

Reproducibility of bolus versus continuous thermodilution for assessment of coronary microvascular function in patients with ANOCA

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KEYWORDS

- clinical research
- fractional flow reserve
- miscellaneous
- stable angina

Abstract

Background: A bolus thermodilution-derived index of microcirculatory resistance (IMR) has emerged as the standard for assessing coronary microvascular dysfunction (CMD). Continuous thermodilution has recently been introduced as a tool to quantify absolute coronary flow and microvascular resistance directly. Microvascular resistance reserve (MRR) derived from continuous thermodilution has been proposed as a novel metric of microvascular function, which is independent of epicardial stenoses and myocardial mass.

Aims: We aimed to assess the reproducibility of bolus and continuous thermodilution in assessing coronary microvascular function.

Methods: Patients with angina and non-obstructive coronary artery disease (ANOCA) at angiography were prospectively enrolled. Bolus and continuous intracoronary thermodilution measurements were obtained in duplicate in the left anterior descending artery (LAD). Patients were randomly assigned in a 1:1 ratio to undergo either bolus thermodilution first or continuous thermodilution first.

Results: A total of 102 patients were enrolled. The mean fractional flow reserve (FFR) was 0.86 ± 0.06 . Coronary flow reserve (CFR) calculated with continuous thermodilution (CFR_{cont}) was significantly lower than bolus thermodilution-derived CFR (CFR_{bolus} ; 2.63 ± 0.65 vs 3.29 ± 1.17 ; $p < 0.001$). CFR_{cont} showed a higher reproducibility than CFR_{bolus} (variability: $12.7 \pm 10.4\%$ continuous vs $31.26 \pm 24.85\%$ bolus; $p < 0.001$). MRR showed a higher reproducibility than IMR (variability $12.4 \pm 10.1\%$ continuous vs $24.2 \pm 19.3\%$ bolus; $p < 0.001$). No correlation was found between MRR and IMR ($r = 0.1$, 95% confidence interval: -0.09 to 0.29 ; $p = 0.305$).

Conclusions: In the assessment of coronary microvascular function, continuous thermodilution demonstrated significantly less variability on repeated measurements than bolus thermodilution.

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Abbreviations

ANOCA	angina and non-obstructive coronary artery disease
CFR	coronary flow reserve
CMD	coronary microvascular dysfunction
IMR	index of microvascular resistance
MRR	microvascular resistance reserve
PET	positron emitted tomography
Q	absolute coronary flow
R	absolute microvascular resistance
RRR	resistance reserve ratio

Introduction

Even in the absence of epicardial stenosis, coronary microvascular dysfunction (CMD) is associated with anginal complaints, reduced quality of life, and a worse prognosis¹. The reported prevalence of CMD is highly variable^{2,3}. Arguably, this variability may relate to the heterogeneous clinical definitions of CMD and to the absence of specific, quantitative, and accurate tools for assessing coronary microvascular resistance.

The quintessential metric of coronary microcirculation is its absolute resistance (R_{μ}). In current practice, microvascular resistance is estimated by combining distal coronary pressure and indirect indices of flow, such as mean transit time⁴⁻⁶. For its ease of application and its outcome prediction capacity in the setting of acute coronary syndromes⁷, the index of microcirculatory resistance (IMR) obtained from bolus thermodilution has emerged as one of the reference standards to define CMD.

More recently, continuous intracoronary thermodilution has been proven to precisely quantify volumetric coronary flow (in mL/min) and absolute microcirculatory resistance (in Wood units [WU])⁸⁻¹⁰. Consequently, the microvascular resistance reserve (MRR) obtained with this technique has been proposed as a specific metric for assessing microvascular function independently from epicardial resistance¹¹. The accuracy of continuous thermodilution-derived coronary flow and resistance measurements have been validated *in vitro*⁹ and *in vivo*¹². Before any measurement tools can be used for research or in a clinical setting, their test-retest reliability must be established. The objective of the present study was to perform a head-to-head comparison of the reproducibility of bolus and continuous thermodilution for functional assessment of coronary microcirculation.

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Materials and methods

STUDY DESIGN

From January 2021 to January 2022, patients with angina and non-obstructive coronary artery (ANOCA) at coronary angiography were included in the study. Exclusion criteria were clinical signs or symptoms of congestive heart failure, severe valvular heart disease requiring either surgical or percutaneous intervention, a history of coronary artery bypass graft, the presence of an angiographically significant epicardial stenosis (diameter stenosis [DS] >50% by visual assessment) and a tortuous coronary anatomy in which wire manipulation could be complex. In all patients, microvascular

function was assessed in the left anterior descending coronary artery (LAD) with bolus and continuous thermodilution. All the measurements were performed in duplicate. Patients were randomly assigned in a 1:1 ratio to undergo a bolus thermodilution first or a continuous thermodilution first. After each measurement, a 2-minute waiting period was mandated before the next measurement. The study design and the main findings are summarised in the **Central illustration**.

The protocol was approved by the institutional review board (IRB of the Onze-Lieve-Vrouw Clinic in Aalst, Belgium, Registration number: 2020/033). All patients provided informed consent. The data supporting the findings of this study are available upon reasonable request.

CORONARY ANGIOGRAPHY

Coronary angiography was performed through either radial or femoral arterial access. A 6 Fr guiding catheter was used, and 0.2 mg of intracoronary isosorbide dinitrate was administered. A guidewire equipped with a pressure/temperature sensor (PressureWire X; Abbott) was connected to dedicated software for tracings analysis (CoroFlow Cardiovascular System; Coroventis) and, after zeroing, was advanced through the guiding catheter. The pressures recorded by the pressure/temperature wire and by the fluid-filled guide catheter were equalised close to the tip of the guiding catheter. Next, the wire was advanced into the distal part of the coronary artery, and the temperature zeroed.

CONTINUOUS THERMODILUTION MEASUREMENT

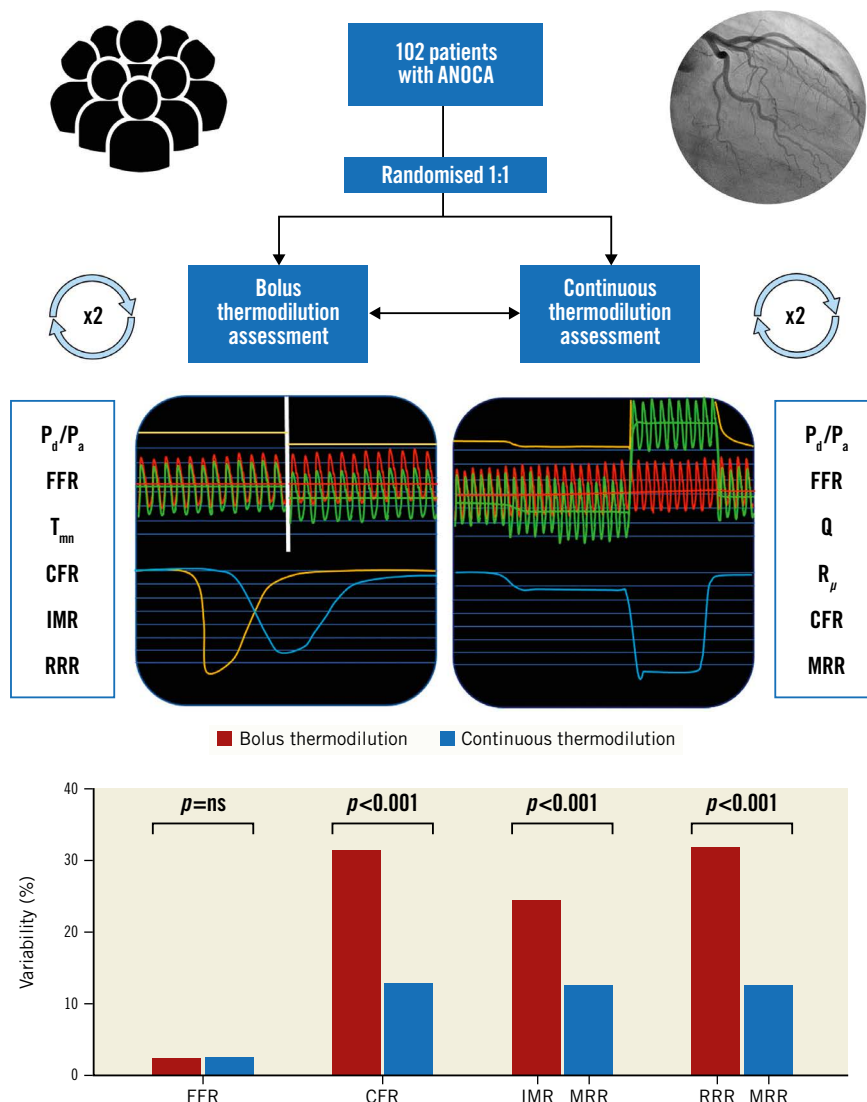
For absolute coronary flow measurement, a dedicated monorail infusion 2.52 Fr microcatheter with 4 distal side holes (RayFlow; HEXACATH) was advanced over the pressure/temperature wire and connected to the 200 cc motorised syringe of an automated injection system (Medrad Stellant; Medrad Inc. [now Bayer]) filled with room temperature saline (typically between 20 and 23°C). The infusion catheter was advanced into the artery being investigated, and its tip was positioned into the first millimetres of the vessel. Absolute resting (Q_{rest}) and hyperaemic (Q_{hyp}) flow measurements were obtained using saline infusion rates of 10 and 20 mL/min, respectively. The infusion pump was automatically programmed to (i) infuse saline at 10 mL/min for 2 minutes to obtain the measurement of the temperature of blood mixed with infused saline (T); then (ii) to switch automatically to 20 mL/min for 1.5 minutes to obtain the measurement of the temperature of blood mixed with infused saline (T) as well as – after a swift pullback of the temperature sensor – the measurement of hyperaemic saline infusion temperature (T_i); and (iii) to switch back to 10 mL/min for 1 minute for the measurement of resting T_i . These techniques allowed for the calculation of resting and hyperaemic flow and resistance in one single procedure¹³.

Absolute coronary flow (Q , mL/min) as derived from continuous thermodilution was calculated by the previously validated equation¹⁴:

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

where Q_i is the infusion rate of saline. Absolute resistance at rest ($R_{\mu,rest}$) and during hyperaemia ($R_{\mu,hyp}$) in WU were calculated as the ratio between the distal coronary pressure (P_d) during each infusion and Q_{rest} or Q_{hyp} , respectively. An $R_{\mu,hyp} >400$ WU was considered

CENTRAL ILLUSTRATION Study design and main results.



CFR: coronary flow reserve; FFR: fractional flow reserve; IMR: index of microvascular resistance; MRR: microvascular resistance reserve; ANOCA: angina and non-obstructive coronary artery; P_d/P_a : aortic pressure; P_d : distal coronary pressure; Q : absolute coronary blood flow; RRR: resistance reserve ratio; R_μ : absolute microvascular resistance; T_{mn} : mean transit time

abnormal¹⁵. Coronary flow reserve, as derived from continuous thermodilution (CFR_{cont}), was calculated as the ratio between Q_{hyp} and Q_{rest} . MRR was calculated as previously described¹¹:

$$MRR = \frac{CFR}{FFR} \frac{P_{a,rest}}{P_{a,hyp}}$$

The formulas used for the calculation of the functional metrics derived from bolus and continuous thermodilution are summarised in **Supplementary Table 1**.

