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The Year in Cardiology 2018: Imaging

Victoria Delgado, Bogdan A. Popescu, Sven Plein, Stephan Achenbach, Juhani Knuuti, Jeroen J. Bax

[1]Heart Lung Centrum, Leiden University Medical Center, The Netherlands; [2]University of Medicine and Pharmacy "Carol Davila" - Euroecolab, Institute of Cardiovascular Diseases „Prof. Dr. C. C. Iliescu", Bucharest, Romania; [3]Multidisciplinary Cardiovascular Research Centre & Division of Biomedical Imaging, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, United Kingdom; [4]Department of Cardiology, Friedrich-Alexander-Universität, Erlangen, Germany; [5]Turku PET Centre, University of Turku and Turku University Hospital

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Correspondence address:
Jeroen J Bax, MD, PhD, Heart Lung Centrum, Leiden University Medical Center
Albinusdreef 2 2300 RC Leiden, The Netherlands
Tel: +31 71 526 2020, Fax: +31 71 526 6809, E-mail: j.j.bax@lumc.nl

In 2018, strain imaging with echocardiography has provided important pathophysiological insights in various cardiovascular disease and the evidence demonstrating its incremental prognostic value over left ventricular ejection fraction is growing. Similarly, tissue characterization with cardiovascular magnetic resonance techniques (late gadolinium enhancement and T_1-mapping) has become an important part in the diagnostic algorithms and risk stratification of patients with cardiomyopathies. In addition, assessment of coronary artery disease with computed tomography (CT) is changing from being exclusively an anatomical test to integrating anatomic (lesion severity and plaque characterization) with functional information (myocardial perfusion and coronary fractional flow reserve) whereas the prognostic implications of quantification of coronary flow reserve with positron emission tomography (PET) have been demonstrated in large scale studies. Technological advances in fusion imaging, such as PET/CT and PET/magnetic resonance, allow for relating anatomical tissue changes with functional alterations in the clinical and pre-clinical setting. Finally, the use of machine learning applied to imaging data to predict cardiovascular events is increasing. This Year in Cardiology review article provides an overview of the most relevant articles published in 2018 on cardiac imaging.

Keywords: echocardiography; positron emission tomography; cardiovascular magnetic resonance; coronary computed tomography

Introduction

This Year in Cardiology review article provides an overview of the most relevant articles published in 2018 on advances in non-invasive cardiac imaging that provided important new insights in the pathophysiology of heart failure, coronary artery disease and cardiomyopathies.

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Echocardiography

Left ventricular (LV) global longitudinal strain (GLS) is becoming part of the routine echocardiographic evaluation of patients with cardiac diseases since it provides accurate assessment of LV systolic function and has important prognostic implications. In 4,172 consecutive patients with acute heart failure (HF) and broad range of LV ejection fractions (LVEF), *Park et al.* demonstrated the greater prognostic value of LV GLS as compared with LVEF (1). Patients were divided according to current classification of HF (HF with reduced LVEF [HFrEF], mildly reduced LVEF [HFmrEF] and preserved LVEF [HFpEF]) and to tertiles of LV GLS (severely reduced GLS ≥–8%), moderately reduced LV GLS (–8.1 to –12.5%) and mildly reduced LV GLS (≤–12.6%). Patients with HFrEF had slightly higher mortality than those with HRmrEF or HFpEF (41%, 38%, and 39%, respectively; p=0.031), whereas patients with severely reduced LV GLS had significantly higher mortality rates at 5-years follow-up as compared with the other tertiles (49% vs. 38% for moderately reduced LV GLS and 34% for mildly reduced LV GLS; p<0.001). In addition, LV GLS demonstrated incremental prognostic value over LVEF by net reclassification improvement analysis (12%, 95% confidence interval [CI] 6.3–15.7%, p<0.001). The prognostic value of LV GLS was also demonstrated in 294 patients with severe aortic stenosis (2). Patients were divided according to a cut-off value of LV GLS of -14%. Patients with more preserved LV GLS (≤–14%) had better survival as compared with patients with more impaired LV GLS (>–14%). Among patients with more impaired LV GLS, there was no significant differences in survival when patients were subdivided according to LVEF (≥55% vs. <55%). Each 1% impairment in LV GLS was independently associated with 17% increased risk of all-cause mortality.

