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Original Article

Comparing stress testing and fractional flow reserve to evaluate presence, location and extent of ischemia in coronary artery disease

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ABSTRACT

Background: FFR provides an accurate and reproducible assessment of the functional severity of coronary stenosis. Whereas stress testing remains the preferred initial modality for assessment of ischemia, there is limited data comparing it with FFR. We sought to determine the correlation between cardiac stress testing and coronary fractional flow reserve (FFR) measurement for assessing the presence, location, and burden of myocardial ischemia in patients referred for evaluation of coronary artery disease (CAD).

Methods: Over 5-year study period, of the 5420 consecutive coronary angiograms that were screened, 326 patients had FFR measurements. Of these, 96 patients with FFR measurements who had a preceding stress test (stress echocardiography [SE] or myocardial perfusion imaging [MPI]) within a year were included.

Results: Of the 96 patients, there were 46 (48%) men and 50 (52%) women with a mean age of 61 ± 10 years. SE was performed in 57 (59.3%) and MPI in 32 (40.7%) of patients. FFR was ≤0.79 in 54 (56%) patients. Stress testing had low sensitivity (55%) and specificity (47%) compared to FFR. The concordance between FFR and stress testing was low for both presence ($k = 0.03$) and location ($k = 0.05$) of the ischemic territory. The number of ischemic vascular territories was correctly estimated in only 39% of the stress tests. SE was more likely to overestimate and MPI more likely to underestimate extent of ischemia.

Conclusions: In patients referred for evaluation of CAD, there was poor correlation between stress testing and FFR. A prospective study comparing these two modalities with FFR is needed.

1. Introduction

Non-invasive cardiac stress testing is currently the recommended modality for the initial evaluation of patients with suspected or known coronary artery disease (CAD). The commonly performed non-invasive stress tests that utilize a combination of stress (delivered by exercise or a pharmacologic agent) and imaging protocols (using echocardiography or myocardial perfusion imaging) have a number of limitations.

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Factors such as the prevalence of CAD, adequacy of stress achieved, quality of the imaging data, as well as inter and intra-observer variability may influence the test results. In addition, myocardial perfusion imaging (MPI), which relies upon the relative uptake of radioactive tracers, can underestimate the burden of ischemia, especially in the presence of multi-vessel disease.

In the evaluation of CAD, the gold standard for diagnostic tests has historically been the anatomic estimation of coronary stenosis by coronary angiography. More recently, fractional flow reserve (FFR) testing performed in the catheterization laboratory has allowed for the functional estimation of coronary stenosis, determined traditionally with non-invasive stress testing. Numerous trials have unequivocally demonstrated the superior cardiovascular outcomes and cost-effectiveness of FFR-guided percutaneous coronary intervention.[1–4] Hence, there is a need to revaluate the role of non-invasive cardiac stress testing in the assessment of myocardial ischemia, by comparing it with FFR-guided estimation of coronary stenosis. There is a striking lack of literature in this regard.[5–9] Therefore, the aim of our study was to compare non-invasive cardiac stress testing and FFR – in determining the presence, location, and the burden of the ischemic vascular territory in patients undergoing evaluation of CAD.

2. Methods

This was a retrospective study, conducted at a tertiary-level academic hospital. A standardized data collection process was used to obtain all information directly from electronic patient medical records (Epic Systems Corporation, Verona, Wisconsin, US) and entered onto a security protected hospital database. The local institutional review board approved the study.

2.1. *Patient selection*

A total of 5420 consecutive coronary angiograms performed over a five-year period at our institute were screened retrospectively using the institutional cardiac catheterization laboratory database. Of these, 326 patients had FFR measurements, of whom 124 patients who had FFR measurements and a preceding non-invasive stress test within a year was evaluated. The clinical, laboratory, and stress imaging data were obtained by reviewing individual patient charts. The angiographer's visual assessment of the coronary anatomy was used to classify the coronary artery lesion as intermediate (50–70% stenosis) or severe (≥70% stenosis). Patients were considered to have CAD if any of the three major epicardial coronary arteries demonstrated at least 50% stenosis. Multi-vessel CAD was defined as the presence of ≥50% stenosis in ≥2 major epicardial vessels. Non-ST elevation myocardial infarction (NSTEMI) was defined as electrocardiographic ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent).[10]