BOLUS THERMODILUTION MEASUREMENT

The basics of CFR and IMR calculation with bolus thermodilution has been described elsewhere^{4,16}. Briefly, three bolus injections

of 3 ml of room temperature saline were performed to assess the mean transit time (T_{mn}) at rest. The three values were averaged. Next, 12 mg of intracoronary papaverine was administered^{17,18}. After reaching steady-state hyperaemia, three bolus injections of 3 ml of saline were repeated to assess the mean transit times at hyperaemia. The software automatically flagged any T_{mn} value that deviated by more than 30% from the average value. These values were replaced with an additional bolus injection. The total number of bolus injections and their respective values were captured in the database. **Supplementary Figure 1** illustrates the total number of bolus injections (accepted and rejected) needed to obtain the final average T_{mn} value. Coronary flow reserve, as derived from bolus

thermodilution (CFR_{bolus}), was calculated as the ratio between the mean transit time at rest ($T_{mn,rest}$) and the mean transit time during hyperaemia ($T_{mn,hyp}$). The IMR was calculated as the product of $P_{d,hyp}$ and $T_{mn,hyp}$. The resistance reserve ratio (RRR) expresses the ratio between basal and hyperaemic microvascular resistance and is calculated as $(P_{d,rest}/T_{mn,rest})/(P_{d,hyp}/T_{mn,hyp})^{19}$. After a 2-minute waiting period, the bolus thermodilution-derived measurements were repeated. An IMR >25 was considered abnormal. The measurement time was defined as the time from the start of the first bolus thermodilution at rest until the completion of the last bolus thermodilution during hyperaemia.

STATISTICS

The distribution of continuous variables was assessed visually by histograms and Q-Q plots. Continuous variables with normal distribution are expressed as mean±standard deviation and non-normally distributed variables as median and interquartile range (IQR). Categorical variables are expressed as count and percentages. Normal ranges are presented as the 5th and 95th percentiles. The Student's t-test and the chi-square test were used to compare differences between continuous and categorical variables, respectively. Pearson's correlation coefficient was used to quantify the associations between individual values for continuous variables. The intraclass correlation coefficient (ICC) was computed using a 2-way mixed-effect model with measures of absolute agreement. A statistical comparison of correlation coefficients was made by using the modified Dunn and Clark's z test for dependent nonoverlapping variables. Variability between two measurements (named A and B) was assessed as relative difference and expressed as a percentage according to the formula:

$$\text{Var}(\%) = \frac{|A-B|}{\frac{(A+B)}{2}} \cdot 100$$

Bland-Altman analysis was used to quantify the agreement between duplicated measurements. Sample size was calculated based on an expected within-subject standard deviation (s_w) of 15%; with a 95% confidence interval and considering 2 measurements (m) performed in each subject (for each method), the minimum required sample size (n) was 85 subjects according to the formula :

$$\frac{1.96}{\sqrt{2n(m-1)}} = 0.15$$

All analyses were performed using R statistical software (R Foundation for Statistical Computing). A p-value <0.05 was considered statistically significant.

Results

BASELINE AND PROCEDURAL DATA

A total of 105 patients were included. In 2 patients, the procedure was aborted due to difficult vessel wiring; in 1 patient, the tracings were not reliable due to kinking of the pressure-wire. The mean age was 66±9 years, and 73 (71.6%) patients were male. The mean left ventricular ejection fraction (LVEF) was 60±10%. The

clinical indications for coronary angiography and for the microvascular function test were anginal chest pain and/or exercise-induced dyspnoea in all patients. Patient characteristics are shown in **Supplementary Table 2**.

Fifty-one patients were randomly assigned to receive bolus thermodilution measurements first and the other 51 to receive continuous thermodilution measurements first. **Table 1** displays bolus and continuous thermodilution-derived measurements. In 15 (14.7%) patients, fractional flow reserve (FFR) was below 0.80 in the distal part of the LAD. The IMR was higher than 25 in 23 (22.5%) patients, and $R_{\mu,hyp}$ was above 400 WU in 45 (44.1%) patients. In 71 (69%) patients, more than three bolus injections were required either for resting or hyperaemic measurements. The number of bolus injections required for each measurement is reported in **Supplementary Figure 1**. The average duration of bolus thermodilution measurements was shorter than continuous thermodilution (2'20"±1'12" vs 4'31"±1'30", respectively; p<0.001).

REPRODUCIBILITY OF THE MEASUREMENTS

Reproducibility data from duplicated measurements of bolus and continuous thermodilution are reported in **Table 1**. **Figure 1**, **Figure 2**, and **Figure 3** illustrate the individual scatter plots, the correlations, and the Bland-Altman analysis of the repeated measurements of Q_{rest} and Q_{hyp} , the repeated measurements of CFR_{cont} and CFR_{bolus} , and the repeated measurements of MRR and IMR, respectively. Multivariable regression analysis showed that none of the clinical factors included in the model influenced the higher variability of CFR_{bolus} (**Supplementary Table 3**). **Supplementary Figure 2-Supplementary Figure 6** display the individual scatter plots, the correlation, and the Bland Altman analysis of all other indices listed in **Table 1**.

Overall, the reproducibility of the hyperaemic values of Q and R_{μ} were significantly better than the corresponding resting values (**Table 1**).

When taking into account only the first T_{mn} for the calculation of IMR and CFR, the reproducibility did not improve (first T_{mn} vs average of the 3 bolus injections: IMR variability=27.3±22.1% vs 24.2±19.3%; p=0.278; CFR variability=34.3±26.8% vs 31.3±24.8%; p=0.407).

COMPARISON BETWEEN BOLUS AND CONTINUOUS THERMODILUTION

The average FFR assessed with the continuous thermodilution was slightly but significantly lower than FFR assessed with intracoronary papaverine (0.82±0.07 vs 0.86±0.06; p<0.001) (**Supplementary Figure 7**).

As illustrated in the **Central Illustration** and **Figure 4**, the test-retest variability of the indices obtained by continuous thermodilution was lower than that of the indices obtained by bolus thermodilution. In particular, the variability of CFR_{cont} was significantly lower than that of CFR_{bolus} (12.8% vs 31.3%; p<0.001). Also, the variability of MRR was significantly smaller than that of IMR and RRR (12.4% vs 23.2% vs 31.8%; p<0.001). Overall,

Table 1. Mean and SD values of bolus and continuous thermodilution measurements performed in duplicates. The order of the measurements was randomly assigned.

	1 st measurement	2 nd measurement	Average	R (95% CI)	Variability (%)	Bias (SD)	ICC (95% CI)
Continuous thermodilution							
P_d/P_a	0.91±0.04	0.90±0.05	0.91±0.04	0.81 (0.73-0.86)	1.79±3.39	0.008 (0.03)	0.77 (0.67-0.84)
FFR	0.82±0.07	0.81±0.07	0.82±0.07	0.91 (0.87-0.94)	2.39±2.75	0.008 (0.03)	0.90 (0.85-0.93)
Q_{rest} (mL/min)	80±27	87±33	83±29	0.80 (0.72-0.86)	17.98±13.99*	-7.35 (19.63)	0.77 (0.64-0.85)
Q_{hyp} (mL/min)	203±66	218±79	211±71	0.89 (0.85-0.93)	11.89±11.54*	-13.92 (35.48)	0.87 (0.78-0.91)
$R_{\mu,rest}$ (WU)	1,142±355	1,104±403	1,121±359	0.78 (0.69-0.85)	16.58±13.51 [†]	38.34 (252.48)	0.78 (0.68-0.84)
$R_{\mu,hyp}$ (WU)	411±139	393±132	401±132	0.89 (0.84-0.92)	11.10±10.84 [†]	14.80 (65.29)	0.88 (0.83-0.92)
CFR_{cont}	2.65±0.69	2.60±0.70	2.62±0.65	0.78 (0.70-0.85)	12.74±10.41 [‡]	0.05 (0.45)	0.78 (0.70-0.85)
MRR	3.18±0.84	3.19±0.85	3.19±0.80	0.81 (0.73-0.87)	12.44±10.06 [§]	-0.006 (0.52)	0.81 (0.74-0.87)
Bolus thermodilution							
P_d/P_a	0.92±0.04	0.92±0.04	0.92±0.04	0.79 (0.71-0.86)	1.74±2.28	0.007 (0.02)	0.78 (0.69-0.85)
FFR	0.86±0.06	0.86±0.06	0.86±0.06	0.88 (0.82-0.92)	2.34±2.95	0.004 (0.03)	0.87 (0.82-0.91)
$T_{mn,rest}$ (s)	0.86±0.38	0.80±0.36	0.83±0.35	0.77 (0.68-0.84)	22.81±20.06	0.05 (0.25)	0.76 (0.67-0.83)
$T_{mn,hyp}$ (s)	0.27±0.14	0.29±0.17	0.28±0.15	0.83 (0.75-0.88)	23.09±18.46	-0.01 (0.09)	0.81 (0.74-0.87)
CFR_{bolus}	3.47±1.44	3.11±1.27	3.27±1.18	0.50 (0.34-0.63)	31.26±24.85 [‡]	0.36 (1.36)	0.48 (0.32-0.62)
IMR	19.42±10.54	20.79±11.64	20.10±10.54	0.81 (0.73-0.86)	24.24±19.27 [‡]	-1.34 (6.97)	0.80 (0.71-0.86)
RRR	4.25 (1.74)	3.76 (1.63)	4.00 (1.45)	0.49 (0.33-0.62)	31.75±26.27 [§]	0.48 (1.70)	0.47 (0.30-0.61)

[†]comparison between CFR_{cont} and CFR_{bolus} , $p<0.001$; *comparison between Q_{rest} and Q_{hyp} , $p<0.001$; [‡]comparison between $R_{\mu,rest}$ and $R_{\mu,hyp}$, $p=0.002$; [§]comparison between MRR and IMR, $p<0.001$; [‡]comparison between MRR and RRR, $p<0.001$. CI: confidence interval; CFR_{bolus} : coronary flow reserve calculated with bolus thermodilution; CFR_{cont} : coronary flow reserve calculated with continuous thermodilution; FFR: fractional flow reserve; ICC: intraclass correlation coefficient; IMR: index of microvascular resistance; MRR: microvascular resistance reserve; P_a : aortic pressure; P_d : distal coronary pressure; Q_{hyp} : absolute hyperaemic coronary flow; Q_{rest} : absolute coronary flow at rest; $R_{\mu,rest}$: absolute microvascular resistance at rest; $R_{\mu,hyp}$: absolute microvascular resistance during hyperaemia; RRR: resistance reserve ratio; R_{μ} : absolute microvascular resistance; s: seconds; $T_{mn,hyp}$: mean transit time during hyperaemia; $T_{mn,rest}$: mean transit time at rest; WU: Wood units

the mean CFR_{cont} was significantly lower than the mean CFR_{bolus} (2.63±0.65 and 3.29±1.17, respectively; $p<0.001$) (**Supplementary Figure 7**). The higher variability of CFR_{bolus} was not influenced by any of the clinical characteristics of the patients and is, therefore, related only to the technique itself (**Supplementary Table 3**). CFR_{cont} and CFR_{bolus} showed a modest correlation and a weak agreement ($R=0.40$; $p<0.001$; $ICC=0.27$ [0.05-0.46]; $p=0.007$) (**Figure 5**). Using a CFR threshold of 2.5 or 2, the percentage of disagreement between CFR_{cont} and CFR_{bolus} was 35.3% and 12.7%, respectively (**Supplementary Figure 8**). MRR showed a mild correlation with the RRR but did not correlate with the IMR (**Figure 6**). There was no correlation between the IMR and $R_{\mu,hyp}$ (**Supplementary Figure 9**).

