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COMPARATIVE REVIEW

A comparative review of coronary computed tomography angiography and myocardial perfusion imaging

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ABSTRACT
Coronary artery disease remains a leading cause of morbidity and mortality worldwide. Non-invasive imaging techniques have revolutionized the diagnosis and management of coronary artery disease. This review aims to compare the utility and effectiveness of two emerging non-invasive imaging modalities: coronary computed tomography angiography and myocardial perfusion imaging. Thus we provide here a comprehensive overview of the advancements in non-invasive imaging techniques for coronary artery disease assessment. In parallel, we discuss the role of coronary computed tomography angiography and myocardial perfusion imaging in the diagnosis and management of coronary artery disease, their comparative efficacy, and their potential to guide subsequent interventions *(Fig. 4, Ref. 70)*. Text in PDF www.elis.sk
KEY WORDS: angiography, heart, perfusion, myocardial blood flow, ischemic heart disease.

Introduction

Coronary artery disease (CAD) stands as a significant global health challenge, accounting for a substantial number of deaths in men, women, regardless of race, ethnicity or country development status. With mortality rates exceeding 600,000 annually in the United States and a staggering 17.8 million deaths worldwide, CAD emerges as a leading cause of mortality and disability (1, 2). While the prevalence of CAD is alarming, its preventable nature warrants comprehensive attention.

In the assessment of CAD, invasive coronary angiography (ICA) has long been regarded as the reference standard for detecting epicardial coronary artery stenoses. However, it presents several limitations, including its cost, inherent procedural risks, and, critically, its inability to provide insight into the physiological impact of a stenosis without direct fractional flow reserve (FFR) measurements. While anatomical criteria classifying severe stenosis typically stipulate ≥50% left main artery stenosis or ≥70% stenosis in other coronary arteries (3), these metrics do not consistently align with the hemodynamic significance of the lesion. It is noteworthy that stenoses meeting or exceeding the 70% threshold may not invariably result in flow limitation, while a substantial proportion of moderate stenoses (50–69% stenosis) does not exhibit flow-limiting characteristics (4). Moreover, the misclassification of the severity of intermediate stenoses is a frequent occurrence in clinical practice. Understanding these limitations in the context of coronary artery (Fig. 1) assessment is essential for improving clinical decision-making, as the anatomical appearance alone may not provide a comprehensive understanding of the functional impact of coronary lesions. This necessitates the integration of physiological assessments, such as FFR, to better inform clinical management and optimize outcomes for patients with CAD.

To ascertain the physiological significance of coronary artery stenosis, a pivotal method involves the invasive assessment of FFR during ICA. Invasive FFR quantifies the ratio of coronary artery pressure distal to a stenosis to aortic pressure under maximal hyperemia. A ratio of ≤0.8, representing a 20% pressure reduction across the stenosis, is indicative of hemodynamic significance (3, 5). This procedure mandates the passage of a coronary pressure guidewire across the stenosis to measure pressures during the intravenous administration of a vasodilator agent, such as adenosine. While generally considered safe, the invasive nature of FFR measurement carries a slight (<1%) risk of coronary artery injury (6). In addition to FFR measurement, there are now other invasive methods available to assess the functional significance of coronary stenosis without the need for adenosine. These methods, known as non-hyperemic pressure ratios, include the increasingly popular iFR or iwFR measurement (instantaneous wave-free ratio) (Fig. 2). This technique leverages a specific diastolic phase

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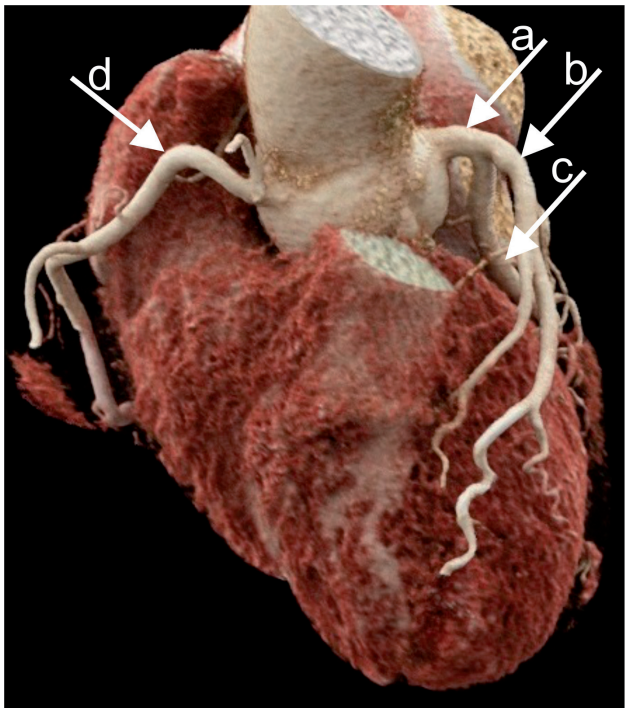

Fig. 1. Computed tomography (CT) images of a 65-year-old woman depicting a 3D reconstruction (using volume rendering technique) of a normal coronary tree (a: LM – left main stem; b: LAD – left anterior descending artery; c: CX – left circumflex artery; d: RCA – right coronary artery), along with multiple 3D reconstructions. The dual source 3rd generation CT Somatom Force device (Siemens Healthcare GmbH) was used to aquire the image.

