Chapter 25
Coronary Heart Disease Diagnosis by FFR$_{CT}$: Engineering Triumphs and Value Chain Analysis

Geoffrey D. Rubin

Coronary heart disease is the leading cause of death throughout the developed world, yet the symptoms that patients experience as a result of coronary disease are often not specific. Determining who are the minority of patients with myocardial ischemia necessitating revascularization is a major activity of many medical centers. This task has traditionally fallen to coronary angiography, which is an expensive and invasive approach to identifying coronary artery lesions necessitating treatment through revascularization with stents or bypass grafts. Recently, computational fluid dynamic methods have been developed for cardiac CT that have been shown to effectively exclude patients from an invasive test when they do not have significant coronary artery disease. This manuscript reviews the technique of CTFFR and discusses some of the challenges of widespread clinical implementation through value chain analysis.

25.1 Coronary Heart Disease Pathophysiology

Development of coronary heart disease occurs over many years with atherosclerotic plaque deposition beginning in childhood and gradually progressing to a stage that can result in narrowing of the coronary arteries that may restrict blood flow to the heart muscle, particularly during high demand such as during exercise. Diminished

G. D. Rubin (✉)
Duke University School of Medicine, Durham, NC, USA
e-mail: grubin@duke.edu

oxygen delivery to the heart muscle causes tissue injury and death. Dead myocardium leads to fatal arrhythmia, pump failure, or in rare instances cardiac rupture.

Common and low-cost testing for coronary heart disease performed with electrocardiography or blood testing are often of limited accuracy. The definitive diagnosis of coronary heart disease rests upon imaging. Imaging is typically performed in two phases. In the first phase, a non-invasive imaging test is typically performed to determine if the patient should proceed to invasive imaging for definitive characterization and management.

Three non-invasive tests are available to assess for coronary heart disease. Two tests center on visualizing functional impairment in the myocardium, whereas one of these tests is capable of direct visualization of coronary artery lesions. The functional tests are radionuclide perfusion imaging (Sabharwal 2017) and stress echocardiography (Elhendy 2018). Both exams are performed during physical or pharmacologic stress and periods of rest to assess for reversible changes in myocardial perfusion or wall motion, respectively. Computed tomography angiography (CTA) is a newer entrance into the field of noninvasive coronary heart disease imaging (Rubin et al. 2014). It has undergone rapid refinement with technological improvement in CT scanners, overcoming limitations related to motion induced blurring to provide three dimensional representations of the coronary artery tree.

In distinction to radionuclide perfusion imaging and echocardiography, CTA allows direct visualization of the coronary artery tree and localization of atherosclerotic plaque, demonstrating both degree of arterial stenosis as well as character of the plaque. These features of CTA provided with the potential to plan therapeutic intervention through transluminal stent-based revascularization or coronary artery bypass grafting. In the absence of an anatomic delineation of coronary artery lesions, radionuclide perfusion imaging and echocardiography require a secondary test to identify treatable coronary artery lesions prior to initiating definitive therapy.

The anatomic mapping required in these latter instances is performed using invasive coronary angiography (ICA). ICA has been the reference standard for coronary artery anatomic visualization since the 1960s when it first became a mainstream clinical test. ICA requires the placement of a catheter into the arterial system with entry point most commonly through the femoral artery located in the groin. A catheter is then advanced in a direction opposite of blood flow until it reaches the heart, whereupon the operator engages the origins of the coronary arteries and directly injects a radio-opaque iodine solution into the coronary arteries while high frequency video is acquired using projectional radiography. Because ICA is a projectional technique, it is susceptible to a number of geometric limitations that hinder detailed evaluation of the coronary artery lumen. In particular, it is incapable of demonstrating discreet arterial cross sections. Its advantage is that it offers a high degree of spatial resolution when compared to noninvasive imaging modalities. Although CTA has substantially lower spatial resolution than ICA, its volumetric acquisition offers substantial advantages by allowing the anatomy to be reconstructed through innumerable projectional view angles and cross sections from a single volumetric acquisition.

An additional and often valuable characteristic of ICA, is that coronary artery access required for coronary angiography is identical to that required for revascularization using transluminal stent deployment. Consequently, patients with significant coronary artery lesions that are amenable to stenting can be treated immediately following their diagnosis as part of a single setting integrated procedure.

