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The year 2017 in the European Heart Journal – Cardiovascular Imaging. Part I --Manuscript Draft--

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Abstract:	<p>The European Heart Journal – Cardiovascular Imaging was launched in 2012. It has gained an impressive impact factor of 8.336 during its first 6 years and is now established as one of the top 10 cardiovascular journals in the world and the most important cardiovascular imaging journal in Europe.</p> <p>The most important studies published in the journal in 2017 will be highlighted in 2 reports. Part I will focus on studies about myocardial function, coronary artery disease and myocardial ischaemia, emerging techniques and applications in cardiovascular imaging, while Part II will focus on valvular heart disease, heart failure, cardiomyopathies, and congenital heart disease.</p>

The year 2017 in the European Heart Journal – Cardiovascular Imaging. Part I.

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The European Heart Journal – Cardiovascular Imaging has successfully evolved as a multimodality imaging journal during its first 6 years. The journal has now an important role as a significant resource for cardiologists, specialists in all imaging modalities, and other physicians working in the field of cardiovascular imaging. The tradition of highlighting the most important studies that were published in the previous year is continued.^{1,2} The most important papers published in the journal in 2017 will be summarized in two articles. Part I is focused on studies about normal reference ranges and myocardial function, coronary disease and myocardial ischaemia, and emerging techniques and applications in cardiovascular imaging.

Normal reference ranges and myocardial function

Normal ranges for 2D echocardiographic measurements of left ventricular (LV) strain from 549 healthy volunteers were published from the European Association of Cardiovascular Imaging (EACVI) NORRE study. The lowest expected values of LV strains (calculated as ± 1.96 standard deviations from the mean) were -16.7% in men and -17.8% in women for longitudinal strain, -22.3% and -23.6% for circumferential strain, and 20.6% and 21.5% for radial strain, respectively. Longitudinal strain decreased with age whereas the opposite occurred with circumferential and radial strain. Male gender was associated with lower strain for longitudinal, circumferential, and radial strain. Inter-vendor differences were observed for circumferential and radial strain despite the use of vendor-independent software. Importantly, no inter-vendor differences were noted in longitudinal strain.³

Analysing data from 440 healthy subjects enrolled in the same NORRE study, the 3D echocardiographic reference ranges for normal LV volumes, function and strain were reported. Upper limits of LV end-diastolic and end-systolic volumes were larger in men (97 and 42 mL/m²) than in women (82 and 35 mL/m²; $P < 0.0001$) and lower limits of LV ejection fraction were higher in women than in men (51% vs. 50%; $P < 0.01$).⁴

Morris and coworkers analysed a large cohort of 238 healthy subjects and 642 patients with heart failure with the purpose of determining the normal range and the usefulness of right ventricular (RV) systolic strain to detect subtle RV systolic abnormalities using 2D speckle-tracking echocardiography. The normal range of RV systolic strain in the healthy subjects was as follows: RV global strain $-24.5 \pm 3.8\%$ and RV free wall strain $-28.5 \pm 4.8\%$ (lowest expected values -17 and -19% , respectively).⁵

Another report from the NORRE study provides normal values of proximal aorta dimensions as assessed by echocardiography. Saura et al reported reference ranges for different anatomical levels using different measurement conventions at different times of the cardiac cycle. Age, gender, and body size were significant determinants of aortic dimensions.⁶

Schaaf et al aimed to evaluate whether 2D and 3D echocardiographic (2DE and 3DE) assessment of left atrial anatomy and function was able to identify patients with paroxysmal atrial fibrillation. Anatomical and functional left atrial remodelling assessed by 2DE and 3DE was independently and strongly associated with paroxysmal atrial fibrillation, suggesting that these parameters can help identify this arrhythmia.⁷

Ternacle et al assessed the time course and mechanisms of metabolic and cardiac modifications induced by short-term high-fat diet in wild-type mice. The high-fat diet promoted early metabolic and cardiac dysfunctions, and adipose and myocardial tissues remodelling.⁸

Maufrais et al analysed the underlying mechanisms of LV and RV functional alterations during several days in high-altitude hypoxia. High-altitude exposure impaired LV diastolic function with the greatest effect observed at day 2, concomitantly with the occurrence of acute mountain sickness. The LV early filling impairments resulted from an increased RV afterload, a decrease in LV filling pressure and a delayed LV untwist.⁹

Two cardiovascular magnetic resonance (CMR) studies provide new insights into different forms of pathological LV hypertrophy. Arenja and colleagues assessed the diagnostic value of myocardial contraction fraction to distinguish left ventricular hypertrophy (LVH) from controls and then specifically to distinguish different aetiologies of LV hypertrophy. The functional measure of myocardial contraction fraction had an excellent area under the curve of 0.96 to detect LVH ranging from 0.92 for hypertensive heart disease, 0.94 for transthyretin amyloidosis, 0.97 for hypertrophic cardiomyopathy and 0.99 for light chain amyloidosis. Interestingly, cut-off values of myocardial contraction fraction <50% allowed the identification of patients with cardiac amyloidosis.¹⁰ Kozor and colleagues included also LVH caused by hypertension, cardiac amyloidosis and hypertrophic cardiomyopathy, but additionally also patients with Fabry disease and aortic stenosis. They found disproportionate hypertrophy of LV papillary muscle in hypertrophic cardiomyopathy and patients without and with LVH linked to Fabry disease.¹¹

A substudy of the Multi-Ethnic Study of Atherosclerosis (MESA) included 536 participants with diabetes mellitus with 11.4 years of follow-up for incident cardiovascular disease. In a multivariate analysis, CMR determined left atrial minimum volume and left atrial function were found to be of prognostic value in these participants free of cardiovascular disease at baseline.¹²

Coronary artery disease and myocardial ischemia

Cardiac computed tomography and CMR led the field of research in the area of imaging in coronary artery disease in 2017. Still, many valuable documents have been published on the role of ultrasound imaging as a first tool for diagnosing and assessing myocardial ischemia.