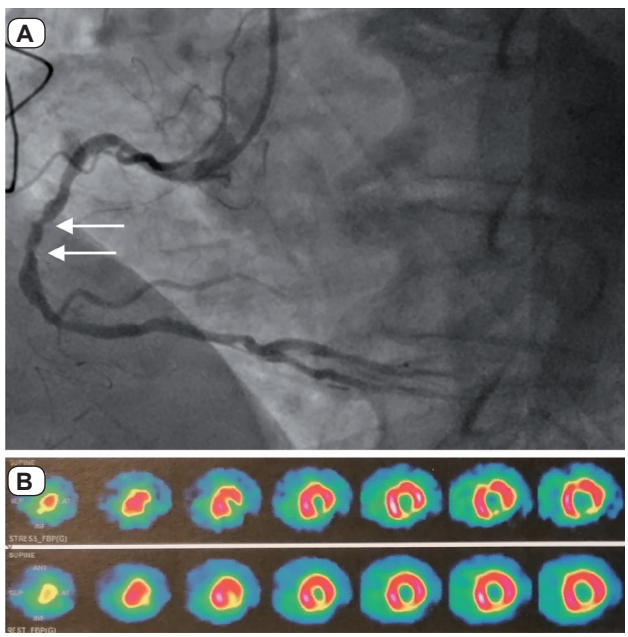

Fig. 2. Coronary angiogram of right coronary artery (A). White arrows show moderate stenosis of the middle part of the right coronary artery. Myocardial perfusion scintigraphy (B) shows reversible perfusion defect during stress phase in the inferior wall area confirming significant stenosis in the middle part of the right coronary artery.

termed the "wave-free period," characterized by naturally low and constant intracoronary resistance, enabling the calculation of a reliable pressure index. Values below 0.9 indicate hemodynamically significant stenosis (7). Alternatively, non-invasive cardiac imaging modalities offer valuable approaches for both anatomical delineation and functional assessment of significant coronary artery stenosis, along with the detection of myocardial infarction (MI). These non-invasive methods serve as important tools in clinical practice, aiding in the comprehensive evaluation of CAD and guiding therapeutic decisions for optimal patient care.

Etiology of coronary artery disease

The etiology of CAD is characterized by a multifaceted interplay of factors. These factors can be categorized into non-modifiable and modifiable elements. Non-modifiable factors, such as gender, age, family history, and genetics, contribute to an individual's predisposition to CAD. It has been observed that males have a higher predisposition to CAD compared to females. Hypercholesterolemia, characterized by elevated levels of low-density lipoproteins (LDL) and decreased levels of high-density lipoproteins (HDL), remains a significant modifiable risk factor for CAD. In contrast, modifiable risk factors encompass variables that can be altered through lifestyle modifications and medical interventions. These modifiable risk factors include smoking, weight and diet control, lipid levels, and psychosocial factors. Given the multifactorial nature of CAD etiology and the presence of modifiable risk factors, the focus of preventive measures should be on interventions aimed at reducing the burden of this disease. Initiatives targeting smoking cessation (8), promoting healthy weight management, optimizing lipid profiles, hypertension control, diabetes mellitus control, sedentary lifestyle prevention and addressing psychosocial variables hold promise in preventing CAD. A novel risk factors have also been subject to research including non-alcoholic fatty liver disease, chronic kidney disease, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, human immunodeficiency virus, thyroid disease, testosterone supplementation, and vitamin D deficiency (1). Notably, markers of inflammation, particularly high sensitivity C-reactive protein (hsCRP), have shown promise as strong indicators of CAD. While the practical application of hsCRP is a subject of controversy, it holds potential as a reliable predictor of CAD (9). By addressing modifiable risk factors through individual and population-level interventions, the incidence and impact of CAD can be significantly mitigated. An individual's 10-year risk of atherosclerotic cardiovascular disease (ASCVD) may be estimated by American Heart Association's ASCVD equation stands.

Pathophysiology of coronary artery disease

CAD is characterized by inadequate blood supply and oxygen delivery to the myocardium due to occlusion of coronary arteries (Fig. 3). The pathophysiology of CAD centers around the formation of atherosclerotic plaques, which progressively restrict blood flow through vessel lumen narrowing. Plaque development begins

with the deposition of lipid-laden macrophages, known as foam cells, in the subendothelial space. Following vascular insult, monocytes migrate to the subendothelial layer and differentiate into macrophages, absorbing oxidized LDL particles and contributing to foam cell formation. The activation of T cells and the release of cytokines further drive the pathological cascade. Growth factors stimulate smooth muscle cells, leading to their uptake of oxidized LDL particles, collagen deposition, and an increased population of foam cells. These processes culminate in the formation of subendothelial plaques. With time, plaques may either grow in size or stabilize if no further endothelial insult occurs. Stable plaques develop fibrous caps and gradually calcify over time (10). As the lumen narrowing becomes significant, myocardial tissue may not receive adequate blood supply during periods of increased demand, resulting in angina symptoms. However, rest allows for a reduction in oxygen requirements, alleviating the symptoms. Angina at rest typically occurs with plaques that have at least 90% stenosis. Rupture of certain plaques exposes tissue factor, triggering thrombosis and potentially causing partial or total lumen occlusion. This can result in the development of acute coronary syndrome (ACS), presenting as unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI), depending on the extent of insult (11)

