

REVIEW

Strange times indeed: the evolving significance of myocardial ischaemia and the dwindling importance of functional imaging

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Abstract: The ISCHEMIA trial is only the latest and most compelling link in a chain of evidence that suggests that myocardial ischaemia per se is not an appropriate treatment target for patients with stable coronary artery disease. This review is trying to make sense of the momentous and sometimes contradictory recent developments in the space of imaging for myocardial ischaemia.

Keywords: myocardial ischaemia, coronary artery disease, imaging.

Rezumat: Studiul ISCHEMIA este doar cea mai recentă și cea mai convingătoare verigă dintr-un lanț de dovezi, care sugerează că ischemia miocardică per se nu este o țintă corectă în abordarea tratamentului pacienților cu boală arterială coronariană stabilă. Acest articol își propune să clarifice cele mai recente și importante, uneori contradictorii, noutăți din domeniul imagisticii ischemiei miocardice.

Cuvinte cheie: ischemia miocardică, boala arterială coronariană, imagistică.

INTRODUCTION

Myocardial revascularisation is arguably the most dynamic, revolutionary area of cardiology and perhaps of clinical medicine. Starting with the first successful anastomosis of the internal thoracic artery to the right coronary artery on February 25, 1964 by (the largely forgotten) Russian surgeon Vasilii Kolessov¹, followed in 1968 by Favarolo's saphenous vein coronary artery by-pass grafting (CABG) I operation, and progressing with Gruntzig's 1977 plain old balloon angioplasty (POBA), Loop's report of the efficacy of left internal mammary as CABG conduit (1986), Sigwart's first implant of a balloon-dilatable stent (1986), Sousa's first drug-eluting stent (DES - 1999)², up to the hybrid algorithm for treating chronic total occlusions (CTO) by percutaneous coronary intervention (PCI) around 2010³, and with the advent and on-going expansion of intracoronary physiological indices such as FFR⁴ and iFR⁵, the field of myocardial revascularisation has persistently pushed the limits of what is deemed feasible,

shattering the barriers of convention and accepted medical wisdom, and reinventing itself successfully countless times.

However, after more than half a century of triumphs, myocardial revascularisation for patients with stable coronary artery disease (CAD) is coming under attack, from multiple angles. Are we about to see its demise in the next few years? And, as imaging specialists, how can we find our way in the rapidly-evolving field of ischaemia imaging?

The conventional paradigm of myocardial ischaemia and its demise

One of the gratifying features of interventional cardiology is its mechanistic simplicity: a coronary stenosis produces myocardial ischaemia, which is associated with symptoms and adverse outcomes. It follows intuitively that the more extensive the ischaemia, the worse the outcomes, and that relieving the obstruction and thus the ischaemia, will necessarily improve symptoms and outcomes⁶.

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Treatment modalities for stable CAD

CABG vs. medical treatment. The superiority of CABG over medical treatment of patients with stable coronary artery disease was established by a meta-analysis covering a relatively small number of 1324 patients assigned to CABG surgery who had better survival than the 1325 assigned to medical management, between 1972 and 1984⁸. However, medical treatment of CAD during that era has almost nothing in common with its contemporary, guideline-directed medical treatment. It is therefore fair to say that we have no data for a comparison of CABG to up-to-date medical treatment of stable coronary disease. Such a trial 'begs' to be done, and would be a very important step in placing the surgical treatment of stable CAD on a solid evidence-basis.

