THE ROLE OF CARDIOVASCULAR MAGNETIC RESONANCE IN CORONARY ARTERY DISEASE

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Ischaemic Heart Disease (IHD) remains the leading cause of death in UK and worldwide. Assessment of IHD is a crucial step in the management of this condition. Over the last decade Cardiac Magnetic Resonance imaging (CMR) has emerged as the most promising non-invasive imaging modality in the assessment of IHD due to its superior spatial resolution, high reproducibility, and non-invasive myocardial tissue characterization property thereby allowing differential diagnosis, guiding clinical decision-making, and improving risk stratification.

The present article describes an educational perspective of the various CMR imaging techniques followed by the current application and evidence for using CMR in acute and chronic IHD [1].

CMR imaging techniques

Cine imaging

CMR is the gold standard method to measure Left and Right Ventricular (LV/RV) volumes and ejection fraction [1,2], which is a 3D assessment based on contouring all the short-axis slices data set (~10-12 slices) obtained from the base to the apex of the ventricles [3].

Steady State Free Precession (SSFP) is the sequence of choice for cine imaging due its clear definition of endocardial and epicardial borders. Regional LV/RV function can be analysed visually [3], detecting the presence and extent of segmental wall motion abnormality, or quantitatively by measuring wall thickening, and myocardial strain [4]. Similarly to echocardiography, cine CMR can be used during low- and high-dose dobutamine to assess myocardial viability and inducible ischemia, respectively [5-7].

T2-Weighted Imaging

Acute Myocardial Infarction (AMI) often leads to myocardial oedema/inflammation and subsequent increase in myocardial water content. In MRI this corresponds to an increase in the T2 relaxation time, a phenomenon that can be imaged with T2-weighted imaging. Demonstration of edema by T2-weighted imaging helps in distinguishing acute from chronic myocardial infarction [8]. In the setting of AMI, the area of myocardial oedema delineated by T2-weighted CMR corresponds to the myocardial Area At Risk (AAR). The presence and extent of myocardial salvage can also be derived with CMR by subtracting the infarcted area from the AAR. Both myocardium at risk and myocardial salvage can be assessed retrospectively shortly after the acute event [9], T2-weighted Short-Tau Inversion Recovery (T2-STIR) is the most commonly used sequence to image oedema in clinical practice. However, it presents some limitation that newer sequence such as ACUT2E (cardiac unified T2 oedema) and T2 mapping could overcome. A recent study by McAlindon et al. demonstrated that the different methods detecting and quantifying myocardial oedema are not interchangeable, and that T2 mapping was the most reproducible method [12].

First-Pass Myocardial Perfusion Imaging

First-pass myocardial perfusion is a method that tracks the transit of a contrast agent through the cardiac chambers and its perfusion in the myocardium [13]. This method is mainly used in conjunction with a stressor to evaluate the presence of inducible perfusion defects (surrogate for inducible myocardial ischemia). These appear in the images as hypointense areas given the lack contrast perfusion due to significant coronary stenosis. Images are often acquired at peak stress and at rest for comparison.

The stress agents most commonly used in stress CMR are vasodilators stressors such as adenosine, dypiridamole (a pro-drug of adenosine) and, more recently, regadenosin. The latter is a more selective agent, which has the potential to reduce the side effects of adenosine.

Due to its high spatial resolution CMR can reliably identifying subendocardial ischemia, and makes the diagnosis of a 3-vessel ischemia possible without encountering the issue of balanced-ischemia that, for example, SPECT sometimes presents. However, dark rim artefacts often mimic genuine perfusion defects and optimizing image quality and experienced reading of the images is essential to maintain diagnostic accuracy. Recent technical developments [14] and the introduction of 3T has improved CMR stress imaging capitalizing on its higher field homogeneity and higher performance gradients than at 1.5T [15,16]. Contraindications for adenosine are infrequent but could lead to serious complications. In the setting of acute coronary syndromes, rest first-pass perfusion can be used to assess the presence of early microvascular obstruction as a marker of microvascular damage.

Late Gadolinium Enhancement (LGE) Imaging

This imaging technique contributes to the myocardial tissue characterization assessment and, particularly in the context of ischemic heart disease, in the detection of myocardial scarring.

