Continuous Thermodilution Method to Assess Coronary Flow Reserve

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Coronary flow reserve (CFR) is a well-validated flow-based physiological parameter that has shown value in clinical risk stratification. CFR can be invasively assessed, classically by Doppler and, more recently, by thermodilution with saline boluses ($CFR_{thermo\text{-}bolus}$). Alternatively, continuous thermodilution is a novel operator-independent, highly-reproducible technique to invasively quantify maximum absolute coronary flow (AF). This study aimed to assess the feasibility of this method to quantify resting AF and to determine CFR ($CFR_{Thermo\text{-}infusion}$) as compared with $CFR_{thermo\text{-}bolus}$. Sixty-two consecutive patients with suspicion of coronary disease and absence of significant epicardial lesions were prospectively investigated. AF at maximal hyperemia (20 mL/min) and at lower infusion rates (6-8-10-12 mL/min) were systematically measured using a dedicated catheter and a temperature/pressure guidewire. The absence of baseline Pd/Pa decrease at 6 (0.15 ± 0.2%), 8 (0.17 ± 0.18%) and 10 mL/min (0.2 ± 0.12%) demonstrated absence of hyperemia at ≤10 mL/min (all p = NS). However, at 12 mL/min hyperemia was confirmed by a significant decrease in Pd/Pa (1.3 ± 1.5%, p <0.01) and increase in AF from 10 mL/min to 12 mL/min (31.4 ± 28.1 mL, p <0.05). All curve tracings at 10 mL/min (129/129, 100%) were adequate versus only (7/15, 53%) and (15/18, 17%) at 6 mL/min, and 8 mL/min, respectively, and this infusion-rate was considered to determine resting-AF. $CFR_{Thermo\text{-}infusion}$ was determined as the ratio of hyperemic-AF (20 mL/min) by resting-AF (10 mL/min). Mean $CFR_{Thermo\text{-}infusion}$ was 2.56 ± 0.9 and $CFR_{thermo\text{-}bolus}$ 2.49 ± 1. Both parameters showed a good correlation (r = 0.76; p <0.001) and intraclass agreement (ICC = 0.76; p <0.001).The continuous thermodilution method enables to quantify resting-AF providing a novel clinical tool to determine CRF. $CFR_{Thermo\text{-}infusion}$ shows a good correlation with $CFR_{thermo\text{-}bolus}$. **(Am J Cardiol 2021;141:31−37)**

Currently, the main index of coronary flow is the coronary flow reserve (CFR) defined as the ratio between coronary flow at maximal hyperemia and coronary flow at rest. CFR has been extensively studied and it is considered a well-validated flow-based physiological parameter that may further assist risk stratification in patients with normal fractional flow reserve (FFR).[1,2] CFR can be invasively assessed by Doppler ($CFR_{Doppler}$) or by thermodilution with saline boluses ($CFR_{thermo\text{-}bolus}$). However, both methods are operator-dependent and require the infusion of adenosine to induce hyperemia.[3−7] Recently, a new method to quantify volumetric absolute coronary flow (AF) and myocardial resistance (MR), based on the principle of thermodilution using continuous saline infusion, has been reported. This method has been validated and proved to be operator-independent. Furthermore, it does not rely on pharmacological agents to induce hyperemia. However, up to now, this method has only been validated at maximal hyperemia and has not been studied to determine CFR.[8−14] In this prospective study, we sought to evaluate the feasibility and safety of this new method to quantify CRF thermodilution with continuous saline infusion ($CRF_{Thermo\text{-}infusion}$). $CFR_{Thermo\text{-}infusion}$ was calculated as the ratio of hyperemic AF and resting AF (determined using a continuous low-flow rate saline infusion) and correlated with CFR obtained by saline boluses injections ($CFR_{thermo\text{-}bolus}$).

Methods

This is a proof-of-concept, validation technique study. A total of 62 consecutive patients undergoing invasive microcirculatory function assessment in 2 in high-volume university centers were prospectively included. All patients had a clinical indication for coronary angiography in the absence of significant epicardial coronary stenosis (<40% diameter stenosis or a normal FFR [>0.8]). Patients with significant valvular disease, contraindication for adenosine infusion, poor general condition, and those with technically nonoptimal physiological studies were excluded. The study

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protocol was approved by the institutional ethics committee of the coordinating center and all patients gave written informed consent. The study protocol consisted of 2 populations. In group 1 (27 patients) the infusion rate that failed to induce microvascular vasodilation and, therefore could be used to estimate basal flow, was investigated. Different saline infusion rates (6, 8, 10, and 12 mL/min) were systematically studied and multiple infusion rates were tested in each patient. Group 2 included 48 patients (13 from group 1 and 35 additional new patients). These 48 patients were investigated with a saline infusion at 10 mL/min (resting-AF) and at 20 mL/min (hyperemic-AF). $CFR_{Thermo\text{-}infusion}$ was determined as the ratio between hyperemic-AF and resting-AF (10 mL/min). Finally, conventional thermodilution with boluses was also determined in all patients. Data on invasive physiological measurements were processed off-line using the CoroFlow console. Offline analysis of thermodilution curves were performed by an independent accredited core-laboratory (Barcelona Cardiac Imaging Core-Laboratory [BARCICORE-lab]) blinded to clinical and angiographic findings.

