Physiology-guided PCI Present status & future perspectives





Takashi Akasaka, MD, PhD, FESC Department of Cardiovascular Medicine Wakayama Medical University



JCR Busan, 2017.12.08. Wakayama Medical University

Disclosure Statement of Financial Interest



Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support
- : Abbott Vascular Japan Goodman Inc. St. Jude Medical Japan Terumo Inc.
- Consulting Fees/Honoraria
- : Daiichi-Sankyo Pharmaceutical Inc. Goodman Inc. St. Jude Medical Japan Terumo Inc.



Concept of FFRmyo

First, it will be p pressure (P_a) and subtraction of ver purpose, suppose in P_v , that $R_s = \infty$ and and $P_d = P_w$ by defin	Because $Q_c^N = 0$:	The contribution calculated as follo Therefore:	Note that for evalue Final stenotic artery after ldiffere better measure than the second stere independent of arter clear that $\frac{\text{FFR}_{cor}^{(2)}}{\text{FFR}_{cor}^{(1)}} = \frac{P_d^{(2)} - P_w^{(1)}}{P_a^{(2)} - P_w^{(1)}}$ or, if of	ally, the theoretical relation between collated ont degrees of stenosis can be obtained. From ear that $Q_c = (P_a - P_d)/R_c$ Therefore: $\frac{Q_c^{(2)}}{Q_c^{(1)}} = \frac{(P_a^{(2)} - P_d^{(2)})/R_c}{(P_a^{(1)} - P_d^{(1)})/R_c} = \frac{\Delta^{(2)}P}{\Delta^{(1)}P}$ correction for pressure changes is made:	eral flow at m Figure 1, (A7a)
and		and because Q_s^N =	$=\left(1-\frac{\Delta}{P_a^{(2)}}\right)$	$\frac{Q_c^{(2)}}{Q_c^{(1)}} = \frac{\Delta^{(2)}P}{P_a^{(2)} - P_v^{(2)}}; \frac{\Delta^{(1)}P}{P_a^{(1)} - P_v^{(1)}}$	(A7b)
Therefore $\frac{P_1}{P_1}$ Equation A1a can forms, which will b	Substitution of tion A1b, gives th FFR _{cor} =-	In case of inter- maximum vasodil pressure $P_a - P_v$. T through the coron intervention (situ	In fa The expression FFI stenose of FFR _{cor} of the dila of the called pressure-correc dial ff previous study. ¹¹ examp Equation A5a can a App the following: be den $\frac{Q_s^{(2)}}{Q_s} = \frac{Q^{(2)} - Q_c^{(2)}}{Examp}$	act, Equation A7 states that decrease of ΔP to is geometry after PTCA induces a proportion relative contribution of collateral flow to to ow, which will be further clarified in the les. Distance of these equations in clinical practi- nonstrated.	y improved tal decrease tal myocar- e following ice also will
and	=		$Q_s^{(1)} \overline{Q^{(1)} - Q_c^{(1)}}$ The and by substituting Ec pTCA Theoretically, maxi dium can be compared (P_w) a Before $Q^{(2)}$ (pressu	first example is based on the simple hemody ch systemic pressures (P_a and P_v) are unchar . Therefore, according to Equation A1a, we lso is constant. ore and after PTCA of one of the corona are measurements are performed by the	ynamic case nged during lge pressure ry arteries, e pressure-
where C_1 , C_2 , and collateral resistanc dial bed supplied t The second step of the stenotic core	Next, fractional calculated as follo FFR _{myo} =	By substitution	$\frac{z}{Q^{(1)}} = \text{monit}$ (induce or, if correction for probe for each of the form of t	by intracoronary administration of paperside by intracoronary administration of papersine. Mean arterial pressure (P_a) is 90 m ΔP is reduced from 50 mm Hg before to the procedure; and venous pressure (P_v) and after the procedure. P_w measured dure on, is 20 mm Hg. Therefore, $P_a^{(1)} = P_a^{(2)} = 40$ mm Hg, $P_d^{(2)} = 80$ mm Hg, $P_v^{(1)} = P_v^{(2)} = 0$ m Hg.	hyperemia baverine or im Hg both essure gra- 10 mm Hg is 0 both ing balloon 90 mm Hg, nm Hg, and
	Equation A3 ha		obtain	ed:	onowing is
Р	ijls N, et al. C	Circulation 19	93;86:1354-1367	Wakayama Medica	University

Measurement of FFRmyo



Advantage of FFR in daily clinical practice

Easy to measure mean coronary pressure by PGW.

