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Safety of absolute coronary flow and microvascular resistance measurements by thermodilution

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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 catheterisation laboratory do not present with significant epicardial stenosis (so-called angina with non-obstructive coronary artery disease [ANOCA])[1].

Most knowledge regarding microvascular resistance has come from non-invasive imaging, from invasive index of microvascular resistance[2], or from Doppler wires[3], all of which are 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 multi-sidehole 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 previously[5]; however, long-term safety and absence of late complications have not yet been described. The present study evaluates the safety of absolute flow measurements, both periprocedural, at 30 days and up to one-year follow-up.

Methods

STUDY DESIGN AND POPULATION

In a total of 100 patients, 213 coronary arteries were assessed, and 467 measurements of absolute blood flow and microvascular resistance were performed. The study was approved by the local independent review board (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 catheterisation, absolute blood flow and resistance measurements were performed according to routine, as previously described **(Figure 1, Supplementary Appendix 1, Supplementary Figure 1)** (complete methods in **Supplementary Appendix 2**)[5,6].

ASSESSMENT OF COMPLICATIONS AND SAFETY AT FOLLOW-UP

During the procedure, clinical, haemodynamic 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 (Hexacath, Rueil-Malmaison, France), an additional coronary angiogram was performed to document vessel integrity which

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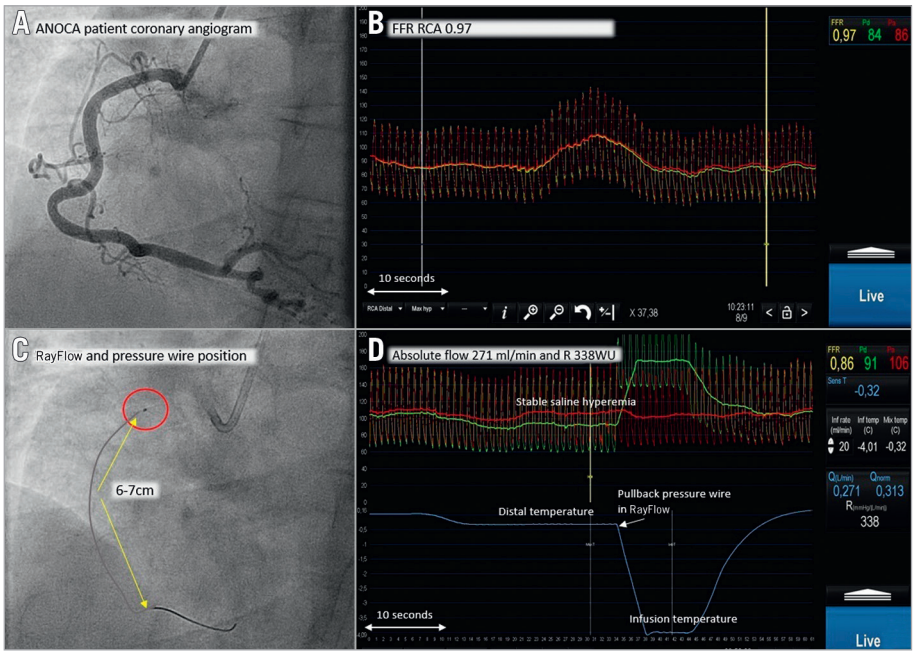

Figure 1. *Procedural example. Normal RCA with FFR and absolute flow/resistance measurements. Extensive legend in Supplementary Appendix 1.*

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.

STATISTICAL ANALYSIS

Statistics are mainly descriptive. Continuous data are summarised as mean±standard deviation (SD) or median with interquartile range, as appropriate. Categorical data are presented as numbers with percentages. Analyses were performed using SPSS Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

POPULATION CHARACTERISTICS

One hundred consecutive patients undergoing these measurements were included between August 2016 and October 2019. Patient characteristics are presented in **Supplementary Table 1**. All measurement details of the 467 absolute flow measurements are shown 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 right coronary artery (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 be the result of Amplatz (Medtronic, Minneapolis, MN, USA) guiding damaging the coronary ostium.

FOLLOW-UP AT 30 DAYS, 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 1,054 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 one year was obtained without any procedure-related adverse events (**Supplementary Appendix 3** for complete patient-specific details).