After completion of a regular radial access coronary angiogram, an intracoronary bolus of at least 200 μg of nitroglycerin was administered. The vessel of interest was instrumented with the pressure-temperature guidewire (PressureWireX Guidewire; Abbott; United States). Adequate pressure and temperature equalization were ensured. Subsequently, the following measurements were systematically performed by protocol:

1. *Low-flow infusion of room temperature saline.* A dedicated rapid exchange coronary infusion microcatheter, Rayflow (Hexacath, France), was positioned in the proximal segment of the vessel. After ensuring that the pressure/temperature sensor-tipped guidewire was positioned at least at 3 cm distal to the catheter tip and Pd/Pa was recorded. Then, to evaluate the feasibility to quantify coronary resting flow (ie, without inducing relevant hyperemia), low infusion rates of saline (6, 8, 10 and 12 mL/min) at room temperature, were started using an automated infusion system. After obtaining a steady temperature state, the pressure/temperature wire was gently pulled back to the tip of the infusion catheter to assess the saline infusate temperature. Pd/Pa was carefully recorded before, during and at the end of the infusions, to confirm the absence of hyperemia induction at these flow rates. A Doppler flow velocity analysis would have been much more sensitive to detect small changes in resting flow but was not obtained in this study.
2. *Hyperemic AF.* To calculate the hyperemic AF the same protocol was repeated but using a saline infusion rate of 20 mL/min. Delta (Δ) Pd/Pa was defined as the absolute difference between basal Pd/Pa and Pd/Pa at the end of the infusion. Delta (Δ) flow was defined as the difference between maximal absolute volumetric flow at hyperemia (20 mL/min infusion rate) and the volumetric coronary flow rate obtained at a low infusion rate whereas % Δflow was defined as the Δflow divided by the flow achieved at maximal hyperemia with saline infusion. Considering that, independently of the infusion rate, when hyperemia is not induced the flow remains unchanged, the absence of Δ flow modification was considered in this study as additional proof to confirm the absence of hyperemia. To assess the reproducibility of 10 mL/min infusion duplicated measurements were obtained in a subgroup of 6 patients after removing the wire from the artery and then readvancing the entire system into the target vessel.
3. *Bolus thermodilution technique.* A coronary thermodilution curve was generated, after removing the infusion microcatheter, taking care that the pressure-temperature wire was exactly located at the same position. Measurements were acquired at rest and maximal hyperemia, induced by peripheral intravenous infusion of adenosine (140 to 180 μgr/kg/min), as previously described[7,15,16] Three consecutive thermodilution curves were obtained by brisk injection of 3 mL of saline at room temperature into the coronary artery. Thermodilution curves were considered satisfactory when a unimodal shape without distortion was observed; poor quality curves were excluded.

Categorical variables were expressed as frequencies (n) and/or percentages (%). Continuous variables were expressed as the mean ± standard deviation or as median (interquartile range). Normality was assessed by using the Kolmogorov-Smirnov. Pearson's correlation coefficient (r) was performed to assess the correlation between $CFR_{Thermo\text{-}infusion}$ and $CFR_{thermo\text{-}bolus}$. The agreement between both methods was also assessed by intraclass correlation coefficients (ICCs) using a 2-way mixed effect model and Bland-Altman plots. Fisher r-to-z transformation was used to assess the significance of the difference between normalized and non-normalized correlation coefficients. Comparisons were performed by either paired Student's *t* test and by one-way ANOVA followed by Tukey's post hoc. Welch's ANOVA test was used for unequal variances. Non-normally distributed continuous variables were analyzed using the Kruskal-Wallis test with a Bonferroni post hoc test. All statistical tests were 2-tailed and a p value of <0.05 was considered significant. All statistical analyses were performed using SPSS software version 23.0 for windows (IBM, Armonk, NY).

