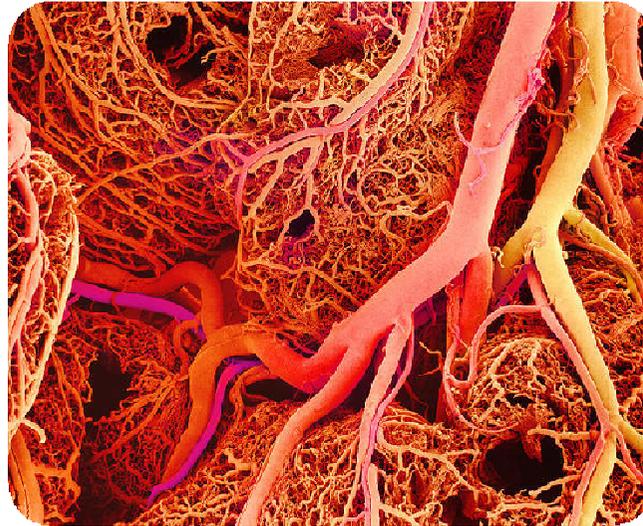




NUEVOS CONCEPTOS DE FISIOLÓGÍA CORONARIA

NUEVAS APROXIMACIONES DIAGNÓSTICAS EN EL ESTUDIO DE LA MICROCIRCULACIÓN CORONARIA

Angel Sanchez Recalde





UN CAMPO DE INVESTIGACIÓN EN AUGE

PubMed.gov

coronary AND microvascular disease



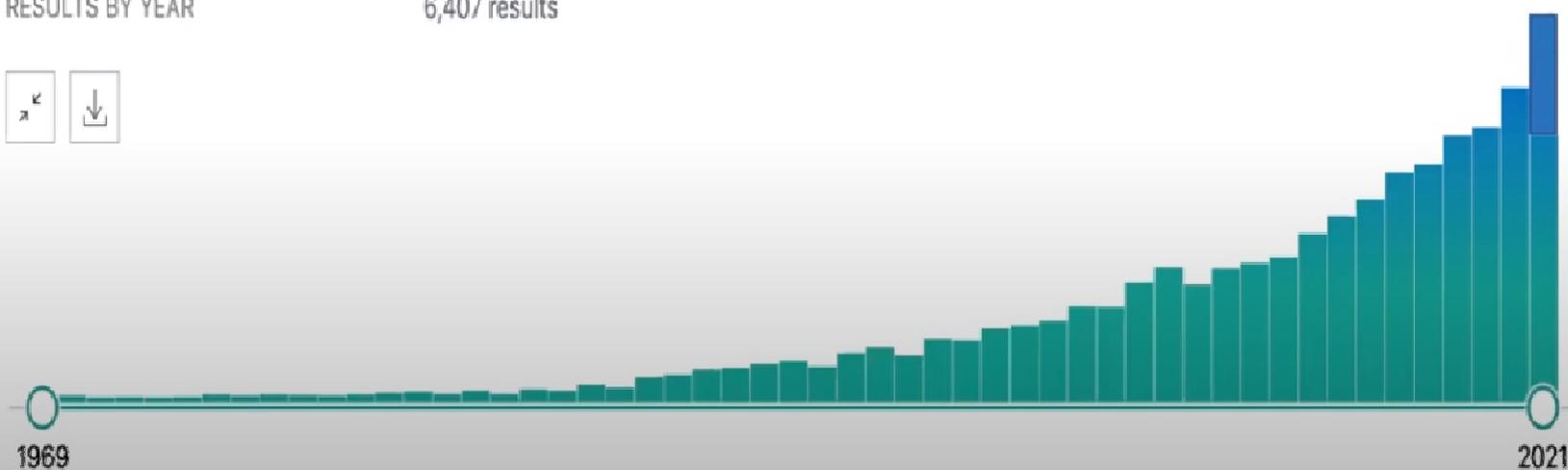
Search

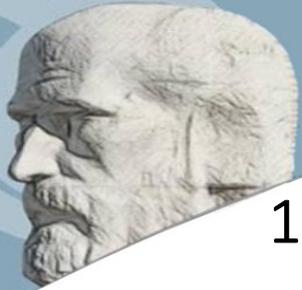
[Advanced](#) [Create alert](#) [Create RSS](#)

[User Guide](#)

RESULTS BY YEAR

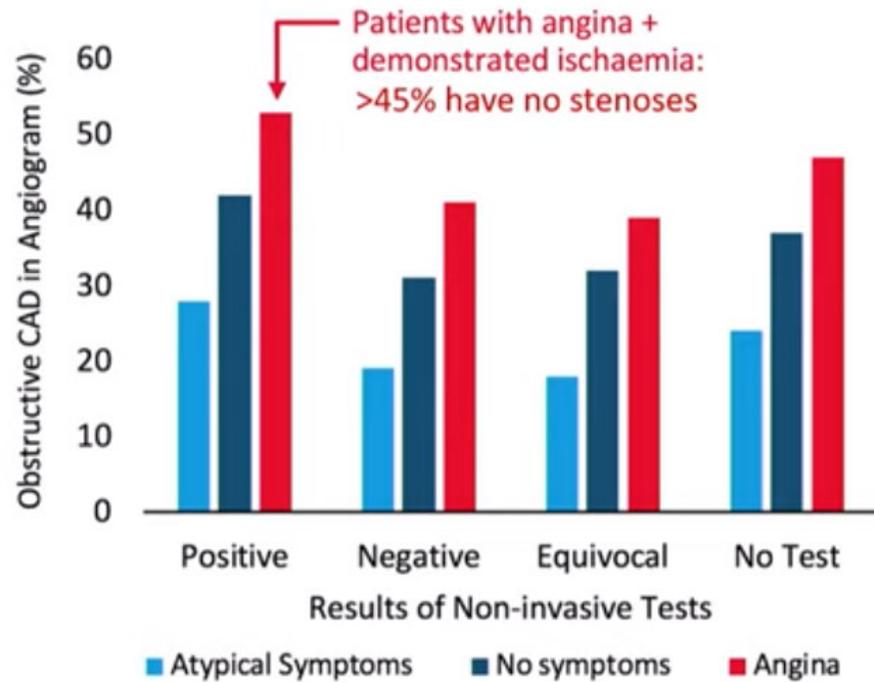
6,407 results





1- INOCA: UN ESCENARIO CLÍNICO CON ALTA PREVALENCIA

Source: 397,954 patients undergoing coronary angiography in the USA

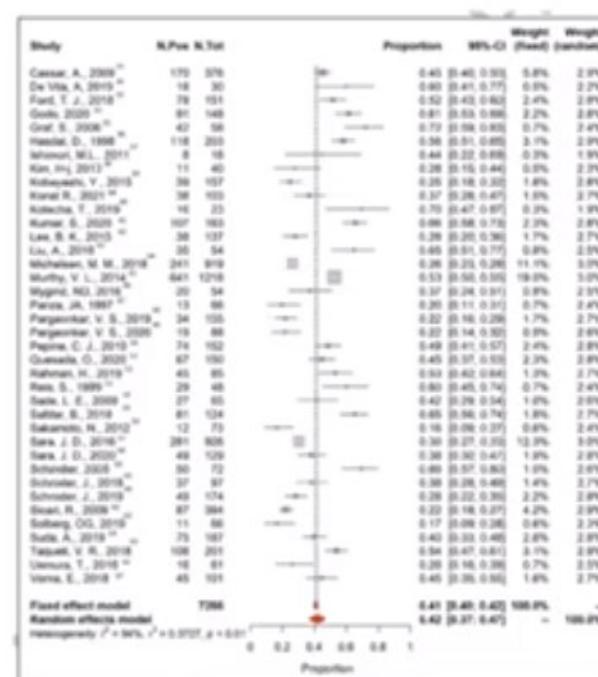
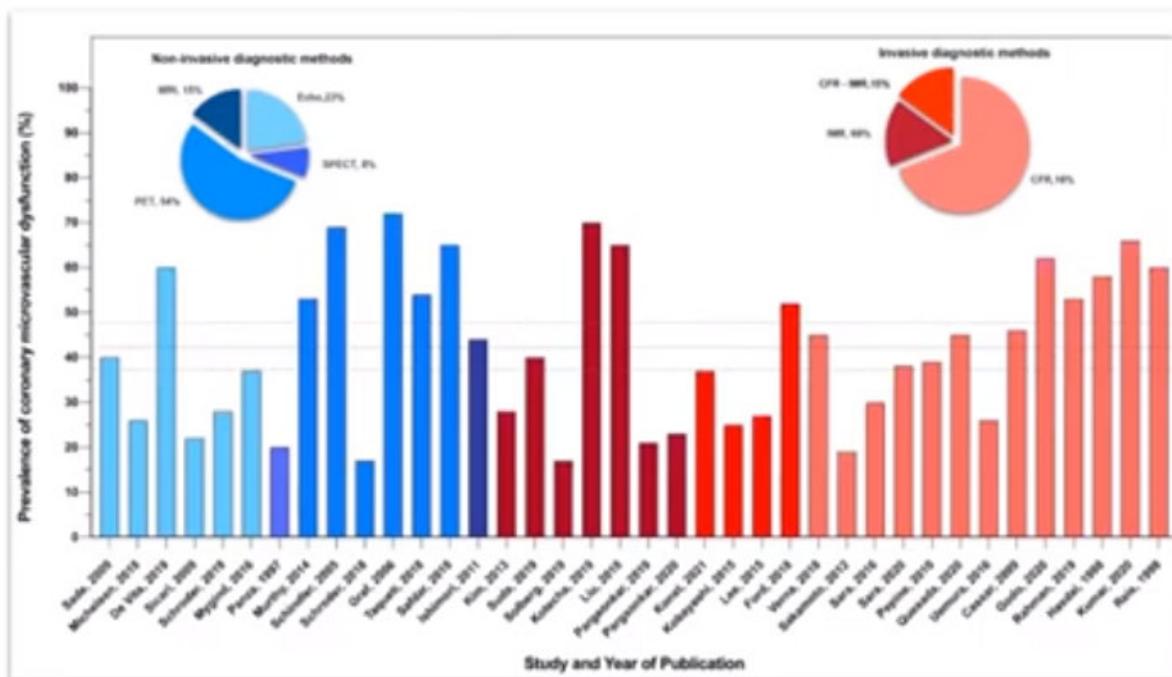


Patel et al: N Engl J Med 362:886, 2010





PREVALENCIA DE DISFUNCIÓN MICROVASCULAR Y VASOESPASMO CORONARIO



In patients with no obstructive coronary artery disease, approximately **42% of the cases** were reported to have CMD and/or coronary spasm.





2-INOCA: LAS CONSECUENCIAS



- INOCA/CMD are rarely correctly diagnosed-misdiagnosis



- No tailored therapy is prescribed for these patients



- Patients continue to experience recurrent angina with impaired quality of life



- Repeated hospitalizations, unnecessary coronary angiography and adverse cardiovascular outcomes in the short and long term



- Paradoxical reassurance by the treating physician
- Physician may even refute the underlying symptoms

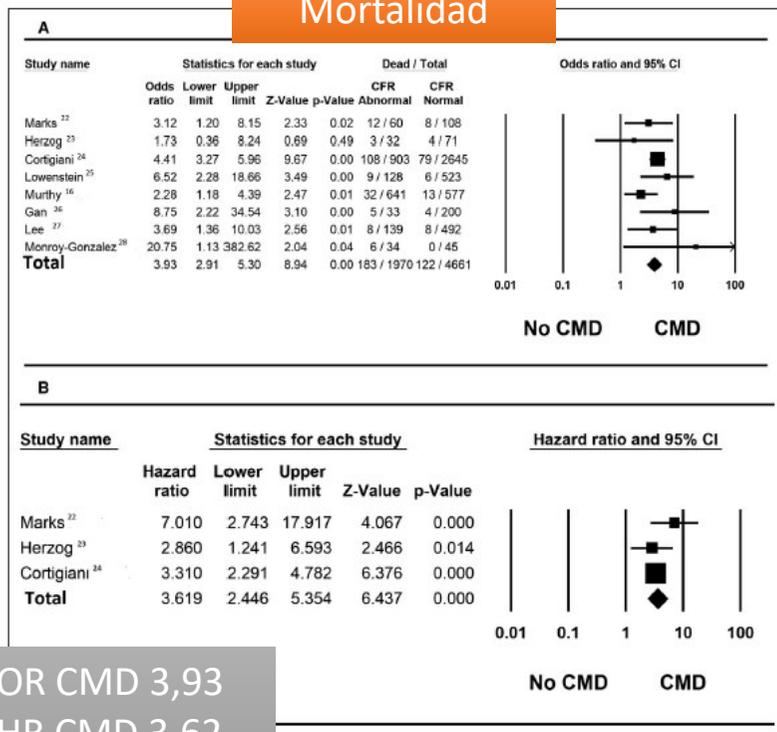
Kunadian et al. EAPCI Consensus Document on INOCA.