In an interesting study, consecutive patients with suspected stable angina, without known coronary artery disease (CAD) were randomized to exercise ECG stress test (194

patients), or exercise echocardiography (191 patients). Exercise echocardiography was more effective and demonstrated superior cost-saving compared with exercise ECG when used as the initial investigation for the evaluation of CAD in patients with new-onset suspected stable angina without known CAD.¹³

In another study, dobutamine stress echocardiography was performed in 250 patients with angina who were afterwards diagnosed with significant coronary artery disease ($\geq 50\%$ stenosis in the left main and/or $\geq 70\%$ in other arteries) at coronary angiography. The study showed that in all phases of dobutamine stress echocardiography global and regional LV peak systolic longitudinal strain were lower in patients with diabetes, independently of the presence of significant coronary artery disease. The diabetic cardiomyopathy is altering the strain values independently of any significant epicardial coronary artery disease.¹⁴

Cortigiani et al sought to investigate the capability of power/mass assessed at peak of dobutamine stress echocardiography to predict mortality in patients with ischaemic cardiomyopathy and no inducible ischaemia. Power/mass assessed allowed effective prognostication in these patients who were test result negative by wall motion criteria. In particular, a peak-stress power/mass ≤ 50 W/100 g was a strong and multivariable predictor of mortality.¹⁵

A large multi-center study has been conducted in Israel on 605 patients, of which 74 (12.2%) had acute coronary syndromes (ACS). The aim was to determine whether 2D-longitudinal strain analysis could assist in the triage of patients with chest pain in the emergency department. Acute coronary syndrome was not among the independent predictors of abnormal 2D longitudinal strain. The area under the curve for global longitudinal strain (GLS) to predict the ACS was only 0.6. Thus, in this study GLS was not a useful tool to rule out ACS in the emergency department.¹⁶

An important recommendation document was published by the EACVI about the modern use of contrast echocardiography.¹⁷ The use of contrast in echocardiography has extended beyond the assessment of cardiac structure and function to the evaluation of myocardial perfusion. The document, based on clinical trials, randomized and multicentre studies and published clinical experience, established clear recommendations for the use of contrast in various clinical conditions with evidence-based protocols.¹⁷

Coronary CT angiography (CTA) is an excellent imaging modality to characterize and quantify coronary atherosclerotic plaques. Adverse plaque characteristics (low plaque attenuation, positive remodelling, napkin-ring sign and spotty calcium) and global coronary plaque burden as assessed by coronary CTA have been associated with future cardiac events. Several studies published in the journal last year consistently demonstrated the long-term prognostic value of adverse plaque characteristics and global plaque burden.

A study on 1469 patients with an overall follow-up time of 7.8 years showed that the prognosis is excellent over a long-term period if coronary CTA is negative and that low-attenuation plaque defined as any voxel with <60 HU and the presence of napkin-ring sign are the most powerful predictors of cardiovascular events even after adjusting for conventional risk factors and CT stenosis severity.¹⁸ In line with these findings a smaller study, with a follow-up time of 8.2 years, concluded that positive remodelling, napkin-ring sign, low attenuation plaque and increased plaque burden are associated with increased risk among patients with non-obstructive CAD.¹⁹ Similarly, a case control study showed that total non-calcified and low-attenuation plaque volumes predict cardiac death during a mean follow-up time of 5 years.²⁰ The CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes: An InteRnational Multicenter) study is one of the largest prospective coronary CTA registry collecting clinical, procedural, and follow-up data of patients undergoing coronary CTA for clinically indicated reasons. The authors demonstrated that the

CONFIRM score combining established clinical risk parameters and the presence of non-obstructive proximal partially calcified or calcified plaques as well as proximal lumen narrowing of $\geq 50\%$ permits a significantly improved prediction of mortality over clinical risk scores for >5 years after coronary CTA.²¹ Importantly, these findings were consistent in a large variety of patient subgroups and were independent of aspirin and statin treatment at baseline. In addition, the CONFIRM investigators demonstrated that early revascularization after coronary CTA is associated with a reduced mortality at 5 years in patients with high-risk CAD. However, they did not find a benefit from early revascularization in patients with low-risk CAD.²²

The prevalence of obstructive CAD in symptomatic patients with zero-coronary calcium score and the associated long-term risk remain controversial. The clinical outcomes of this challenging patient population were investigated in a study on 3914 patients with a follow-up time of 5.2 years. The study demonstrated that zero calcium score has a negative predictive value of 99.5% for excluding $>70\%$ stenosis on coronary CTA and the annual event rate was 0.3% for those with zero compared with 1.2% for non-zero calcium scores. Based on these observations it seems that the presence of non-calcified plaque on coronary CTA in patients with zero calcium score does not affect prognosis, therefore zero calcium score may be a safe ‘gatekeeper’ in this patient cohort obviating the need for additional expensive tests.²³

