Pharmacologic Agents for Maximal Hyperemia

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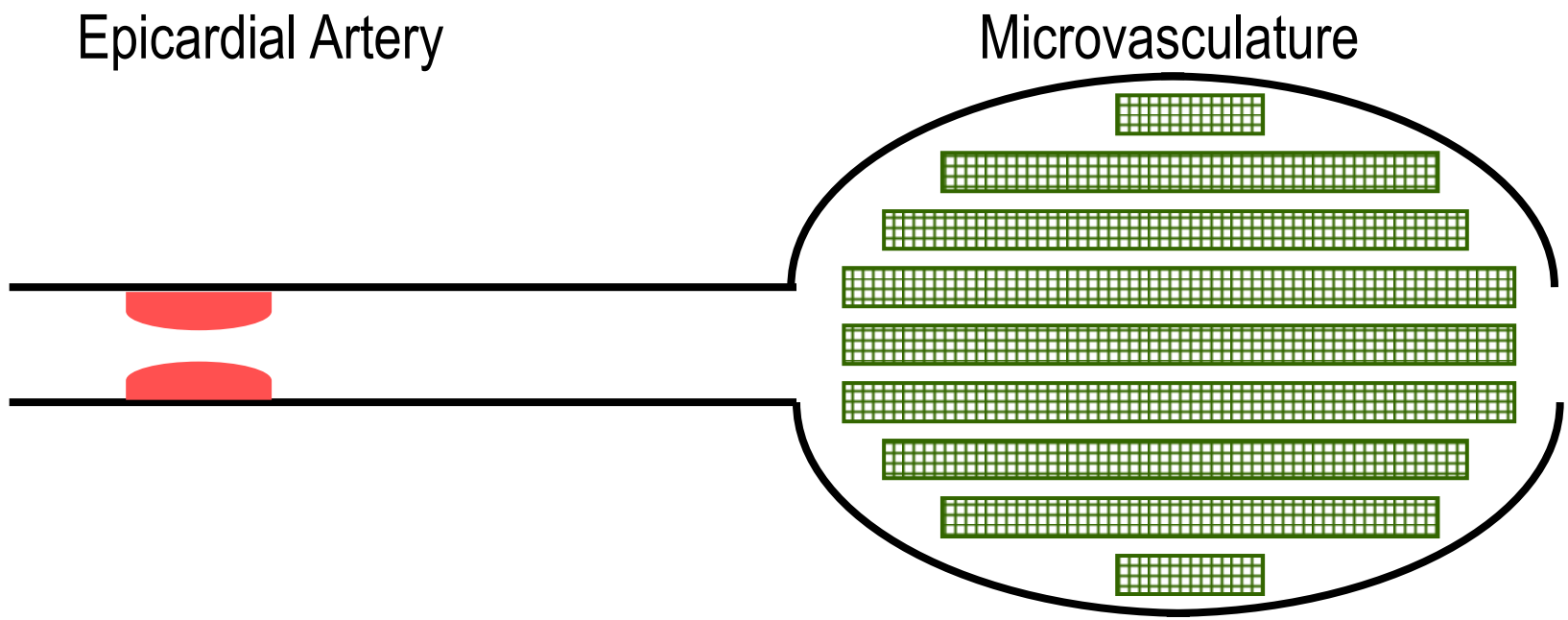
Cardiovascular Center

Maximal hyperemia is essential for FFR measurement



Maximal hyperemia: Which and How?

Intravenous infusion

- **Adenosine, ATP**	140 μg/kg/min
- Dobutamine	20-40 μg/kg/min

Intracoronary bolus

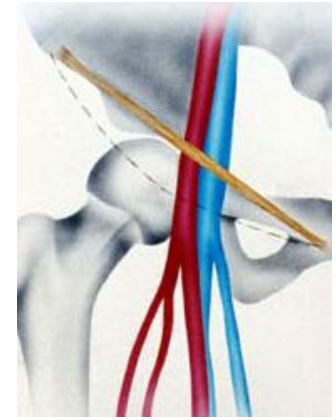
- Papaverine	10 - 20 mg
- **Adenosine, ATP**	20-720 μg
- Nitroprusside	0.3-0.9 μg/kg
- Nicorandil	**2mg**

