

# The year 2013 in the *European Heart Journal* – *Cardiovascular Imaging*: Part II

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The new multi-modality 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 has summarized studies in myocardial function, myocardial ischaemia, and emerging techniques in cardiovascular imaging. Part II is focussed on valvular heart diseases, heart failure, cardiomyopathies, and congenital heart diseases.

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## Introduction

The multi-modality *European Heart Journal and Cardiovascular Imaging* has successfully transitioned from an exclusive echocardiographic journal two 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 II is focussed on valvular heart diseases, heart failure, cardiomyopathies, and congenital heart diseases.

## Valvular heart disease

With the growth of the elderly population, valvular heart disease (VHD) has become an important cause of cardiovascular morbidity and mortality.<sup>1</sup> Multi-imaging modality plays a major role in the diagnosis, management, and risk stratification of patients with VHD.<sup>2</sup> Doppler echocardiography is crucial to initial and longitudinal assessment of patients with VHD. It provides detailed anatomic and functional information, and clarifies the mechanisms of regurgitation and the potential for valve repair. Mitral valve prolapse (MVP) is one of the most frequent valve lesions requiring surgery. Clefts in the mitral leaflets are known to represent a risk factor for early failure of mitral valve repair. Ring *et al.*<sup>3</sup> showed that clefts are frequently seen in MVP and may play an important role in the

development of MVP. Lancellotti *et al.*<sup>1</sup> have reported the recommendations for the echocardiographic assessment of native VHD. The key points were: (i) the evaluation of valvular regurgitation requires the use of different echocardiographic modalities, including 3D echocardiography, when available; (ii) the evaluation should integrate multiple parameters to assess its severity—qualitative, semi-quantitative, quantitative, chronicity of the disease—and should be combined with clinical data. The assessment of tricuspid regurgitation (TR) remains challenging because standards for determining TR severity are less robust than for left-sided valvular regurgitation. In fact, algorithms for relating colour flow-derived parameters to TR severity are less well developed. Adjunctive parameters may help to consolidate about the severity of TR. Mutlak *et al.*<sup>4</sup> have reported that excessive respiratory changes in Doppler measurements of TR systolic velocities ( $\geq 0.6$  m/s) were a specific sign of severe TR. Left-ventricular (LV) ejection is known to underestimate the extent of intrinsic myocardial dysfunction in patients with VHD.<sup>5</sup> 2D speckle-tracking imaging of myocardial deformation has gained growing interest in VHD and detects more accurately the presence of subtle LV myocardial dysfunction.<sup>6</sup> Layer-specific strain analysis enables to evaluate myocardial deformation from endocardial to epicardial myocardial layers. Kaneko *et al.*<sup>7</sup> showed that transmural and inner-half strains but not outer-half strains were reduced in patients with chronic severe aortic regurgitation and preserved LV ejection fraction; these parameters improved after aortic valve surgery suggesting that they could be used to determine the