Eur Heart J. 2020 Oct 1;41(37):3504-3520; EuroIntervention. 2021 Jan 20;16(13):1049-1069



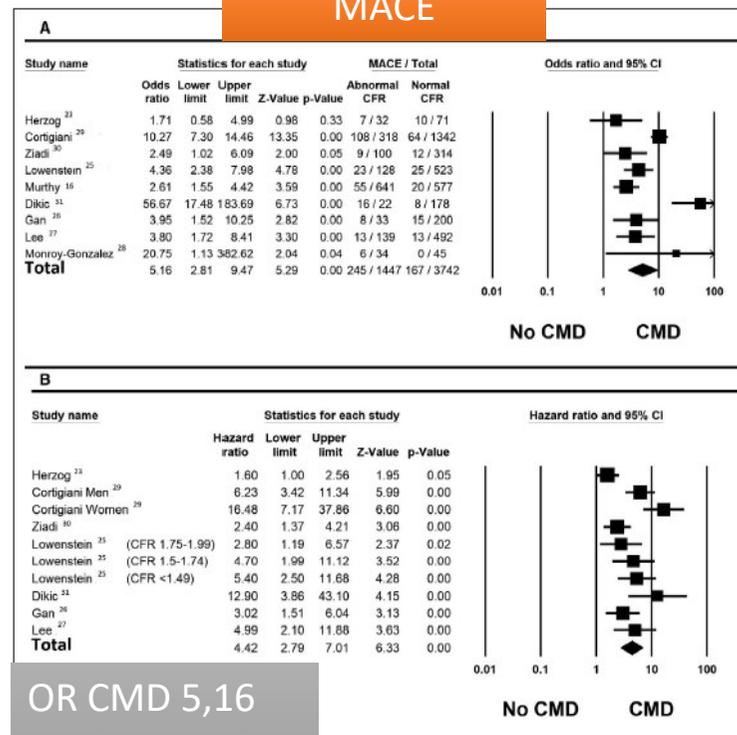
PRONÓSTICO DE LA DISFUNCIÓN MICROVASCULAR EN PACIENTES SIN ENFERMEDAD CORONARIA OBSTRUCTIVA

Mortalidad



OR CMD 3,93
HR CMD 3,62
P < 0,001

MACE

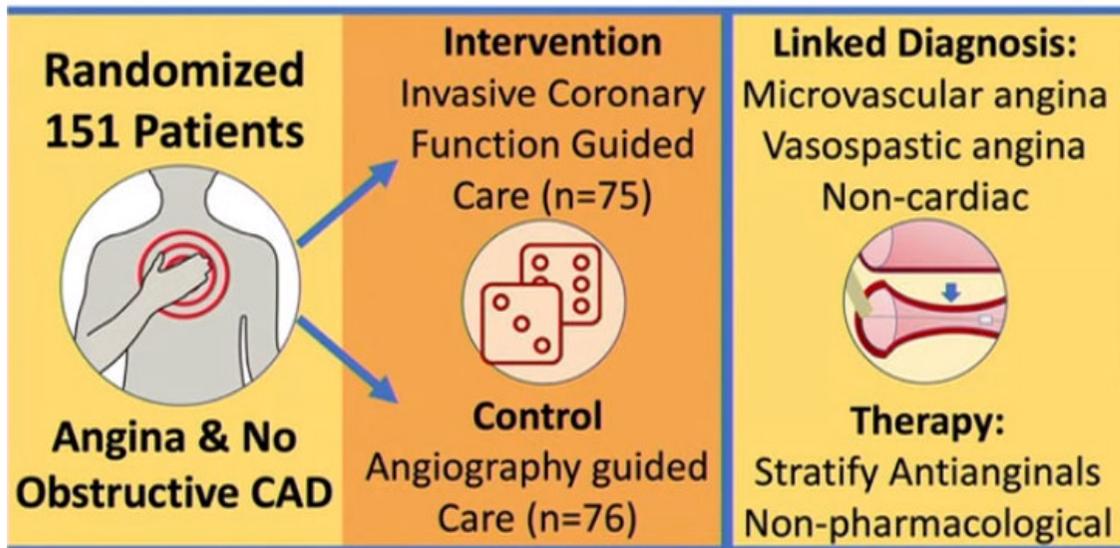


OR CMD 5,16
HR CMD 4,42
P < 0,001

Mayor mortalidad y riesgo de MACE en pacientes con MCD

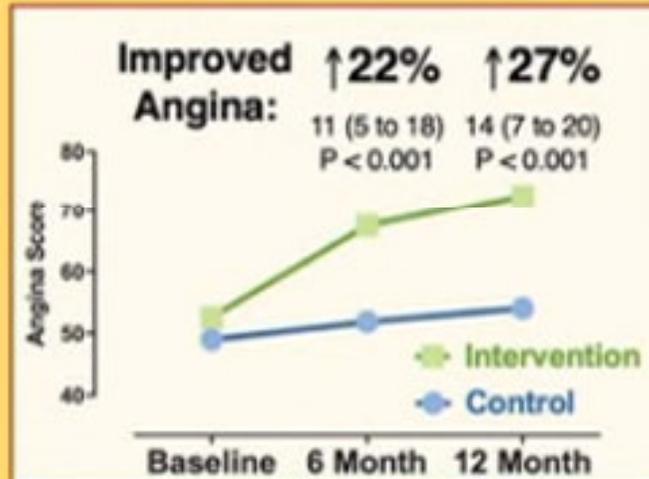
3- TRATAMIENTO DIRIGIDO

Invasive Coronary Function Testing in Angina (CorMicA): One Year RCT Outcomes



Ford, Berry et al. JACC 2018; ACC CV Int. 2019

Main Results:



**Sustained Benefits:
Improved Angina and
Quality of Life**

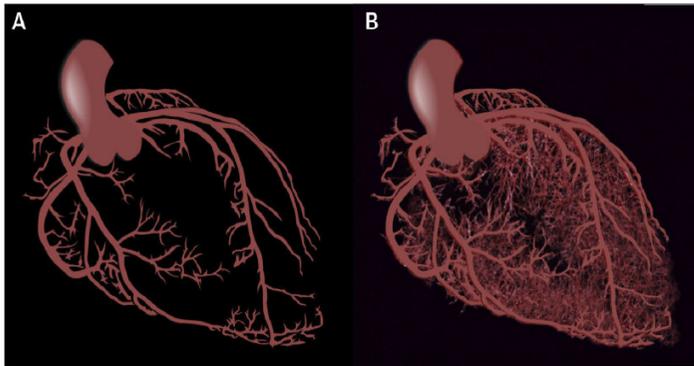


MICROCIRCULACIÓN: AUTOREGULACIÓN DEL FLUJO CORONARIO

Arteriole

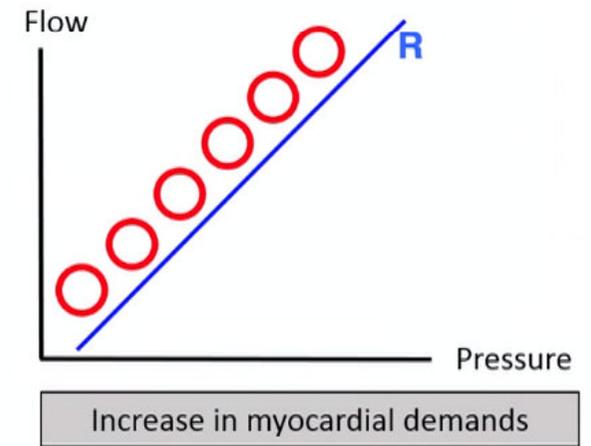
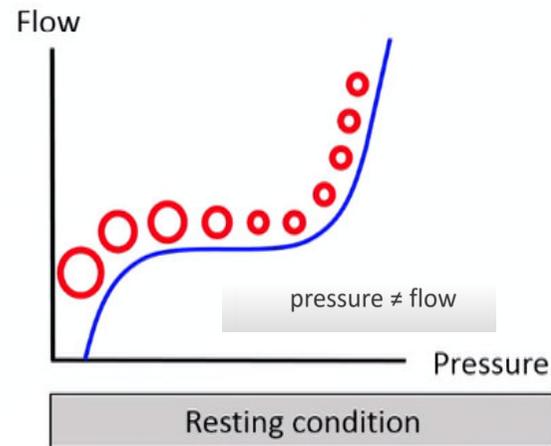


Changes in the arteriole tone



CONDUCTANCIA

AUTOREGULACIÓN



Para valorar y cuantificar el compartimento microvascular necesitamos medir **FLUJO Y RESISTENCIAS**
" Capacidad de autoregulación"

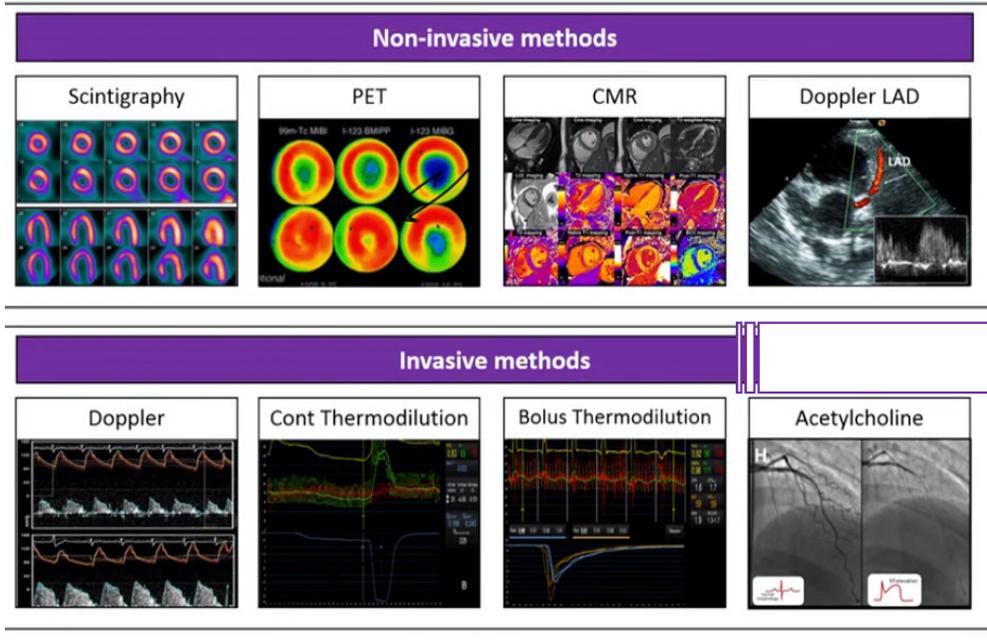


¿Cómo exploramos la microcirculación?

EDITORIAL

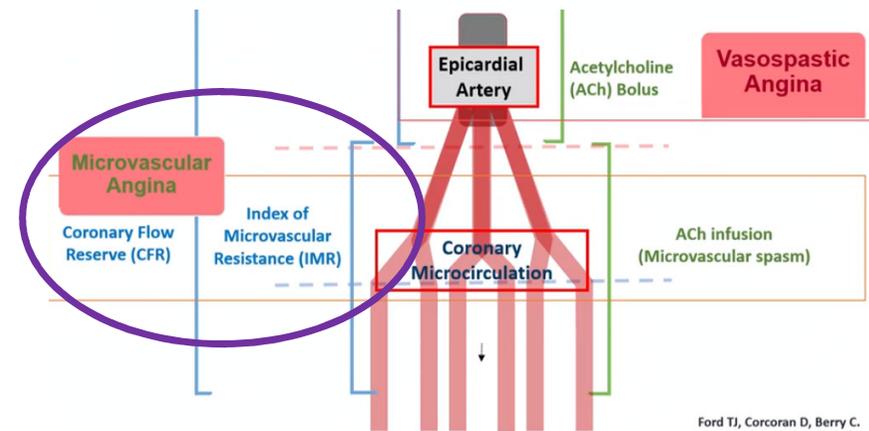
Macro-Confusion About the Coronary Microcirculation

Allen Jeremias, MD, MSc; Ziad A. Ali, MD, DPhil



ESC guidelines, Chronic Coronary Syndromes Angina without obstructive disease in the epicardial coronary arteries - INOCA

Recommendations	Class	Level
Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR.	Ia	B
Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm.	IIb	B
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.	IIb	B



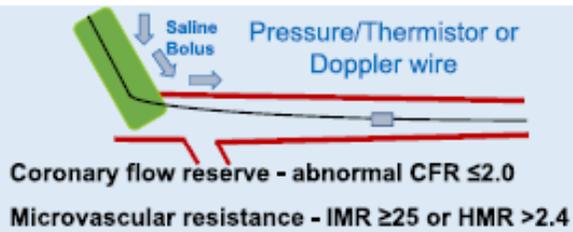
Ford TJ, Corcoran D, Berry C. Heart 2017;0:1-9

Invasive Coronary Assessment in INOCA

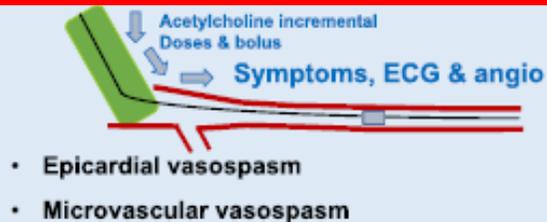
1 Coronary Angiography

- Consider:
 - Obstructive CAD
 - Myocardial bridging
 - 'Flush' ostial branch occlusion

2 Guidewire (adenosine)



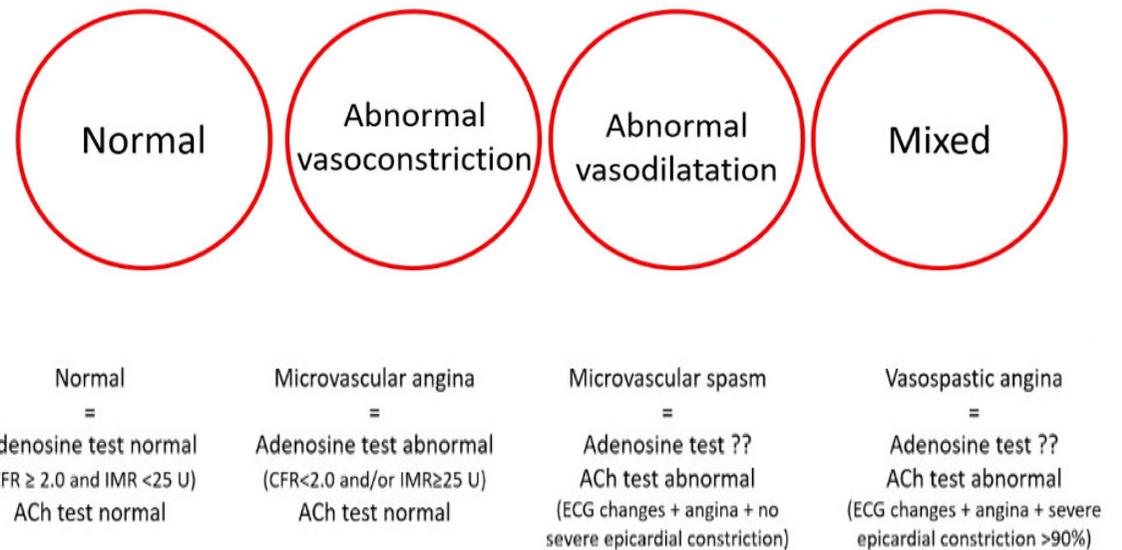
3 Vasoreactivity (acetylcholine)



