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CURRENT OPINION

The Year in Cardiology

The Year in Cardiology 2013: imaging in ischaemic heart disease

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This article focuses on some of the most important studies published in the year 2013 in cardiac imaging related to ischemic heart disease. Many of the studies across the various imaging techniques addressed the prognostic impact of imaging data on outcome in patients with this disease.

Keywords Non-invasive cardiac imaging • Echocardiography • Coronary computed tomography • Cardiac magnetic resonance • Myocardial positron emission tomography

Introduction

The purpose of this review is to provide the readership of the journal with a comprehensive overview of the clinically most relevant publications in the field of cardiovascular imaging in 2013 including echocardiography, cardiovascular magnetic resonance (CMR), coronary computed tomography angiography (CCTA), and radionuclide imaging. This year has witnessed important contributions of cardiac imaging to the diagnosis and management of heart failure and of valvular lesions. There has also been an increasing awareness of the impact of imaging findings on the diagnosis, prognosis, and treatment of ischaemic heart disease (IHD), which has served to solidify the clinical value of non-invasive imaging modalities and will thus be the main focus of this manuscript. The 2013 ESC guidelines on the management of stable coronary artery disease (CAD)[1] have further emphasized the role of non-invasive imaging to guide CAD treatment compared with previous guidelines, and are recommended for a more in-depth appraisal of the appropriate use of these technologies.

Echocardiography

Ischaemic cardiomyopathy is a frequent cause of left ventricular dyssynchrony. Analysis of contractile reserve has been applied to predict the response to cardiac resynchronization therapy. In a single-centre study of 58 guideline selected cardiac resynchronisation therapy (CRT) candidates, this approach has now been expanded by the assessment of apical rocking,[2] a parameter integrating the effect of both scar tissue and activation delays on the pattern of left ventricular contraction. The amplitude of apical rocking during low-dose dobutamine stress echo was associated with the response to CRT over a mean follow-up of 41 months, while the changes in left ventricular ejection fraction induced by dobutamine were not. An increase in apical rocking, but not in left ventricular ejection fraction, was also associated with improved long-term survival in CRT patients. Thus, parameters more sophisticated than ejection fraction may need to be applied for gaining an adequate functional understanding of a dyssynchronous ventricle.

In patients with CAD, accurate diagnosis of myocardial ischaemia is mandatory for appropriate therapy. A decrease in myocardial perfusion can be diagnosed earlier than wall motion abnormalities, which may be a reason why single photon emission computed tomography (SPECT) tends to be more sensitive than stress echo for detection of CAD.[3] Myocardial contrast echo, however, provides information on both perfusion and function. Thus, a large European multicentre study in 628 patients compared sulfur hexafluoride microbubble-enhanced myocardial contrast echo with SPECT for the detection of significant CAD. The trial was performed in a population exhibiting an intermediate-to-high prevalence of CAD with all the patients receiving myocardial contrast echo, SPECT, and coronary angiography within 1 month. Myocardial contrast echo displayed superior sensitivity (*Figure 1*), but lower specificity for detection of CAD when