On the other hand, ICA is expensive. It requires multiple skilled personnel to perform a procedure that lasts between 1 and 3 h. It requires a patient to take a full day from work. There is discomfort associated with having a catheter inserted into the groin and manipulated during the procedure as well as pressure being applied for hemostasis over several hours after the procedure. Finally, there is a small but measurable risk of coronary artery injury due to the insertion of the catheter which can result in myocardial infarction or cardiac rhythm disturbances.

25.2 Invasive Coronary Angiography Is Inefficient

Because ICA is the reference standard for depicting coronary artery lesions and is a prerequisite for performing revascularization in patients with suspected coronary heart disease characterized with either SPECT or echocardiography, it has been a critical path for the management or coronary heart disease for many years. Because it is an invasive examination, ICA is more expensive than non-invasive imaging tests owing to the greater intensity of personnel required to perform an ICA, the overhead costs associated with a catheterization laboratory, and requirements for pre and post procedural care. In addition to financial expense, ICA exposes patients to greater risk owing to its invasive nature. While in experienced hands, the likelihood of complications from ICA is very low, it is still substantially higher than for non-invasive examinations.

In 2010, an analysis of almost 400,000 elective ICAs performed at 663 United States hospitals between 2004 and 2008 revealed that only 38% of subjects had obstructive coronary lesions and thus warranted intervention (Patel et al. 2010). Characterized based upon a visual assessment of at least 50% luminal narrowing, significant coronary artery lesions were found in only 38% of subjects.

While a positivity rate of only 38% is seen to represent an inefficient use of invasive testing for treatment planning, the value of visually assessed luminal stenosis at ICA is further degraded when considering the results of multiple studies reported in a meta-analysis (Stergiopoulos et al. 2014), which revealed that patients with stable chest pain who were re-vascularized based upon ICA did not have better health outcomes than patients who were managed with non-operative medical (pharmacologic) therapy. Suggesting that the appearance of a "significant" narrowing at ICA was not a reasonable determinant of the need for re-vascularization.

25.3 Fractional Flow Reserve

Until recently, the assessment of coronary artery disease using ICA was restricted to an image-based assessment of variations in coronary artery diameter. Particularly given the fact that conventional angiography is a projectional technique obtained using fluoroscopy, the ability to accurately represent flow-limiting arterial stenosis is limited. The introduction of the physiologic measurement, fractional flow reserve (FFR), has been revolutionary for the characterization of patients being assessed with ICA.

Obtained during infusion of the vasodilator adenosine to maximize coronary flow, FFR represents the ratio of the mean arterial pressure obtained immediately beyond a region of arterial narrowing to the mean arterial pressure within the root of the aorta (Pijls et al. 1996). These measurements provide an indication of the pressure drop along the length of the coronary artery. An FFR of 0.8 or lower is the most common threshold for considering a coronary lesion to be flow limiting.

The value of FFR guided coronary revascularization was established with publication of 2-year outcomes from the FAME trial in 2010 (Pijls et al. 2010). In FAME patients with multi-vessel coronary artery disease, defied as coronary artery stenosis with greater than 50% diameter reduction in at least two of the three major coronary arteries, were randomized to one of two treatment planning approaches. Half the 1205 subjects underwent percutaneous coronary revascularization based upon the visual appearance of the coronary angiogram while the other half underwent percutaneous coronary intervention based upon the FFR measurement.

Two years following treatment, there was a 33% reduction in the risk of death or major cardiac events amongst the patients who were treated based upon FFR guidance vs appearance guided coronary artery revascularization. Amongst the patients in whom FFR measurements were made, only 38% of lesions suspected to be significant based upon their appearance were positive by FFR criteria, this explains the result that despite a greater frequency of death or mild myocardial infarction, 42% more stents were placed on average in patients with appearance guided revascularization when compared to FFR guided revascularization.

As a result of the FAME trial and other subsequent clinical investigations, FFR has become the established standard for determining which coronary lesions merit revascularization. Moreover, when considering that only 38% of patients referred to US hospitals have obstructive coronary artery disease, multiplied by the observations through FAME that 30% of those lesions are FFR positive, it is possible to extrapolate a prevalence of 11% of patients referred to ICA having disease necessitating revascularization.

These results underscore the inefficient and ultimately expensive practice of using ICA as a means of determining which patients will need revascularization. Thus, a gate-keeper to inter-coronary angiography is needed. A noninvasive gate-keeper that reliably predicts FFR positive coronary artery lesions with a minimum of false positive results should have a substantial impact on the quality and cost of care for patients suspected of having significant coronary artery disease.