The last year brought several interesting and innovative projects in the field of functional assessment of CAD with cardiac CT. The evidence supporting CT based FFR simulation (FFRCT) and myocardial perfusion imaging (MPI) is accumulating.²⁴ It has been demonstrated by several large multicentre trials that FFRCT has high diagnostic performance in stable CAD. A recent study has analysed the diagnostic performance of FFRCT, in patients with hypertension and diabetes, who are at risk of microvascular impairment. The

investigators found that FFRCT is a robust method in a broad stable CAD population, including patients at high risk for microvascular disease.²⁵ Another study has investigated the utility of FFRCT in the follow-up of patients with second iteration bioresorbable vascular scaffold (BVS). Cardiac CT was performed at 18 months and 72 months in 53 patients with BVS. Interestingly, in 39 patients with serial coronary CTA analyses, the minimal luminal area increased significantly from the first to the second follow-up coronary CTA (delta = 0.80mm^2 , $P=0.002$) (Figure 1). The study showed that long-term serial coronary CTA with FFRCT assessment of bioresorbable scaffold is feasible and the results demonstrated late lumen enlargement with the persistence of normalization of the FFRCT.²⁶ Stress CT perfusion in patients with obstructive CAD at coronary CTA in the same setting reduced the referral rate for invasive coronary angiography and revascularization.²⁷ Importantly, the authors demonstrated that the occurrence of major cardiovascular events at 12 months follow-up in patients with normal stress CTP is low, thus deferral of invasive coronary angiography based on negative stress CTP seems to be a safe diagnostic strategy with an extra effective radiation dose of 3.1 (2.3–4.4) mSv ($k=0.014\text{ mSv/mGy/cm}$). The same group has investigated the influence of heart rate, medication use, and patient characteristics on image interpretability of stress myocardial CTP examinations and concluded that increasing heart rate during the acquisition of adenosine stress myocardial CTP is related to worse image interpretability.²⁸

Another challenging clinical scenario is represented by patients with stable chest pain and absence of obstructive CAD, which raises the suspicion of coronary microvascular dysfunction (CMD). In a prospective study, 189 patients with intermediate pre-test probability of CAD underwent hybrid imaging with coronary CTA and quantitative ^{15}O -water PET perfusion imaging followed by invasive coronary angiography, and assessment of fractional flow reserve. The study demonstrated that CMD identified as abnormal vasodilator

capacity by PET perfusion imaging exists in 9% of patients with stable chest pain and suspected CAD. Importantly, CMD without any coronary atherosclerosis was rare (1%) in this population (Figure 2).²⁹ On the other hand, chronic coronary total occlusions (CTO) are quite common and are encountered in up to one-third of patients with known or suspected CAD. A ¹⁵O-water PET study of 76 consecutive patients with CTO has demonstrated that even in the presence of angiographically well-developed collateral arteries, the vast majority of CTO patients with preserved LVEF display significantly impaired perfusion. These results suggest that collateral function during increased blood flow demand in viable myocardium is predominantly insufficient and that revascularization should be considered.³⁰ The importance of respiratory phase matching between single-photon-emission computed tomography myocardial perfusion imaging (SPECT-MPI) and low-dose computed tomography (CT) for attenuation correction (AC) was assessed in a prospective study. Forty patients underwent 1-day ^{99m}Tc-tetrofosmin pharmacological stress/rest SPECT-MPI using a cadmium–zinc–telluride gamma camera. Low-dose CT for AC was performed at deep-inspiration breath-hold. SPECT-MPI was acquired once with free-breathing (FB) and repeated at deep-inspiration breath-hold (BH) to match the respiratory phase of AC. Compared with non-corrected breath-hold SPECT-MPI and with free-breathing AC SPECT-MPI, respiratory-phase- matched AC SPECT-MPI significantly affected segmental semi-quantitative uptake, increased the frequency of normal scans, yielded the best interobserver agreement and significantly improved image quality. These findings suggest a potential role of respiratory triggered SPECT-MPI in clinical routine.³¹

Splenic perfusion is reduced during adenosine and on CMR stress perfusion this can be observed as the ‘splenic switch off’ phenomenon. Hosking and colleagues validated splenic switch-off in a cohort derived from over 23,000 patients with CMR perfusion scans in whom follow-up data was available including invasive coronary angiograms within 12 months if

performed. The rate of lack of splenic switch-off was 20.7% in patients with false negative adenosine CMR stress perfusion scans and only 13.1% in patients with true positive adenosine CMR stress perfusion scans. Splenic switch-off can easily be visually assessed, but also quantification is simple and fast. A cut-off of 0.4 for spleen intensity ratio (comparison between adenosine stress and rest signal intensity in the spleen) has 82.5% sensitivity and 92.3% specificity to identify splenic switch-off. Thus, splenic switch-off is a promising and now commonly used method to determine whether adenosine response is adequate.³²

