The Influence of Contrast Media Dose and Osmolality on the Diagnostic Performance of Contrast Fractional Flow Reserve

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Abstract

Background: Both contrast media dose and osmolality may affect the degree of hyperemia and therefore diagnostic accuracy achieved with contrast fractional flow reserve (cFFR).

Methods and Results: A total of 763 patients were prospectively enrolled from 12 institutions. cFFR, instantaneous wave-free ratio (iFR), distal pressure/aortic pressure (Pd/Pa) at rest and FFR were measured. Patients were categorized by the osmolality and volume of contrast media: low- and iso-osmolality (n=574 and 189); low (<8 milliliters) and high volume (n=341 and 422). We compared the diagnostic performance of cFFR between the low- and iso-osmolality and between low and high volume contrast, and investigated its superiority over other resting indices using FFR ≤0.80 as a reference standard. Both the low- and iso-osmolality groups showed comparable diagnostic accuracy of cFFR (84.8% versus 88.8%) as did both the low and high contrast volume groups (83.2% versus 87.9%). By receiver operator characteristics curve analysis, cFFR provided better diagnostic performance than resting indices regardless of contrast osmolality and volume (P<0.001 versus iFR and Pd/Pa for all groups). There was no significant difference between the area under the curve of cFFR in the low- and iso-osmolality groups (0.938 versus 0.957, P=0.40) and in the low and high volume contrast groups (0.939 versus 0.949, P=0.61). Multivariable logistic regression analysis showed that neither contrast osmolality nor volume significantly affected the diagnostic accuracy of cFFR.

Conclusions: Contrast volume and osmolality do not affect the diagnostic accuracy of cFFR. These data suggest that cFFR can be broadly applied in most catheterization laboratories.

Clinical Trial Registration URL: **https://www.clinicaltrials.gov**. Unique identifier: NCT02184117.

Introduction

Pressure-derived fractional flow reserve (FFR) is the reference standard in catheterization laboratories to assess the physiologic severity of coronary artery stenosis.[1,2] FFR-guided therapy has been shown to improve patient outcomes by determining the appropriate selection of patients for percutaneous coronary intervention (PCI).[3,4] For its accurate calculation, FFR requires maximal coronary hyperemia, usually achieved with adenosine.[5-7] However, cost, time, side effects or practical reasons associated with adenosine may limit the widespread utilization of FFR. Therefore, adenosine-free pressure-derived indices have been drawing attention.[8-16]

The pressure ratio between the distal coronary artery and aorta during submaximal hyperemia induced by intracoronary injection of contrast medium, so-called contrast FFR (cFFR) emerged as an adenosine-free index and has been shown to be superior to other adenosine-free indices obtained at pure resting status in predicting FFR and reducing the use of adenosine.[13-16] In addition, cFFR is immediately available using conventional contrast media routinely administered for coronary angiography and does not require special software or an electrocardiogram tracing.[15,16]

However, there is a theoretical concern that both contrast dose and osmolality may affect the degree of hyperemia and therefore the diagnostic accuracy achieved with cFFR. In clinical practice, the type and dose of contrast media used for cardiac catheterization varies. We, therefore, performed this analysis to investigate the impact of contrast osmolality and dose on the diagnostic performance of cFFR.

Methods

Study design and population.

The CONTRAST (Can contrast injection better approximate FFR compared to pure resting physiology?) study[16] is a multi-center, prospective, investigator-initiated observational study, designed to evaluate the diagnostic performance of contrast FFR (cFFR), resting distal coronary pressure to aortic or proximal coronary pressure (Pd/Pa), and the instantaneous

wave-free ratio (iFR) to predict FFR (registered at clinicaltrials.gov: identifier NCT02184117).

The current study enrolled 763 patients from the CONTRAST study who were 18 years of age or older and underwent routine FFR assessment for standard indications. In cases of multivessel disease, only the first lesion studied using FFR was included. Exclusion criteria included prior coronary artery bypass surgery, known severe left ventricular hypertrophy (septal wall thickness >13 mm) or dysfunction (left ventricular ejection fraction <30%), extremely tortuous or calcified coronary arteries precluding intracoronary physiologic measurement, contraindication to adenosine, recent (within 3 weeks prior to cardiac catheterization) ST-segment elevation myocardial infarction, or renal insufficiency such that additional contrast would pose unwarranted risk. Culprit lesions for acute infarction were also excluded. This study was approved by an institutional review committee from each participating site, and each patient provided written informed consent.