Normal value to FFR is 1.0.

Cut-off value for demonstrating ischemia is 0.75.

Cut-off value for revascularization is 0.8.



Clinical Evidence in FFR

Intracoronary imaging & physiology in ESC guideline 2014



DEFER:J Am Coll Cardiol 2007;49:2105-2111

Recommendations	Class ^a	Level [▶]	Ref. ^c
FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available.	I	A	50,51,713
FFR-guided PCI in patients with multivessel disease.	lla	В	54
IVUS in selected patients to optimize stent implantation.	lla	В	702,703,706
IVUS to assess severity and optimize treatment of unprotected left main lesions.	lla	В	705
IVUS or OCT to assess mechanisms of stent failure.	lla	С	
OCT in selected patients to optimize stent implantation.	ШЬ	С	

Eur Heart J. 2014;35:2541-2619 Wakayama Medical University



Relationship between FFR & functional tests



(N.H.J.Pijls, et al. N Engl J Med 1996;334:1703-1708)



Relationship between FFR & other tests

Best cut-off

Wakayama Medical University

eroniu/A	Namper	lschemic tests	งยุกษ	Accuracy
Pijls et al.	60	X-ECG	0.74	97
DeBruyne et al.	60	X-ECG/SPECT	0.72	85
Pijls et al.	45	X-ECG/SPECT/pacing/DSE	0.75	93
Bartunek et al.	37	DSE	0.68	90
Abe et al.	46	SPECT	0.75	91
Chamuleau et al.	127	SPECT	0.74	77
Caymaz et al.	40	SPECT	0.76	95
Jimenez-Navarro et al.	21	DSE	0.75	90
Usui et al.	167	SPECT	0.75	79
Yanagisawa et al.	167	SPECT	0.75	76
Meuwissen et al.	151	SPECT	0.74	85
DeBruyne et al.	57	MIBI-SPECT post-MI	0.78	85
Samady et al.	48	MIBI-SPECT post-MI	0.78	85

(Kern MJ & Samady H. J Am Coll Cardiol 2010;55:173-185)



Conceptual relationship between FFR & outcomes





Johnson NP, et al. J Am Coll Caridol 2014;64:1641-1654 Wakayama Medical University

Hazard Ratio of MACE in each FFR



Ahn JM, et al. Circulation in press (CIRCULATIONAHA.116.024433) Wakayama Medical University



Key integrated information from hundreds of studies

Risk to die or experience myocardial infarction in the next 5 years related to a coronary stenosis:

- Non-ischemic stenosis <1% per year NUCLEAR studies, DEFER, FAME, PROSPECT, CCTA)
- Ischemic stenosis, if left untreated 5-10% per year Many historical registries, ACIP, etc.)
- Stented stenosis; 2-3% per year after 2 years (e.g. DEFER, FAME, SYNTAX, many large studies & registries)



Incidence of MACE in deferred lesions according to each FFR group



Ahn JM, et al. Circulation in press (CIRCULATIONAHA.116.024433) Wakayama Medical University



Representative Examples of FFRct (NXT trial)





Norgaard BL, et al. J Am Coll Cardiol 2014;63:1145 - 1155 Wakayama Medical University

Correlation and Bland-Altman Plots of FFR and FFRCT in Vessels Having FFR Measured (n = 51)



Nørgaard BL, et al. J Am Coll Cardiol Cardiovasc Imag 2016, doi.org/10.1016/j.jcmg.2015.11.025



The DeFACTO Study: Intermediate Stenoses (30-70%)





 $FFR_{CT} 0.71 = Lesion-specific ischemia of an intermediate stenosis (30-70%) - Concordant and in agreement with invasive FFR$



SROC curves of the diagnostic accuracy of cardiac imaging compared with FFR





Ibrahim Danad et al. Eur Heart J 2016;eurheartj.ehw095

FFRCT Decision-Rule Algorithm in patients with new-onset chest pain without known coronary artery disease





Nørgaard BL, et al. J Am Coll Cardiol Cardiovasc Imag 2016, doi.org/10.1016/j.jcmg.2015.11.025 Wakayama Medical University





Wakayama Medical University

Comparison of FFRCTA Results Before and After Simulated PCI With Stent Implantation before (A) and after (B) PCI.



