The year in cardiology 2014: imaging

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Preamble

Non-invasive cardiac imaging is pivotal for the diagnosis and decision making of patients with cardiovascular diseases. Recent innovations in echocardiography, nuclear imaging, computed tomography, and cardiac magnetic resonance have provided novel pathophysiological insights that may impact on the clinical management of patients. The current review provides a summary of selected articles on technological innovations in imaging and emerging clinical applications.

Introduction

In 2014, many articles were published on the use of non-invasive cardiovascular imaging, including echocardiography, nuclear imaging, computed tomography (CT), and cardiac magnetic resonance (CMR) imaging. A selection of these articles is presented here. The focus is on technical innovations and emerging applications in clinical cardiology.

Echocardiography

Accumulating data have demonstrated the role of speckle tracking echocardiography (STE) in characterization left ventricular (LV) mechanics and risk stratification of patients with various cardiac diseases. Geske et al. demonstrated that LV septal morphology rather than genetic basis is the main determinant of regional LV strain abnormalities in patients with hypertrophic cardiomyopathy (HCM). Genotype-positive HCM patients (n = 51) were more likely to have reverse curve morphology of the interventricular septum (59%) whereas genotype-negative patients (n = 80) had more frequently sigmoidal septal curvature (49%). Interestingly, while global LV strain (GLS) was not significantly different between groups, regional strain analysis revealed that genotype-positive HCM patients had significantly more impaired longitudinal strain in the mid inferoseptal, basal inferoseptal, and basal anteroseptal regions compared with genotype-negative patients. When patients were divided according to genotype and LV septal morphology, LV GLS was significantly more impaired among genotype-positive HCM patients with a reverse septal curvature than in genotype-negative HCM patients with a sigmoid septal morphology (Figure 1).

Quarta et al. also observed a negative correlation between LV septal thickness and GLS in 172 patients with cardiac amyloidosis. Despite showing relatively preserved LV ejection fraction, LV GLS significantly impaired with increasing tertiles of LV septal thickness. At regional level, only basal and mid ventricular segments significantly worsened with increasing LV septal thickness while apical segments showed preserved longitudinal strain values. When analysing the data based on type of cardiac amyloidosis, patients with mutant-type transthyretin-related (TTR) cardiac amyloidosis showed more preserved LV GLS compared with patients with wild-type TTR and immunoglobulin amyloid light-chain cardiac amyloidosis. On multivariate analysis, immunoglobulin amyloid light-chain cardiac amyloidosis, renal dysfunction, New York Heart Association functional classes III–IV, and LV GLS were independently associated with long-term survival.

In heart failure patients with preserved left ventricular ejection fraction (LVEF) and diastolic dysfunction, STE has also helped to understand the pathophysiology of this growing epidemic. Kraigher-Krainer et al. showed that these patients have significantly impaired LV GLS and circumferential strain compared with controls. Interestingly, abnormal LV GLS (defined as > 2 SD below the mean value of controls) was more prevalent than abnormal circumferential strain (43 vs. 22% for patients with an LVEF ≤ 55%). Both longitudinal and circumferential strains were independently associated with LV mass index.

Left ventricular GLS has been proposed as a surrogate of myocardial infarct size, an important determinant of LV dilatation after ST-segment elevation myocardial infarction (STEMI). Joyce et al. demonstrated that STEMI patients with LV GLS > −15% (n = 520) had significantly larger LV volumes at follow-up compared with patients with more preserved GLS (≤ −15%) (n = 521). Left ventricular GLS was independently associated with LV dilatation post-STEMI after correcting for various demographic, clinical and echocardiographic variables. Furthermore, Ersboll et al. showed that STE-derived diastolic indexes were associated with long-term prognosis of 1048 patients with myocardial infarction. Using STE strain rate, the early diastolic peak strain rate (e’sr) was measured and the ratio between transmural pulsed wave Doppler early peak velocity (E) and e’sr was derived as an index of LV filling pressures.