In brief, a gadolinium-chelate contrast agent is administered intravenously, it then promptly diffuses into the extracellular tissue compartment. Its effect is to reduce the T1, and to a lesser degree the T2, relaxation times of the myocardium. Being an extracellular contrast agent, the gadolinium-chelate molecules accumulate in areas of increased extracellular space. In normal myocardium, contrast promptly washes out from the tissue, whereas in infarcted myocardium it will accumulate having a longer wash out period (infarcted myocardium = ruptured myocyte membrane, i.e. increased extracellular space). Gadolinium-chelates accumulate in both acute and chronic myocardial infarctions. In the images, infarcted myocardium will appear as hyperintense (bright) area and normal myocardium as a hypointense ("bright is dead"). In the setting of acute myocardial infarction, the LGE sequence can also detect areas of hypointensity within the infarcted area, representing persistent MicroVascular Obstruction (MVO).

In a patient with ischemic heart disease the CMR imaging protocol always includes cine and LGE imaging, with oedema and first-pass perfusion added depending on the clinical question; the scan duration is ~45min (fig. 1 and 2).

CMR in Non ST Elevation Acute Coronary Syndrome (NSTE-ACS)

The evidence for using CMR in NSTE-ACS is growing. The current ESC guideline on the management of NSTE-ACS suggests use of CMR in the following settings: a) patients without recurrence of pain, normal ECG findings, negative troponins tests, and a low risk score, before deciding on an invasive strategy, b) to assess viability and c) to detect myocarditis [17].

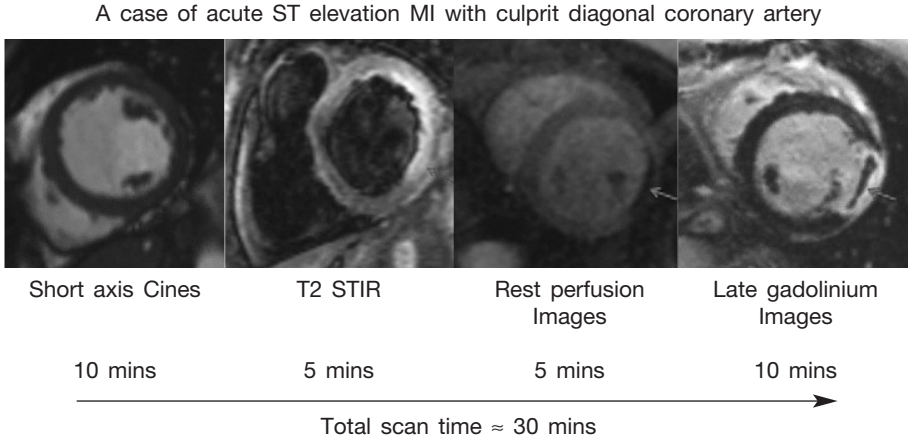

Fig. 1. A case of acute ST elevation MI with culprit diagonal coronary artery. The short axis cines showing the wall motion abnormality, T2 STIR imaging showing myocardial oedema or area at risk (arrow), rest perfusion showing early microvascular obstruction (arrow) and late gadolinium imaging showing lateral wall transmural enhancement with microvascular obstruction (arrow).

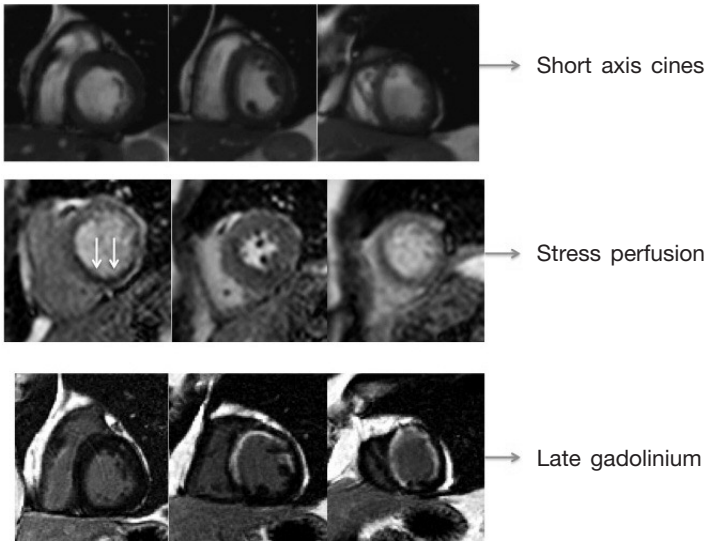

Fig. 2. Assessment of chronic ischaemic heart disease: A patient with previous anterior myocardial infarction assessed for ischaemic heart disease. Stress perfusion imaging showed basal inferior perfusion defect (arrow), and late enhancement imaging showed transmural myocardial infarction in the mid-distal LAD territory with viable inferior wall.

