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Automation of intracoronary continuous thermodilution for absolute coronary flow and microvascular resistance measurements

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Abstract

Aim: Microvascular resistance reserve (MRR) as derived from continuous intracoronary thermodilution specifically quantifies microvasculature function. As originally described, the technique necessitates reinstrumentation of the artery and manual reprogramming of the infusion pump when performing resting and hyperemic measurements. To simplify and to render this procedure operator-independent, we developed a fully automated method. The aim of the present study is to validate the automated procedure against the originally described one.

Methods and Results: For the automated procedure, an infusion pump was preprogrammed to allow paired resting-hyperemic thermodilution assessment without interruption. To validate the accuracy of this new approach, 20 automated measurements were compared to those obtained in the same vessels with conventional paired resting-hyperemic thermodilution measurements (i.e., with a sensor pullback at each infusion rate and manual reprogramming of the infusion pump).

A close correlation between the conventional and the automated measuring technique was found for resting flow (Q_{rest} : $r = 0.89$, mean bias = 2.52; SD = 15.47), hyperemic flow (Q_{hyper} : $r = 0.88$, mean bias = -2.65; SD = 27.96), resting microvascular resistance ($R_{\mu-rest}$: $r = 0.90$, mean bias = 52.14; SD = 228.29), hyperemic microvascular resistance ($R_{\mu-hyper}$: $r = 0.92$, mean bias = 12.95; SD = 57.80), and MRR (MRR: $r = 0.89$, mean bias = 0.04, SD = 0.59).

Procedural time was significantly shorter with the automated method ($5'25'' \pm 1'23''$ vs. $4'36'' \pm 0'33''$, $p = 0.013$).

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; ICC, intraclass correlation coefficient; IQR, interquartile range; MRR, microvascular resistance reserve; Q, absolute coronary flow; Q_{rest} , resting absolute coronary flow; Q_{hyper} , hyperemic absolute coronary flow; R_{μ} , absolute microvascular resistance; $R_{\mu-rest}$, resting absolute microvascular resistance; $R_{\mu-hyper}$, hyperemic microvascular resistance; SD, standard deviation; T, temperature of blood mixed with infused saline; T_i , temperature of infused saline.

Conclusion: Continuous intracoronary thermodilution-derived measurements of absolute flow, absolute resistance, and MRR can be fully automated. This further shortens and simplifies the procedure when performing paired resting-hyperemic measurements.

KEYWORDS

continuous intracoronary thermodilution, coronary flow reserve, coronary physiology, microvascular function, microvascular resistance reserve

1 | INTRODUCTION

Recent studies validated continuous coronary thermodilution for the invasive measurement of absolute coronary flow (Q , in ml/min). The measurements can be obtained during hyperemia^{1,2} and at rest.³ From these volumetric flow measurements and the simultaneous measurements of distal coronary pressure, microvascular resistance (R_{μ} , in Wood units), fractional flow reserve (FFR), coronary flow

reserve (CFR), and microvascular resistance reserve (MRR) can be simultaneously computed, providing a comprehensive framework of epicardial and microvascular coronary physiology.^{4,5}

A number of technical developments have been introduced to allow absolute Q and R_{μ} measurements to be easily applied in humans: (a) a combined pressure and temperature sensor-tipped guidewire, (b) a dedicated monorail infusion microcatheter to enable immediate and complete mixing of saline and blood, (c) a