Taylor CA, et al., J Am Coll Cardiol 2013;61:2233–2241



Computation of FFR From 3D QCA and TIMI Frame Count (A,B) X-ray angiography



Tu S, et al. JACC: Cardiovasc Interv, 2014; 7: 768–777



Correlation and Agreement Between FFR and the Computed FFRQCAA



Tu S, et al. JACC: Cardiovasc Interv, 2014; 7: 768–777



Penetration of FFR



Rough estimates expressed in percentage of number of PCI



iFR





Diastolic pressure – flow relationship & FFR





Coronary flow velocity recordings

Aortic stenosis*

HCM**



- * Yoshikawa J, Akasaka T, et al. J Am Soc Echocardiogr 1993; 6:516-524
- ** Akasaka T, Yoshikawa J, et al. J Am Soc Echocardiogr 1994; 7:9-19 Wakayama Medical University



Relationship Between iFR & FFR and Pd /Pa & FFR Jeremias A, et. Al. J Am Coll Cardiol, 2014;63:1253-1261





Sen et al. CLARIFY. J Am Coll Cardiol. 2013;61(13):1409-1420

iFR has similar diagnostic accuracy to FFR



iFR and FFR have similar diagnostic accuracies





<u>Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation</u>

Intermediate lesion requiring physiological assessment In ACS : intermediate *non-culprit* lesion





Patients enrollment in DEFINE-FLAIR study





Davies JE, et al. N Engl J Med 2017;376:1824-34.

Cumulative Risk of the Primary Endpoint



No. at Risk

iFR	1242	1149	1131	1122	1118	1111	1088	1052	1037	1027	1019	995	764
FFR	1250	1169	1156	1149	1144	1141	1119	1081	1066	1055	1046	1017	793



Superiority of iFR to FFR

Variable	iFR Group (N=1242)	FFR Group (N=1250)	P Value†
Stents placed with postdilation — no. (% of total stents placed)	407 (49.5)	425 (46.9)	0.28
PCI procedures performed with pressure wire — no. (% of total stents placed)	261 (31.8)	278 (30.7)	0.63
Patient-reported adverse procedural symptoms or signs — no. of patients (%)	39 (3.1)	385 (30.8)	<0.001
Patient-reported dyspnea — no. of patients (%)	13 (1.0)	250 (20.0)	
Patient-reported chest pain — no. of patients (%)	19 (1.5)	90 (7.2)	
Physician-reported adverse procedural signs — no. of patients (%)			
Heart-rhythm disturbance	2 (0.2)	60 (4.8)	
Significant hypotension	4 (0.3)	13 (1.0)	
Vomiting or nausea	1 (0.1)	11 (0.9)	
Ventricular arrhythmia or bronchospasm¶	1 (0.1)	8 (0.6)	
Other	4 (0.3)	38 (3.0)	



Superiority of iFR to FFR	iFR Group	FFR Group	
Variable	(N=1242)	(N=1250)	P Value†
Radial-artery approach — no. of patients (%)	896 (72.1)	888 (71.0)	0.54
Procedure time — min			
Median	40.5	45.0	0.001
Interquartile range	27.0–60.0	30.0–66.0	
Hyperemic agent administered — no. of patients (% of total no. who received a hyperemic agent)			
Total	NA	1608 (100)	
Intracoronary adenosine	NA	455 (28.3)	
Intravenous adenosine	NA	950 (59.1)	
Other agent	NA	203 (12.6)	
Multivessel disease — no. of patients (%)	505 (40.7)	519 (41.5)	0.66
Type of vessel evaluated — no. (% of total vessels evaluated) \ddagger			
Total	1575 (100)	1608 (100)	0.58
Left anterior descending artery	844 (53.6)	845 (52.5)	0.56
Left circumflex artery	323 (20.5)	333 (20.7)	0.89
Right coronary artery	374 (23.7)	393 (24.4)	0.65
Other	33 (2.1)	31 (1.9)	0.74
Unknown	1 (0.1)	6 (0.4)	0.06



Total no. of vessels evaluated or treated:	1879	1940	0.42
No. of vessels evaluated or treated per patient <u>:</u>	1.51±0.76	1.55 ± 0.80	0.42
Functionally significant lesions — no. (% of total vessels evaluated) \S	451 (28.6)	557 (34.6)	0.004
≥1 Functionally significant lesions present — no. of patients (%)§	426 (34.3)	486 (38.9)	0.02
Mean iFR	0.91±0.09	NA	
Mean FFR	NA	0.83±0.09	
Percent of lesions within the FFR range Any issues in	iFR compa	ared with	FFR?
<0.60	NA	1.96	
0.60–0.90	NA	75.08	
>0.90	NA	22.96	
Revascularization performed — no. of patients (%)			
Total	590 (47.5)	667 (53.4)	0.003
CABG	25 (2.0)	42 (3.4)	0.04
PCI	565 (45.5)	625 (50.0)	0.02
Stents placed — no. (% of total stents placed)			
Total	822 (100)	906 (100)	0.86
Drug-eluting stent	811 (98.7)	893 (98.6)	
Bioresorbable vascular scaffold	11 (1.3)	13 (1.4)	
No. of stents placed per patient	0.66±0.92	0.72±0.96	0.09