Results

A total of 62 consecutive patients who fulfilled the inclusion criteria were prospectively recruited from June 2019 to March 2020. Clinical and angiographic characteristics of these patients are described in Table 1. A total of 162 volumetric absolute flow quantifications were performed in 62 arteries: 62 measurements were performed under hyperemic conditions (by using saline at room temperature at 20 mL/min) and 100 measurements were obtained using lower infusion rates (≤12 mL/min). Adequate thermodilution curves were obtained in all arteries during saline infusion at 10 to 20 mL/min (100%, 129/129). However, when lower infusion rates were performed fewer adequate temperature curves were obtained, mainly because mean mixed temperature below reference temperature was too low (Figure 2).

$CFR_{thermo\text{-}bolus}$ could be successfully obtained in all investigated arteries in the group-2 (100%, 48/48). The

Table 1
Baseline characteristics

Age ± SD (years)	62.6 ± 13
Women	23 (37%)
Body mass index (kg/m^2) ± SD	17.6 ± 6
Hypertension	46 (74%)
Diabetes mellitus	16 (26%)
Dyslipidemia	34 (55%)
Smoker (current or past)	28 (45%)
Previous PCI	32 (52%)
Prior Myocardial infarction	29 (47%)
LVEF (%) ± SD	58.1 ± 11
Clinical presentation	
-Stable disease	49 (79%)
-Unstable angina	5 (8%)
-NSTEMI	8 (13%)
Target coronary vessel	
-Left anterior descending	47 (76%)
-Left circumflex	5 (8%)
-Right coronary artery	10 (16%)

average bias between the 2 measurements at 10 mL/min was 1.4% ± 1.4%. One patient developed atrioventricular block during the saline infusion in the right coronary artery (at 20 mL/min) that was immediately resolved by stopping the infusion and the study was uneventfully performed at 15 mL/min. No other complications were observed. Adequate thermodilution curves with saline boluses were obtained in 349 out of 372 studies, corresponding to 94% of the curves. Figure 1 depicts a typical case example

A higher decrease in mean aortic pressure was induced with intravenous adenosine infusion than with intracoronary saline infusion (Table 2). The difference between both mean aortic pressure reductions was 3.7 mm Hg, (95% CI 0.97 to 6.44, p <0.005).

Functional parameters obtained during the different infusion rates are shown in Table 2. ΔPd/Pa and % ΔPd/Pa differed according to the use of low-rate saline infusions (p <0.001 for both parameters) (Figure 3). Notably, % ΔPd/Pa and ΔPd/Pa remained equal when saline was infused at 6, 8 and 10 mL/min (p = NS for all comparisons). At those infusion rates, ΔPd/Pa and % ΔPd/Pa were both negligible (0.20 ± 0.24 mm Hg, 0.17 ± 0.18 mm Hg, 0.21 ± 0.1 mm Hg) and (0.15 ± 0.2%, 0.17 ± 0.2%, 0.22 ± 0.1%) respectively. However, when an infusion of 12 mL/min was used, some degree of hyperemia was detected and confirmed by a significant decrease in ΔPd/Pa (1 ± 1.6%, p <0.01). Paired comparisons showed that saline infusion at 10 mL/min produced a numeric (non-statistically significant) increase in AF compared with 8 mL/min and 6 mL/min. However, above this value, coronary flow significantly increased and