A few studies published in this journal in 2017 reported the high diagnostic accuracy of CMR in significant CAD. Adenosine CMR first pass myocardial perfusion imaging allows assessment of global and regional alterations in myocardial blood flow. Theoretically, balanced ischaemia in three vessel disease may be visually missed on CMR first pass perfusion imaging. Global myocardial blood flow reserve can also be determined by assessing the flow in the coronary sinus during adenosine and at rest. Shomanova and colleagues performed a study using these two approaches in patients with and without obstructive coronary artery disease and found that the combination provided higher diagnostic yield compared to myocardial first pass perfusion reserve alone. However, on its own the coronary sinus blood flow based approach cannot determine the location of obstructive coronary disease.³³

In a multi-centre study of 106 female and 251 male patients who underwent 3D CMR first-pass perfusion imaging which was compared to invasive fractional flow reserve assessment as the reference standard, Harmada and colleagues showed that diagnostic accuracy was at least as good in women (sensitivity/specificity 95%/84%) as in men (sensitivity/specificity 83%/82%). Thus, whole-heart first-pass 3D CMR stress perfusion imaging has high diagnostic accuracy irrespective of gender.³⁴

CMR stress perfusion has been shown in the past to have excellent prognostic value with negative studies having a very low annualised event rate. This has now been confirmed in a meta-analysis comparing the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease.³⁵ Coronary CT angiography, CMR, exercise and pharmacological stress echocardiography and single-photon emission tomography all have very low annualised event rates, in particular after adjusting for population event risk and prevalence of obstructive CAD.

The Tayside Screening for Cardiac Events study enrolled 5000 volunteers aged >40 years with no prior history of coronary artery disease and a low to intermediate 10-year risk of cardiovascular events and performed CMR scans including late gadolinium enhancement. In this middle aged population - unlike in previously described studies of older people including patients with coronary artery disease - they observed that the prevalence of silent myocardial infarction was very low (0.2%).³⁶

Contrast-enhanced CMR was used to assess area at risk, infarct size and microvascular obstruction in patients following reperfused ST-elevation myocardial infarction. 41% of the 727 patients were smokers. Reinstadler and colleagues demonstrated that there is little evidence to support the ‘smoker’s paradox’, which claimed that smokers have better myocardial tissue perfusion and outcomes after myocardial infarction. The CMR area at risk, infarct size and microvascular obstruction and major adverse cardiac events (after adjustment for baseline differences) were similar between smokers and nonsmokers.³⁷

Emerging techniques and applications in cardiovascular imaging

Using 2D speckle tracking echocardiography (STE) Huttin et al³⁸ tried to demonstrate the relations between mitral valve prolapse (MVP) and LV deformation. There was no significant difference between control subjects and patients with MVP with respect to global and regional peak LV longitudinal strain ($-23.7 \pm 3.2\%$ vs. $-23.1 \pm 2.2\%$). In contrast,

patients with MVP had significantly higher values of global pre-stretch index (3.2 ± 4.1 vs. 1.3 ± 1.2 ; $P = 0.01$) and global post-systolic index (3.2 ± 0.4 vs. 1.7 ± 1.1 ; $P = 0.05$) compared with controls, located mainly in the lateral wall and basal segments. Both anterior and posterior MVP were responsible for post-systolic index in basal inferior segments and pre-stretch index in anterior ones. Changes in mid-wall segmental deformation pattern were mainly observed at the level of the segments adjacent to the papillary muscle. Pathological early-systolic shortening and late/post-systolic deformation is attributed to an increased interaction between wall deformation and mitral valve events in patients with MVP.³⁸

Analysing 41 consecutive genotyped family members of hypertrophic cardiomyopathy patients without LVH, Kauer et al³⁹ found no significant differences between genotype +, LVH – (G+/LVH–) and control subjects in maximal systolic twist and global longitudinal strain. In diastole, the early peak untwist rate was significantly lower in G+/LVH– subjects compared with control subjects ($62 \pm 19^\circ\text{s}^{-1}$ vs. $76 \pm 30^\circ\text{s}^{-1}$, $P < 0.05$), whereas the late peak untwist rate tended to be higher. Untwist from maximal twist until the first 20% of diastole was delayed in G+/LVH– subjects compared with controls ($39.3 \pm 12.9\%$ vs. $51.3 \pm 15.6\%$, $P < 0.005$). Late diastolic strain rate was significantly higher in G+/LVH– subjects in the inferoseptal, the inferolateral, and the anteroseptal walls. Strain from maximal twist until the first 20% of diastole was delayed in G+/LVH– subjects in the inferoseptal, inferolateral, and anteroseptal segments. In mutation carriers for HCM, LV untwist and early diastolic strain are delayed, while untwist rate and diastolic strain rate are decreased.³⁹

A new software tool for automated segmentation and quantification of the left atrium (LA) from 3D echocardiography was validated by Almeida et al.⁴⁰ The LA segmentation tool uses a dual-chamber model of the left side of the heart to automatically detect and track the

atrio-ventricular plane and the LA endocardium in transthoracic 3D echocardiography. The automated tool required no user interaction in 93% of the recordings.⁴⁰