Patients enrollment in iFR SWEDEHEART Clinical Trials



Gotberg M, et al. N Engl J Med 2017;376:1813-23. Wakayama Medical University



Kaplan-Meier Curve for the Primary Endpoint



Gotberg M, et al. N Engl J Med 2017;376:1813-23.. Wakayama Medical University



Characteristic	Superiority of iFR to FFR	iFR Group (N=1012)	FFR Group (N = 1007)	P Value
Radial-artery approach —	no. of patients (%)	841 (83.1)	811 (80.5)	0.13
Contrast material used pe	er patient — ml			0.10
Median		110	115	
Interquartile range		80–155	80–160	
Procedure time — min†				0.09
Median		50.8	53.1	
Interquartile range		13.8-87.8	18.1-88.1	
Fluoroscopy time — min				0.57
Median		10.5	10.2	
Interquartile range		6.3-16.8	6.5-16.0	
Intravenous adenosine ac	lministered — no. of patients (%)	NA	695 (69.0)	
Total no. of lesions evalua	ated	1568	1436	
Chest discomfort during p	procedure			<0.001†
None		982 (97.0)	319 (31.7)	
Mild		26 (2.6)	316 (31.4)	
Moderate		2 (0.2)	285 (28.3)	
Severe		2 (0.2)	87 (8.6)	



Gotberg M, et al. N Engl J Med 2017;376:1813-23. Wakayama Medical University

No. of lesions evaluated per patient	1.55 ± 0.86	1.43 ± 0.70	0.002	
Hemodynamically important lesions — no. (% of total lesions evaluated) <u></u>	457 (29.1)	528 (36.8)	<0.001	
No. of hemodynamically important lesions per patient‡	0.45 ± 0.71	0.52±0.68	0.05	
Mean iFR	0.91±0.10	NA		
Mean iFR in hemodynamically important lesions‡	0.80±0.13	NA		
Mean FFR	NA	0.82±0.10		
Mean FFR in hemodynamically important lesions‡	NA	0.72±0.08		
Lesion complexity according to the ACC-AHA claser issues — no./total no. of treated lesions (%)§¶	in iFR co	mpared w	יith₀₽FR	?
A	61/915 (6.7)	73/980 (7.4)		
B1	304/915 (33.2)	320/980 (32.7)		
B2	284/915 (31.0)	300/980 (30.6)		
С	139/915 (15.2)	165/980 (16.8)		
Missing data	127/915 (13.9)	122/980 (12.4)		
Lesions treated in the vessel — no./total no. of treated lesions (%) \P			0.68	
Left main coronary artery	14/915 (1.5)	16/980 (1.6)		
Left anterior descending artery	434/915 (47.4)	469/980 (47.9)		
Left circumflex artery	176/915 (19.2)	179/980 (18.3)		
Right coronary artery	164/915 (17.9)	196/980 (20.0)		
Missing data	127/915 (13.9)	120/980 (12.2)		
Total no. of stents placed	698	787		
No. of stents placed per patient undergoing PCI	1.58 ± 1.08	1.73±1.19	0.05	



FFR (prePCI)









Xience V : 3.5x15mm Wakayama Medical University



FFR (after stenting to #6)









Xience V : 2.5x8mm Wakayama Medical University

FFR (after stenting to #7)

Pullback curve by iFR

iFR Pullback

Nijjer S, et al. JACCint 2014; 12: 1386-1396.

Advantages of iFR pullback

• The most significant lesion could be identified by the finding of maximum pressure (iFR value) difference.

PCI case with iFR co-registration

PCI case with iFR co-registration

PCI case with iFR co-registration

Prediction of post PCI iFR by Syncvision

Prediction of post PCI iFR by Syncvision

We chose a short stent.

CLARIFY an ADVISE sub-study

Summary of microvascular resistance (MVR) reduction with & without hyperemia by adenosine infusion in cases with or without significant stenosis

Although reduction of MVR in iFR is grater than FFR in cases with stenosis, much more reduction in MVR is demonstrated during hyperemia in cases with & without stenosis in iFR.