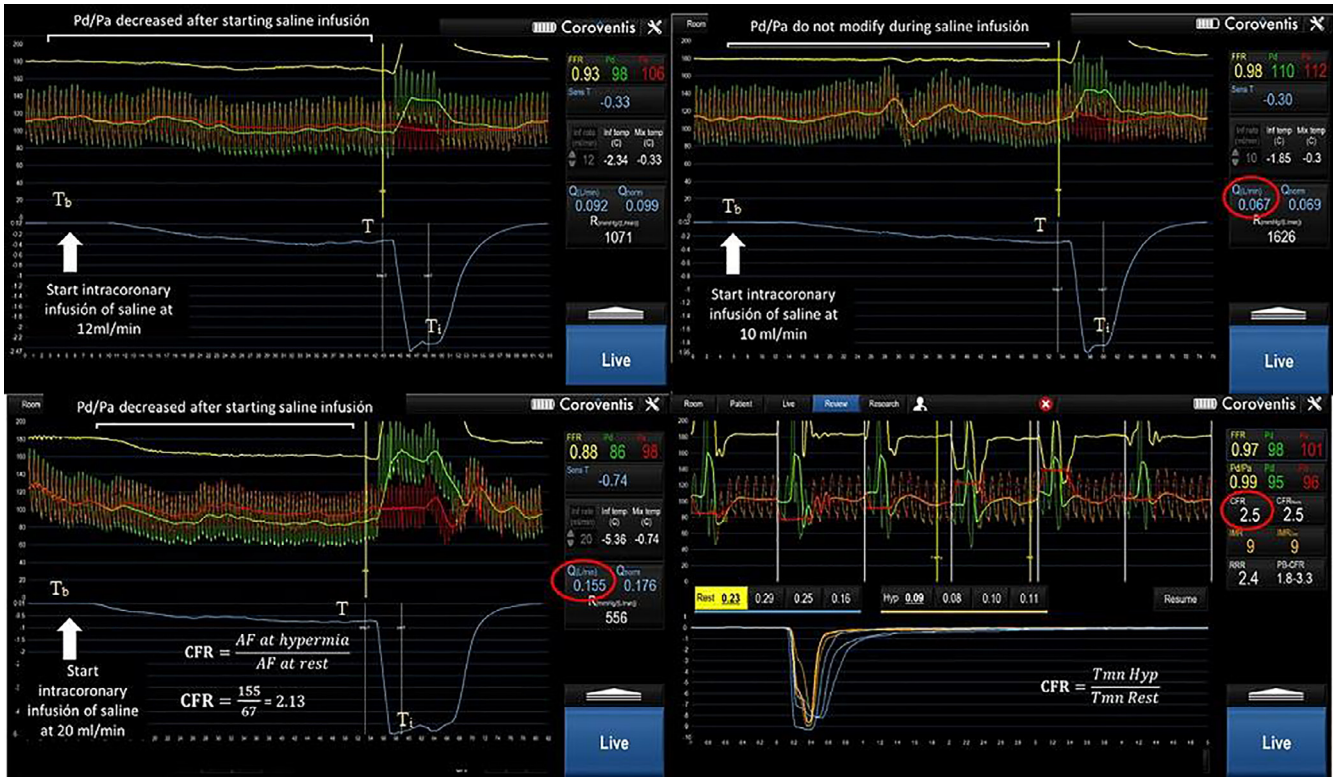

Figure 1. A representative case example.
Room temperature saline solution is infused into the coronary artery through a specific catheter. The screen displays a real-time readout of the baseline temperature (Tb) and, after the infusion begins, there is a gradual decrease in temperature (T). Once the temperature stabilizes, the guidewire is positioned at the microcatheter tip to measure the infusion temperature (Ti). This allows the quantitative measurement of AF according to the formula Qb = 1.08 Ti/T Qi, where Qi is the preset saline infusion rate. Aortic pressure (red trace), distal coronary pressure (green trace), and Pd/Pa ratio (yellow trace) are monitored simultaneously. (**A**) Saline infusion at 12 mL/min reflected a Pd/Pa decrease during the infusion and a higher AF compare with AF assessed at 10 mL/min (**3B**) hence, a certain degree of hyperemia was induced at 12 mL/min. (**B**) At 10 mL/min hyperemia was not induced as evidenced by the fact that Pd/Pa did not modify during the infusion. (**C**) Saline infusion at 20 mL/min induces maximal hyperemia. Therefore $CFR_{Thermo\text{-}infusion}$ is obtained by dividing AF at maximal hyperemia by resting-AF at 10 mL/min. **D**) $CFR_{thermo\text{-}bolus}$, as previously described, is calculated by dividing Tmn at ret by Tmn at hyperemia.

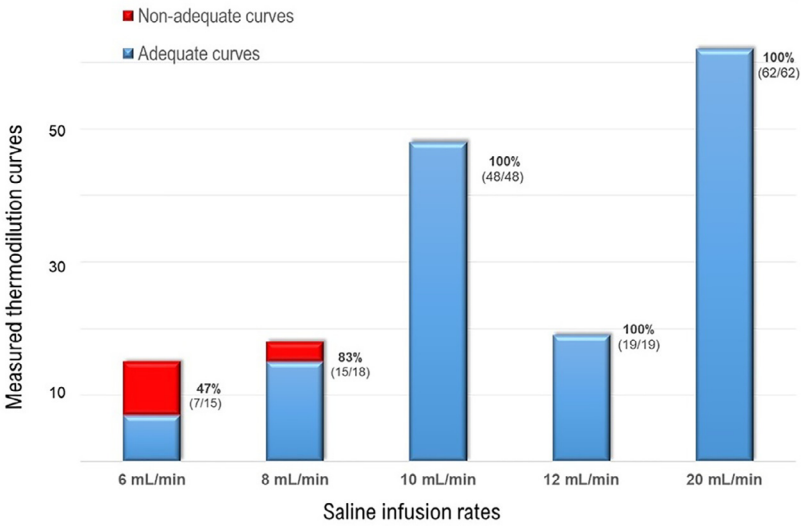

Figure 2. Measured thermodilution curves.
Adequate thermodilution curves obtained according to the room temperature saline infusion-rate.

the higher the infusion rate the higher the AF (31.4 ± 28.1mL, p <0.05 from 10 mL/min to 12 mL/min) (Supplementary figure). Concordantly Δflow significantly differed at higher infusion rates but not when rated at ≤10 mL/min (Figure 4).

