

# Can Resting Indices Obviate the Need for Hyperemia and Promote the Routine Use of Physiologically Guided Revascularization?

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## KEYWORDS

• iFR • FFR • Hyperemia • Adenosine

## KEY POINTS

- Physiologically guided revascularization improves outcomes and reduces cost.
- Current use of hyperemic indices, such as fractional flow reserve, is low.
- Hyperemia-free indices, such as instant wave-free ratio, have the potential to improve adoption by making assessment faster and easier.
- Comparison of iFR and FFR with a spectrum of invasive and noninvasive ischemia tests has demonstrated equivalent diagnostic accuracy.
- Clinical outcome studies are currently recruiting to definitively determine the role of iFR in the clinical domain.

## INTRODUCTION

The appearance of a coronary stenosis on angiography relates poorly to its effect on underlying coronary flow.<sup>1,2</sup> This has led to the development and validation of several intracoronary indices of stenosis severity over the last 20 years.<sup>3–8</sup> Fractional flow reserve (FFR) is the most widely used clinical index. Its methodical validation has led to its incorporation into revascularization guidelines; however, despite this, the proportion of revascularization procedures guided by FFR is low.<sup>9</sup>

Recently, taking advantage of improved intracoronary wire technology and computational power, newer indices have been introduced into clinical practice.<sup>10,11</sup> By making stenosis assessment easier and faster, these indices aim to further increase the adoption of physiologic guided revascularization into routine clinical practice. Of these indices, instant wave-free ratio (iFR) is the most widely used alternative to FFR because it provides a measure of physiologic stenosis severity, using a standard pressure wire, and is calculated without the need of

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administration of powerful vasodilator agents, such as adenosine.<sup>10,12</sup> Its introduction has challenged the paradigms supporting the very use of FFR and justifiably has led to much debate about the need for hyperemia in stenosis assessment.<sup>13–16</sup>

This article assesses the data from contemporary human studies to address some of the common assumptions regarding hyperemic and baseline physiology in the context of the baseline pressure-derived index of iFR and the hyperemic index of FFR. We aim to determine if the available evidence supports the continued investigation, development, and use of baseline indices.

**IS HYPEREMIA PHYSIOLOGICALLY ESSENTIAL FOR THE PRESSURE-ONLY ASSESSMENT OF A STENOSIS?**

Intracoronary physiologic indices aim to determine the effect of a stenosis on blood flow within the vessel. However, measuring true volumetric blood flow is difficult, and accurate, reproducible measurements are challenging, time consuming, and largely used in the research laboratory. In contrast, pressure measurements are easier to obtain, more reproducible, and less time consuming to measure.<sup>17</sup> Overall this makes pressure-based indices more attractive for routine clinical use.

For a pressure-derived index to make inferences about underlying flow, intracoronary conditions need to be created where pressure and flow are proportional.<sup>18</sup> Under such conditions pressure can be used as a surrogate for flow, permitting assessment of the physiologic significance of the lesion using pressure alone. This circumvents the problems of measuring flow and provides a simpler, more clinically attractive tool.

The physiologic cornerstone of FFR relies on the principle that the pressure drop across a stenosis ( $\Delta P$ ) is proportional to flow ( $Q$ ) when microvascular resistance ( $R$ ) is stable (Equation 1), a condition that is achieved during the administration of hyperemic agents, such as adenosine, or alternatives, such as papaverine<sup>18</sup> (Equation 2).

$$\Delta P = QR \tag{1}$$

When resistance is constant ( $R$ ):  $\Delta P \propto Q \tag{2}$

FFR is therefore highly dependent on hyperemic agents for its accurate calculation.<sup>19</sup> This dependence of FFR on hyperemia has been translated into the assumption that the

physiologic condition requisite for pressure to be used as a surrogate to flow can only be achieved during hyperemia.<sup>13,15,20</sup>

However, this is in contrast to the original physiologic studies that have defined the understanding of coronary hemodynamics.<sup>21,22</sup> Using meticulous manual analysis of pressure-flow data, it has been demonstrated that it is indeed possible to categorize stenoses as mild, moderate, and severe without the need for hyperemia.<sup>21</sup> Gould<sup>21</sup> demonstrated that the most appropriate period for the assessment of a coronary stenosis is when intracoronary pressure is not confounded by the contraction and relaxation of the myocardium, thereby isolating a phase when the myocardium is passive and intracoronary pressure and flow velocity have an almost linear relationship. However, indices derived using such an approach had limited clinical applicability because they could only be identified from simultaneous measurement of pressure and flow velocity.<sup>8,23</sup>

Recently, the derivation of iFR demonstrated that it was possible to identify a phase in the cardiac cycle where the characteristic features ideal for stenosis assessment are found. The key advance was the demonstration that it was possible to automate the identification of the phase using sophisticated computational algorithms in real time on a beat-to-beat basis using the pressure wave-form alone (Fig. 1A).<sup>10</sup> Combining the simplicity of automation, the need to only measure pressure (rather than simultaneous pressure and flow) and absence of the need to induce hyperemia makes iFR highly attractive for routine clinical practice.<sup>24</sup>

Essential to the success of iFR was achieving conditions of stable microvascular resistance under resting conditions, because only under these conditions is pressure proportionate to flow. ADVISE showed that during the iFR wave-free period window the stability of resting resistance is equivalent to that achieved with adenosine-mediated hyperemia during the calculation of FFR (see Fig. 1B).<sup>10</sup> These findings suggested for the first time that, using contemporary phasic analysis to isolate the iFR wave-free period window, pressure can be used as a surrogate to flow under baseline conditions. In doing so ADVISE demonstrated that by using advanced computational algorithms, it was possible to obviate hyperemic agents, thereby providing a framework to challenge the underlying assumption that hyperemia is required for pressure-only stenosis assessment.

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