4 Diagnosis & Management

1. Microvascular angina
2. Vasospastic angina
3. Mixed angina
4. Non-Cardiac (normal IDP)

4 endotypes as a guide to therapy covering all possible results of CFT



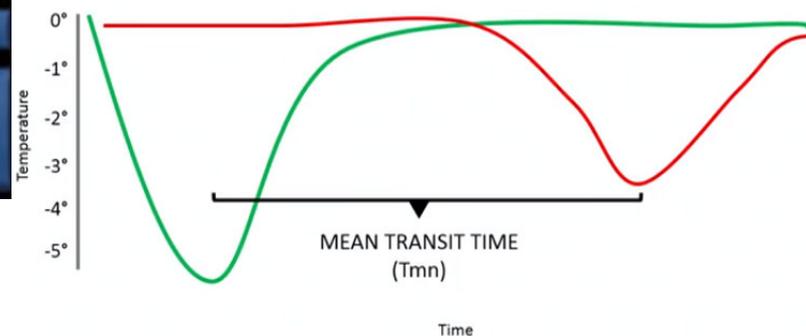
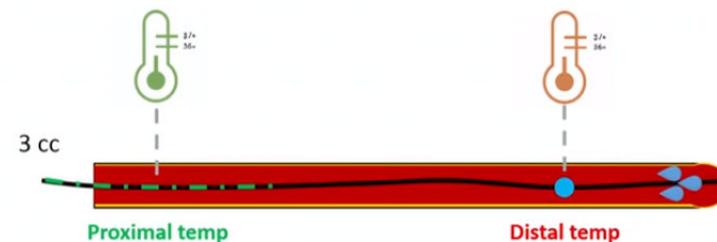
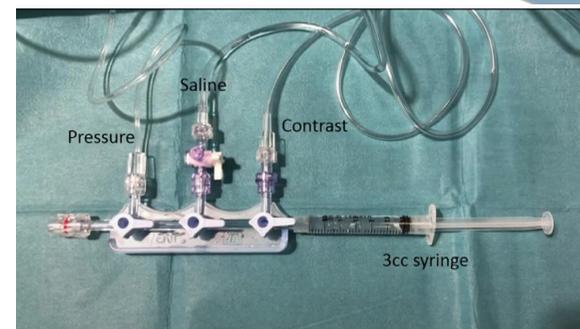
* Russell C, Baillie JK. Current Opinion in Systems Biology. 2017(3):139-

"WASH OUT" 24 HORAS ANTES



CFR / IMR

Termodilución con bolos de salino



La medición es operador dependiente



CFR / IMR

Termodilución con bolos de salino

Hyperemic Agent



IC Adenosine 100 μ g in the RCA and 200 μ g in the left coronary artery

IV Adenosine 140 mcg/Kg/min





CFR / IMR

Termodilución con bolos de salino

CFR (Coronary flow reserve)

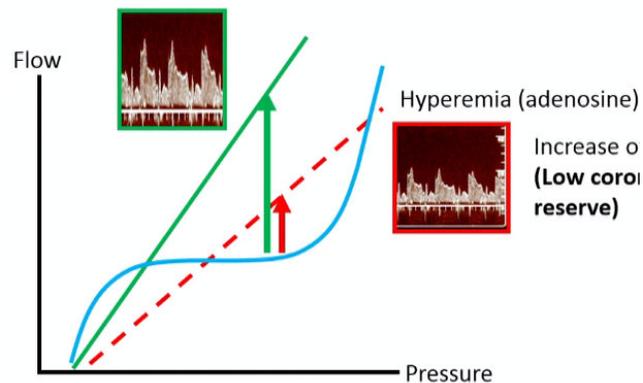
- Dinamicidad microcirculación

Hyperemic flow / resting flow

T_{nm} reposo / T_{nm} hiperemia

Valor normal > 2

(Normal coronary flow reserve)



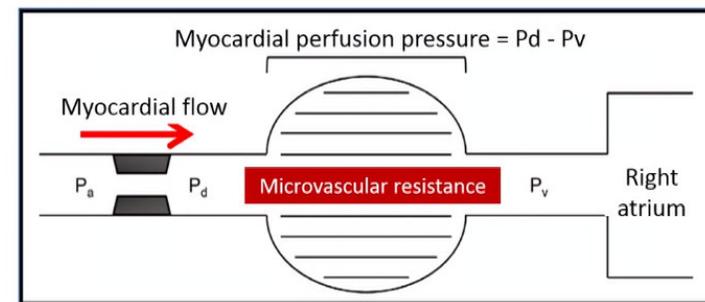
IMR (Miocardial Resistance Index)

- *Mecanismos estructurales*

$$R_{\mu} = \frac{P_d}{Q}$$

Presión distal x T_{nm} hiperemia

Valor normal < 25

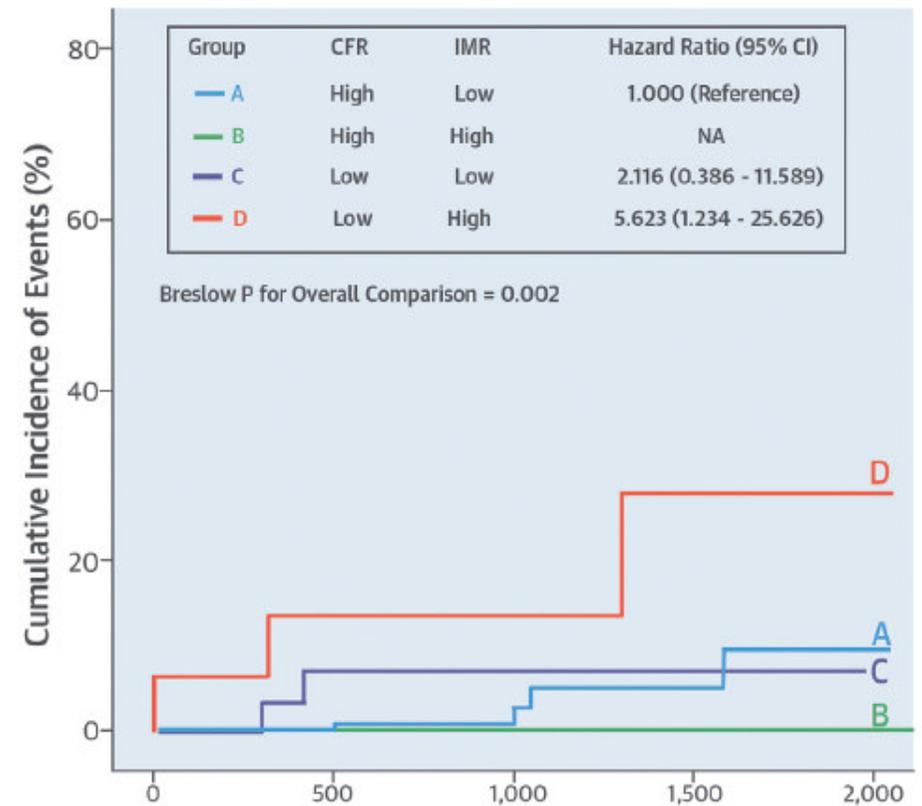




Limitaciones

- Operador dependiente: variabilidad
- Necesidad de adenosina
- Son índices, no valores absolutos
 - CFR
 - No específico de la microcirculación
 - Alta dependencia de **condiciones en reposo**
 - Flujo basal aumentado
 - Tiempo diastólico acortado
 - Presión intracavitaria aumentada
 - IMR
 - Depende de la existencia de circulación colateral
- A veces **la interpretación** de los resultados es difícil....

Un 37% con resultado de CFR e IMR discordante



Lee Joo Myung, Journal of the American College of Cardiology. 2016 Mar 15;67(10)



SECOND-GENERATION CORONARY PHYSIOLOGY

Absolute flow and absolute resistences
MRR index



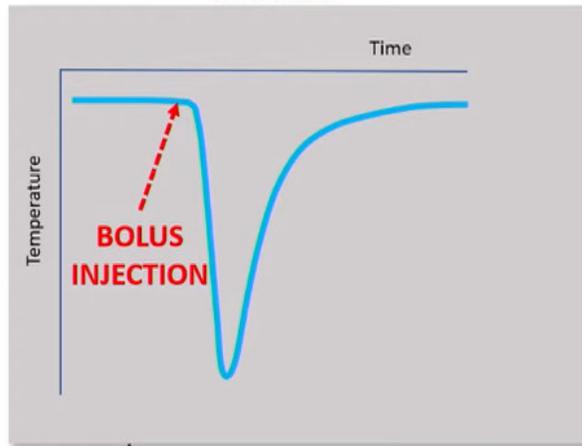


Un paso más allá: De la termodilución en bolos a la termodilución continua

Indicator Dilution Theory

The 'indicator' must be mixed to blood instantaneously to be completely representative of blood flow

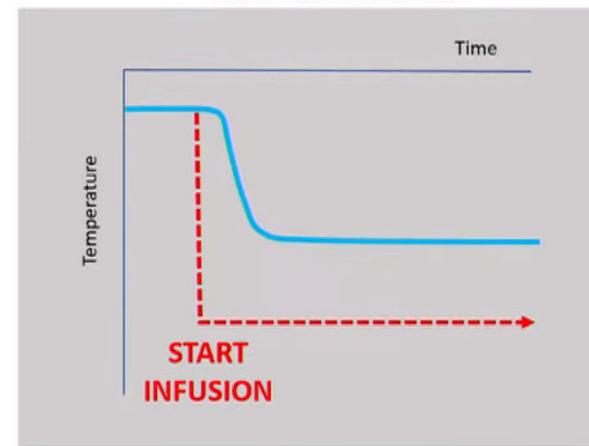
Bolus



$$Q = M / \int c(t) dt \quad \text{or} \quad Q = V / T_{mm}$$

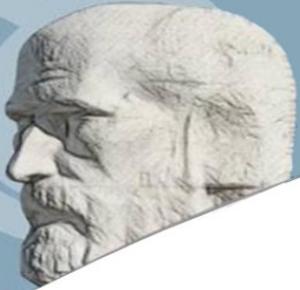
Thermodilution

Continuous



$$Q = Q_i \times \frac{T_i}{T} \times 1.08$$

FLUJO CORONARIO ABSOLUTO (ml/min) Y RESISTENCIAS CORONARIAS ABSOLUTAS (UW)



Journal of the American College of Cardiology
Volume 50, Issue 24, 11 December 2007, Pages 2294-2304



Clinical Research
Invasive Cardiology

Direct Volumetric Blood Flow Measurement in Coronary Arteries by Thermodilution

Wilbert Aarnoudse MD, PhD ^{†, 1}, Marcel van't Veer MSc ^{†, 1}, Nico H.J. Pijls MD, PhD ^{†, 2, 3, 4}, Joost ter Woort MD [‡], Steven Vercauteren MD [§], Pim Tonino MD [‡], Maartje Geven MSc [†], Marcel Rutten PhD [†], Eduard van Hagen RN [‡], Bernard de Bruyne MD, PhD [§], Frans van de Vosse PhD [†]

Circulation: Cardiovascular Interventions
Volume 11, Issue 3, March 2018
<https://doi.org/10.1161/CIRCINTERVENTIONS.117.006194>