Considering $CFR_{thermo\text{-}bolus}$ as a reference value and using a CFR cut-off value of 2, $CFR_{Thermo\text{-}infusion}$ misclassified 11 patients. Average value of $CFR_{thermo\text{-}bolus}$ and $CFR_{Thermo\text{-}infusion}$ at 10 mL/min were similar (Table 2). A strong correlation was found between $CFR_{thermo\text{-}bolus}$ and $CFR_{Thermo\text{-}infusion}$ (r=0.76; p <0.001) (Figure 5) with good agreement (ICC = 0.76; p <0.001). The Bland−Altman plot showed a trend for slightly higher values with $CFR_{Thermo\text{-}infusion}$ than with $CFR_{thermo\text{-}bolus}$.

Discussion

The present study demonstrates for the first time, the feasibility of using thermodilution by continuous infusion of saline through a novel microcatheter at a low-flow rate (≤10 mL/min) to quantify volumetric resting AF and MR. Using this technique, CFR can be derived from direct measurements of coronary flow rather than from indirect pressure data.

Thermodilution technique for coronary blood flow measurement was proposed more than 30 years ago [17] However, this method, was limited by several technical difficulties, that hamper its routine clinical application[9,13] Recently, the development of a special microcatheter together with a specific dedicated software have significantly simplified the procedure. This new method has several advantages over the conventional indirect flow measurements: It is operator independent and easy to perform; it does not need adenosine and its reproducibility is remarkably better than conventional flow measurements[10−13,16,18−22] In agreement with previously reported studies,[10−13,16,18−22] we found that this method was feasible and safe in a real-world cohort of 62 patients with no significant adverse effects or procedural-related complications. Up to now, thermodilution by continuous infusion of saline through a dedicated catheter has only been validated to quantify the maximum volumetric coronary flow at maximal hyperemia (≥15 mL/min), however, its value under resting conditions remains unknown[8−10,13,20] In the present study, we found that Pd/Pa remains unchanged during low-flow saline infusions (6, 8, and 10 mL/min). Likewise % ΔPd/Pa and ΔPd/Pa also remains unchanged when saline was infused at ≤10 mL/min. Altogether, these

Table 2
Physiological measurements

Infusion rate (mL/min)	8 (n = 15)	10 (n = 48)	12 (n = 12)	20 (n = 48)	Bolus (n = 48)
Pd/Pa	0.95 ± 0.03	0.95 ± 0.03	0.94 ± 0.03	NA	NA
ΔPd/Pa	0.17 ± 0.2	0.2 ± 0.1	1.3 ± 1.5	7 ± 5	NA
ΔPd/Pa %	0.17 ± 0.2	0.2 ± 0.1	1 ± 1.6	8.5 ± 1.5	NA
ΔPa (hyperemic Pa - resting Pa)	NA	NA	NA	0.7 ± 1.4	4.5 ± 2.4
FFR ± SD	NA	NA	NA	0.88 ± 0.05	0.89 ± 0.04
Absolute flow mL/min ± SD	100±35	93 ±38	130±22	223 ± 81	NA
Myocardial resistance (Wood Units) ± SD	1201±886	1108 ± 430	764 ± 246	419 ± 227	NA
IMR_{corr} ± SD	NA	NA	NA	NA	20.8 ± 21
CFR ± SD	2.55 ± 0.8	2.56 ± 0.9	1.5 ± 0.4	NA	2.49 ± 1
$CFR_{normalized}$ ±SD	2.78 ± 1	2.64 ± 0.9	1.54 ± 0.4	NA	2.74 ±1

Δ Pd/Pa %: Pd/Pa at the end of the infusion minus Pd/Pa at the beginning expressed as percentage of initial Pd/Pa.

