History and Development of Coronary Flow Reserve and Fractional Flow Reserve for Clinical Applications

Nils P. Johnson, MD, MS*, Richard L. Kirkeeide, PhD, K. Lance Gould, MD

KEYWORDS

• Clinical coronary physiology • Coronary flow reserve • Fractional flow reserve
• Historical development

KEY POINTS

- Clinical coronary physiology developed as an applied branch of pure physiology with a specific goal of diagnosing and treating patients with coronary artery disease.
- The historical development of clinical coronary physiology can be understood though a focus on both clinical motivations and technologic advances.
- Revascularization risk and angiographic ambiguity motivated the development of clinical coronary physiology, whereas the development of flow and pressure sensors made it a reality.
- Coronary flow reserve (CFR) equals the ratio of flow between hyperemia and resting conditions and first linked anatomic severity to physiologic reserve.
- Fractional flow reserve (FFR) equals the ratio of maximum flow between the stenotic artery and the same artery free from stenosis and, under certain conditions, can be measured before intervention with pressure sensors.

INTRODUCTION

In this review we discuss the history and development of clinical, invasive coronary physiology. By emphasizing the word *clinical*, we draw an immediate distinction between medicine (an applied field whose goal is patient care) and pure physiology (a branch of science devoted to understanding the functional mechanisms of life). Like engineering from physics, clinical medicine borrows from physiology but with the distinct purpose of practical intervention instead of rigorous description. Unlike a controlled animal model, humans typically display a host of simultaneous variations that we cannot quantify perfectly. Nevertheless, such patients appear in our clinics, emergency departments, and hospital wards requiring diagnosis and treatment. Therefore, *clinical* physiology sacrifices purity for pragmatism – summarized by the quotation, "all models are wrong, but some are useful."[1]

Our review begins with the motivating forces behind clinical coronary physiology. Next we detail the evolution of technical developments, both pharmacologic and sensors. Finally, we place the conceptual development of CFR and FFR in a historical context, linked to clinical motivations and technical developments. We focus on CFR and FFR because these 2 metrics have the longest history and broadest application. As summarized in

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Division of Cardiology, Department of Medicine, Weatherhead PET Center for Preventing and Reversing Atherosclerosis, Memorial Hermann Hospital, University of Texas Medical School at Houston, 6431 Fannin Street, Room MSB 4.256, Houston, TX 77030, USA
* Corresponding author.
E-mail address: Nils.Johnson@uth.tmc.edu

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Table 1, a large number of invasive metrics has been proposed for studying coronary physiology. CFR and FFR stand apart, however, for their longevity and depth of study. As stated presciently in 1997, "The preference for one physiologic technique may come from advances in guide wire capabilities and handling characteristics, ease of signal interpretation and integration into the specific catheterization laboratory system."[2]

CLINICAL MOTIVATIONS

Two clinical forces have spurred development of clinical coronary physiology: risk of revascularization and angiographic ambiguity. Excerpts from a 1997 article[2] capture these elements:

- Procedural risk: "… in so performing [percutaneous transluminal coronary angioplasty], a previously stable (and functionally not significant) lesion might be activated and a deleterious 'restenosis' process triggered. In fact, it is expected that in 20% to 30% of such patients, a clinically relevant restenosis will occur within 6 months. It is therefore unclear whether the risk of dilating a functionally

Table 1
Proposed indexes for invasive coronary physiology

Index	Full Name	Year	Developer(s)	Reference	Publications[a]
CFR (or CFVR)	Coronary flow (velocity) reserve	1974	Gould	53	>2000
ΔP	Translesion pressure gradient	1979[b]	Grüntzig	4	N/A[c]
Pd/Pa	Various terms, usually simply Pd/Pa	1985[b]	Wijns	73	
IHDVPS	Instant, hyperemic, diastolic velocity/pressure slope	1989	Mancini	74	<10
FFR	Fractional flow reserve	1993	Pijls and De Bruyne	63	>1000
d-FFR	Diastolic FFR	2000	Abe	75	<10
HMR	Hyperemic microvascular resistance	2001	AMC[d]	76	≈50
HSR (and BSR)	Hyperemic (and basal) stenosis resistance	2002 (and 2012)		77	≈10
PFLA	Pressure-flow loop area	2002	Ovadia-Blechman	78	<10
PTC	Pulse transmission coefficient	2002	Lerman	79	<10
IMR	Index of microcirculatory resistance	2003	Fearon	80	≈50
DCVR	Diastolic coronary vasodilator reserve	2004	Serruys	81	<10
dp_{v50}	Translesion gradient at 50 cm/s	2006	Marques	82	<10
CDP (or LFC)	Pressure drop (or lesion flow) coefficient (equivalent to the Euler number)	2007	Banerjee	83	≈20
iFR	Instantaneous wave-free ratio	2012	Davies	84	≈20

Abbreviations: Pa, aortic pressure; Pd, distal coronary pressure.
[a] Approximate PubMed search on full or related name in title or abstract or Scopus search for citations of primary reference.
[b] Refers to its clinical application in humans, as the index had been proposed previously.
[c] These measures have become so common that specific publication counts are not applicable.
[d] Academic Medical Center in Amsterdam, Netherlands, including Meuwissen, Piek, Siebes, Spaan, and van de Hoef.
Data from Refs.[4,53,63,73–84]