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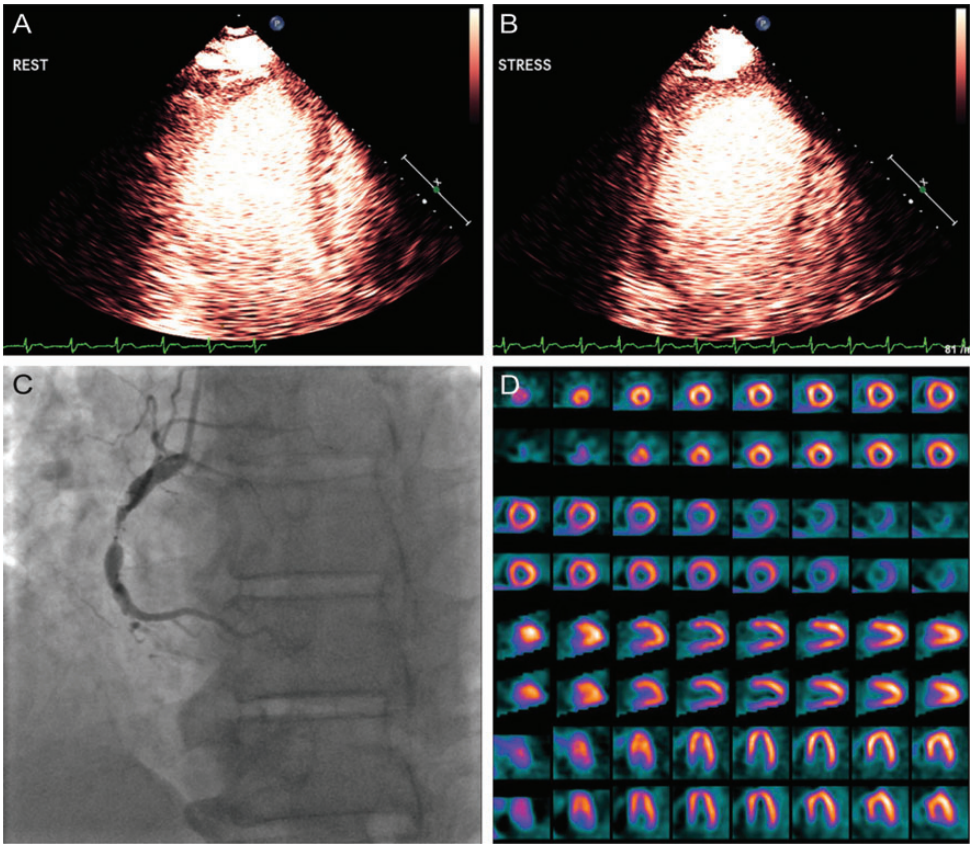

Figure 1 A 52-year-old man with significant reversible defect of the inferior wall shown by myocardial contrast echocardiography at rest (*A*) and under stress (*B*), corresponding to an 80% stenosis of the right coronary artery on quantitative coronary angiography (*C*). SPECT (*D*) revealed no abnormalities. From Senior *et al.* [3] with permission from the journal.

compared with SPECT. This study strongly encourages the application of microbubble echo contrast not only for improved wall motion detection, but also for combining the latter with myocardial perfusion imaging.

A prospective single-centre randomized trial performed in 2014 patients at intermediate-to-high risk for cardiac events confirmed that the combination of myocardial perfusion imaging with wall motion analysis improved the detection of CAD when compared with conventional stress echo in which contrast was only used when two continuous segments could not be visualized.[4] The combined approach was superior in detecting abnormalities, resulted more often in revascularization, and was better in predicting cardiac events.

Pharmacological stress echo is a strong predictor of events in patients with left bundle branch block (LBBB). Doppler-derived coronary flow reserve (CFR) determined during pharmacological stress echo adds prognostic information to stress echo in patients with diabetes mellitus or with arterial hypertension. A large multicentre study performed in 324 patients with known or suspected CAD and LBBB examined whether the superior prognostic power of additional Doppler measurements was also seen in patients with LBBB.[5] Indeed, an abnormal CFR in the left anterior descending coronary artery (LAD) was independently associated with a markedly increased risk for cardiac events even in the patients on therapy with a stress echo negative for ischaemia. This study thus emphasizes that the assessment of CFR in the LAD should be more often included in armamentarium of stress echocardiography. Along this line, another multicentre study in 718 patients determined whether the addition of myocardial perfusion and CFR in the LAD to wall motion analysis increased prognostic information.[6] Multivariate analysis demonstrated that risk stratification was indeed progressively improved with the sequential addition of the parameters mentioned above. The authors recommend this multiparametric approach for today's intensively treated patients arguing that the average risk for cardiac events is so low that methods with a higher predictive sensitivity than that available with standalone wall motion assessment are required.

Appropriate use criteria decision support tools have been developed to guide physicians in selecting the appropriate imaging modality for evaluating patients with suspected CAD. A prospective multicentre cohort study tested the impact of such a tool on clinical practice.[7] Appropriateness ratings for stress echo, myocardial perfusion scintigraphy, and CCTA were provided. At the end of the test period, the percentage of appropriate tests increased, while that of inappropriate tests decreased, suggesting that such a tool may improve education of physicians.

