European Heart Journal (2004) **25**, 219–223

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

Clinical research

Validation of coronary flow reserve measurements by thermodilution in clinical practice

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Received 24 July 2003; received in revised form 31 October 2003; accepted 6 November 2003

KEYWORDS
Coronary flow reserve;
Coronary artery disease;
Fractional flow reserve;
Ischaemia;
Thermodilution

Background Coronary flow reserve (CFR) and fractional flow reserve (FFR) provide complementary information on the coronary circulation. Using a pressure wire, it is possible to calculate CFR by thermodilution (CFR_{thermo}), so that FFR and CFR can be measured with a single guide wire. The present multicentric study was performed to compare the feasibility of CFR_{thermo} obtained with an improved algorithm and a standardized injection technique and its agreement with Doppler-derived CFR ($CFR_{Doppler}$).
Methods and results In 86 patients with coronary artery disease recruited during 1 week in eight centres FFR, CFR_{thermo} and $CFR_{Doppler}$ were measured. FFR could be obtained in all patients (100%). An optimal $CFR_{Doppler}$ could be obtained in 69% of the patients. CFR_{thermo} could be obtained in 97% of the patients. A significant correlation was found between $CFR_{Doppler}$ and CFR_{thermo} (r=0.79, P<0.0001) but CFR_{thermo} tended to be higher than $CFR_{Doppler}$.
Conclusions In a setting close to 'real world' practice, this multicentric study confirms the feasibility and reliability of thermodilution-derived CFR. In addition, the safety and the swiftness of assessing FFR and CFR with one single guide wire makes the latter a unique clinical tool for the evaluation of the coronary circulation.

Introduction

Coronary flow reserve (CFR) and fractional flow reserve (FFR) have been proposed to evaluate coronary artery disease[1–9] as they provide complementary information on the status of the coronary circulation. So far, assessing both indices simultaneously requires two guide wires (a Doppler wire and a pressure wire), which is cumbersome and expensive. We have recently validated a coronary thermodilution technique enabling the assessment of CFR (CFR_{thermo}) and FFR with the same wire.[10,11] CFR_{thermo} is defined as the ratio between the resting mean transit time ($T_{mn\ rest}$) and hyperaemic mean transit time ($T_{mn\ hyperaemic}$). Despite a fair correlation between

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0195-668X/04/$ - see front matter © 2003 Published by Elsevier Ltd on behalf of The European Society of Cardiology.
doi:10.1016/j.ehj.2003.11.009

CFR_{thermo} and CFR measured by Doppler ($CFR_{Doppler}$), some scatter persists in the first validation study. Several factors may account for this scatter: first, the algorithm used to calculate T_{mn} tends to underestimate CFR; second, a non-standardized injection technique of the bolus of IC saline might account for some variability; and finally, suboptimal quality of some Doppler signals might decrease the correlation between CFR_{thermo} and $CFR_{Doppler}$. In addition, the thermodilution technique has so far been validated in two experienced centres, which may not reflect the more widespread applicability of CFR_{thermo}.

Accordingly, the aim of the present study was twofold: (1) to compare the feasibility of CFR_{thermo} and $CFR_{Doppler}$ in a multicentric setting closer to 'real world' practice; and (2) to compare the results of CFR_{thermo} obtained with an improved algorithm and a standardized injection technique to $CFR_{Doppler}$ derived from high-quality Doppler tracings.

Methods

Patient population

The study was conducted in eight hospitals in five countries. Between March 25 and 29 2002 (week 25), all patients referred in these centres for physiological assessment and/or angioplasty of at least one coronary stenosis were included unless they were unstable, if marked tortuosities were present, or if the lesion to be treated was a total occlusion. A total of 86 patients were included in the study. To investigate the feasibility of CFR_{thermo} and of $CFR_{Doppler}$ in a setting representative of the 'real world', all the measurements obtained were taken into account for analysis. However, to compare CFR_{thermo} to $CFR_{Doppler}$, only the data from patients in whom an optimal Doppler tracing could be obtained were taken into account (see below).

