Efficacy of coronary fractional flow reserve using contrast medium compared to adenosine

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Abstract

Introduction: Coronary fractional flow reserve (FFR) is recommended as the gold standard method in evaluating intermediate coronary stenoses. However, there are significant debates concerning the agents and the timing of the measurement.

Aim: To compare the contrast medium induced Pd/Pa ratio (CMR) with the FFR.

Material and methods: We enrolled 28 consecutive patients with 34 intermediate lesions who underwent coronary FFR measurement by intracoronary (*i.c.*) adenosine. After baseline Pd/Pa was calculated, a single contrast medium (Iomeron) injection of 6 ml (3 ml/s) was performed manually. Within 10 s after the contrast medium injection, the CMR was calculated. Bolus injection of *i.c.* adenosine was performed to induce maximal hyperemia (from 60 µg to 600 µg), and when it was ≤ 0.80, the intermediate lesion was considered as significant.

Results: After bolus *i.c.* adenosine, 12 lesions of 34 (35.3%) were identified as significant. The CMR value was 0.86 ±0.06 (range: 0.71–0.97). There were no significant differences between FFR and CMR values (p = 0.108). A substantial positive correlation between adenosine and contrast values was detected (0.886 and p < 0.001). Good agreement in Bland-Altman analysis was revealed (mean bias was 0.027, 95% confidence interval 0.038–0.092). Receiver operating characteristics curve analysis showed 90.9% sensitivity and 91.7% specificity for a cut-off value of 0.85 for the CMR compared to FFR (≤ 0.80).

Conclusions: Our study showed that measuring the CMR is a feasible method compared to FFR. The CMR may be used in situations where adenosine cannot be administered.

Key words: adenosine, fractional flow reserve, contrast medium.

Introduction

Coronary fractional flow reserve (FFR) is the gold standard in evaluating the hemodynamic significance of intermediate coronary lesions [1]. In many clinical studies FFR-guided percutaneous coronary intervention (PCI) has proven a positive effect on patient long-term outcomes [2, 3]. Maximal hyperemia is essential to ensure FFR measurements; therefore intravenous (*i.v.*) adenosine infusion is accepted as a gold standard method [4]. However, the search for a different hyperemic agent began due to the fact that *i.v.* adenosine is expensive and has potential side effects. Intracoronary (*i.c.*) adenosine, papaverine, sodium nitroprusside and nicorandil have been tested as alternatives [5]. Intracoronary adenosine was accepted as an alternative method to *i.v.* adenosine [6, 7]. Recently, coronary hemodynamic assessment methods without a hyperemic agent, such as the instantaneous wave free ratio, have been studied widely. However, there is still controversy about the use of this method [1, 4]. Non-ionic contrast media are routinely used in coronary angiography. Hyperemic effects of these agents have long been known. Two encouraging studies demonstrated that measurement of the significance of intermediate stenoses was feasible by using contrast medium instead of adenosine [8, 9].

Aim

Our study aimed to compare contrast medium induced Pd/Pa ratio (CMR) with the FFR in the evaluation

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of hemodynamic significance of angiographically intermediate stenosis.

Material and methods

Study population

From September 2015 to December 2015, 28 consecutive patients with 34 angiographically intermediate stenoses who underwent FFR were enrolled.

All patients had 50–70% stenoses of at least one major epicardial artery by visual assessment. Exclusion criteria were: saphenous venous graft stenosis, recent (< 7 days) acute coronary syndrome, left main coronary stenosis, tandem lesions in epicardial artery, baseline Pd/Pa ≤ 0.80 and absolute contraindications to adenosine. The study was approved by the local ethics committee and conformed to the Declaration of Helsinki on human research.

Pressure measurements and study protocol

All interventions were performed from the femoral artery. 100 IU/kg unfractionated heparin (UFH) and 0.1–0.2 µg *i.c.* nitroglycerin (NTG) were injected and a 0.014" pressure wire (Volcano Corporation, San Diego, California) was calibrated, then it was nulled and introduced via a guiding catheter. Before passing the lesion both curves (aortic pressure and the wire pressure curve) were equalized. After that the wire was introduced distal to the stenosis and the baseline Pd/Pa was calculated (Pd: mean coronary pressure distal to coronary lesion, Pa: mean aortic pressure).

Measurement of CMR

After baseline Pd/Pa was calculated, single contrast medium (Iomeron) injection of 6 ml (3 ml/s) was performed manually. Ten seconds after the contrast medium injection, Pd/Pa was calculated. Afterwards, the guiding catheter was flushed with saline.