Coronary Physiology Procedure.

All coronary physiologic parameters were measured with a 0.014-inch pressure sensor guidewire (PressureWire Certus or Aeris wire and the QUANTIEN system, St. Jude Medical). The pressure guidewire was advanced distal to the target lesion. The first measurements were made for at least 1 minute to record resting physiology. Next, an IC bolus of contrast medium was injected either manually or with an injector. The volume and type of IC contrast medium was not mandated but with a recommendation for 6 to 10 ml. Then, 100-200 μg of intracoronary adenosine was injected.[17] Finally, intravenous (IV) adenosine was administered at140 μg/kg/min for 2 minutes via either a central or large-bore peripheral IV line. Each measurement was repeated twice in the same way with at least a one minute interval to ensure pressure recovery. Operators were encouraged to perform both IC and IV adenosine measurements in duplicate, but all 4 were not mandatory as long as at least one technique was repeated. All physiologic tracings were sent to an independent core laboratory (Cardiovascular Research Foundation, New York) for off-line analysis. The quality of pressure tracings and electrocardiographic data were carefully evaluated. FFR was measured as mean distal coronary pressure divided by aortic or proximal coronary pressure during maximal hyperemia with IC injection and IV infusion of adenosine; cFFR was

measured during submaximal hyperemia with IC injection of contrast; and Pd/Pa was measured at rest. The iFR was defined as the ratio of distal coronary pressure to aortic pressure during the wave-free period (approximately 75% of late diastole) at rest [8], automatically calculated by the core laboratory using HARVEST software (Volcano Corporation). Because there could be as many as 4 FFR values for each subject (2 IC and 2 IV), a summary FFR value was computed by the following hierarchy: the average of 2 IV values, a single IV value, the average of 2 IC values, or a single IC value. When both test and retest values were present, their average was used.

Study Endpoints.

The primary purpose of this analysis was to investigate whether the osmolality and dose of contrast media impact the diagnostic performance of cFFR. The patients were categorized by the osmolality of contrast media used for cFFR measurement into two groups: low-osmolality (including Iobitridol, Iohexol, iomeprol, iopamidol, iopromide, ioversol, ioxaglate) and iso-osmolality group (including Iodixanol) and by the median value of contrast volume: high contrast volume (≥8 ml) and low contrast volume (<8 ml).

The significance of a coronary artery lesion based on adenosine-free indices was defined as cFFR ≤0.83, iFR <0.90, and Pd/Pa <0.92 according to previous studies.[10,16] We explored the diagnostic performance of the hybrid strategy in which adenosine can be avoided for values above or below a defined threshold, but must be administered when the value falls within those limits (adenosine zone). The range of 0.83-0.88, 0.87-0.94 and 0.89-0.95 was chosen for cFFR, iFR and Pd/Pa adenosine zone as used to achieve 94% rounded accuracy in CONTRAST study cohort.[16]

Statistical Analysis.

Continuous variables are presented as a median and interquartile range (IQR) and were compared with Mann-Whitney U test. Categorical variables are presented as counts and percentages and were compared using the Fisher's exact test. Correlations between FFR and adenosine-free indices were tested with Pearson's correlation coefficient. Receiver-operating characteristics (ROC) curve analysis was used to examine the diagnostic performance of cFFR, iFR and Pd/Pa as a predictor of FFR ≤0.80. The area

under the ROC curve (AUC) was compared with the method of DeLong et al. or Hanley & McNeil for correlated or uncorrelated curves, respectively.[18,19] Multivariable logistic regression models were used to assess whether contrast osmolality and volume were predictors of diagnostic performance of cFFR. In the models, the diagnostic agreement between cFFR and FFR (agreement or not) in positive FFR, negative FFR, and entire patients were used as a dependent variable for sensitivity, specificity and accuracy, respectively, while contrast osmolality (iso- vs. low-osmolality) and volume (high vs. low volume) were used for independent variables. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered significant.