25.4   CT Angiography

CT scanners provide an opportunity to acquire volumetric coronary angiograms following a single injection of an iodine solution into a peripheral vein. With recent generation scanners CTAs encompassing the entirety of the heart frequently require less than 5 s to acquire and offer a temporal resolution as low as 70 ms (Rubin et al. 2014).

Multiple clinical studies have established the diagnostic performance of CT angiography with a very high negative predictive value of between 0.97 and 0.99. However, the positive predictive value of CT angiography when interpreted using a visual assessment akin to that of conventional angiography suffers from false positive results that provide a positive predictive value of 0.64–0.86 (Budoff et al. 2008; Miller et al. 2008; Meijboom et al. 2008a). While this diagnostic performance is fair, it falls off substantially when the reference standard for coronary artery disease is FFR rather than the visual assessment of the coronary lesion at ICA. In fact, when using an FFR greater than 0.8 as the reference standard for significant coronary lesions, 75% of lesions that appear to be narrowed by at least 50% on CT angiography are falsely positive, resulting in a positive predictive value of only 0.25 (Meijboom et al. 2008b). If CT angiography is to serve as an effective gatekeeper for ICA, an additional technology is needed to determine which of the apparently significant coronary lesions on CTA are actually flow limiting. That technology has recently become available based upon the use of computational fluid dynamics applied to the CT scan data resulting in the modeling of FFR from the CT data, referred to as FFR$_{CT}$.

Relying upon a painstakingly segmented anatomic model of the coronary arteries and the aggregate myocardial mass, the application of computational fluid dynamics has provided the basis for predicting FFR values along the length of the coronary arteries, both at baseline and maximal flow conditions, simulating the intra-arterial injection of adenosine that is used with invasive FFR measurement. This is accomplished by solving Navier–Stokes equations of blood flow where mass and momentum are conserved as they are applied to the movement of viscous fluid. Mean coronary artery pressure is thus derived along the length of the coronary arteries allowing for the calculation of FFR by dividing mean coronary pressures by the aortic pressure (Taylor et al. 2013). When compared to invasive FFR, FFR$_{CT}$ slightly underestimates the FFR value with a mean difference of 0.03 but correlates with FFR with a Pearson's correlation coefficient of 0.82 (P-0.001) (Norgaard et al. 2014).

When applied to a cohort of 103 patients with stable chest pain, FFR$_{CT}$ results improved the specificity of coronary CT angiographic evaluation from 25% to 82%, raised the positive predictive value from 58% to 85%, and overall improved the accuracy of the exam by 26%. In aggregate, the frequency of false positive results was reduced by 70% with FFR$_{CT}$ when compared to visual interpretation of the coronary CT angiograms with reclassification of those false positive results as true negatives (Koo et al. 2011). In a subsequent clinical trial focused on characterizing

visually equivocal 30–70% arterial narrowing observed at CT angiography, FFR_{CT} similarly improved specificity from 32% to 85% and positive predictive value from 37% to 63% (Norgaard et al. 2014). Figures 25.1 and 25.2 illustrate coronary CT angiograms and associated FFR_{CT} calculations.

Most recently, a prospective cohort of patients deemed to have an intermediate likelihood of significant coronary artery disease but without known disease was assembled across 11 European sites. Patients were enrolled into two testing arms, one receiving usual care and testing and the other receiving CTA/FFR_{CT} testing.

Amongst the 187 patients with usual care testing who then went on for ICA, 32% underwent coronary revascularization either with coronary artery stenting performed in the catheterization lab (42 patients) or surgical coronary bypass grafting (17 patients). Consequently, 68% of patients undergoing ICA in the usual care cohort were determined not to have significant disease (Douglas et al. 2015).

