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REVIEW

The year 2013 in the *European Heart Journal – Cardiovascular Imaging*. Part I

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The new multimodality cardiovascular imaging journal, *European Heart Journal – Cardiovascular Imaging*, was created in 2012. Here, we summarize the most important studies from the journal's second year in two articles. Part I of the review will focus on studies in myocardial function, myocardial ischaemia, and emerging techniques in cardiovascular imaging, and Part II will focus on valvular heart diseases, heart failure, cardiomyopathies, and congenital heart diseases.

Keywords multimodality cardiovascular imaging • echocardiography • nuclear • CMR • CT

Introduction

The multimodality *European Heart Journal – Cardiovascular Imaging* has successfully transitioned from an exclusive echocardiographic journal 2 years ago. The journal now serves as an important resource for general cardiologists, specialists in all imaging modalities, and other physicians working in the field of cardiovascular imaging. In two articles, we highlight the most important studies that were published in the journal in 2013. Part I is focused on studies in myocardial function, myocardial ischaemia, and emerging techniques in cardiovascular imaging.

Recommendations from the European Association of Cardiovascular Imaging

In addition to publishing original scientific studies, another important assignment for *European Heart Journal – Cardiovascular Imaging* is to publish position papers, recommendations and expert consensus papers from the European Association of Cardiovascular Imaging (EACVI). In 2013, the EACVI published three recommendations on echocardiographic topics[1–3] and one expert consensus in the field of multimodality imaging.[4]

Myocardial function

During the last few years, it has been apparent that assessment of myocardial deformation by speckle-tracking echocardiography adds important information to functional assessment by ejection fraction (EF) only.[5–7] Knowledge of myocardial function is pivotal in the diagnosis and risk stratification of patients with decreased myocardial function.[8] The most powerful method is left ventricular (LV) global longitudinal strain (GLS) by two-dimensional (2D) speckle-tracking strain. This was further confirmed in a prospective study of 425 patients referred for cardiac surgery.[9] This study demonstrated that GLS was an independent predictor, superior to EF, for early postoperative mortality after adjustment to EuroSCORE.

In an era of multimodality imaging, it is important to know how values compare between imaging modalities. A study by Puntmann *et al.*[10] compared cardiovascular magnetic resonance (CMR) with transthoracic echocardiography (TTE) derived measurements of LV chamber dimensions and wall thickness. In 101 subjects, including 33 patients with dilated LV, good agreement between CMR and TTE, with a three-chamber CMR approach agreeing best with TTE.

Knowledge of myocardial function in cancer survivors after anthracycline treatment is important. A study from Yu *et al.*[11] showed that children had impaired subendocardial circumferential deformation and apical rotation with consequential reduction of transmural circumferential strain and rotation gradients.

Current strain technology by different vendors is not compliant and different absolute strain values have been reported when comparing equipment from two or more vendors. It seems, however, that longitudinal strain is very reproducible, while other deformation directions show poorer reproducibility data. Therefore, the EACVI initiated a standardized approach to deformation imaging jointly

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with the American Society of Echocardiography (ASE).[12] The leaders of the EACVI and the ASE invited representatives from all vendors to participate in a concerted effort to reduce intervendor variability of strain measurement. The experience of the committee so far has demonstrated the potential for co-operation among vendors and the imaging societies. The first report will be published during 2014 in our journal. A recent comparison between 3D strain from two different vendors showed that the agreement was poor except for longitudinal strain assessment[13] and confirmed the need for a standardization process.

Echocardiographic machines and software are constantly improving in regard to image quality, spatial resolution, and more. These improvements might lead to slightly different measurements. It will therefore be important to check normal ranges with newer equipment and software. The aim of the Normal Reference Ranges for Echocardiography Study (NORRE Study) is to obtain a set of 'normal values' for cardiac chamber geometry and function in a large cohort of healthy Caucasian individuals (25–75 years) using both conventional and advanced echocardiographic techniques.[14] The first results were published in the journal in the beginning of 2014.[15] The NORRE Study was performed in 22 laboratories accredited by the EACVI and in one laboratory in the USA accredited by Intersocietal Commission for the Accreditation of Echocardiography Laboratories. The final sample size was 734 normal subjects, in whom M-mode, 2D, and 3D imaging, colour Doppler, pulsed-wave Doppler, pulsed-wave tissue Doppler, and colour tissue Doppler imaging data were assessed. All studies were analysed in a central echocardiographic core laboratory for quantitative analysis. The first article presented a comprehensive analysis of chamber quantification in the large NORRE cohort. Another study provides normative values for right atrial volumes and function measured by 3D and 2D speckle-tracking echocardiography.[16] Assessment of left atrial (LA) mechanical function using speckle-tracking echocardiography was found to be a valid approach and clinically feasible compared with transoesophageal echocardiography.[17]