Results

Patient characteristics are presented in Tables 1A and 1B. There were 574 patients in the low-osmolality group versus 189 patients in the iso-osmolality group and 341 patients in the low contrast volume group versus 422 patients in the high contrast volume group. The median IC contrast volume was similar in the low- and iso-osmolality groups (8 [6-8] ml versus 8 [6-10] ml, P = 0.12). Iso-osmolality contrast was more frequently used in patients with advanced age, renal insufficiency, female sex, and dyslipidemia. Low volume contrast was more frequently used in patients with advanced age, female sex, hypertension, diabetes mellitus and dyslipidemia but without family history of coronary artery disease. The cFFR value was lower in the iso-osmolality group compared to the low-osmolality group. Pd/Pa, iFR, and FFR values were not significantly different between the two osmolality groups (Table 2A). The Pd/Pa, iFR and cFFR values were higher in the low contrast volume group compared to the high contrast volume group. The FFR value was not significantly different between the low and high contrast volume groups (Table 2B).

Correlation and Agreement between the Adenosine-Free Indices and FFR.

cFFR correlated well with FFR in both low- and iso-osmolality groups, as well as in both low and high volume contrast groups. Among the three adenosine-free indices, cFFR showed the highest correlation coefficient with FFR (Figure 1 and 2) and the best agreement with FFR with the smallest scatter of data by the Bland-Altman Plots (Figure 3 and 4) in all

groups.

Comparisons of Diagnostic Accuracy of the Adenosine-Free Indices

The results of the ROC analysis of cFFR, iFR, and Pd/Pa to predict FFR ≤0.80 are shown in Figure 5 and 6. When comparing AUC, cFFR provided better diagnostic performance than resting indices regardless of contrast osmolality or volume (P <0.001 versus iFR and Pd/Pa for all groups). There was no significant difference between the AUC of cFFR in the low- and iso-osmolality groups (0.938 versus 0.957, P = 0.40) and in the low and high volume contrast groups (0.939 versus 0.949, P = 0.61).

Application of Binary Strategies and Effect of Contrast Osmolality and Volume

When using a binary strategy with a defined threshold of cFFR ≤0.83, low osmolality contrast had lower sensitivity and slightly higher specificity than iso-osmolality contrast, as did low contrast volume compared to high contrast volume (Table 3). Multivariable logistic regression models showed that contrast osmolality and volume independently affected sensitivity and specificity of cFFR (Table 4). Sensitivity was likely to increase, and specificity was likely to decrease as contrast volume increased, or Iso-osmolalar contrast was used (versus low-osmolar). However, the overall diagnostic accuracy of cFFR was not significantly affected by contrast volume and osmolality.

Application of Hybrid Strategies

When employing a hybrid strategy, the diagnostic accuracy of cFFR-FFR hybrid strategy achieved similarly high values of 94.9% and 95.3% in the low- and iso-osmolality and 94.4 % and 95.4% in the low and high contrast volume groups with high sensitivity (91.4% and 97.4% in the low- and iso-osmolality; and 89.7% and 95.4% in the low and high contrast volume groups) and high specificity (98.4% and 93.6% in the low- and iso-osmolality; and 95.4% and 99.3% in the low and high contrast volume groups). Furthermore, the percentages of patients requiring adenosine were less than 30% in all groups: 25.5% and 28.4% in the low- and iso-osmolality and 22.4% and 29.4% in the low and high contrast volume groups. On the other hand, 42.8 or 46.0% of patients needed adenosine for iFR-FFR or Pd/Pa-FFR hybrid strategies. Multivariable logistic regression revealed that neither contrast osmolality (Odds ratio 1.089 [95% confidence interval: 0.483 − 2.45]) nor volume

(Odds ratio 1.237 [0.620 − 2.466]) was associated with the diagnostic agreement of cFFR-FFR hybrid strategy with a minimal effect of contrast osmolality and volume on sensitivity (odds ratio of osmolality 3.955 [0.901 – 17.326] and odds ratio of volume 2.618 [1.080 – 6.341]) and specificity (odds ratio of osmolality 0.274 [0.075 – 1.006] and odds ratio of volume 0.165 [0.020 – 1.329]).