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optimal timing for surgery. In patients with primary mitral regurgitation (MR), Witkowski *et al.*<sup>8</sup> reported that the use of contemporary indication criteria for mitral valve repair (MVR) was associated with a low incidence of long-term post-operative LV dysfunction. Interestingly, they showed that a reduced pre-operative global longitudinal strain (GLS:  $-19.9\%$ ) emerged as a powerful independent predictor of post-operative LV systolic dysfunction. In secondary MR, the relationship between left atrial (LA) function and recurrent MR after MVR has been poorly investigated. Van Garsse *et al.*<sup>9</sup> observed an irreversible impairment in LA reservoir function due to reduced compliance in patients with recurrent MR after MVR. The assessment of LA strain can be used as an additional finding to identify patients who are unlikely to benefit from mitral annuloplasty. Of note, in patients with chronic primary MR, LA becomes more spherical with increasing severity of MR, suggesting a decrease in LA eccentricity index in relation to the decreased LA systolic function.<sup>10</sup> In aortic stenosis (AS), the increase in LV afterload does not only result from outflow obstruction but also from reduced systemic arterial compliance.<sup>11</sup> In these patients, the circumferential ascending aortic strain estimated by 2D speckle tracking is reduced and correlates with stroke volume index and LV afterload-related variables such as valvulo-arterial impedance and aortic valve area.<sup>12</sup> Garcia *et al.*<sup>13</sup> demonstrated in 71 patients with AS that cardiac magnetic resonance (CMR) may be an alternative to echocardiography, e.g. in patients with poor acoustic windows, for the evaluation of aortic valve kinetics (valve opening and closing slope) with low observer variability. Bicuspid aortic valve (BAV) represents the most frequent congenital cardiac abnormality resulting in premature valvular degeneration and aortic dilatation. Meierhofer *et al.*<sup>14</sup> showed using CMR that wall shear stress and flow patterns in the ascending aorta in patients with BAVs differ significantly from tricuspid aortic valves. The significantly higher shear stress may have an impact on the development of aortic dilation in these patients. Infective endocarditis remains a dangerous condition in which imaging plays a key role. Identification of prosthetic valve endocarditis (PVE) remains challenging. The use of radiolabelled leucocyte scintigraphy carries an excellent positive predictive value for the detection of PVE in patients with inconclusive echocardiography.<sup>15</sup> Therefore, the intensity of radiolabelled leucocyte accumulation in the perivalvular area represents an interesting marker of local infectious activity and extension. Selection of candidates for mitral valve/transcatheter aortic intervention (TAVI) is complex and often involves a multi-modality imaging strategy. Echocardiography is the primary imaging modality used at all stages of the percutaneous MitraClip and TAVI procedures, complementing fluoroscopy. This has been elegantly addressed in two review articles.<sup>16</sup> MitraClip therapy has proven successful in reducing the degree and severity of MR. Whether MR downgrading relates to immediate change in mitral ring geometry is unknown. Schmidt *et al.*<sup>17</sup> showed a significant reduction in mitral annulus size in the antero-posterior region but not in the latero-medial region after MitraClip implantation in patients with secondary but not primary MR. Tsang *et al.*<sup>18</sup> reported that AS can affect the mitro-aortic coupling. Moreover, TAVI does not result in recovery of mitral valve structure/function as the prosthetic aortic ring compresses the calcified aortic valve in the aortic-mitral fibrous continuity. These features have implications in the future TAVI valve development. Maffessanti *et al.*<sup>19</sup> were able to compare mitral and tricuspid valve morphology and dynamics

in the same patients and in the same conditions using a novel semi-automatic algorithm based on cine CMR images for point tracking and 3D reconstruction. The methodology was feasible and accurate when compared with manual assessment and holds great promise.

## VHD and cardiac computed tomography

Coronary computed tomography (CT) angiography (CTCA) may be considered as an alternative to invasive coronary angiography to rule out significant coronary artery disease (CAD) before non-coronary cardiac surgery. An analysis of Catalan *et al.*<sup>20</sup> was based on the results of four European studies and indicated that in experienced hands, the use of initial pre-operative CTCA could have avoided many invasive coronary angiographies and resulted in a more cost-effective strategy than the conventional invasive coronary angiography strategy.