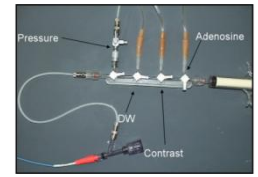
Intracoronary infusion

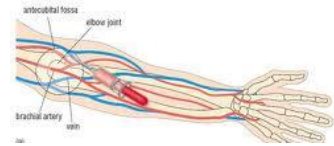
- **Adenosine**	240μg/min

Intravenous bolus

- Regadenoson	400μg







Comparison of vasodilatory stimuli

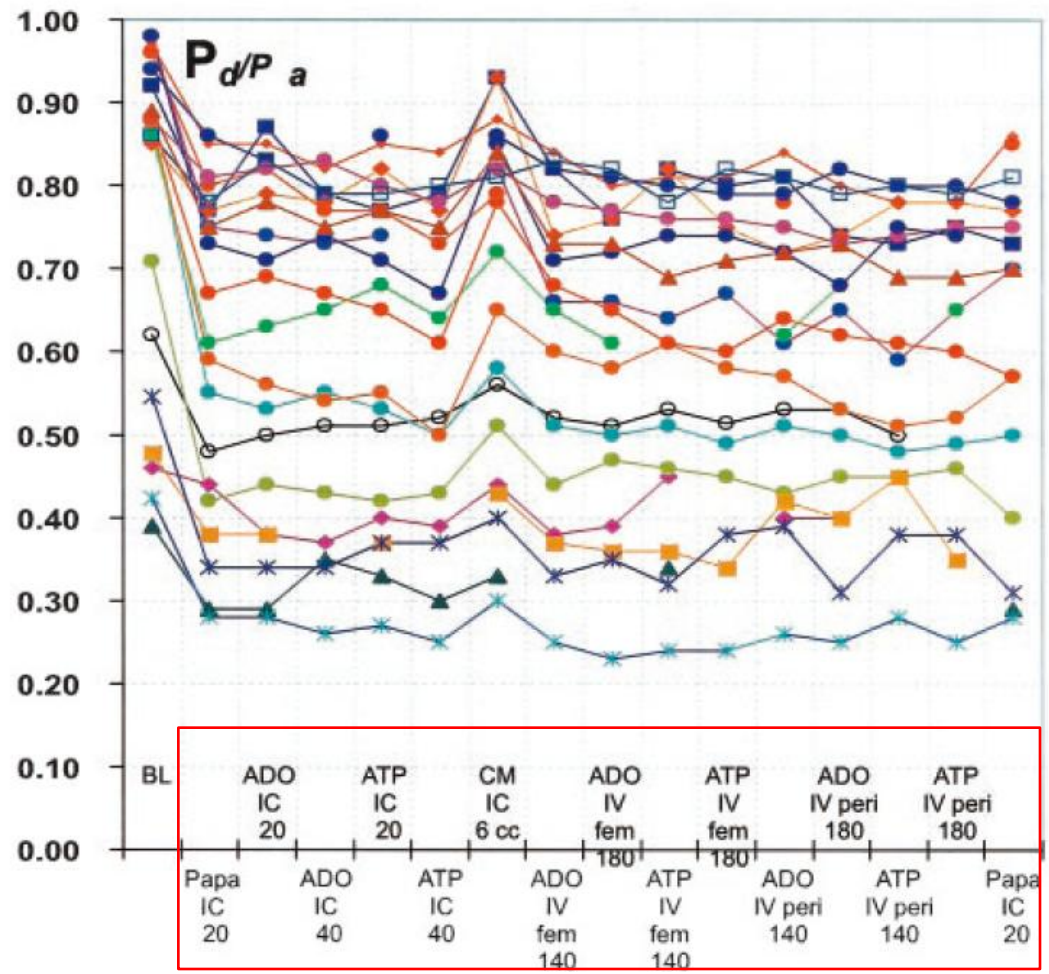
Intracoronary and Intravenous Adenosine 5′-Triphosphate, Adenosine, Papaverine, and Contrast Medium to Assess Fractional Flow Reserve in Humans

Bernard De Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD; Emanu
Jozef Bartunek, MD, PhD; Jan-Willem Bech, MD
William Wijns, MD, PhD; Guy R. Heyndrickx, MD,

Background—Inducing both maximal and steady-state coronary hyperemia is of clinical i of fractional flow reserve measurements. The present study compares different dosage adenosine 5′-triphosphate (ATP), adenosine, contrast medium, and papaverine regardi maximal and steady-state hyperemia.

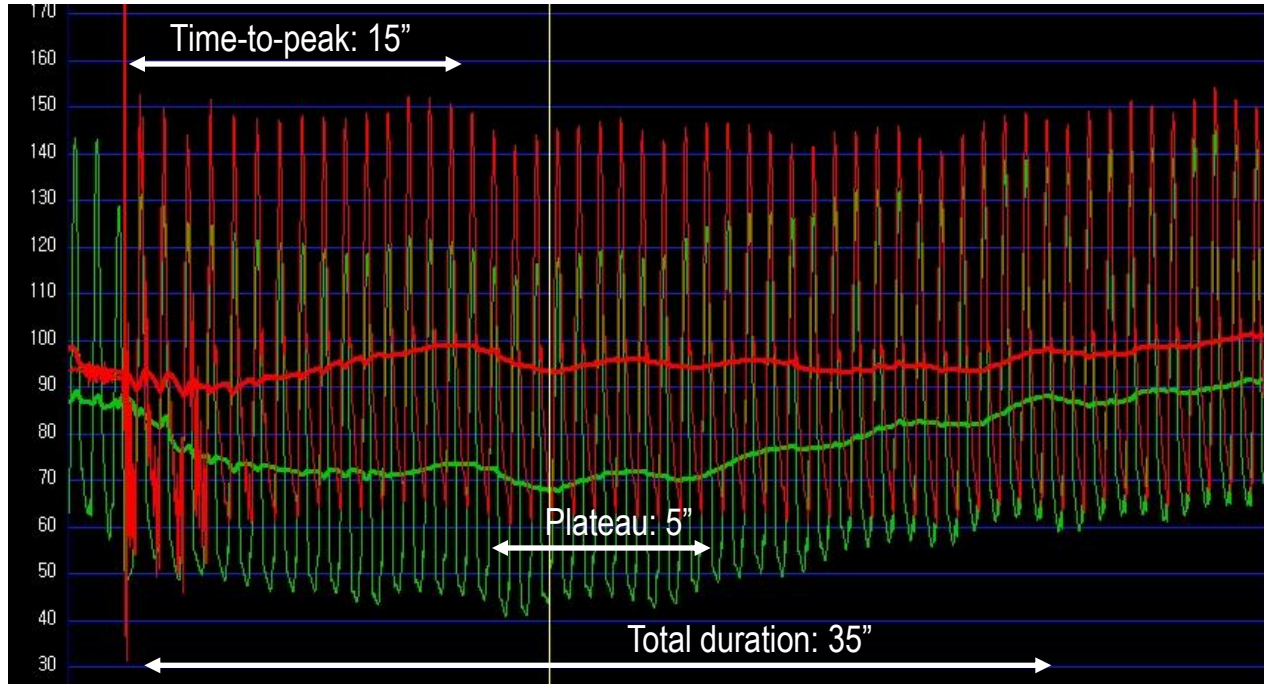
Methods and Results—In 21 patients with an isolated coronary stenosis, coronary vasod by papaverine (20 mg intracoronary), adenosine (20 and 40 μg intracoronary), ATI iohexol (6 mL intracoronary), adenosine or ATP through an antecubital vein (140 adenosine or ATP through a femoral vein (140 and 180 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Because ve the ratio of distal coronary pressure (P_d) to aortic pressure (P_a) was used as an index of 0.77±0.21 at rest and decreased to 0.61±0.21 after papaverine. P_d/P_a decreased t vasodilators, except with contrast medium (0.68±0.21; $P<0.01$ versus papaverine). St be obtained by intracoronary papaverine and by intravenous ATP or adenosine. In an infusion of ATP was varied from 0 to 280 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At doses >140 $\mu g \cdot kg^{-1} \cdot$ decrease in P_d/P_a ratio nor a further increase in coronary flow velocities.