Discussion

The present data demonstrate the 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. No vessel-related events such as cardiac death, myocardial infarction (MI), or index vessel-related revascularisation had occurred at 30-day and one-year follow-up. Our study extends the experience of Xaplanteris et al[5] and Everaars et al[4] on the safety of this methodology.

HYPERAEMIA AND CHEST DISCOMFORT

In our study, mild chest discomfort was noted in only two patients. This is in contrast to the frequently observed chest pain observed during hyperaemia induced by intravenous (IV) adenosine[7].

Table 1. Periprocedural events.

Variables										Total number of measurements
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-day follow-up (n=100)	
Death	0 (0%)
Acute coronary syndrome	0 (0%)
Revascularisation	0 (0%)
Repeat 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%)*
Revascularisation	2 (2.8%)*
Repeat 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%)
Revascularisation	0 (0%)
Repeat angiography	1 (1.4%)*
Emergency ward visit	5 (7.2%)*

* None of them was classified as procedure-related. Summary values represent number (%).

WIRE-RELATED COMPLICATIONS

As with every intracoronary technique, a small risk of 0.5-2%[8] of vessel damage is associated with guidewire manipulations. In our study, only one 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 of any guidewire-based measurements.

INFUSION CATHETER-RELATED COMPLICATIONS

The RayFlow catheter has a diameter of 0.84 mm, comparable to optical 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, no catheter-related complication could be attributed to the catheter, either periprocedurally or 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; however, 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 multicentre registries.

Conclusion

Selective measurement of absolute coronary blood flow and microvascular resistance with thermodilution and using a specific

multi-sidehole infusion catheter is safe and not related to noticeable adverse events either periprocedurally or at follow-up.

Impact on daily practice

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

Conflict of interest statement

N. Pijls reports institutional grants from Abbott and Hexacath, being a consultant for Abbott, Opsens, and GE, and holding minor equity in Philips, ASML and HeartFlow. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Extensive legend for Figure 1.
Supplementary Appendix 2. Methods.
Supplementary Appendix 3. Follow-up.
Supplementary Figure 1. Infusion catheter profile.
Supplementary Table 1. Baseline characteristics.
Supplementary Table 2. Procedural characteristics.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00074

Supplementary data

Supplementary Appendix 1. Extensive legend for Figure 1

Example of absolute blood flow and resistance measurement. Panel A shows a normal right coronary artery of a patient presenting in the catheterisation 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 in the proximal coronary artery. The RayFlow catheter is recognisable by a radiopaque dot at the location of the side holes at 1 cm from its tip (red circle). The distance between the pressure/temperature sensor and tip of the infusion catheter is preferably 6-7 cm 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 (20 ml/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 271 ml/min and resistance of the RCA territory as 338 Wood units.

Supplementary Appendix 2. Methods

Absolute blood flow and resistance measurement

Cardiac catheterisation, absolute blood flow and resistance measurements were performed according to routine. Guiding catheters were advanced as usual and a pressure/temperature wire (PressureWire™ X; Abbott Vascular, Santa Clara, CA, USA) was introduced into the ostium of the coronary artery. After proper equalisation of pressures, the dedicated RayFlow catheter (Hexacath, Paris, France) was advanced over the pressure wire and positioned with its tip in the proximal part of the coronary artery **(Figure 1, Supplementary Figure 3)**. 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 into 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 hyperaemic coronary blood flow in ml/min and 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 distal coronary pressure (Pd) is also 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 cath lab monitor by software (CoroFlow®; Coroventis, Uppsala, Sweden) **(Figure 1)**.

