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Current Developments and Future Applications of Intracoronary Hemodynamics

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Abstract

Intracoronary hemodynamic assessment of the physiologic significance of coronary lesions improves clinical outcomes in patients with coronary artery disease. Coronary flow velocity reserve (CFVR), fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), and index of microcirculatory resistance (IMR) utilize sensor-mounted guidewires to approximate coronary flow. CFVR and FFR rely on pharmacologic administration of adenosine to achieve hyperemia and diagnose epicardial lesion severity. As an adenosine-free index, iFR utilizes a wave-free period in mid-late diastole during which resistance is constant and low to assess lesion significance. IMR combines hyperemic pressure measurements with thermodilution to quantify microvascular resistance. We review the physiology, clinical trials, and clinical applications of these invasive hemodynamic assessments.

Keywords

Fractional Flow Reserve; Instantaneous Wave-Free Ratio; Coronary Flow Reserve; Index of Microcirculatory Resistance; Hemodynamics; Coronary Artery Disease

Introduction

Recent review articles outline the benefits of a nonangiographic-based assessment of coronary artery disease. Matsuzawa and Lerman discuss the ability of non-invasive measures of peripheral endothelial dysfunction to predict the presence of and complications from atherosclerotic coronary disease.[1] Ahmed provides an extensive overview of the assessment of coronary microvascular dysfunction by both non-invasive and invasive assessments.[2] Rassi et al address practical uses for invasive assessment by fractional flow reserve and optical coherence topography in diagnosing and treating coronary disease.[3] In this review, we expand upon the non-angiographic assessment by focusing on emerging modalities to assess hemodynamic severity of coronary artery lesions in the cardiac catheterization lab. We summarize current and ongoing clinical trials addressing fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) and address their current and future roles in clinical practice. Furthermore, we discuss the data with regards to index of

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microcirculatory resistance (IMR) and its potential as an invasive measure of microvascular disease and dysfunction.

Catheter-based assessment of coronary fluid hemodynamics has gained widespread translation to the clinical realm as an effective tool for diagnosing coronary artery disease severity.[4] Visual estimation of severity by angiography is an imperfect method with high interobserver variability and poor correlation with objective measurements such as quantitative coronary angiography and fractional flow reserve.[5; 6] While intravascular ultrasound and optical coherence tomography are available to improve the anatomic assessment, the catheterization lab has also adopted the physiologic assessment of lesion significance.[7] Translesional hemodynamics may be safely and reproducibly assessed by crossing a coronary lesion with a sensor-tipped guidewire to directly assess for ischemia, an assessment traditionally limited to non-invasive exercise and pharmacological stress testing.[8] Furthermore, large-scale, randomized clinical trials suggest that hemodynamic assessment of coronary artery lesions improves clinical outcomes.[9–11]

Coronary Hemodynamics

Direct measurement of intracoronary hemodynamics is readily achieved in the cardiac catheterization lab. Pressure waves are transmitted through a fluid-filled catheter and analyzed by a pressure transducer or, in the case of pressure wires, measured by a pressure sensor 3cm from the tip.[12] Similar coronary guide-wires have been created that are mounted with thermistors [13] or Doppler sensors [14] for temperature or flow velocity assessment, respectively.

Ischemia is driven by a mismatch between myocardial oxygen demand and myocardial oxygen supply. Wall stress, heart rate, and contractility influence demand, while supply is related to arterial oxygen content and coronary blood flow. Increasing myocardial oxygen supply relies primarily on compensatory increases in coronary blood flow.[15] Coronary blood flow is best defined according to Poiseuille's Law, wherein flow is determined by the perfusion pressure and resistance of a vessel ($\text{Pressure} = \text{Flow} / \text{Resistance}$). [16] Nearly all of the coronary vascular resistance in an undiseased vessel is due to microvascular resistance.[17] Resistance is influenced by both external compression, as occurs naturally in systole or pathologically in left ventricular hypertrophy, and intrinsically by endothelial smooth muscle response to local metabolites and neural innervation.[15]

Coronary perfusion pressure is derived primarily by aortic blood pressure. When perfusion pressure decreases, arteriolar vasodilation maintains constant blood flow by a process termed autoregulation. In the setting of epicardial stenosis, transcoronary pressure decreases but flow is maintained via vasodilation up to the maximal threshold, at which point coronary flow cannot match demand and ischemia occurs.[18] Vasodilatory agents may be administered to achieve maximal dilation and minimize microvascular resistance. During hyperemia, coronary pressure has a linear correlation with coronary flow (Figure 1).[19; 20] Coronary flow reserve (CFR), fractional flow reserve (FFR), and instantaneous wave-free ratio (iFR) all utilize this principle of a correlative relationship between pressure and flow at points of minimal resistance to estimate the severity of a coronary artery lesion.