Coronary imaging with two or three imaging modalities is time consuming and is associated with risk of complications. However, it provides incremental information about plaque pathology and biology allowing complete and comprehensive assessment of plaque morphology. Michail et al⁴¹ review the current clinical evidence supporting the use of multimodality intravascular imaging in the study of atherosclerosis, summarize the key findings of the first invasive imaging studies that utilize hybrid dual-probe catheters, and discuss the limitations of combined intravascular imaging that restrict its wider application in both the clinical and the research arena.⁴¹

The diagnosis of intraplaque haemorrhage, a major contributor to lesion progression, is very challenging. Matsumura et al⁴² have analysed the role of intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS), comparing the results obtained with these two emerging techniques with histopathology. Segments with intraplaque haemorrhage had more fibroatheromas (FAs) with a greater IVUS plaque burden, a greater prevalence of IVUS echolucent zones, and a higher NIRS-lipid core burden index (LCBI) compared to segments without intraplaque haemorrhage.⁴²

The fusion imaging of coronary anatomy by coronary CTA with 3D echocardiography (3DE)-derived resting myocardial deformation was tested by Maffesanti et al⁴³ in 28 patients with chest pain, referred for coronary CTA (256 Philips scanner) who underwent 3DE and regadenoson stress. To obtain a reference for stenosis significance, coronary arteries were also fused with colour maps of stress myocardial perfusion. 3D displays were used to detect stress perfusion defect and/or resting strain abnormality in each territory. Fusion of coronary CTA and 3DE-derived data allows direct visualization of each coronary artery and strain in its territory. In this feasibility study, resting strain showed good agreement with stress

perfusion (79% agreement), indicating that it may be potentially used to assess the haemodynamic impact of coronary stenosis, as an alternative to stress testing that entails additional radiation exposure.⁴³

CMR late gadolinium enhancement is one of the CMR bread and butter techniques which allows detection of regional myocardial fibrosis or scar in the left myocardium. Atrial late gadolinium enhancement is far more challenging given the thinness of the atrial wall. To date, no attempt had been made in humans *in vivo* to image fibrotic structures within the atrial wall, such as the sinoatrial node. Csepe and colleagues used 3D contrast-enhanced CMR at 3 Tesla in healthy volunteers with a spatial resolution of $0.625 \times 0.625 \times 1.25 \text{ mm}^3$ and were able to depict an ellipsoid fibrotic region of $23.6 \times 7.2 \times 2.9 \text{ mm}^3$ corresponding to the location of the sinoatrial node. This method was then validated in the same manuscript in explanted donor hearts *ex vivo* at 9.4 Tesla and the same findings of an ellipsoid fibrotic region correlated with histological specimens of the sinoatrial node.⁴⁴

Structural heart disease imaging and intervention planning became a mainstream application of cardiac CT imaging. Calcification is the dominant mechanism of progressive aortic valve obstruction in the majority of elderly patients with severe aortic stenosis (AS). Nonetheless, in some cases patients with low aortic valve calcification are diagnosed with haemodynamically severe AS. In a retrospective study of 563 patients with severe symptomatic AS that underwent balloon-expandable transcatheter aortic valve implantation (TAVI) the authors assessed the clinical and haemodynamic characteristics and outcome of patients with severe AS and low valve calcification. Patients with severe AS and low aortic valve calcification were found to be younger and to have a higher BMI. Importantly, balloon-expandable TAVI in patients with mildly calcified aortic valve was not associated with increased risk of valve embolization. In addition, the authors demonstrated a high device success and lower rates of paravalvular regurgitation for these patients.⁴⁵ Another important

aspect of pre-procedural TAVI planning with cardiac CT is the possibility to determine the optimal fluoroscopic projection for prosthesis implantation, which reduces the volume of periprocedural contrast agent compared with an angiography-based approach without an increase of complications.⁴⁶ Beyond TAVI planning, cardiac CT became indispensable in sizing work-up for percutaneous left atrial appendage closure. A single-centre registry demonstrated that the routine incorporation of CT is associated with excellent outcomes for procedural safety and no major residual leak was observed. The authors suggested that a particular value of CT in left atrial appendage closure may be the detection and subsequent avoidance of gross sizing error by 2D TOE that occurs in a small but important proportion of cases.⁴⁷ Among original articles regarding the assessment of the myocardium using CT an ex vivo small animal study on X-ray phase-contrast CT showed us the latest directions of CT development. Phase contrast images are formed not only by X-ray absorption by the tissue but also by wave propagation phenomena, enhancing structural information, thus allowing to raise tissue contrast to an unprecedented level. In this ex vivo study small animal hearts' micro-structure at myofibre resolution was imaged (Figure 3). This superior imaging approach opens up new possibilities for a systems approach towards analysing cardiac structure and function.⁴⁸

