jaa Just accepted article

EuroIntervention

Title: **Safety of Absolute Coronary Flow And Microvascular Resistance Measurements by Thermodilution.**

Authors: Daniëlle CJ Keulards, M.D; Marcel van 't Veer, MSc, PhD; Jo M Zelis, M.D; Mohamed el Farissi, M.D; Frederik M Zimmermann, M.D; Annemiek de Vos, M.D; Koen Teeuwen, M.D, PhD; Guus Brueren, M.D, PhD; Inge Wijnbergen, M.D, PhD; Pieter-Jan Vlaar, M.D, PhD; Pim AL Tonino, M.D, PhD; Nico HJ Pijls, M.D, PhD

DOI: 10.4244/EIJ-D-20-00074

Citation: Keulards DCJ, van 't Veer M, Zelis JM, el Farissi M, Zimmermann FM, de Vos A, Teeuwen K, Brueren G, Wijnbergen I, Vlaar PJ, Tonino PAL, Pijls NHJ. Safety of Absolute Coronary Flow And Microvascular Resistance Measurements by Thermodilution. *EuroIntervention* 2020; Jaa-734 2020, doi: 10.4244/EIJ-D-20-00074

Manuscript submission date: 13 January 2020

Revisions received: 29 January 2020

Accepted date: 17 February 2020

Online publication date: 25 February 2020

Safety of Absolute Coronary Flow And Microvascular Resistance Measurements by Thermodilution

Short title: Safety of microvascular resistance measurements

Daniëlle CJ Keulards, M.D[1]; Marcel van 't Veer, MSc, PhD[1,2]; Jo M Zelis, M.D[1]; Mohamed el Farissi, M.D[1]; Frederik M Zimmermann, M.D[1]; Annemiek de Vos, M.D[1]; Koen Teeuwen, M.D,PhD[1]; Guus Brueren, M.D,PhD[1]; Inge Wijnbergen, M.D,PhD[1]; Pieter-Jan Vlaar, M.D,PhD[1]; Pim AL Tonino, M.D,PhD[1,2]; Nico HJ Pijls, M.D,PhD[1,2]

1. Catharina Hospital Eindhoven, The Netherlands
2. Eindhoven University of Technology, The Netherlands

Correspondence address:
Nico H.J.Pijls
Catharina Hospital
Michelangelolaan 2
5623 EJ Eindhoven
nico.pijls@xs4all.nl

Classifications

Miscellaneous, Fractional flow reserve, Other technique

Abbreviations

ANOCA	Angina Non Obstructive Coronary arteries
FFR	Fractional Flow Reserve
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending
LCx	Ramus Circumflex
OCT	Optical coherence tomography
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
RCA	Right Coronary Artery

Introduction

Assessment of the microcirculation of the heart has gained interest over recent years. This is partly due to the fact that up to 50% of patients with chest pain visiting the catherization laboratory do not present with significant epicardial stenosis (so-called Angina with Non Obstructive Coronary Artery disease (ANOCA).[1]

Most knowledge regarding microvascular resistance came from non-invasive imaging, from invasive index of microvascular resistance[2], or from doppler wires[3], both being semi-quantitative and operator dependent.

Recently, direct quantitative measurement of coronary blood flow and microvascular resistance has become possible by thermodilution with saline infusion, using a pressure-temperature guidewire and a multisidehole infusion catheter. Such measurements have been validated versus Positron Emission Tomography (PET)[4], have a high reproducibility and are operator independent.[5] Procedural safety has been reported before[5], but long term safety and absence of late complications have not been described yet. The present study evaluates the safety of absolute flow measurements, both periprocedural, at 30 days and to one year follow-up.

Methods

Study design and population

In a total of 100 patients, 213 coronaries arteries were assessed and 467 measurements of absolute blood flow and microvascular resistance were performed. The study was approved by the local IRB and informed consent was obtained from all patients to use their data for this post-hoc safety analysis.