Catheterization procedure

The coronary ostium was cannulated with a 6F angioplasty guiding catheter through which central aortic pressure (P_a) was continuously recorded. After administration of 200 µg IC isosorbide dinitrate (ISDN), an angiogram was obtained. $CFR_{Doppler}$ was obtained as follows: a Doppler guide wire (Flowire, Jomed) was advanced in the distal part of the artery and manipulated to obtain optimal Doppler flow velocity tracings. After recording baseline flow velocity, adenosine IV was infused during at least 4 min to obtain steady state maximal hyperaemia. Adenosine was then turned off during 5 min. If the Doppler velocity tracings were considered of high quality by the operator (see below), the Doppler wire was removed and a Pressure/Temperature sensor (Pressure Wire 4, Radi Medical Systems, accuracy of 0.05 °C within a temperature range from 15 to 42 °C) was advanced at the same location where the Doppler crystal was located. Distal coronary pressure (P_d) was continuously monitored. CFR_{thermo} was obtained as follows: first, the correct position of the guiding catheter into the coronary ostium is checked and the lines (catheters, syringe, manifold and connecting tubes) are carefully flushed with saline to avoid the administration of contrast medium. Then, the syringe that usually serves to inject contrast medium is filled with 3 to 4 ml of saline at room temperature. These syringes usually have a safety-volume that avoids injecting air bubbles. The bolus of saline is then briskly injected (less than 0.25 s) into the coronary tree. This allows us to obtain a first thermodilution curve at rest. Three resting thermodilution curves are obtained at rest, the injection of saline being separated from each other with an interval of approximately 8–10 s. Adenosine is then switched on again and a second series of hyperaemic thermodilution curves are obtained. Thereafter the procedure was completed according to the clinical needs.

Optimization of $CFR_{Doppler}$

An example of pressure, thermodilution and Doppler velocity recordings is shown in Fig. 1. Doppler tracings were graded on a 1 to 5 scale (from very poor to optimal). Because in the present study $CFR_{Doppler}$ was the reference method, only patients with good or optimal Doppler flow velocity tracings were considered. The selection process of the Doppler flow tracings was performed beforehand in two steps: (1) the operator was urged not to proceed with the protocol if the Doppler tracings were not classified as good or optimal. In this case, the patient was excluded from further analysis; (2) in addition, for the purpose of the comparison between CFR_{thermo} and $CFR_{Doppler}$, all tracings were blindly reviewed in a core laboratory. Ethical Committees of the participating centres approved the study, and an informed consent was obtained from all patients.

Data analysis

The Pressure Wire actually includes two temperature sensors: the shaft of the catheter that enables the recording of the input signal, and the distal sensor located at the junction between the radiopaque and the non-radiopaque part of the wire. In our first validation studies, T_{mn} had been defined as the time elapsed between half of the saline has been injected (defined as t_0, and determined on the temperature curve from the shaft of the wire), and half of the saline has passed the sensor.[10,11] Yet, in vitro experiments have shown that 6 to 8 s after injecting 3 ml of saline at room temperature, the temperature of the shaft of the pressure wire (used as reference) returned to the baseline (body temperature). Accordingly, the first 2 ml of saline (the volume contained in the catheter) did not actually impact on the thermodilution curve. Therefore, in the modified algorithm (used in this study), t_0 has been shifted rightwards to the nadir of the shaft temperature curve in order not to take into account the extra-time due to the first 2 ml of saline. T_{mn} as used in the present was defined as the time elapsed between T_0 and the centre of gravity of area under the thermodilution curve obtained in the distal part of the vessel. Experiments performed in vitro (not shown) have demonstrated a better concordance (especially in the high values of CFR) between CFR calculated by measurements of absolute flow with thermodilution-derived flow reserve as calculated by the modified algorithm (CFR_{thermo}=0.99 CFR −0.01, R^2=0.91) than with the old algorithm (CFR_{thermo}=0.70 CFR −0.39, R^2=0.96).