In diagnosis

CMR has a role in detection of ACS in low risk patients presenting with chest pain, normal ECG, normal cardiac biomarkers and prior to deciding on an invasive strategy. A study by Kwong et al. looked at the diagnostic accuracy of CMR in 161 consecutive patients presenting to the emergency room with cardiac chest pain but no evidence of MI [18]. The study suggested that CMR could identify ACS more accurately than conventional markers. CMR performed within 12 hours of presentation included rest first-pass myocardial perfusion, cine, and LGE imaging. The study reported a sensitivity and specificity for detecting subsequent ACS of 84% and 85%, respectively. Cury et al. looked at 62 low risk patients presenting with chest pain. By adding a T2 weighted imaging technique to rest first-pass perfusion, cine and LGE imaging, the diagnostic accuracy to detect ACS increased from 84% to 93% when compared to conventional CMR protocol [19].

In risk stratification and management

Ingkanisorn et al. demonstrated the high negative predictive value of a normal adenosine stress CMR test in patients with troponin-negative chest pain presenting to the emergency room [20].

Plein et al. demonstrated that in patients with NSTEMI, CMR (cines, stress and rest perfusion, LGE and coronary MRA) could reliably predict the presence of coronary stenosis requiring revascularization (sensitivity, 96%; specificity, 83%). Moreover, CMR assessment was superior to the prediction based on the TIMI risk score [21].

Raman et al. demonstrated that the T2-weighted sequence could identify the acutely ischemic myocardium, therefore helping in identifying the culprit vessel in patients with multivessel disease [22].

CMR in ACS with unobstructed coronaries

In 7-15% of patients presenting with ACS, no significant coronary obstruction on coronary angiography is identified, representing a diagnostic and clinical dilemma [23,24].

Patients with unobstructed coronaries are thought to have a better prognosis, therefore they do not always receive secondary prevention medications [25]. However, recent studies suggest that the recurrence of infarction or death was around 2% [26,27,23]. CMR can play an important role in detecting the underlying diagnosis, which can span from acute/chronic myocarditis, acute Myocardial Infarction (MI) with spontaneous recanalization/embolus, stress cardiomyopathy (Tako Tsubo) or other cardiomyopathies [28-30]. However, in 1/3 of these patients the CMR scan is normal [28].

CMR in ST-Elevation Myocardial Infarction (STEMI)

The mortality from STEMI varies according to patient factors and treatment factors. Those with a larger infarct have increased risk of heart failure and death. Infarct size is directly associated with mortality and patients with an infarct >12% of the Left Ventricle (LV) have a 7% mortality at 2 years compared to 0% with an infarct <12% of the LV [31]. Infarct size measured by LGE is directly associated with outcome. A study by Tarantini et al. demonstrated that the amount of transmural scar on LGE CMR predicted adverse LV remodeling, with significant additional predictive value over troponin [32]. Another study by Roes et al. confirmed the finding that infarct size on LGE CMR was a stronger predictor of all-cause mortality than LV ejection fraction and LV volumes in a population of 231 healed MI patients [33]. Transmurality of infarction also was associated with worse outcome, and it has been demonstrated that CMR derived acute infarct size is a stronger predictor of future events than measures of LV systolic performance [34]. Francone et al. showed that the extent of reversible and irreversible myocardial injury as assessed by CMR in STEMI patients treated with Primary Percutaneous Coronary Intervention (PPCI), is determined by time to reperfusion. Particularly, salvaged myocardium is markedly reduced when reperfusion occurs >90 min of coronary occlusion [35].

There is increasing data on the prognostic value of CMR derived infarct size and myocardial salvage [36,37].