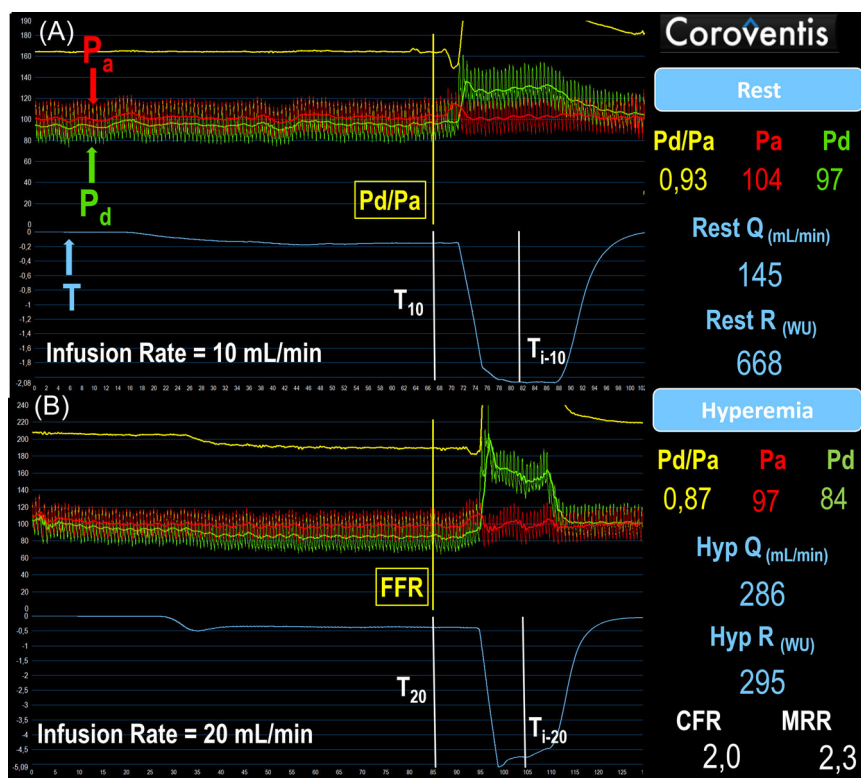


FIGURE 1 Conventional paired resting-hyperemic coronary flow measurement with continuous intracoronary thermodilution. Example of resting (upper panel) and hyperemic (lower panel) continuous thermodilution measurements necessitating two pullback maneuvers of the sensor (conventional method). For the execution of continuous thermodilution at rest, the infusion pump is programmed to provide infusion of saline at a flow rate of 10 ml/min, during which the temperature of blood mixed with saline at 10 ml/min (T_{10}) is measured distally in the vessel. After a swiftly proximal withdraw of the sensor at the tip of the infusion microcatheter, also the temperature of infused saline at 10 ml/min (T_{i-10}) is measured. The resting measurement is completed. For the execution of continuous thermodilution during hyperemia, the coronary artery is rewired to place the coronary wire distally in the coronary artery. The infusion pump is reprogrammed to provide infusion of saline at a flow rate of 20 ml/min, which elicits a stable hyperemic state. Now, the temperature of blood mixed with saline at 20 ml/min (T_{20}) is measured distally in the vessel and, again, after a swiftly proximal withdraw of the sensor at the tip of the infusion microcatheter, the temperature of infused saline at 20 ml/min (T_{i-20}) is measured. The hyperemic measurement is completed. FFR, fractional flow reserve; MRR, microvascular resistance reserve. [Color figure can be viewed at wileyonlinelibrary.com]

dedicated software, which integrates all signals and provides all metrics online.⁶

Nevertheless, paired resting-hyperemic Q measurements require two wire pullback maneuvers, one distal rewiring of the artery and the reprogramming of the infusion pump (Figure 1), hence introducing some wire manipulations and operator interference.

In the present study we propose and validate a method to obtain paired resting-hyperemic continuous thermodilution measurements in an automated manner (Figure 2).

2 | METHODS

2.1 | Study population

Patients undergoing clinically indicated physiological assessment of the coronary circulation^{7,8} were recruited at two participating institutions. The study was approved by the local ethics committee, and all patients gave written informed consent.

2.2 | Conventional procedure for resting and hyperemic Q measurement

Continuous intracoronary thermodilution was performed with saline at an infusion rate of 10 ml/min for resting Q and R_{μ} calculations³ and—after distal rewiring of the vessel—at an infusion rate of 20 ml/min

for hyperemic Q and R,⁹ see Figure 1. FFR, CFR, and MRR were calculated as previously described.^{4,5}