CABG vs. PCI. Evidently, patients prefer minimally invasive procedures to major surgery, and PCI offers a very attractive alternative to open-heart CABG. This situation has the perfect ingredients for a bitter turf war between surgeons and interventionalists⁹ which is exacerbated by a stream of contradictory data: after the initial enthusiasm and unreserved, hurried adoption of DES for off-licence indications, a concerted attack on DES ('the firestorm of Barcelona')¹⁰ was launched at the World Congress of Cardiology in 2006. The interventional community regrouped and, with the emergence of the Academic Research Consortium, PCI entered the era of rigorous trial design and analysis¹¹, convincingly refuting the accusations that DES sharply increase mortality compared to bare-metal stents (BMS)¹². In spite of thorough trials¹³ and meta-analyses comparing PCI to CABG in various anatomic subsets including the left main stem^{14,15} the controversy is not settled and recriminations between surgeons and interventionists continue, as recently seen in the acrimonious aftermath of the EXCEL trial publication¹⁶. The choice of the modality of coronary revascularisation remains thus extremely complex, even for patients with diabetes mellitus, for whom conventional wisdom had long established that CABG is superior to PCI¹⁷. The number of possible permutations involving coronary anatomy, acuity of presentation, patient characteristics, stent platforms, type and kinetics of drug eluted by the stent, procedural parameters, antiplatelet regimes, and concomitant cardioactive treatments is so large that unequivocal answers to the question „PCI or CABG?“ will still take years to emerge.

PCI vs. medical treatment. This is perhaps the most intriguing and counterintuitive area, in that increasing

proof is accumulating that PCI-based revascularisation of patients with stable CAD confers no benefit over guideline-driven medical therapy. BARI-2D¹⁸ (BMS in diabetics), STICH¹⁹ (CABG and surgical LV remodelling in patients with ischaemic LV dysfunction), COURAGE²⁰ (patients with stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia) each produced enormous controversy and turmoil in the interventional community because they questioned the universally-accepted and intuitively-compelling „ischaemic paradigm“, according to which relief of ischaemia would improve quality of life and survival.

Nothing, however, compares to the impact of the two most recent trials, ORBITA and ISCHEMIA.

ORBITA²¹ was the first PCI trial that used a sham procedure in the control arm. All patients had coronary angiography, but those randomised to medical treatment also had a cath-lab based sham PCI procedure, so they did not know whether they had received stents or not. This was done in order to remove the powerful placebo effect associated with PCI. The primary endpoint was improvement in treadmill exercise time between inclusion and follow up at six-weeks and there was no difference between patients who received a stent and those who had only a sham procedure. None of the secondary endpoints (peak oxygen uptake, change in exercise time to 1 mm ST-segment depression, angina CCS class, limitation of exercise, stability and frequency of angina, quality of life scores and Duke Treadmill score) was different between groups. The only parameter that reached marginal statistical significance was an improvement in the wall motion score index by dobutamine stress echo in patients who had stents. These results have subsequently been presented as the „final nail in the coffin of PCI“, and made it among the headlines of major news programmes.

ISCHEMIA²² is the most expensive medical RCT ever conducted (it cost 100 million USD)²³ and randomised >5000 patients with moderate or severe ischaemia (diagnosed by functional imaging or ETT) and screened by CT coronary angiography to rule out left main stem disease, to revascularisation (approx. 2/3 by PCI and 1/3 by CABG) or medical treatment. Over 5 years there was no difference in the primary endpoint of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure (adjusted HR 0.93; 95% CI 0.80–1.08), no significant differences in other combinations

of endpoints or the endpoints individually, and there was no subgroup that benefitted from revascularisation. The ISCHEMIA-CKD²⁴ study also showed no reduction in cardiac events with an invasive strategy and additionally, no improvement in symptoms or quality of life in patients with chronic renal failure.

Both ORBITA²⁵ and ISCHEMIA²⁶ have been criticised on multiple fronts but, notwithstanding their imperfections, there is no doubt that, jointly, they have dealt a severe blow to the conventional paradigm of ischaemia in stable CAD, by suggesting that inducible myocardial ischaemia is not, after all, an appropriate target for treatment and therefore for imaging, as relieving ischaemia does not appear to improve outcomes or symptoms in the era of aggressive medical treatment.

What is the cardiac imaging specialist supposed to do in this strange, new and shifting landscape?