Measurement of FFR

Bolus injection of *i.c.* adenosine was performed to induce maximal hyperemia (from 60 µg to 600 µg). Incremental boli of *i.c.* adenosine (60 µg, 300 µg, 600 µg) were administered with each successive dose given at least 60 s apart from the previous one or after returning to baseline hemodynamic conditions. Each administration was performed in 5 to 10 s followed by a rapid flush of saline. The FFR ≤ 0.80 was considered significant.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, categorical variables were expressed as percentages. To test the distribution of continuous data, the Kolmogorov-Smirnov test was used. Statistical significance of the relationship between CMR and FFR was assessed by Student's *t*-test. The relationship between CMR and FFR was quantified with Pearson's correlation coefficient. Agreement between CMR and FFR was assessed by Bland-Altman plots and 95% confidence intervals. Receiver operating characteristics (ROC) curve analysis was performed to determine the cut-off value for CMR in prediction of hemodynamically significant lesions determined by FFR. A p-value < 0.05 was considered statistically significant. SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Twenty-eight patients with 34 intermediate coronary lesions were enrolled in this study (age: 63.4 ±12.8; 79% were male). Main characteristics of the study population are summarized in Table I. Baseline Pd/Pa was 0.92 ±0.04 (range: 0.84–0.99). The FFR was 0.83 ±0.07 (range: 0.69–0.96). Twelve (35.3%) lesions were significant (FFR ≤ 0.80). Of those 9 patients underwent PCI and three patients underwent CABG. Transient atrioventricular block was observed in 12 patients, and 18 patients experienced angina and/or dyspnea. The CMR was 0.86 ±0.06 (range: 0.71–0.97) (Figure 1). According to baseline Pd/Pa, both adenosine and the contrast medium caused significant hyperemia and lowered hyperemic Pd/Pa values (FFR and CMR). There were no significant differences between FFR and CMR values (p = 0.108). A substantial positive correlation between FFR and CMR was detected (r = 0.886 and p < 0.001) (Figure 2).

Good agreement in Bland-Altman analysis was revealed (mean bias was 0.027, 95% confidence interval (CI) –0.038 to 0.092) (Figure 3). In addition there was a significant correlation between Pd/Pa, FFR and CMR values (r = 0.777, p < 0.001 and r = 0.915, p < 0.001, respectively).

Table I. Baseline clinical and angiographic characteristics of study population

Parameter	Value
Age, mean ± SD	63.4 ±12.8
Sex – male (%)	79
Hypertension (%)	39
Diabetes mellitus (%)	18
Smoking (%)	61
Previous CAD (%)	46
Previous PCI (%)	32
Vessels (%):	
LAD	62
RCA	24
LCx	14

