Can Computed Fractional Flow Reserve Coronary CT Angiography (FFRCT) Offer an Accurate Noninvasive Comparison to Invasive Coronary Angiography (ICA)? "The Noninvasive CATH." A Comprehensive Review

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Abstract: Invasive coronary angiography (ICA) serves as a very important tool in the diagnosis of coronary artery disease (CAD) and provides information for further intervention. Fractional Flow Reserve (FFR) at the time of ICA is the gold standard to analyze the hemodynamic and physiologic significance of moderate coronary stenosis. The dawn of coronary CT angiography (CTA) has helped in visualizing the anatomy of coronary arteries. Computed Fractional Flow Reserve (FFRCT) from such an imaging study shows promise in providing valuable data about physiology on top of the anatomy noninvasively; which can guide decision-making process for revascularization. This manuscript aims to review the accuracy of FFRCT obtained from a coronary CTA in the diagnosis of hemodynamically significant coronary artery stenosis and ruling out nonsignificant coronary artery stenosis when compared to the Gold standard of FFR obtained during ICA. We conducted a Medline search using various combinations of "FFRCT," "ICA" "noninvasive," "significant stenosis," and "CAD" to

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identify pivotal randomized trials published before May 1, 2020, for inclusion in this review. Concurrently, major practice guidelines, trial bibliographies, and pertinent reviews were examined to ensure inclusion of relevant trials. A consensus among the authors was used to choose items for narrative inclusion. The following section reviews data from pivotal trials to determine a noninvasive strategy in appropriate patients to accurately detect functionally significant stenosis. For these trials, the sensitivity, specificity, and accuracy are compared. Trials reviewed: CTA, FFRCT, ICA, CT-myocardial perfusion imaging. FFRCT is a novel noninvasive modality which localizes significant "ischemia-causing" stenosis (≤0.80) by means of crystal fluid dynamics eliminating the need for vasodilators. The analysis of FFRCT by DISCOVER FLOW, DeFACTO, NXT trials revealed high sensitivity, negative predictive value, and good accuracy. The ADVANCE registry showed significantly lower events of CV death or myocardial infarction with a negative FFRCT (>0.80 study). The PLATFORM trial showed significant reduction in negative ICA with negative FFRCT, thus ultimately reducing the number of unnecessary percutaneous coronary intervention. Decrease in healthcare costs was noted with FFRCT, decreasing downstream testing, and invasive procedures. FFRCT is a novel modality for analyzing significant stenosis in CAD noninvasively. The high sensitivity of this modality could make it a good rule out tool to avoid unnecessary intervention in physiologically insignificant lesions. Limitations of this modality include low specificity, double exposure to contrast, turnaround time, and upfront costs. Further query into this matter is warranted. (Curr Probl Cardiol 2021;46:100642.)

Introduction

Cardiovascular disease remains the number one cause of death globally, responsible for 31% of mortality annually.[1] Coronary artery disease (CAD) is the most common type of heart disease in the United States.[2] Statistically 1 person suffers from myocardial infarction (MI) every 40 seconds in the United States and about 805,000 annually.[3] About 647,000 lives are lost to heart disease every year.[3] Not only does heart disease cause significant morbidity and mortality but also increased healthcare spending about $219 billion each year from 2014 to 2015.[3]

Humongous strides have been made in the diagnosis of CAD in imaging and invasive techniques. Invasive coronary angiography (ICA) serves as a very important tool in the diagnosis of CAD and provides information for further intervention. Fractional Flow Reserve (FFR) at the time of ICA is the gold standard to analyze the hemodynamic and physiologic significance of moderate coronary stenosis. The dawn of coronary CT angiography (CCTA) has helped in visualizing the anatomy of coronary arteries. Computed Fractional Flow Reserve (FFRCT) from such an imaging study shows promise in providing valuable data about physiology on top of the anatomy noninvasively; which can guide decision-making process for revascularization.