Implications for ischaemia imaging of recent trial data

It would be premature to declare functional imaging for ischaemia dead²⁷. Neither ORBITA nor ISCHEMIA were set up to compare the role of different imaging modalities in the management of CAD, so any conclusions about imaging utilisation based on their findings are only preliminary and derivative. It is still very relevant to perform functional imaging in many clinical contexts. For instance, a normal ischaemic imaging test carries a powerful and positive prognostic significance, while an abnormal test can explain symptoms and provide reassurance that a pathway to treatment has opened up. An important key to the correct utilisation of diagnostic imaging is to take into account the pre-test probability of ischaemia, as well as the diagnostic performance of each modality, for instance expressed through receiver-operating characteristics²⁸.

Potential impact of ISCHEMIA on clinical practice²⁷

How are we to use the findings of ISCHEMIA in our day-to-day approach to patients with suspected CAD?

One option would be to stop testing for ischaemia altogether, given the futility demonstrated by ISCHEMIA and the other large and well-conducted contemporary RCTs quoted earlier. The pitfall is that without demonstration of ischaemia in the individual patient it is difficult to justify prescribing medical treatment, which involves a multitude of life-long tablets, each with its side-effects. Moreover, with an increasingly well-informed patient population, practitioners may come under increasing pressure from the patients

themselves to investigate symptoms with ischaemia imaging or invasive angiography. And how can we be sure there is no LMS disease without further testing?

Another option is to perform CT angiography to rule out LMS disease, and then treat medically if it is absent, without any further investigations. This would replicate the approach shown to be safe and effective in ISCHEMIA; revascularisation would be reserved for those patients (free from LMS disease) who still experience intrusive symptoms while on maximal guideline-driven medical therapy, and would not require further imaging before proceeding to PCI or CABG. A potential problem with this approach is that a recent study of the external applicability of the ISCHEMIA trial found that only 4% of patients in a large registry fulfilled ISCHEMIA inclusion criteria²⁶; moreover, they had a much lower incidence of major adverse cardiac events (MACE) during follow-up than those outside the ISCHEMIA inclusion criteria. This is the first indication that the type of patient for whom the conclusions of ISCHEMIA apply may not be that easy to find in the 'real world'; clearly further validation is needed before we can apply 'mechanically' the ISCHEMIA algorithm.

Finally, there is the option to continue as before, i.e. only perform invasive angiography if pre-test evidence of ischaemia has been obtained non-invasively. This approach is, however, unlikely to prevail, both because the results of ISCHEMIA reduce the pressure to perform functional imaging, and, more importantly, because FFR and especially the much-simpler-to-perform iFR now allow immediate diagnosis of functionally significant coronary stenoses in the cath lab, where immediate revascularisation can be carried out seamlessly in the same procedure.

Non-invasive imaging methods for diagnosing stable CAD

Functional imaging tests for the diagnosis of coronary artery disease involve acquisition of data both at rest and during a physiological stress (exercise, vasodilator, inotropic stimulant). They visualise either myocardial perfusion by tracking the rest and stress myocardial distribution of an intravenously-injected tracer, or the response of the myocardium to a relative imbalance between metabolic demand and supply during stress, which will manifest as localised or global myocardial systolic dysfunction – hypo-, a- or dyskinesia of myocardial segments.

By contrast, anatomical imaging visualises the coronary arteries, and ideally should be coupled with some

form of functional assessment in order to ascertain the significance of stenoses of moderate severity (50-70%). Fractional flow reserve (FFR)⁴ and instantaneous wave-free ratio (iFR)⁵ have emerged as invasive „gold standard” tests for the physiological assessment of coronary artery stenoses. Initially these were exclusively invasive tests, performed to guide PCI, but now hybrid imaging allows the acquisition of a CT coronary angiogram (an anatomical test) coupled with either CT-FFR (based on complex hydrodynamic modelling) and/or perfusion imaging (based on the direct proportionality of the image „brightness” to the amount of contrast agent visualised).

In a meta-analysis comparing multiple methods of functional cardiac imaging directly to FFR, MRI had the highest performance for diagnosing CAD causing myocardial ischaemia, with lower performance for SPECT and SE. Anatomic imaging (CTCA and invasive coronary angiography) had lower specificity, while functional assessment with stress echo, SPECT, and CT-FFR increased diagnostic accuracy²⁸. However, CT perfusion imaging and CT-FFR are not yet widely available or fully validated.