From the Normal Reference Ranges for Echocardiography (NORRE) study, Sugimoto and coworkers provided the normal reference limits for 2D and 3D mea-

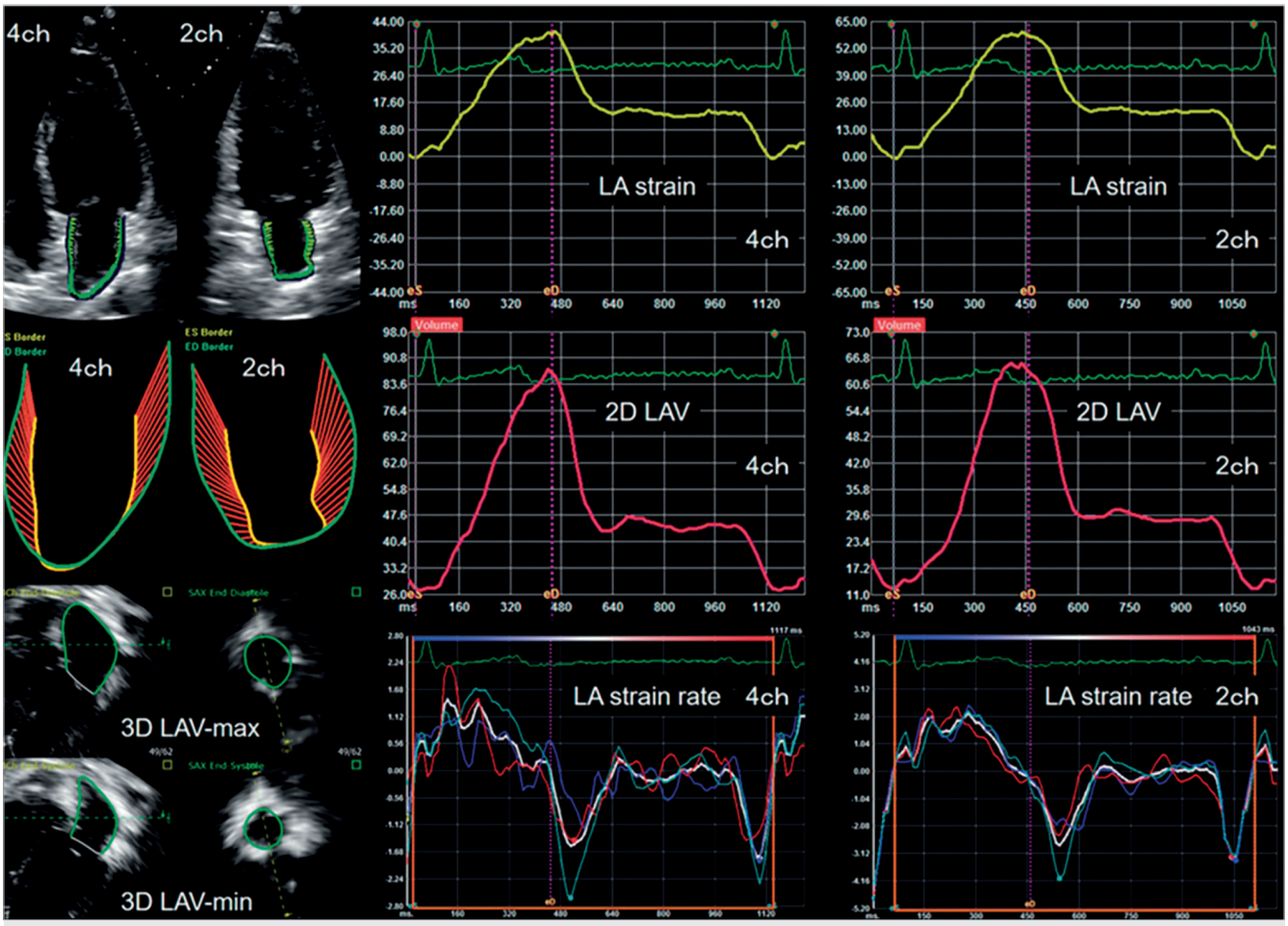

FIGURE 1. Measurements of left atrial volumes and strain with vendor-independent software. From the apical 4- and 2-chamber views, the endocardial border of the left atrium (LA) is traced and the software tracks the movement of the endocardium generating the time-strain, time-volume and time-strain rate curves. The maximum (LAV-max) and the minimum (LAV-min) LA volumes were measured from 3-dimensional (3D) datasets. Reproduced with permission from Sugimoto et al. (3)