Coronary computed tomography angiography

In the context of diagnosing CAD, ICA has traditionally held the position of the gold standard. Nevertheless, the emergence of coronary computed tomography angiography (CCTA) has presented an increasingly viable non-invasive alternative. CCTA offers distinct advantages by circumventing the risks associated with invasive procedures while also providing a faster and potentially more cost-effective means of assessing patients with intermediate CAD risk. Notably, epicardial coronary arteries, characterized by their small millimeter-scale diameters,

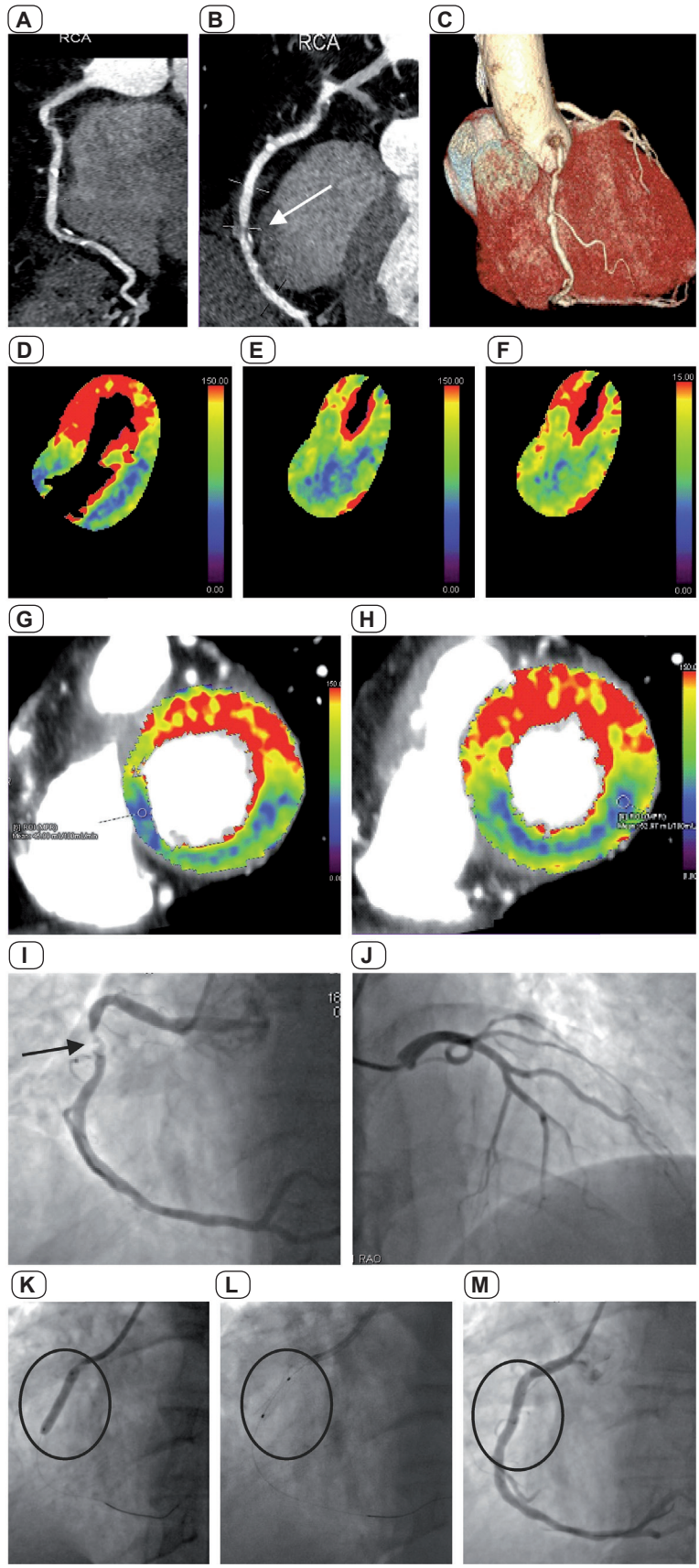

Fig. 3. Myocardial perfusion imaging and invasive coronary angiography. CT (A-C) right coronary artery stenosis and (D-H) perfusion CT with hypoperfusion in examined region of right coronary artery images of representative patient subsequently indicated for (E-M) PTCA and (K-M) stent placement. CT, computerized tomography; PTCA, percutaneous transluminal coronary angioplasty. The dual source 3rd generation CT Somatom Force device (Siemens Healthcare GmbH) was used to aquire the images A-H. Figures are adopted from Gibarti et al. Exp Ther Med. 2023;25(5):192 with kind permision of Spandidos Publications.