0.4 0.5 0.6 0.7 0.8 0.9 1.0 iFR values

Petraco R et al. EuroIntervention. 2013 Feb 22;8(10):1157-65

SYNTAX II

*FFR with adenosine, iFR/FFR in side branches, all at discretion of the operator

European Heart Journal (2017) **00**, 1–11 doi:10.1093/eurheartj/ehx512 FASTTRACK CLINICAL RESEARCH ESC Late Breaking Science in PCI 1

4

3

2

1

0

Lesion treatment ater iFR/FFR interrogation (n=1177)

Interventional cardiology

Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with *de novo* three vessel disease: 1-year results of the SYNTAX II study

Javier Escaned¹, Carlos Collet², Nicola Ryan¹, Giovanni Luigi De Maria³, Simon Walsh⁴, Manel Sabate⁵, Justin Davies⁶, Maciej Lesiak⁷, Raul Moreno⁸, Ignacio Cruz-Gonzalez⁹, Stephan P. Hoole¹⁰, Nick Ej West¹⁰, J. J. Piek², Azfar Zaman¹¹, Farzin Fath-Ordoubadi¹², Rodney H. Stables¹³, Clare Appleby¹³, Nicolas van Mieghem¹⁴, Robert Jm. van Geuns¹⁴, Neal Uren¹⁵, Javier Zueco¹⁶, Pawel Buszman¹⁷, Andres Iniguez¹⁸, Javier Goicolea¹⁹, D; Andrzej Ochala²¹, Dariusz Dudek²², Colm Hanratty⁴, Rat Arie Pieter Kappetein¹⁴, David P. Taggart³, Gerrit-Anne v Marie-Angele Morel²³, Ton de Vries²³, Yoshinobu Onuma Patrick W. Serruys⁶*, and Adrian P. Banning³

¹Hospital Clinico San Carlos IDISSC and Universidad Complutense de Madrid, Madrid, Spain; Calle Profesor Martín Lag Academic Medical Center of Amsterdam, Cardiology, Amsterdam, the Netherlands; Meibergdreef 9, 1105 AZ Amsterda Cardiology, John Radcliffe Hospital, Cardiology, Oxford, UK; Headley Way, Headington, Oxford OX3 9DU, UK; ⁴Depar Belfast, UK; Knockbracken Healthcare Park, Saintfield Rd, Belfast BT8 8BH, UK; ⁵Hospital Clinic I Provincial de Barcelona Barcelona, Spain: ⁶Department of Cardiology, Imperial College London, London, UK; Kensington, London SW7 2AZ, UK

Cases of three-vessel PCI (%) in SYNTAX II and SYNTAX I

Primary endpoint: MACCE

Exploratory End-Point: MACCE PCI vs. CABG

*Non-inferiority margin of 5% with a one-sided alpha of 5%

Unresolved issue

Case: 64 y.o., female, NSTEMI (anterior)

QFR=0.73

FFR CT=0.79

Comparison between FFR & iFR at present

	FFR	iFR
Pressure Wire	Ο	0
Hyperemia free	×	0
Typical measurement time	5-10 min	1-2 min
Pressure damping unlikely	×	Ο
Cost saving(add to FAME)	×	Adenosine / Time Equipment
Optimized for pullback	×	0
Peri-PCI assessment	0	×
Evidence against ischemia	Ο	Δ
Clinical outcome data	0	Coming soon !

Comparison among FFRs & iFR

	Imaging modality	On-Line	Pressure- wire use	Analysis time	Hyperemia
FFR p-wire	Angio	Yes	Yes	<5mim	Yes
FFR CTA-HF	СТА	Νο	Νο	24 hrs	Νο
FFR CTA-SM	СТА	Νο	Νο	>35min	Νο
QFR	3D-Angio	Yes	Νο	<4min	Νο
iFR	Angio	Yes	Yes	<5min	No/yes

Take home message

- Although FFR might have a limitation based on diastolic coronary pressure-flow relationship, there are many evidence demonstrating clinical usefulness.
- Furthermore, several non-invasive FFR measurement systems are developing according to the evidence of invasive FFR, and clinical evidence have been demonstrated by these methods.
- Although timing of measurement is thought to be ideal in iFR based on diastolic coronary pressure-flow relationship, there are a only few data demonstrating clinical usefulness.
- Although non-inferiority of iFR for PCI guidance compared with FRR has been reported in DEFINE-FLAIR study and iFR SWEDEHEART Trials, there are still unresolved issues which should be resolved adequately and further investigation would be required in the future.