In comparison, 193 patients assigned to undergo ICA first underwent FFR_{CT} measurement. Based upon the FFR_{CT} value, catheterization was not performed in 61%. Amongst the remaining 39% that went on to ICA, 70% of subjects had
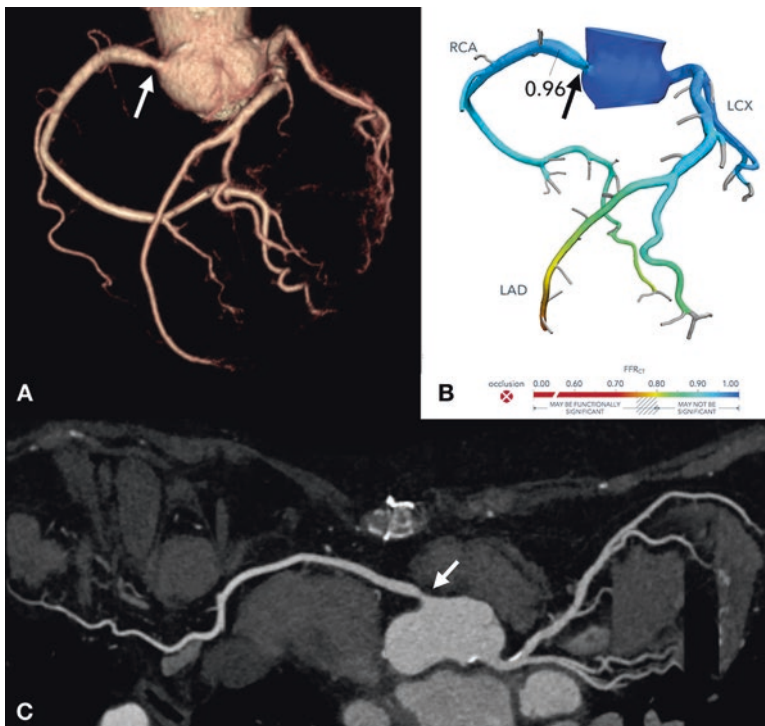

Fig. 25.1 CT angiogram from a patient with chest pain. (**a**) Three-dimensional volume rendering and (**c**) curved reformation shows narrowing at the origin of the right coronary artery (arrow). (**b**) Three-dimensional surface representation uses color overlay to indicate FFR_{CT} values along the length of the major coronary arteries. A value of 0.96 just distal to the right coronary artery origin indicates that it is not hemodynamically significant. No further testing was required
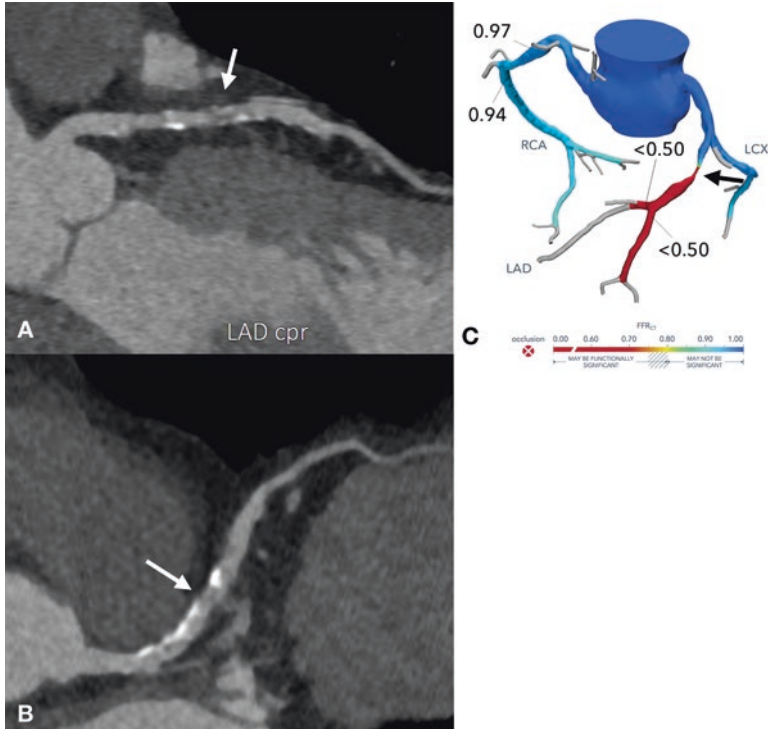
Fig. 25.2 CT angiogram from a different patient with chest pain. (**a**, **b**) Curved reformations through the centerline of the left anterior descending coronary artery and oriented 90° to one another reveal an area of heterogeneity in the artery which is not clearly represented as a significant narrowing (arrow). (**c**) The same region is associated with a significant drop in FFRCT to <0.50 (arrow), indicating an area of significant flow limitation

obstructive coronary artery disease necessitating revascularization while only 30% of patients referred to ICA based upon FFR$_{CT}$ measurements or 12% of all patients undergoing FFR$_{CT}$ underwent ICA without demonstration of a significant coronary lesion. These results correspond to a six-fold reduction in negative ICAs when FFR$_{CT}$ served as gatekeeper to the angiography suite, while the percentage of significant obstructive disease was identical to the patients referred to ICA following the usual care. Moreover, when assessed after 1 year and despite a sixfold reduction in the number of patients undergoing invasive catheterization within the FFR$_{CT}$ arm of the study, there was no difference in the frequency of major cardiac events (1% for both usual and CT groups) nor was there a difference in quality of life measure or in aggregate risk for future events (11, 12).