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Increasing quartiles of $E/e’$sr were associated with significantly larger infarct size (based on troponin concentrations), lower LVEF, and more impaired LV GLS. Patients with an $E/e’$sr $> 1.25$ had four-fold higher mortality risk than patients with an $E/e’$sr $< 1.25$. The expression $E/e’$sr was independently associated with long-term survival [hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.05–2.13; $P = 0.02$]. As Tschoöpe et al.\(^6\) indicated in an accompanying editorial, these findings indicate that diastolic LV strain rate parameters may be more sensitive than systolic parameters to predict adverse outcomes since diastolic LV relaxation is an energy-dependent mechanism that impairs after the onset of ischaemia earlier than systolic parameters.

In asymptomatic patients with moderate and severe primary mitral regurgitation and preserved LV GLS, the presence of LV contractile reserve during peak exercise has been associated with better prognosis. Magne et al.\(^7\) showed that LV contractile reserve defined by $>2\%$ improvement in LV GLS was superior in predicting long-term outcome of 115 patients with moderate (37%) and severe (63%) primary mitral regurgitation than a definition based on $>4\%$ increase in LVEF. After adjusting for several clinical and echocardiographic parameters proposed by current guidelines to indicate need for surgical mitral valve repair,\(^8\) the presence of LV contractile reserve based on LV GLS was independently associated with better outcome (HR 1.6, 95% CI 1.1–2.3; $P = 0.01$).
The clinical application of 3D STE was demonstrated by Smith et al.\textsuperscript{9} evaluating right ventricular (RV) mechanics in patients with pulmonary hypertension. The peculiar 3D disposition of the RV challenges its functional assessment. With this novel imaging technique, patients with pulmonary hypertension showed significantly impaired area strain and multidirectional strains (longitudinal, circumferential, and radial) compared with healthy controls. In addition, area strain was independently associated with prognosis in these patients.

Finally, a recent innovation in echocardiography is the development of pocket-size ultrasound devices. Gianstefani et al.\textsuperscript{10} showed that the use of these devices resulted in shorter scanning and reporting times while keeping good accuracy in evaluating LV systolic function and wall motion abnormalities and in diagnosing significant pericardial effusion and valvular heart disease. In addition, pocket-size ultrasound devices were associated with an overall cost saving per scan of 76% compared with high-end ultrasound systems.

**Nuclear imaging**

Single photon emission computed tomography (SPECT) and other non-invasive imaging have been used for decades to detect or exclude coronary artery disease (CAD). Thom et al.\textsuperscript{11} compared 2-year outcomes and cost-effectiveness of SPECT, stress echocardiography, and stress perfusion CMR as the initial imaging strategy vs. direct angiography in the management of 898 patients with stable chest pain in a prospective randomized trial. Compared with angiography, the HR for mortality in patients randomized to CMR was 2.6 (95% CI 1.1–6.2, \( P = 0.032 \)), 1.0 (95% CI 0.4–2.9, \( P = \text{ns} \)) for SPECT, and 1.6 (95% CI 0.6–4.0, \( P = \text{ns} \)) for stress echocardiography. Considering recent advances in imaging techniques in the last decade, this study demonstrates that non-invasive imaging could be used safely as the initial test to diagnose CAD, without adverse effects on patient outcomes or increased costs, relative to angiography.

Other recent publications in nuclear cardiology concern innovation in technology and use of advanced imaging techniques in cardiovascular disease. The recent introduction of gamma cameras using multipinhole collimation and cadmium–zinc–telluride (CZT) detectors permits ultrafast myocardial perfusion imaging. Chowdhury et al.\textsuperscript{12} reported a diagnostic accuracy of 82% in 165 patients with obstructive CAD on invasive angiography; moreover, in 1109 patients with median follow-up of 624 days, the cardiac event rate (death, non-fatal infarction) was 0.4% in patients with a normal scan, vs. 6.8% when the scan was abnormal. Importantly, the acquisition time was very short: 322 ± 51 s. Gimelli et al.\textsuperscript{13} also demonstrated in 247 patients undergoing gated rest–stress myocardial perfusion imaging with CZT detectors that this new technology also permits assessment of diastolic function. The peak filling rate and the time to time peak filling rate were derived from gated CZT images as measures of LV filling dynamics, and compared well with routine measures for diastolic function derived from echocardiography.