Discussion

SUMMARY OF RESULTS

This is the first study to compare head-to-head the reproducibility of bolus and continuous thermodilution in assessing coronary microvascular function. Overall, the indices obtained by continuous coronary thermodilution have a higher reproducibility than corresponding indices derived from bolus thermodilution. In particular, the variability of CFR is approximately three times lower when derived from continuous thermodilution than when derived from bolus thermodilution, and the variability of MRR is approximately two times lower than that of the IMR. In addition, the

absolute value of CFR obtained by continuous thermodilution was lower than the CFR derived from bolus thermodilution. Finally, hyperaemic measurements of Q , R_{μ} , and T_{mn} tend to be more reproducible than their corresponding resting measurements.

ACCURACY AND REPRODUCIBILITY

The clinical utility of any measurement depends on both accuracy (i.e., how close a measured value is to the true value) and reproducibility (i.e., the degree to which repeated measurements give the same results). The accuracy of Q as derived from continuous thermodilution has been validated *in vitro* for values ranging from 50 to 350 mL/min¹⁴. These values cover the range of flow commonly encountered in coronary arteries at rest and during hyperaemia. The accuracy of Q and microvascular R as derived from continuous thermodilution has been also validated in humans by using [¹⁵O₂]H₂O positron emitted tomography (PET) during hyperaemia by Everaars et al¹².

When the noise of repeated measurements is large (low reproducibility), individual decision-making will be noisy as well²⁰. In addition, any mechanistic study or therapeutic trial, which would both involve repeated measurements, would be flawed. In the field of CMD, of which the pathophysiology remains largely unknown and for which any specific treatment is lacking, the usage of a metric with a high degree of accuracy and reproducibility is required. The present data indicate that, overall, continuous thermodilution is more reproducible than bolus thermodilution to assess coronary

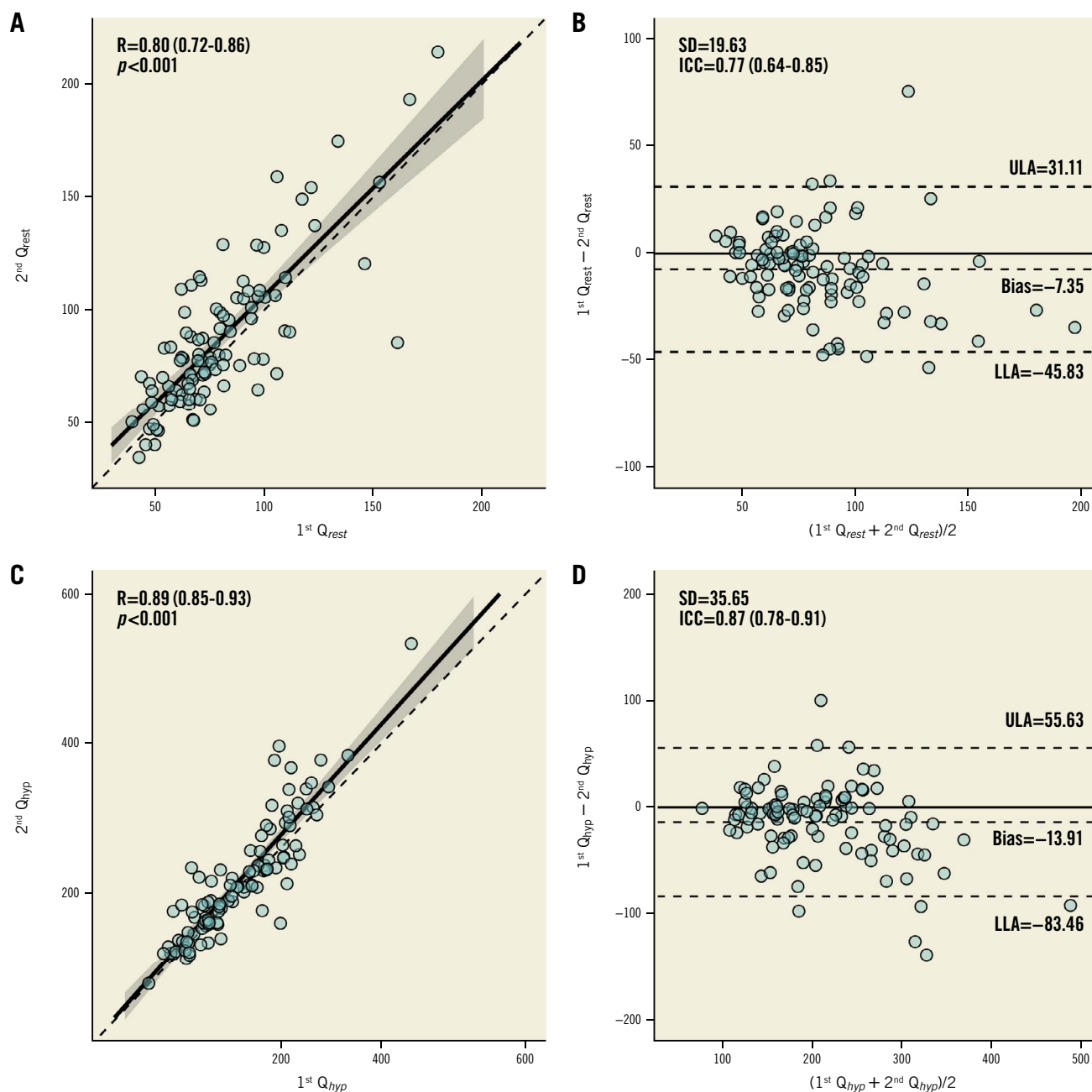


Figure 1. Reproducibility of Q_{rest} and Q_{hyp} . Scatter plots (A,C) and Bland-Altman plots (B,D) for repeated measurements of Q_{rest} and Q_{hyp} . ICC: intraclass correlation coefficient; LLA: lower limit of agreement; Q_{hyp} : absolute hyperaemic coronary flow; Q_{rest} : absolute coronary flow at rest; R: Pearson correlation coefficient; SD: standard deviation; ULA: upper limit of agreement

microvascular function. It can be speculated that this relates to the fact that continuous thermodilution is almost operator-independent. In addition, during continuous thermodilution, a prolonged steady-state is reached, while bolus thermodilution relies on the decay of a thermodilution curve that lasts less than one cardiac cycle. We have to note, however, that the reproducibility of pressure-derived metrics like FFR remains markedly higher than that of coronary flow. This likely relates to the stability of pressure measurements, the simultaneous assessment of P_d and P_a , and the linear relationship between P_d and P_a during hyperaemia.

THERMODILUTION TO ASSESS MICROVASCULAR FUNCTION

Coronary microvascular dysfunction is increasingly recognised as an important factor of chest pain and additional medical costs. The development of new therapeutic strategies for improving CMD is hampered by the absence of appropriate animal models and of direct visualisation of the microcirculation, but even more fundamentally, by the difficulties in quantifying microvascular resistance. The latter can currently be approximated by indices using surrogates of flow, among which is the T_{mn} derived from bolus thermodilution⁴.

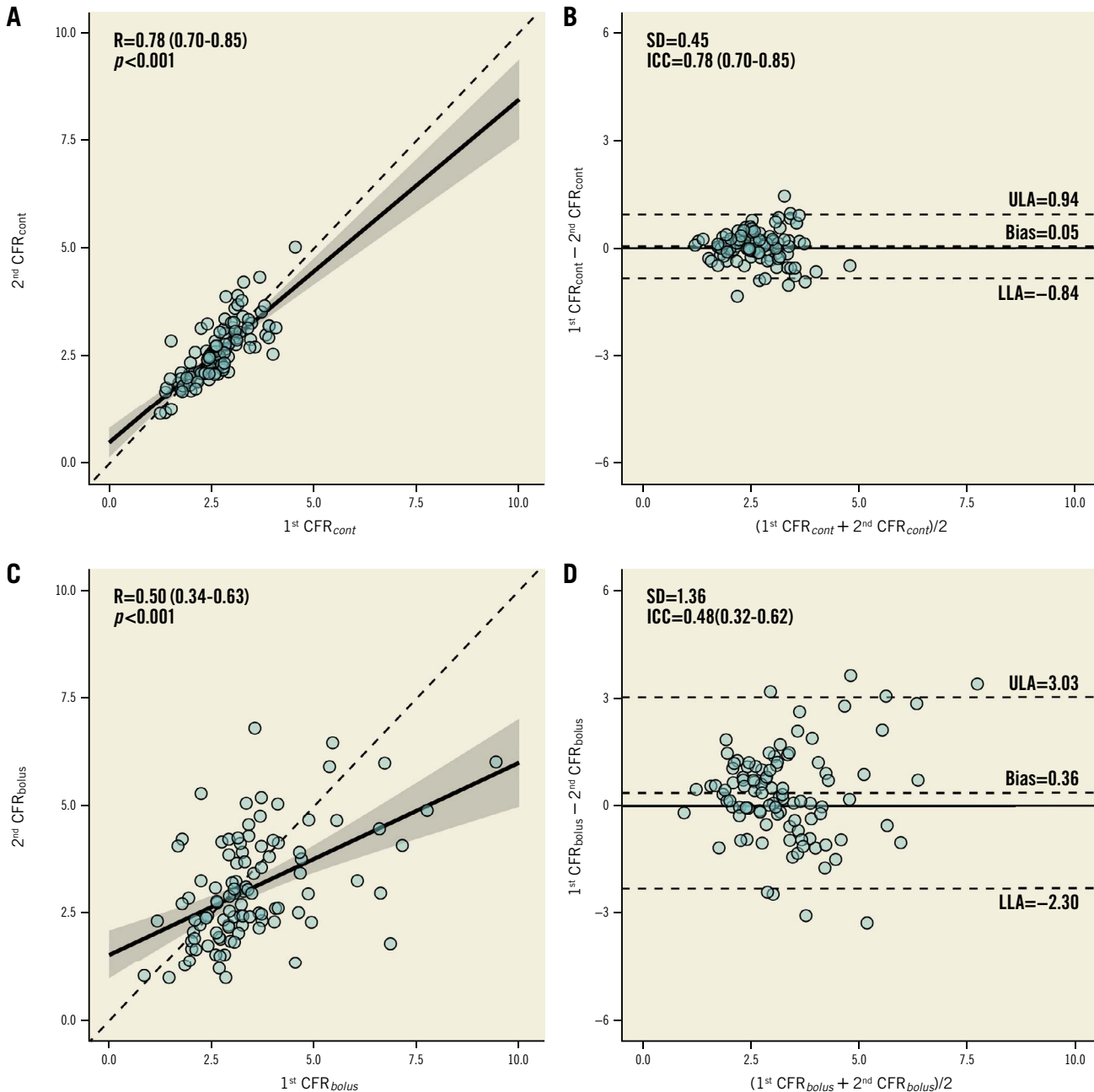


Figure 2. Reproducibility of CFR_{cont} and CFR_{bolus} . Scatter plots and Bland-Altman plots for repeated measurements of CFR_{cont} (A,B) and CFR_{bolus} (C,D). CFR_{cont} : coronary flow reserve calculated with continuous thermodilution; CFR_{bolus} : coronary flow reserve calculated with bolus thermodilution; ICC: intraclass correlation coefficient; LLA: lower limit of agreement; R: Pearson correlation coefficient; SD: standard deviation; ULA: upper limit of agreement

Currently, the IMR^5 derived from the T_{mn} and distal coronary pressure is easy to obtain and is considered the invasive standard of reference to diagnose CMD^{1,6}. This technique, however, presents some limitations, mainly related to the fact that manual injection of saline accounts for some variance in the measurements²¹. In addition, the duration of the measurements is shorter than the duration of one single heart beat. This is why both resting and hyperaemic measurements are repeated three times and the values averaged when the agreement between these values is

acceptable (i.e., less than 30% deviation from each other). In the present study, this agreement between the three resting values and the three hyperaemic values was obtained in a minority of cases. In 69% of patients, more than three bolus injections were required.