Discussion

The main finding of this study is that the diagnostic accuracy of cFFR in comparison to FFR is not affected by contrast osmolality or volume. cFFR has better diagnostic accuracy than iFR and Pd/Pa regardless of whether low- or iso-osmolalar contrast is used and whether low or high volume contrast is injected. Both contrast osmolality and volume affect sensitivity and specificity of cFFR, but in opposite directions such that the overall diagnostic accuracy is not different between the low or iso-osmolar agents or between low or high volume injection.

Previous studies have shown that cFFR has greater diagnostic accuracy than other resting adenosine-free indices, however the contrast osmolality and volume used to measure cFFR in those studies varied.[13-16] In theory, both contrast osmolality and volume injected might affect the degree of hyperemia achieved when measuring cFFR and therefore impact its diagnostic accuracy.[20,21] The mechanism by which contrast media induce submaximal hyperemia is not entirely clear but presumed to be partially due to transient hypoxia from replacement of oxygenated blood and partially due to stimulating endothelial paracrine pathways.[17]

In the present study, greater contrast volume and lower osmolality were associated with an upward trend in sensitivity and a downward trend in specificity, which may mean that higher contrast volume and lower osmolar contrast result in greater hyperemia. With respect to the hyperemic effect of contrast osmolality, one might think that higher osmolar contrast would be more hyperemic, however iodixanol an iso-osmolar contrast (lower osmolality than

low osmolar contrast agents), has higher viscosity than the low-osmolality contrast media,[22] which might contribute to its greater hyperemia since viscosity of the contrast media directly influences the endothelium-derived vasodilatory response of the coronary vasculature and therefore the degree of hyperemia.[23]

Previous studies have investigated the influence of contrast dose on contrast-induced hyperemia, but mostly using older contrast agents different from contemporary, lower osmolar contrast.[21,24] A recent study tested progressive contrast doses (3, 6, 10, and 15 ml) of iodixanol in 12 left coronary lesions, showing that the percentage of cFFR relative to Pd/Pa decreased as contrast dose increased from 3, 6 to 10 ml.[14] The result was in line with our study, suggesting the presence of a dose-response relationship between contrast volume and degree of contrast-induced hyperemia in the dose range typically used during coronary angiography. Although the overall diagnostic accuracy of cFFR did not change based on the volume or osmolality of the contrast media injected, Table 3 shows that the sensitivity of cFFR was higher in patients receiving higher contrast volume, while specificity was lower. Likewise, the sensitivity of cFFR was higher in patients receiving iso-osmolar contrast compared to those receiving low osmolar contrast. It is important to note that the same patients were not randomized to high or low volume contrast or to low or iso-osmolar contrast. For this reason, the patients who received higher volumes of contrast were different from those who received lower volume contrast, for example, and these differences contribute to the changes in sensitivity and specificity which were observed.

Because the relationship between sensitivity and specificity is a trade-off relation, our threshold of cFFR≤0.83 was chosen to maximize accuracy, not to maximize either just sensitivity or just specificity. . Another method of using cFFR simply applies the FFR threshold, namely cFFR≤0.80. In this case, cFFR reaches 100% specificity (all cFFR positive lesions are FFR positive) but with reduced sensitivity (some cFFR negative lesions are still FFR positive due to more potent hyperemia with adenosine). Therefore the

differences in sensitivity and specificity represent tradeoffs on the ROC curve, which different operators may weight differently (a 'rule-in' versus 'rule-out' threshold) from our choice to maximize accuracy. Although contrast volume and osmolality affect the sensitivity and specificity of cFFR, because these parameters change in opposite directions the overall diagnostic performance of the binary strategy of cFFR is not affected to a great degree by contrast volume injected or osmolality. However, if one is most interested in achieving a high sensitivity then a higher contrast volume and a lower osmolality increase the sensitivity of cFFR. Likewise, if one is most interested in achieving a high specificity then a lower contrast volume and a higher osmolality increase the specificity of cFFR.