Conclusion—Provided sufficient dosages are used, ATP, adenosine, and papaverine (b maximal hyperemia and are therefore suitable to assess fractional flow reserve. On intravenous ATP or adenosine induce steady-state hyperemia enabling a pressure pul assessing diffuse coronary atherosclerosis. **(*Circulation*. 2003;107:1877-1883.)**



de Bruyne et al. Circulation 2003

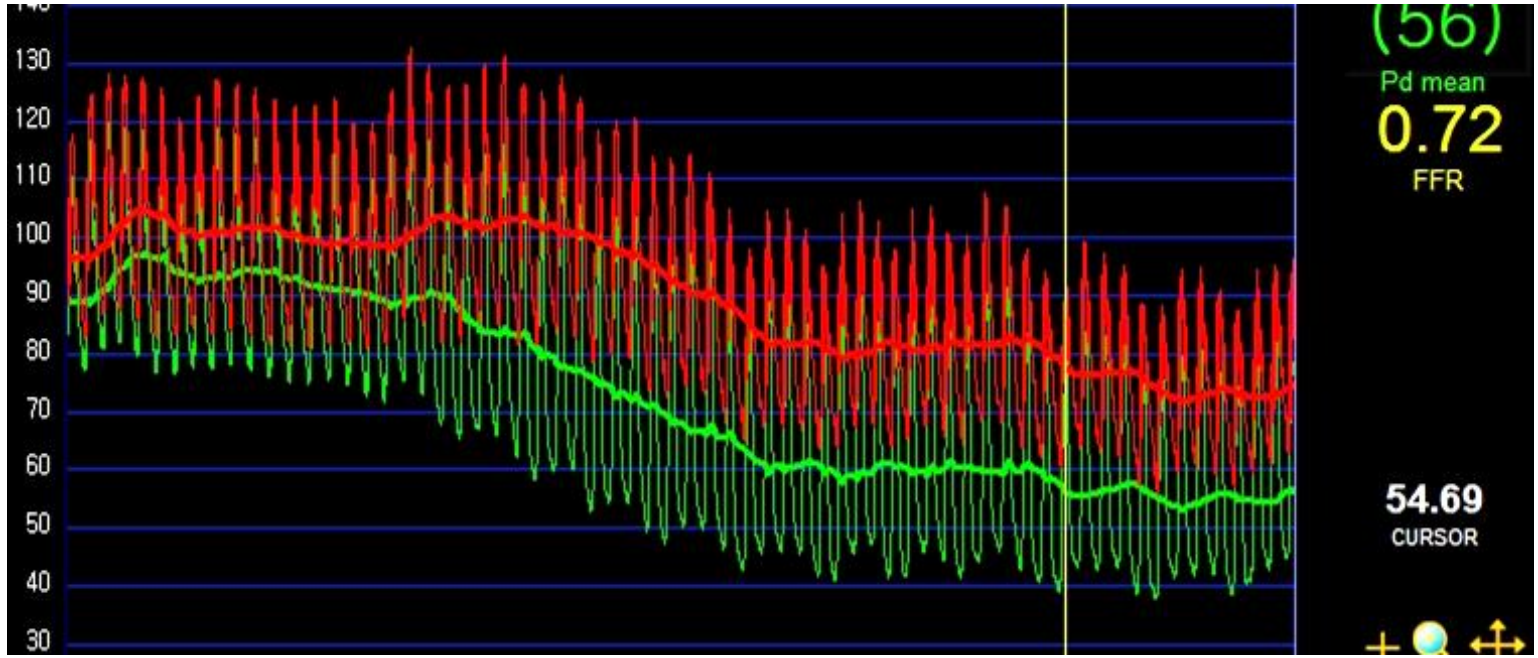
IC adenosine: the easiest, but not the best



- **Simple and inexpensive**
- Short action time, not adequate for pressure pullback and IMR/CFR
- Less effective than IV infusion in some patients
- Difficult to use in patients with ostial disease
- Inaccurate with side hole guiding catheter
- More frequent AV block than with IV infusion

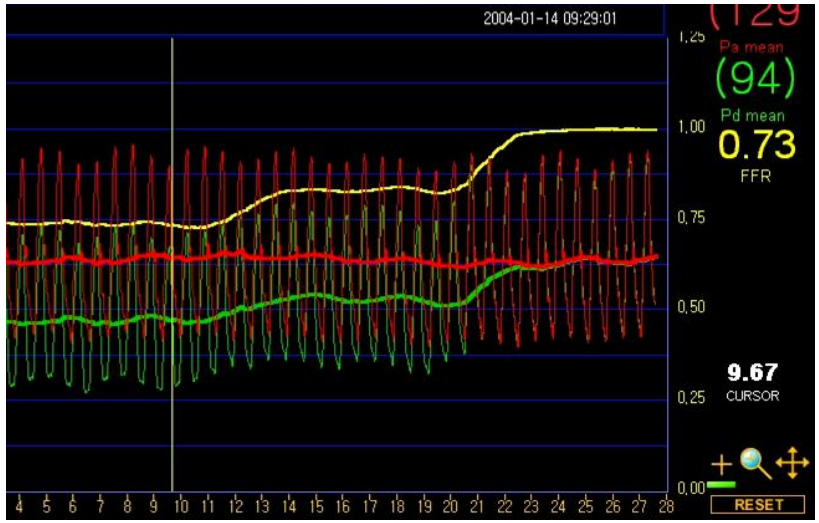
IV adenosine: “Gold standard”