Absolute blood flow and resistance measurement

Cardiac catheterization, absolute blood flow and resistance measurements were performed according to routine and as previously described (Figure 1 and **supplementary figure 1**) (complete methods **see supplements**).[5,6]

Assessment of complications and safety at follow up

During the procedure, clinical, hemodynamic and electrocardiographic variables were recorded as usual. Special attention was paid to the occurrence of bradycardia/atrioventricular conduction abnormality. After removal of the Rayflow catheter and guidewire, an additional coronary angiogram was made to document vessel integrity which was reviewed by an independent reviewer. Out-patient visits were scheduled at 30 days and at one year and follow up data were obtained from the electronic patient files.

Statistics

Statistics are mainly descriptive. Continuous data were summarized with the mean ± standard deviation (SD) or median with interquartile range as appropriate. Categorical data was presented as number with percentage (SPSS 25.0, Chicago, USA).

Results

Populations characteristics

One hundred consecutive patients undergoing these measurements were included between august 2016 and October 2019. The median follow up period was: 511 days (range 99 to 1054 days). The patient characteristics are presented in **supplementary table 1**. All measurement details of the 467 absolute flow measurements are outlined in **supplementary table 2**.

Periprocedural safety

Measurements were successful and well-tolerated in all patients. Procedural complications are displayed per measurement and infusion rate in **table 1**.

Only two patients experienced chest discomfort during infusion without electrocardiographic abnormalities. In 2.6% of all measurements (N=12), bradycardia or atrioventricular block occurred.

In one patient, dissection of the RCA was observed, more proximal than the tip of the infusion catheter. The dissection caused angina and transient ST-elevation and required stenting. After review by two independent interventionalists this complication was adjudicated to the Amplatz-guiding damaging the coronary ostium.

Follow up 30 days, at 12 months and beyond 12 months

Follow up at 30 days was obtained in all patients and follow up of at least one year in 71 patients. The median follow up period was 511 days for all patients (range from 99 to 1054 days). Events at follow-up are presented in **table 2**. None of the events occurred in the index coronary artery. In 71 patients follow-up beyond 1 year was obtained without any procedure related adverse events (see **supplements** for complete patient specific details).

Discussion

The present data demonstrate safety of invasive measurement of coronary blood flow and microvascular resistance. Except for short transient conduction disturbances in 2.6% of measurements, no noticeable periprocedural side effects were observed and at follow-up at 30 days and 1 year, not any vessel-related event like cardiac death, MI, or index vessel related revascularization had occurred. Our study extends the experience of Xaplantaris et al[5] and Everaars et al[4] on the safety of this methodology.

Hyperemia and chest discomfort

In our study in only 2 patients mild chest discomfort was noted. This is in contrast to the frequently observed chest pain observed during hyperemia induced by IV adenosine[7].

Wire related complications

As with every intracoronary technique, a small risk of 0.5 %– 2%[8] for vessel damage is associated with guidewire manipulations. In our study, only 1 case of coronary ostium dissection occurred and was most likely caused by the Amplatz#2-catheter. Therefore, the risk of the present technique, does not seem to be different from the very small risk any guide wire based measurements.

Infusion catheter related complications

The Rayflow catheter has a diameter of 0.84mm, comparable to optimal coherence tomography (OCT) or intravascular ultrasound (IVUS) probes with a risk for vessel damage of 0.5-2% in a general population.[9] In our study, not any catheter related complication could be attributed to the catheter, neither periprocedural nor at follow-up.

Limitations

Post-procedure integrity of the coronary artery was assessed by angiography and not with IVUS/OCT. Therefore, minimal vessel injury undetected by the post procedural angiogram cannot be excluded but its clinical relevance would be minimal given the complete absence of any vessel related complications at follow-up. Finally, the results of this study should be confirmed in large multicenter registries.

Conclusion

Selective measurement of absolute coronary blood flow and microvascular resistance with thermodilution and using a specific multisidehole infusion catheter is safe and not related to noticeable adverse events neither periprocedural nor at follow-up.

Impact on daily practice

The results show that this method for invasive assessment of the coronary microcirculation can be used in daily catheterization laboratory practice without noticeable risk or discomfort for the patient.