In the present study, higher values of CFR were observed when derived from bolus thermodilution than from continuous thermodilution. It is likely that a hand injection of a bolus of saline in a system with a very low resistance may exaggerate the acceleration

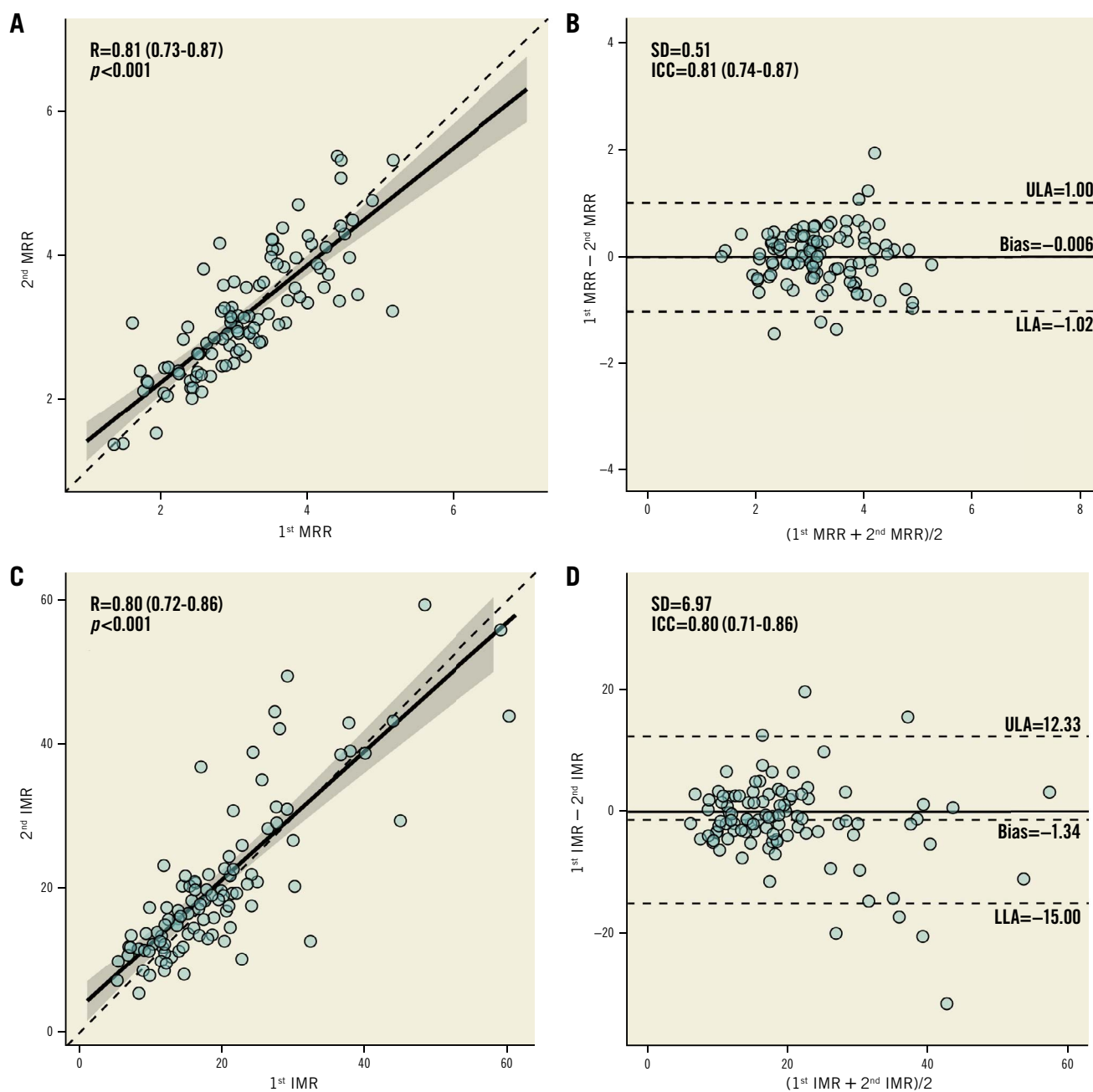


Figure 3. Reproducibility of MRR and IMR. Scatter plots and Bland-Altman plots for repeated measurements of MRR (A,B) and IMR (C,D). ICC: intraclass correlation coefficient; IMR: index of microvascular resistance; LLA: lower limit of agreement; MRR: microvascular resistance reserve; R: Pearson correlation coefficient; RRR: resistance reserve ratio; SD: standard deviation; ULA: upper limit of agreement

of coronary flow, thus leading to a shorter T_{mn} and higher CFR values. Other authors recently reported supraphysiological values of CFR when derived from bolus thermodilution²². Previous studies have shown that CFR_{bolus} tends to overestimate Doppler-derived CFR with a very modest correlation between the two parameters^{21,22}. Similarly, Everaars et al found a weaker correlation between CFR_{bolus} and PET-derived CFR²¹ than between Doppler-derived CFR and PET-derived CFR. Taking into account only the first T_{mn} value to calculate CFR and the IMR did not improve the reproducibility of the measurements. Furthermore, it has been

shown that the IMR does not correlate with $R_{\mu, hyp}^{23}$. Alternatively, it might be speculated that the presence of an infusion catheter might increase epicardial resistance and, consequently, reduce hyperaemic flow and CFR_{cont} . This was not observed in the present study (**Supplementary Table 4**), but it cannot be formally excluded when measurements are obtained in vessels with smaller diameters. Yet, while the presence of the infusion catheter might influence CFR, it does not influence MRR, precisely because any epicardial resistance is accounted for, thus making MRR specific for the microcirculation.

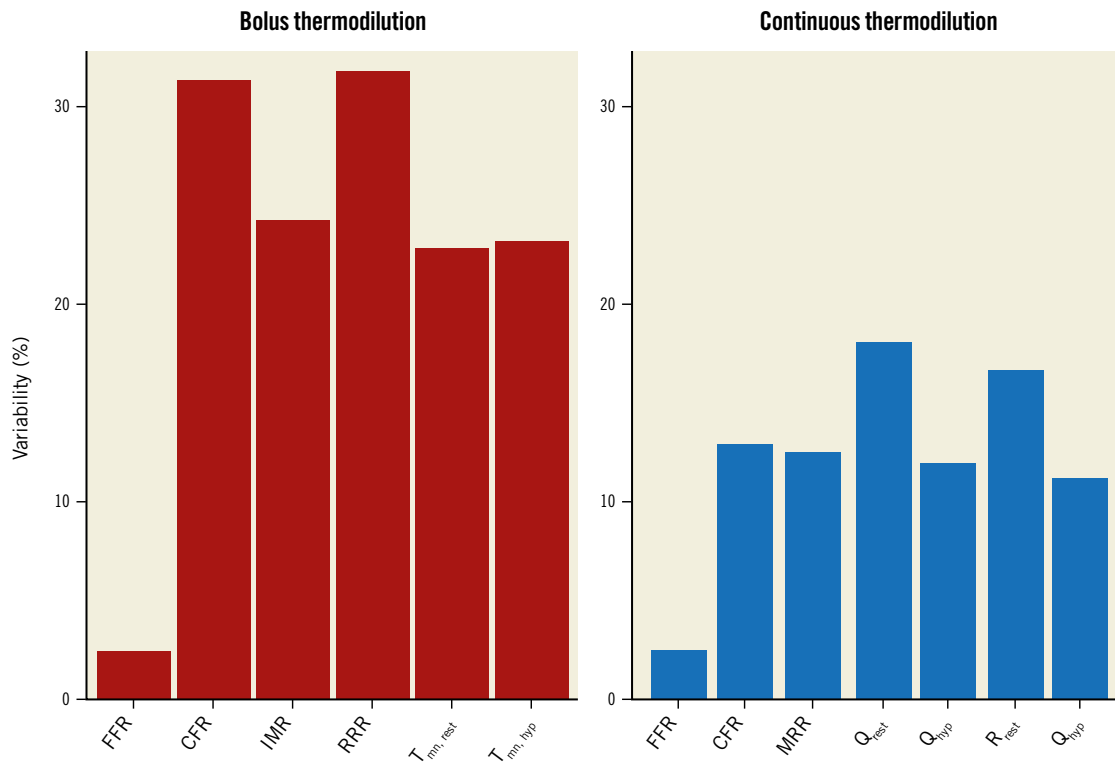


Figure 4. Variability of bolus thermodilution- and continuous thermodilution-derived measurements. Barplots with the variability (expressed as %) of the main indices derived by bolus and continuous thermodilution. CFR: coronary flow reserve; FFR: fractional flow reserve; IMR: index of microvascular resistance; MRR: microvascular resistance reserve; Q_{hyp} : absolute hyperaemic coronary flow; Q_{rest} : absolute coronary flow at rest; RRR: resistance reserve ratio; $R_{\mu,hyp}$: absolute resistance during hyperaemia; $R_{\mu,rest}$: absolute resistance at rest; $T_{mn,hyp}$: mean transit time during hyperaemia; $T_{mn,rest}$: mean transit time at rest

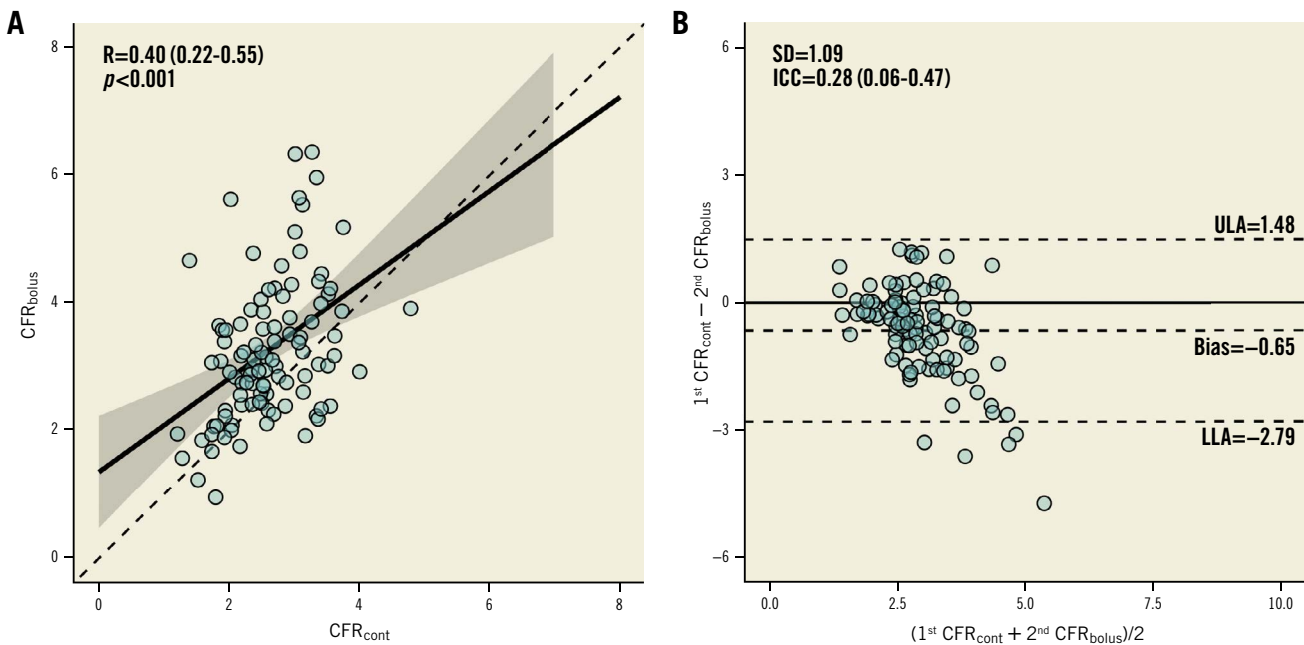


Figure 5. Correlation between bolus and continuous thermodilution-derived CFR. A scatter plot (A) and a Bland-Altman plot (B) showing the correlation and the agreement between CFR_{cont} and CFR_{bolus} . CFR_{bolus} : coronary flow reserve calculated with bolus thermodilution; CFR_{cont} : coronary flow reserve calculated with continuous thermodilution; ICC: intraclass correlation coefficient; LLA: lower limit of agreement; R: Pearson correlation coefficient; SD: standard deviation; ULA: upper limit of agreement