## Heart failure

In 2013, several studies have addressed the role of imaging in heart failure (HF). Dobutamine stress echocardiography is widely used to evaluate the presence and extent of myocardial functional reserve in HF patients. The relationship between dobutamine-induced changes in long-axis function as evaluated by tissue Doppler mitral annular velocities ( $s'$ ) and exercise capacity was reported by Ciampi *et al.*<sup>21</sup> The weaker the change, the weaker the contractile recruitment, and the lower the exercise tolerance. LV systolic shortening velocity was also closely associated with invasive measurements of cardiac output, whereas changes in  $E/e'$  ratios did not correlate with pulmonary capillary wedge pressure. This latter observation warrants some caution in converting changes in  $E/e'$  into changes in LV filling pressure.<sup>22</sup> Conversely, changes in  $E/e'$  during exercise are well correlated with exercise capacity;  $E/e'$  has greater specificity for raised filling pressure and could be used to rule out cardiac reasons as a cause for dyspnoea on exertion.<sup>23</sup> Reduced peak oxygen uptake (peak  $VO_2$ ) is one of the most important predictors of cardiovascular events in HF. In healthy subjects, coronary flow reserve (CFR) is well correlated with peak  $VO_2$ . In HF, CFR,  $E/e'$  and  $s'$  but not traditional measures of LV systolic function (i.e. LV ejection fraction) are correlated with peak  $VO_2$ . CFR is thus likely to be a limiting factor in functional capacity in HF.<sup>24</sup> Abnormal glucose metabolism as estimated by oral glucose tolerance testing is also associated with reduced LV contractile reserve and exercise tolerance in HF. Egstrup *et al.*<sup>25</sup> have underscored such an association in 161 patients with systolic HF. This observation may offer one explanation for the excess mortality related to diabetes in HF. Preliminary data suggested that the persistence of vortex (echo-contrast particle image velocimetry) from late diastole into isovolumic contraction could be a marker of the fluid continuum of the cardiac cycle and help coupling diastole to systole. The change in vortex strength may have prognostic value in HF.<sup>26</sup> The most frequent clinical manifestation of anti-cancer drugs-related cardiotoxicity is symptomatic or asymptomatic LV dysfunction that can progress to HF. Anthracycline-induced cardiomyopathy has been associated with the worst prognosis. Stoodley *et al.*<sup>27</sup> described an immediate alteration in LV diastolic function that correlated with LV systolic dysfunction after the administration of therapeutic doses of anthracycline chemotherapy. Therefore, recognition of altered diastolic function could serve as an indicator of altered LV systolic function, and

thereby identifying a subset of patients who should benefit from a closer follow-up. LV dyssynchrony is frequent in HF and largely affects response to cardiac resynchronisation therapy.<sup>28</sup> To date, no standardized methods have been shown to be superior to another to evaluate LV dyssynchrony. Beyond differences between methods, variability could also result from the vendor-specific software used to estimate the degree of mechanical dispersion. Aly *et al.*<sup>29</sup> compared TomTec and QLAB software packages for 3D echocardiographic assessment of LV dyssynchrony including their ability to predict response to CRT. They concluded that these 3D software packages are not interchangeable; TomTec software seemed more accurate than QLAB for the prediction of response to CRT. Obtaining an optimal LV lead position in CRT can be challenging. Shetty *et al.*<sup>30</sup> used CMR to guide LV lead positioning by overlaying three latest activated segments with <50% scar on late-gadolinium enhanced images (LGE) on to live fluoroscopy. Long-term response to CRT was improved with the use of this technique. After CRT implantation, long-term survival depends on several factors; the reduction in LV end-systolic volume is a better predictor when compared with the improvement in clinical status.<sup>31</sup> However, mechanical radial discoordination rather than mechanical dyssynchrony carried incremental predictive value over classical baseline characteristics (i.e. QRS morphology) for response to CRT.<sup>32</sup> LV dyssynchrony can vary during exercise.<sup>33</sup> In patients with LV systolic dysfunction, dynamic LV dyssynchrony is correlated with dynamic MR and exercise intolerance. In patients with dilated cardiomyopathy and narrow QRS, the dynamic increase in LV dyssynchrony during exercise echocardiography also emerged as a strong predictor of less favourable event-free survival.<sup>34</sup>

## Cardiomyopathy

The measurement of myocardial strain and strain rate can be obtained by different imaging methods. Interestingly, decreased strain parameters may identify pre-clinical ventricular dysfunction at a stage when conventional studies remain normal. Both colour Doppler myocardial imaging and 2D speckle-tracking analysis have been used in a series of obese children and adolescents. Compared with non-obese, sex- and age-matched controls, LV longitudinal strain by both methods was lower, in the absence of other comorbidities, although LV ejection fraction was not different between the two groups.<sup>35</sup> Another study confirmed these findings, indicating that childhood obesity may be responsible for early alteration in both longitudinal and circumferential LV strain.<sup>36</sup>