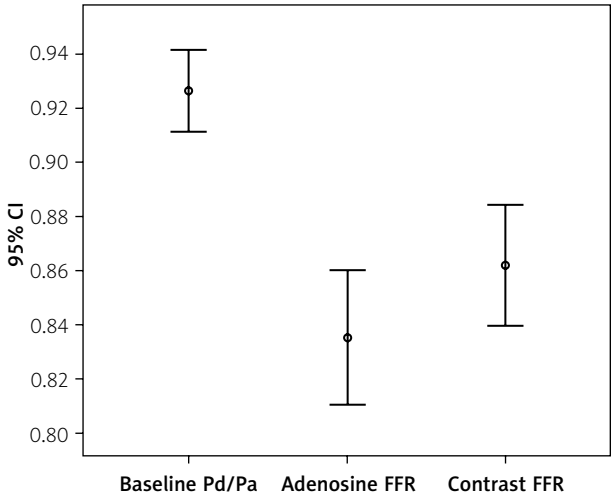

Figure 1. Error plot for baseline Pd/Pa, adenosine FFR and contrast FFR

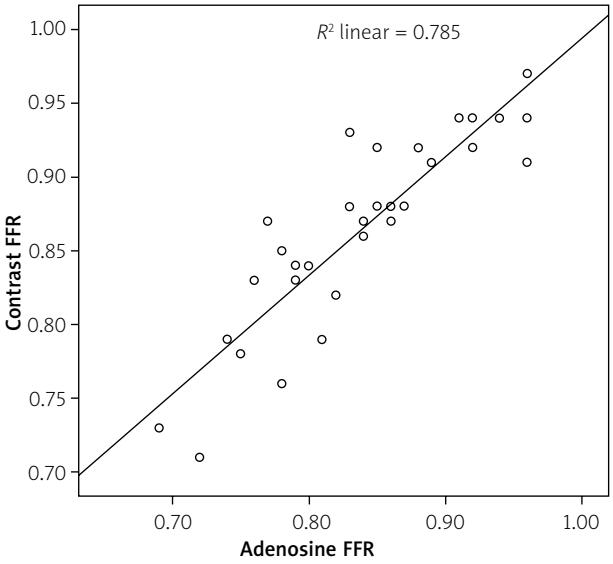

Figure 2. Correlation plot between adenosine and contrast FFR

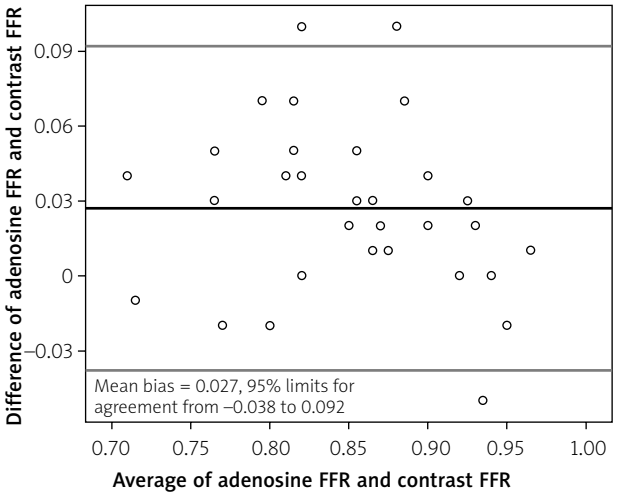

Figure 3. Bland-Altman plot showed a good agreement between contrast FFR and adenosine FFR

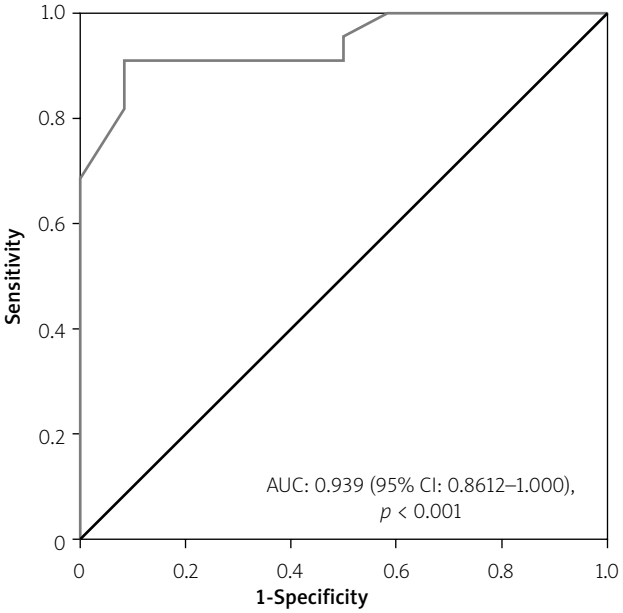

Figure 4. ROC curve analysis for contrast FFR in prediction of hemodynamically significant coronary lesion assessed by adenosine FFR

The ROC curve analysis showed 90.9% sensitivity and 91.7% specificity for a cut-off value of 0.85 for the CMR in comparison to FFR ≤ 0.80 (Figure 4). The overall accuracy was 91.2%, positive predictive value was 91.2%, negative predictive value was 91.1% and Bayesian post-test probability was 91% (Figure 5). The false positive rate was 2/13 and the false negative rate was 1/21.

Discussion

Our study demonstrated that CMR measurements using contrast medium are feasible and represent a new index in the measurement of hemodynamically significant coronary stenoses as an alternative to adenosine. Using the cut-off value of 0.85 for the CMR could be a viable option in patients who have a contraindication to the administration of adenosine. The FFR is regarded as the gold standard in the hemodynamic evaluation of intermediate coronary lesions [7, 10–12]. Long-term CV risk was found to be lower for FFR-guided PCI when compared to angiographically guided PCI [2, 3]. For FFR measurements maximal hyperemia induced by adenosine is mandatory [4, 6, 13]. Because of potential side effects and *i.v.* adenosine challenges (*i.v.* infusion, time consuming, etc.), the use of various alternative agents

has been studied (*i.c.* adenosine, regadenoson, nitroprusside, etc.) [5, 14]. Furthermore, in order to overcome financial difficulties or side effects associated with the use of medications, a new adenosine-free index based on the measurement of the resting gradient called the instantaneous wave free ratio (iFR) was suggested [15]. However, there are still ongoing debates regarding the results of iFR studies.