References

1. Edvardsen T, Donal E, Bucciarelli-Ducci C, Maurovich-Horvat P, Maurer G, Popescu BA. The years 2015–2016 in the European Heart Journal—Cardiovascular Imaging. Part I. Eur Heart J Cardiovasc Imaging 2017;18(10):1092-1098.
2. Edvardsen T, Gerber B, Donal E, Maurovich-Horvat P, Maurer G, Popescu BA. The year 2015-16 in the European Heart Journal-Cardiovascular Imaging. Part II. Eur Heart J Cardiovasc Imaging 2017;18(12):1322–30.
3. Sugimoto T, Dulgheru R, Bernard A, Ilardi F, Contu L, Addetia K et al. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2017;18(8):833-840.
4. Bernard A, Addetia K, Dulgheru R, Caballero L, Sugimoto T, Akhaladze N et al. 3D echocardiographic reference ranges for normal left ventricular volumes and strain: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2017;18(4):475-483.
5. Morris DA, Krisper M, Nakatani S, Köhncke C, Otsuji C, Belyavskiy E et al. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. Eur Heart J Cardiovasc Imaging. 2017;18(2):212-223.
6. Saura D, Dulgheru R, Caballero L, Bernard A, Kou S, Gonjilashvili N et al. Two-dimensional transthoracic echocardiographic normal reference ranges for proximal aorta dimensions: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2017;18(2):167-179
7. Schaaf M, Andre P, Altman M, Maucort-Boulch D, Placide J, Chevalier P et al. Left atrial remodelling assessed by 2D and 3D echocardiography identifies paroxysmal atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2017;18(1):46-53.

8. Ternacle J, Wan F, Sawaki D, Surenaud M, Pini M, Mercedes R et al. Short-term high-fat diet compromises myocardial function: a radial strain rate imaging study. *Eur Heart J Cardiovasc Imaging*. 2017;18(11):1283-1291,
9. Maufrais C, Rupp T, Bouzat P, Doucende G, Verges S, Nottin S et al. Heart mechanics at high altitude: 6 days on the top of Europe. *Eur Heart J Cardiovasc Imaging*. 2017;18(12):1369-1377.
10. Arenja N, Fritz T, Andre F, Riffel JH, aus dem Siepen F, Ochs M et al. Myocardial contraction fraction derived from cardiovascular magnetic resonance cine images-reference values and performance in patients with heart failure and left ventricular hypertrophy. *European Heart Journal - Cardiovascular Imaging* 2017;18:1414–1422.
11. Kozor R, Nordin S, Treibel TA, Rosmini S, Castelletti S, Fontana M et al. Insight into hypertrophied hearts: a cardiovascular magnetic resonance study of papillary muscle mass and T1 mapping. *European Heart Journal - Cardiovascular Imaging* 2017;18:1034–1040.
12. Markman TM, Habibi M, Venkatesh BA, Zareian M, Wu C, Heckbert SR et al. Association of left atrial structure and function and incident cardiovascular disease in patients with diabetes mellitus: results from multi-ethnic study of atherosclerosis (MESA). *European Heart Journal - Cardiovascular Imaging* 2017;18:1138–1144.
13. Zacharias K, Ahmed A, Shah BN, Gurunathan S, Young G, Acosta D et al. Relative clinical and economic impact of exercise echocardiography vs. exercise electrocardiography, as first line investigation in patients without known coronary artery disease and new stable angina: a randomized prospective study. *Eur Heart J Cardiovasc Imaging*. 2017;18:195-202.
14. Wierzbowska-Drabik K, Trzos E, Kurpesa M, Rehcinski T, Miskowiec D, Cieslik-Guerra U et al. Diabetes as an independent predictor of left ventricular longitudinal strain reduction

- at rest and during dobutamine stress test in patients with significant coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2017. Dec 9. [Epub ahead of print]
15. Cortigiani L, Sorbo S, Miccoli M, Scali MC, Simioniuc A, Morrone D et al. Prognostic value of cardiac power output to left ventricular mass in patients with left ventricular dysfunction and dobutamine stress echo negative by wall motion criteria. *Eur Heart J Cardiovasc Imaging*. 2017;18(2):153-158.
 16. Shiran A, Blondheim DS, Shimoni S, Jabarren M, Rosenmann D, Sagie A et al. Two-dimensional strain echocardiography for diagnosing chest pain in the emergency room: a multicentre prospective study by the Israeli echo research group. *Eur Heart J Cardiovasc Imaging*. 2017;18:1016-1024.
 17. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL et al. Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017. *Eur Heart J Cardiovasc Imaging*. 2017;18:1205-1205af.
 18. Feuchtner G, Kerber J, Burghard P, Dichtl W, Friedrich G, Bonaros N, et al. The high-risk criteria low-attenuation plaque <60 HU and the napkin-ring sign are the most powerful predictors of MACE: a long-term follow-up study. *Eur Heart J Cardiovasc Imaging* 2017;18(7):772-779.
 19. Conte E, Annoni A, Pontone G, Mushtaq S, Guglielmo M, Baggiano A, et al. Evaluation of coronary plaque characteristics with coronary computed tomography angiography in patients with non-obstructive coronary artery disease: a long-term follow-up study. *Eur Heart J Cardiovasc Imaging* 2017;18(10):1170-1178.
 20. Hell MM, Motwani M, Otaki Y, Cadet S, Gransar H, Miranda-Peats R, et al. Quantitative global plaque characteristics from coronary computed tomography angiography for the