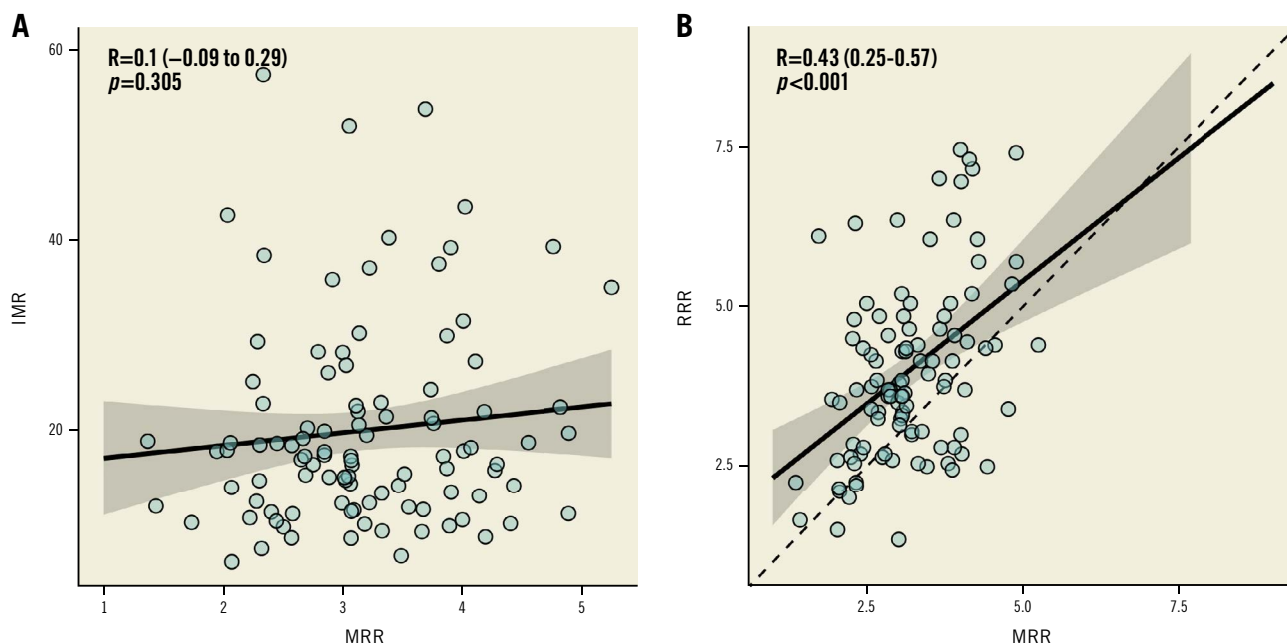


Figure 6. Correlation between MRR and IMR-RRR. Scatter plot showing the correlation between MRR and IMR (A) or RRR (B). IMR: index of microvascular resistance; MRR: microvascular resistance reserve; R: Pearson correlation coefficient; RRR: resistance reserve ratio

No correlation was found between MRR and the IMR. This likely relates to conceptual differences between these two indices. As the IMR reflects hyperaemic microvascular resistance while MRR reflects the vasodilatory capacity of the microcirculation, thus accounting for resting conditions.

THERMODILUTION AND CLINICAL OUTCOME

The relation between the IMR and clinical outcome has been shown in patients with ST-elevation myocardial infarction (STEMI). An IMR value above 40 after primary percutaneous coronary intervention (PCI) has been associated with significantly higher mortality as compared to lower post-PCI IMR values⁷. In patients with STEMI, it is well established that a post-PCI “sluggish flow” or “no-reflow” observed at angiography after a successful primary PCI is a sign of a poor recovery of left ventricular function and a poor clinical outcome. This “no-reflow” phenomenon has been ascribed to intravascular factors as well as to perivascular oedema²⁴. Since the T_{mn} is the reverse of flow velocity and is, therefore, the physiological counterpart of the progression of contrast medium in the epicardial conduit, the presence of “no-reflow” goes along with significantly prolonged T_{mn} and, thus, with very high values of the IMR²⁵. In patients with STEMI, IMR values above 40 immediately after recanalisation of the artery by primary PCI were associated with higher mortality after one year⁷. In these patients, extreme values of IMR (median 60.5, IQR 44.1-74.5) were found, and the IMR value correlated negatively with the global left ventricular ejection fraction after 6 months²⁶. In stable patients, however, the pathophysiology of abnormal resistance is quite different and depends on several, mainly extravascular, factors. The range of

IMR values found in chronic coronary syndrome (CCS) patients is markedly lower. In addition, an IMR value of 25 was proposed as a threshold for distinguishing normal from abnormal microvascular function in CCS patients, almost twice as low as the threshold used after primary PCI^{27,28}.

Consequently, in these stable patients, the relationship between IMR values and clinical outcome is weaker than in the acute setting¹. We recently proposed a new approach based on continuous thermodilution and allowing the measurement of coronary flow and microvascular resistances in absolute terms¹⁴. Yet, even when quantified in absolute terms, Q , R_{μ} , and CFR depend on myocardial mass and the presence of epicardial stenoses²⁹. Therefore, the concept of MRR was developed to be specific to the coronary microcirculation, i.e., independent of myocardial mass and epicardial resistance¹¹. On top of these theoretical advantages, the present study indicates that MRR based on continuous thermodilution is two to three times more reproducible than the IMR and RRR derived from bolus thermodilution.

Limitations

The present study only assessed and compared the reproducibility of bolus and continuous thermodilution. The study did not investigate the accuracy of the results by comparison with a standard of reference. Both bolus and continuous thermodilution have been previously compared separately with [¹⁵O]H₂O PET^{12,21}.

Also, interobserver reproducibility of the results of bolus and continuous thermodilution was not assessed.

In the present study, papaverine was used as hyperaemic agent. Although there is no direct comparison, the hyperaemic effects of

papaverine and saline (as infused by the RayFlow catheter) can be assumed to be similar since the hyperaemic effects of saline and adenosine are similar^{17,30}.

Finally, despite the accuracy and reproducibility of continuous thermodilution, its adoption is currently limited by the availability and cost of the RayFlow catheter.

Conclusions

The reproducibility of continuous thermodilution-derived measurements of Q, R_μ, CFR, and MRR is superior to similar measurements derived from bolus thermodilution. MRR derived from continuous thermodilution was shown to be highly reproducible for assessing the function of the microcirculation. Future prospective studies are warranted to address the clinical impact of these metrics.

Impact on daily practice

Accuracy and reproducibility are indispensable prerequisites for the clinical utility of any new metrics. Our findings illustrate that the reproducibility of continuous intracoronary thermodilution is higher than for bolus thermodilution, mainly because the former technique is operator independent.

Conflict of interest statement

G. Esposito is supported by a research grant from the CardioPaTh PhD Program. P. Paolisso is supported by a research grant from the CardioPaTh PhD Program. D. Bertolone is supported by a research grant from the CardioPaTh PhD Program. E. Barbato declares speaker fees from Abbott Vascular, Boston Scientific, and GE Healthcare. C. Collet reports receiving research grants from Biosensor, GE Healthcare, Medis Medical Imaging, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott Vascular; and consultancy fees from HeartFlow, OpSens, Pie Medical Imaging, Abbott Vascular, and Philips. B. De Bruyne has an institutional consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens, GE Healthcare, and Corovantis Research; has received institutional research grants from Abbott Vascular, Corovantis Research, CathWorks, and Boston Scientific; and holds minor equities in Philips, Siemens, GE Healthcare, Edwards Lifesciences, HeartFlow, OpSens, and Celiad. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Functional metrics derived from bolus and continuous thermodilution.

Supplementary Table 2. Baseline characteristics.

Supplementary Table 3. Multivariate analysis for the predictors of the variability of CFR_{bolus} .

Supplementary Table 4. Effect of the infusion microcatheter on flow and CFR.

Supplementary Figure 1. Number of bolus injections performed.

Supplementary Figure 2. P_d/P_a agreement with both continuous and bolus thermodilution.

Supplementary Figure 3. FFR agreement with both continuous and bolus thermodilution.

Supplementary Figure 4. Scatter plot and Bland-Altman plot for repeated measurements of microvascular resistance.

Supplementary Figure 5. Repeatability of T_{mn} at rest and during hyperaemia.

Supplementary Figure 6. Reproducibility of RRR.

Supplementary Figure 7. Comparison of physiological indices assessed with bolus and continuous thermodilution.

Supplementary Figure 8. Reclassification rate.

Supplementary Figure 9. IMR and $R_{\mu,hyp}$.

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Supplementary data

Supplementary Table 1. Functional metrics derived from bolus and continuous thermodilution.

Q (mL/min)	$1.08 \cdot \frac{T_i}{T} \cdot Q_i$
R_μ (WU)	$\frac{P_d}{Q}$
CFR_{cont}	$\frac{Q_{rest}}{Q_{hyp}}$
MRR	$\frac{CFR}{FFR} \cdot \frac{P_{a,rest}}{P_{a,hyp}}$
CFR_{bolus}	$\frac{T_{mn,rest}}{T_{mn,hyp}}$
IMR	$P_{d,hyp} \cdot T_{mn,hyp}$
RRR	$\frac{P_{d,rest} \cdot T_{mn,rest}}{P_{d,hyp} \cdot T_{mn,hyp}}$

Q: absolute coronary blood flow; R_μ : absolute microvascular resistance; T_i : infusion temperature; T: mixed temperature; P_d : distal coronary pressure; FFR: fractional flow reserve; P_a : aortic pressure; CFR_{cont} : coronary flow reserve (derived from continuous thermodilution); MRR: microvascular resistance reserve; CFR_{bolus} : coronary flow reserve (derived from bolus thermodilution); T_{mn} : mean transit time; IMR: index of microvascular resistance; RRR: resistance reserve ratio.

Supplementary Table 2. Baseline characteristics.

	Overall (N=102)
Gender Male	73 (71.6)
Age	65.9 ± 9.3
Bmi	29.5 ± 20.9
Smoker	36 (35.3)
Current Smoker	20 (19.6)
Hypertension	68 (66.7)
Diabetes	19 (18.6)
Dyslipidaemia	74 (72.5)
CAD History	14 (13.7)
Previous PCI	20 (19.6)
Previous MI	13 (12.7)
Previous PCI LAD	16 (15.7)
Previous MI LAD	9 (8.8)
Creatinine	0.94 ± 0.22
GFR	78.3 ± 15.7
CCS	
0 (or exercise-induced dyspnoea)	6 (6)
1	61 (61)
2	23 (23)
3	4 (3)
4	6 (6)
Atrial fibrillation	4 (4.0)
LVEF	59.7 ± 9.9
ACEI/ARBS	51 (50)
Statins	66 (64.7)
Beta-Blockers	41 (40.2)
Calcium Blockers	27 (26.5)
Insulin	4 (3.9)
Oral Antidiabetic	9 (8.8)
Anticoagulation	10 (9.8)
Aspirin	42 (41.2)
P2Y12 Inhibitor	14 (13.7)

CAD: Coronary Artery Disease. PCI: Percutaneous Coronary Interventions. MI: Myocardial infarction. LAD: Left Anterior Descending Artery. GFR: Glomerular Filtration Rate. CCS: Canadian Cardiovascular Society Angina Class. LVEF: Left Ventricular Ejection Fraction. ACEI: Angiotensin-converting enzyme inhibitors. ARBs: Angiotensin II Receptor Blockers.