Coronary Flow Reserve

The degree to which the coronary circulation dilates in response to pharmacologic stimulation is termed coronary flow reserve. [19] Coronary flow reserve can be estimated by intracoronary Doppler velocity (CFVR) [21–23] or thermodilution flow measurements.[24–26] Absolute coronary flow reserve is the ratio of maximal hyperemic flow to resting coronary flow and therefore is influenced by conditions that influence maximal flow.[27] Flow reserve is decreased in the setting of epicardial coronary stenosis due to higher resting vasodilation and therefore correlates with epicardial resistance and severity of stenosis.[28]

However, the measurement is influenced by resting flow hemodynamics such as blood pressure and heart rate.[29; 30] (Figure 1) Furthermore, coronary flow reserve also is unable to distinguish between the influence of microvascular disease and epicardial disease on coronary flow.[27] The significant overlap between risk factors for epicardial coronary disease and risk factors for microcirculatory dysfunction (i.e. diabetes, hypercholesterolemia, left ventricular hypertrophy), limits the efficacy of absolute coronary flow to isolate the significance of epicardial disease.[31] To mediate the influence of microvascular resistance, an indexed value (relative CFVR) has been used by taking the ratio of the CFVR in a target vessel to the CFVR in an undiseased vessel. However, this requires the presence of a normal, undiseased vessel, and wiring it adds additional procedural time and risk.[27] The physiologic influences and procedural requirements have hindered the adoption of absolute or relative CFVR for wide-scale clinical use.

Fractional Flow Reserve (FFR)

Physiology

Myocardial fractional flow reserve (FFR) was developed as an index of lesion severity by comparing post-stenosis blood flow in a vessel to a theoretical normal maximal flow in the same vessel distribution.[32] This is achieved by advancing an interventional pressure wire past the stenosis and deriving a ratio of the mean distal pressure (Pd) to the mean aortic pressure (Pa). The pressure gradient approximates coronary blood flow when maximal hyperemia is achieved by administration of nitroglycerin and adenosine.[33; 34] Unlike CFVR, FFR is independent of changes in hemodynamic or ionotropic conditions.[30]

Several limitations have been proposed. FFR relies on the assumption that pressure approximates flow in states where microvascular resistance can be minimized and coronary venous flow is low.[30] Conditions that increase microvascular resistance or decrease arteriolar vasodilatory reserve may limit the ability of adenosine to reliably achieve maximal hyperemia and may falsely influence the FFR value.[35; 36] Large, acute non-ST elevation MI or ST elevation MI damages coronary vasodilatory function.[36] In left ventricular hypertrophy, the increase in myocardial mass is disproportionate to the growth of the microvasculature, increasing myocardial resistance and inhibiting maximal vasodilation.[34] Notably, these two subgroups have been excluded from clinical trials.[9; 10] Elevated left ventricular end-diastolic pressure restricts coronary flow during diastole and influences the pressure-flow relationship during hyperemia (Figures 1 and 2A).[37–39] Furthermore, a paradoxical response to adenosine may be seen in severe stenosis or severely impaired

microvascular resistance (Figure 2B).[40] Thus far, the influence of these subgroup characteristics on FFR values appears small, limiting their overall impact on clinical outcomes from a FFR-based revascularization strategy.