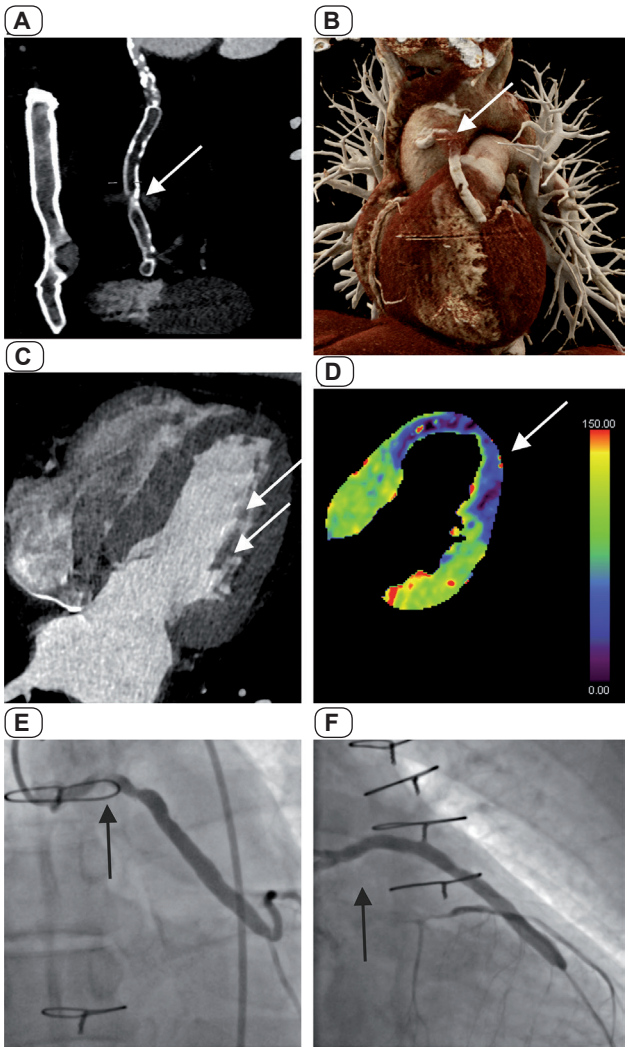

Fig. 4. Representative images of a 71-year-old man with post-coronary artery bypass grafting to the LAD (left anterior descending artery), revealing significant stenosis in the vein graft resulting in scar formation in the lateral wall of the left vetricle. MIP (maximal intensity projection) (A) and corresponding 3D reconstruction VRT (volume rendering technique) (B). MPR (multiplanar recontruction) (C) along with reduced perfusion (D) evaluated using computed tomography perfusion (CTP). The dual source 3rd generation CT Somatom Force device (Siemens Healthcare GmbH) was used to aquire the image. The images bellow display percutaneous transluminal coronary angioplasty before (E) and after (F) stent implantation into the vein graft.

demand exceptional spatial and temporal resolution for accurate visualization. CCTA, driven by innovations such as 64-slice multi-detector CT (64-MDCT) systems and more contemporary technologies, has achieved the necessary temporal and spatial resolution capabilities to delineate even the distal segments of the coronary artery tree (12).

In evaluating the diagnostic prowess of CCTA, research has predominantly centered on its capacity to discern significant coronary lesions (those exceeding 50% blockage) in comparison to lesions subsequently identified through ICA in the same cohort of patients. Early investigations involving 64-slice multi-detector CT (64-MDCT) technology unveiled promising results, showcasing diagnostic sensitivity, specificity, positive predictive value, and negative predictive value in of 99%, 64%, 86%, and 97%, (patient-based analysis) and 88%, 90%, 47% and 99% (segment-based analysis), respectively (13). It is pertinent to note that these initial studies typically excluded individuals with factors such as atrial fibrillation, atrial premature contractions, ventricular premature contractions, prior history of CAD, and those unable to tolerate beta-blockade.

In our centre, we recorded overall sensitivity at 95.42%, 92.31%, and 80.00% as well as specificity at 30.71%, 49.58%, and 75.82%, corresponding to the three significant stenosis thresholds (≥50%, ≥60%, and ≥70%, respectively) (14). Accordingly, the overall negative predicting values were recorded at 93.36%, 90.77% and 86.05%. In summary, CCTA may be found useful in detecting significant coronary stenosis selecting patients for subsequent invasive procedure based on significant stenosis. We conclude that lumen reduction of ≥60% presents a fine balance between negative predicting value and sensitivity/specificity in the environment of our centre (East-Slovak Institute of Cardiovascular Diseases, Inc.). These findings underscore the potential of CCTA as a valuable diagnostic tool, albeit with some considerations as a positive 64-slice CTCA scan often overestimates the severity of atherosclerotic obstructions and requires further testing to guide patient management (15).

Additionally, CCTA can be employed to measure the Coronary Artery Calcium (CAC) score. CAC score represents a crucial diagnostic tool in contemporary clinical practice. This score effectively quantifies the presence of calcified plaque within the coronary arteries through the utilization of non-contrast CT scans, yielding a numerical value that correlates with the potential risk of future cardiac events. The categorization is straightforward: CAC scores of 0, 1 to 10, 11 to 100, 101 to 400, and those exceeding 400 correspond to no, mild, moderate, and severe CAD, respectively (16). Notably, patients bearing CAC scores of 0 or 1 to 10 are associated with a low lifetime risk of adverse cardiovascular events. However, intriguing findings have spotlighted the increased risk that individuals with mild CAC scores (1 to 10) face, demonstrating a threefold elevated risk of CAD development in comparison to those with CAC scores of zero. These revelations have spurred a deeper exploration into the roles played by non-calcified coronary artery plaque, rapid atherosclerosis, and plaque destabilization in the genesis of CAD. Importantly, assessing these additional plaque features, particularly non-calcified coronary artery plaques that span from non-obstructive to significantly stenotic, proves to be challenging via CAC scoring alone (17). Moreover, it holds particular significance for patients possessing a family history of premature CAD, offering a valuable instrument for risk evaluation (18). Notably, the CAC Score emerges as an essential diagnostic element in cases where patients present with atypical chest pain, especially following conventional functional tests such as stress echocardiograms or myocardial perfusion scans. In such instances, the CAC score provides supplementary insights, enhancing the diagnostic process (19). However, it is imperative to acknowledge

the limitations associated with the CAC Score. One such constraint pertains to the exposure of patients to ionizing radiation during the examination process, albeit at a lower dose compared to CCTA. Furthermore, the CAC score is confined in its ability to detect non-calcified plaque, an important contributor to CAD, which underscores the need for complementary diagnostic modalities. Additionally, it is crucial to emphasize that the CAC score does not provide insights into the severity of luminal narrowing or the extent of blood flow impairment (20).