Discussion

Current Guidelines

Diagnostic approach for stable CAD can be broadly divided into anatomical, functional/physiological or a combination of both. Current ACC/AHA guidelines after obtaining the pretest probability (PTP) of CAD, favor functional status assessment using stress test, preferably exercise, as the initial diagnostic test.[4] Standard ECG stress testing is preferred in low or intermediate likelihood of CAD while myocardial perfusion imaging/echocardiogram/cardiac magnetic resonance imaging (CMR) is recommended in intermediate to high likelihood CAD based on assessment of risk.[4] ICA is reserved for persistence of symptoms despite guideline-directed medical therapy (GDMT) and further intervention decision is guided by the presence of lesions and its significance, percutaneous coronary intervention (PCI) vs coronary artery bypass graft.[4]

In contrast, European Society of Cardiology (ESC) 2019 guidelines mandate resting echocardiogram in all patients and offer CCTA (anatomical imaging) in low, intermediate PTP and clinical likelihood in the front end of diagnostic testing, with ischemia evaluation using imaging preferred in intermediate to high risk, and finally ICA with FFR or instantaneous wave-free ratio in very high risk patients. Hence, obtaining anatomical data of the lesion is also part of the guidelines.[5] The addition of FFR component to CCTA with FFRCT is mentioned to improve diagnosing hemodynamically significant stenosis.[5]

Thus, while the American guidelines are more geared toward assessing functional or physiological testing, whereas the Europeans adopt a combination approach. To tackle the question of the better approach comparing the various anatomical, functional, and combination approaches, we are analyzing the different modalities and how FFRCT can play a significant role.

What Is FFRCT?

FFR is the ratio of blood flow through coronary artery in the presence of stenosis to blood flow through the coronary artery in the absence of stenosis.[6] By application of Poiseuille's law, it is obtained by the ratio arterial pressure distal to the stenosis to the arterial pressure proximal to the stenosis.[6] Studies revealed that reversible myocardial ischemia was revealed with FFR obtained during ICA in combination with noninvasive stress test with a sensitivity of 88%, specificity of 100%, accuracy of 93%.[7]

The decision of intervention in case of coronary stenosis using FFR obtained during ICA compared to the basis of anatomic severity of the lesion was proved by the FAME trial. Using FFR-guided decision making (<0.8) yielded a 72% relative risk reduction in the composite endpoint of death, myocardial infarction, and repeat vascularization at 1 year of follow-up, in this randomized control trial.[8] FAME 2 trial further demonstrated that the approach of FFR with GDMT compared to GDMT alone led to significant absolute risk reduction of 7.9% in the composite endpoint of death, myocardial infarction, and repeat vascularization at 1 year of follow-up.[9] FFR remains is the Gold standard for assessing hemodynamic significance of a lesion and is a Class I recommendation in the American 2014 guidelines for significant stenosis (<0.80).[10]

In reference to the current AHA guidelines, functional testing using either Stress ECG or stress imaging seems to be the first step in the diagnosis of CAD. The advent of CCTA has provided anatomical data, which is quite useful in visualizing presence of CAD, but lacks the hemodynamics data that is required to decide whether the visualized lesion is causing significant obstruction hence ischemia. FFRCT seems to be the solution for obtaining both anatomic and functional data with good correlation to the actual ICA derived FFR. It involves getting a CCTA for obtaining anatomic data of coronary vasculature, epicardial vessels, and aortic root. Allometric scaling and the myocardial mass derived from the CCTA data helps in calculating resting coronary blood flow and cardiac output, while the mean aortic pressure is obtained from noninvasive blood pressure measurement from the brachial artery. An environment of hyperemia is simulated to match the effect of adenosine-driven pharmacological stress test. Thus, the pressures distal and proximal to stenosis are obtained from which FFR is calculated using computational fluid dynamics (CFD).[11] This technique involves uploading the data obtained from CCTA to Heartflow servers where the image based CFD is run, which is the FDA approved means of deriving FFRCT. This process has a turnaround time which is usually hours. The alternative to this would be having on site machine-learning approach, which studies show a good correlation with CFDs and can have quicker turnaround times.[12]