Myocardial 2D strain echocardiography was measured in children with acute lymphoblastic leukaemia treated with anthracycline therapy. All strain parameters—global longitudinal, radial, and circumferential strains—decreased significantly. N-terminal pro-brain natriuretic peptide was not related to strain parameters and cardiac troponin T was not a predictor of abnormal strain 1 year after anthracyclines, indicating the importance of combining strain parameters and cardiac biomarkers in this setting.<sup>37</sup>

In a cohort of children with Kawasaki disease, systolic LV myocardial strain and strain rate were obtained by velocity vector imaging. Routine echocardiographic measurements were normal. Compared with controls, patients had lower GLS and strain rate, particularly in

patients with coronary artery dilation and resistance to treatment with intravenous immunoglobulin.<sup>38</sup>

The experience with 3D speckle-tracking echocardiography (STE) is increasing. This method may be a more accurate tool than 2D STE in particular when a marked translational motion of the heart inside the chest occurs during the cardiac cycle, such as in transplant recipients. This was confirmed in a series of 36 heart transplant recipients. GLS was lower with 3D STE when compared with 2D STE: the inferolateral wall was a source of variation between the two methods. 3D—but not 2D STE-derived longitudinal strain—was independently associated with NYHA class, suggesting a clinically relevant relationship between functional status and myocardial mechanism in these patients.<sup>39</sup>

The clinical course of patients with hypertrophic cardiomyopathy (HCM) can be influenced in part by subendocardial ischaemia and atrial fibrillation. Myocardial ischaemia is a major cause of chest symptoms in these patients and its assessment remains difficult. Subendocardial perfusion abnormality may be reflected by transient LV cavity dilation during exercise, which can be quantified by Tc-99m tetrofosmin scintigraphy. The results of this method have been compared with ultrasonic tissue characterization using cyclic variation of integrated backscatter (CV-IB) and LGE CMR. Right and left halves of the ventricular septum were analysed. CV-IB in the right halves of the ventricular septum was predominant in patients with subendocardial ischaemia, whereas a reverse predominance was observed in patients without subendocardial ischaemia. LGE CMR was not associated with subendocardial ischaemia, suggesting that repetitive subendocardial ischaemic episodes did not induce myocardial fibrosis in patients with HCM.<sup>40</sup>

The identification of HCM patients at risk of paroxysmal atrial fibrillation is clinically important. The combination of enlarged LA antero-posterior diameter, decreased peak strain rate of the LA lateral wall in the reservoir phase, and a prolonged P-wave duration in the Z-lead yielded an area under the curve of 0.90 for identifying patients with documented episode(s) of atrial fibrillation.<sup>41</sup>

Several characteristics are known to be useful for predicting cardiac events in HCM patients: HCM-related death, HF, stroke, or worsening of symptoms. A tissue Doppler imaging study showed that a short deceleration time of E wave (<197 ms) and a high septal  $E/e'$  (>9.65) are independent predictors of cardiovascular events in HCM patients.<sup>42</sup>

Mitochondrial disease is associated with morphological abnormalities and HF and early detection is important for risk stratification. Bates *et al.*<sup>43</sup> showed that CMR detects functional (strain parameters) and metabolic (measured with MR Spectroscopy) abnormalities in carriers of the m.3243A>G mutation without known cardiac involvement. Importantly, the mutation load correlated with abnormalities, in particular the LV mass index.