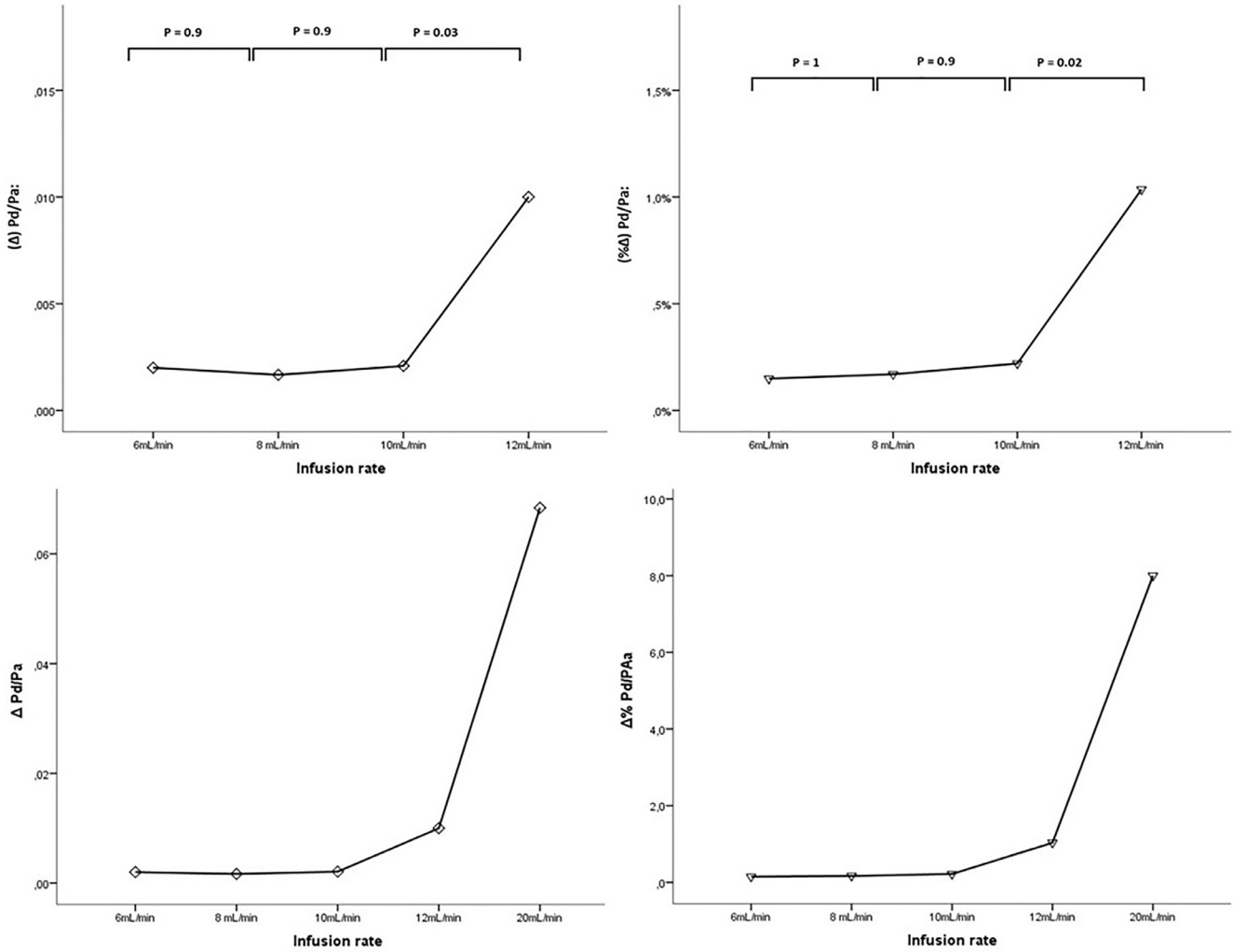

Figure 3. Delta PD/Pa values during saline infusions.
Average values of Δ Pd/Pa (Pd/Pa at the end of the infusion minus baseline Pd/Pa) during infusion of saline at room temperature at flow rates of 6, 8, 10, and 12 mL/min. The values are expressed as an absolute value (**A**) and as percentages (**B**). P values refer to pairwise comparisons after adjustment for multiple comparisons.

findings provide compelling evidence suggesting at those low infusion rates, intracoronary saline infusion at room temperature does not induce significant coronary hyperemia. Conversely, when the pump infusion was set at 12 mL/min, a relevant degree of hyperemia was systematically induced, as reflected by 2 key findings. First, a slight, but consistent and significant, decrease in Pd/Pa was observed during the infusion (1% reduction vs 0.2% at 10 mL/min, $p < 0.05$). Second, volumetric coronary flow and delta flow were quite similar at 8 and 10 mL/min, however, at a rate of 12 mL/h AF, a significant increase (2% increase from 8 to 10 mL/min vs 26.6% from 10 to 12 mL/min, $p < 0.01$), was detected. Our findings strongly suggest that a relevant degree of hyperemia was reached at 12 mL/min but not at ≤10 mL/min.