Assessment and interpretation of diastolic function remain difficult. The introduction of e' was launched as a solution to many of these problems, but controversies about its value persist. The value of e'/a' is not yet determined, but an important contribution to a better knowledge on how to use this ratio was proposed by Kim *et al.*[18] They studied determinants of preserved diastolic function at the lateral annulus in in 1166 consecutive patients with isolated diastolic dysfunction. They found that patients with lateral $e'/a' > 1$ were younger, male, and had a lower prevalence of diabetes and hypertension and showed less evidence of LV diastolic dysfunction and structural remodelling as LV hypertrophy and LA enlargement, than those with a lateral $e'/a' < 1$. It is also controversial whether septal or lateral e' should be the preferred measurement. Galderisi *et al.*[19] showed that the lateral e' was the most accurate parameter to predict increased LV filling pressure in patients with coronary artery disease (CAD).

The complicated structure of the right ventricle (RV) makes it difficult to image with echocardiography. It consists of an inflow part including the tricuspid valve apparatus; a trabecular part that includes pronounced trabeculations; and an outflow tract consisting of a muscular infundibulum, separating the tricuspid from the pulmonary valve.[20]

The evaluation of the RV function has a very significant role as a prognostic factor in patients with myocardial infarction (MI). Three-dimensional echocardiography may offer benefits for RV assessment than 2D echocardiography. In a recent study of 85 patients with RV infarct and also with inferior myocardial infarct,[21] the use of RV s' as a parameter of RV performance was of similar value to discover RV MI as the use of 3D echocardiography.

Knowledge of RV and atrial function is also important in pulmonary hypertension. In a porcine model of RV chronic pressure overload, Guihaire *et al.*[22] found that non-invasive indices of RV function are markers of ventricular–arterial coupling rather than ventricular contractility. The widely used RV fractional area change, tricuspid annular plane systolic excursion, peak systolic tricuspid annular velocity $(s)'$, and the RV myocardial performance index were all found to better correlate to ventricular–arterial coupling as assessed by RV end-systolic elastance/pulmonary arterial elastance.

Ischaemic heart disease

The mortality from atherosclerotic cardiovascular diseases (CVDs) is steadily decreasing in many countries in Western Europe. CVD remains, however, the major cause of death worldwide.[23] This patient group is also the largest group undergoing cardiac imaging procedures in Europe. Traditional risk scores have many limitations and are less accurate in subgroups as diabetics, women, younger patients, and elderly subjects. The role of cardiovascular imaging in detecting subclinical atherosclerosis is increasing and detection of *de facto* initial disease might overcome some limitations of conventional risk stratification.

CMR has an expanding range of indications and clinical applications.[24] It is particularly useful for *in vivo* imaging of MI with methods available for delineation of myocardial oedema, necrosis/fibrosis, and ischaemia. In an *ex vivo* pig model of acute MI, Ubachs *et al.* validated T_2-weighted CMR for the quantification of myocardium at risk against single-photon emission computed tomography (SPECT) and infarct size against a histological reference standard. The study showed that CMR accurately determined area at risk, infarct size, and the derived measure of myocardial salvage.[25]

Several studies published in 2013 confirmed the prognostic value of CMR in risk stratification after acute MI. In 309 patients, 3-month infarct size $\geq$ median by late gadolinium enhancement (LGE) CMR was a strong and independent predictor of outcome with an adjusted hazard ratio of 1.13 per 1% increase.[26] In a second study of 199 patients with acute ST elevation (STE) MI, CMR measures on LA function were independently associated with the outcome.[27]

Other studies highlighted the value of combined low-dose dobutamine and LGE CMR in the prediction of remodelling,[28] which was also the topic of a meta-analysis,[29] and the infarct border zone by LGE in the prediction of hard clinical endpoints.[30] Other CMR outcome measures were reviewed in the *European Heart Journal – Cardiovascular Imaging* by Mavrogeni *et al.*[31]