Microvascular obstruction

In up to 30% of patients with STEMI the angiographic phenomenon of 'no-reflow' is observed, resulting from absent/incomplete distal myocardial reperfusion, despite successful vessel recanalization [38]. In CMR this is known as MicroVascular Obstruction (MVO) and it is observed on rest first-pass perfusion, but also in LGE images. The presence and extent of MVO after AMI

is associated with adverse LV remodeling and poor clinical outcome [39-41], and myocardial segments presenting MVO are more likely to develop wall thinning and no functional recovery [42]. Nijveldt et al. confirmed that MVO in LGE proved a more powerful predictor of global and regional functional recovery than the transmural extent of infarction.

Intramyocardial hemorrhage

Depending on the severity of the ischemic injury, microvascular injury can lead to: 1) MicroVascular Obstruction (MVO) only, or 2) MVO with IntraMyocardial Hemorrhage (IMH). IMH appears as MVO in the rest first-pass perfusion and LGE images. The distinctive aspect of IHM vs MVO is the hypointense signal in the T2-weighted images caused by the hemoglobin breakdown products (not seen in MVO). Therefore T2-weighted images are essential for making the differential diagnosis IHM vs MVO.

Infarct size, myocardial salvage, MVO and IMH measured by CMR are being increasingly used as surrogate endpoints in clinical trials of acute myocardial infarction [43]. For example, the EXPIRA trial showed that in STEMI thrombectomy prevents thrombus embolization and preserves microvascular integrity by reducing the presence and extent of MVO and infarct size measured by CMR [44].

STEMI with multivessel disease

It is estimated that 40-65% of the patients presenting with STEMI have MultiVessel Disease (MVD) at PPCI [45,46]. The current ESC guideline on STEMI suggests bystander disease a stress imaging guided approach (including CMR) to guide complete revascularization. In a recent study adenosine stress CMR 1-5 days post PPCI was shown to be an effective modality for detection of inducible myocardial ischemia in non-culprit coronary stenosis with excellent overall diagnostic accuracy of 96% (sensitivity 99%, specificity 67%, positive and negative predictive value 97% and 86% respectively) [47]. Dastidar et al. demonstrated that, less than 40% patients undergoing PPCI with moderate to severe bystander non-culprit coronary artery disease need further revascularization. As a gatekeeper to complete revascularization, stress CMR was also found to be a cheaper management strategy in a cost analysis model when UK or US–based costs were assumed [48].

Complications of ACS by CMR

CMR is superior to echocardiography for the identification of ventricular thrombi, particularly when they are small and apical. They are easily identifiable early after contrast administration when both the cavity and the myocardium still appear bright, whilst the thrombus appears hypointense (lack of contrast uptake given that it is avascular) [49,50]. CMR is also able to detect other complications of MI including ventricular aneurysm, pseudoaneurysms, papillary muscle infarction with subsequent mitral regurgitation and ventricular septal defects that could lead to cardiac rupture [51].

The high spatial resolution of CMR allows the detection of right ventricular involvement in acute MI [52], which has been demonstrating that that early

post-infarction RV ischemic injury is common and is characterized by myocardial oedema, LGE, and functional abnormalities. RV injury is not limited to inferior infarcts but is commonly found in anterior infarcts as well [53]. RV infarction detected by CMR was a strong and independent predictor of clinical outcome after acute reperfused STEMI [54,55].

CMR for Myocardial viability

Numerous studies have demonstrated that LV dysfunction in patients with CAD may be a reversible phenomenon related to myocardial stunning or myocardial hibernation, thereby establishing that not all dysfunctional myocardium in ischemic heart disease is irreversible [56].

LGE CMR allows the differentiation of viable vs non-viable myocardium, identifying those myocardial segments that could benefit from revascularization.

However, not every patient with CAD and severe LV dilatation regains meaningful systolic function following revascularization. A study by Bax et al. showed that extensive LV remodelling (LV end-systolic volume >141ml) limits functional improvement after revascularization, with negative long-term prognostic effects, despite the presence of viability [57].

Hibernated myocardium is in a down-regulated functional state as a consequence of chronic ischaemia, but maintains the possibility to regaining function if coronary blood flow is restored. Therefore, establishing the presence of viability is of utmost clinical importance to guide surgical revascularization. This concept is supported by a meta-analysis demonstrating significant survival benefit of revascularizing patients with ischaemic cardiomyopathy and viable myocardium over medical management, and no significant difference between the treatments in patients with non-viable myocardium [58]. Furthermore, the role of assessing for myocardial viability to guide management of patients with chronic ischaemic systolic LV dysfunction is recognized in the 2014 ESC/EACTS guidelines on myocardial revascularization [59].