Technical aspects of the non-invasive methods for diagnosing inducible myocardial ischaemia are shown in Table 1²⁹ and a metanalysis-based comparison of their diagnostic performance in Table 2³⁰.

Differential impact of test strategy on patient outcomes

Initial research on the diagnostic performance of ischaemia imaging focused on reproducibility, sensitivity, specificity and similar metrics of the tests. Lately, research has appeared on the effect that the choice of test has on the final outcome/type of treatment for the patient. This is an intriguing concept – why would the diagnostic test sequence impact the outcome? After all, regardless of the pathway by which we arrive at the diagnosis, one would hope that each specific

Table 2. Diagnostic performance of imaging modalities for the diagnosis of inducible myocardial ischaemia (modified from reference 30)

Modality	Sensitivity	Specificity
Exercise ECG	0.66	0.75
Stress Echo	0.80	0.84
SPECT	0.61	0.84
Real-time myocardial contrast TTE	0.75	0.52
CMR	0.87	0.91
CCTA	0.78	0.86

condition is consistently and appropriately treated in everybody who has it.

Nevertheless, this seems to be the case indeed, reflecting the wide variation in practices and the role that immeasurable variables such as „clinical judgement” play in the choice of investigations and treatments. For instance, in the SCOT HEART trial³¹, patients with stable chest pain who also had CTCA on top of standard care experienced a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years than those receiving standard care alone, without a higher rate of coronary angiography or coronary revascularization. The explanation seems to be that patients in the CTCA group had received preventive and anti-anginal drugs more frequently than the controls.

In PROMISE³² 10,003 patients with chest pain were randomly assigned to a strategy of initial anatomical testing with coronary computed tomographic angiography or to functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography). The composite primary end point was death, myocardial infarction, hospitalization for unstable angina, or major procedural complication. Over a follow-up of 2 years, the CTCA-first strategy offered no benefits over the functional testing strategy, with identical

Table 1. Overview of functional imaging modalities. Modified from reference 29

Method	Limitations	Advantages	Spatial resolution
SPECT	Radiation, spatial resolution, limited quantification, attenuation	Widely available, well tested, robust and reproducible	10x10x10mm
PET	Lower spatial resolution of quantitative ¹⁵ O ₂ -water PET	Gold standard for perfusion imaging, best for quantitation	4x4x4mm
MRI	Costly, not widely available, interference from pacemakers, claustrophobia, poor image quality in irregular heart rhythms	Non-invasive biopsy, unlimited field of view, extensive assessment of cardiac and intrathoracic structures	1x2x6-8mm
ECHO	Variable image quality, operator-dependence	Versatility, repeatability, widely available, relatively simple and cheap setup	1x1-3x3-6mm

occurrence of the primary endpoints in both arms of the trial, but with more invasive coronary angiograms in the CTCA arm. The divergence from the results of the smaller SCOT HEART trial has been accounted for by the significantly lower prevalence of obstructive CAD in PROMISE (half the level in SCOT HEART) as well as by the directionally opposing effects of myocardial infarction and hospitalisation for unstable angina, leading to an overall neutral effect³³. Moreover, the PROMISE investigators did report that CCTA was associated with a 34% relative reduction in all-cause death and myocardial infarction at 12 months.

Finally, three meta-analyses^{31,34,35} agree that, compared with functional stress testing, the use of CCTA appears to associate with a lower incidence of myocardial infarction but also with an increase in the usage of invasive coronary angiography, revascularization procedures (of which some may have been unnecessary), CAD diagnoses, and new prescriptions for aspirin and statins. Despite these differences, CCTA overall is not associated with a reduction in all-cause mortality or cardiac hospitalizations.

If not myocardial ischaemia, what should be our imaging target in CAD now?

In the aftermath of ISCHEMIA this has become an existential question for imaging specialists. The tenets of half a century of practice based on the conventional wisdom that relieving myocardial ischaemia improves outcomes are crumbling away – what is there to replace them?