It is challenging to determine the reason for the lower cFFR in patients receiving higher volume of contrast (Table 2B). At first glance, one might conclude that this is a result of greater hyperemia with a larger volume of contrast. However, unfortunately patients were not randomized to lower or higher volumes of contrast, which means that we cannot assume the difference is due to a greater hyperemic effect in patients receiving a higher volume of contrast, because it may be due to the significant differences in baseline characteristics between the two groups (Table 1B). For example, there were significantly more diabetic, hypertensive, dyslipidemic, and female patients who received a lower volume of contrast. All of these clinical characteristics have been associated with microvascular dysfunction; this may explain the higher cFFR value in the patients who received the lower volume of contrast. It may also explain the significantly higher Pd/Pa and iFR seen in the low volume contrast group compared to the high volume contrast group, differences which clearly are not related to contrast volume. Why FFR did not change as well may be due to higher resting flow in the patients who received high volume contrast, which could explain the lower values recorded with the adenosine-free indices. Once adenosine is administered, it abolishes any contribution of resting flow and FFR values may therefore be no different between the two groups.

With respect to the higher cFFR seen in the low osmolality group compared with the iso-osmolality group (Table 2A), again we cannot assume that this is due to an effect of the

osmolality. This is because the patients were not randomized to low osmolality or iso-osmolality contrast and therefore, as mentioned above, differences in baseline clinical characteristics might explain the difference in cFFR.

As FFR is the reference standard, a binary strategy of cFFR during submaximal hyperemia achieved a diagnostic accuracy of 85 to 90%.[13-16] Employing a cFFR-FFR hybrid strategy can raise the accuracy to around 95%.[13-16] The present study showed that the diagnostic accuracy of the hybrid strategy was not significantly affected by contrast volume or osmolality, and avoids adenosine in over 70% of patients.

Limitations

Our study has several limitations. First, the present study is a non-randomized, post hoc analysis of the CONTRAST study. Therefore, the results should be interpreted as hypothesis generating. A randomized study comparing volume and osmolality of contrast media injected in the same patients would help to clarify whether or not any real differences exist in diagnostic accuracy, as well as sensitivity and specificity of cFFR. Second, we did not investigate the impact of the differences in other factors of contrast media such as pH or ionicity. Third, because the cutoff values for both binary and hybrid strategies are derived from the CONTRAST study, the reproducibility of the results should be evaluated in other cohorts. Fourth, contrast volume between 6 to 10 ml was used in almost 98% of cases in the CONTRAST study, thus, the result of this study cannot be extrapolated to smaller or larger contrast volume. Fifth, because the protocol did not stipulate that operators measure the exact amount of contrast used with each cFFR measurement, but asked operators to provide an estimate of the contrast volume, there is some degree of uncertainty surrounding the volume administered. Finally, the diagnostic accuracy is influenced by disease prevalence (i.e. in this study the prevalence of positive FFR [≤0.80]). However, as the prevalence of positive FFR was similar between iso- and low-osmolality groups, we used the models for accuracy to look at the effect of osmolality and volume on the accuracy of cFFR.

Conclusion

Neither contrast volume nor osmolality significantly affect the overall diagnostic accuracy of cFFR. cFFR should be broadly applicable in clinical practice when operators prefer to avoid adenosine for physiological lesion assessment. However, if one is most interested in achieving either high sensitivity alone or high specificity alone for cFFR, then contrast volume and osmolality can be important.

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Table 1A. Patient Characteristics in Low and Iso-osmolality Groups.