Advanced imaging techniques such as positron emission tomography (PET) and PET-CT are increasingly used in clinical studies. Blankstein et al.\textsuperscript{14} evaluated 118 patients with sarcoidosis (without history of coronary artery disease) for the presence of cardiac inflammation or focal perfusion defects on PET using $^{18}$F-fluorodeoxyglucose (FDG) and rubidium-82, respectively. Cardiac involvement was detected in 60% of patients, whereas extra-cardiac lesions were present in 26%. During a median follow-up of 1.5 years, 31 events were noted (27 sustained ventricular tachycardias (VT) and 8 deaths); cardiac involvement on PET-predicted events (after adjustment for clinical criteria or LVEF). Particularly, the combination of cardiac perfusion defects and abnormal FDG uptake were predictive of outcome, whereas extra-cardiac lesions were not. The findings suggest that PET can identify patients with sarcoidosis at high risk of VT or death.

Fallalvola et al.\textsuperscript{15} reported the results of the prediction of arrhythmic events with positron emission tomography study. In 204 patients with ischaemic cardiomyopathy (LVEF 27 ± 9%) who received an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death (SCD), PET was performed to assess cardiac sympathetic innervation (with $^{11}$C-metahydroxyephedrine) and combined perfusion—FDG imaging to assess scar. During 4.1 years follow-up, 16.2% of patients experienced an SCD event (arrhythmic death or ICD discharge for ventricular fibrillation or...
Computed tomography

Coronary artery calcium (CAC) imaging continues to raise interest in 2014 as a means for more personalized risk stratification beyond traditional risk factors and biomarkers. In a substudy of the large Multi-Ethnic Study of Atherosclerosis trial, Martin et al.18 explored the interaction between CAC scores and lipid abnormalities. In patients with CAC score ≥ 100, incident cardiovascular disease rates were high (22.7 – 29.5 per 1000 person-years) regardless of presence or severity of lipid abnormalities. In contrast, with CAC score of 0, event rates varied from 2.7 to 5.9 per 1000 person-years across lipid abnormality categories. Individuals with no lipid abnormalities and CAC score ≥ 100 had a higher event rate than individuals with extensive lipid abnormalities but CAC = 0, suggesting that CAC scores should be strongly considered when matching statin therapy to absolute cardiovascular risk. Often the question arises, whether CAC imaging should be supplemented by CT coronary angiography (CTCA) for screening and risk stratification. This question was addressed by two studies including different populations: the FACTOR-64-randomized clinical trial20 and the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry).21 Recently presented at the 2014 American Heart Association Scientific Sessions meeting, the FACTOR-64 trial-randomized 900 patients with type 1 and type 2 diabetes mellitus and without CAD symptoms to screening for CAD using CTCA or to standard national-guidelines based optimal diabetes care.20 Standard therapy or aggressive therapy (± invasive coronary angiography) of patients randomized to the CTCA screening was based on CTCA findings. Among the 395 patients who underwent CTCA, 46, 12, and 11% showed mild, moderate, and severe CAD, respectively. After a mean follow-up of 4 ± 1.7 years, there were no differences in the primary endpoint event rate (composite of all-cause mortality, non-fatal myocardial infarction, or unstable angina requiring hospitalization): 6.2 vs. 7.6% of the CTCA screened patients and control patients, respectively (intention-to-treat analysis HR 0.8, 95% CI 0.49 – 1.32, P = 0.38). Moreover, the substudy of the large multi-national multi-ethnic CONFIRM registry which followed 8627 symptomatic patients undergoing CAC and CTCA scanning for a median of 25 months showed that CTCA information on plaque extent and severity (both non-obstructive and obstructive) was a strong and independent predictor of cardiac death and myocardial infarction after correcting for patients’ clinical variables and CAC score.21 In the Heinz-Nixdorf Recall Study, Erbel and colleagues explored CAC progression among 3481 asymptomatic subjects (aged 45 – 74) who underwent two CAC scans 5 years apart.22 Coronary artery calcium progression occurred at a predictable rate along well-defined exponential percentiles for age, gender, and baseline CAC. Neither cardiovascular risk factors nor medical treatment (including lipid lowering and antihypertensive therapy) had any significant influence on CAC progression. This allowed the development of a mathematical tool for prediction of individual CAC progression, enabling anticipation of the age when CAC thresholds of high risk are reached.