Supplementary Table 3. Multivariate analysis for the predictors of the variability of CFR_{bolus}.

Multivariate analysis shows none of the clinical factors included in the model is an independent predictor of the higher variability of CFR_{bolus}

	Beta Coeff	STD Error	T value	P
Intercept	85.0	36.47	2.33	0.022
Male sex	-1.11	6.13	-0.18	0.856
Age	-0.50	0.32	-1.55	0.125
Diabetes	-2.45	6.76	-0.36	0.717
Dyslipidemia	-8.00	5.85	-1.37	0.174
Previous PCI LAD	3.28	10.21	0.32	0.748
Previous MI LAD	-5.78	12.98	-0.44	0.657
GFR	-0.25	0.19	-1.38	0.168
Sinus Rhythm	6.59	13.15	0.50	0.617
F statistic 0.824. P-value 0.583. Residual standard error 25.02				

PCI: percutaneous coronary intervention. LAD: left anterior descending artery. MI: Myocardial Infarction. GRD: glomerular filtration rate.

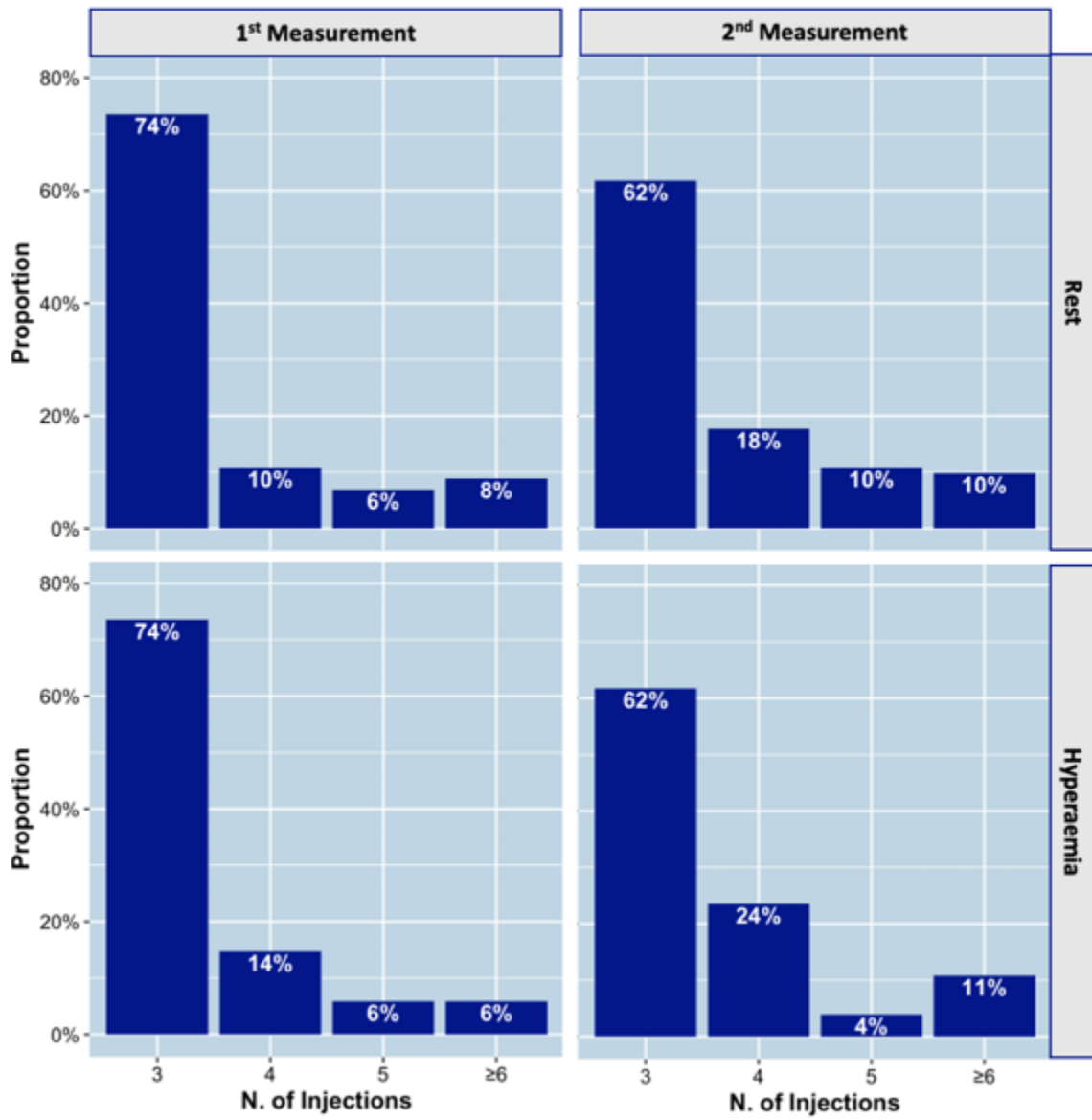
Supplementary Table 4. Effect of the infusion microcatheter on flow and CFR.

As the infusion catheter itself may limit the coronary flow, absolute flow and coronary flow reserve were calculated with and without the microcatheter according to the following formulas:

- Q is the absolute coronary flow calculated as $Q=1.08*(Ti/T)*Qi$
- $Q_N = Q/FFR_{cont}$ (FFR measured with the Rayflow)
- $Q_C = Q_N \cdot FFR$ (FFR measured without the Rayflow)

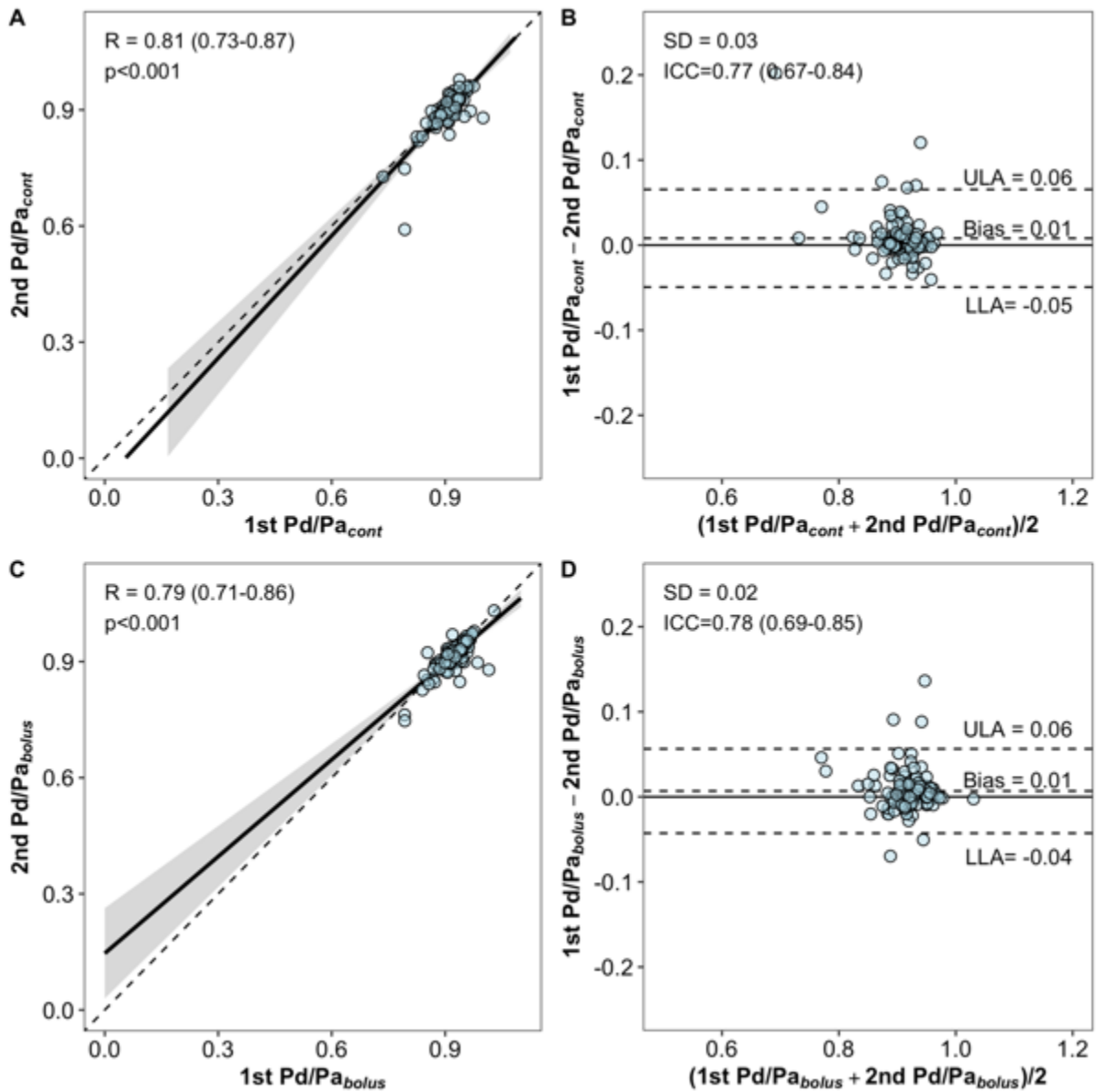
$Q_{rest} = 83 \pm 29$ ml/min	$Q_{rest} = 83 \pm 29$ ml/min	p=0.723
$Q_{hyp} = 211 \pm 71$ ml/min	$Q_{c,hyp} = 220 \pm 74$ ml/min	p=0.320
CFR = 2.62±0.65	CFR _c = 2.69±0.68	p=0.461

Q_N : absolute coronary flow normalized for the FFR measured by continuous thermodilution,
 Q_{rest} : absolute coronary flow at rest; Q_{hyp} : absolute hyperemic coronary flow; $Q_{c,hyp}$: absolute hyperemic flow calculated in the absence of the Rayflow catheter in-situ; CFR: coronary flow reserve; CFR_c: coronary flow reserve calculated in the absence of the RayFlow Catheter in situ.