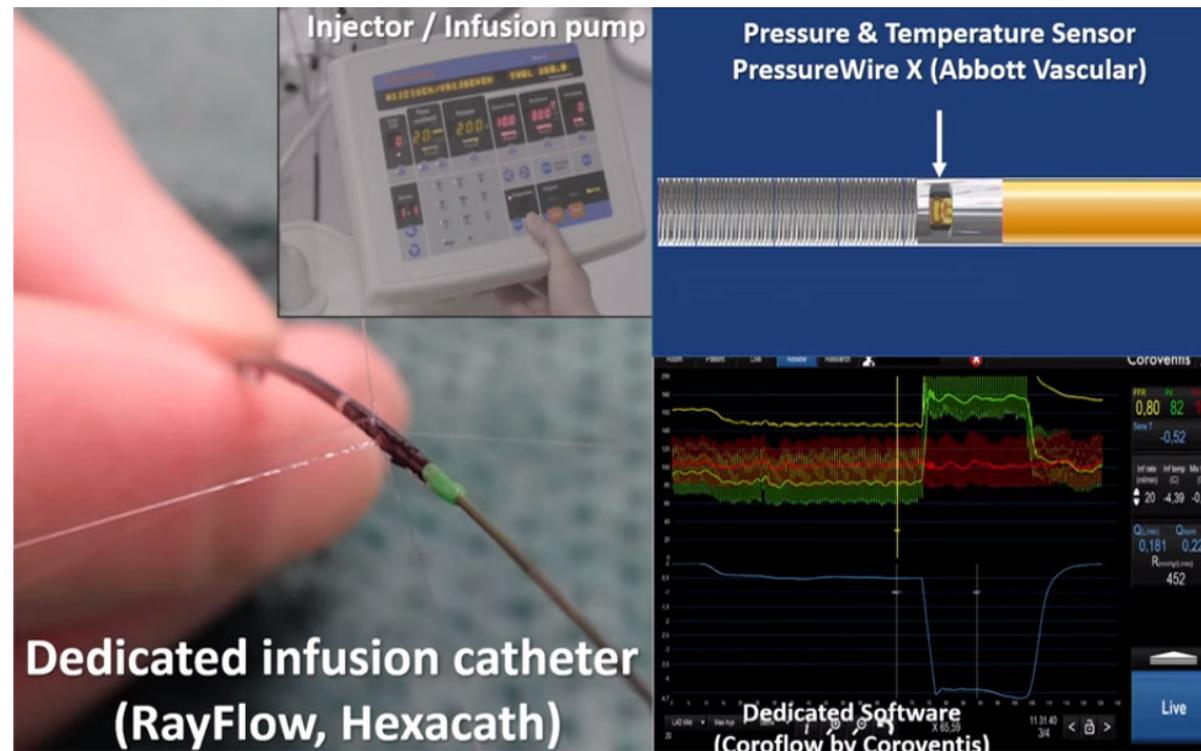


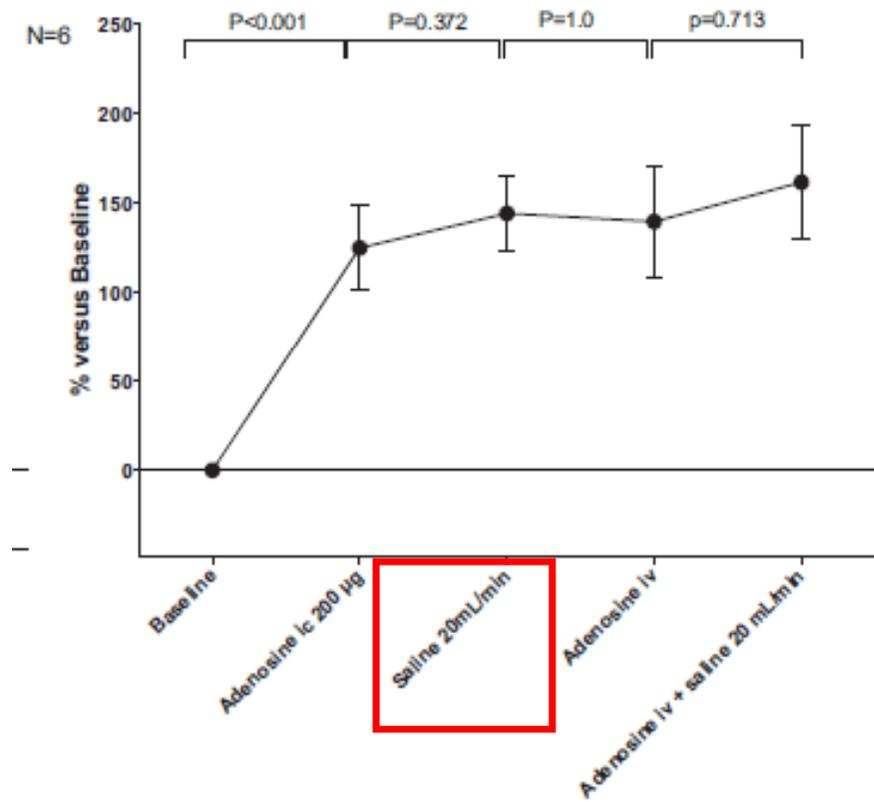
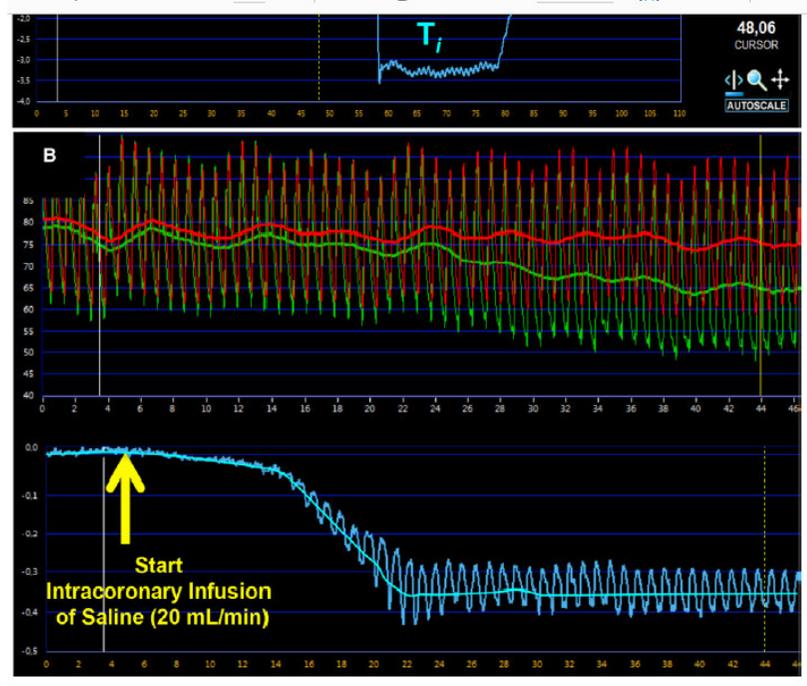
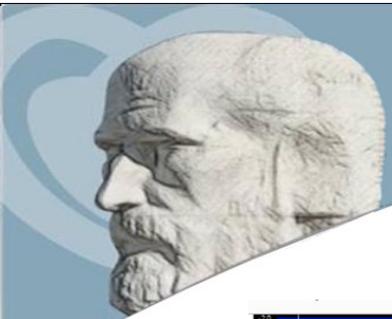
ORIGINAL ARTICLE

Catheter-Based Measurements of Absolute Coronary Blood Flow and Microvascular Resistance

Feasibility, Safety, and Reproducibility in Humans

Panagiotis Xaplanteris, MD, PhD, Stephane Fournier, MD, Daniëlle C.J. Keulards, MD, Julien Adjedj, MD, Giovanni Ciccarelli, MD, Anastasios Milkas, MD, Mariano Pellicano, MD, Marcel van't Veer, MSc, PhD, Emanuele Barbato, MD, PhD, Nico H.J. Pijls, MD, PhD, and Bernard De Bruyne, MD, PhD





LA INFUSIÓN CONTINUA DE SALINO GENERA UN ESTADO DE HIPEREMIA MÁXIMA ESTABLE SIN NECESIDAD DE ADENOSINA



Flujo coronario y resistencias vasculares

Termodilución con infusión continua salino

Flujo coronario absoluto (Q) (termodilución)

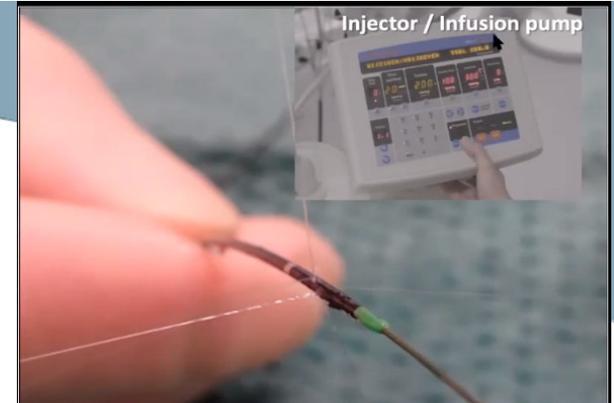
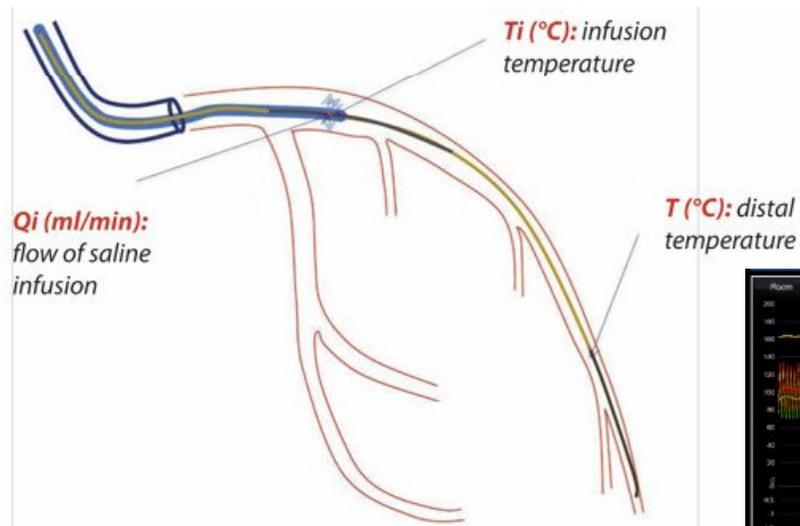
- T= temperatura de la sangre homogénea mezclada con el s salino
- Ti = temperatura del s salino infundido medida en la salida del catéter
- Qi= ritmo de infusión del s salino

$$Q = \frac{T_i}{T} \times 1,08 \times Q_i \text{ (ml/min)}$$

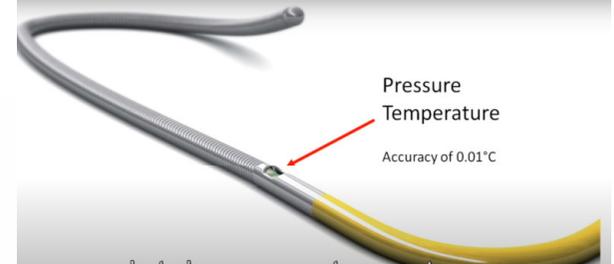
$$R = \frac{P}{Q} \text{ (mm Hg.min.mL}^{-1}\text{)}$$

Resistencias (Ohm)

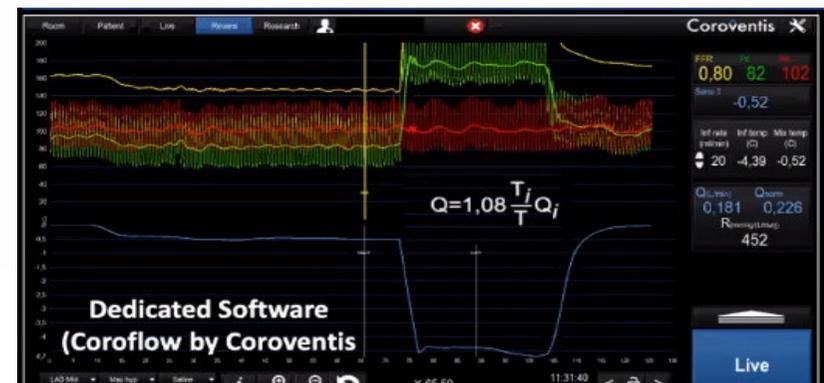
- Pd= presión en coronaria distal
- Q=flujo coronario



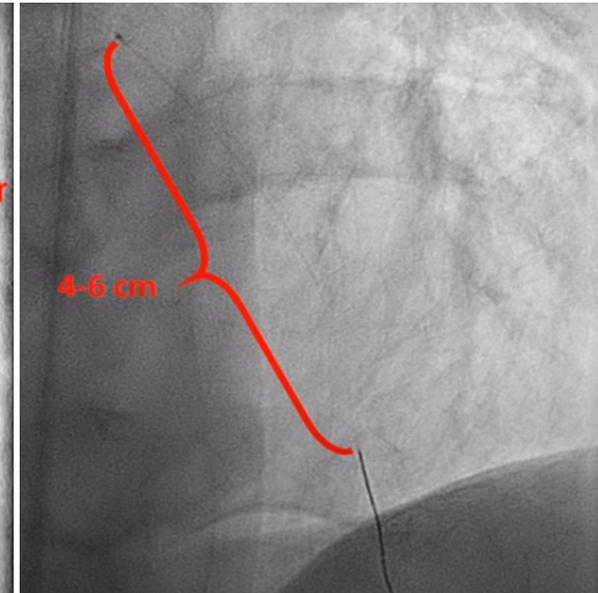
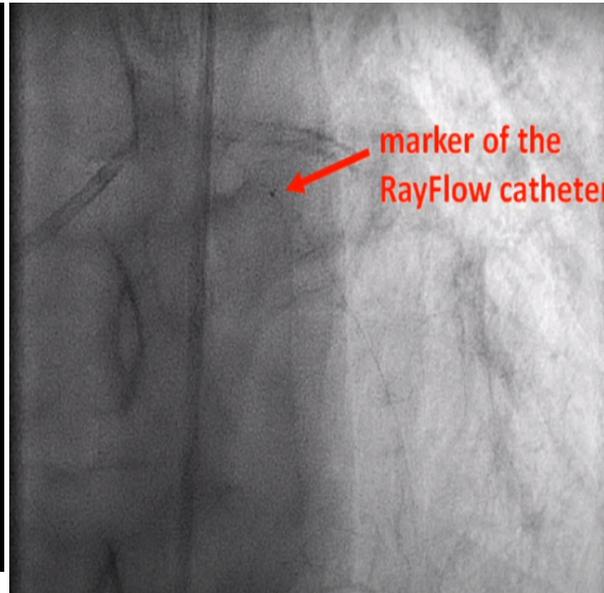
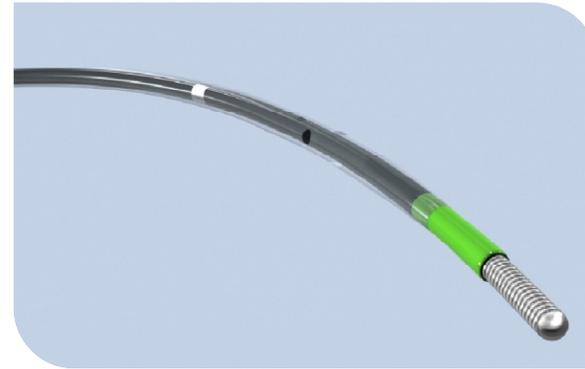
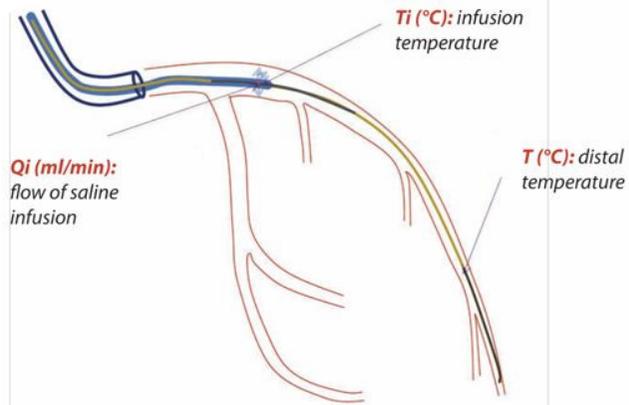
Dedicated infusión catheter



Pressure- Temperature Wire

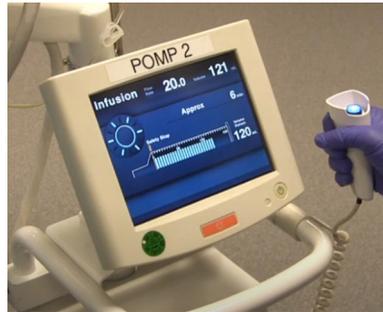


Dedicated software (Coroflow by Coroventis)