Previously, De Bruyne et al found a linear correlation between the extent of hyperemia and the rate of continuous saline infusion, the higher the rate, the higher the hyperemia[8] In the present study, the hyperemic stimulus at 10 mL/min was negligible or nonexistent. Likewise, in the study by De Bruyne et al, flow velocity did not significantly increase from 5 mL/min to 10 mL/min. Besides, flow velocity was notably and significantly increased from 10 mL/min to 15 mL/min[8]

Lower infusion rates (6 to 8 mL/min), certainly did not induce hyperemia, although, in some cases, such low infusion rates do not enable to obtain adequate thermodilution curves. Consequently, our findings suggest that saline infusion rated at 10 mL/min emerges as the most reliable infusion rate to accurately quantify volumetric resting-AF.

As we were able to quantify maximal and resting volumetric AF, a direct CFR determination could be readily obtained, as the ratio between maximum AF and resting AF. $CFR_{thermo\text{-}bolus}$ and $CFR_{Thermo\text{-}infusion}$ showed a good correlation ($r = 0.76$). It should be noted, however, that $CFR_{thermo\text{-}bolus}$ does not provide a true gold standard for CFR in humans and has an intrinsic variability of at least 15% to 20%. Although $CFR_{Doppler}$, represents an alternative method, $CFR_{Doppler}$, is neither a true gold standard and, in fact, has even shown a suboptimal correlation with direct flow measurements. Moreover, this technique is technically demanding and therefore suffer from interobserver variability[4] The use of PET could have yielded a definitive gold

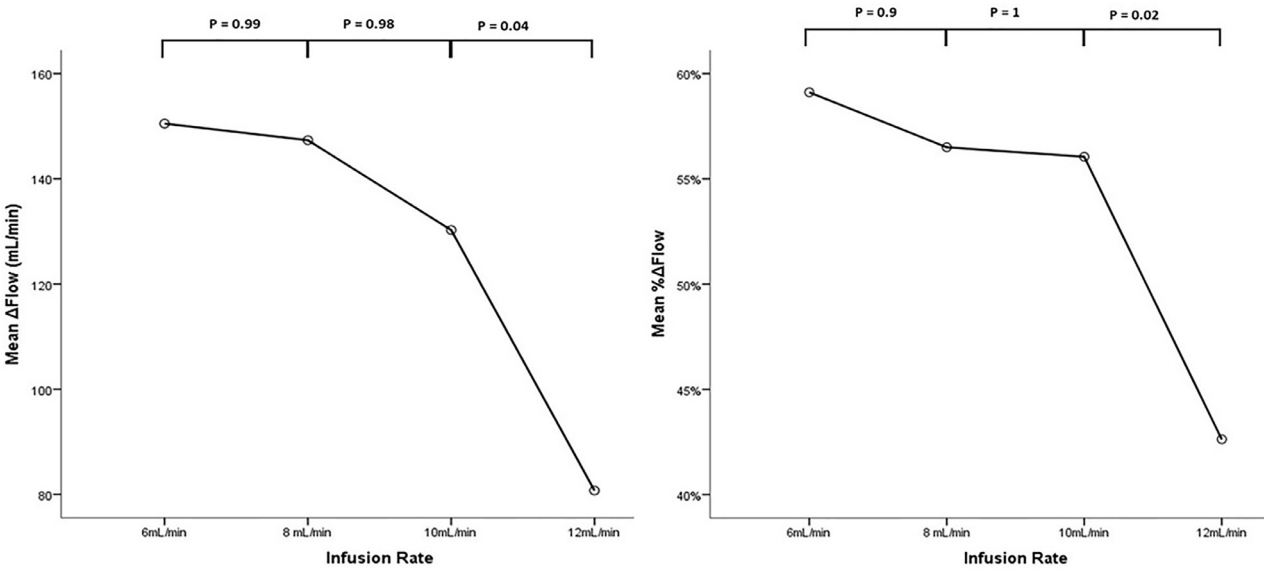

Figure 4. Mean Delta AF during saline infusions.
(A,and B) Mean Δ Flow (difference between hyperemic maximum flow and "resting-flow") at low infusion rates. Δ AF significantly decreased at 12 mL/min but not at ≤10 mL/min. (C,and D) Mean Δ AF was similar at ≤ 10 mL/min but not at 12 mL/min suggesting that at this rate hyperemia was induced by the room-temperature saline infusion. The values are expressed as an absolute value (*left*) and as a percentage (*right*). p values refer to pairwise comparisons after adjustment for multiple comparisons.