The differential diagnosis between Tako-Tsubo cardiomyopathy (TTC) and acute anterior infarction is challenging before coronary angiography. Before coronary angiography, left anterior descending artery distal flow by transthoracic Doppler echocardiography was visible in all patients with TTC and in only 36% of patients with acute myocardial infarction. The combination of distal flow and the pattern of wall motion characteristics provided a diagnostic accuracy of 86%. In addition, CFR assessed within 1 day after admission was less

severely impaired in the TTC group when compared with the acute infarction group.<sup>44</sup>

The development of multi-dimensional flow assessment and derived estimates of kinetic energy (KE) by CMR is beginning to demonstrate clinical utility. In 10 patients with dilated CM, Erikson et al.<sup>45</sup> demonstrated changes in the diastolic flow route in the LV and changes to inflow KE compared with 10 control subjects. These observations are potential subclinical markers of LV dysfunction.

Cardiovascular complications of radiotherapy include pericardial, myocardial, valve, and CADs. The role of multi-modality imaging has been proposed and reported in the Journal from the European Association of Cardiovascular Imaging and the American Society of Echocardiography.<sup>46</sup>

## Congenital heart disease

Multi-modality imaging is essential for the diagnosis and follow-up of congenital heart disease. A European certification process for echocardiography of congenital heart disease has been endorsed by the European Association of Cardiovascular Imaging formerly the European Association of Echocardiography, the Association for European Paediatric and Congenital Cardiology, and the Grown-up Congenital Heart Working Group of the European Society of Cardiology. The flowchart of certification includes several steps for candidates: initiation of the process, log of cases, registration for examination, certification examination, submission of additional documentation, and confirmation of certification. This process has proved feasible.<sup>47</sup>

Like echocardiography, CMR has become an essential tool in the management of patients with congenital heart disease. In addition to morphological and functional assessment, CMR can demonstrate myocardial scar and fibrosis and methods for estimation of interstitial myocardial volume based on T1 mapping have been developed. In patients with Tetralogy of Fallot (TOF), Munkhammar et al.<sup>48</sup> showed with LGE CMR that fibrosis of the RVOT is strongly associated with restrictive RV physiology.

Using T1 mapping, Plymen et al.<sup>49</sup> reported that in adults who had undergone atrial redirection surgery for transposition of the great arteries (TGA), CMR showed interstitial expansion in the interventricular septum compared with age- and sex-matched healthy volunteers. Although it was not possible to measure the interstitial volume of the right ventricle in this study, its findings go some way in explaining the long-term consequences of atrial redirection surgery.

Although anatomic correction of complete TGA by arterial switch operation is successful, a significant proportion of patients have impaired exercise capacity. Dynamic changes in LV contractility have been assessed by the measurement of LV myocardial isovolumic acceleration at rest and at different heart rates during exercise, leading to the determination of LV force–frequency relationship (FFR). The curve of patients was shown to be flattened compared with a positive FFR reference curve observed in a healthy paediatric cohort. LV contractile reserve was worse in patients having variant coronary arterial anatomy.<sup>50</sup>

Patients with hypoplastic left heart syndrome may require tricuspid valve repair for correcting tricuspid valve insufficiency, a consequence of important structural abnormalities of the valve. Although 2D echocardiography can identify several of these

abnormalities, echocardiography is sensitive to detect leaflet motion abnormalities but not leaflet structural abnormalities, leading to significant discrepancies between echocardiographic and surgical findings.<sup>51</sup>

Right atrial anatomy is complex. Catheter-based interventions for right atrial structural or electrical disorders require a good understanding of right atrial anatomy. Anatomical details can be provided by 3D transoesophageal echocardiography, cardiac computed tomography or magnetic resonance imaging. A review article has described the normal anatomy and variants of right atrial structures.<sup>52</sup> Another review article has described the peri-interventional echocardiographic assessments for device closure of interatrial communications. Intracardiac echocardiography is safe and spares the patient the risks and discomfort of general anaesthesia, but the costs of catheters remain an important limitation.<sup>53</sup>

## Conclusion

This review has summarized the studies in VHDs, HF, cardiomyopathies, and congenital heart diseases published in 2013 in the *European Heart Journal - Cardiovascular Imaging*.

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