Background

NEED FOR IMPROVED CORONARY ARTERY DISEASE (CAD) TESTING

Cardiologists use a number of noninvasive diagnostic tests including exercise treadmill, stress echocardiography, and nuclear SPECT in order to determine which patients have coronary artery disease and who may benefit from revascularization. However, Patel et al. (2014) found that despite widespread use of these tools, 58.4% of patients sent to invasive coronary angiography (ICA) did not have significant CAD. In fact, Chinnaiyan et al. found that stress test results were not predictive of which patients had significant CAD and provided no predictive value beyond traditional cardiovascular risk factors such as high blood pressure or a history of smoking.

In a recent study performed by Vavalle et al., researchers found that only 48% (7,564 of 15,766) of patients had obstructive disease at the time of ICA. Furthermore, patients with positive stress test results were less likely to undergo revascularization (35.2%) than patients with negative results (47.9%) or no stress test at all (40.3%). These studies underscore the need for a better noninvasive test that more accurately determines who may benefit from invasive evaluation.

Effect of the Presence and Type of Angina on Cardiovascular Events in Patients Without Known Coronary Artery Disease Referred for Elective Coronary Angiography. Vavalle, J.P. et al. (2016). JAMA Cardiology.

INVASIVE FRACTIONAL FLOW RESERVE (FFR)

Fractional Flow Reserve (FFR), measured during ICA, serves as the gold standard for identifying vessel-specific ischemia and is used to identify patients who may benefit from coronary revascularization. The FAME study (Tonino et al.) randomized patients with multivessel CAD to angiography-guided Percutaneous Coronary Intervention (PCI) or FFR-guided PCI. The FFR-guided group, in which stents were placed only when a stenosis was associated with FFR < 0.80, had a significantly lower rate of adverse clinical events. In the FAME II study (De Bruyne et al.), patients in whom at least one stenosis was functionally significant (FFR < 0.80) were randomized to FFR-guided PCI or best available medical therapy. Patients in the FFR-guided group had a significantly lower rate of adverse clinical events.

Data from the prospective IRIS-FFR registry performed by Ahn et al. confirmed the superior outcomes of FFR-guided care in 5,846 patients. The authors report that for lesions with a low FFR, the risk of an adverse cardiac event was much lower if the lesion was revascularized. Conversely, for lesions with a high FFR, the data strongly supports medical treatment as a reasonable and safe treatment strategy. A recent meta-analysis performed by Nagaraja et al. showed that the availability of FFR data changed the management strategy in 22-48% of patients compared to an angiography-guided strategy. These studies demonstrate the ability for FFR to guide treatment safely and effectively for patients with stable CAD.

Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: How consistent is the effect? Nagaraja, V. et al. (2017). Cardiovasc Revasc Med.
Scientific Basis

**HOW THE FFR<sub>CT</sub> ANALYSIS WORKS**

Taylor et al. have described the scientific basis for the noninvasive FFR<sub>CT</sub> analysis, explaining how recent advances in computational fluid dynamics and image-based modeling underlie the ability to calculate FFR values mathematically. When these methods are applied to standard coronary CT angiograms (cCTA), the result is a color-coded 3 dimensional map of FFR<sub>CT</sub> values at every point in the coronary arterial tree. Visualization of FFR<sub>CT</sub> values in patient-specific anatomy enables physicians to identify ischemia-producing coronary lesions.


**Validation of FFR<sub>CT</sub>**

HeartFlow FFR<sub>CT</sub> has been evaluated in three multicenter prospective clinical trials that directly compared FFR<sub>CT</sub> values with invasively measured FFR values in over 600 patients at major medical centers worldwide. Clinical data from the landmark NXT study (Nørgaard et al. 2014) utilized the most current version, and showed that the HeartFlow FFR<sub>CT</sub> Analysis had a greater ability to determine whether significant CAD is present and whether a coronary stenosis is obstructing blood flow, i.e. low FFR, as compared to cCTA alone. The HeartFlow Analysis had higher diagnostic accuracy (86%) than cCTA (65%) and ICA showed only 71% accuracy in the study. When compared with other noninvasive testing methods, FFR<sub>CT</sub> demonstrated significantly higher diagnostic accuracy (Nørgaard et al. 2015).