$CFR_{Doppler}$ was defined as the ratio between the average peak velocity (APV) at hyperaemia and the APV at rest. CFR_{thermo} was defined as the ratio between the resting mean transit time ($T_{mn\ rest}$) and hyperaemic mean transit time ($T_{mn\ hyperaemia}$).

Statistical analysis

All data are presented as mean±SD. Variability between three measurements was defined as follows:

$$Var(a_1,a_2,a_3)=\max_{1,2,3}\frac{|ai-\bar{a}|}{\bar{a}}$$

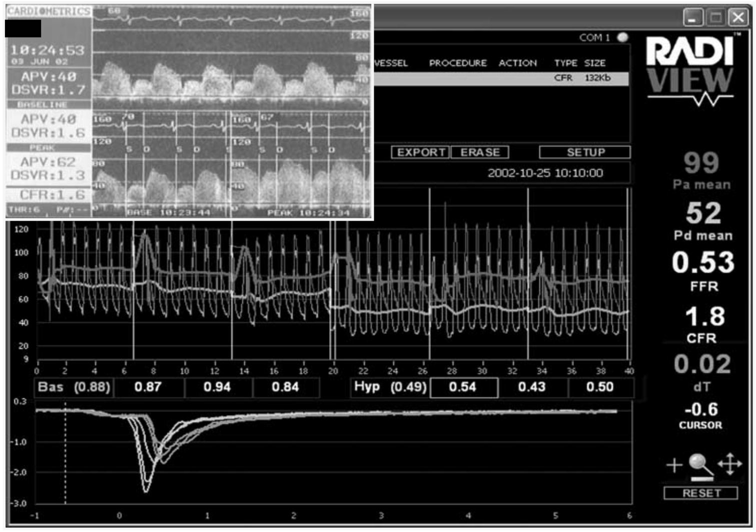

Fig. 1 Simultaneous pressure (upper part) and thermodilution curves (lower part) in a stenotic coronary artery. FFR equals 0.53, CFR_{thermo} equals 1.8. The baseline thermodilution curves are displayed in blue, the hyperaemic curves in green. Only the thermodilution curves recorded by the distal sensor are displayed. The x-axis under the thermodilution curves represents the time expressed in seconds after T_0. The thermodilution curve obtained by the shaft of the wire and which enables to determine T_0 are not displayed. The corresponding Doppler tracings are given in the upper left corner.

Variability at baseline and hyperaemia was compared by the Wilcoxon signed-rank test. All values of CFR are provided by vessel and can therefore be considered independent from each other. CFR_{thermo} was compared with $CFR_{Doppler}$ by linear regression analysis. A Bland—Altman plot is provided. This plot depicts the relationship between the average value between $CFR_{Doppler}$ and CFR_{thermo} and the absolute difference between $CFR_{Doppler}$ and CFR_{thermo}.

The mean times needed to obtain the measurements were compared by paired t-test analysis. A $P<0.05$ was defined as statistically significant.

Results

Feasibility data

Eighty-six patients were included. Twenty-seven were excluded due to sub-optimal quality of Doppler tracings as assessed by the operator. Among the remainder 59 patients with an optimal Doppler tracing (69%), FFR could be obtained in all patients (100%) and CFR_{thermo} could be obtained in 57 patients (97%). The average time to perform the measurements was 5±1 min for CFR_{thermo} and 6±2 min for $CFR_{Doppler}$ ($P=0.073$). Adequate thermodilution curves were obtained in 381 out of 408 studies, corresponding to 93% of the curves. The variability of T_{mn} within each set of three consecutive measurements was 14±8% at baseline and 17±11% at hyperaemia ($P<0.01$). In all but two cases, a good thermodilution curve could be obtained by repeating the injections, or by increasing the volume of the bolus to 4 ml. The main reason for non-adequate curves was a too low amplitude of the thermodilution curve and a too slow injection of the bolus of saline.