Assessment and quantification of myocardial blood flow (MBF) by CMR is increasingly used in clinical practice and now enshrined in European guidelines. Ebersberger *et al.* evaluated perfusion CMR at 3 T in 116 patients with suspected or known CAD against the invasive reference standard of pressure-wire-derived fractional flow reserve (FFR). CMR had a sensitivity, specificity, and positive and negative

predictive values at the patient level of 85, 87, 77, and 92%, respectively.[32] In an accompanying editorial, Plein and Motwani discussed the appropriateness of using FFR as an endpoint for non-invasive imaging studies, pointing out that FFR was initially validated against non-invasive imaging. The authors propose that validated imaging tests such as positron emission tomography may be more appropriate endpoints for such studies.[33]

The use of regional GLS by echocardiography in patients with MI has been extensively studied. The superiority of these parameters to wall motion score index and EF in patients with acute STE MI and relatively preserved LV function was recently demonstrated by Cimino *et al.*[34]

Recent echocardiographic machines have the ability to assess deformation parameters from the different myocardial layers. However, the techniques differ between vendors and their clinical value is not established. A study comparing strain-encoded (SENC) CMR and 2D speckle-tracking echocardiography demonstrates that both methods can discriminate between different transmurality categories of MI with similar accuracy.[35] An experimental study could not show superiority of multilayer analyses in the assessment of reperfusion.[36]

Coronary flow reserve (CFR) assessment by transthoracic ultrasound of the left anterior descending (LAD) artery during dipyridamole stress echocardiography has extensively been studied. In a further study, CFR could predict adverse events when added to standard evaluation in patients with acute coronary syndrome (ACS) even in the absence of LAD disease.[37]

Intravascular ultrasound (IVUS) is not routinely in use in most of the patient groups, but has an important role in research. Culprit lesion-positive arterial remodelling by IVUS was associated with a poor long-term prognosis in patients with ACS.[38] This technique may be a clinically useful marker of vulnerable patients.

The use of mitral annular plane systolic excursion measurement is still helpful to evaluate LV systolic function in the case of poor sonographic windows.[39]

It has been commonly believed that reduced myocardial flow reserve (MFR) as a sign of early coronary dysfunction is linked with the subsequent development of CAD. In a study by Uusitalo *et al.*,[40] coronary calcium score (CCS) was measured 11 years after measurement of CFR in 77 healthy, lean, normotensive, non-smoking, and non-diabetic men (mean age 35 years). Thirty-nine percent of subjects had a CCS > 0, but none had clinical symptoms or evidence of ischaemia in stress echocardiography. At baseline, the average CFR was comparable in individuals with or without coronary calcium in the follow-up study, suggesting that coronary reactivity does not predict the presence of coronary calcification in asymptomatic men with very low likelihood of CAD at least with 11 years of follow-up.

Farhad *et al.*[41] investigated the added value of the quantitative MBF and the MFR in predicting major adverse cardiovascular events in patients with suspected myocardial ischaemia. MBF was quantitated using ^{82}Rb and positron emission tomography in 351 patients. During a median follow-up of 624 days, 35 major adverse cardiac events (MACEs) occurred. As expected, MACE rate was higher in patients with ischaemia than those without, but the quantitative MBF had independent prognostic power in addition to standard analysis. The authors concluded that MBF quantification has an added value allowing further risk stratification in patients with normal and abnormal perfusion images.

Adenosine stress CT myocardial perfusion imaging could enable the detection of haemodynamic significance of intermediate coronary stenosis detected by CT coronary angiography (CTCA). An experimental study demonstrated that dynamic dual source CT can quantitatively measure MBF and identify regional reductions of MBF during adenosine stress over a wide range of flow-limiting coronary artery obstruction severities with a good correlation to coronary blood flow obtained with intracoronary flow probe or FFR measurements.[42]

The combined or hybrid imaging of myocardial perfusion is gaining increasing interest and various combinations (CT + SPECT, CT + PET, and CT + CMR) have been investigated. In a study by Schaap *et al.*,[43] hybrid SPECT and CT coronary angiography were evaluated in 98 patients and the results of the hybrid approach were compared with standalone SPECT and CTCA for the diagnosis of significant CAD. Parallel to what has been shown earlier, the sensitivities of SPECT and CT angiography were high (93 and 98%), but the specificities were lower (79 and 62%). Hybrid analysis of SPECT and CT angiography improved the overall performance but especially the specificity (95%) without losing sensitivity (96%). The authors confirmed that the combination of anatomy and function improves the performance of the diagnostic test.