25.5   Comparing Costs

The reduction in invasive catheterization associated with CT use has been shown to impact the future cost of care as well. When considering 2015 United States Medicare Reimbursement Rates as a proxy for costs, a standard ICA costs $2838 or more than nine times that of a CT angiogram ($301). Without accommodating for the costs of performing FFR_{CT}, this suggests that if only one negative coronary artery angiogram were avoided for every nine CTs performed, then the aggregate cost of diagnosis would be less when FFR_{CT} serves as gatekeeper to ICA (Douglas et al. 2016). However, this analysis oversimplifies the issue of cost measurement as it does not address downstream utilization of medical resources, which may vary following diagnosis with CT versus ICA.

The PLATFORM trial provides a basis for understanding the potential impact of FFR_{CT} on acute and downstream costs. One year following diagnostic testing, the average cost of cardiac care was 33% lower for FFR_{CT} ($8127) versus ICA ($12,145). However, when examining median costs, which avoid the skew associated with the high cost of treating patients with coronary artery disease, the FFR_{CT} pathway cost 12 times less than the ICA pathway ($546 versus $6472). As long as the cost of FFRCT is limited to less than 15 times that of performing and interpreting the CT scan, the use of FFR_{CT} as a gateway to ICA would still result in diminished cost of care when compared to the standard approach of today (Douglas et al. 2016).

25.6   Economic Considerations for Translation to Routine Care

Based upon the aforementioned results, it appears that the use of FFR_{CT} as a determinant of who should undergo ICA is a compelling application that should reduce costs and improve care of patients with coronary heart disease. Nevertheless, the practicality of transitioning current medical practice to a future state based upon FFR_{CT} is fraught with barriers. In order to understand where these barriers might appear, it is useful to consider value chain analysis for FFR_{CT}. Specifically, value chain analysis (Rubin 2017) examines all industry participants in the production of FFR_{CT} as it provides its ultimate impact on individual patients and society as a whole.

As a first step, when considering value to the patient, where value is conceptualized as benefit divided by costs, the patient benefits from the availability of a quicker and less invasive diagnostic test that should result in the same clinical outcomes and quality of life downstream. Assuming that the lower cost of performing FFR_{CT} compared to ICA are passed on to the patient in the form of lower pricing, patients costs are diminished while benefits increase, resulting in substantial increase in value.

When aggregating this value across many patients, society stands to gain from a lower cost of care for coronary heart disease resulting in savings that might be used to support other healthcare priorities or reduce taxes required to support healthcare. Thus, societal value appears to be enhanced as well.

It is the interaction between four distinct entities upstream from the patient in the value chain that lend complexity to our economic considerations. These four entities represent the diagnostic imager, the cardiac interventionalist who performs ICA and coronary stenting, the hospital facility where catheterization laboratories represent an important capital asset, and healthcare payers, both private and public.

For the imager, the performance of FFR$_{CT}$ requires extra effort which diminishes time available for other activities. Incremental support should be provided to accommodate the added work of FFR$_{CT}$. When physicians are compensated based upon a fee-for-service model, uncompensated additional work associated with FFR$_{CT}$ analysis may reduce net revenue to imaging providers unless their efforts are mitigated by an overall increase in CT referrals and the allocation of revenue from those CT referrals provided to offset the added effort required to perform the FFR$_{CT}$ analysis.

The interventionalist stands to lose substantial revenue by performing fewer diagnostic ICAs. In order to offset this loss of activity and revenue, interventionalists will need to identify other activities to compensate and backfill their new-found availability. Paradoxically, over time there may be an increase in the need for diagnostic ICA if FFR$_{CT}$ is applied widely to the population identifying patients at risk, allowing detection of patients at a treatable stage, prior to their suffering from a serious cardiac event such as sudden death.