Patients were excluded if there was, a) an episode of NSTEMI in the time interval between the stress test and cardiac catheterization ($n = 6$); or, b) an indeterminate stress test result ($n = 2$); or c) difficulty in correlation of a vessel with its corresponding vascular territory either due to a prior coronary artery bypass grafting ($n = 15$) or due significant disease (≥50% stenosis) in the left main coronary artery ($n = 5$). The remaining 96 patients were included in the analysis.

2.2. *Stress echocardiography and myocardial perfusion imaging*

Stress echocardiography (SE) was performed using standard stress protocols utilizing either treadmill exercise or administration of dobutamine (atropine supplementation when necessary). Similarly, stress MPI was performed with standard techniques using either treadmill exercise or adenosine vasodilation. Images were evaluated using the 17-segment model.[11] Stress tests were interpreted by staff cardiologists and/or radiologists not directly involved in patient care, for the presence of stress-induced ischemia, its location, and the number of vascular territories involved.

2.3. *Estimation of FFR*

FFR measurements were performed on lesions that were of intermediate severity as determined by the angiographer's visual assessment of the coronary anatomy. A 6 French guiding catheter without side-holes was used to engage the coronary arteries. Heparin or bivalirudin was administered intravenously for anticoagulation. FFR was performed using either a 0.014-inch sensor-tipped high-fidelity Pressure Wire™ (RADI Medical Systems AB, Uppsala, Sweden) or the 0.014-inch sensor-tipped Volcano Prime Wire Prestige® Pressure Guidewire (VOLCANO Corp, Rancho Cordova, CA). The transducer was normalized first with the catheter tip to ensure identical pressure recordings from the pressure wire and coronary catheter. The pressure sensor was then positioned distal to the stenosis. The guide catheter was flushed completely of any contrast material before the measurements and intracoronary nitroglycerine was administered prior to induction of coronary hyperemia. Aortic pressure (phasic and mean) and coronary pressure distal to the stenosis (phasic and mean) were recorded at baseline and under maximum coronary hyperemia. Coronary hyperemia was induced by adenosine, administered by intracoronary route (using boluses of 24 mcg–96 mcg) or, less frequently, intravenously (at an infusion rate of 140 mcg/kg/min) at the discretion of the operator. Hemodynamic data were digitally stored on an electronic database (Horizon Cardiology™, McKeeson Corporation) for off-line analysis. FFR was calculated as the ratio of the mean distal intracoronary pressure to the mean aortic pressure at peak hyperemia.[2]

An FFR measurement of ≤0.79 was considered abnormal.[1,12] Since FFR measurements are not routinely performed in vessels with either severe or no disease, we imputed FFR values for these vessels for the purposes of the study. Coronary vessels with total occlusion were assigned an FFR of 0.50 ($n = 8$ vessels); vessels with >70% angiographic stenosis were assigned a value of 0.79 ($n = 29$ vessels); whereas angiographically normal vessels were assigned a value of 0.95 ($n = 135$ vessels).[6]

2.4. *Evaluating the presence and location of ischemia, and the ischemic burden*

The results of the stress test and FFR were used to determine which, if any, of the three epicardial vascular territories or combinations thereof were identified as ischemic. The stress test was considered to have identified the presence of ischemia if it demonstrated 'any ischemia' i.e. if any one of the vascular territories were abnormal on the stress test in the presence of an abnormal FFR in any one of three epicardial vessels. For evaluating the location of ischemic territories involved, we noted the exact ischemic territory, if any, or territories identified by the stress test and the FFR. For estimation of the ischemic burden, the stress test was considered to have 'underestimated' or 'overestimated' the ischemic burden if it identified significantly fewer or greater ischemic vascular territories respectively, compared to the FFR.