Myocardial perfusion imaging

Myocardial perfusion imaging (MPI) serves as a comprehensive tool capturing the collective impact of pathology on epicardial coronary arteries, small vessels, and endothelium, thus providing a holistic evaluation of the overall burden of ischemic heart disease (IHD) (21). This noninvasive approach is employed for the early diagnosis of asymptomatic CAD and assessing the functional significance of known CAD. Compelling evidence suggests that the early detection of myocardial perfusion abnormalities, coupled with aggressive intervention against cardiovascular risk factors, may contribute to the restoration of myocardial perfusion, subsequently reducing morbidity and mortality. While cardiac myocardial perfusion single-photon emission computed tomography (myocardial perfusion scintigraphy, MPS) has been a gold standard in this domain for decades, newer modalities, including positron emission tomography (PET), cardiac magnetic resonance imaging (CMR), computed tomography perfusion (CTP), and myocardial contrast echocardiography (MCE), are emerging. intermodal comparisons, and evaluations relative to ICA.

Stress induction

Myocardial perfusion imaging has gained prominence leveraging pharmacological stress through vasodilators like adenosine, regadenoson, or dobutamine (22-24). Formerly, adenosine and dipyridamole stood as standard pharmacologic stress agents inducing vasodilatation during CTP (25). Adenosine, an endogenous purine nucleoside, stimulates adenosine receptors on the arteriolar vascular smooth muscle cells while dipyridamole, a nucleoside transport inhibitor and a phosphodiesterase enzyme 3 inhibitor, blocks reuptake of adenosine into platelets, red blood cells, and endothelial cells, inadvertently leading to increased extracellular concentrations of adenosine receptors (25). Further pharmacological agent include dobutamine, a synthetic catecholamine with a potent β_1-receptor and mild α_1- and β_2-receptor agonist activity. Due to their short half-lives (10 s for adenosine (22), 3–12 min for dipyridamole (23), and 2 min for dobutamin (24)), adenosine, dipyridamole, and dobutamine are administered as continuous infusions.

However, their application is often accompanied with the frequent occurrence of adverse events, with mild events such as flushes, chest pain, dyspnea, dizziness, and nausea, affecting up to 80% of patients, and rarer but serious events including bronchospasm, atrioventricular block, and peripheral vasodilation (26). In response to these challenges, clinicians have begun shifting towards the use of regadenoson, a selective A_{2A} receptor agonist (27). Notably, regadenoson presents an improved safety and tolerability profile in comparison to adenosine, which acts non-selectively on A_1, A_{2A}, A_{2B}, and A_3 receptors (28).

Regadenoson holds a substantial advantage over adenosine, dipyridamole, and dobutamin in terms of administration, as it is delivered as a single bolus (0.4 mg), contrasting with the weight-adjusted infusions required for adenosine and dipyridamole (29). This shift to regadenoson marks a pivotal advancement, not only streamlining the administration process but also mitigating the incidence of adverse events, thereby enhancing the overall safety and tolerability of pharmacologic stress agents in the context of CTP (30).

Myocardial perfusion scintigraphy and positron emission tomography

Myocardial perfusion scintigraphy (MPS) and positron emission tomography (PET) imaging, performed post-physical or pharmacologic stress and during rest, serve to discern regional disparities in coronary blood flow, offering a qualitative and semi-quantitative evaluation of regional perfusion defects (31). With a rich history spanning over three decades, MPS has entrenched itself in clinical practice, supported by extensive literature attesting to its diagnostic prowess, value in risk stratification, and prognostic utility. Notably, MPI tracers illustrate a linear relationship between peak stress myocardial blood flow (MBF) and myocardial tracer concentration uptake. However, this correlation faces challenges in clinical application due to the "roll-off phenomenon," where increase in coronary flow beyond 1.5–2-fold do not proportionally elevate tracer uptake. MPS effectively detects ischemia when stenosis has the potential to induce a reduction in blood flow, occurring typically when stenosis diameter exceeds ~50–70%. In the early literature, encompassing an analysis of 79 studies involving nearly 9000 patients, MPS demonstrated a sensitivity of 86% and specificity of 74% in detecting angiographic stenosis exceeding 50% (32).

MPS serves as a valuable tool providing incremental value in risk assessment for patients with known or suspected CAD. The linear relationship between the extent and severity of perfusion abnormalities observed in MPS and the risk of cardiac death and myocardial infarction (MI) underscores its prognostic significance. A meta-analysis involving nearly 40,000 patients revealed that a normal or low-risk MPS study correlated with a low major adverse cardiovascular event rate (0.6% per year), akin to event rates in the general population without CAD evidence (33). Recent prospective research has further emphasized the predictive power of MPS, indicating a substantial increase in death rates (9.2% vs 2.6%), MI rates (11.8% vs 3.3%), and revascularization rates (24.7% vs 2.7%) for individuals with abnormal scans (34).