2.3 | Automated procedure for resting and hyperemic Q measurement

The simplification procedure consisted in measuring both resting and hyperemic infusion temperatures (T_i) at the end of the continuous thermodilution measurement, thus allowing one single sensor pullback. This is obtained by programming the automatic infusion pump (i) to infuse saline at 10 ml/min for 2 min for the measurement of the temperature of blood mixed with infused saline; then (ii) to automatically switch to 20 ml/min for 1.5 min for the measurement of the temperature of blood mixed with infused saline (T) as well as—after a swift pullback of the temperature-sensor—for the measurement of hyperemic T_i ; and (iii) to automatically switch back to 10 ml/min for 1 min for the measurement of resting T_i . For the right coronary artery hyperemic and resting infusion rates at 15 and 8 ml/min were used, as previously reported.³ The procedure is represented in Figure 2. Details on the pump programming are provided in the Supporting Information materials.

To evaluate the agreement between the conventional and automated procedures, the measurements were performed sequentially in the same vessel while keeping the position of the intracoronary infusion microcatheter (RayFlow, Hexacath Inc.) constant. The order of the type of measurement (conventional vs. automated) was randomly assigned.

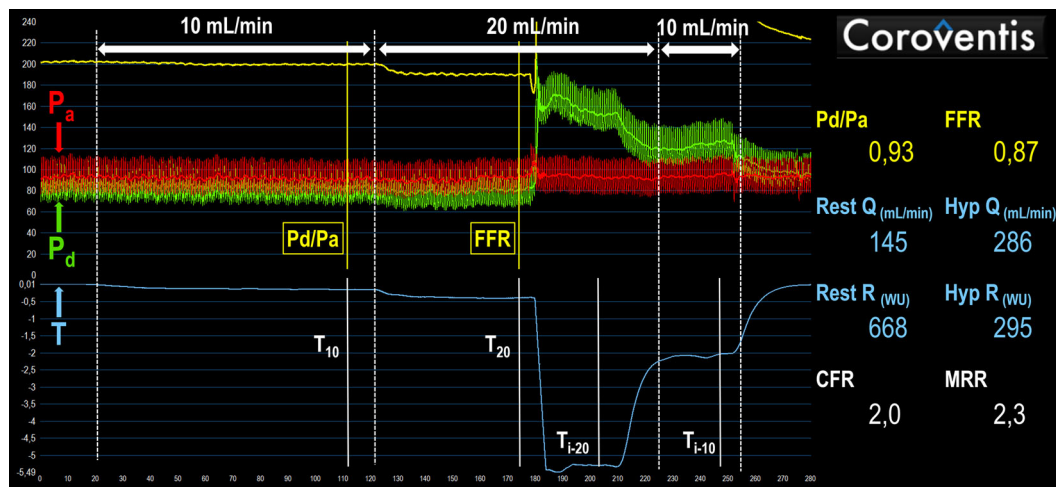


FIGURE 2 Automated paired resting-hyperemic coronary flow measurement with continuous intracoronary thermodilution. Example of paired resting-hyperemic thermodilution tracing obtained with a single pullback of the sensor (automated method). The infusion pump was preprogrammed in order (i) to provide first an infusion of saline at a flow rate of 10 ml/min, during which the temperature of blood mixed with saline at 10 ml/min (T_{10}) is measured distally in the vessel; (ii) next the pump automatically switches to an infusion of saline at a flow rate of 20 ml/min, during which the temperature of blood mixed with infused saline at 20 ml/min (T_{20}) is measured distally in the vessel and, after a swiftly proximal withdraw of the sensor at the tip of the infusion microcatheter, also the temperature of infused saline at 20 ml/min (T_{i-20}) is measured; (iii) finally, the pump automatically switches back to an infusion of saline at a flow rate of 10 ml/min, during which the temperature of infused saline at 10 ml/min (T_{i-10}) is measured. The paired resting-hyperemic thermodilution measurement is completed. Only one pullback at the end of the measurement is needed to collect both blood temperatures (T) and both infusion temperatures (T_i). FFR, fractional flow reserve; MRR, microvascular resistance reserve. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline clinical characteristics of patients undergoing continuous thermodilution assessment (patient N = 19)