INFUSIÓN SSF 20 ml/min



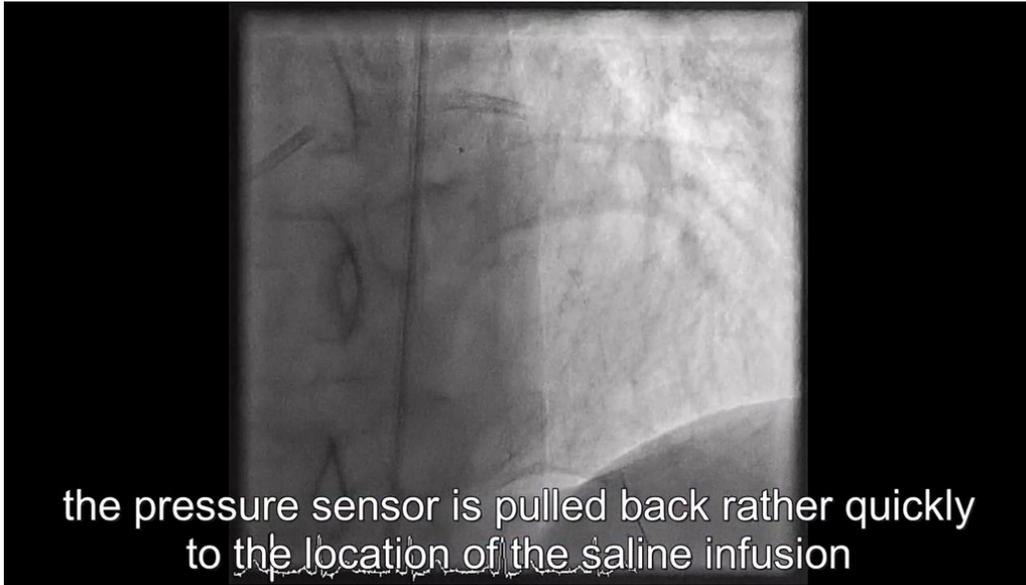
30 seg



HIPEREMIA MÁXIMA
VASODILATACIÓN MÁXIMA
DE LA MICROCIRCULACIÓN

ADENOSINA



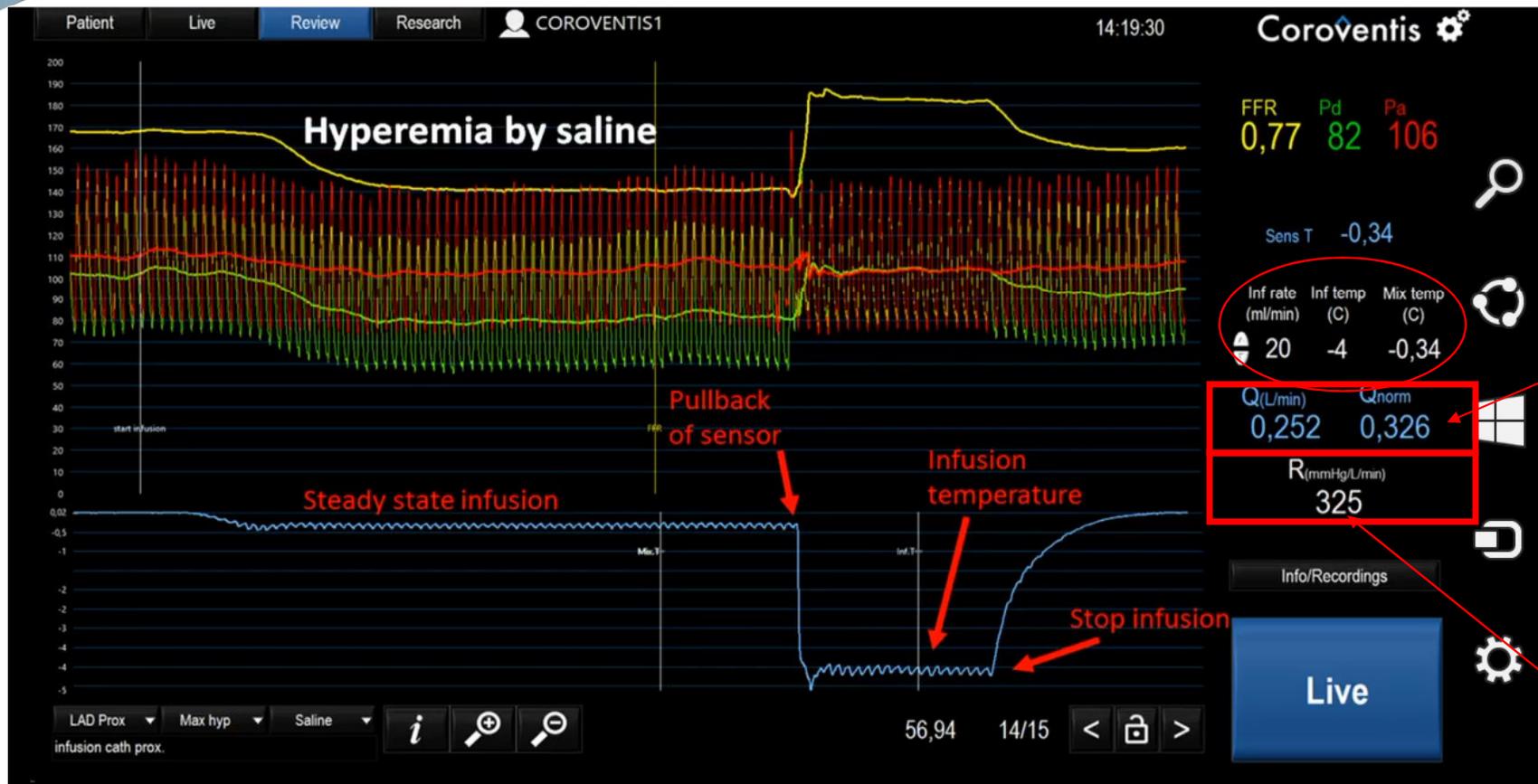


the pressure sensor is pulled back rather quickly to the location of the saline infusion



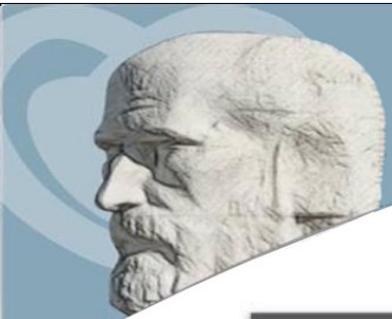


Flujo coronario absoluto y resistencias microvasculares absolutas



$$Q = 1.08 \frac{T}{T_i} Q_i$$

$$R = \frac{P_d}{Q}$$



Bolus thermodilution IMR

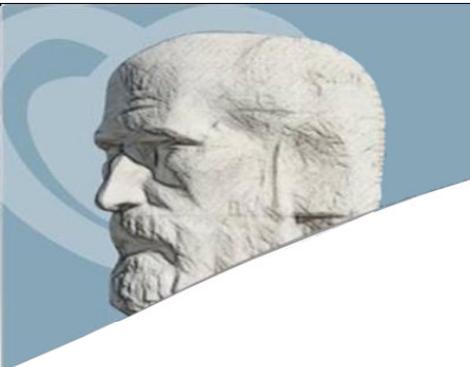


- Easy
- Fast (1-2 min)
- No extra material
- Operator dependant
- Non-Quantitative

Continuous thermodilution Absolute Flow, Resistance, and MRR



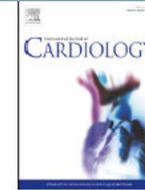
- Easy
- Longer (4-5 min)
- Dedicated infusion catheter
- Operator independant
- Quantitative (mL/min)
- Highly reproducible



Contents lists available at ScienceDirect

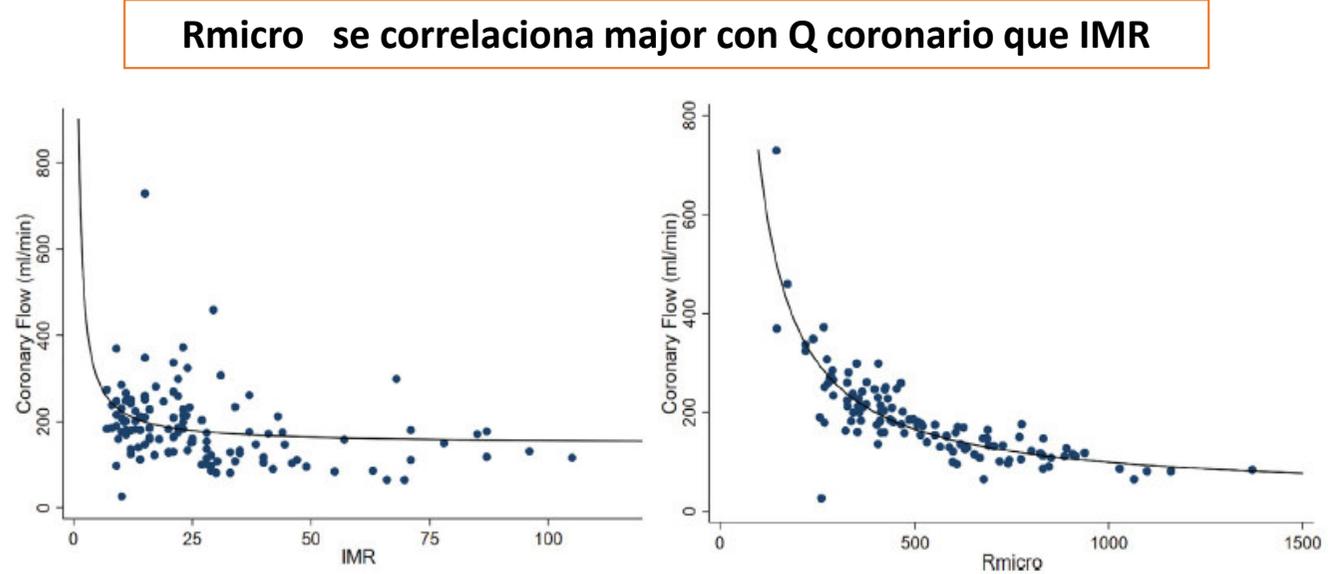
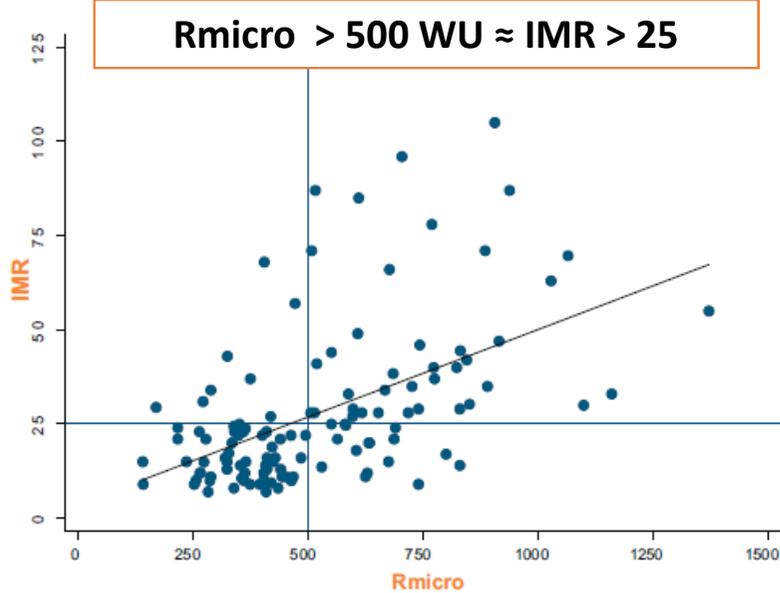
International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Coronary microvascular dysfunction assessed by continuous intracoronary thermodilution: A comparative study with index of microvascular resistance

Fernando Rivero^a, Alejandro Gutiérrez-Barrios^b, Josep Gomez-Lara^c, Manuel Fuentes-Ferrer^d, Javier Cuesta^a, Danielle C.J. Keulards^e, Ana Pardo-Sanz^f, Teresa Bastante^a, Elena Izaga-Torralba^b, Joan-Antoni Gomez-Hospital^c, Marcos García-Guimaraes^g, Nico H.J. Pijls^e, Fernando Alfonso^{a,*}



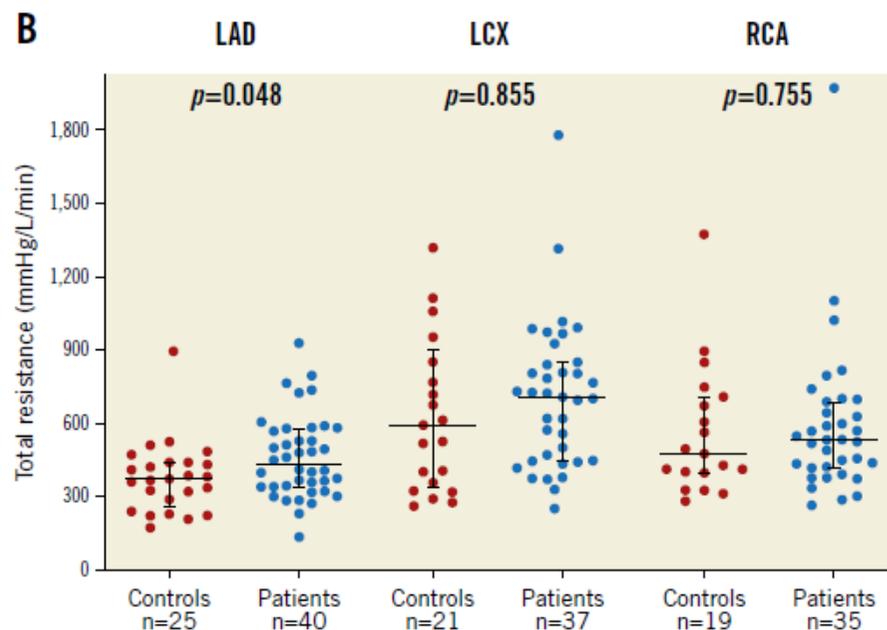
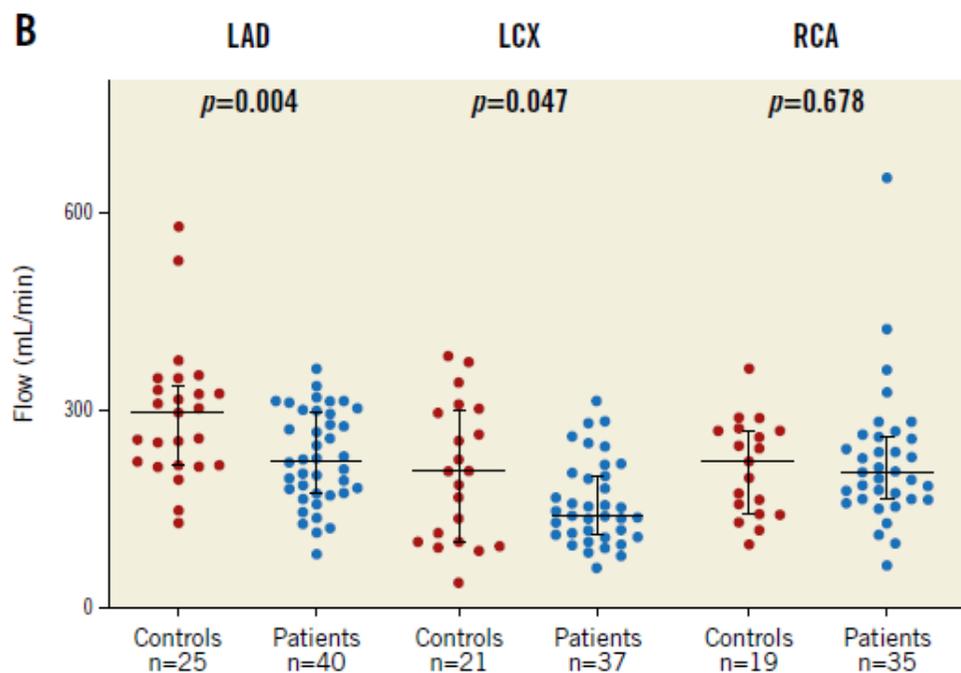