The STICH trial recently questioned the role of viability demonstrating that in patients with CAD and LV dysfunction assessment of myocardial viability did not identify patients with a differential survival benefit from CABG, as compared with medical therapy alone. However, viability was not assessed by CMR, and the study received many additional criticisms, and other studies are planned to clarify this question.

There are multiple imaging modalities available to assess viability, such as dobutamine stress echocardiography, SPECT and positron emission tomography (PET) [58]. However, the ESC/EACTS guidelines on myocardial revascularization [59] recognize the high diagnostic accuracy of CMR for assessing the transmurality of myocardial scar of CMR combined with its ability to assess contractile reserve. CMR has the highest spatial resolution in comparison to these other established techniques, enabling to detect up to 1 gram of infarcted myocardium in comparison to the lower limit of SPECT of approximately 10g [60]. In addition, the reproducibility of CMR assessment of chronic infarct is excellent [61]. However, the guidelines also concede that the overall differences in performance between modalities are small and that local experience and availability are likely major determinants of which technique should be used [59].

There are mainly two CMR parameters that can be used to assess myocardial viability: infarct transmurality with LGE, and contractile reserve with dobutamine CMR.

The importance of LGE transmurality in assessing viability in chronic CAD was established by Kim et al. [62], when they demonstrated that, in patients with ischaemic LV dysfunction the transmural extent of LGE predicted LV functional recovery after revascularization. In particular, the absence of LGE corresponded to a 78% chance of segmental functional recovery at 3 months after revascularization. In comparison, myocardial segments with 51-75% transmurality of LGE, only 10% segments recovered in function, falling to 2% with >75% transmural LGE. However, where the extent of LGE is 1-50%, the chance of functional recovery was indeterminate and approximately 50%. Very similar results were reproduced by other groups [63].

Kwong et al. [64] demonstrated the presence of any degree of LGE in chronic MI patients increased the risk of major adverse cardiac events by six-fold. The number of segments demonstrating LGE is also important. In a multicenter, international study of 1.560 patients, multivariate analysis demonstrated than the number of segments with LGE was an independent predictor of mortality over a 2.4 year follow-up period [65]. In patients with chronic CAD, the presence of LGE may be a better prognostic marker than traditional ejection fraction [65,66].

In addition to detecting the presence/absence of a myocardial infarction, CMR allows its precise transmural distribution and quantification either in absolute grams or in % of LV mass. Several methods exist to quantify transmurality, including semi-automated objective techniques, which can be used in the research studies [67].

End-Diastolic Wall Thickness (EDWT)

Myocardial thinning often represents myocardial scarring from previous infarction [69] with EDWT <6mm carrying a low probability of post-revascularization functional recovery [70]. However, the clinical utility of this parameter is limited by the fact that thinned myocardium could also represent myocardial hibernation and indeed viable myocardium. Shah et al. demonstrated that among patients with CAD with regional wall thinning referred for CMR, limited scar burden was present in 18% and was associated with improved contractility and recovery of wall thickness after revascularization [71]. Therefore wall thickness (thinning) per sé should not represent a marker of viability.

Regional Wall Motion Abnormality (RWMA)/contractile reserve

Regional wall motion abnormality is only present when the transmural infarct extension is >50% [72] and not in the presence of smaller infarctions. Thus, RWMA in isolation underestimate infarct size.

Conversely, improvement of RWMA during low-dose dobutamine represent a marker of myocardial viability [73].

As a beta-agonist, dobutamine results in an increase in myocardial contractility, heart rate and stroke volume. The protocol used in CMR is similar to echocardiography.

The principle of dobutamine stress CMR is that the agent is administered

at increasing doses with interval imaging until target heart rate (which may require the administration of atropine) is achieved or angina symptoms are experienced.

In the presence of a flow-limiting coronary stenosis, the myocardium will display new RWMA as a surrogate for ischemia. On the other hand, the regain of function of baseline RWMA represents contractile reserve in hibernating myocardium. Using this approach sensitivity and specificity can be significantly improved compared with dobutamine stress echo [90]. Quantifying RWMA by myocardial tagging in this context has been demonstrated to increase diagnostic accuracy [74,91].