Age	63.47 ± 11.52
Male sex	16 (84.2)
BMI	27.32 ± 3.24
Current smoker	6 (31.6)
Previous smoker	3 (15.8)
Hypertension	11 (57.9)
Diabetes	3 (15.8)
Dyslipidaemia	9 (47.4)
Previous PCI	6 (31.6)
Previous MI	5 (26.3)
CCS	
- Class 1	14 (73.7)
- Class 2	4 (21.1)
- Class 3	0 (0.0)
- Class 4	1 (5.3)
LVEF	64.38 ± 14.25
eGFR	70.67 ± 21.34
Aspirin	10 (52.6)
Statins	11 (57.9)
ACEI/ARBs	12 (63.2)
Beta-blockers	3 (15.8)
Calcium-channel blockers	2 (10.5)
Oral antidiabetic	3 (15.8)

Note: Values are n (%) or mean ± SD.

Abbreviations: ACE-I, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index in Kg/m²; CCS, Canadian Cardiovascular Society grading of angina; eGFR, estimated glomerular filtration rate in ml/mm²; LVEF, left ventricle ejection fraction in %; MI, myocardial infarction; PCI, percutaneous coronary intervention.

2.4 | Supplemental procedure for calculation of T_i at rest from hyperemic T_i

In addition to the simplification described in the main manuscript, we also propose and validated a second simplification procedure which also avoids the need for a rewiring of the artery and that could be applied if the infusion pump cannot be programmed. The method is based on the derivation of T_i at rest from the measured hyperemic T_i. All details about the method and its results are given in the Supporting Information materials.

2.5 | Statistical methods

Vessels were considered independent observations. Continuous variables are presented as mean ± standard deviation (SD) and interquartile range, and their distributions compared with parametric (t-test) and nonparametric tests (Mann–Whitney test), as appropriate. Agreement analysis was performed with the Bland–Altman method. Linear correlation was assessed with Pearson's R or Spearman's ρ method as appropriate and with intraclass correlation coefficients. A 0.05 level of significance was assumed. All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing).

3 | RESULTS

A total of 20 vessels (19 patients) had both resting and hyperemic Q measured obtained by the conventional method and by the automated method. Measurement protocol with automated and conventional thermodilution was completed in all cases. No complication occurred during the measurements.

Baseline characteristics of the overall populations are shown in Table 1. Sixteen (84.2%) patients were male with a mean age of 63.5 years. Moderate to severe anginal complaints were present in a fourth of cases (Canadian Cardiovascular Society ≥2 in ca. 26%).

TABLE 2 Hemodynamic data collected with tested conventional versus automated continuous intracoronary thermodilution

	Conventional continuous thermodilution (vessel N = 20)	Automated continuous thermodilution (vessel N = 20)	p Value
Q _{rest} (ml/min)	89.49 [59.16–112.25]	83.00 [71.35–87.37]	0.493
Q _{hyp} (ml/min)	209.55 [163.07–257.16]	210.80 [183.8–283.1]	0.680
R _{rest} (WU)	941.6 [797.3–1501.5]	949.1 [815.8–1332.3]	0.321
R _{hyp} (WU)	393.7 [280.4–513.1]	380.3 [298.0–483.4]	0.327
FFR	0.81 [0.75–0.85]	0.83 [0.78–0.87]	0.170
CFR	2.57 [2.00–2.73]	2.52 [2.20–2.73]	0.902
MRR	3.02 [2.22–3.69]	3.06 [2.53–3.76]	0.729

Note: Data are presented as median [IQR].

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; MRR, microvascular resistance reserve; Q, absolute flow; R, absolute microvascular resistance; WU, Wood unit.