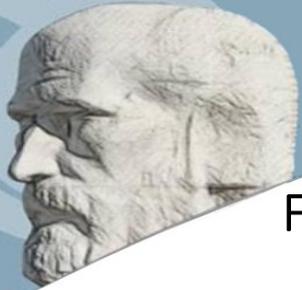
Limitaciones: EFECTO MASA

- **Flujo absoluto y resistencias dependen de la masa miocárdica:** a mayor masa miocárdica , mayor flujo coronario y menores resistencias
- La masa miocárdica tiene **gran variabilidad interindividual** y para cada territorio vascular
- Por lo tanto, **un gran rango de “valores normales”** de flujo y resistencias son esperables
- Para salvar esta limitación, necesitamos:
 - Ajustar por masa miocárdica
 - Normalizar los valores en hiperemia a los valores en reposo correspondientes: **concepto de “RESERVA” de flujo (CFR) y resistencias (MMR)**

Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans

Stephane Fournier^{1,2,3}, MD; Danielle C.J. Keulards⁴, MD; Marcel van't Veer⁴, MSc, PhD; Iginio Colaïori¹, MD; Giuseppe Di Gioia^{1,3}, MD; Frederik M. Zimmermann⁴, MD; Takuya Mizukami¹, MD, PhD; Sakura Nagumo¹, MD; Monika Kodeboina¹, MD; Mohamed El Farissi⁴, MD; Jo M. Zelis⁴, MD; Jeroen Sonck^{1,3}, MD; Carlos Collet¹, MD, PhD; Nico H.J. Pijls^{4,5}, MD, PhD; Bernard De Bruyne^{1,2*}, MD, PhD



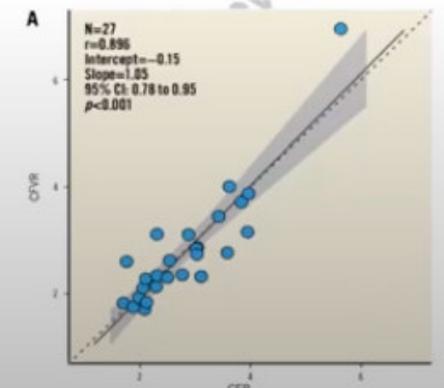
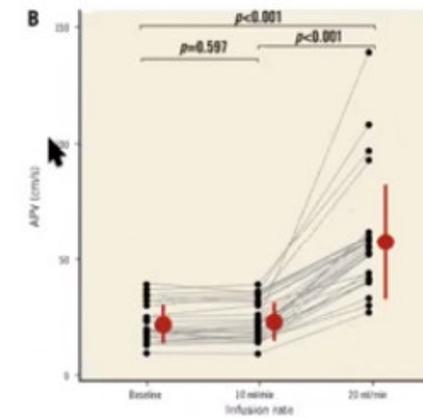
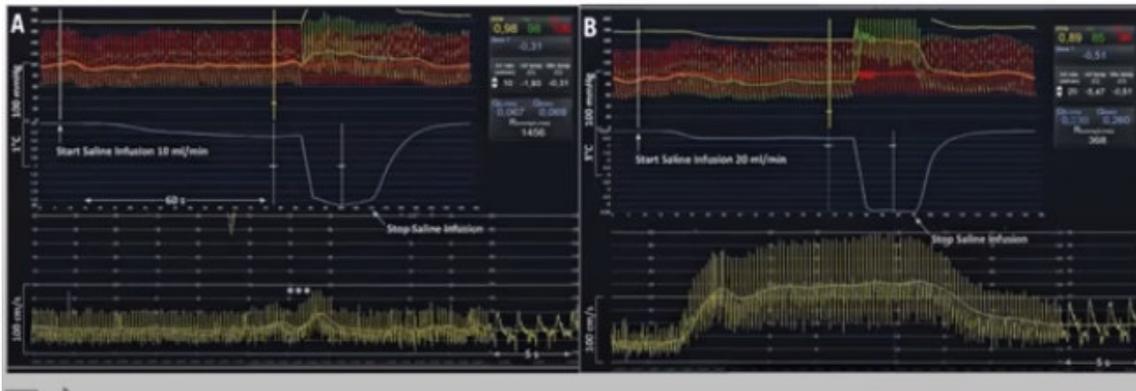


FLUJO CORONARIO BASAL: talón de Aquiles de la fisiología coronaria

Thermodilution-derived volumetric resting coronary blood flow measurement in humans

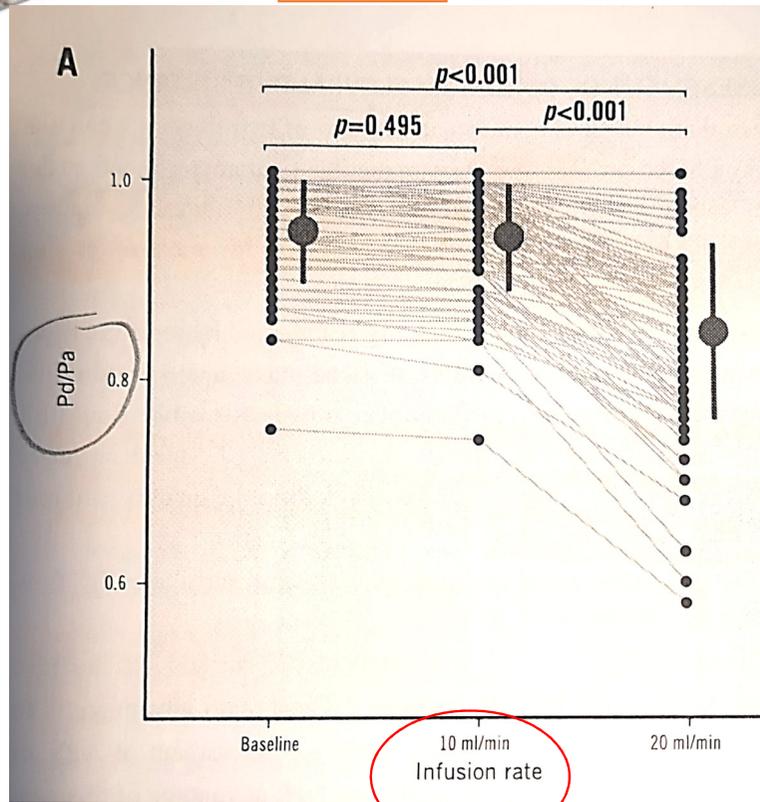
Emanuele Gallinoro^{1,2}, MD; Alessandro Candreva¹, MD; Iginio Colaïori¹, MD; Monika Kodeboina^{1,3}, MD; Stephane Fournier^{3,4}, MD; Olivier Nelis¹, MT; Giuseppe Di Gioia^{1,3}, MD; Jeroen Sonck^{1,3}, MD; Marcel van 't Veer^{5,6}, MSc, PhD; Nico H.J. Pijls^{5,6}, MD, PhD; Carlos Collet¹, MD, PhD; Bernard De Bruyne^{1,4*}, MD, PhD

1. Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium; 2. Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; 3. Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; 4. Department of Cardiology, Lausanne University Hospital, Lausanne, Switzerland; 5. Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands; 6. Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands

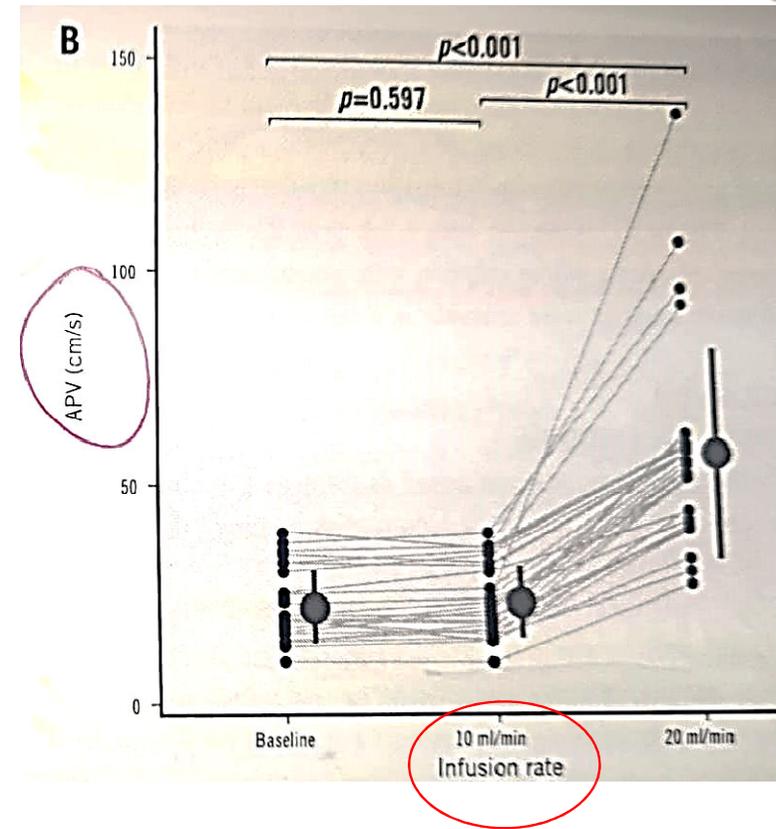




Pd/Pa

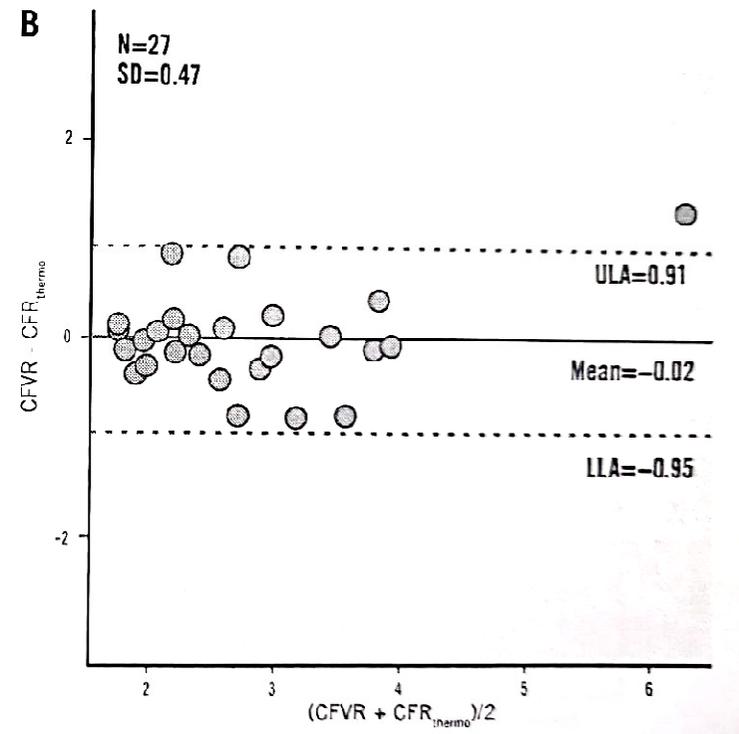
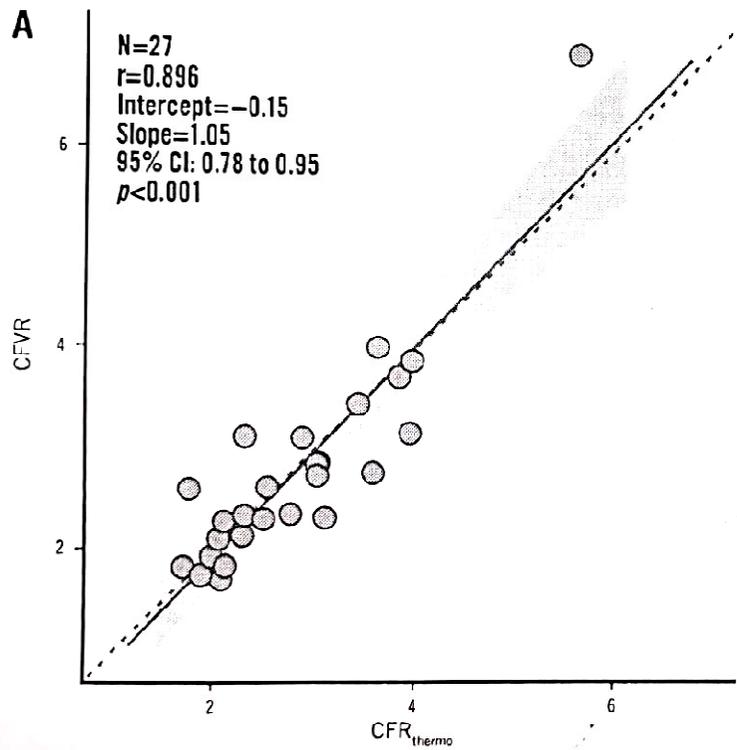


Vel. Doppler



LA TERMODILUCIÓN CONTINUA CON SALINO A UN RITMO DE INFUSIÓN BAJO (10 ml/min) PERMITE CALCULAR FLUJO CORONARIO ABSOLUTO Y RESISTENCIAS ABSOLUTAS EN REPOSO