FFRCT in Detecting Ischemia

FFRCT has been studied to analyze the sensitivity, specificity, accuracy in diagnosing significant ischemia in CAD while comparing it with ICA derived FFR. A significant FFR value of $\leq$0.80 was used as ischemia-causing stenoses in multiple prospective trials. The Discover FLOW trial was a prospective study with a cohort of 103 patients with either known and suspected CAD. They underwent CCTA, FFRCT followed by comparison to ICA derived FFR. The CT FFR had a sensitivity of 87.9%, specificity of 82.2%, and accuracy of 84.3%, when compared to CCTA the sensitivity of 91.4%, specificity of 39.6%, and accuracy of 58.5%.[13] Another prospective study of 252 patient with either diagnosed or suspected CAD underwent the same as the above trial. In this trial, FFRCT had per patient basis sensitivity of 87.9%, specificity of 82.2%, and accuracy of 84.3% vs CCTA with had a sensitivity of 90%, specificity of 54%, and accuracy of 73%.[14] A similar prospective multicenter study called NXT trial with 254 patients was conducted which showed sensitivity, specificity, and accuracy of 88%, 79%, and 81%, respectively, for FFRCT compared to 94%, 34%, 53%, respectively, for CCTA.[15] Thus, DISCOVER FLOW, DeFACTO, NXT trials showed improved specificity and accuracy of FFRCT when compared to CCTA.[13-15] In regards to the positive predictive value and negative predictive value of FFRCT compared to CCTA, a prospective study with 42 patients derived at 74% vs 60%, respectively, and 89% vs 88%, respectively.[16]

Pooled studies in the form of meta-analyses also revealed FFRCT having higher per patient specificity, 77%[17] and accuracy, 82%[18] when compared to CCTA. FFRCT obtained by machine-learning approach was also tested. A prospective analysis of 72 patients comparing machine-learning approach that could be obtained onsite and CCTA revealed sensitivities and specificities of 87% and 77% as compared with 94% and 66% for FFRCT from machine-learning approach to CCTA alone, respectively.[19] Another prospective study looking to compare FFRCT from machine-based learning approach and CCTA demonstrated better in specificity and accuracy of FFRCT and also the accuracy was close to 90% when FFRCT cut off was less than 0.74 as compared to the usual ≤0.80.[20] All these point toward FFRCT either being a reliable and accurate modality in determining ischemia-causing stenosis when compared to anatomical imaging.

Anatomical Imaging

CCTA is a noninvasive, contrast based study to visualize coronary arteries and detect luminal abnormalities. The PROMISE trial, a prospective randomized trial, did not show any difference in event rate in the CCTA group compared to functional testing group.[21] But following evidence pointed toward a difference between the groups as in SCOT heart trial, a randomized, multicenter, parallel-group trial, where there was a significant decrease in combined endpoint of MI or cardiovascular death 2.3% vs 3.9% during 5-year follow-up when compared to standard care.[22] CRESCENT trial established that CCTA and calcium imaging are effective alternatives in diagnosis of stable CAD with less downstream testing and diagnostic cost when compared to functional tests,[23] and in CRESCENT II trial it was demonstrated CCTA was associated with a greater positive diagnostic yield of invasive angiography and reduction in the proportion of angiograms when compared to functional testing.[24] Also, a randomized prospective study comparing CCTA with functional stress ECG, found out that fewer downstream testing and re-hospitalization where CCTA was utilized.[25]