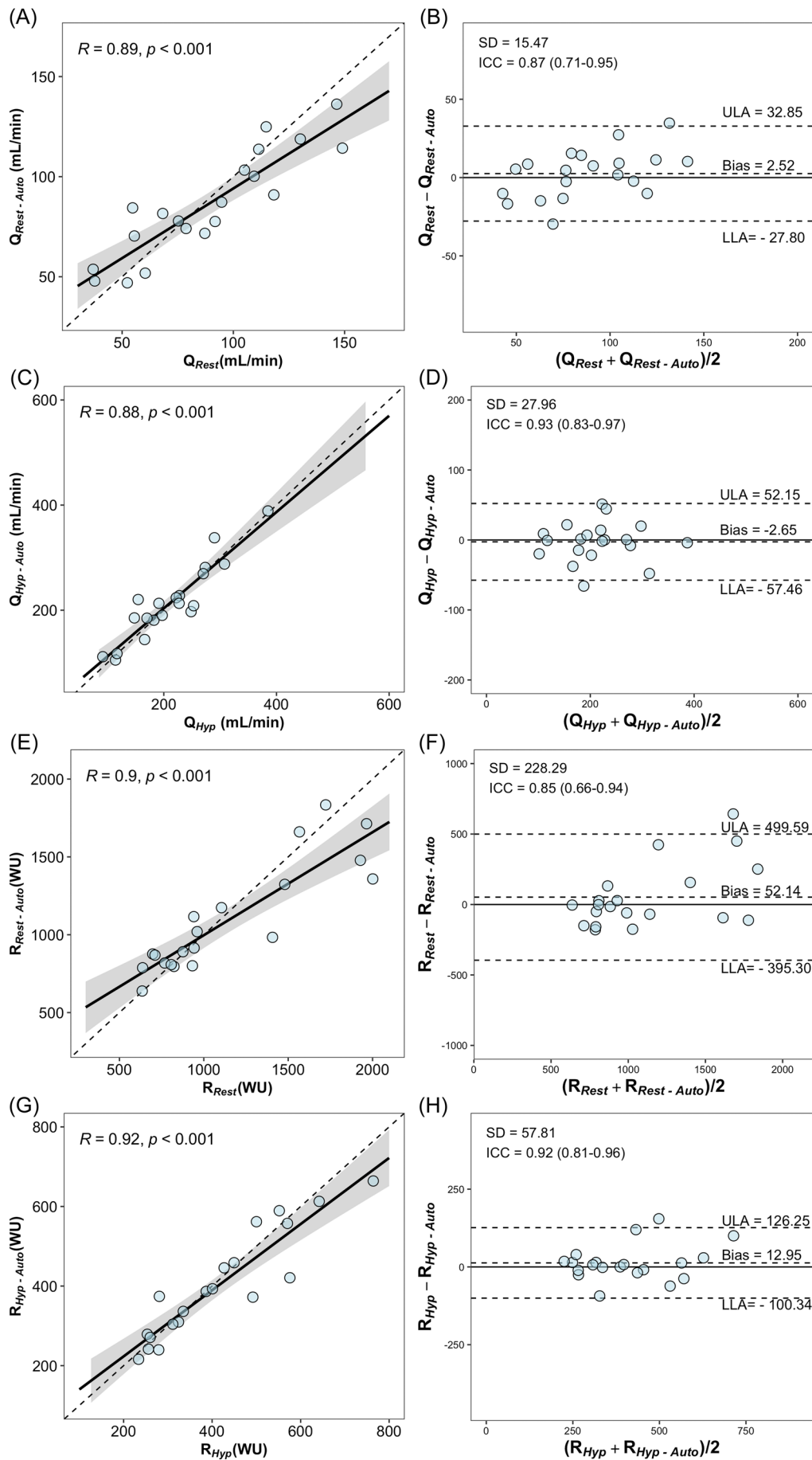


FIGURE 3 (See caption on next page)