Clinical Trials

Multiple clinical trials have evaluated the efficacy of an FFR-based treatment strategy on reducing clinical outcomes (Table 1). The DEFER trial built on a prior established association of FFR with stress testing.[32; 41; 42] In the study, 325 patients undergoing planned percutaneous coronary intervention (PCI) underwent FFR. Patients with a lesions with an FFR <0.75 underwent PCI as planned and were considered part of a reference group. Patients with a lesion with an FFR > 0.75 were randomized to percutaneous intervention or medical management. One and five year follow-up has been published, showing no difference in a broadly defined major adverse cardiac events (MACE) primary outcome between patients conservatively managed versus undergoing PCI in the group above >0.75. The rate of composite endpoints, cardiac death and acute myocardial infarction in the group conservatively managed due to an FFR >0.75 remained an extremely low 3.3% at five years. [43]

The FAME trial randomly assigned 1005 patients with multivessel coronary artery disease to angiography-guided versus FFR-guided PCI or optimal medical therapy.[44] Basing PCI treatment strategy on an FFR $\geq$ 0.80 resulted in a 5% absolute risk reduction ($p = 0.02$, NNT 19) in all-cause death, myocardial infarction, or repeat revascularization. The group randomized to an FFR-based strategy also had lower mean numbers of stents placed (1.9 v 2.7, $p < 0.001$), lower procedural costs (\$5,332 v. \$6,007, $p < 0.001$) and sustained one year cost-effectiveness (\$14,315 v \$16,700, $p < 0.001$).[44–46]

FAME 2 randomized 888 patients with stable coronary artery disease and an FFR $\geq$ 0.80 and to PCI versus optimal medical therapy alone. Enrollment was halted prematurely when interim analysis found a significant reduction in the primary outcome of all-cause death, myocardial infarction, or urgent revascularization (HR 0.39, 95% CI [0.26,0.57]) among patients who underwent PCI. The risk reduction was driven primarily by a reduction in urgent revascularization (PCI group 4.0% v. medical therapy group 16.3%, $p < 0.001$). There was no significant difference in outcomes between patients who underwent PCI based on a FFR $\geq$ 0.80 and a registry cohort ($n=166$) of patients who underwent medical therapy based on a FFR > 0.80 (95% CI [0.49,3.39]; $p=0.61$). [47]

These trials led to widespread adoption of invasive physiologic measurements for diagnosing ischemic lesions in current guidelines. Currently, the Society of Cardiovascular Angiography and Interventions Guidelines 2011 includes a IIA recommendation for the use of FFR as an adjunct to angiography in assessing intermediate (50–70%) coronary lesions for revascularization therapy.[48] Similarly, the European Society of Cardiology 2014 Guidelines provide a IA recommendation for FFR to identify coronary lesions in the absence of prior stress testing and IIA recommendation for FFR-guided PCI in patients with multivessel coronary artery disease.[49]

Future Investigations

Several ongoing clinical trials are investigating further uses for FFR (Table 1). FAME 3 (NCT02100722) is currently enrolling patients with multivessel coronary artery disease (> 50% stenosis) randomized to coronary artery bypass grafting versus an FFR-based PCI approach with a primary outcome of death, myocardial infarction, stroke, or repeat revascularization at one year.[50] The FORZA trial (NCT01824030) will randomize patients to FFR-guided versus OCT-guided severity assessment for intermediate coronary lesions.[51] SYNTAX II is a multicenter trial (NCT02015832) that will utilize FFR (and iFR) to guide the PCI arm in a score-based approach to treat multivessel coronary artery disease. Secondary outcomes from MITNECB5 (NCT01972360) will add to the data comparing FFR with non-invasive testing, namely coronary CT, stress echocardiography, cardiac MRI perfusion, and technetium-99m SPECT.[52]

Instantaneous Wave-Free Ratio (iFR)

Physiology

Over the last three years, there has been increasing interest in the use of hyperemia-free indices of severity. The hyperemia-free hemodynamic assessment has been proposed to benefit over FFR or CFVR by obviating the need for the temporary discomfort of adenosine to patients, shortening procedural time and decreasing costs.[53; 54]

The instantaneous wave-free ratio (iFR) is derived from a period of low and constant coronary resistance in mid to late diastole (Figure 3).[53] The mean pressure during this diastolic wave-free period is obtained distal to the lesion and indexed to the simultaneous aortic pressure. At this time point, the influence of coronary resistance is constant and low, allowing for pressure to correlate with coronary flow. Furthermore, isolation of the pressure measurement to a diastolic period improves variability [30; 53] by eliminating the interaction between the myocardium and coronary microvasculature in systole, during which the microvasculature is compressed and intracoronary resistance increases.[53; 55; 56]