2.5. *Statistical analysis*

Categorical variables are reported as counts and percentages and were compared using chi-square statistics. Continuous variables are presented as means ± SD and were compared using student's t-test or Wilcoxon nonparametric statistic. p value of <0.05 was considered to indicate statistical significance. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to assess the ability of stress testing modality to identify myocardial ischemia in comparison with an abnormal FFR (i.e. FFR $\leq$0.79). The results were analyzed separately on per-patient and per-vessel basis. Evaluation of per-patient and per-vessel concordance for ischemia between stress testing and FFR was done by determining k statistic values: a k statistic of $+1$ indicating perfect agreement, 0 indicating agreement as expected by chance, and -1 indicating complete disagreement. The mean number of ischemic territories detected by stress testing and FFR were compared using the Mann–Whitney U test. Data were analyzed using PASW Statistics version 18 (SPSS Inc, Chicago, IL, USA).

3. Results

Baseline characteristics of the 96 patients included in the study are presented in Table 1. Of these, 45 patients had multi-vessel disease (Supplementary Table 1).

3.1. *Diagnostic accuracy of non-invasive stress testing*

When compared with FFR-guided estimation of CAD, non-invasive stress testing had a sensitivity of 57%, specificity of 45%, positive predictive value of 57% and a negative predictive value of 45% (Table 2). Similar evaluations were performed for various sub-groups, i.e. males, females, obese (BMI > 30 kg/m^2), diabetics, and the type of stress test (i.e. SE and MPI) (See Table 3). In the enriched subset of patients with multi-vessel disease, stress test results had a higher sensitivity and positive predictive values along with lower specificity and negative predictive values compared to the cohort that included patients with less extensive disease (See Table 3).

Table 1 – Baseline characteristics of all patients ($n = 96$).

Variable	
Age (years)	61 ± 10
Males	46 (48%)
Race	
Caucasian	46 (48%)
African–American	32 (33%)
Body mass index (kg/m^2)	31.2 ± 7.2
Cardiovascular risk factors	
Hypertension	74 (77%)
Dyslipidemia	64 (67%)
Diabetes	35 (36%)
Smoking	71 (74%)
Family history of coronary artery disease	59 (61%)
History of ischemic heart disease	41 (43%)
Serum creatinine (mg/dL)	0.9 ± 0.3
Mean time interval between cardiac stress and catheterization (days)	72 ± 93
Stress testing	
Pharmacological	52 (54%)
Exercise	44 (46%)
Abnormal stress test	54 (56%)
Angiographic characteristics	
LAD	63 (66%)
LCx	29 (30%)
RCA	46 (48%)
Mean fractional flow reserve	0.84 ± 0.01
Fractional flow reserve $\leq$0.79	54 (56%)

LAD = Left anterior descending artery; LCx = Left circumflex artery; RCA = Right coronary artery.

3.2. *Estimation of the ischemic burden*

Of the overall group of 96 patients, in 38 (39%) patients, stress testing and FFR detected identical ischemic territories (mean number of territories = 0.68 ± 0.81 in both; $p = 1.00$). In 26 patients (27%), stress testing underestimated the number of ischemic territories (mean number of territories by stress testing = 0.15 ± 0.37 vs. by FFR = 1.35 ± 0.63; $p < 0.001$). In the remaining 32 patients (33%), stress testing overestimated (mean number of territories by stress test = 1.72 ± 0.81; by FFR = 0.38 ± 0.66; $p < 0.001$) the number of ischemic territories compared to FFR. Estimation of the ischemic burden was further analyzed based on the type of stress imaging: i.e. MPI ($n = 39$) and SE ($n = 57$). The proportion of patients with concordant estimations of the ischemic burden was similar between the two studies, with MPI correctly identifying the

Table 2 – Diagnostic accuracy of stress test results compared with fractional flow reserve (FFR) measurement.

		FFR Abnormal	Normal
Stress testing results	Abnormal	31	23
	Normal	23	19

Values in cells represent number of patients.