Improved quantification can also be offered by novel post-processing feature tracking software on standard cine images [75].

The importance of integrating CMR parameters for viability assessment is highlighted in the meta-analysis of 24 studies including 698 patients by Romero et al. [76], demonstrating that LGE provided the highest sensitivity (95%) and negative predictive value (90%), whereas low-dose dobutamine offered the best specificity (91%) and positive predictive value (93%).

Inducible myocardial ischaemia

The FAME study [77] established that revascularization of patients with symptomatic stable CAD guided by the presence of myocardial ischaemia measured invasivally by Fractional Flow Reserve (FFR) is prognostically important.

Furthermore, a meta-analysis of 11.636 patients with suspected CAD demonstrated that the absence of ischaemia confers prognostic benefit, with very low annualized event rates for cardiovascular death (0.3%) and MI (0.4%) [78]. The ongoing MR-INFORM study is assessing whether in patients with stable CAD a CMR stress perfusion strategy is non-inferior to FFR to guide patients' management [79]. The ongoing ISCHEMIA trial will demonstrate whether patients with moderate-severe ischemia on stress imaging will benefit from coronary angiography and revascularization [80].

Vasodilator stress CMR has been demonstrated to correlate well with FFR [81]. When compared to PET, CMR was demonstrated to provide a similar diagnostic accuracy (pooled sensitivity 89% with 95% confidence interval: 88-91% and pool specificity 76% with 95% confidence interval: 73-78%) to PET, which achieved the highest diagnostic performance, but without exposure to ionizing radiation [82]. The large, prospective, CE-MARC study has recently established CMR's high diagnostic accuracy in coronary heart disease and its superiority over SPECT: CMR had a sensitivity of 86.5%, specificity 83.4%, positive predictive value 77.2%, and negative predictive value 90.5% compared to sensitivity of 66.5%, specificity 82.6%, positive predictive value 71.4%, and negative predictive value 79.1% for SPECT [83]. In both genders, CMR has greater sensitivity than SPECT without significant differences between males and females [84]. Stress CMR also performs favorably in cost-effective analyses assessing diagnostic pathways for the work-up of suspected CAD [85].

The role of stress CMR in ischaemia assessment has been recognised in

international guidelines on the assessment of CAD. The 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD lists stress perfusion CMR as one of the suggested modalities to assess patients with a pre-test probability of CAD of 15-85% (class I recommendation) [86]. The National Institute for Health and Care Excellence (NICE) recommends non-invasive ischaemia imaging (including stress CMR) in patients with intermediate risk of CAD (30-60%) and in patients with an estimated likelihood of CAD of 61-90% after resting ECG, providing revascularization is not being considered or if invasive angiography is not clinically appropriate or acceptable to the person [87]. A small study by Dastidar et al. showed that the prevalence of myocardial ischaemia is not different in the intermediate and high likelihood of CAD [88]. Stress CMR receives class IIa recommendations in several clinical settings in the 2012 ACC/AHA chest pain guidelines, with class I recommendations for exercise ECG, nuclear perfusion and stress echocardiography [89].

In clinical practice, detection of inducible ischaemia is usually based on visual assessment of the stress and rest images, reporting its presence and extent following the myocardial segmentation model. Interpreting stress CMR images can be challenging as artefacts mimic genuine perfusion defects. Both standardization in reporting and significant experience in reading the images are important [84].

Semi-quantitative and quantitative perfusion measurement are possible but currently technically challenging, time consuming and mainly used in research.

Recently exercise stress cardiac MRI has been investigated by Thavendiranathan et al. The study in healthy volunteers showed that peak exercise wall motion assessed by exercise stress cardiac MR is feasible and can be performed at least as rapidly as stress echo [95].

Conclusion

CMR is a well-established comprehensive non-invasive imaging modality in the assessment of patients with CAD. CMR can assess cardiac anatomy, function, myocardial perfusion and tissue viability, without exposure to ionising radiation and in <1h scan. Its use in IHD is supported by strong and rapidly expanding evidence. The real challenge is to delineate how CMR can improve patient management and impact upon clinical outcomes, whilst proving to be cost-effective.

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