Clinical Trials

Multiple clinical trials have compared iFR with FFR. The ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study formed the derivation cohort for the calculation of the instantaneous wave-free ratio. The study compared iFR to FFR, finding relatively good agreement ($R = 0.91$, $p < 0.0001$) and ability to predict an $FFR < 0.80$ (c-statistic 0.93).[53] However, this level of agreement has yet to be replicated in multiple subsequent clinical trials with correlation coefficients ranging from 0.77–0.91 (Table 2).[53; 57–61] The largest study, RESOLVE, combined clinical trial (ADVISE, VERIFY) and institutional data to compare iFR, resting Pd/Pa and hyperemic FFR at a core laboratory, ultimately evaluating 1,593 lesions from 15 clinical sites. Interestingly, there was an extremely high correlation between non-hyperemic FFR (Pd/Pa) and iFR measurements ($R^2 = 0.95$, $p < 0.001$); however, limited correlation with hyperemic FFR ($R^2 = 0.66$, $p < 0.001$). Using an iFR cutoff of 0.90 to predict an FFR of 0.80 classified 80% of the lesions appropriately.[60]

While its correlation with FFR is limited, the diagnostic ability of iFR to diagnose ischemia may be similar to FFR. Utilizing a reference standard of myocardial perfusion scintigraphy, iFR appears to be similar in predicting ischemia when compared to FFR (iFR AUC 0.81 v. FFR AUC 0.85, $p=0.29$; $n=85$).[62] The ability of iFR and FFR to predict physiologic significance defined by hyperemic stenosis resistance (HSR) was also shown to be similar (iFR AUC 0.93 v. FFR AUC 0.96, $p=0.48$; $n=51$).[63] Coronary flow velocity reserve was found to have higher agreement with iFR than FFR ($r=0.68$ v. $r=0.50$, $p<0.001$)[64], although the use of CFVR as standard for ischemia is limited as previously addressed.[65] While there is suggestion of non-inferiority from these small studies, definitive conclusions must be tempered pending further validation and larger sample-size studies.

Several studies have proposed novel uses for iFR. Nijjer et al described the role of iFR in assessment of serial lesions and diffuse disease via pressure-wire pullback technique to predict the hemodynamic effect of PCI. Such a strategy may ultimately be valuable in decreasing number of stents required or shortening stent length.[66] Use of iFR may rapidly document improvement in coronary hemodynamics following PCI, showing similar pre- and post- changes as FFR after PCI. [67] ADVISE II, a recently completed clinical trial utilized a “Hybrid” iFR/FFR approach wherein treatment was based on iFR values of 0.86 (PCI) or 0.94 (medical therapy) with FFR utilized in the “adenosine zone” of 0.86–0.93. Early reported results have boasted a 94% classification match to FFR-guided therapy, saving 65.1% of patients from hyperemic therapy.[68]

Future Investigations

The DEFINE REAL study (NCT02281110) will enroll 3000 patients in an observational registry to establish the ability of iFR to predict hemodynamic severity as assessed by FFR <0.80 , planning for the largest scale head-to-head assessment of correlation between iFR and FFR to date. Two trials currently registered plan to compare clinical outcomes based on an iFR versus FFR guided PCI strategy. iFR Swedeheart (NCT02166736) will utilize 2000 patients with stable angina or acute coronary syndrome from the Swedish angiography and angioplasty registry to conduct a registry-based randomized clinical trial ultimately comparing one year outcomes of death, myocardial infarction or unplanned revascularization between iFR and FFR groups. Similarly, the DEFINE-FLAIR trial (NCT02053038) will randomly assign 2500 patients with intermediate lesions (40–70%) to an FFR or iFR guided PCI strategy with plans to compare clinical outcomes (MACE) and cost between the two modalities. J-Define (NCT02002910) will further explore the cost-effectiveness of a hybrid FFR/iFR approach. SYNTAX II, PROSPECT II, ORBITA, MITNEC will also utilize invasive physiologic assessments in their clinical protocols with plans for comparisons between iFR and FFR in secondary analyses.[52]