CCTA has excellent sensitivity, however, has lower specificity and accuracy when compared to ICA FFR when standing alone as compared to FFRCT.[13-19] Thus, using CCTA is a great tool for diagnosis of CAD, though the ability to detect the functional significance of stenoses as a standalone test is low. Also, the use of CCTA is limited in severe coronary calcifications, obesity, irregular heart rate, inability to breath-hold, and previous revascularizations (stents, bypass grafts).[26,27]

Functional Stress ECG

Exercise ECG plays a pivotal role in the ACC/AHA guidelines.[4] Data suggests stress ECG in diagnosis of CAD is inferior to diagnostic imaging.[28] The sensitivity and specificity of stress ECG in anatomically significant CAD from pooled data is 58% (95% CI: 46%-69%) and 62% (95% CI: 54%-69%).[28] Comparatively the positive and negative likelihood ratio also is inferior when compared to the different imaging modalities.[28] Stress ECG also had inferior diagnostic power to rule-in, where a very high PTP 80% (76-83) is required, or rule-out, where a very low PTP $\leq$ 19% (15-25) is required, significant CAD.[28] The limitations of this modality include inability to diagnose CAD if there are baseline ECG abnormalities. Thus, the new ESC guidelines recommend the use of diagnostic imaging as the initial test.[5]

However, the advantage of exercise ECG is the ability to assess the patient's functional capacity. The ability to exercise and, more importantly, exercise capacity are strong predictors of cardiovascular events. Exercise ECG also provides information about symptoms, arrhythmias, changes in blood pressure, ST-segment changes which can be used to complement in evaluation and determining the appropriate intervention.[29] These data like decreased exercise capacity, ST depression at low workloads, or symptoms of angina, ventricular arrhythmias, abnormal response in blood pressure all predict high event risk in a patient.[29] Given the advantages, the low sensitivity, specificity, and likelihood ratio in comparison with imaging modalities, cautions to use stress ECG as additional information rather than the sole modality from which decisions are to be made.

Functional Stress Imaging

Functional imaging comprises single-photon emission computed tomography or positron emission computed tomography (PET), stress echocardiography, or stress CMR imaging assessing myocardial perfusion and/or wall motion. Functional imaging tests are better at detecting ischemia-causing stenoses and also have the added advantage of localizing the lesion site compared to exercise ECG. Pooled data analysis reveals PET and stress CMR having the highest sensitivities of 89% (95% CI: of 82-93) and 89% (95% CI: 85-92), respectively, highest negative likelihood ratio of 0.13 (0.08-0.22) and 0.13 (0.09-0.18), respectively, while stress CMR having the highest specificity 87% (95% CI: 83%-91%), positive likelihood ratio of 7.10 (5.07-9.95) among the functional stress imaging modalities in detecting functionally significant CAD when compared to FFR derived from ICA ($\leq$ 0.80).[28] Single-photon emission computed tomography is a commonly used modality, while it has good sensitivity, 87% (95% CI: 83%-90%), in diagnosing anatomically significant CAD (>50% stenosis), its sensitivity, 73% (95% CI:

62%-82%), decreases in diagnosing functionally significant CAD.[28] Given the normal test is associated with decreased rate of MI and cardiovascular test,[28] functional imaging modality would be a better option in diagnosing CAD and also further PET, stress CMR offer insight into functional significance of the lesion, when compared to either functional stress ECG or anatomical imaging.

The Significance of FFRCT Post-ISCHEMIA Trial

ISCHEMIA trial, a randomized, parallel study, was conducted to evaluate major adverse ischemic events in routine invasive therapy, PCI, when compared to optimal medical therapy in patients with stable CAD and moderate to severe ischemia on noninvasive testing.[30] The trial revealed no significant difference in major adverse ischemic events, cardiovascular mortality, and all-cause mortality, between the groups, and routine invasive strategy was associated with increased 6 months periprocedural MI.[30] There was benefit in angina in the invasive group as well as decrease in MI at 4 years.[30-31] This trial echoes the prior evidence in COURAGE trial[32] and Bari 2D trial[33] where PCI was not associated with decreased MI or death.