Lowering radiation dose from CTCA is important. Novel iterative image reconstruction algorithms are now available which allow effective noise suppression and thereby scanning at very low tube current and voltage. One of these algorithms, model-based iterative reconstruction, was recently validated in 36 nonselected patients undergoing CTCA and invasive coronary angiography.23 Computed tomography coronary angiography images were acquired using low tube voltage (80 – 100 kV) and current (150 – 210 mA) at an effective average dose of 0.29 mSv (equivalent of 10 chest X-rays). Image quality was very good with 97% interpretable segments and a high diagnostic accuracy compared with invasive angiography. A limitation of CTCA is the lack of information on haemodynamic significance of the stenosis. The CORE320 trial is a large multi-centric imaging study to assess the diagnostic accuracy of CT perfusion combined with CTCA for the diagnosis of flow-limiting CAD using a comprehensive gold standard of invasive coronary angiography combined with SPECT myocardial perfusion imaging (Figure 3).24 Image analysis was performed in independent core labs. When CT perfusion was added to CTCA, the diagnostic accuracy (measured by receiver operating characteristic curve analysis) increased significantly [area under the curve (AUC) 0.87 compared with 0.84 for CTCA alone,
Figure 3  Computed tomography coronary angiography combined with computed tomography perfusion in a symptomatic 64-year-old male with suspected coronary artery disease. The left anterior descending coronary artery revealed a 96% diameter stenosis by computed tomography coronary angiography (A) and an 85% diameter stenosis by invasive coronary angiography (B). The computed tomography perfusion (C) study revealed a mild defect in the distal anteroseptal wall, and moderate defects in the basal anteroseptal, the basal anterior, the distal anterior, and apical walls, while the single photon emission computed tomography (D) study revealed moderate defects in the distal anterior, the distal anteroseptal, the basal anteroseptal, and apical walls. The left circumflex artery revealed an 87% diameter stenosis by computed tomography coronary angiography (A), a 79% diameter stenosis by invasive coronary angiography (B), mild defects in the distal inferoseptal and distal inferolateral walls, and moderate defects in the distal anterolateral and distal anterior walls by computed tomography perfusion (C), and a moderate defect in the distal anterior wall by single photon emission computed tomography (D). The right coronary artery revealed a 60% diameter stenosis by computed tomography coronary angiography (A), a 77% diameter stenosis by invasive coronary angiography (B), a mild defect in the distal inferoseptal wall by computed tomography perfusion (C), and no myocardial perfusion defects by single photon emission computed tomography (D). Reproduced with permission from Rochitte et al.24
CT-derived fractional flow reserve (FFR_{CT}) continues to raise attention in 2014. The second-generation version of the software has been tested in its third multi-centric validation study, the Heart-FlowNXt study, vs. invasive FFR. This study included 254 patients scheduled for invasive coronary angiography who underwent CTCA. The diagnostic accuracy by receiver operating characteristic curve analysis was significantly higher for FFR_{CT} compared with CTCA alone (AUC 0.90 vs. 0.81). Adding FFR_{CT} to CTCA increased particularly the specificity (from 34 to 79%) and positive predictive value (40–65%) for diagnosing flow-limiting coronary lesions. Finally, the transluminal attenuation gradient (TAG) has emerged as another tool to evaluate the haemodynamic relevance of coronary stenoses by CTCA. This approach allows estimating functional significance based on the rate by which intraluminal contrast attenuation decreases along a coronary vessel downstream from a given stenosis. In a recent study by Wong et al., TAG was compared with CT perfusion against the gold standard of invasive coronary angiography plus FFR in 75 patients. Both showed very comparable diagnostic accuracy (AUC 0.84 and 0.85, respectively). However, an integrated CT protocol combining TAG with CT perfusion and CTCA yielded the highest diagnostic accuracy (AUC 0.91).