Index of Microcirculatory Resistance

There is increasing interest into invasive hemodynamic assessment of microvascular dysfunction, an often unrecognized cause of cardiovascular symptoms and adverse cardiovascular outcomes.[69–72] While prior evaluations of microcirculatory resistance required Doppler flow/velocity measurements, an index of microcirculatory resistance (IMR) has been validated using a pressure and temperature sensor-mounted wire.[73]

Maximal hyperemia is achieved with intravenous adenosine and the mean distal coronary pressure and mean transit time via thermodilution are measured. IMR is then calculated by multiplying the average Pd by the average transit time.[74] In the setting of an epicardial stenosis, a measurement is also obtained during coronary balloon inflation to estimate coronary wedge pressure.[75]

The clinical applicability for IMR is still being defined. The largest focus of clinical investigations has been on its ability to predict the prognosis of patients undergoing PCI. For instance, Fearon *et al.* showed that patients undergoing primary PCI for STEMI with a culprit vessel IMR >40, had an increased risk of death or rehospitalization for heart failure (HR 2.1 [1.1–1.41]). Impressively, the effect of an elevated IMR on mortality was independent of clinical or procedural characteristics.[75] Additionally, IMR has been shown to predict peri-procedural MI and outcomes in stable CAD in patients undergoing PCI.[76; 77] As we increase our understanding of the prognostic significance of microvascular dysfunction, IMR-tailored therapies or interventions may lead to improvement of outcomes in patients with coronary artery disease.[78]

Summary

Over 40 years of research into invasive coronary physiology has contributed to the emergence of intracoronary hemodynamic assessment as one of the most promising tools to diagnose ischemia and improve patient outcomes. Fractional flow reserve is a proven methodology with large-scale clinical data to support it. iFR and adenosine-free assessment shows promise, the appropriateness of which will be addressed with ongoing investigations and clinical trials. IMR may finally draw attention to the clinical importance of microvascular disease. Regardless of the modality, the outlook for intracoronary hemodynamic assessment appears promising.

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Figure 1. Intracoronary pressure and flow relationship illustrated

The resting intracoronary pressure to flow relationship is illustrated by the thick, dark line. As coronary pressure declines, autoregulation maintains steady coronary flow until a point that maximum vasodilation is achieved. At this point, microvascular resistance is minimized and pressure correlates linearly with flow (thin, dark line). Pharmacologic vasodilation may allow pressure to approximate flow while pressure is still physiologic and microvascular resistance maintaining flow (dark arrow). Clinical conditions, such as LVH or elevated left-ventricular end-diastolic period may impair microvascular dilation under pharmacologic

conditions, altering the slope of the pressure and flow relationships (dotted line). Basal coronary flow increases in clinical conditions such as tachycardia, hypertension, and anemia (curved dotted line). The size of the dark arrow to the dotted arrow represents the potential influence of these conditions on coronary flow reserve, while the change in slope between the dark line and dotted line represents the influence of fractional flow reserve.

Figure 2. Discordance between iFR and FFR

A. This case of a 63 year-old male with ischemic cardiomyopathy (ejection fraction of 25%) with unstable angina illustrates discordance between iFR and FFR in a 70% RCA lesion.

B. This case of a 50 year-old with end-stage renal disease and prior PCI presented with unstable angina, noted to have diffuse atherosclerosis with serial lesions to the left anterior descending artery. iFR categorized a physiologically significant lesion (0.81) while fractional flow reserve categorized it as insignificant (0.82). The hyperemic wave-free pressure ratio was noted to be higher after adenosine administration illustrating a paradoxical response to adenosine in this patient.

Figure 3. Intracoronary pressure and resistance measurements during the cardiac cycle
 The instantaneous wave-free ratio (iFR) is derived from a period of low and constant coronary resistance in mid to late diastole. *Figure reproduced with permission from Journal of American College of Cardiology, Vol. 59, Sen et al., Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis. Copyright Elsevier 2012.[53]*

Prior and ongoing randomized-control trials investigating the clinical efficacy of fractional flow reserve for evaluating the severity of coronary artery lesions.