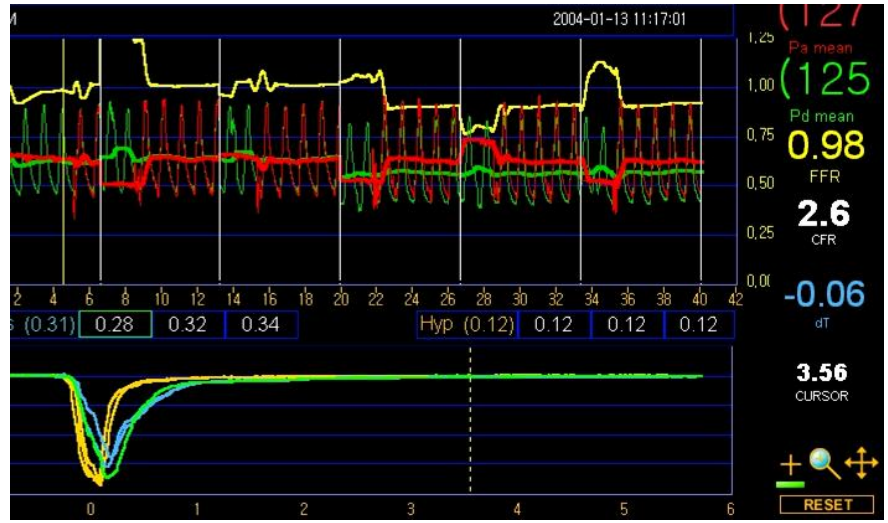
- IV infusion of adenosine: coronary vasodilator of choice
- Central venous access is recommended
  - A 4 - 6 Fr sheath in the femoral vein is adequate
  - A large gauge IV line in peripheral veins may be used



Adenosine IV: Advantages

- Very good safety profile; less AV block than IC bolus
- One dose (140 ug/kg/min) is adequate for almost all patients
- Sustained hyperemia for ‘pressure pullback’ recording and IMR

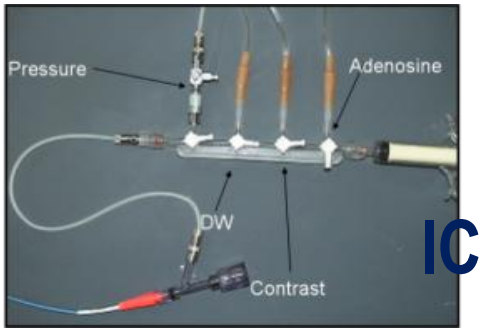




Requires at least > 20-30seconds

Inconvenience with Adenosine IV via Femoral vein

- Needs central vein access
- Chest pain, bronchospasm, AV block
- Requires large amount of adenosine (cost)
- Difficult to use during trans-radial procedures



IC infusion of adenosine via guiding catheter

Inconvenience with Adenosine IV via Femoral vein

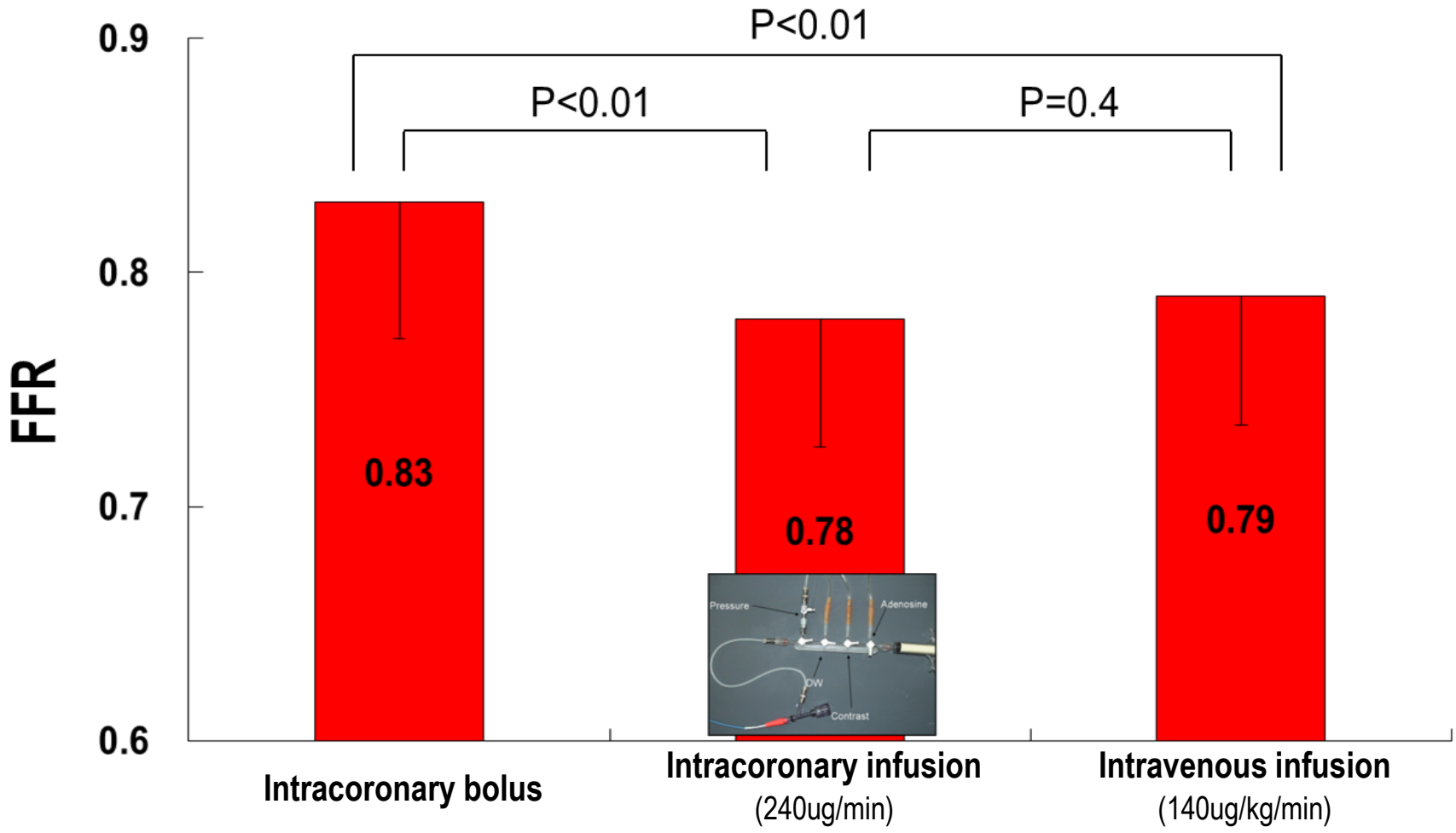
- ~~Needs central vein access~~
- Chest pain, bronchospasm, AV block
- ~~Requires large amount of adenosine (cost)~~
- ~~Difficult to use during trans-radial procedures~~