MPS not only excels as a prognostication tool but also plays a pivotal role in treatment decisions. In a sizable observational study encompassing more than 10 thousands patients with suspected CAD, those with minimal stress-induced ischemia demonstrated a survival advantage with medical therapy. Conversely, patients with extensive ischemia (>10–12.5%) exhibited enhanced survival benefits with revascularization (35). The association between the

extent and severity of hibernating myocardium, post-test treatment, and subsequent patient survival further underscores MPS's relevance. Patients with limited hibernating myocardium derive substantial benefits from medical therapy, while those with extensive hibernating myocardium (>10%) may experience enhanced outcomes with revascularization (36).

Additionally, MPS proves to be an excellent tool for preoperative risk stratification, offering a high negative predictive value. A normal preoperative MPS result not only indicates a low perioperative risk but also suggests a low long-term risk. A recent extensive retrospective observational study of 322,688 patients undergoing noncardiac surgery underscores the significance of abnormal myocardial perfusion as a notable risk factor for adverse postoperative events (37). Overall, MPS stands as a versatile and robust diagnostic modality, providing critical insights for risk assessment, treatment decisions, and preoperative considerations in the management of cardiovascular health.

Cardiac magnetic resonance imaging

Cardiac Magnetic Resonance Imaging (CMR) has gained prominence leveraging pharmacological stress through vasodilators. Vasodilator methods entail intravenous gadolinium contrast administration during vasodilator infusion, revealing perfusion defects in ischemic territories during hyperemia. CMR also adeptly detects wall motion abnormalities in the presence of ischemia (38). While CMR assessment is primarily qualitative, employing visual inspection for ischemia presence and extent, efforts to enhance diagnostic accuracy include quantitative measurements of perfusion. These methods range from semi-quantitative, utilizing signal intensity differences, to fully quantitative, measuring absolute blood flow (39). In a study of 84 patients undergoing rest and vasodilator stress imaging, CMR's measurement of myocardial perfusion reserve exhibited a sensitivity of 88% and specificity of 90%, compared to ICA (40). It demonstrated excellent concordance with PET for detecting obstructive epicardial CAD (41). Recent meta-analyses, comparing CMR, PET, and MPS, indicate their similar sensitivity with varying specificities. CMR, with a sensitivity of 89% and specificity of 76%, appeared to surpass MPS in diagnostic accuracy (42). Trials like MR-IMPACT and CE-MARC consistently underline CMR's superior diagnostic accuracy and risk reduction potential (43, 44). Moreover, a recent meta-analysis found CMR's sensitivity and specificity at the per-patient level equivalent to CT and PET (45). Moreover, CMR emerges as a potent risk stratification tool. A meta-analysis involving 25,497 patients demonstrated CMR's ability to predict adverse events, including all-cause death, through findings such as wall motion abnormalities, stress-induced perfusion defects, and low left ventricle ejection fration (46). Accepted as the noninvasive gold standard for cardiac structure and function assessment, CMR outshines echocardiography, providing a comprehensive evaluation (47).

Myocardial contrast echocardiography

Echocardiography, a longstanding tool for studying heart anatomy and function, has evolved with the introduction of lipid microspheres as contrast agents. These microspheres, distinguished by their outer shell composition and gas content, offer unique echogenic properties (21). Upon injection into the systemic circulation, ultrasound-induced oscillation generates distinctive echoes, facilitating differentiation of blood, myocardium, and other tissues. Following left ventricle cavity opacification, a high-intensity ultrasound pulse destructs the microspheres. In normal myocardium, contrast replenishment takes approximately 5 seconds, while under hyperemic conditions, it typically takes less than 2 seconds. Coronary stenosis-induced decreased MBF prolongs replenishment time (48). MCE has exhibited robust diagnostic performance compared to ICA. A meta-analysis involving approximately 1700 patients from 20 trials reported a sensitivity of 83% and specificity of 80% for CAD diagnosis (49). Concordance with MPI was also notable, with kappa values of 0.81 at the patient level and 0.86 at the vessel level (50). In individuals suspected of acute coronary syndrome with normal troponin levels and a non-diagnostic electrocardiogram, the presence of abnormal wall motion and myocardial perfusion was associated with a substantial hazard ratio for predicting future cardiac events (51). MCE's capability to measure CFR adds a valuable dimension to evaluating patients with microcirculatory disease, effectively discriminating between ischemic and nonischemic cardiomyopathy. The multifaceted utility of MCE positions it as a powerful and versatile tool in contemporary cardiovascular assessment.

Computed tomography perfusion

Computed Tomography Perfusion (CTP) (Fig. 4), akin to other MPI modalities, employs a multidetector CT system capturing sequential images to delineate the kinetics of iodinated contrast in arterial blood and myocardium (Figs 3 and 4). Infarcted or ischemic areas manifest as hypodense in contrast to healthy myocardium (52). In human studies using adenosine stress, combined CCTA/CTP, in comparison to ICA and MPS, exhibited 86% sensitivity and 92% specificity for identifying atherosclerosis-induced perfusion abnormalities (53). While CCTA/CTP demonstrated higher specificity and overall accuracy than CCTA alone (54), a recent study comparing CTP and Cardiac Magnetic Resonance (CMR) against quantitative ICA and MPS found similar diagnostic performance between CTP and CMR (55).