Funding

None

Conflict statement

DK, MV, JZ, MF, FM, AV, KT, GB, IW, PV, PT: none

NP: Institutional grant; Abbott, Hexacath. Consultant; Abbott, Opsens, GE. Minor equities Philips, ASML, Heartflow.

References

1. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*2010;**362**:886–895.

2. Fearon WF, Balsam LB, Farouque HMO, Caffarelli AD, Robbins RC, Fitzgerald PJ, Yock PG, Yeung AC. Novel index for invasively assessing the coronary microcirculation. *Circulation*2003;**107**:3129–3132.

3. Doucette JW, Corl PD, Payne HM, Flynn AE, Goto M, Nassi M, Segal J. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation*1992;**85**:1899–1911.

4. Everaars H, Waard GA de, Schumacher SP, Zimmermann FM, Bom MJ, Ven PM van de, Raijmakers PG, Lammertsma AA, Götte MJ, Rossum AC van, Kurata A, Marques KMJ, Pijls NHJ, Royen N van, Knaapen P. Continuous thermodilution to assess absolute flow and microvascular resistance: validation in humans using [15O]H2O positron emission tomography. *Eur Heart J*2019;**40**:2350–2359.

5. Xaplanteris P, Fournier S, Keulards DCJ, Adjedj J, Ciccarelli G, Milkas A, Pellicano M, Van't Veer M, Barbato E, Pijls NHJ, De Bruyne B. Catheter-Based Measurements of Absolute Coronary Blood Flow and Microvascular Resistance: Feasibility, Safety, and Reproducibility in Humans. *Circ Cardiovasc Interv*2018;**11**:e006194.

6. Veer M van 't, Adjedj J, Wijnbergen I, Tóth GG, Rutten MCM, Barbato E, Nunen LX van, Pijls NHJ, De Bruyne B. Novel monorail infusion catheter for volumetric coronary blood flow measurement in humans: in vitro validation. *EuroIntervention*2016;**12**:701–707.

7. Lachmann V, Heimann M, Jung C, Zeus T, Verde PE, Kelm M, Bönner F. Feasibility, safety and effectiveness in measuring microvascular resistance with regadenoson. *Clin Hemorheol Microcirc*2019;**71**:299–310.

8. Shaukat A, Tajti P, Sandoval Y, Stanberry L, Garberich R, Burke MN, Gössl M, Henry T, Mooney M, Sorajja P, Traverse J, Bradley SM, Brilakis ES. Incidence, predictors, management and outcomes of coronary perforations. *Catheterization and Cardiovascular Interventions*2019;**93**:48–56.

9. Sijde JN van der, Karanasos A, Ditzhuijzen NS van, Okamura T, Geuns R-J van, Valgimigli M, Ligthart JMR, Witberg KT, Wemelsfelder S, Fam JM, Zhang B, Diletti R, Jaegere PP de, Mieghem NM van, Soest G van, Zijlstra F, Domburg RT van, Regar E. Safety of optical coherence tomography in daily practice: a comparison with intravascular ultrasound. *Eur Heart J Cardiovasc Imaging*2017;**18**:467–474.

Figure 1 legend: Normal RCA with FFR and absolute flow/resistance measurements.

Extensive legend in **online supplements.**

Take-home Table 1: periprocedural events

Variables										Total number of measurements
Periprocedural										
Vessel Measured	**LAD**			**LCx**			**RCA**			
Infusion rate (ml/min)	**15 n=6**	**20 n=119**	**25 n=41**	**15 n=34**	**20 n=103**	**25 n=10**	**15 n=65**	**20 n=82**	**25 n=7**	**Total n=467**
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Perforation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Dissection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)	**1 (0.2)**
Cerebrovascular accident	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Air embolus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Thrombus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
procedural myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Ventricle tachycardia/ Ventricle fibrillation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Vessel spasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
AV-block	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	3 (3.6)	6 (86)	**10 (2.1)**
Bradycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.4)	0 (0)	**2 (0.4)**
Slow flow	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0 (0)**
Frequent ventricular extra systole	0 (0)	1 (0.8)	0 (0)	0 (0)	2 (1.9)	0 (0)	1 (1.5)	2 (2.4)	0 (0)	**6 (1.3)**
Chest pain	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	**2 (0.4)**