Circ J 2005; 69: 908–912

Intracoronary Continuous Adenosine Infusion
— A Novel and Effective Way of Inducing Maximal Hyperemia for Fractional Flow Reserve Measurement —

Bon-Kwon Koo, MD, PhD; Cheol-Ho Kim, MD, PhD*; Sang-Hun Na, MD;
Tae-Jin Youn, MD, PhD*; In-Ho Chae, MD, PhD*; Dong-Ju Choi, MD, PhD*;
Hyo-Soo Kim, MD, PhD; Myoung-Mook Lee, MD, PhD; Chung-Hee Oh, MD, PhD;
Young-Bae Park, MD, PhD; Yun-Shik Choi, MD, PhD; Seung-Ja [illegible], PhD

IC infusion of adenosine via guiding catheter

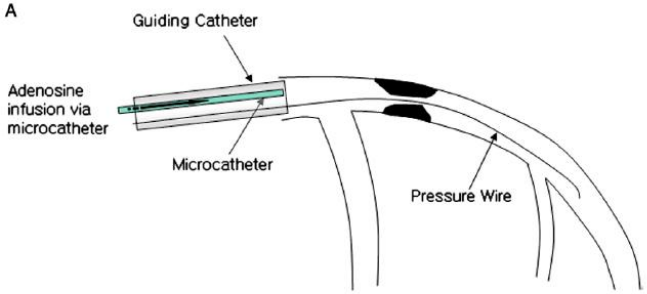


Koo BK, et al. Circulation J 2005

Comparison of the intracoronary continuous infusion method using a microcatheter and the intravenous continuous adenosine infusion method for inducing maximal hyperemia for fractional flow reserve measurement

Myeong-Ho Yoon, MD, PhD, Seung-Jea Tahk, MD, PhD, Hyoung-Mo Yang, MD, Jin-Sun Park, MD, Mingri Zheng, MD, Hong-Seok Lim, MD, PhD, Byoung-Joo Choi, MD, So-Yeon Choi, MD, PhD, Un-Jung Choi, MD, Joung-Won Hwang, MD, Soo-Jin Kang, MD, PhD, Gyo-Seung Hwang, MD, PhD, and Joon-Han Shin, MD *Suwon, Korea*

A



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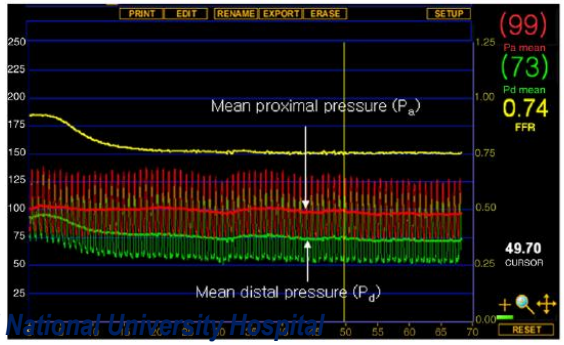
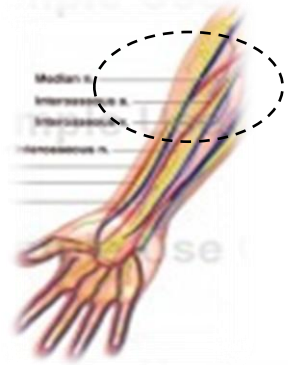


Table III. Changes of functional significance induced by the different methods of adenosine administration and different doses of adenosine infusion

	No. of lesions	
	FFR <0.75	FFR ≥0.75
IC bolus	11 (25%)	33 (75%)
IV infusion	16 (36%)	28 (64%)
IC infusion		
60 μg/min	12 (27%)	32 (73%)
120 μg/min	14 (32%)	30 (68%)
180 μg/min	19 (43%)	25 (57%)
240 μg/min	21 (48%)	23 (52%)
300 μg/min	21 (48%)	23 (52%)
360 μg/min	21 (48%)	23 (52%)



Adenosine infusion via Peripheral vein

Inconvenience with Adenosine IV via Femoral vein

- ~~Needs central vein access~~
- Chest pain, bronchospasm, AV block
- Requires large amount of adenosine (cost)
- ~~Difficult to use during trans-radial procedures~~

Adenosine infusion via Antecubital vein

Clin Res Cardiol (2009) 98:717–723
DOI 10.1007/s00392-009-0056-7

ORIGINAL PAPER

Adenosine-induced maximal coronary hyperemia for myocardial fractional flow reserve measurements: comparison of administration by femoral venous versus antecubital venous access

Michael Lindstaedt · Waldemar Bojara ·
Tim Holland-Letz · Aydan Yazar · Thomas Fadgyas ·
Lucie Müller · Andreas Mügge · Alfried Germing

Table 2 Data on FFR measurement results in 50 patients with respect to different applications of the hyperemic stimulus

Adenosine application	FFR		Time to peak hyperemia (s)	
	Mean	STD	Mean	STD
A140	0.7504	0.11	61	27
A170	0.7440	0.11	52	23
F140	0.7388	0.11	66	25