**Cardiac magnetic resonance imaging**

Cardiac magnetic resonance imaging is currently considered the gold standard for quantification of LV dimension and function. Atharovski et al. used CMR to accurately assess the changes in LV systolic and diastolic function in 16 patients with Takotsubo cardiomyopathy. CMR-derived diastolic parameters included LV peak filling rate and left atrial emptying volumes. In contrast to LV systolic function, which showed a significant increase at pre-discharge, LV diastolic dysfunction persisted at hospital discharge and normalized only at 3 months follow-up.

The prognostic implications of the presence and extent of myocardial scar assessed with late gadolinium enhancement (LGE) CMR was explored in various pathologies. Chan et al. studied the prognostic value of myocardial scar in 1293 patients with HCM (60% with low risk for SCD). Myocardial scar was present in 42% of patients (mean LGE extent 10 ± 9% of the LV mass). During a median follow-up of 3.3 years, 37 (3%) patients experienced SCD. Myocardial scar was present in 70% of those patients. The adjusted risk for SCD increased proportionally with the LGE extent; each 10% increase in LGE was associated with 40% increase in the risk of SCD. In addition, even in the low-risk patients who experienced SCD, the risk of SCD was also associated with increasing extent of myocardial scar (HR 1.66, 95% CI 1.24–2.23; P = 0.0007). These results suggest that not only the presence but also the extent of myocardial scar can be used to optimize risk stratification, particularly in low-risk HCM patients.

Barone-Rochette et al. evaluated whether myocardial scar was an independent predictor of all-cause mortality in 154 patients with severe aortic stenosis (AS) without prior myocardial infarction who underwent surgical aortic valve replacement (AVR). Myocardial scar was observed in 29% of patients (mean LGE extent 3.5 ± 2.3%). After a median follow-up of 2.9 years after AVR, 21 patients died. The extent of myocardial LGE (HR 2.8, 95% CI:1.3–6.9; P = 0.025) and NYHA functional classes III–IV (HR 3.2: 95% CI:1.1–8.1; P < 0.01) were the only independent predictors of all-cause mortality, suggesting that myocardial scar might optimize the pre-operative risk assessment of patients with severe AS. Furthermore, Neilan et al. studied the prognostic value of LV myocardial scar in 664 patients with atrial fibrillation without known previous myocardial infarction who were treated with radiofrequency catheter ablation. Left ventricular myocardial scar was detected in 13% of patients with a mean LGE extent of 5.9 ± 3% (50% of myocardial scars following the coronary artery distribution suggesting ischaemic origin). During a median follow-up of 42 months, 22 patients with myocardial scar died. In multivariate analysis, age and LV LGE extent were independent predictors of mortality. Particularly, each 1% increase in LV LGE extent was associated with 15% increased risk of all-cause mortality.

Furthermore, accurate identification of the extent and location of LV scar using LGE may be helpful to decide on endo- or epicardial catheter ablation in patients with VT. Andreu et al. evaluated the accuracy of LGE CMR to predict the origin of VT based on the endocardial, epicardial, transmural, or mid-myocardial location of scar in 80 patients with VT (36% non-ischaemic cardiomyopathy) undergoing catheter ablation. The presence of epicardial LV LGE could identify the epicardial origin of the VT with 80% sensitivity and 88.7% specificity (Figure 4). The findings are particularly relevant in non-ischaemic patients with non-inducible VT, since the origin of VT can be accurately identified with LGE CMR, when myocardial scar is located at the epicardium, an epicardial ablation can be considered.