Table 3 – Diagnostic accuracies of stress testing compared with FFR in the study sub-groups.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Men ($n = 46$)	63	47	63	47
Women ($n = 50$)	52	44	52	43
Diabetics ($n = 35$)	50	53	59	44
Obese ($n = 54$)	53	45	62	36
Coronary artery disease ($n = 82$)	57	43	66	34
Multi-vessel disease ($n = 45$)	67	22	77	14
Type of stress testing				
Stress echocardiography ($n = 57$)	62	39	51	50
Exercise echocardiography ($n = 37$)	63	39	52	50
Dobutamine echocardiography ($n = 20$)	60	40	50	50
Adenosine MPI ($n = 32$)	54	40	67	29

MPI = myocardial perfusion imaging.

burden of ischemia in 18 (46%) studies, and SE in 20 (35%) studies ($p = 0.30$). However, among patients who had discordance ($n = 21$ for MPI and 37 for SE), there was a significant difference between SE and MPI, with underestimation of the burden of ischemia more likely with MPI (14 [36%] patients) than with SE (12 [21%] patients), and overestimation of the burden of ischemia more likely with SE (25 [44%] patients) than with MPI (7 [18%]) ($p < 0.05$ for all comparisons of discordance).

3.3. *Estimation of presence and location of ischemia*

The per-patient concordance between stress testing and FFR for diagnosing the presence of any ischemia was poor ($k = 0.03$ [95% CI: −0.17 to 0.23]). Similarly, the per-patient concordance between stress testing and FFR to correctly identify the location of the ischemic vascular territory(ies) was also poor ($k = 0.05$ [95% CI: −0.06 to 0.16]). Even in patients with multi-vessel disease, the correlation between stress testing and FFR remained low for diagnosing the presence of any ischemia ($k = -0.09$ [95% CI: −0.35 to 0.17]) as well as for correctly identifying the location of the ischemic vascular territories ($k = -0.02$ [95% CI: −0.14 to 0.09]).

3.4. *Per-vessel analysis*

Per-vessel analysis was done to compare the FFR value of a vessel with the non-invasive stress test result in the corresponding vascular territory. Of the 288 vessels evaluated, FFR values were not available for 28 vessels. These were vessels with intermediate lesions in patients who underwent PCI for severe lesions in another vessel. Per-vessel analysis was performed on the remaining 260 vessels. Concordant results were noted in 153 (59%) vessels which had a normal FFR and a normal stress test in the corresponding territory, and in 20 (8%) vessels with an abnormal FFR and an abnormal stress test in the corresponding vascular territory. In contrast, discordant results were noted in 37 (14%) vessels, which had a normal FFR and an abnormal stress test, and 50 (19%) vessels with an abnormal FFR and a normal stress test. The concordance between the two forms of testing for correctly identifying ischemia in the vascular territory of the individual vessel (i.e. per-vessel analysis) was poor ($k = 0.10$ [95% CI: −0.03 to 0.22]). Importantly, the level of agreement remained poor for the important territory of left anterior descending (LAD) artery ($n = 89$ vessels) ($k = 0.07$ [95% CI: −0.14 to 0.28]). The sensitivity, specificity, and predictive accuracies for the various subgroups of vessels are shown in Table 4.

4. Discussion

The main results of our study can be summarized as follows. In identifying the presence and location of the ischemic vascular territory, there was poor correlation between non-invasive stress testing and FFR. The ischemic burden was correctly estimated in 39% of stress tests, and not significantly influenced by the type of imaging (i.e. SE or MPI). Among stress tests, SE was more likely to overestimate and MPI more likely to underestimate the burden of ischemia.

Poor correlation between stress testing and FFR in diagnosing ischemia has been demonstrated in several studies.[5–8,13,14] However, there are limited data comparing the two methods in their ability to estimate the burden of ischemia. In addition, there are scant data addressing higher-risk subgroups, such as those with multi-vessel or significant LAD disease. Our study provides useful insights into these previously unstudied populations. It is worth emphasizing that we noted a poor correlation between stress testing and FFR in these high-risk sub-groups. These data suggest that in a

Table 4 – Diagnostic accuracies of stress testing compared with FFR for various vascular territories.