A notable advancement is Computed Tomography Fractional Flow Reserve (CTFFR), leveraging computational fluid dynamics to predict invasive FFR (56). In the PLATFORM trial, CTFFR, as part of a strategy comparing CTCA with standard care, emerged as a feasible and safe alternative to ICA, significantly reducing instances of ICA showing no obstructive CAD (57). CTCA when compared to usual care, reduced ICA referrals, maintaining similar clinical outcomes at one year and lower costs (58).

Advances (and limitations) of MPI over CCTA

Further clinical studies have explored the additional value of combining CCTA with CTP compared to CCTA alone. It was demonstrated an increase in accuracy with the combined assessment in diagnosing significant coronary stenosis (59). The addition of

Myocardial CTP to the strategy enhanced accuracy from 0.77 to 0.90 (area under the ROC curve) in detecting stenoses. In contrast to CCTA, MPI has the limitation of identifying only the coronary territory supplied by the most severe stenosis, potentially leading to reduced sensitivity, particularly in cases of multivessel disease. Addressing this limitation, PET MPI emerges as a promising alternative with distinct advantages. The superior quality and accuracy of PET, attributed to its finer spatial resolution and attenuation correction, position it as a transformative technology (60). PET MPI not only outperforms MPS but also provides absolute quantitation of MBF and Coronary Flow Reserve (CFR). CFR, a comprehensive measure of coronary vasomotor dysfunction, integrates the effects of focal, diffuse, large and small-vessel CAD, and endothelial dysfunction on myocardial perfusion, offering a holistic understanding of IHD rather than focusing solely on CAD.

In a meta-analysis encompassing 177 studies with nearly 12,000 patients, PET demonstrated higher sensitivity compared to MPS (92.6% vs 88.3%) for detecting >50% epicardial stenosis, while maintaining comparable specificity (61). Although the clinical impact of this sensitivity difference may be modest, it underscores the superior diagnostic potential of PET. Another meta-analysis involving 114 MPS and 15 PET studies corroborated these findings, emphasizing the enhanced sensitivity of PET MPI (61). CFR measurements by PET play a pivotal role in risk stratification, distinguishing patients at low or high risk for serious adverse events, including cardiovascular death, beyond traditional clinical assessments. Notably, CFR measurement aids in the risk reclassification of approximately 35% of intermediate-risk patients, with CFR values of <2 and <1.5 associated with a 3.4 and 5.6-fold increased risk of cardiac death, respectively (62). The multifaceted capabilities of PET MPI establish it as a transformative technology in the realm of myocardial perfusion imaging, offering a more comprehensive and nuanced understanding of cardiovascular health.

Numerous studies glorify the remarkable accuracy of CCTA in non-invasive angiography. However, many of these comparisons with nuclear imaging involved patients already slated for cardiac catheterization, thereby introducing referral and selection bias. Thus, the diagnostic precision of 64-row CCTA for detecting obstructive coronary stenosis was systematically evaluated against MPS, with quantitative coronary angiography (QCA) serving as the reference standard (63) in 230 patients (49% male, mean age 57.8 years) with chest pain. This prospective multicenter trial, uniquely comparing 64-row CCTA to MPI in the same patients, unequivocally demonstrates the superior diagnostic accuracy of CCTA over MPI. In detail, ICA revealed stenosis ≥50% in 52.1% (25 of 48) of cases. CCTA exhibited significantly higher sensitivity than nuclear imaging (92.0% vs 54.5%, p<0.001), with comparable specificity (87.0% vs 78.3%) when defining obstructive disease as ≥50%. For stenosis ≥70%, CCTA provided superior sensitivity (92.6% vs 59.3%, p<0.001) and similar specificity (88.9% vs 81.5%). The odds ratio for ICA disease was significantly higher with CCTA for ≥50% stenosis (51.75, 95% CI=8.50–314.94, p<0.001) and for summed stress score ≥5% (12.73, 95% CI=2.43–66.55, p<0.001). Receiver operating characteristic curve analysis confirmed the superior ability of CCTA over MPI in classifying obstructive CAD disease (area=0.85 vs 0.71, p<0.0001). These findings affirm CCTA as a reliable modality for detecting >50% and >70% stenosis in stable chest pain patients.

Another restrospective study compared the efficacy of MPS and CCTA in individuals with a low pretest likelihood of obstructive CAD and occupations associated with a high risk (64). In detail, the study encompassed 512 MPS and 170 CCTA studies meeting the inclusion criteria. Referral to ICA occurred in 15.8% (81/512) following MPS, compared to 2.4% (4/170) with CCTA (p<0.001). Among those referred for ICA, the false-positive rate was 93% (75/81) for MPI and 50% (2/4) for CCTA, indicating a significant difference (p=0.043). These results show that in symptomatic individuals with a low likelihood of CAD but high occupational risk, CCTA demonstrated a significant reduction in ICA referrals and false-positive rates compared to MPI.