Cardiovascular magnetic resonance

A new algorithm to improve the accuracy of detecting significant stenoses in patients with suspected CAD uses the combination of CMR and CCTA.[8] In this single-centre study of 192 patients with low-to-intermediate pre-test probability for CAD invasive coronary angiography (ICA) was only performed if there was obstructive CAD detected by coronary CTA combined with myocardial ischaemia on CMR (*Figure 2*) or if CMR showed myocardial ischaemia without evidence of obstructive CAD on coronary CTA. The combination with CMR improved specificity and overall accuracy from 39 to 57% for coronary CTA alone to 94 and 91%. Invasive coronary angiography could be avoided in more than half of the patients based on coronary CTA and CMR results. These patients had no cardiac events during a follow-up of 18 $\pm$ 6 months. Furthermore, this combined imaging strategy provided an alternative diagnosis in 10% of patients. The downside of this strategy is the need for substantial imaging resources.

Several recent guidelines recommend the use of stress imaging techniques for determining the risk of adverse events in patients with an intermediate likelihood for obstructive CAD.[1] Based on such risk stratification, the guidelines do or do not recommend revascularization. The use of CMR for the purpose of risk stratification is supported by a 2013 study in a cohort of 815 patients. Cardiovascular magnetic resonance demonstrated a strong association with major adverse cardiac events when inducible ischaemia was found.[9] This was true both for those with suspected stable CAD and those with recurrent or increasing symptoms and known CAD. Cardiovascular magnetic resonance reclassified 91.5% of patients with intermediate pre-test risk (65.7% to low risk, 25.8% to high risk) with corresponding changes in the observed event rates (0.3 and 4.9%/year for low- and high-risk post-test, respectively). In a meta-analysis based on 19 studies involving a total of 11 636 patients, Lipinski *et al.*[10] found that patients with CMR verified ischaemia had a higher incidence of myocardial infarction [odds ratio (OR): 7.7; $P < 0.0001$], cardiovascular death (OR: 7,0; $P < 0.0001$), and the combined endpoint (OR: 6.5; $P < 0.0001$) compared with those with a negative study. The presence of late gadolinium enhancement was also significantly associated with a worse prognosis. These data put CMR with respect to prognostication in a similar category as SPECT perfusion and stress echocardiographic studies. The latter already have a large data base showing that negative studies are associated with very low event rates $<$1%/year for MI and death.

Coronary computed tomography angiography

Two 2013 papers enable us to better understand the prognostic value of CCTA in patients with suspected CAD. In the large