The hospital faces similar pressures as does the interventionalist. There is the risk of an empty cardiac catheterization lab challenging the institution to support the fixed costs of the laboratory and its supporting personnel with lower payment from payers in response to the lower ICA volumes. The hospital will not be motivated to support FFR$_{CT}$ adoption unless they can find other procedures to backfill the volume within the catheterization lab as a basis for generating revenue to cover their costs.

Finally, the payer stands to gain substantially from the introduction of FFR$_{CT}$. When considering the prevalence of coronary heart disease across a payers' pool of beneficiaries, the reduction in ICA represents a basis for substantial cost reductions across the pool of beneficiaries. These cost reductions may translate into greater overall profit for shareholders, and an opportunity to lower insurance premiums to enhance competitiveness, or the application of excess revenue to other expense-generating priorities.

When considered across the whole of the value chain, the aggregate reduction in costs with what is assumed to be minimal change in healthcare outcomes provides a basis for substantial value to the patient, the payer, and society as a whole. While the imager is most likely to experience a net increase in value as well, the interventionalist and the hospital are positioned to potentially experience a reduction in value which, without mitigating economic intervention, might hinder the adoption of FFR$_{CT}$. Consequently, a value chain based examination of FFR$_{CT}$ delivery and its

economic impact suggests that payers may need to incent interventionalists and hospitals to adopt FFR$_{CT}$ by sharing some of their cost savings with the interventionalists and the hospitals in order to help them transition to a value preserving state (Fig. 25.3).
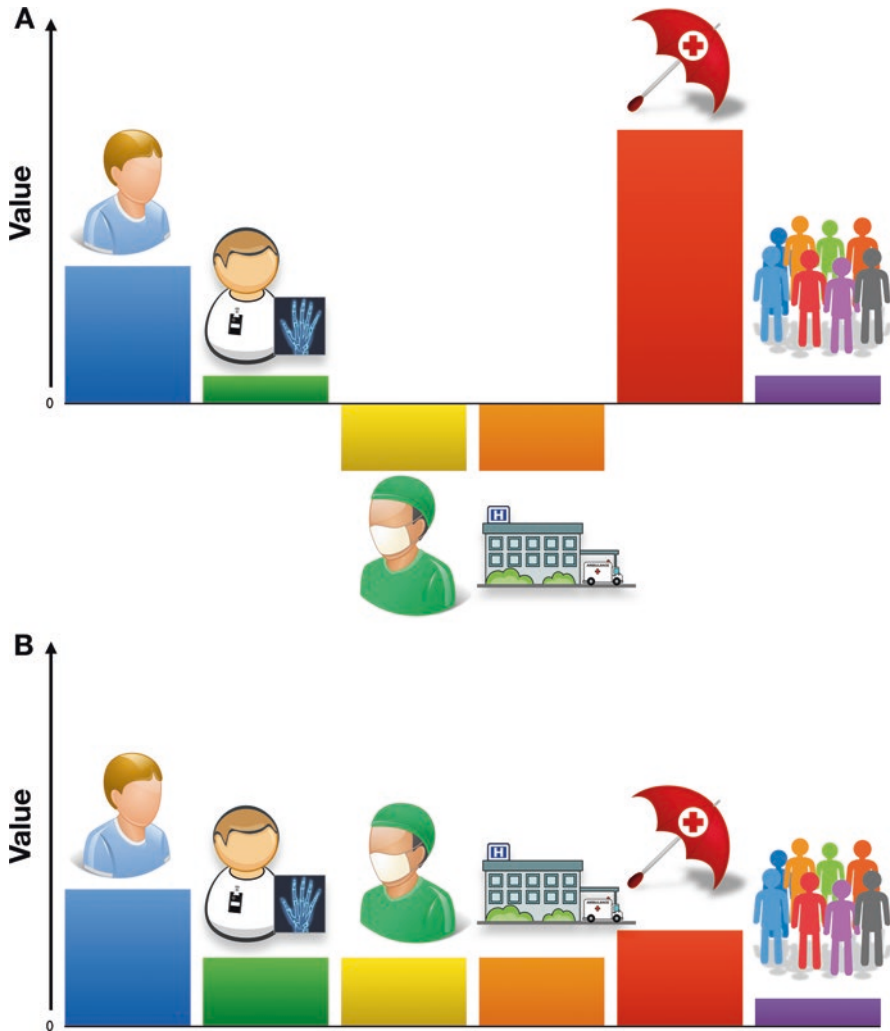