Supplementary Appendix 3. Patient-specific follow-up data

Follow-up at 30 days and at 12 months

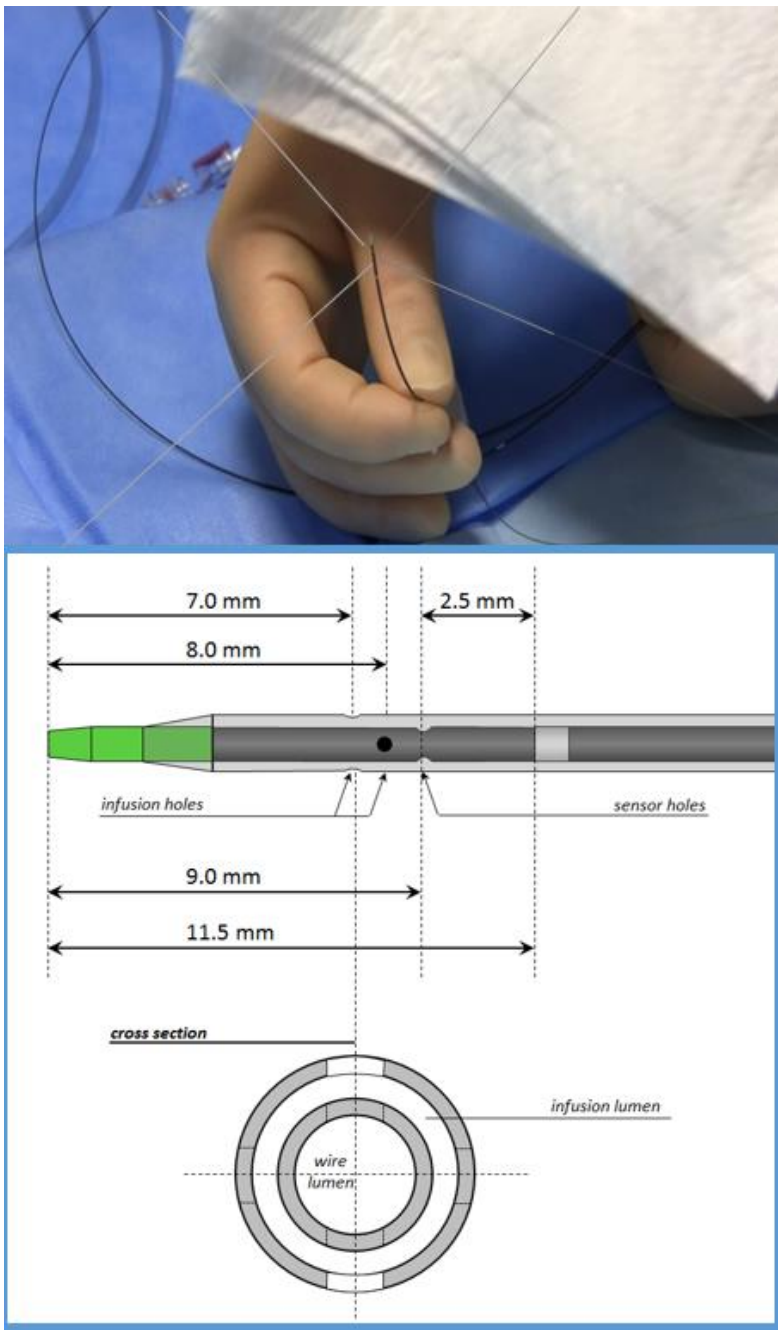
One patient visited the emergency department with chest complaints and went home the same day with an alternative diagnosis of angina with non-obstructive coronary artery disease (ANOCA).

Three other patients 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 fractional flow reserve (FFR) during the initial catheterisation.

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 been 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

Follow-up beyond one year was obtained in 71 patients. In this period (367-1,054 days), five patients visited the emergency department with chest complaints, none of which was classified as an acute coronary syndrome. One patient underwent re-angiography where no obstructive coronary artery disease was found. One patient died because of lung cancer.



Supplementary Figure 1. Infusion catheter profile.

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 Table 1. Baseline characteristics.

Number of patients	**100**
Number of coronary arteries	**213**
Number of measurements	**467**
Male gender, n (%)	45 (45)
Age, years, 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)
Dyslipidaemia, n (%)	37 (37)
Family history of CAD, n (%)	34 (34)
ANOCA/syndrome X	37 (37)
Participation in a clinical trial	43 (43)
Diffuse coronary artery disease	20 (20)

Summary values represent number (%) or mean±standard deviation.
ANOCA: angina with non-obstructive coronary artery disease; CAD: coronary artery disease; CAG: coronary angiogram

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)
Haemodynamic 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

Summary values represent number (%) or mean±standard deviation.
LAD: left anterior descending artery; LCx: left circumflex artery; Pa: central aortic pressure; Pd: distal coronary pressure; Qi: infusion rate of saline; R: microvascular resistance; RCA: right coronary artery; T: distal coronary temperature during continuous thermodilution; Ti: infusion temperature of saline entering into the coronary artery; WU: Wood unit (1 Wood unit=1 mmHg/ml/min=80 dynes/s/cm^{-5})