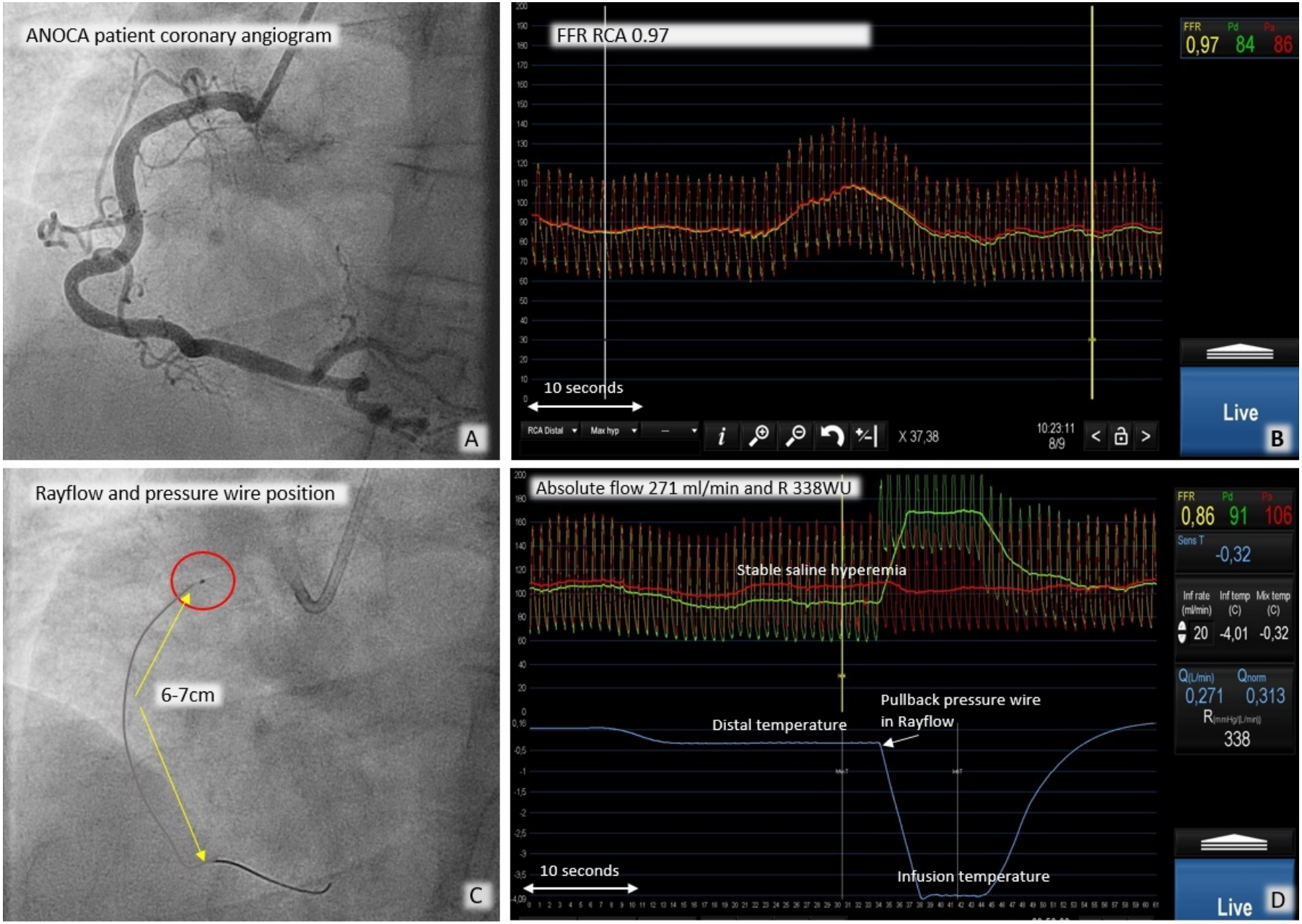
Summary values represent number (%)