Vascular territories (number of vessels)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
LAD ($n = 89$)	37	71	39	68
LCx ($n = 83$)	10	89	11	88
RCA ($n = 89$)	27	80	40	68
Diabetic vessels ($n = 93$)	27	84	39	75

significant proportion of patients, non-invasive stress testing cannot be used in isolation to make confident therapeutic decisions regarding the functional significance of coronary lesions.

Notably, there was significant overestimation of ischemia by stress testing. This was especially true with stress echocardiography. It is plausible that an abnormal stress test may result from stress-induced physiologic and microvascular abnormalities despite relatively preserved epicardial flow, resulting in a correspondingly normal FFR. In this setting, measurement of the coronary flow reserve, which assays absolute rather than relative changes in coronary blood flow, can help reconcile the discrepancy. The discrepant results may in part due to the limitations of FFR in accounting for microvascular disease. Studies indicate that microvascular disease, which may result in an abnormal stress test, is associated with worse cardiovascular outcomes.[15] An abnormal non-invasive stress test can be of incremental value in identifying a higher risk cohort despite the coronary angiographic data.[16] However, it remains unknown whether an abnormal stress test would be of similar incremental prognostic value in patients with a normal FFR measurement. We also noted an underestimation of ischemia by stress testing compared to FFR and this was significantly more common with MPI. This corroborates the established mechanism of ischemia detection with MPI, reliant upon the relative uptake of radioactive tracers.

Discrepancies between non-invasive and invasive methods of assessment of the functional significance of coronary stenoses may have major prognostic and therapeutic implications. While it may be intuitive to consider revascularization in patients with an abnormal FFR and despite a normal non-invasive stress test, this approach is not currently supported by evidence. However, in patients with stable coronary disease who also have an abnormal FFR (<0.80), randomization to deferred (medical management) and baseline revascularization leads to a much higher urgent revascularization rates in the deferral group.[12] Also, it is worth noting that in the absence of FFR-guided assessment of CAD, vessels with intermediate lesions (i.e. 50–70% stenosis) with a prior abnormal non-invasive stress test are currently deemed revascularization appropriate by the ACC/AHA guideline. However, if FFR measurements were performed and found normal in this patient group, the potential benefits, risks and costs of deferred versus index PCI are unclear. Our study was not designed to address these questions but the findings highlight these important areas for future trials.

5. Limitations

Our study has several limitations. In our study, we imputed FFR values for severely stenosed, occluded and normal vessels. An FFR estimation of such vessels is often neither clinically prudent nor indicated, either due to therapeutic futility (occluded vessel), clinically indicated PCI (angiographically severe disease) or potential for harm from needless instrumentation (angiographically normal vessels). Moreover, similar imputations have been previously reported.[6] Therefore, we believe the assumptions we made are unlikely to have significantly influenced the results of the study and also reflect real-world clinical practice. Second, we did not use quantitative angiography to determine the anatomical significance of lesions. However, we did not think this was necessary as our protocol of using visual assessment for determining the need for FFR assessment has been previously validated in large trials.[1,4] Thirdly, stress test and FFR estimations were not performed simultaneously. While interval progression of CAD could potentially impact the results, with the time interval between the two procedures being less than a year (mean 72 days), disease progression is unlikely to have played a significant role.[17] Moreover, the small numbers of patients whose disease did progress clinically in the time interval between stress testing and angiography and resulted in an acute coronary syndrome were excluded from the study.

6. Conclusion

In patients undergoing evaluation for CAD, there was poor correlation between non-invasive stress testing and FFR estimation for the diagnosis and location of ischemia. Compared with FFR-guided estimation of the extent of ischemia, the MPI significantly underestimated the burden of ischemia while SE led to significant overestimation. The increasing utilization of FFR underscores the need for a large prospective study comparing FFR with non-invasive stress testing for their diagnostic and prognostic roles in the assessment of CAD.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ihj.2015.02.010.

Conflicts of interest

All authors have none to declare.

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