Plaque burden, vulnerable plaque

CCTA. Increasingly, the emphasis is shifting from the assessment of myocardial ischaemia and of coronary stenoses to that of the overall amount of atheroma in the coronary tree. Coronary calcium scoring by EBCT has long been validated as a risk-prediction tool, but recently it was shown that “plaque burden, not stenosis per se, is the main predictor of risk for CVD events and death. Thus, patients with a comparable calcified atherosclerosis burden, generally, carry on a similar risk for CVD events regardless of whether they have non-obstructive or obstructive CAD”³⁶.

Conversely, in patients with a calcium score of zero, it is the presence or absence of obstructive CAD that correlates with outcomes³⁷.

Plaque remodelling (PR) (defined as diameter of plaque 10% larger than reference vessel), low attenuation plaque (LAP) (less than 30 HU), a „napkin ring” appearance and spotty calcification are CT features of vulnerable plaque, a predictor of ACS^{38,39}.

CMR. Although CMR can image the proximal coronary arteries⁴⁰ as well as plaque composition (high intensity plaque in particular appears to correlate with ACS⁴¹) with good accuracy⁴², there is much less data on CMR than on CT for prognosticating outcomes based on arterial appearances in patients with CAD. This is partly explained by the poorer spatial resolution of CMR compared with CT (although acquisition at 3T⁴³ seems to resolve the problem) and partly by the longer, more laborious acquisition protocols. Moreover, CT acquires genuine 3D volumes, while CMR reconstructs volumes by acquisition of sequential slices, „stitched” together by reference to the R wave on the ECG, thus being vulnerable to respiratory motion and to irregular heart rhythms. However, the well-validated ability of stress-perfusion CMR to offer high specificity and high sensitivity assessment of myocardial ischaemia means it has the potential to offer the mythical non-invasive „one-stop shop”, which delivers anatomical and functional data with a single investigation, the real ‘Holy Grail’ of imaging.

Perivascular adipose tissue

There is increasing understanding of the „toxicity” of adipose tissue for vascular health, by the release of cytokines and of other biologically active mediators that promote atheroma formation and plaque instability. The fat attenuation index (FAI) is a novel parameter that can be measured by CT in the epicardial adipose tissue (EAT) around the coronaries and correlates to plaque instability and outcomes⁴⁴. In the CRISP CT study⁴⁵ patients with abnormally high perivascular FAI had ~9 times higher risk for cardiac mortality. This improved prediction of mortality was well above the current state of the art assessment of risk using CTCA, including clinical risk factors, calcium score, the extent of coronary atherosclerosis and the presence of high-risk plaque features.

CONCLUSIONS

Under the pressure of data from randomised controlled trials, the mechanistic paradigm that has underpinned the practice of cardiology in the space of stable coronary artery disease is shifting. The call to drop our „obsession with coronary luminology”, articulated by Topol and Nissen in 1995⁴⁶, has finally borne fruit, as we move from „detecting the vulnerable plaque to managing the vulnerable patient”⁴⁷. Our focus in imaging is shifting from stenoses, inducible myocardial ischaemia and plaques to atheroma burden and its metabolic activity in conjunction to that of the perivas-

cular adipose tissue. A new era of atheroma and metabolic-focused imaging is starting, and as an imaging community we should be ready to embrace it.

Abbreviations

ACS	acute coronary syndrome
BMS	bare-metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCS	Canadian Cardiac Society
CMR	Cardiac magnetic resonance
CTCA	computer-tomography coronary angiogram
CVD	cardiovascular disease
DES	drug-eluting stent
EAT	epicardial adipose tissue
EBCT	electron-beam computer tomography
ETT	exercise tolerance test
FAI	fat attenuation index
FFR	fractional flow reserve
HU	Hounsfield units
IFR	instantaneous wave-free ratio
LAP	low attenuation plaque
LMS	left main stem
LV	left ventricle
MACE	major adverse cardiac events
MRI	magnetic resonance imaging
PCI	percutaneous coronary intervention
PR	plaque remodelling
RCT	randomised controlled trial
SPECT	single-photon emission computer tomography

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