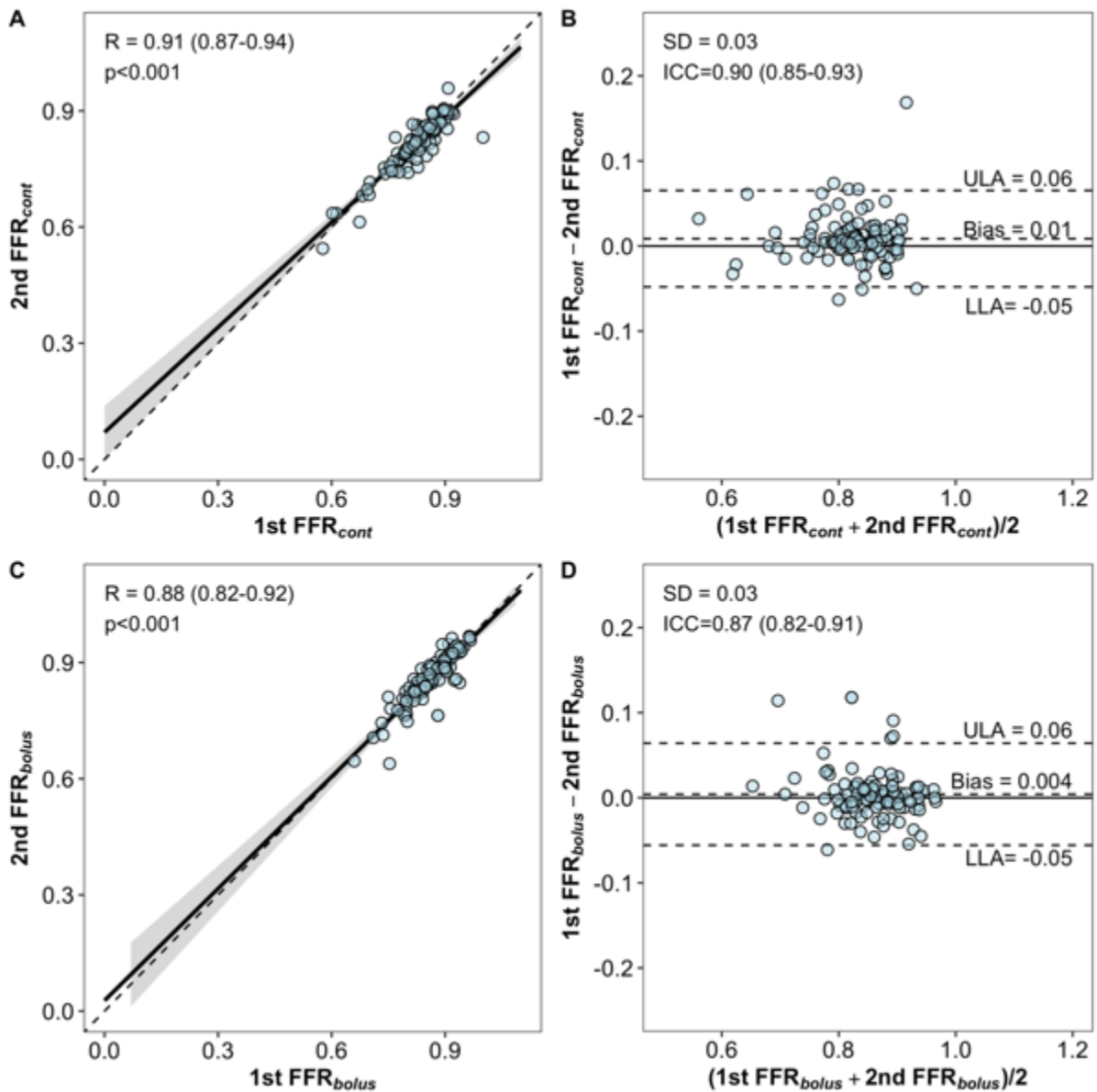
Supplementary Figure 1. Number of bolus injections performed.

Bar plot showing the proportion of bolus injections required for each bolus thermodilution measurement.



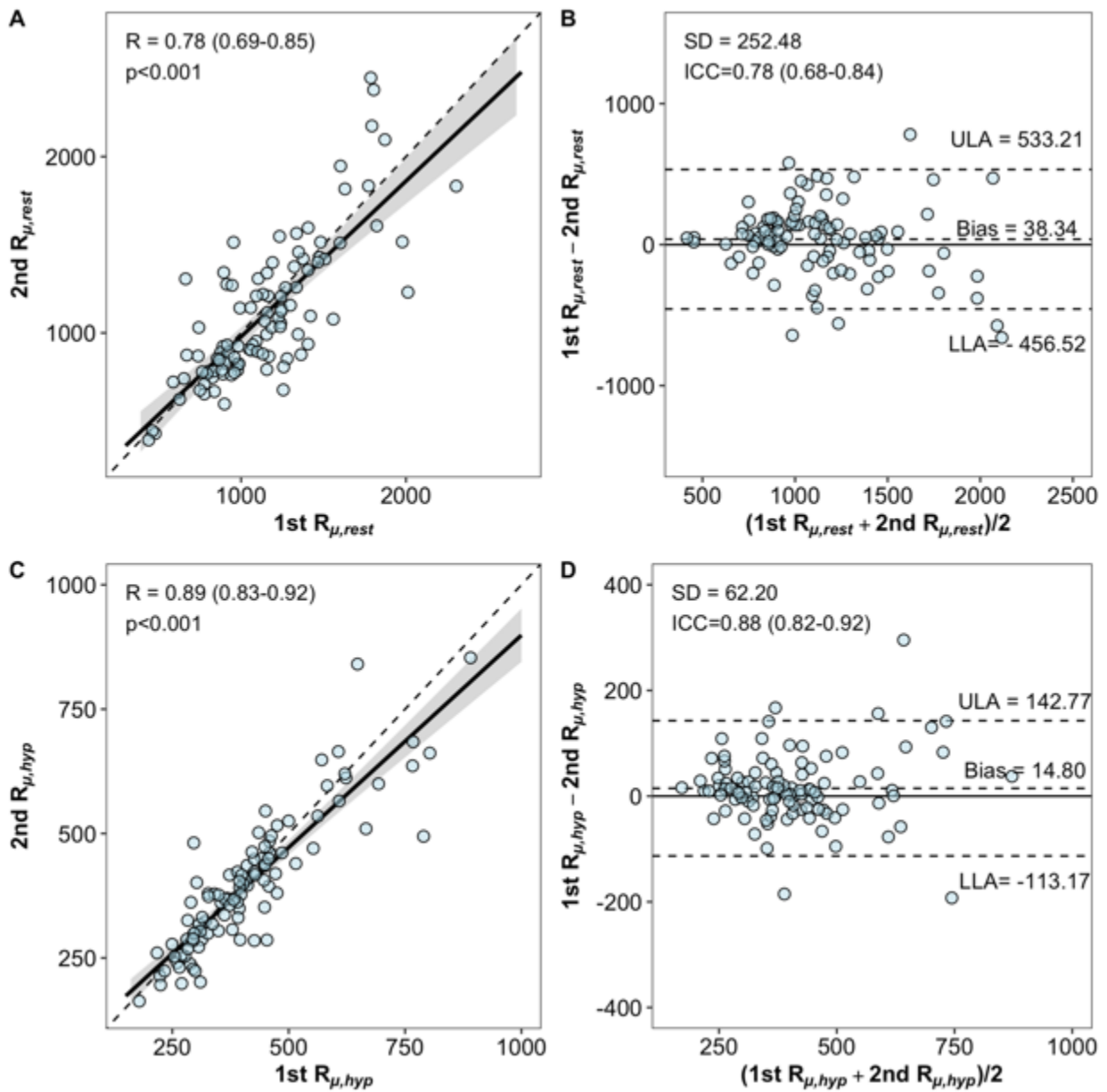
Supplementary Figure 2. P_d/P_a agreement with both continuous and bolus thermodilution.

Linear correlation and Bland-Altman plot of the P_d/P_a assessed with continuous intracoronary thermodilution (panel A and B) and with bolus thermodilution (panel C and D)



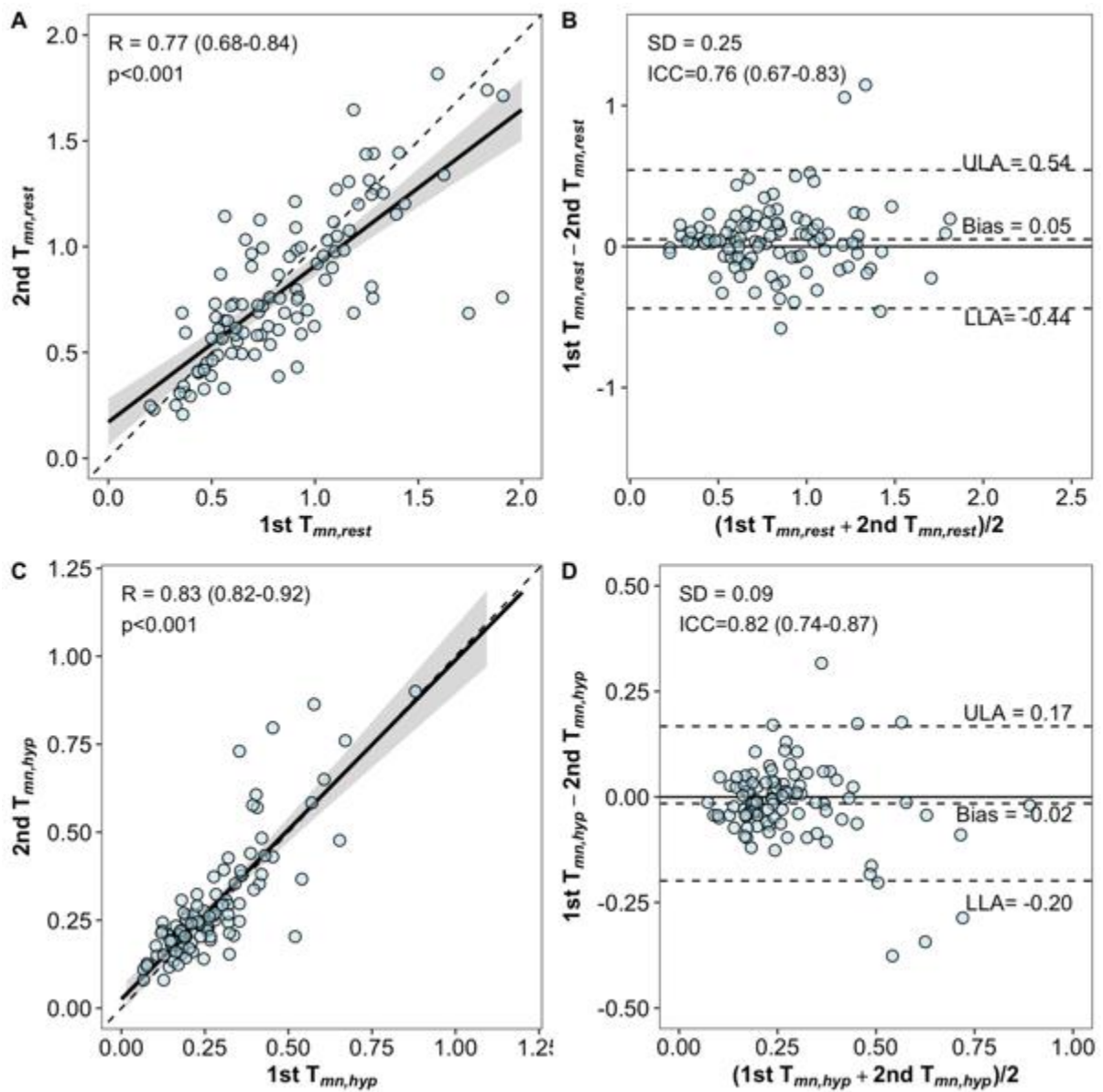
Supplementary Figure 3. FFR agreement with both continuous and bolus thermodilution.