As the ISCHEMIA trial does not show any benefit in intervention even in the presence of diagnosis of moderate to severe ischemia in functional imaging studies, it is enforced that PCI might not be the answer from a pure mortality or events perspective.

This creates a need for a noninvasive test that can signal intervention in case of significant stenosis. The ADVANCE registry showed significantly lower events of CV death or MI with a negative FFRCT (>0.80)[34] and also the ability to detect major adverse ischemic events FFRCT was positive (≤0.80) was demonstrated by a Danish study[35] The PLATFORM trial showed significant reduction in negative ICA with negative FFRCT, thus ultimately reducing the number of unnecessary PCI.[36] FFRCT RIPCORD demonstrated change in management strategy in 36% of patients with CCTA when FFRCT data was revealed[37]. Since FAME 2[9] demonstrated mortality benefit, FFRCT can be the modality to be used for both accurate diagnosis and detection of significant stenosis by implementing FFR noninvasively, thus avoiding unnecessary invasive intervention.

Conclusion

FFRCT is a highly effective test that can be implemented as a first line modality given its ability to provide anatomical and physiological information at the same time. FFRCT's sensitivity is high as proven by the different studies complemented by high negative predictive value. Decrease in healthcare costs where demonstrated with FFRCT, decreasing downstream testing and invasive procedures.[13,36] Thus, as a rule out test to exclude functionally significant CAD, this test helps in reducing need for invasive interventions, thus ultimately decreasing healthcare costs and patient anxiety.

FFRCT is not without limitations. Specifically, its average specificity and positive predictive value as a test, when compared to all modalities including invasive methods (Table 1), limits its use as one test to rule out and confirm a functionally significant lesion. Also, FFRCT involves use of contrast which could be a limiting factor in patients with chronic kidney disease. FFRCT relies heavily on the quality of the initial CCTA image. Low quality images are not optimal for use and can skew the result. Heartflow is the FDA-approved method of obtaining FFRCT with a turnaround time of hours. Though machine-based learning methods of FFRCT can solve the problem by providing on-site methods of obtaining the result, further research is needed.

Thanks to technology, noninvasive cardiac test has improved at an exponential rate. Given the evidence of the superiority of functional imaging over functional stress ECG, and its adoption by the ESC, it is logical to assume such changes or recommendations will be reflected in the upcoming update on diagnosis of stable CAD from ACC/AHA.

TABLE 1. Sensitivities and specificities of different diagnostic modalities in functionally significant lesion (FFR of ≤0.80)

Diagnostic modality	Sensitivity	Specificity
FFRCT		
Discover Flow 2011[13]	87.9 (95% CI: 76.7-95.0)	82.2 (95% CI: 73.3-89.1)
DeFACTO 2013[14]	90% (95% CI: 84%-95%)	54% (95% CI: 46%-83%)
NXT 2014[15]	86% (95% CI: 77%-92%)	79% (95% CI: 72%-84%)
CCTA		
DISCOVER FLOW 2011[13]	91.4% (95% CI: 81.0-97.1)	39.6% (95% CI: 30.0-49.8)
NXT, 2014[15]	94% (86-97)	34% (95% CI: 27%-41%)
Knuuti et al., 2018[28]	93% (95% CI: 89-96)	53 (95% CI: 37-68)
SPECT		
Knuuti et al., 2018[28]	73% (95% CI: 62-82)	83% (95% CI: 71%-90%)
Stress CMR	89% (95% CI: 85-92)	87% (95% CI: 83%-91%)
Knuuti et al., 2018[28]		
PET	89% (95% CI: 82-93)	85% (95% CI: 81%–88%)
Knuuti et al., 2018[28]		

FFRCT, given its efficacy and the virtue of being a noninvasive method of obtaining FFR, can be a novel accurate "rule-out" test for functionally significant stenosis/CAD.

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