Currently, there are many studies being conducted with the aim of finding a cheaper and easy-to-use method for the evaluation of hemodynamic significance of coronary stenoses comparable to FFR. One of them is the CMR [5, 14]. It has been known for a long time that the contrast medium is a hyperemic agent [14]. Even though it was reported that the contrast medium causes only submaximal hyperemia [14], it has been determined recently that it causes effective enough hyperemia and could be used in the evaluation of intermediate coronary stenoses [9, 16]. In the RINASCI study, a substantial correlation (r = 0.98) and good agreement (mean bias: 0.02, 95% CI: –0.03 to 0.07) were determined in the measurements of 102 intermediate lesions between FFR and the CMR [16]. Similarly, in the study by Spagnoli *et al.* a substantial correlation was determined (r = 0.90) [17]. The same was confirmed in our study. We determined a substantial correlation (r = 0.886) and good agreement (mean bias: 0.027, 95% CI: –0.038 to 0.092) between the FFR and the CMR measurements. Besides contrast medium, iFR has emerged as an alternative method to FFR [15]. In the recent ADVISE study, a strong correlation (0.90) and a good agreement (0.05 ±0.19) between iFR and FFR were established [18]. However, the agreement was lower than in our and RINASCI studies. In a comprehensive study Kanaji *et al.* (CMR, iFR and contrast iFR) determined r = 0.85, mean bias: 0.016 ±0.055 between CMR and FFR; r = 0.74, mean bias: 0.072 ±0.064 between iFR and FFR; and r = 0.93, mean bias: 0.038 ±0.051 between contrast iFR and FFR. In their study, contrast iFR had no superiority regarding the compliance with FFR, whereas the correlation was found to be stronger [9].

Our study had several limitations. The most important limitation was a low number of patients. Secondly, unlike other studies in the literature, we used *i.c.* adenosine instead of *i.v.* Thirdly, while determining the CMR, contrast medium was injected manually. Manual administration is more common in daily practice, which may be important in terms of demonstrating the effect of administering the contrast medium rather than being considered as a limitation. For the CMR to become a standard method in the evaluation of hemodynamic significance of coronary stenoses, the method should be standardized and validated with more comprehensive studies, measurement time should be evaluated (end-diastolic or mean), and more importantly, its relationship with the long-term clinical outcomes should be determined.

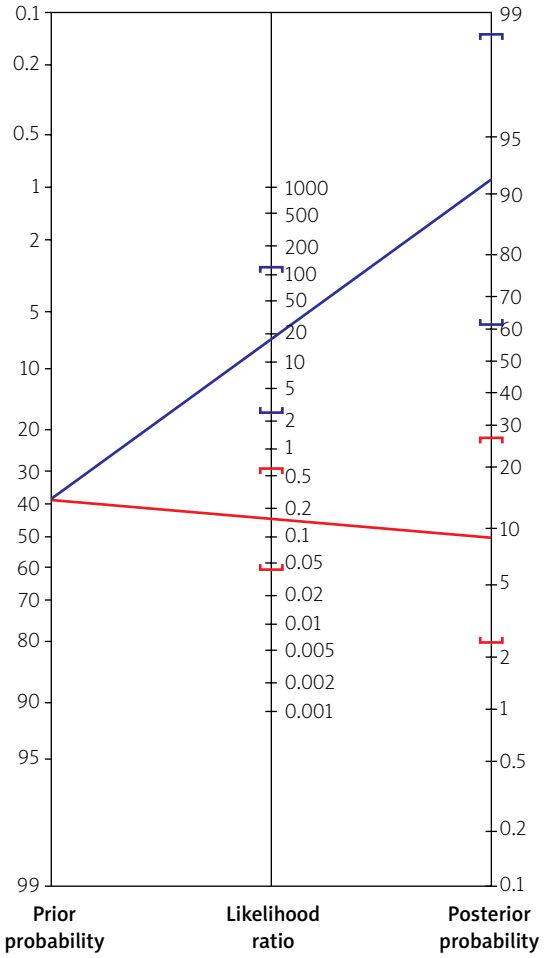

Figure 5. Bayesian nomogram (a straight line through the pretest probability of 38% and the LR+ of 17 yields a posttest probability of 91.2%; a straight line through the pretest probability of 38% and the LR– of 0.16 yields a posttest probability of 8.8%)

Conclusions

Our study suggests that the CMR with manually administered contrast medium is feasible and that the CMR may be used in situations where the administration of adenosine is contraindicated.

Conflict of interest

The authors declare no conflict of interest.

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