Linear correlation and Bland-Altman plot of the FFR assessed with continuous intracoronary thermodilution (panel A and B) and with bolus thermodilution (panel C and D)



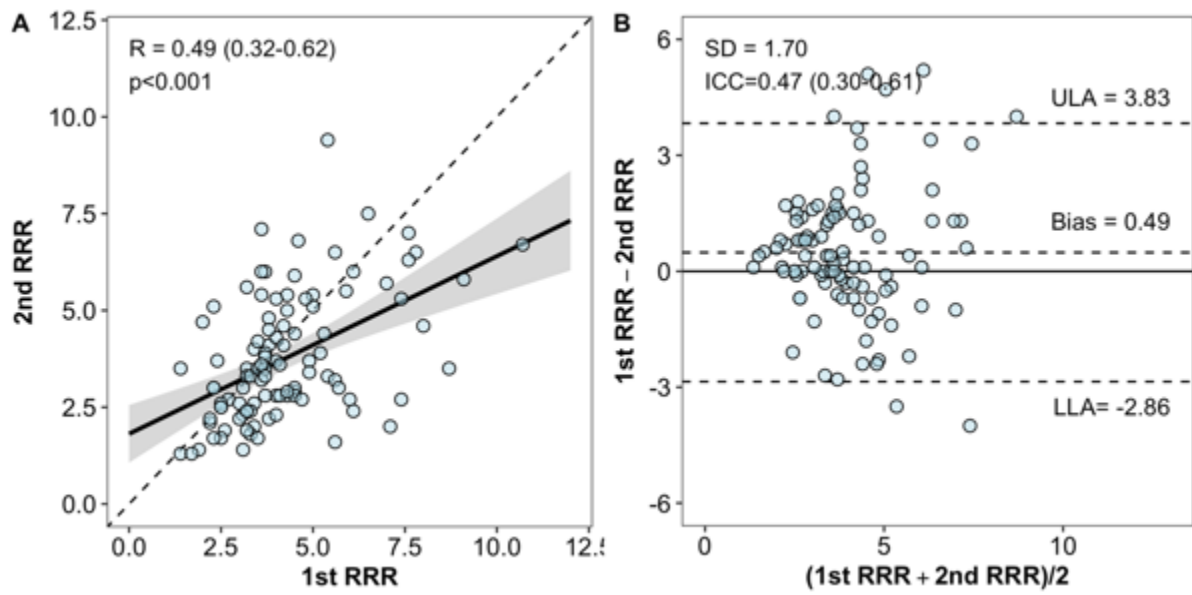
Supplementary Figure 4. Scatter plot and Bland-Altman plot for repeated measurements of microvascular resistance.

Absolute microvascular resistance can be measured with intracoronary continuous thermodilution. Correlation and agreement of $R_{\mu,rest}$ and $R_{\mu,hyp}$ are shown in panel A-B and C-D respectively.



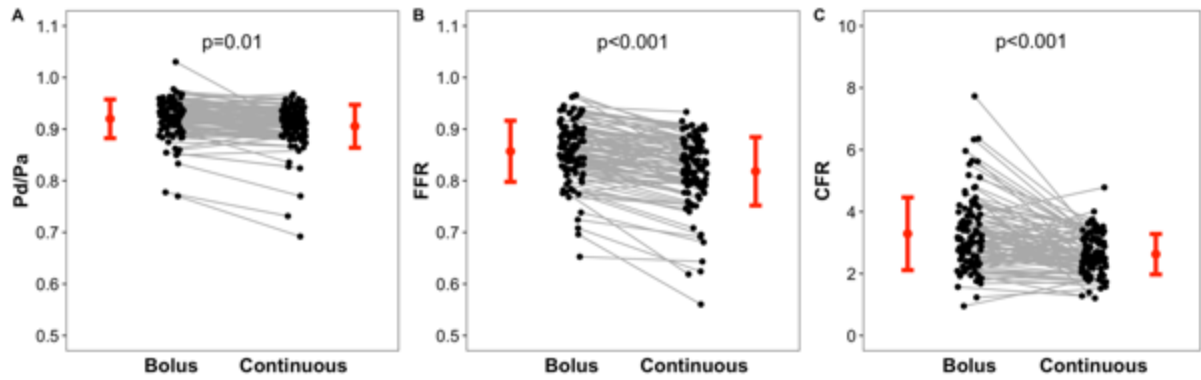
Supplementary Figure 5. Repeatability of T_{mn} at rest and during hyperaemia.

Scatter Plot and Bland-Altman Plot for repeated measurements of T_{mn} at rest (panel A and B) and during hyperemia (panel C and D).



Supplementary Figure 6. Reproducibility of RRR.

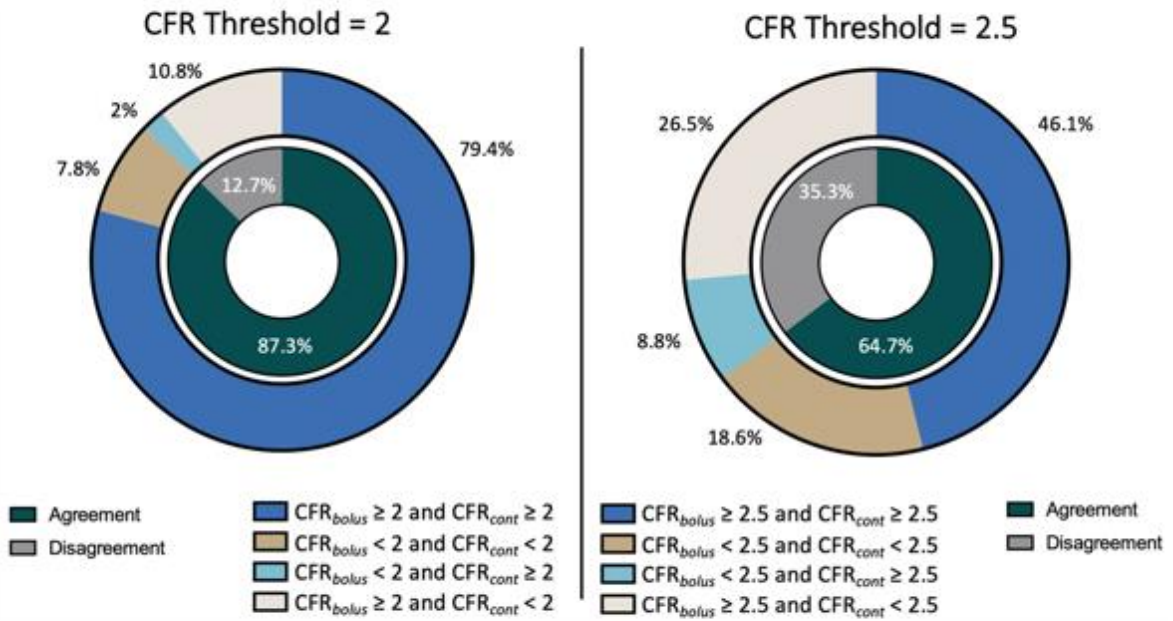
Scatter Plot (panel A) and Bland-Altman Plot (panel B) for repeated measurements of RRR.



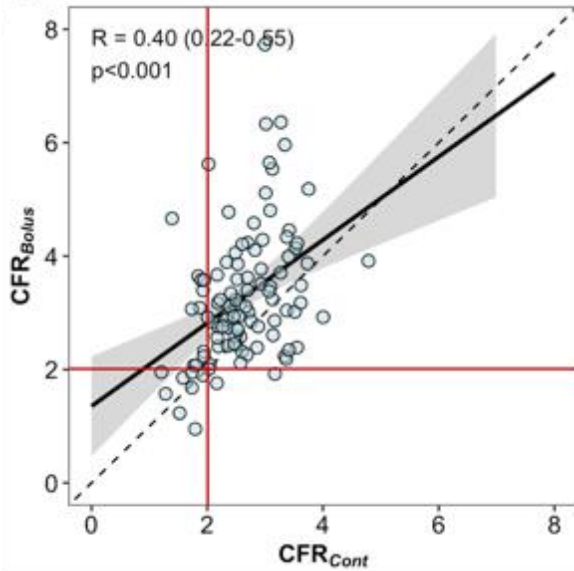
Supplementary Figure 7. Comparison of physiological indices assessed with bolus and continuous thermodilution.

Strip-chart showing mean, standard deviation and individual values of Pd/Pa (panel A), FFR (panel B) and CFR (panel C) assessed with both bolus and continuous thermodilution. Overall, mean values of all the three indices were significantly lower when assessed with continuous thermodilution as compared to bolus thermodilution.

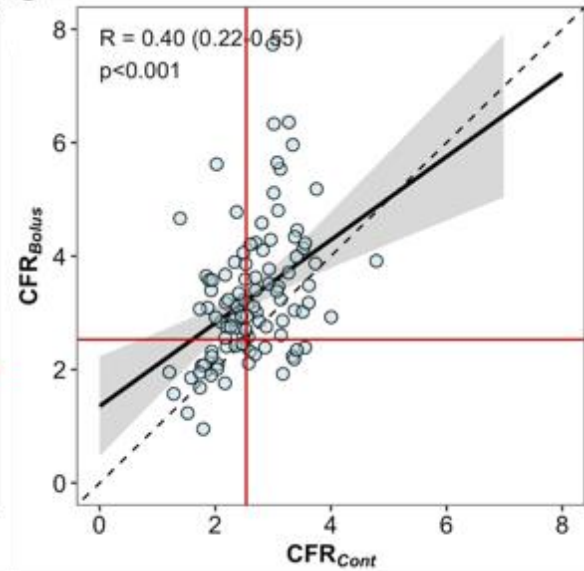
A



B



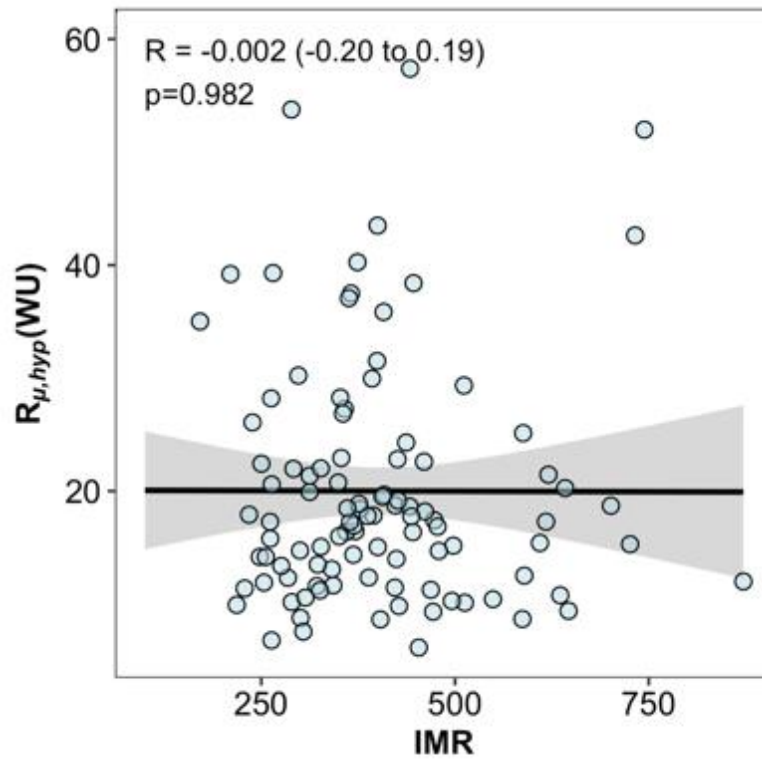
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Supplementary Figure 8. Reclassification rate.

A) Donut Chart showing the agreement between bolus and continuous thermodilution when using a CFR threshold of 2 or 2.5. B) and C) Scatter plot of the correlation between CFR_{cont} and CFR_{bolus} with the red lines showing the intercept for CFR threshold of 2 and 2.5 respectively.

CFR_{cont} : Coronary flow reserve assessed by continuous thermodilution; CFR_{bolus} : Coronary Flow reserve assessed by bolus thermodilution.



Supplementary Figure 9. IMR and $R_{\mu,hyp}$.

Scatter Plot showing the correlation between IMR and $R_{\mu,hyp}$.