ABSOLUTE FLOW-DERIVED CFR



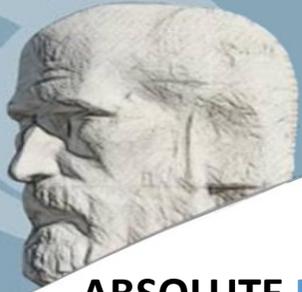


Termodilución continua: flujo absoluto en reposo



10 ml/min - LAD





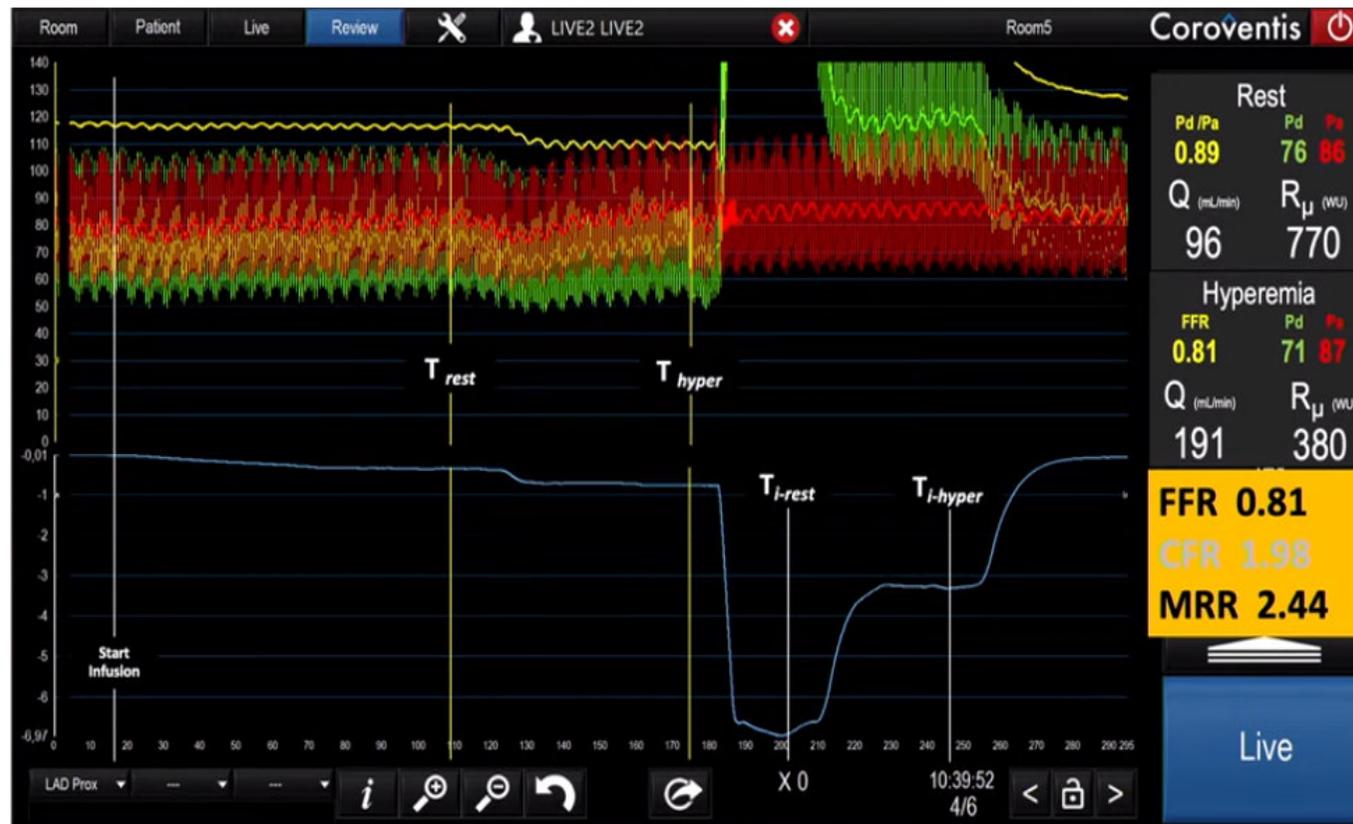
ABSOLUTE RESTING FLOW AND RESISTENCE 10 ml/min



ABSOLUTE HIPEREMIC FLOW AND RESISTENCE 20 ml/min



Absolute flow derived CFR, MRR



De Bruyne, Pijls, Fearon et al JACC 2021:1541

Procedimiento operador INDEPENDIENTE



MRR: primer índice específico de la microcirculación derivado del flujo absoluto

Microvascular Resistance Reserve for Assessment of Coronary Microvascular Function

JACC Technology Corner

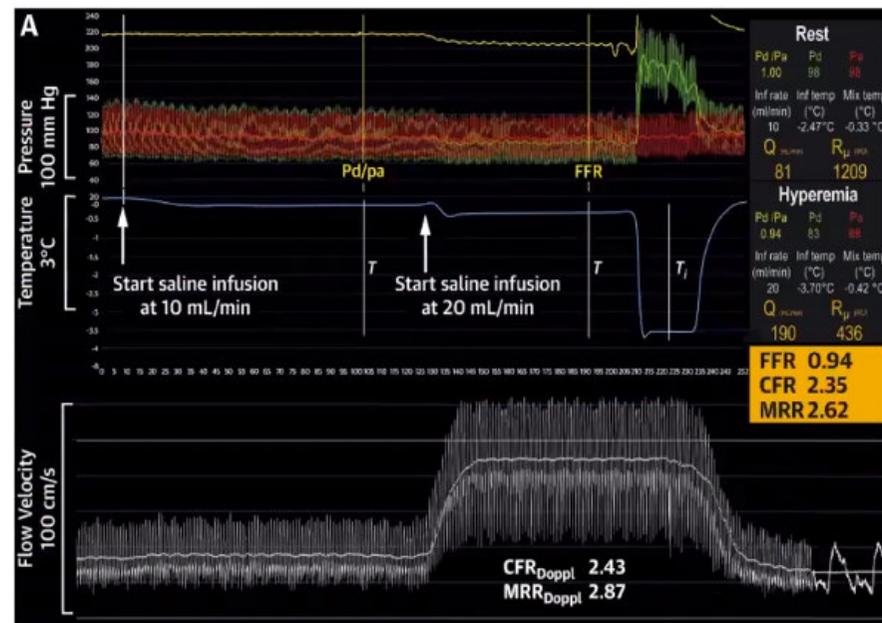
Bernard De Bruyne, MD, PhD,^{a,b,*} Nico H.J. Pijls, MD, PhD,^{c,*} Emanuele Gallinoro, MD,^{a,d} Alessandro Candreva, MD,^a Stephane Fourmier, MD,^b Danielle C.J. Keulards, MD,^e Jeroen Sonck, MD,^{a,e} Marcel van't Veer, MS, PhD,^{c,f} Emanuele Barbato, MD, PhD,^{a,g} Jozef Bartunek, MD, PhD,^h Marc Vanderheyden, MD,^g Eric Wyffels, MD,^g Annemieke De Vos, MD,^c Mohamed El Farissi, MD,^c Pim A.L. Tonino, MD, PhD,^c Olivier Muller, MD, PhD,^b Carlos Collet, MD, PhD,^a William F. Fearon, MD^g



MMR

- Parámetro cuantitativo
- 100% Específico de microcirculación
- Independiente de las resistencias epicárdicas
- Independiente de masa miocárdica
- Independiente de cambios en presión arterial
- Independiente de operador
- Procedimiento sencillo y rápido

CENTRAL ILLUSTRATION: Simultaneous Registration of Pressures, Temperature, and Flow Velocity in the Right Coronary Artery



B

$$Q = 1.08 \cdot \frac{T_i}{T} \cdot Q_i$$

$$R_{\mu,rest} = P_a / Q_{rest}$$

$$R_{\mu,hyper} = P_d / Q_{hyper}$$

$$MRR = \frac{Q_{hyper}}{Q_{rest}} \cdot \frac{P_{a,rest}}{P_{d,hyper}}$$

C



De Bruyne, B. et al. J Am Coll Cardiol. 2021;78(15):1541-1549.

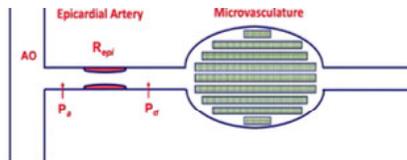


MMR: específico de la microcirculación

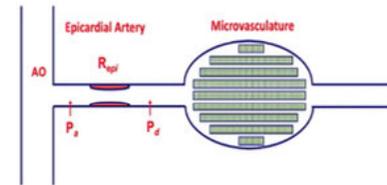
$$: \text{MRR} = (\text{true}) R_{\mu, \text{rest}} / R_{\mu, \text{hyper}}$$

Resistencias microvasculares verdaderas (como serían en el hipotético caso de arterias epicárdicas completamente normales) / Resistencias microvasculares en hiperemia

How to calculate
(true) $R_{\mu, \text{rest}}$???



How to calculate
 $R_{\mu, \text{hyper}}$???



- En caso de ausencia total de enfermedad epicárdica: $P_a = P_d$
- En caso de enfermedad epicárdica: $R_{\mu, \text{rest}}$ estarían disminuídas por un estado compensador (autoregulación)

- Las resistencias en hiperemia no se ven afectadas por la presencia de enfermedad epicárdica

$$(\text{true}) R_{\mu, \text{rest}} = P_{a, \text{rest}} / Q_{\text{rest}} \quad (\text{eq 1})$$

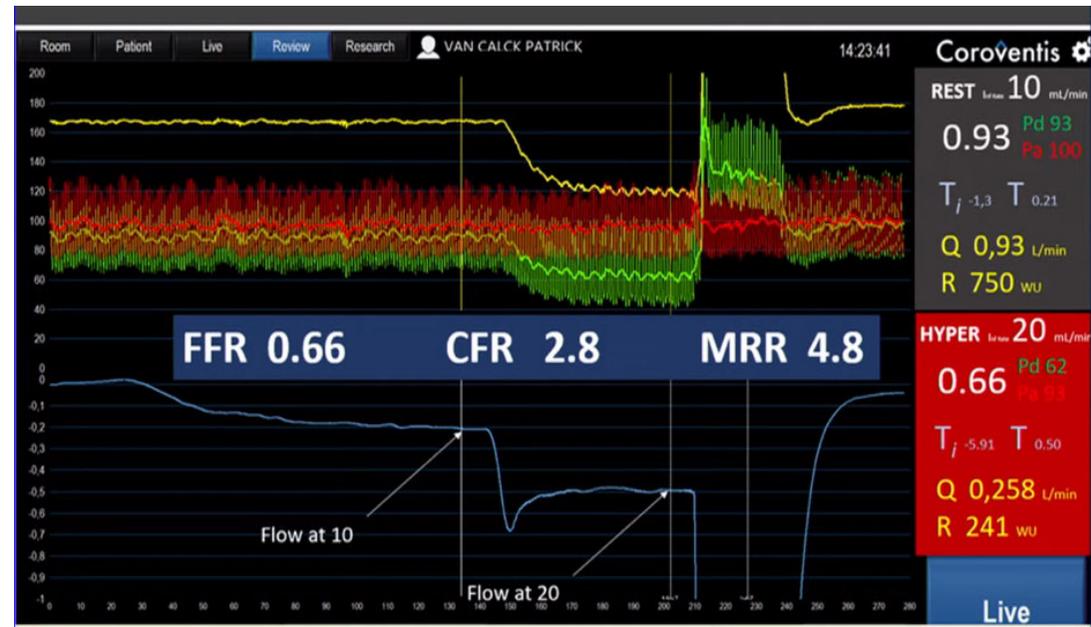
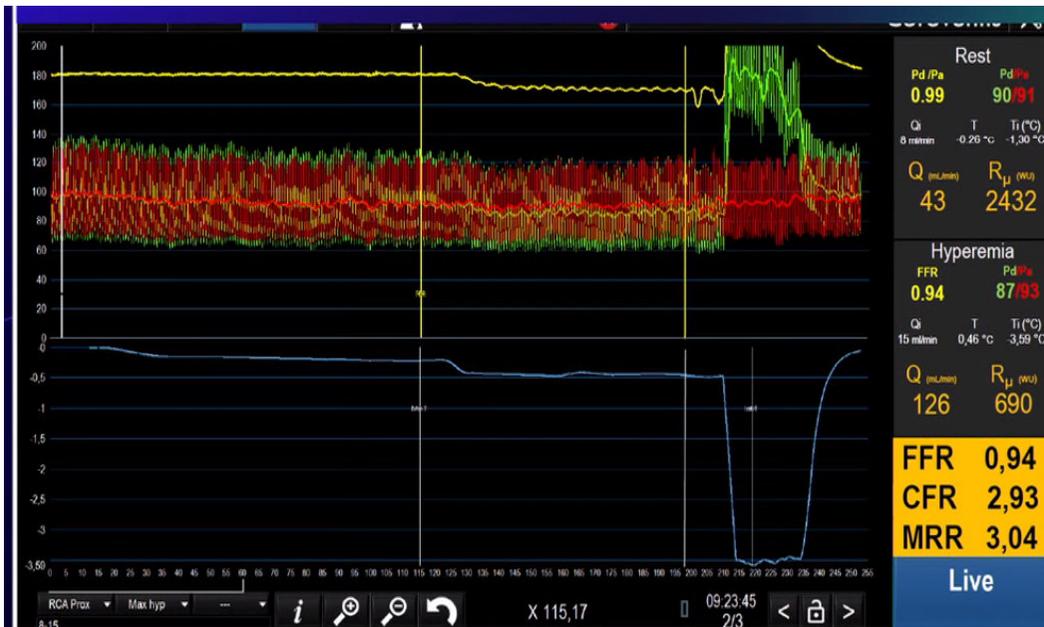
$$R_{\mu, \text{hyper}} = P_{d, \text{hyper}} / Q_{\text{max}} \quad \text{equation(2)}$$