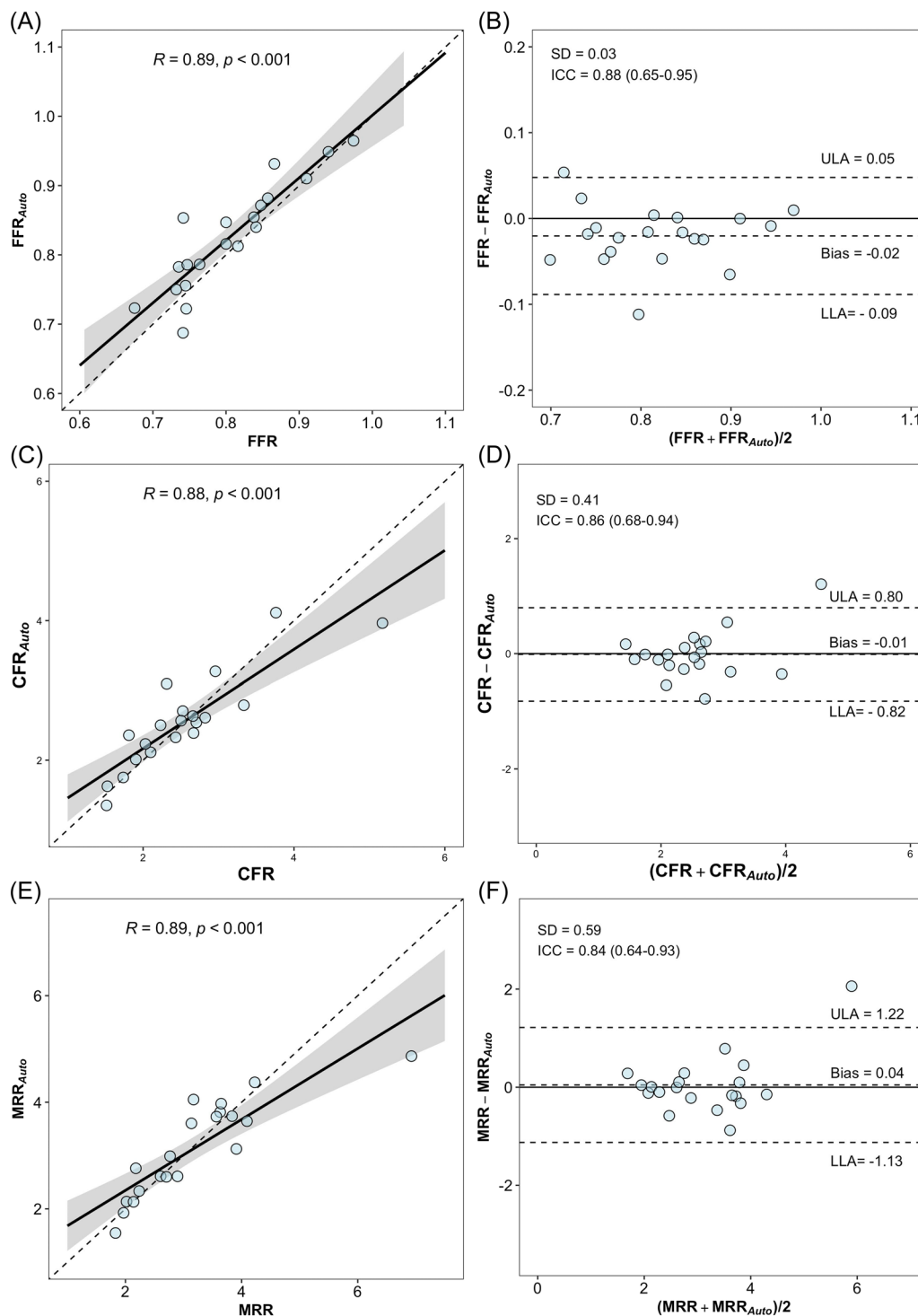


FIGURE 4 Agreement between conventional and automated procedures for continuous intracoronary thermodilution—fractional flow reserve (FFR), coronary flow reserve (CFR), and microvascular resistance reserve (MRR). Linear correlation and Bland–Altman plot for FFR, (A) and (B), CFR, (C) and (D) and for microvascular resistance reserve (MRR), (E) and (F) measured with the conventional and with the automated continuous intracoronary thermodilution procedures. Automated measurements marked with the subscript “*auto*.” ICC, intraclass correlation coefficients; LLA, lower limit of agreement; SD, standard deviation; ULA, upper limit of agreement. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Agreement between conventional and automated procedures for continuous intracoronary thermodilution—absolute coronary flow (Q) and microvascular resistance (R). Bland–Altman plots for resting and hyperemic flow (Q in ml/min; [A, B] and [C, D], respectively) and for resting and hyperemic resistance (R in WU; [E, F] and Panels [G, H], respectively) measured with the conventional and with the automated continuous intracoronary thermodilution procedures. Automated measurements marked with the subscript “*auto*.” ICC, intraclass correlation coefficients; LLA, lower limit of agreement; SD, standard deviation; ULA, upper limit of agreement. [Color figure can be viewed at wileyonlinelibrary.com]

Resting and hyperemic measurements were obtained with infusion rates at 10 and 20 ml/min, respectively, in 18 (90%) left anterior ascending arteries and with reduced infusion rates at 8 and 15 ml/min in 2 (10%) right coronary arteries.