Fig. 25.3 (**a**) Graphical representation of relative value changes resulting from a transition from current diagnostic patterns that result in many non-actionable ICAs to the use of FFR$_{CT}$ as a determinant of referral to ICA. The stakeholders from left to right respectively are the patient, the imager, the interventionalist, the ICA facility, the insurer, and society as a whole. Relative value is representational and not quantitative. The reduction in value experienced by interventionalists and facilities might block the realization of value for other participants in the value chain. A redistribution of value as represented in (**b**) would substantially reduce economic barriers and align interests for adoption

25.7   Conclusion

As a leading cause of death across the developed world, coronary heart disease is a major public health problem. The traditional methods for diagnosis leading to therapy are inefficient and expensive. The development of computational fluid dynamic methods applied to high resolution volumetric CT data provide a means for estimating the physiologic impact of coronary artery narrowing by quantifying FFR$_{CT}$ values. Preliminary clinical testing supports the idea that FFR$_{CT}$ should be an excellent gatekeeper for entry into catheterization laboratories so that fewer negative ICAs are performed. In this scenario, ICA would be largely used as a prelude to needed coronary revascularization while patients who do not undergo ICA are safely managed with medical therapy. Despite the remarkable technical and clinical advances that would seem to compel the widespread adoption of FFR$_{CT}$, economic drivers must be understood and addressed to assure that patients and society will receive whatever benefits might be achieved through the widespread adoptions of this technology.

References

Budoff MJ, Dowe D, Jollis JG et al (2008) Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 52:1724–1732. https://doi.org/10.1016/j.jacc.2008.07.031

Douglas PS, Pontone G, Hlatky MA et al (2015) Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRct: outcome and resource impacts study. Eur Heart J 36:ehv444–ehv449. https://doi.org/10.1093/eurheartj/ehv444

Douglas PS, De Bruyne B, Pontone G et al (2016) 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM study. J Am Coll Cardiol 68:435–445. https://doi.org/10.1016/j.jacc.2016.05.057

Elhendy A (2018) The power of stress echocardiography and myocardial perfusion scintigraphy in predicting long-term outcome. Nothing lasts forever. J Nucl Cardiol 25:480–482. https://doi.org/10.1007/s12350-016-0621-1

Koo B-K, Erglis A, Doh J-H et al (2011) Diagnosis of ischemia-causing coronary stenoses by non-invasive fractional flow reserve computed from coronary computed tomographic angiograms results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 58:1989–1997. https://doi.org/10.1016/j.jacc.2011.06.066

Meijboom WB, Meijs MFL, Schuijf JD et al (2008a) Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 52:2135–2144. https://doi.org/10.1016/j.jacc.2008.08.058

Meijboom WB, van Mieghem CAG, van Pelt N et al (2008b) Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 52:636–643. https://doi.org/10.1016/j.jacc.2008.05.024

Miller JM, Rochitte CE, Dewey M et al (2008) Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 359:2324–2336. https://doi.org/10.1056/NEJMoa0806576

Norgaard BL, Gaur S, Leipsic J et al (2014) Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 63:1145–1155. https://doi.org/10.1016/j.jacc.2013.11.043

Patel MR, Peterson ED, Dai D et al (2010) Low diagnostic yield of elective coronary angiography. N Engl J Med 362:886–895. https://doi.org/10.1056/NEJMoa0907272

Pijls NH, De Bruyne B, Peels K et al (1996) Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 334:1703–1708. https://doi.org/10.1056/NEJM199606273342604

Pijls NHJ, Fearon WF, Tonino PAL et al (2010) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 56:177–184. https://doi.org/10.1016/j.jacc.2010.04.012

Rubin GD (2017) Costing in radiology and health care: rationale, relativity, rudiments, and realities. Radiology 282:333–347. https://doi.org/10.1148/radiol.2016160749

Rubin GD, Leipsic J, Joseph Schoepf U et al (2014) CT angiography after 20 years: a transformation in cardiovascular disease characterization continues to advance. Radiology 271:633–652. https://doi.org/10.1148/radiol.14132232

Sabharwal NK (2017) State of the art in nuclear cardiology. Heart 103:790–799. https://doi.org/10.1136/heartjnl-2015-308670

Stergiopoulos K, Boden WE, Hartigan P et al (2014) Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. JAMA Intern Med 174:232–240. https://doi.org/10.1001/jamainternmed.2013.12855

Taylor CA, Fonte TA, Min JK (2013) Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol 61:2233–2241. https://doi.org/10.1016/j.jacc.2012.11.083