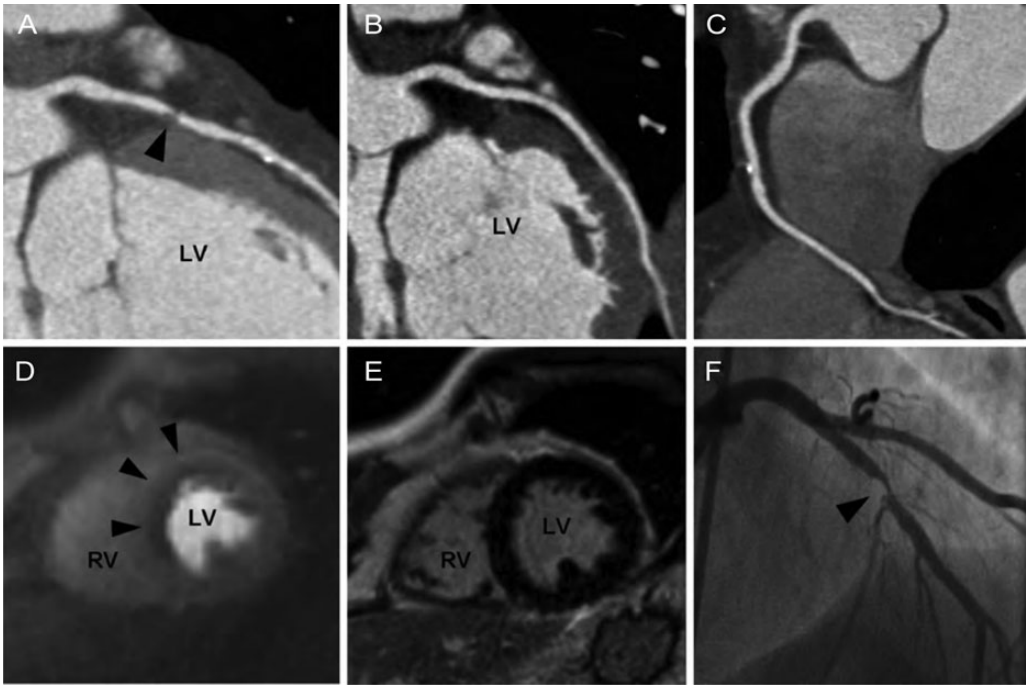

Figure 2 Case example. A patient with obstructive coronary artery disease on computed tomography coronary angiography in the left anterior descending coronary artery (*A*), normal circumflex coronary artery (*B*), and non-obstructive coronary artery disease in the right coronary artery (*C*). Cardiovascular magnetic resonance imaging showed an adenosine stress-induced perfusion defect in the anterior and anteroseptal myocardial wall (*D*, mid-ventricular short-axis orientation) and the absence of myocardial fibrosis on gadolinium late enhancement imaging (*E*). Invasive coronary angiography (*F*) confirmed significant coronary artery disease in left anterior descending coronary artery. LV, left ventricle; RV, right ventricle. From Groothuis *et al.*[8]

CONFIRM registry of ~20 000 patients, 347 patients died during a median follow-up of 2.3 years.[11] The best CCTA parameter for predicting mortality was the number of proximal segments with mixed or calcified plaque and the number of proximal segments with a stenosis ≥50%. A proximal coronary segment containing either a mixed or calcified plaque or a stenosis had an equivalent prognostic impact as a 5-year increase in age or the risk of smoking. Longer follow-up was available in a smaller study with 1584 patients followed for 5.6 years.[12] The severity of CAD (categorized as normal, non-obstructive, one-vessel, two-vessel, and three-vessel obstructive) and the total number of plaques were the best predictors for death and non-fatal MI. The annual event rate was nevertheless low at 1.5% even for patients with CAD and extensive plaque load (>5 segments). However, in patients without CAD the annual event rate was only 0.24%. These studies show that CCTA may add prognostic value even when compared with ICA as CCTA detects non-stenotic plaque more readily than invasive angiography.

The use of CCTA in the emergency department continued to be a hot topic in 2013. In a retrospective study from two risk-matched cohorts of 894 emergency department patients presenting with chest pain, CCTA was shown to significantly reduce the overall admission rate (14 vs. 40%, $P < 0.001$).[13] Moreover, the expected length of stay in the emergency department was 1.6 times longer with the standard evaluation ($P < 0.001$). Although there were no differences in the rates of death and acute MI within 30 days of the index visit, the likelihood of returning to the emergency department within 30 days for recurrent chest pain was five times greater with the standard evaluation ($P = 0.022$). This study adds to the growing evidence that the routine use of CCTA in the emergency department reduces healthcare resource utilization. This important finding in an increasingly cost conscious environment is further substantiated by a meta-analysis including four large randomized studies looking at a total of 3266 patients.[14] All studies showed decreased length of stay with CCTA and three of the four studies reported cost savings. Based on these trials, it can be expected that the use of CCTA in the emergency department will continue to grow in order to shorten the time to diagnosis, lower cost and improve diagnostic precision in patients presenting with acute chest pain.

CT fractional flow reserve (CT_{FFR}) continues to raise interest in 2013. This technique allows to determine a 'virtual' FFR value for a given coronary stenosis from a standard CT coronary angiogram using computational fluid dynamics. After the promising results of the first pilot study, the DISCOVER-FLOW study, the enthusiasm was somewhat tempered by the results of the larger DeFACTO trial last year, which failed to meet the non-inferiority endpoint. A recently published substudy of the DeFACTO trial assessed the diagnostic accuracy of intermediate lesions (defined as 30–69% stenosis) in 407 vessels from 252 patients.[15] Using invasive FFR as the standard of reference, CT_{FFR} demonstrated superior diagnostic accuracy compared with CT stenosis on per-patient (AUC: 0.81 vs. 0.50, $P = 0.0001$) and per-vessel basis (AUC: 0.79 vs. 0.53, $P < 0.0001$).