In contrast to macroscopic scar detection with LGE, T1 mapping (with or without the use of contrast) is a technique recently introduced to assess LV extracellular volume (ECV), which is a marker of myocardial interstitial fibrosis. Wong et al. assessed LV ECV from pre- and post-contrast T1 measurements in 231 diabetic patients and compared them with 945 patients without diabetes mellitus. The authors noted that diabetic patients had higher LV ECV compared with non-diabetics (30.2 vs. 28.1%, P < 0.001). Diabetes was significantly associated with LV ECV after correcting for several demographic and echocardiographic parameters, cardiovascular risk factors, myocardial infarct size and medications (β = 1.26; P < 0.001). Furthermore, the use of renin–angiotensin–aldosterone system blockers was independently associated with lower LV ECV (β = −0.6; P = 0.028). During a median follow-up of 1.3 years, 24 deaths and 21 heart failure hospital admissions occurred among diabetics. Every 3% increase in LV ECV was associated with 50% increase in the risk of all-cause mortality or heart failure hospitalization.

White et al. tested the diagnostic and prognostic value of a rapid, post-contrast T1-based visual assessment of diffuse myocardial hyper-enhancement in 90 patients with suspected cardiac amyloidosis. A frame-by-frame visual comparison of myocardial and blood pool signal was performed over the range of increasing inversion times to determine the relative T1. Diffuse myocardial hyper-enhancement was defined as >50% of the LV with abnormally short T1 in an area without a typical coronary artery distribution (non-ischaemic). Forty-eight (81%) patients had diffuse myocardial hyper-enhancement based on visual T1 assessment. Over a median
follow-up of 29 months, 56% of patients died. Diffuse myocardial hyper-enhancement was the strongest predictor of all-cause mortality in this population (HR 5.5, 95% CI 2.7–11.0; P < 0.0001).

Recent developments in CMR included the introduction of high-resolution myocardial perfusion imaging which has higher overall diagnostic accuracy in detecting significant CAD compared with standard-resolution imaging. Motwani et al.\textsuperscript{34} compared the diagnostic accuracy of high-resolution and standard-resolution perfusion CMR in 35 patients with angiographic three-vessel CAD. High-resolution perfusion CMR detected (subendocardial) ischaemia in all three coronary artery territories in 57% of patients whereas only 29% of patients were identified with standard-resolution perfusion CMR. The AUC to detect three-vessel CAD was significantly higher for high-resolution compared with standard-resolution perfusion CMR (0.9 vs. 0.69, P < 0.001).

Finally, 3D phase-contrast CMR with three-directional velocity encoding (4D flow CMR) may have important applications in valvular heart disease. Mahadevia et al.\textsuperscript{35} used this technique to correlate

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**Figure 4** Identification of the origin of ventricular tachycardia combining ECG, late gadolinium enhancement-cardiac magnetic resonance and electroanatomical mapping data. (A) The ECG of the ventricular tachycardias showing an origin in the inferoapical part of the septum (anterior infarction with late progression of the R wave in the precordial leads, left bundle branch block and left superior axis). (B) The late gadolinium enhancement-cardiac magnetic resonance left ventricular short-axis view with endocardial scar in the inferior wall (arrow) and extensive transmural scar in the septum and endocardial in the anterior wall. (C) The electrical activation map during the ventricular tachycardias, identifying the origin of the ventricular tachycardias at the apical part of the inferoseptum. Reproduced with permission from Andreu et al.\textsuperscript{31}
altered flow and haemodynamics in the ascending aorta with the type of cusp fusion in 30 patients with bicuspid aortic valve (15 with right–left cusp fusion and 15 with right-non-coronary cusp fusion). Eccentric outflow jet patterns were identified with increased wall shear stress of the right anterior wall of the ascending aorta in patients with right–left cusp fusion and increased wall shear stress of the right posterior wall in patients with right-non-coronary cusp fusion. These findings were associated with the type of aortopathy. While 87% of patients with right–left cusp fusion showed dilation of the aortic root only or the entire ascending aorta and arch, 87% of patients with right-non-coronary cusp fusion showed dilation only of the tubular portion of the ascending aorta.

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