limitations, on-going technical advancements are awaited to optimally identify the potential of simultaneous pressure and flow velocity measurements in clinical practice.
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