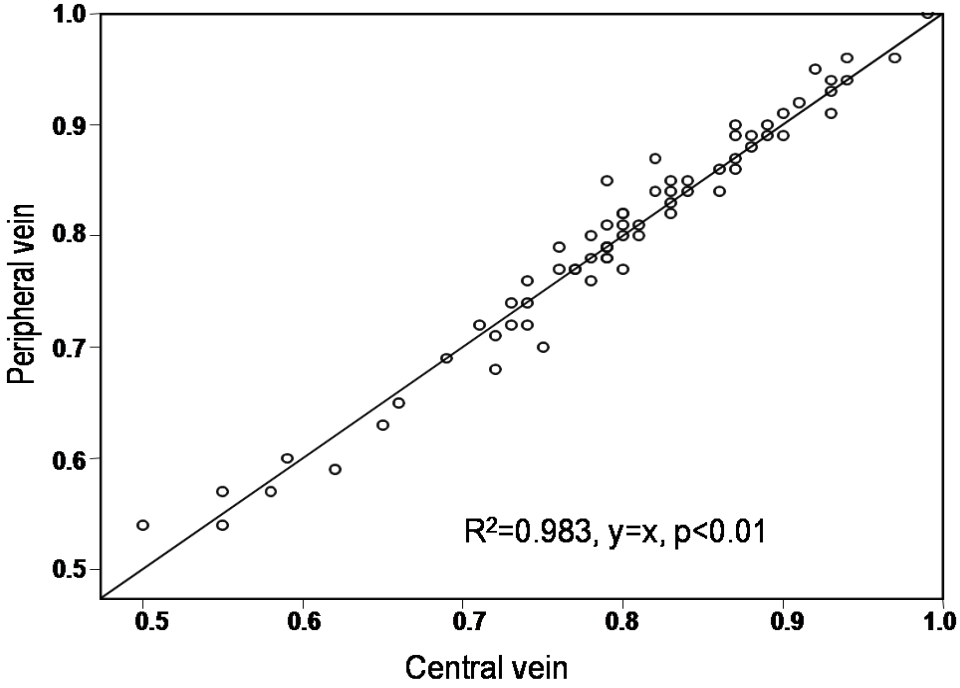
Circulation
Cardiovascular Interventions
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Comparison of Hyperemic Efficacy Between Central and Peripheral Venous Adenosine Infusion for Fractional Flow Reserve Measurement

Myung-Ki Seo, Bon-Kwon Koo, Ji-Hyun Kim, Dong-Ho Shin, Han-Mo Yang, Kyung-Woo Park, Hae-Young Lee, Hyun-Jae Kang, Hyo-Soo Kim, Byung-Hee Oh and Young-Bae Park

Adenosine infusion via forearm vein

(most commonly used venous access)



	Femoral vein	Forearm vein	P value
FFR	0.80±0.10	0.80±0.11	0.95
FFR <0.8	27 (44%)	26 (42%)	1.0
IMR	11.8±10.9	11.3±9.2	0.58

Seo MK, Koo BK, et al. Circulation intervention, 2012

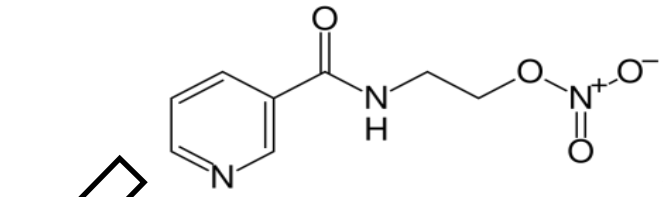
FFR with more convenient hyperemia

Inconvenience with Adenosine IV via Femoral vein

- ~~Needs central vein access~~
- Chest pain, bronchospasm, AV block
- ~~Requires large amount of adenosine (cost)~~
- ~~Difficult to use during trans-radial procedures~~

FFR with more convenient hyperemia

Nicorandil
(Sigmart®)

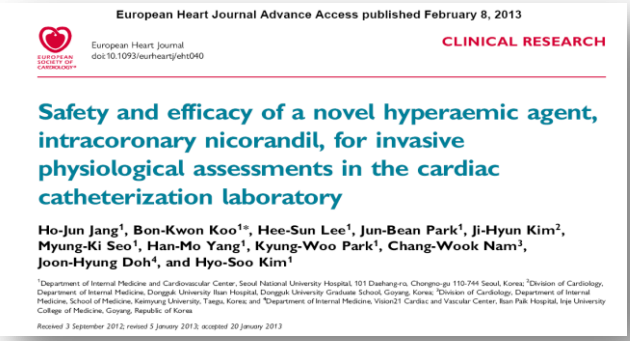


ATP-sensitive K^+ ch activator

: dilatation of coronary resistant arterioles

Nitrate-like action

: dilatation of epicardial coronary artery



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CLINICAL RESEARCH

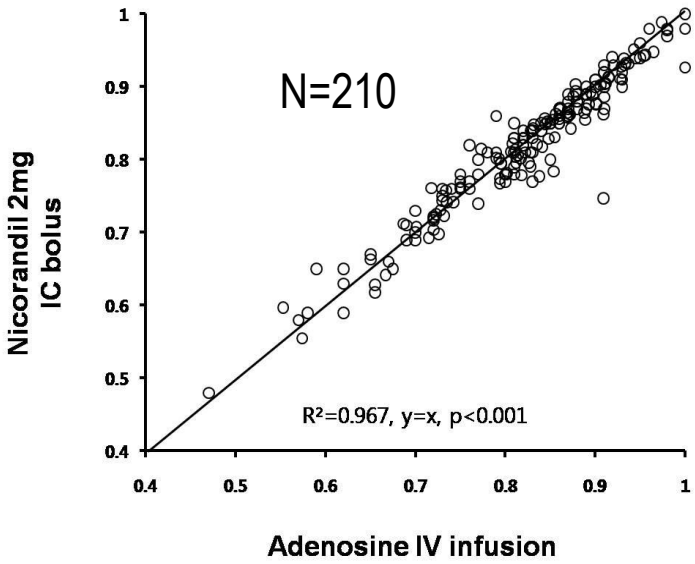
Safety and efficacy of a novel hyperaemic agent, intracoronary nicorandil, for invasive physiological assessments in the cardiac catheterization laboratory