Cardiac CT and CAD

CTCA is a useful tool for the detection and especially ruling out obstructive CAD in selected patients with stable angina pectoris. In a retrospective cohort of 498 stable, symptomatic patients with a low-intermediate probability of CAD referred for either CTCA or exercise-stress test, a frontline diagnostic strategy using CT incurred lower costs related to downstream diagnostic utilization, ambulatory visits, and cardiovascular medication than exercise-stress test-based strategy.[44] Meta-analyses of randomized controlled trials showed that CTCA can be effective and safe as the first imaging test to exclude significant CAD also in low-to-intermediate risk patients with acute chest pain in the emergency department. However, downstream utilization of resources is still a matter of debate since different results in the use of subsequent invasive coronary angiographies and revascularizations have been detected.[45,46]

Evaluation of coronary stents by CTCA remains challenging because partial volume or blooming artefacts from the highly attenuated stent struts cause problems for the delineation of the coronary stent lumen. The study by Gebhard *et al.*[47] suggested that adaptive statistical iterative reconstruction may be useful in CTCA evaluation of these patients by improving intra-stent luminal area, diameter visualization, and image quality compared with the standard filtered back projection reconstruction.

Myocardial bridging, i.e. intramyocardial course of a coronary artery causing it to be covered by a bridge of myocardium, can be detected by CTCA. Rubishtein *et al.*[48] found a relatively high (35%) prevalence of myocardial bridging among a cohort of 334 symptomatic patients referred for CCTA and no obstructive CAD. However, there was no association between myocardial bridging and increased risk for cardiovascular death or MI during 6 years of follow-up.

Cardiac CT has potential to improve cardiovascular risk assessment over conventional risk factors of CAD by the detection of coronary calcium and non-calcified plaque as reviewed by Mureddu

et al.[23] Obesity is associated with the presence of CAD, but the relationships between body mass index (BMI) and conventional risk factors that often co-exist with obesity are complex. In a multi-ethnic, asymptomatic population of 1212 young men, obesity was associated with the presence of coronary artery calcium independently of the conventional risk factors of CAD.[49] Similarly, among 13 874 patients without known CAD undergoing CTCA, individuals with increased BMI had greater prevalence, extent, and severity of CAD that was not fully explained by the presence of traditional risk factors.[50] Furthermore, a higher BMI was independently associated with increased risk of MI during an average of 2.4-year follow-up. In a cohort of 1535 individuals without clinically manifested CAD, the presence of chronic obstructive pulmonary disease in long-term smokers was associated with that of subclinical CAD measured by CCS independently of traditional cardiovascular risk factors.[51] Although CAD is one of the underlying mechanisms of atrial fibrillation, Den Uijl *et al.*[52] found that in the CTCA prior to radiofrequency catheter ablation for atrial fibrillation, obstructive CAD or the presence of coronary atherosclerosis was not associated with a higher risk for atrial fibrillation recurrence after ablation.

Low-attenuation plaque has been widely investigated as a marker for atherosclerotic plaque vulnerability. Comparison with histology in explanted hearts showed that low-attenuation plaque in CTA can be used as a marker for lipid core plaque, i.e. plaque with a large lipid/necrotic core.[53] However, the (semi)-automated plaque assessment tools based on measurement of the area between the inner and outer vessel walls are prone to errors if cross-sections without any visually apparent plaque are included in the image analysis.

Recent imaging techniques

Pocket-size imaging devices

The miniaturization and improvements in technology have led to the development of pocket-size imaging devices (PSIDs) with good image quality and excellent portability. PSIDs are now widely available, and their potential role in a hospital environment has been investigated but still remains undefined.[54] One study demonstrated that PSID can provide a valuable alternative to TTE in the presence of focused clinical questions and can provide an efficient way of delivering a ward-based transthoracic echo service. Another study showed that the use of PSID after only brief bedside training greatly improved the clinical diagnosis of medical students and junior doctors, over and above history, physical examination, and ECG findings.[55] A third study showed that PSID used by a trained cardiologist has good diagnostic accuracy in the emergency setting compared with a high-end echocardiograph.[56]

Contrast echocardiography

Myocardial contrast echocardiography has many advantages and allows better assessment of wall motion, LV opacification and in many patients myocardial perfusion.[57] One major disadvantage is the price of the contrast agents. The use of contrast agents in the UK is, however, limited to $<4\%$ of all transthoracic echocardiographic studies.[58] Major barriers to the implementation of contrast use are the absence of cardiac imaging specialists directly supervising echocardiography departments and the training of sonographers to independently administer contrast. A new area for contrast was