- prediction of future cardiac mortality during long-term follow-up. *Eur Heart J Cardiovasc Imaging* 2017;18(12):1331-1339.
21. Deseive S, Shaw LJ, Min JK, Achenbach S, Andreini D, Al-Mallah MH, et al. Improved 5-year prediction of all-cause mortality by coronary CT angiography applying the CONFIRM score. *Eur Heart J Cardiovasc Imaging* 2017;18(3):286-293.
 22. Schulman-Marcus J, Lin FY, Gransar H, Berman D, Callister T, DeLago A, et al. Coronary revascularization vs. medical therapy following coronary-computed tomographic angiography in patients with low-, intermediate- and high-risk coronary artery disease: results from the CONFIRM long-term registry. *Eur Heart J Cardiovasc Imaging* 2017;18(8):841-848.
 23. Mittal TK, Pottle A, Nicol E, Barbir M, Ariff B, Mirsadraee S, et al. Prevalence of obstructive coronary artery disease and prognosis in patients with stable symptoms and a zero-coronary calcium score. *Eur Heart J Cardiovasc Imaging* 2017;18(8):922-929.
 24. Packard RR, Li D, Budoff MJ, Karlsberg RP. Fractional flow reserve by computerized tomography and subsequent coronary revascularization. *Eur Heart J Cardiovasc Imaging* 2017;18(2):145-152.
 25. Eftekhari A, Min J, Achenbach S, Marwan M, Budoff M, Leipsic J, et al. Fractional flow reserve derived from coronary computed tomography angiography: diagnostic performance in hypertensive and diabetic patients. *Eur Heart J Cardiovasc Imaging* 2017;18(12):1351-1360.
 26. Onuma Y, Collet C, van Geuns RJ, de Bruyne B, Christiansen E, Koolen J, et al. Long-term serial non-invasive multislice computed tomography angiography with functional evaluation after coronary implantation of a bioresorbable everolimus-eluting scaffold: the ABSORB cohort B MSCT substudy. *Eur Heart J Cardiovasc Imaging* 2017;18(8):870-879.

27. van Rosendael AR, Dimitriu-Leen AC, de Graaf MA, van Zwet EW, Jukema JW, Bax JJ, et al. Impact of computed tomography myocardial perfusion following computed tomography coronary angiography on downstream referral for invasive coronary angiography, revascularization and, outcome at 12 months. *Eur Heart J Cardiovasc Imaging* 2017;18(9):969-977.
28. van Rosendael AR, de Graaf MA, Dimitriu-Leen AC, van Zwet EW, van den Hoogen IJ, Kharbanda RK, et al. The influence of clinical and acquisition parameters on the interpretability of adenosine stress myocardial computed tomography perfusion. *Eur Heart J Cardiovasc Imaging* 2017;18(2):203-211.
29. Stenstrom I, Maaniitty T, Uusitalo V, Pietila M, Ukkonen H, Kajander S, et al. Frequency and angiographic characteristics of coronary microvascular dysfunction in stable angina: a hybrid imaging study. *Eur Heart J Cardiovasc Imaging* 2017;18(11):1206-1213.
30. Stuijzand WJ, Driessen RS, Raijmakers PG, Rijnierse MT, Maeremans J, Hollander MR, et al. Prevalence of ischaemia in patients with a chronic total occlusion and preserved left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging* 2017;18(9):1025-1033.
31. Clerc OF, Fuchs TA, Possner M, Vontobel J, Mikulicic F, Stehli J, et al. Real-time respiratory triggered SPECT myocardial perfusion imaging using CZT technology: impact of respiratory phase matching between SPECT and low-dose CT for attenuation correction. *Eur Heart J Cardiovasc Imaging* 2017;18(1):31-38.
32. Hosking A, Koulouroudias M, Zemrak F, Moon JC, Rossi A, Lee A et al. Evaluation of splenic switch off in a tertiary imaging centre: validation and assessment of utility. *Eur Heart J Cardiovasc Imaging*. 2017 Nov 1;18(11):1216-1221.
33. Shomanova Z, Florian A, Bietenbeck M, Waltenberger J, Sechtem U, Yilmaz A. Diagnostic value of global myocardial perfusion reserve assessment based on coronary sinus flow

- measurements using cardiovascular magnetic resonance in addition to myocardial stress perfusion imaging. *European Heart Journal - Cardiovascular Imaging* 2017;18:851–859.
34. Hamada S, Gotschy A, Wissmann L, Paetsch I, Jahnke C, Plein S et al. Multi-centre study of whole-heart dynamic 3D cardiac magnetic resonance perfusion imaging for the detection of coronary artery disease defined by fractional flow reserve: gender based analysis of diagnostic performance. *European Heart Journal - Cardiovascular Imaging* 2017;18:1099–1106.
35. Smulders MW, Jaarsma C, Nelemans PJ, Bekkers SCAM, Bucerius J, Leiner T et al. Comparison of the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease-a meta-analysis. *European Heart Journal - Cardiovascular Imaging* 2017;18:980–987.
36. Weir-McCall JR, Fitzgerald K, Papagiorcopulo CJ, Gandy SJ, Lambert M, Belch JJF et al. Prevalence of unrecognized myocardial infarction in a low-intermediate risk asymptomatic cohort and its relation to systemic atherosclerosis. *European Heart Journal - Cardiovascular Imaging* 2017;18:657–662.
37. Reinstadler SJ, Eitel C, Fuernau G, de Waha S, Desch S, Mende M et al. Association of smoking with myocardial injury and clinical outcome in patients undergoing mechanical reperfusion for ST-elevation myocardial infarction. *European Heart Journal - Cardiovascular Imaging* 2017;18:39–45.
38. Huttin O, Pierre S, Venner C, Voilliot D, Sellal JM, Aliot E et al. Interactions between mitral valve and left ventricle analysed by 2D speckle tracking in patients with mitral valve prolapse: one more piece to the puzzle. *Eur Heart J Cardiovasc Imaging*. 2017;18(3):323-331.