Ho-Jun Jang[1], Bon-Kwon Koo[1]*, Hee-Sun Lee[1], Jun-Bean Park[1], Ji-Hyun Kim[2], Myung-Ki Seo[1], Han-Mo Yang[1], Kyung-Woo Park[1], Chang-Wook Nam[3], Joon-Hyung Doh[4], and Hyo-Soo Kim[1]

[1]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehang-ro, Chongno-gu 110-744 Seoul, Korea; [2]Division of Cardiology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University Graduate School, Goyang, Korea; [3]Division of Cardiology, Department of Internal Medicine, School of Medicine, Keimyung University, Taegu, Korea; and [4]Department of Internal Medicine, Vision21 Cardiac and Vascular Center, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea

Received 3 September 2012; revised 5 January 2013; accepted 20 January 2013

Hyperemic efficacy



	Nicorandil bolus 2 mg	Adenosine IV infusion	P value
Fractional Flow Reserve	**0.82 ± 0.10**	**0.82 ± 0.10**	**0.33**
Time to max hyperemia, s	**18.3 ± 6.1**	**43.8 ± 16.0**	**<0.001**
Plateau time, s	**27.3 (IQR 17-33)**	**-**	
IMR	**17.2 ± 7.6**	**18.3 ± 8.7**	**0.29**

Jang HJ, Koo BK, et al. Eur Heart J 2013

Safety Parameters

	Adenosine infusion	Nicorandil Bolus 2 mg	P value
Δ Blood pressure	-16.8±9.3	-13.2±5.6	<0.001
Δ Heart rate	5.7±7.1	2.5±5.8	<0.001
Δ PR interval	7.5±13.1	4.7±12.3	0.034
Δ QTc interval	16.7±17.0	1.3±19.5	<0.001
VAS pain score	2.1±2.6	0.9±1.9	<0.001

VAS, visual analogue scale.

Transient AV block

- IC bolus of adenosine: 12 patient
- IV infusion of adenosine: 4 patient
- Nicorandil IC bolus: NONE

Jang HJ, Koo BK, et al. Eur Heart J 2013

Maximal hyperemia: **Which and How?**

Intravenous infusion

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Intracoronary infusion

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Intravenous bolus

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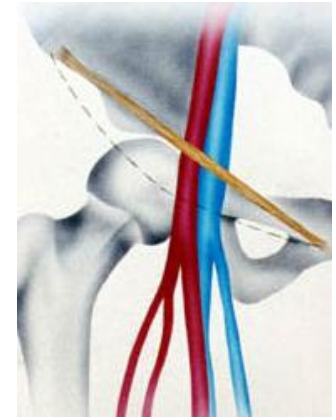

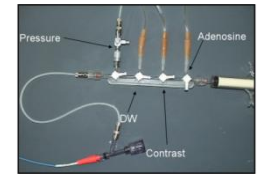

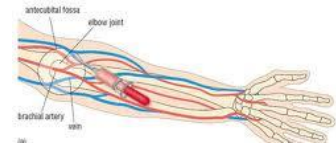

Is hyperemia maximal, reliable and reproducible?

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CLINICAL RESEARCH

Fractional Flow Reserve–Guided Revascularization

Practical Implications of a Diagnostic Gray Zone and Measurement Variability on Clinical Decisions

Ricardo Petraco, MD,* Savan Sen, MBBS,* Sukhjinder Nijjer, MBChB,*

REVIEWS

Fractional flow reserve as a surrogate for inducible myocardial ischaemia

Tim P. van de Hoef, Martijn Meuwissen, Javier Escaned, Justin E. Davies, Maria Siebes, Jos A. E. Spaan

Results Outside the [0.75 to 0.85] FFR range, measurement certainty of a single FFR result is >95%. However, closer to its cut-off, certainty falls to less than 80% within 0.77 to 0.83, reaching a nadir of 50% around 0.8. In clinical practice, that means that each time a single FFR value falls between 0.75 and 0.85, there is a chance that the FFR-derived revascularization recommendation will change if the

Adenosine and coronary vasodilatation

The assumption that the administration of adenosine in a standardized dose induces complete elimination of vascular tone in all patients is challenged by several well-known mechanisms that have an important role in daily clinical practice. First, α-adrenergic vasoconstric-

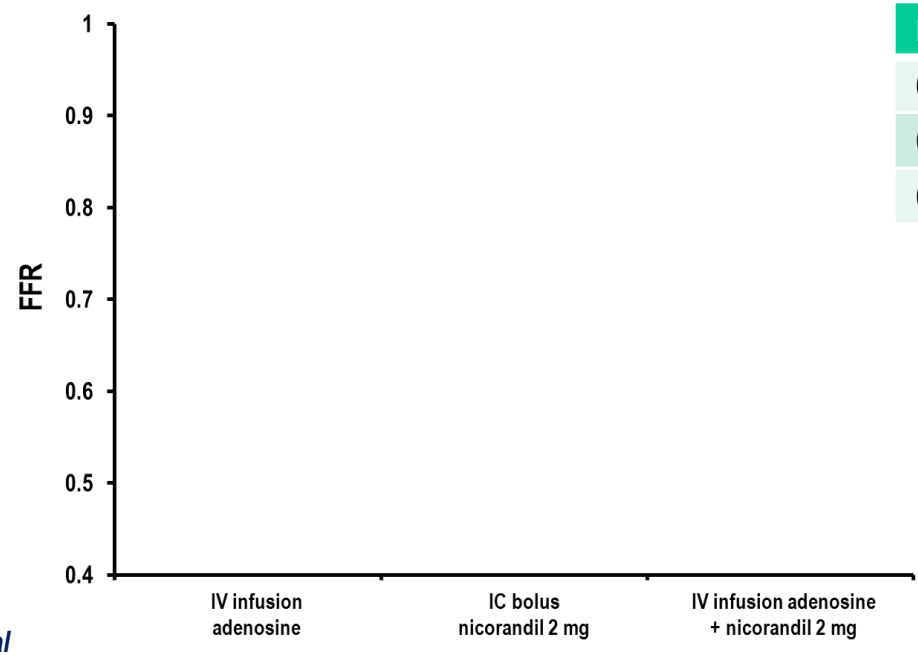
aemic state in the coronary circulation.[93] Consistent with this theory, hyperaemic microvascular resistance during vasodilatation induced by a standardized dose of adenosine is highly variable between patients,[62] and even between adjacent perfusion territories within the same patient.[63,64] Ultimately, the extent of the hyperaemic