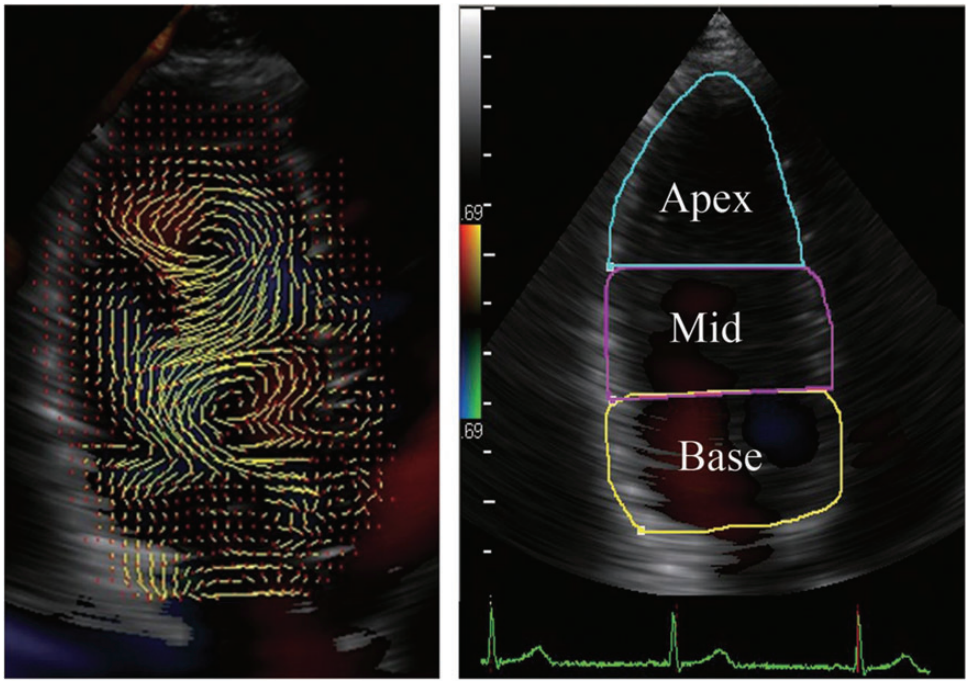

Figure 1: Images of VFM. Velocity vectors were identified without angle dependency (left panel). The left ventricle was divided into three segments: base, mid, and apex (right panel).[59]

demonstrated by Rutz *et al*. They showed that contrast could assist in detecting chronic heart transplant rejection, i.e. cardiac allograft vasculopathy.

New imaging techniques

There is growing interest for intracardiac flow visualization. Recently developed vector flow mapping (VFM) enables evaluation of local flow dynamics without angle dependency.[59]

Retarded apical kinetic energy fluid dynamics could be detected using VFM and were shown to be closely associated with LV spherical remodelling in patients with high LA pressure (*Figure 1*).

Optical coherence tomography (OCT) is a recently developed intravascular imaging modality that allows detailed assessment of atherosclerotic plaque morphology, coronary stents, and abnormal tissue reactions associated with stent implantation. Kawamori *et al.*[60] found that most cases of stent malapposition with a short distance between the strut and vessel wall, thrombus, tissue prolapse, or minor stent edge dissection improved during the 8-month follow-up. Park *et al.*[61] found that the presence of intra-stent thrombi was seen as often in patients with or without aspirin/clopidogrel resistance 195 days after implantation of a drug-eluting stent. A study of Habara *et al.*[62] revealed that the OCT morphological characteristics of drug-eluting stent restenotic tissue varied depending on time after stent implantation. Heterogeneous appearance of intima, thin-cap fibroatheroma-like pattern image, and intra-intimal microvessels were increased from the early (<1 year) to the very late (>3 years) phase. Matsuo *et al.*[63] found that circulating levels of malondialdehyde-modified low-density lipoprotein, which is an oxidized low-density lipoprotein, were associated with the presence of thin-cap fibroatheroma plaque morphology in OCT in patients with either stable angina pectoris or ACS.

Conclusion

This review has summarized the studies in myocardial function, myocardial ischaemia, and emerging techniques published in 2013 in the *European Heart Journal – Cardiovascular Imaging*. Part II of the review will focus on valvular heart diseases, heart failure, cardiomyopathies, and congenital heart diseases.

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