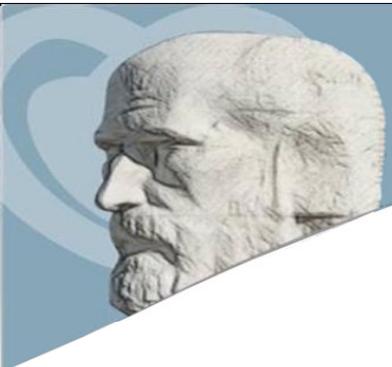
$$\text{MRR} = Q_{\text{max}} / Q_{\text{rest}} \times P_{a, \text{rest}} / P_{d, \text{hyp}}$$

equation(3)



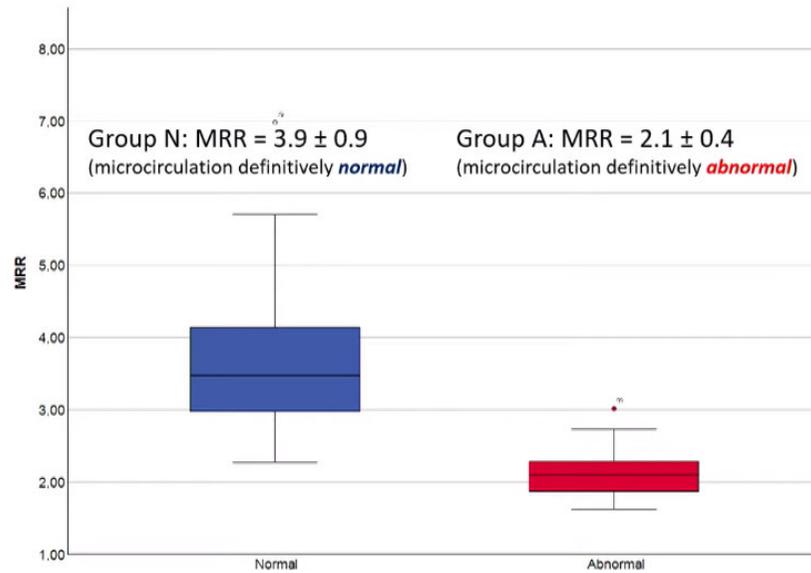
MRR en términos de CFR y RFR



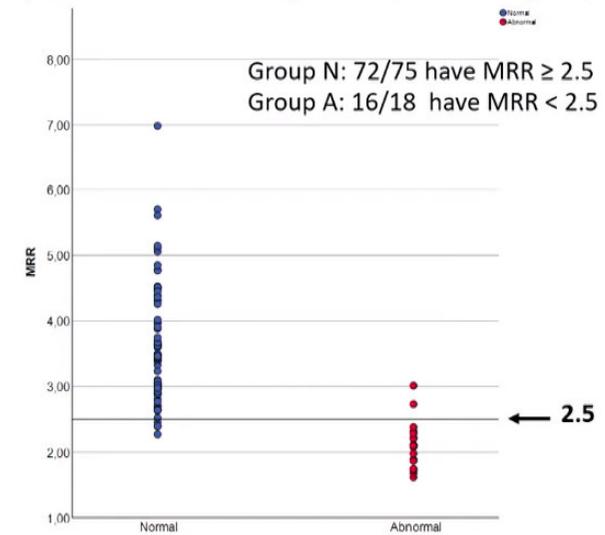


NL-CFT Trial:

Dutch Registry in patients suspected of *ANOCA/MINOCA*, which is presently performed in the



Diagnostic Accuracy of MRR to correctly classify MVD in group N and A



In these highly selected patients, diagnostic accuracy of MRR of < 2.5 or ≥ 2.5 to correctly indicate or exclude microvascular disease, is **95 %**

Futuras líneas: → **EUROCRFT project**
EUROpean Coronary Resistance & Absolute Flow Trial

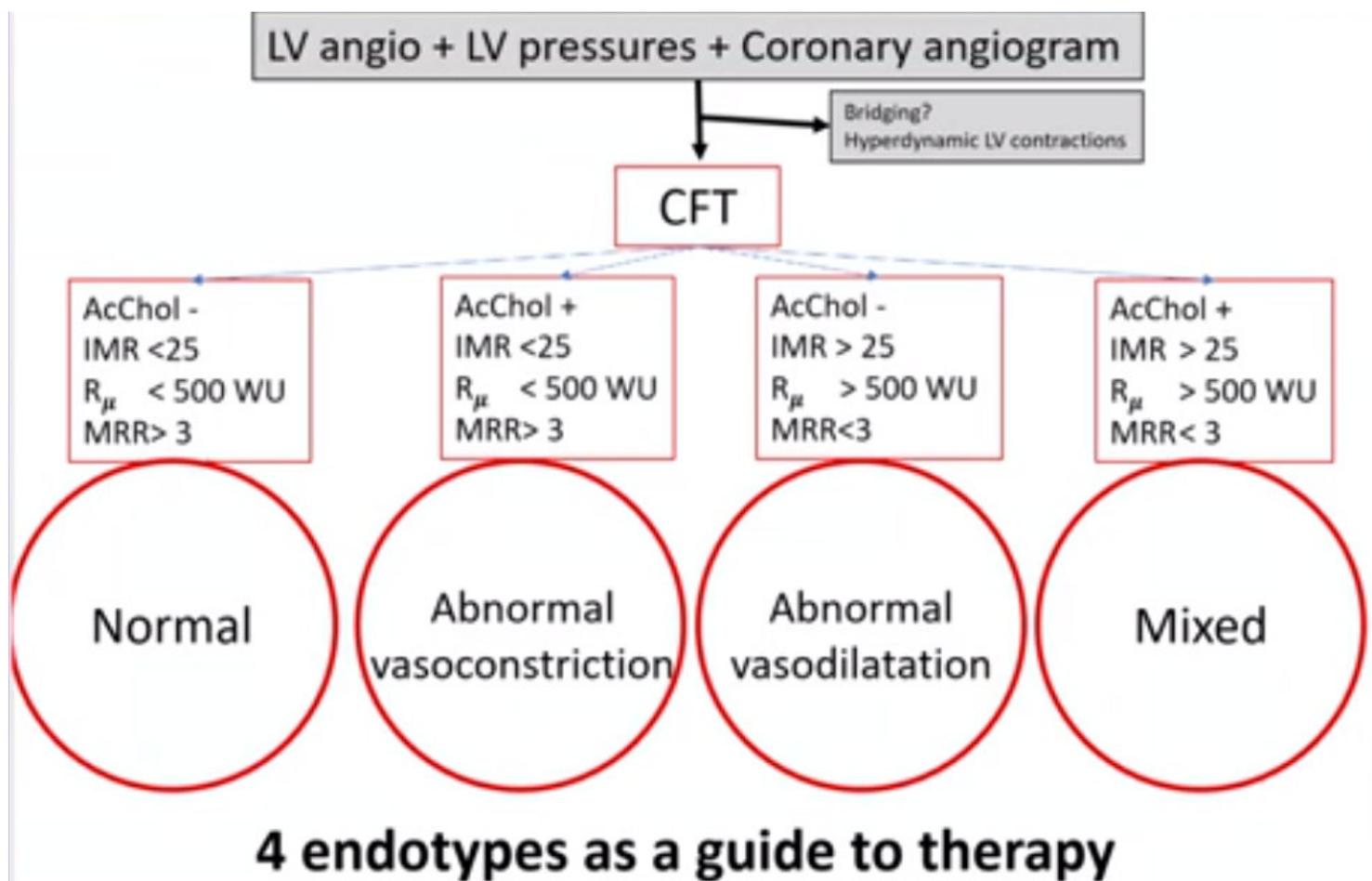


MRR

- **Parámetro preciso, cuantitativo y reproducible**
- **100% Especifico de la microcirculación, de la masa miocárdica y de los cambios en presión arterial**
- **En personas sanas MRR es similar a CFR**
- **En pacientes con enfermedad coronaria epicárdica, es un “super-CRF” específico de microcirculación y ajustado a los cambios hemodinámicos, e independiente de la enfermedad epicárdica**
- **Las variaciones de CFR debidas a heterogeneidad genética, edad siguen estando presentes en MRR**
- **Una dicotomía del 100% de los pacientes es difícil de alcanzar pero nos permite un diagnóstico más preciso de enfermedad microvascular**
- **Se quieren investigaciones futuras que validen su aplicación clínica**

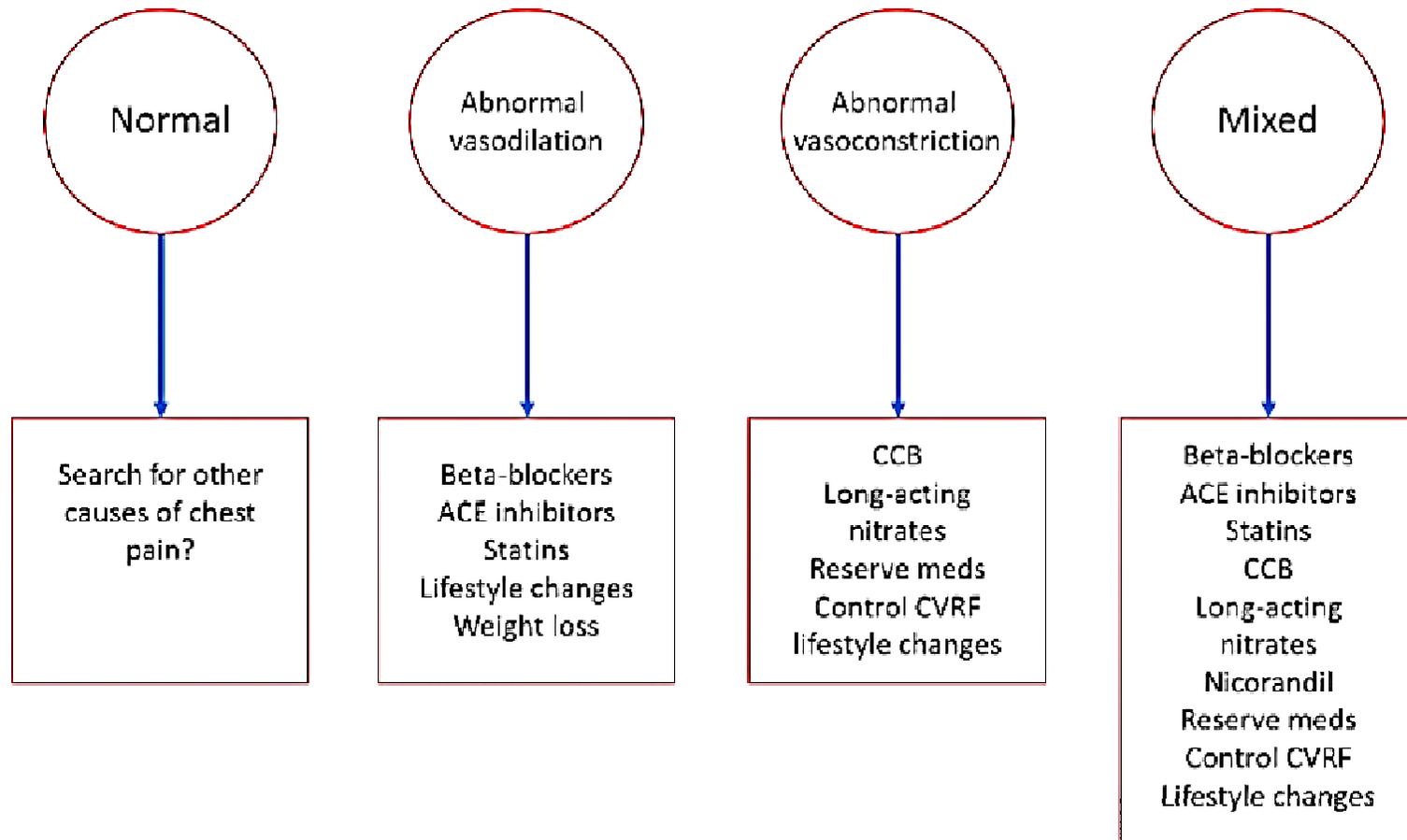


Una nueva aproximación diagnóstica...





TRATAMIENTO SEGÚN ENDOTIPO





CONCLUSIONES

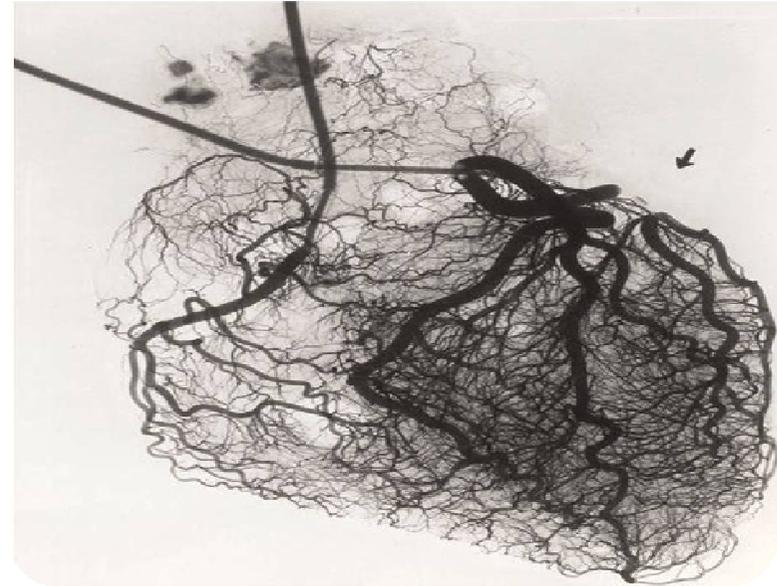
- La **disfunción microvascular** es probablemente una condición muy frecuente pero su prevalencia, relevancia y fisiopatología exactas todavía son poco conocidos en parte debido a la ausencia de **medidas cuantitativas**.
- **En la era de la medicina de precisión, necesitamos parámetros cuantitativos.**
- Los **test diagnósticos de segunda generación** suponen una expansión de nuestras herramientas para explorar la microcirculación.
- El método de **termodilución continua y la estimación del flujo coronario absoluto y resistencias absolutas** representan una forma nueva, cuantitativa y operador independiente para la valoración específica de la función microvascular.
- MMR se presenta como un nuevo índice objetivo de la **dinamicidad microvascular** salvando las limitaciones del CFR.
- Estos nuevos parámetros pueden ser útiles para caracterizar correctamente y estandarizar el diagnóstico de disfunción microvascular, así como para guiar su tratamiento.



What you see . . .



What you don't see . . .



GRACIAS