of endothelin-1.[92] Nevertheless, and contrary to common belief, adenosine could be intrinsically unable to induce true maximal vasodilatation of the coronary vascular bed and, therefore, to induce a true maximal hyperaemic state in the coronary circulation.[93] Consistent

Stability and reproducibility of FFR (n=389)

with different hyperemic drugs, different routes and different time

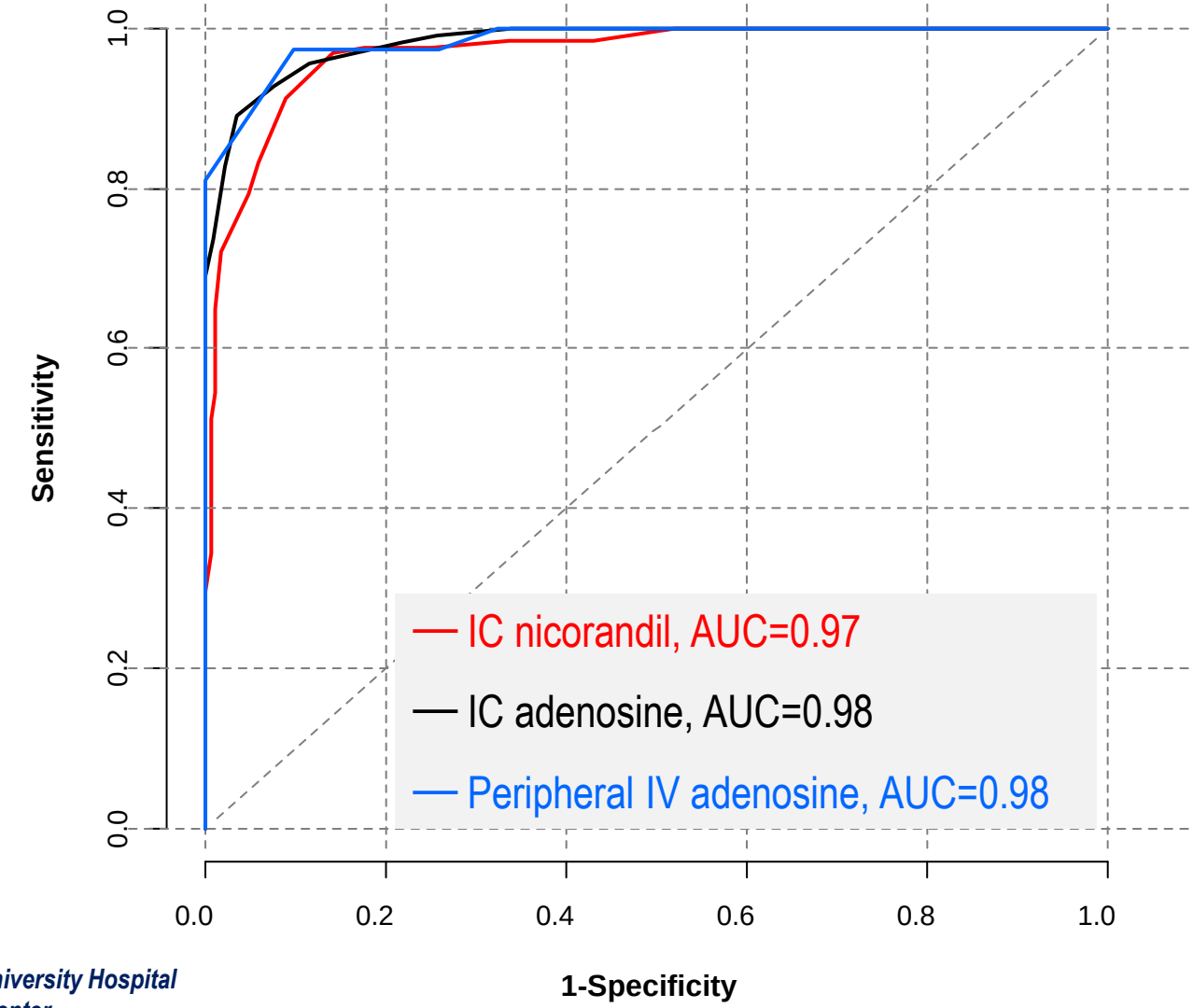
	Kappa	P-value
Adenosine vs. Nicorandil	**0.80**	<0.001
ATP vs. Nicorandil	**0.84**	<0.001
Adenosine: Central vs. Periph IV	**0.82**	<0.001



Kappa	Interpretation
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
0.81 – 1.00	Almost perfect agreement

Classification agreement

: IV adenosine vs. each alternative methods



Maximal Hyperemia for FFR

1. Maximal epicardial and microvascular vasodilation is the key for accurate measurement of FFR.
2. IV infusion of adenosine is the gold standard for FFR/CFR/IMR measurement.
3. Other routes and drugs can be used when needed,
    - Adenosine: IV infusion via large peripheral vein, IC bolus, IC infusion
    - Sigmart, papaverine IC bolus
    - Regadenosone IV bolus
4. Importance of maximal hyperemia cannot be overemphasized, so when you doubt about maximal hyperemia,

    1) Check the infusion system and solution

    2) Increase the dose of hyperemic agent

    3) Use the different route of adminstration or different drug