	Overall (n = 763)	Low-osmolality (n = 574)	Iso-osmolality (n = 189)	P value
Age, years	67 (58-73)	66 (57-73)	68 (63-74)	0.002
Male, n (%)	547 (72)	433 (75)	114 (60)	<0.001
Current smoking, n (%)	146 (19)	114 (20)	32 (17)	0.40
Hypertension, n (%)	545 (71)	406 (71)	139 (74)	0.52
Dyslipidemia, n (%)	508 (67)	366 (64)	142(75)	0.004
Diabetes mellitus, n (%)	219 (29)	162 (28)	57 (30)	0.64
Family history, n (%)	191 (25)	164 (29)	27 (14)	<0.001
Renal insufficiency, n (%)	74 (10)	37 (7)	37 (20)	<0.001
Previous MI	198 (26)	158 (28)	40 (21)	0.086
Coronary vessel				0.59
Left main	25 (3)	21 (4)	4 (2)	
LAD	460 (60)	339 (59)	121 (64)	
LCx	138 (18)	105 (18)	33 (18)	
RCA	140 (18)	109 (19)	31 (16)	
Contrast volume	8 (6-10)	8 (6-10)	8 (6-8)	0.12
Stenosis Classification by Angiography				0.27
≤70%	677 (88.7)	512 (89.2)	165 (87.3)	
71 – 90%	77 (10.1)	57 (9.9)	20 (10.6)	
91 – 99%	5 (0.7)	2 (0.4)	3 (1.6)	
unknown	4 (0.5)	3 (0.5)	1 (0.5)	

Values are median (interquartile range) or n (%). IC, intracoronary; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; MI, myocardial infarction, RCA, right coronary artery.

Table 1B. Patient Characteristics in Low and High Contrast Volume Groups.

	Overall (n = 763)	Low volume (n = 341)	High volume (n = 422)	P value
Age, years	67 (58-73)	66 (58-73)	67 (59-73)	0.002
Male, n (%)	547 (72)	223 (65)	324 (77)	0.001
Current smoking, n (%)	146 (19)	70 (21)	76 (18)	0.41
Hypertension, n (%)	545 (71)	269 (79)	276 (65)	<0.001
Dyslipidemia, n (%)	508 (67)	252 (74)	256(61)	0.001
Diabetes mellitus, n (%)	219 (29)	114 (33)	105 (25)	0.010
Family history, n (%)	191 (25)	73 (21)	118 (28)	0.044
Renal insufficiency, n (%)	74 (10)	38 (11)	36 (9)	0.27
Previous MI	198 (26)	92 (27)	106 (25)	0.56
Coronary vessel				0.34
Left main	25 (3)	10 (3)	15 (4)	
LAD	460 (60)	195 (57)	265 (63)	
LCx	138 (18)	69 (20)	69 (16)	
RCA	140 (18)	67 (20)	73 (17)	
Contrast volume	8 (6-10)	6 (6-7)	10 (8-10)	<0.001
Iso-osmolality contrast	189 (25)	81 (24)	108 (26)	0.61
Stenosis Classification by Angiography				0.32
≤70%	677 (88.7)	303 (88.9)	374 (88.6)	
71 – 90%	77 (10.1)	35 (10.3)	42 (10.0)	
91 – 99%	5 (0.7)	3 (0.9)	2 (0.5)	
unknown	4 (0.5)	0 (0.0)	4 (1.0)	

Values are median (interquartile range) or n (%). IC, intracoronary; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; MI, myocardial infarction, RCA, right coronary artery.

Table 2A. Pressure Wire Indices in Low and Iso-osmolality Groups.

	Overall (n = 763)	Low osmolality (n = 574)	Iso osmolality (n = 189)	P value
Pd/Pa	0.92 (0.88 – 0.95)	0.92 (0.88 – 0.93)	0.92 (0.88 – 0.95)	0.16
iFR	0.90 (0.85 – 0.94)	0.90 (0.85 – 0.95)	0.89 (0.84 – 0.94)	0.060
cFFR	0.86 (0.79 – 0.91)	0.86 (0.80 – 0.91)	0.84 (0.78 – 0.90)	0.029
FFR	0.81 (0.74 – 0.87)	0.80 (0.73 – 0.86)	0.83 (0.74 – 0.88)	0.21

Values are median (interquartile range). cFFR, contrast-based fractional flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; Pd/Pa, distal pressure / aortic pressure.

Table 2B. Pressure Wire Indices in Low and High Contrast Volume Groups.