CT perfusion imaging (CTP) has emerged as a novel and promising modality for detecting myocardial ischaemia. Rief *et al.*[16] assessed the value of CTP added to CCTA in patients in 91 consecutive patients with coronary stents scheduled for invasive coronary angiography. Coronary computed tomography angiography alone resulted in 22% non-diagnostic studies (metal artifacts). Adding CTP to CCTA increased the diagnostic accuracy from 61 to 87% and the area under the ROC curve from 0.69 to 0.82, mainly because of a reduction in non-diagnostic examinations (gold standard: quantitative coronary angiography). Hence, CTP and/or CT_{FFR} may become valuable assets to improve the diagnostic yield of CT in the future in patients with equivocal, intermediate, or stented lesions, but larger trials are needed before wide adoption of these techniques can be advocated.

Radionuclide imaging

In 2013, the increasing availability of solid-state detector technology (cadmium zinc telluride, CZT) for myocardial perfusion SPECT (single-photon emission computed tomography) imaging has offered several advantages with regard to patient comfort, radiation safety, and duration of image acquisition. The prognostic value of such high-speed SPECT has now also been established by Nakazato *et al.*[17] who followed-up 1613 consecutive patients undergoing high-speed SPECT on a CZT camera for a mean of 2.6 years. Annualized death rates increased progressively with increasing stress total perfusion deficit (sTPD): 0.87% or sTPD of 0%, 1.94% for sTPD of 1–4%, 3.10% for sTPD of 5–10%, and 5.33% for sTPD >10%. After adjusting for several clinical baseline variables, sTPD remained a significant predictor of all-cause mortality.

Radiation protection issues remain a hot topic in 2013 for all modalities that generate ionizing radiation and in particular for myocardial perfusion SPECT. Strategies to lower radiation exposure to patients and staff include the aforementioned CZT technology which allows significant reduction in administered radionuclide doses and patient-tailored protocols such as selective stress-only imaging. Recent data from the Mount Sinai Medical Center reported a significant reduction in administered radionuclide doses (10 746 vs. 7174 mCi), and approximately a 40% reduction in the dose equivalent across all staff members after the introduction of CZT technology and stress-only protocols in their centre.[18] These changes occurred despite a 10% increase in patient volume and were accompanied by a significant faster patient throughput.

Although myocardial perfusion imaging using positron emission tomography (PET) is less frequent in Europe than in the USA, a number of publications deserve attention. Positron emission tomography has the unique property of being able to assess coronary vascular function by measuring MBF at rest and coronary hyperaemia. In 901 patients with chest pain or an abnormal exercise stress ECG and yet normal PET myocardial perfusion imaging (no regional perfusion defects), CFR was measured with ^{82}Rubidium PET and coronary artery calcium score (CACS) determined by CT.[19] With increasing CACS, CFR decreased. Over a median follow-up of 1.5 years, annual risk-adjusted major adverse cardiac events (MACE) rates were higher for patients with CFR <2.0 compared with those having a CFR ≥2.0 (5.5 vs. 1.9%/year). MACE rates also increased for increasing calcium scores, but this increase was only borderline statistically significant. Even for patients with a calcium score of 0, an impaired CFR tripled the annualized adjusted MACE rate from 1.4 to 5.2%. This study underscores the mounting evidence that CFR is an important risk factor for hard cardiac endpoints. It

appears that at least on a short-term follow-up of 1.5 years, CFR is an even more powerful predictor of cardiac events than CACS.

A large multicentre registry examined the prognostic value of stress myocardial perfusion PET in patients with suspected or known CAD.[20] There were a total of 7061 patients from four centres who had a median follow-up of 2.2 years. The risk of experiencing cardiac death increased with an increasing extent of myocardium found to be abnormal at stress PET. Adding the information of per cent myocardium ischaemic and per cent myocardium scarred to a large body of clinical information improved model performance and risk reclassification for cardiac death. The improvement in risk assessment gained by adding PET data was smaller for all-cause death.

The use of myocardial perfusion PET may increase in Europe with the introduction of new ^{18}F-fluorinated perfusion compounds which are currently under clinical evaluation.[21] In a multicentre study of 86 patients, PET myocardial perfusion imaging with flurpiridaz F 18 was safe and superior to SPECT MPI for image quality, interpretative certainty, and overall CAD diagnosis.

Conclusion

Imaging studies in the year 2013 underscored the value of imaging for making the diagnosis and predicting the prognosis in patients with suspected and established CAD. However, appropriately sized prospective randomized trials to prove the impact of cardiac imaging on patient management and clinical outcomes are still eagerly awaited.

Conflict of interest: none declared.

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