39. Kauer F, van Dalen B, Michels M, Schinkel AFL, Vletter WB, van Slegtenhorst M et al. Delayed and decreased LV untwist and unstrain rate in mutation carriers for hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging*. 2017;18(4):383-389.
40. Almeida N, Papachristidis A, Pearson P, Sarvari SI, Engvall J, Edvardsen T et al. Left atrial volumetric assessment using a novel automated framework for 3D echocardiography: a multi-centre analysis. *Eur Heart J Cardiovasc Imaging*. 2017;18(9):1008-1015.
41. Michail M, Serruys PW, Stettler R, Crake T, Torii R, Tenekecioglu E et al. Intravascular multimodality imaging: feasibility and role in the evaluation of coronary plaque pathology. *Eur Heart J Cardiovasc Imaging*. 2017;18(6):613-620.
42. Matsumura M, Mintz GS, Kang SJ, Sum ST, Madden SP, Burke AP et al. Intravascular ultrasound and near-infrared spectroscopic features of coronary lesions with intraplaque haemorrhage. *Eur Heart J Cardiovasc Imaging*. 2017;18(11):1222-1228.
43. Maffessanti F, Patel AR, Patel MB, Walter JJ, Mediratta A, Medvedofsky D et al. Non-invasive assessment of the haemodynamic significance of coronary stenosis using fusion of cardiac computed tomography and 3D echocardiography. *Eur Heart J Cardiovasc Imaging*. 2017;18(6):670-680.
44. Csepe TA, Zhao J, Sul LV, Wang Y, Hansen BJ, Li N et al. Novel application of 3D contrast-enhanced CMR to define fibrotic structure of the human sinoatrial node in vivo. *European Heart Journal - Cardiovascular Imaging* 2017;18:862–869.
45. Abramowitz Y, Jilaihawi H, Pibarot P, Chakravarty T, Kashif M, Kazuno Y, et al. Severe aortic stenosis with low aortic valve calcification: characteristics and outcome following transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging* 2017;18(6):639-647.

46. Hell MM, Biburger L, Marwan M, Schuhbaeck A, Achenbach S, Lell M, et al. Prediction of fluoroscopic angulations for transcatheter aortic valve implantation by CT angiography: influence on procedural parameters. *Eur Heart J Cardiovasc Imaging* 2017;18(8):906-914.
47. Rajwani A, Nelson AJ, Shirazi MG, Disney PJS, Teo KSL, Wong DTL, et al. CT sizing for left atrial appendage closure is associated with favourable outcomes for procedural safety. *Eur Heart J Cardiovasc Imaging* 2017;18(12):1361-1368.
48. Gonzalez-Tendero A, Zhang C, Balicevic V, Cardenes R, Loncaric S, Butakoff C, et al. Whole heart detailed and quantitative anatomy, myofibre structure and vasculature from X-ray phase-contrast synchrotron radiation-based micro computed tomography. *Eur Heart J Cardiovasc Imaging* 2017;18(7):732-741.

Figure legends

Figure 1. Case example of serial coronary CTA with FFRCT improvement at follow-up. Case example of a patient treated with a Bioresorbable Vascular Scaffold (white arrows) in the proximal segment of the LAD. Coronary CTA at 18 months showed a moderate in-scaffold stenosis with MLA 3.4 mm² (dash line C) with area stenosis of 64%. At 72-month Coronary CTA follow-up, showed an increased MLA to 7.0 mm² (dash line C) and area stenosis of 30%. This late lumen enlargement had a significant impact on FFRCT distal to the scaffold. FFRCT, Non-invasive fractional flow reserve derived from coronary computed tomography angiography; LAD, Left anterior descending artery; MLA, Minimal lumen area. (Modified from Onuma et al.²⁶).

Figure 2. Coronary microvascular dysfunction in the absence of atherosclerosis in a 58-year-old man with atypical angina pectoris, history of smoking, family history of coronary artery disease, and ischaemia on exercise ECG. Myocardial blood flow (MBF) during adenosine stress was moderately reduced in all vessel areas (A, global MBF 1.9 mL/g/min). MBF at rest was homogenously distributed (B) and CFR was reduced being 2.2. Coronary CT angiography images show the absence of atherosclerosis in the left anterior descending (C) and circumflex (D) arteries and the right coronary artery (E). Invasive coronary angiogram shows non-obstructed left (F) and right (G) coronary arteries. (Modified from Stenstrom et al.²⁹).

Figure 3. Fibre orientation X-ray phase contrast CTT imaging. Fibre angles change across the walls within a slice in fetal rabbit control (A) and in intrauterine growth restriction (B) hearts. Fibre angles change from endo- to epi-cardium from +60° to -60°. In the C and D, a visualization of the 3D fibre structure of the IUGR rabbit heart is shown (left: fibre angles within one slice; right: 3D fibre tracking within the wall). IUGR: intrauterine growth restriction. (Modified from Gonzalez-Tendero et al.⁴⁸).

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