Table 2: events at follow up

Clinical outcomes at 30 days follow-up (n=100)	
Death	0 (0%)
Acute Coronary Syndrome	0 (0%)
Revascularization	0 (0%)
Repeated angiography	0 (0%)
Emergency ward visit	0 (0%)
Clinical outcomes at 12 month follow-up (n=71)	
Death	1 (1.4%)*
Cardiac death	0 (0%)
Non-cardiac death	1 (1.4%)*
Acute Coronary Syndrome	1 (1.4%)*
Revascularization	2 (2.8%)*
Repeated angiography	3 (4.2%)*
Emergency ward visit	1 (1.4%)*
Clinical outcomes beyond 12 months (n=71)	
Death	1 (1.4%)*
Cardiac death	0 (0%)
Non-cardiac death	1 (1.4%)*
Acute Coronary Syndrome	0 (0%)
Revascularization	0 (0%)
Repeated angiography	1 (1.4%)*
Emergency ward visit	5 (7.2%)*

* None of them classified as procedure related

Summary values represent number (%)



Supplements Safety study

Overview of contents

Methods

Absolute blood flow and resistance measurement

Cardiac catheterization, absolute blood flow and resistance measurements were performed according to routine. Guiding catheters were advanced as usual and a pressure/temperature wire (Pressure wire X™ Abbott, Saint Paul, USA) was introduced in the ostium of the coronary artery. After proper equalization of pressures, the dedicated Rayflow catheter (Hexacath, Paris) was advanced over the pressure wire and positioned with its tip in the proximal part of the coronary artery (Figure 1 and appendix figure 2). Before saline infusion starts, the temperature is calibrated and body temperature is set to 'zero' (reference temperature). Next, saline infusion is started at a rate of 15-25 ml/min and absolute blood flow in the coronary artery is calculated as previously described.[5,6]

Measurement in short: during steady-state infusion, the temperature of the completely mixed blood and saline (T) is measured in the distal coronary artery and after a steady-state has been reached, the pressure wire is pulled back in the Rayflow catheter to determine the infusion temperature of the saline (Ti). Absolute blood flow is then calculated by the equation:

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

Where Qb is the hyperemic coronary blood flow in ml/min. Ti is the infusion temperature of the saline as measured at the infusion holes of the Rayflow catheter. T is the distal coronary temperature after complete mixing of blood and saline measured by the pressure wire. Qi is the infusion rate of saline in ml/min. The constant 1.08 relates to the difference between the specific heats and densities of blood and saline.

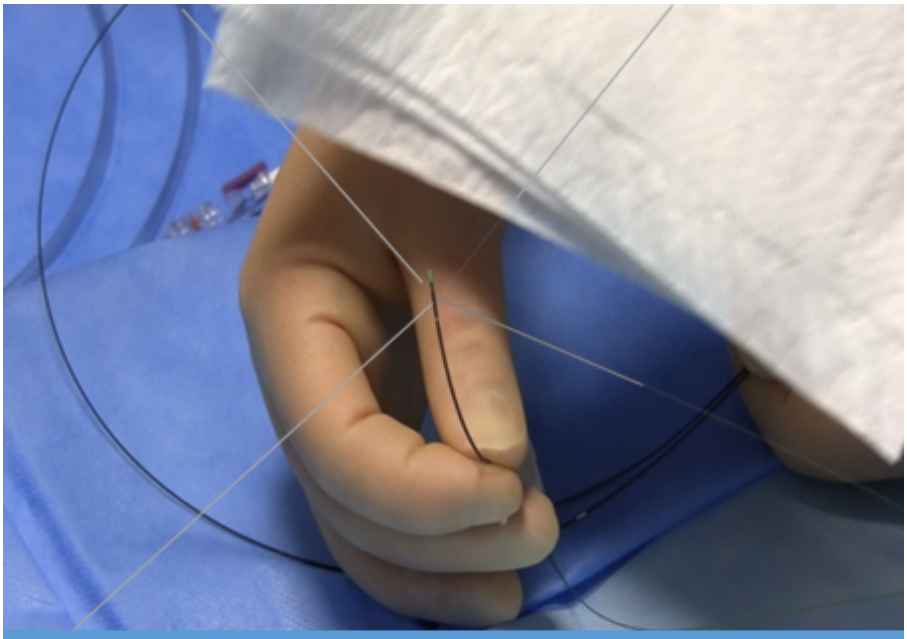
Because also distal coronary pressure (Pd) is recorded simultaneously, the microvascular resistance (R in mmHg/ml/min or Wood Units) can be calculated in analogy to Ohm's law by dividing the distal pressure and flow by the simplified equation below:

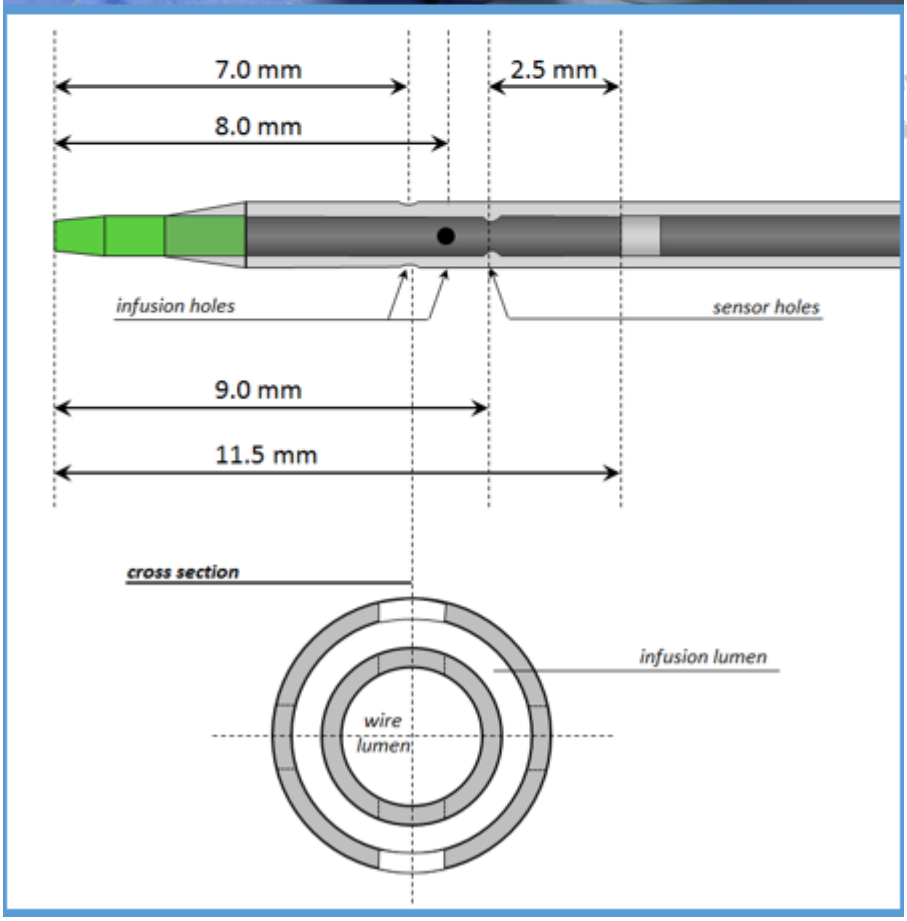
$$R = \frac{Pd}{Qb}$$

All signals are instantaneously displayed on the regular cathlab monitor by software (Coroflow ®, Coroventis, Uppsala, Sweden; figure 1).

Legend: the upper panel shows the homogeneous infusion of saline through the outer catheter holes**.** In the lower panel, a longitudinal and transverse cross-section of the distal part of the infusion catheter is shown.