	Overall (n = 763)	Low volume (n = 341)	High volume (n = 422)	P value
Pd/Pa	0.92 (0.88 – 0.95)	0.93 (0.89 – 0.96)	0.92 (0.88 – 0.95)	0.004
iFR	0.90 (0.85 – 0.94)	0.91 (0.86 – 0.95)	0.89 (0.83 – 0.94)	0.001
cFFR	0.86 (0.79 – 0.91)	0.87 (0.80 – 0.92)	0.85 (0.79 – 0.89)	0.001
FFR	0.81 (0.74 – 0.87)	0.80 (0.74 – 0.87)	0.81 (0.73 – 0.87)	0.88

Values are median (interquartile range). cFFR, contrast-based fractional flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; Pd/Pa, distal pressure / aortic pressure.

Table 3. Diagnostic performance of cFFR using a binary threshold of cFFR≤0.83 and AUC of cFFR for predicting FFR ≤0.80.

	Sensitivity	Specificity	Accuracy	AUC
Low-osmolality group	72.6%	97.2%	84.8%	0.938
Iso-osmolality group	86.8%	90.3%	88.8%	0.957
Low contrast volume	68.6%	98.6%	83.2%	0.939
High contrast volume	82.3%	92.9%	87.9%	0.949

AUC, area under the receiver operating characteristic curve; cFFR, contrast-based fractional flow reserve; FFR, fractional flow reserve.

Table 4. Effects of contrast osmolality and volume on the diagnostic performance of cFFR.

		Odds ratio	95% CI	P value
Sensitivity				
Contrast osmolality (iso vs. low)	86.8% vs. 72.6%	2.839	1.364 – 5.908	0.005
Contrast volume (high vs. low)	82.3% vs. 68.6%	2.343	1.386 – 3.961	0.002
Specificity				
Contrast osmolality (iso vs. low)	90.3% vs. 97.2%	0.308	0.110 – 0.864	0.025
Contrast volume (high vs. low)	92.9% vs. 98.6%	0.204	0.045 – 0.919	0.039
Accuracy				
Contrast osmolality (iso vs. low)	88.8% vs. 84.8%	1.414	0.827 – 2.418	0.21
Contrast volume (high vs. low)	87.9% vs. 83.2%	1.462	0.947 – 2.256	0.086

cFFR, contrast-based fractional flow reserve; CI, confidence interval.

Figure 1. Correlation between Fractional Flow Reserve and Adenosine-free Indices in Low- and Iso-osmolality Contrast.

cFFR, contrast-based fractional flow reserve; iFR, instantaneous wave-free ratio; FFR, fractional flow reserve; Pd/Pa, distal pressure / aortic pressure at rest.

Figure 2. Correlation between Fractional Flow Reserve and Adenosine-free Indices in Low and High Contrast Volume.

Abbreviations were same as Figure 1.

Figure 3. Bland-Altman Plot between Fractional Flow Reserve and Adenosine-free Indices in Low- and Iso-osmolality Contrast.

Bias (mean difference) between two indices is shown in solid line and 95% limits of agreement (LOA) are shown in dotted lines. cFFR, contrast-based fractional flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LOA, 95% limits for agreement; Pd/Pa=rest distal pressure/aortic pressure.

Figure 4. Bland-Altman plot between fractional flow reserve and adenosine-free indices in low and high contrast volume.

Abbreviations were same as Figure 3.

Figure 5. Receiver operator characteristics curve analysis of adenosine-free indices to predict fractional flow reserve ≤0.80 in low- and iso-osmolality contrast groups.

The AUC of cFFR was the greatest among the adenosine-free indices in both low- and iso-osmolality group (all P <0.001). There was no significant difference between the AUC of cFFR in the low- and iso-osmolality group (P = 0.40).

AUC, area under the receiver operator characteristics curve; cFFR, contrast-based fractional flow reserve; CI, confidence interval; iFR, instantaneous wave-free ratio; FFR,

fractional flow reserve; Pd/Pa, distal pressure/aortic pressure at rest.

Figure 6. Receiver Operator Characteristics Curve Analysis of Adenosine-free Indices to Predict Fractional Flow Reserve ≤0.80 in the Low and High Contrast Volume Groups.

The AUC of cFFR was the greatest among the adenosine-free indices in both low and high contrast volume groups (all P <0.001). There was no significant difference between the AUC of cFFR in the low- and iso-osmolality group (P = 0.61).

Abbreviations were same as Figure 5.