**Clinical Use of the HeartFlow Analysis**

The HeartFlow FFR<sub>CT</sub> Analysis has been shown to significantly affect treatment decisions for patients with suspected CAD. In the FFR<sub>CT</sub> RIPCORD study, Curzen et al. reported that treatment decisions based on cCTA changed in 44% of patients when FFR<sub>CT</sub> data were made available.

The prospective controlled clinical utility and cost effectiveness PLATFORM trial (Douglas et al. 2015) showed that in patients scheduled for ICA the addition of FFR<sub>CT</sub> data was associated with cancellation of the invasive procedure in 61% of patients. In addition, the proportion of patients who underwent ICA only to find no obstructive CAD dropped from 73% in the usual care group to 12% in the group guided by a pathway incorporating cCTA and FFR<sub>CT</sub>. Importantly, there were no adverse events during 1 year of follow-up in the 117 patients whose ICA was cancelled based on FFR<sub>CT</sub> findings (Douglas et al. 2016). By reducing the number of unnecessary invasive procedures performed, Benton et al. argue that FFR<sub>CT</sub> has the ability to lower health care expenditures and become the true gatekeeper to ICA.


Health Economics

There is also evidence that the HeartFlow Analysis can reduce costs associated with diagnosing and treating CAD. One year follow-up of the PLATFORM study performed by Douglas et al. found that for patients with a planned ICA, evaluation via a pathway incorporating cCTA and FFR_{CT} led to significantly lower costs of care compared with standard treatment ($8,127 vs. $12,145, a reduction of 33%). When the $1500 cost of FFR_{CT} was included, total savings to the healthcare system was 26%. In addition, evaluation via a pathway incorporating cCTA and FFR_{CT} was associated with improved Quality of Life compared with a strategy of evaluation with ICA or other noninvasive tests (Hlatky et al. 2015).

An earlier health economic analysis performed by Hlatky et al. (2013) found that incorporating FFR_{CT} into patient management could lead to 30% lower costs and a 12% reduction in the rate of death and heart attack over a period of one year. Rajani et al. and Kimura et al. published similar findings using UK and Japanese health economic models respectively.


Real World Experience with the FFR_{CT} Analysis

Nørgaard et al. (2016) recently shared their experience using cCTA and FFR_{CT} as the initial diagnostic modality to evaluate patients with new onset chest pain and no known CAD. In this population with a low to intermediate pre-test likelihood of disease, FFR_{CT} was ordered for 189 patients (15.1%) who had one or two intermediate coronary stenoses (lumen narrowing 30% to 70%) found by cCTA. Conclusive FFR_{CT} results were obtained in 98% of patients and 123 patients (65%) had their ICA deferred based on the results. The authors report no adverse clinical events for these patients through a median follow-up period of 12 months. In a follow-up report (2017) the authors report that switching from MPI to FFR_{CT} to evaluate patients with intermediate stenoses led to a reduction in patients who needed a second noninvasive test, a reduction in ICA utilization, a decrease in the rate of finding no obstructive CAD at ICA, and an increase in the number of ICAs performed with functional information available.

Jensen et al. examined the impact of adopting a diagnostic strategy composed of cCTA with selective FFR_{CT} testing for all symptomatic patients with suspected CAD (N = 774). This replaced an earlier strategy that used frontline cCTA for patients with a low-intermediate risk of CAD and referred patients with high risk directly to ICA. Of the 181 patients with a high risk of CAD, use of cCTA and FFR_{CT} led to cancellation of 75% (115/153) of planned ICAs. In the 593 patients with a low-intermediate risk of CAD, cCTA with selective FFR_{CT} safely kept 91% of patients out of the cath lab. The authors reported four adverse events, none of which occurred in a patient who had an ICA cancelled based on FFR_{CT} results.


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