Supplementary figure 1: infusion catheter profile





Supplementary table 1: baseline characteristics

Number of patients	**100**
Number of coronary arteries	**213**
Number of measurements	**467**
Male gender, N (%)	45 (45)
Age, mean (SD)	62.1 ± 9.5
Medical history	
Hypertension, n (%)	34 (34)
Current smoking, n (%)	10 (10)
Previous smoking, n (%)	25 (25)
Diabetes Mellitus, n (%)	12 (12)
Dyslipidemia, n (%)	37 (37)
Family history of CAD, n (%)	34 (34)
Clinical indication FFR, flow, resistance measurements	
ANOCA/syndrome X	37 (37)
Participation in a clinical trial	43 (43)
Diffuse coronary artery disease	20 (20)

CAD: Coronary Artery disease

CAG: Coronary angiogram

ANOCA: Angina Non Obstructive Coronary Arteries

Summary values represent number (%) or mean ± standard deviation

Supplementary table 2: procedural characteristics

Variables			
	LAD	**LCx**	**RCA**
Coronary arteries n=213	75 (35.2)	67 (31.5)	71 (33.3)
Measurements N=467	166 (35.2)	147 (31.5)	154 (33.3)
Invasive measurements			
Infusion rate			
Qi 15 ml/min	6 (3.6)	34 (23.1)	65 (42.2)
Qi 20 ml/min	119 (71.7)	103 (72.8)	82 (53.2)
Qi 25 ml/min	41 (24.7)	10 (6.8)	7 (4.5)
Hemodynamic parameters			
Pd (mmHg)	78.6 ± 16.1	82.9 ± 16.8	79.5 ± 15.9
Pa (mmHg)	97.8 ± 13.7	95.8 ± 15.3	90.9 ± 16.1
Ti (°C)	4.71 ± 0.81	4.26 ± 0.94	3.94 ±0.95
T (°C)	0.55 ± 0.27	0.65 ± 0.31	0.47 ± 0.22
Q_b (ml/min)	277 ± 100	201 ± 145	215 ± 95
R (WU)	399 ± 175	611 ± 375	508 ± 274

LAD: left anterior descending artery; LCx: left circumflex artery; Pa: central aortic pressure; Pd: distal coronary pressure; Qi: infusion rate of saline; RCA: right coronary artery; R: microvascular resistance; T: distal coronary temperature during continuous thermodilution; Ti: infusion temperature of saline entering into the coronary artery; WU: WoodUnit. 1 Woodunit = 1mmHg/ml/min = 80 dynes/s/cm^{-5}

Summary values represent number (%) or mean ± standard deviation

Follow up

Follow up 30 days and at 12 months

One patient visited the emergency department with chest complaints and went home the same day with an alternative diagnosis of ANOCA.

Three other patient were referred for re-angiography within the first year which revealed identical non-obstructive epicardial coronary anatomy. Two patients underwent **Coronary Artery Bypass** Grafting because of functional significant disease discovered by FFR during the initial catheterization.

One patient presented with an inferior wall infarction due to an in stent thrombosis of the RCA. This ST-elevation myocardial infarction was not procedure-related since measurements had not performed in that particular vessel in this patient. One patient, a 78 year old male, died at home due to pneumonia.

Follow up beyond 12 months

In 71 patients follow-up beyond 1 year was obtained. In this period (367-1054 days) 5 patients visited the emergency department with chest complaints, none of which were classified as an acute coronary syndrome. One patient underwent re-angiography were no obstructive coronary artery disease was found. One patient died because of lung cancer.

Figure legends

Figure 1: Example of absolute blood flow and resistance measurement. Panel A shows a normal right coronary artery of a patient presenting in the catheterization laboratory with chest pain. Panel B shows the FFR measurement in this artery, with a normal FFR of 0.97. Next the Rayflow catheter is advanced over the pressure wire (Panel C) and positioned into the proximal coronary artery. The Rayflow catheter is recognizable by a radiopaque dot at the location of the sideholes at 1cm from its tip (red circle). The distance between the pressure/temperature sensor and tip of the infusion catheter is preferably 6-7cm as shown. In panel D, the actual performance of the measurement is shown. The blue tracing indicates the coronary temperature, which is set to zero before the start of the procedure (left part of panel D). After starting the infusion (20ml/min) and mixture of blood and saline, steady state distal temperature is rapidly achieved (-0.32°C). Next, the wire is pulled back to the tip of the infusion catheter and the temperature of the infused saline is recorded (-4.01°C). All relevant parameters are displayed instantaneously (Panel D, right side). Flow in this RCA is calculated as 271ml/min and resistance of the RCA-territory as 338 Wood Units.