Furthermore, an international randomized trial study on a total of 303 patients (151 MPS and 152 CCTA) was published investigating the hypothesis that, in the initial assessment of patients with suspected CAD, stress MPI would lead to fewer downstream tests compared to CCTA (65). In detail, mildly symptomatic patients with an intermediate likelihood of CAD, and asymptomatic patients at intermediate risk of cardiac events, were randomly assigned to undergo either initial stress-rest MPI or CCTA. The primary outcome was downstream noninvasive or invasive testing at 6 months. Secondary outcomes included cumulative effective radiation dose (ERD) and costs at 12 months. The initial MPI was abnormal in 29% (41/143) and CCTA in 56% (79/141) of patients. Patients undergoing initial stress-rest MPI had significantly fewer downstream tests at 6 months (adjusted OR 0.51, 95% CI 0.28–0.91, p=0.023). There was a slight increase in the median cumulative ERD with MPI (9.6 vs 8.8 mSv, p=0.04), but no significant difference in costs between the two strategies at 12 months. Results of this study show that in the management of patients with suspected CAD, a strategy of initial stress MPI is considerably less likely to necessitate further downstream testing compared to initial testing with CCTA.

In summary, the MPI examination offers advantages when combined with anatomical assessment of the coronary arteries, providing a comprehensive evaluation. However, it has limitations when used in isolation due to exposure to ionizing radiation and iodinated contrast, which are avoidable with other diagnostic methods. Myocardial CTP, while enhancing diagnostic accuracy, necessitates additional doses of radiation and contrast compared to CCTA alone, warranting caution in patients with renal failure or undergoing repeated radiation-based examinations. The use of vasodilatory pharmacological stress requires careful assessment in patients with clinical or hemodynamic instability, as well as those with atrioventricular blocks, chronic obstructive pulmonary disease, and/or asthma (66).

Future directions

The ever-evolving landscape of cardiovascular medicine underscores the continuous quest for more accurate and efficient diagnostic approaches. As such, recent strides in medical imag-

ing technology have sparked considerable interest in exploring novel methodologies to enhance the detection and assessment of coronary artery disease (CAD). Traditional diagnostic modalities, while valuable, may have limitations in terms of sensitivity, specificity, or the ability to provide a comprehensive evaluation of CAD. Hence, there is a pressing need to search for new approaches that can address these limitations and offer improved diagnostic precision. Newly introduced gamma camera systems, characterized by optimized acquisition geometry, collimator designs, and advanced reconstruction techniques, hold promise for significant enhancements in image quality (67). Particularly noteworthy are the advancements with Cadmium-Zinc-Telluride (CZT) detectors, which boast superior energy and spatial resolution. Demonstrating a remarkable sensitivity of 95% and accuracy of 69% in detecting obstructive CAD (68), these cameras exhibit heightened sensitivity, allowing for shorter imaging times even with reduced radioactivity administration. The CZT camera facilitates rapid perfusion imaging and enables the acquisition of serial dynamic images, facilitating the measurement of MBF and CFR.

Hybrid imaging cameras mark a notable milestone by integrating anatomical and functional images, exemplified in the combination of MPS with CCTA. A meta-analysis involving 951 patients and 1973 vessels underscores the improved diagnostic specificity of hybrid imaging for detecting obstructive CAD compared to standalone CCTA (69). In detail, in a per-patient evaluation, the pooled sensitivity of hybrid imaging demonstrated parity with CCTA (91% vs 90%; p=0.28). Notably, specificity was markedly higher for hybrid imaging compared to CCTA (93% vs 66%; p<0.001). Assessing on a per-vessel basis, sensitivity for hybrid imaging versus CCTA was akin (84% vs 89%; p=0.29). Remarkably, hybrid imaging exhibited a specificity of 95%, surpassing the 83% specificity observed with CCTA (p<0.001). Summary receiver-operating characteristic curves underscored the enhanced discriminatory capacity of hybrid imaging over CCTA alone on a per-vessel basis (area under the curve: 0.97 vs 0.93; p=0.047). However, this improvement was not as pronounced on a per-patient level (area under the curve: 0.97 vs 0.93; p=0.132). These findings highlight the superior specificity of hybrid imaging, signifying its potential as a robust diagnostic tool for CAD detection compared to CCTA.

In cases where patients with a normal MPS study underwent concomitant CCTA, an abnormal CCTA was correlated with a higher event rate, emphasizing the synergistic diagnostic value of combining anatomical and functional information (70). These technological advancements not only enhance the precision of CAD detection but also pave the way for more efficient and comprehensive cardiovascular assessments.

Conclusion

Computed Tomography Perfusion represents a significant advancement in cardiovascular imaging, offering a comprehensive assessment of both anatomy and physiology in a single imaging session. Studies have demonstrated its diagnostic accuracy in identifying atherosclerosis-induced perfusion abnormalities, particularly when combined with CCTA. Furthermore, the emergence of CTFFR holds promise as a non-invasive alternative for predicting invasive FFR, thus aiding in treatment decisions. These findings underscore the growing role of CTP and CTFFR in reshaping clinical practice, providing clinicians with valuable insights for the management of patients with suspected coronary artery disease.

Learning points

Coronary artery disease stands as a significant global health challenge with mortality rates exceeding 17 millions anually.

Investigations involving CT technology unveiled promising results, showcasing high negative predictive value.

Ongoing advancements in computational fluid dynamics-based techniques like CT fractional flow reserve hold promise for enhancing the assessment of coronary artery disease.

Combining myocardial perfusion single-photon emission computed tomography with coronary computed tomography angiography enhances specificity.

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