Results of the coronary physiology assessment with the conventional and with the automatic continuous thermodilution procedures are reported in Table 2. Variable distributions did not differ significantly (FFR = 0.81 [0.75–0.85] vs. 0.83 [0.78–0.87], $p = 0.170$; CFR = 2.57 [2.00–2.73] vs. 2.52 [2.20–2.73], $p = 0.902$; MRR = 3.02 [2.22–3.69] vs. 3.06 [2.53–3.76], $p = 0.729$). The agreement between the parameters measured by either the conventional approach or the automated approach are reported in Figure 3 (resting and hyperemic Q and R_{μ}) and Figure 4 (FFR, CFR, and MRR). A significant reduction in procedural time was observed with the automated method (5'25" \pm 1'23" vs. 4'36" \pm 0'33", $p = 0.013$).

Detailed results related to the derivation of T_i at rest from the actual hyperemic T_i , the derivation and the validation of the regression equation are presented in the Supporting Information materials.

4 | DISCUSSION

The present data show that paired resting-hyperemic continuous intracoronary thermodilution measurements can be accurately obtained in a fully automated manner. In addition, this automated approach simplifies and shortens these measurements.

Intracoronary continuous thermodilution allows a direct and volumetric assessment of absolute coronary Q and R_{μ} at rest³ and during the hyperemic steady state induced by intracoronary infusion of saline at 15 ml/min or more.⁹ Paired resting-hyperemic thermodilution measurements allow the invasive derivation of CFR⁶ and, more recently, of MRR, a specific index for microvascular function independent from myocardial mass.⁵ Along with FFR, the assessment of CFR and MRR is essential for a comprehensive evaluation of the coronary functional status.^{5,10}

Measuring CFR and MRR from absolute Q and R_{μ} values requires paired resting and hyperemic thermodilution measurements. Conventionally, this is achieved by a first pullback maneuver of the sensor into the infusion microcatheter to measure resting T_i , distal rewiring of the artery, and a second pullback maneuver to measure hyperemic T_i . These manipulations are unpractical and the infusion microcatheter could be displaced during vessel reinstrumentation, potentially impairing measurement accuracy, as previously described.²

Hence, the proposed single-pullback simplification protocol with a programmed automated pump setting for resting and hyperemic Q measurement overcomes these limitations by minimizing human interference to a quick pullback of the sensor after 3 min of infusion.

What appears to be a small technical detail, greatly facilitates and standardizes the application of continuous intracoronary thermodilution, and sets the stage for increased operator-independency and

automation of the paired resting-hyperemic thermodilution measurements.

5 | CONCLUSION

The present data indicate that continuous thermodilution-derived FFR, CFR, and MRR measurements can be performed with a programmed pump setting and a single wire pullback without vessel rewiring. The measurement is short (approximately 4.5 min) and virtually automated.

CONFLICTS OF INTEREST

Dr. Candreva reports receiving research grants from Medyria. Dr. Collet reports receiving research grants from Biosensors, HeartFlow Inc., ShockWave Medical, Pie Medical Imaging, Siemens, GE, Medis Medical Imaging, and Abbott Vascular and consultancy fees from Opsens, Boston Scientific, Medyria, HeartFlow Inc., and Philips Volcano. Dr. De Bruyne discloses institutional consulting fees from Abbott Vascular and Boston Scientific and equities in Philips, Siemens, GE, Bayer, HeartFlow, Edwards Lifesciences, and Ceyliad. The remaining authors declare no conflict of interest.


DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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