Table 1 Angiographic and haemodynamic data

All vessels ($n=42$)	
FFR	0.75±0.2
$CFR_{Doppler}$	2.0±0.8
CFR_{thermo}	2.2±0.9
Reference vessels ($n=16$)	
LAD/LCX/RCA	8/4/4
Reference diameter, mm	2.8±0.6
FFR	0.89±0.08
$CFR_{Doppler}$	2.4±1.0
CFR_{thermo}	2.8±1.0[a]
Stenotic vessels ($n=26$)	
LAD/LCX/RCA	12/5/9
Reference diameter, mm	2.9±0.6
Minimal lumen diameter, mm	1.3±0.4
% stenosis	59±17
FFR	0.66±0.16
$CFR_{Doppler}$	1.7±0.6
CFR_{thermo}	1.8±0.6

[a] $P<0.05$ versus $CFR_{Doppler}$

Comparison of CFR_{thermo} and $CFR_{Doppler}$

Because $CFR_{Doppler}$ was the reference method, all Doppler tracings were reviewed again in the core laboratory. Only the tracings which were rated optimal both at rest and at hyperaemia ($n=42$ in 34 patients) were kept for comparison with CFR_{thermo}. In these arteries the average value of CFR_{thermo} and $CFR_{Doppler}$ were similar (Table 1). A fair correlation was found between $CFR_{Doppler}$ and CFR_{thermo} as shown in Fig. 2. The Bland—Altman plot shows the trend for measuring higher values of CFR by thermodilution than by Doppler velocitometry, especially in the higher range of values. Accordingly, If only non-stenotic vessels were considered, the values of CFR_{thermo} were significantly higher than the corresponding values of $CFR_{Doppler}$.

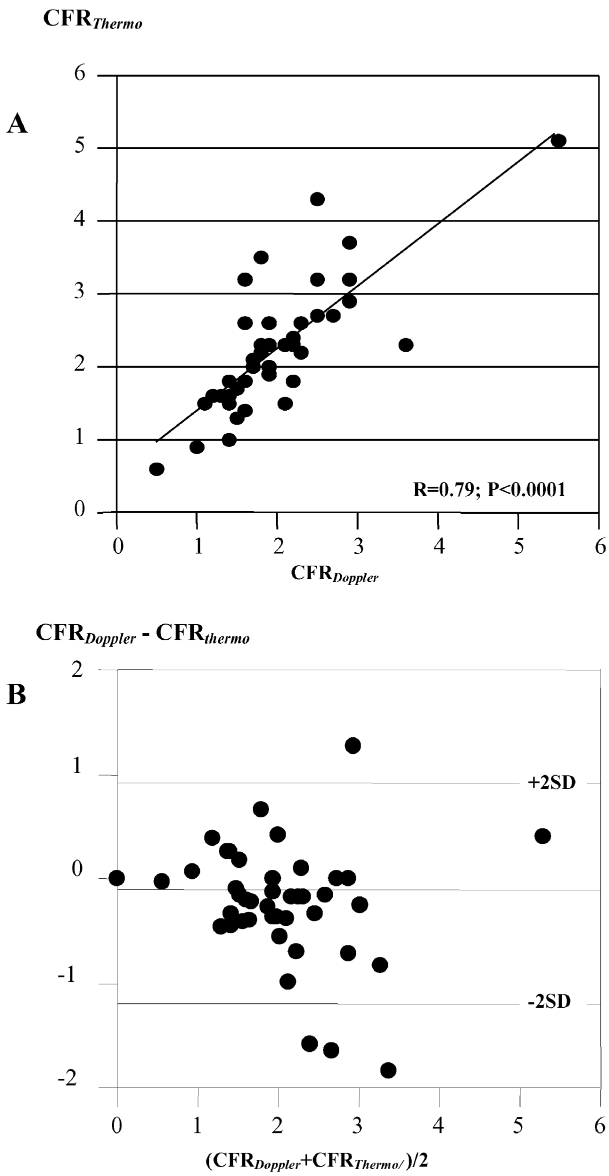

Fig. 2 Panel A: Correlation between CFR measured by Doppler ($CFR_{Doppler}$) and CFR measured by thermodilution (CFR_{thermo}). Panel B: Bland—Altman plot of the relationship between $CFR_{Doppler}$ and CFR_{thermo}. The x-axis depicts the average value between $CFR_{Doppler}$ and CFR_{thermo}, while the y-axis depicts the absolute difference between $CFR_{Doppler}$ and CFR_{thermo}.