Table 1

Previous Trials						
Study Title	Author (Primary, Senior)	Publication Date	Journal	Sample Size	Lesions	Randomization
FAME 2	De Bruyne, Fearon	Sept, 2012	NEJM [7]	1220	Stable, all stenoses	FFR-Guided v. Medical Therapy
						Primary Outcomes: Death, MI, Urgent Revascularization at 1 year
						Result: FFR-guided therapy resulted in significant reduction in primary endpoint (HR 0.23(0.26,0.57))
FAME	Tonino, Fearon	Jan, 2009	JACC [6]	1005	Multivessel CAD	FFR-Guided v. Angiographically-Guided
						Primary Outcomes: Death, MI, Repeat Revascularization at 1 year
						Result: FFR-guided therapy resulted in significant reduction in primary outcomes (13.2 v. 18.3%, p=0.02)
DEFER	Bech, Pijls	April, 2001	Circulation [40]	325	>50% Lesions	FFR 0.75 (Deferral v. PCI)
						Primary Outcomes: Death, MI, CABG, Angioplasty, Procedural Complication at 1 year
						Result: Similar survival in deferred group as PCI group (89% v. 92%, p=NS)
Ongoing Trials						
	Primary Investigator	Estimated Completion Date	ClinicalTrials.gov Identifier	Estimated Enrollment	Lesions	Randomization
FAME 3	Fearon, Pijls, De Bruyne	Aug, 2017	NCT02100722	1500	Multivessel CAD, >50% Lesions	FFR-Guided PCI v. CABG
						Primary Outcomes: Death, MI, Stroke, and Repeat Revascularization at 1 year
FORZA	Burzotta	April, 2016	NCT01824030	400	Intermediate Lesions	FFR-Guided PCI v. OCT-Guided PCI
						Primary Outcomes: Angina Score at 13 months

Previous Trials								
Study Title	Author (Primary, Senior)	Publication Date	Journal	Sample Size	Lesions	Randomization	Primary Outcomes	Result
SYNTAX II	van Es	Dec, 2015	NCT02015832	450	Multivessel CAD	FFR-, iFR-, and OCT-Assisted Therapy v. Historical (SYNTAX I) Control	Death, MI, Stroke, and Repeat Revascularization at 1 year	
Compare -Acute	Smits	Jan, 2017	NCT01399736	885	STEMI, Non-Culprit Lesions	FFR-Guided PCI v. Angiographically-Guided PCI	Death, MI, Stroke, and Repeat Revascularization at 1 year	
DEFINE -FLAIR	Davies, Sen	Nov, 2019	NCT02053038	2500	Intermediate Lesions	FFR-Guided PCI v. iFR-Guided PCI	Death, MI, and Unplanned Revascularization at 1 year	
iFR -SWEDEHEART	Götberg	May, 2015	NCT02166736	2000	Intermediate Lesions	FFR-Guided PCI v. iFR-Guided PCI	Death, MI, and Unplanned Revascularization at 1 year	

Table 2

Clinical trials comparing the fractional flow reserve and the instantaneous wave-free ratio.

Study Title	Author (Primary, Senior)	Publication Date	Journal	Number of lesions	Study Design	Lesion Characteristics	R ²	iFR Cutpoint	AUC	Sensitivity	Specificity
<i>Advise In Practice</i>	Petraco, Davies	Nov, 2014	Am Heart J [59]	392	Observational	Intermediate	NA	0.90	0.87	81%	79%
RESOLVE	Jeremias, Stone	April, 2014	JACC [60]	1593	Meta-Analysis	All Lesions	0.66	0.90	0.81	79%	82%
Seoul Registry	Park, Koo	Oct, 2013	Int J Cardiol [58]	238	Observational	Intermediate	0.60	0.90	0.90	76%	86%
VERIFY Prospective	Berry, Oldroyd	April, 2013	JACC [57]	206	Observational	All Lesions	0.70	0.83	0.87	54%	96%
ADVISE Registry	Petraco, Davies	May, 2013	EuroIntervention [61]	339	Observational	Intermediate	NA	0.89	0.86	NA	NA
ADVISE	Sen, Davies	April, 2012	JACC [53]	157	Observational	All Lesions	0.80	0.83	0.93	85%	91%