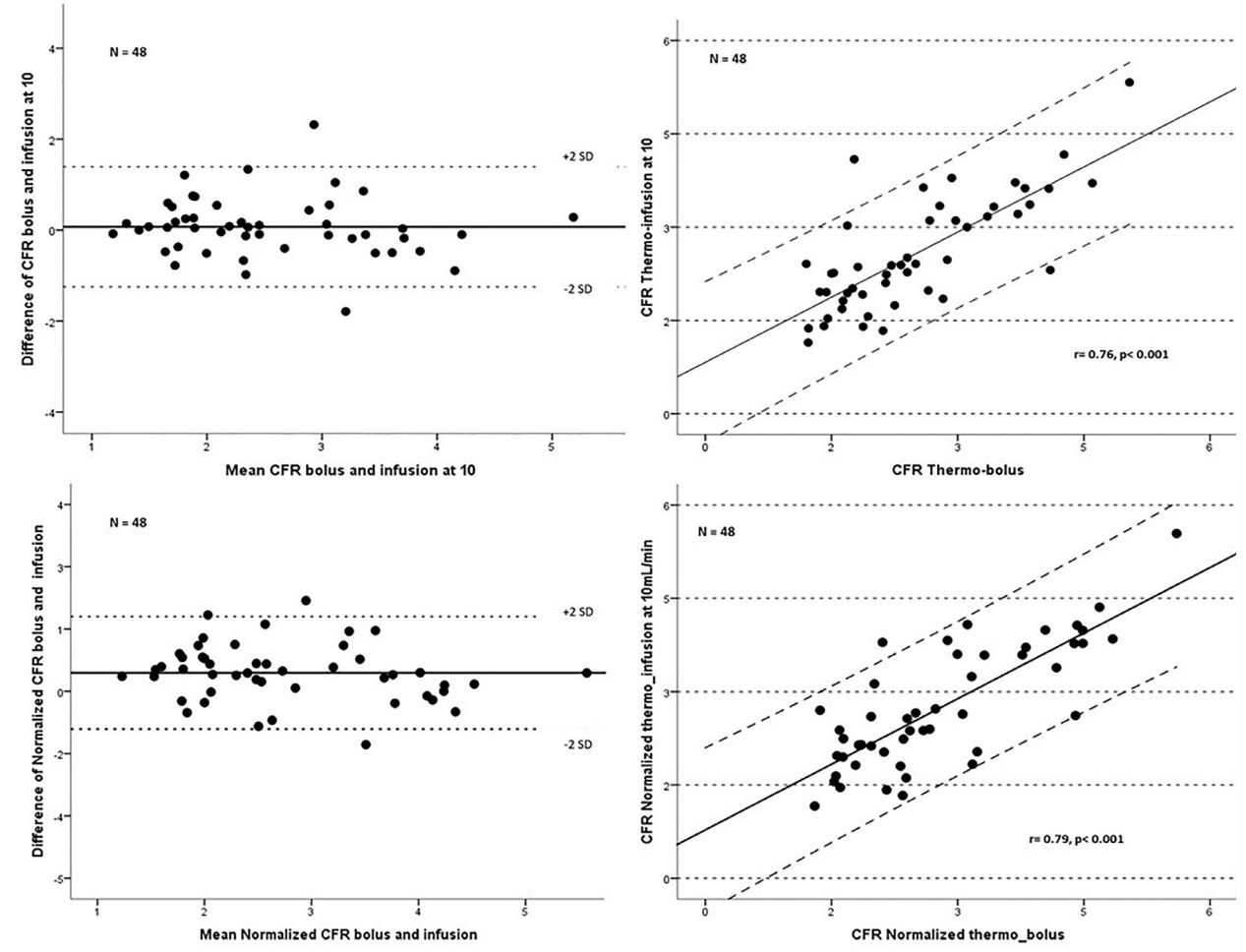

Figure 5. $CFR_{Thermo\text{-}infusion}$ and $CFR_{thermo\text{-}bolus}$ correlation.
Scatter and Bland−Altman plots comparing both thermodilution based methods non-normalized (A, B) and after normalized values according to FFR (C, D). P values refer to pairwise comparisons after adjustment for multiple comparisons.

standard for CFR, but in that case, simultaneous acquisition of $CFR_{Thermo\text{-}infusion}$ would not have been possible[16] Interestingly, the correlation we found between $CFR_{thermo\text{-}bolus}$ and $CFR_{Thermo\text{-}infusion}$ ($r = 0.76$) was very close to the previously reported correlations between in-vitro ($r = 0.75$) and in-animal ($r = 0.85$) AF obtained by a direct measurement and indirect flow assessment by mean transit time (Tmn).[4,7] Our results, therefore, confirm the recently reported strong correlation between direct measured and calculated flow.[10,14]

In conclusion, the present study demonstrates, for the first time, the feasibility and reliability of coronary AF volumetric quantification at resting conditions using continuous thermodilution method at 10 mL/min. Furthermore, our results demonstrate that CFR can be accurately calculated using this novel method. This method is operator independent, accurate, and easy to perform, avoiding the need for microvascular vasodilator drugs.

Disclosures

The authors declare no conflicts of interest.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.011.

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