Discussion

The present study was conducted over a 5-day period in eight centres, six of them without previous experience in coronary thermodilution, but all of them with an extensive experience with intracoronary Doppler and pressure measurements.

Feasibility of CFR_{thermo}

In order to compare the feasibility of CFR_{thermo} and $CFR_{Doppler}$ in a setting close to everyday clinical practice 86 consecutive patients scheduled for PCI or functional assessment were included. The data obtained in these unselected patient cohort (except for unstable syndromes, total occlusion of the target lesion and extreme tortuosities) indicate that CFR_{thermo} is easy to obtain in the vast majority of patients, significantly more than $CFR_{Doppler}$. In 31% of cases the operator considered the Doppler tracings sub-optimal. Optimal thermodilution curves could be obtained in 97% of patients. Several factors may contribute to this high success rate: in contrast to Doppler measurements, the exact position of the pressure/temperature sensor in the vessel lumen does not influence the T_{mn}. In addition, neither the exact volume nor the exact temperatures of the bolus influence T_{mn} as long as a well-defined thermodilution curve can be recorded and that the injection of saline does not modify the flow in itself.

CFR_{thermo} versus $CFR_{Doppler}$

In order to validate the CFR_{thermo} (obtained with a new standardized injection technique and by using a modified algorithm for T_{mn} calculation) only patients in whom an optimal Doppler tracing was obtained were taken into account. The results confirm a fair correlation between CFR_{thermo} and $CFR_{Doppler}$. In order to obtain an optimal reference method, only high quality Doppler tracings were selected without knowledge of the corresponding thermodilution tracings. In addition, the algorithm used for calculating T_{mn} was slightly modified according to new data obtained in vitro. Finally, a standardized and simplified injection technique of the bolus of saline was applied.

Limitations

Several limitations related to the study design or to the thermodilution technique should be taken into account: first, only 34 of the 86 patients included were finally considered for the validation of CFR_{thermo} by $CFR_{Doppler}$. The severity of the inclusion criteria was justified by the need for an optimal gold standard to gauge CFR_{thermo}. This, however, introduces a bias toward a higher feasibility of CFR_{thermo}.

Second, the variability of the T_{mn} is limited albeit not negligible so that it is recommended, very much like for cardiac output measurement by pulmonary thermodilution, to calculate the mean value of three consecutive measurements of T_{mn} for the calculation of CFR_{thermo}. Third, since CFR is the ratio of hyperaemic to resting flow, it is paramount to obtain truly baseline flow. In particular, contrast medium-induced hyperaemia should be avoided by flushing the catheter with saline at least 30 s before the acquisition of the first thermodilution curve. Also, the bolus of saline should not exceed 4 ml, to avoid any flow disturbances induced by the bolus of saline itself.

Fourth, CFR_{thermo} tends to overestimate $CFR_{Doppler}$ especially in non-stenotic vessel. This should be taken into account because these normal or near normal arteries are precisely those in which measuring CFR will be most desirable.

Fifth, in a minority of patients, two vessels were assessed. Therefore, the possible dependence of these measurements might lead to an underestimation of the variability.

Finally, the emergence of a major side branch between the guiding catheter and the stenosis may artificially increase the value of CFR when measured by thermodilution.

Conclusion

The present study confirms the feasibility and reliability of thermodilution-derived CFR measurements in a multicentric setting. The values of CFR obtained by thermodilution tend to be higher than those used to obtain Doppler flow velocity measurements. A single guide wire allowing simultaneous assessment of FFR and CFR represents a unique tool for a better understanding of the relative contribution of epicardial stenosis and microvascular impairment to myocardial ischaemia.

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