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surements of LA function using vendor-independent software *(Figure 1)* and investigated the influence of age and sex on LA function measurements (3). LA reservoir and conduit function decreased with age whereas LA pump function increased. Sex did not have any influence on LA functional parameters. These reference values are important to understand the abnormalities in LA function in various clinical scenarios. In 1,361 patients with atrial fibrillation, *Leung et al.* (4) showed that LA reservoir strain was more impaired and the time delay between the electrical and mechanical activation of the LA myocardium (so-called PA-TDI) was longer in those who had ischemic stroke as compared to patients without stroke (14.5% vs. 18.9%, p=0.005 and 166 ms vs. 141 ms, p<0.001; respectively). LA reservoir strain and PA-TDI were independently associated with risk of stroke in a model including CHA_2DS_2-VASc score, age and use of anticoagulants.

Characterization of the morphology of the patent foramen ovale with transoesophageal echocardiography is important to select patients with cryptogenic stroke who may benefit from transcatheter closure of the patent foramen ovale . In the Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENSE-PRO) study (5), patients with large patent foramen ovale, atrial septal aneurysm or hypermobility were randomized to PFO closure vs. medical therapy. The rate of the combined primary endpoint (stroke, vascular death or Thrombolysis In Myocardial Infarction-defined major bleeding) at 2 years follow-up was 0 in the patent foramen ovale closure arm vs. 12.9% in the medical treatment arm.

The use of machine learning is increasing in the field of cardiovascular imaging (6). Comprehensive unsupervised machine learning algorithm using LV myocardial long-axis velocity patterns at rest and exercise may help the diagnosis of HFpEF. *Sanchez-Martinez et al.* (7) examined 156 patients referred to stress echocardiography. Machine learning algorithm identified a continuum from health to disease. Clinical validation revealed good correlation with the current clinical criteria for diagnosis of HFpEF. Furthermore, cluster analysis was applied to develop a model of LV diastolic function from conventional Doppler echocardiographic data and speckle tracking analysis of simultaneous changes in volumes, strain and strain rate of the LV and LA in 130 patients (8). The model was validated in 44 patients undergoing invasive measurements of pulmonary capillary wedge pressure and LV end-diastolic pressure. Cluster patterns of speckle tracking-derived data provided accurate phenotypic characterization of LV diastolic function in patients with various grades of LV diastolic dysfunction as assessed with 2D and Doppler based indices. Therefore, the current multiparametric algorithm to assess LV diastolic dysfunction which includes 2D, Doppler and tissue Doppler data could be simplified by clustering and classification algorithms based on speckle tracking echocardiographic data. In addition, on receiver operator characteristic curve analysis, the clustering model had a good accuracy to predict elevated pulmonary capillary wedge pressure in the validation cohort (area under the curve 0.86).

In the field of valvular heart disease, echocardiographic studies have provided new evidence. The prognostic value of flow status in patients with severe aortic stenosis has been confirmed in a large series of patients with severe aortic stenosis. *Rusinaru et al.* (9) showed that a stroke volume index <30 ml/m^2 was associated with poor outcome in patients with severe aortic stenosis and preserved LVEF regardless of the treatment. Point-of-care smartphone-connected devices, including pocket-echocardiography, smartphone-connected-electrocardiogram, activity monitoring, and portable brain natriuretic peptide laboratory testing, has shown to reduce the time to referral for therapy with percutaneous valvuloplasty or surgical valve replacement (83 vs. 180 days; p<0.001), and with a lower risk of a hospitalization and/or death on follow-up (15% vs. 28%; p=0.013) as compared to standard of care in patients with structural heart diseases (10). Finally, a retrospective case-control single center study showed that the majority of patients with thrombosis of bioprostheses are asymptomatic at the moment of echocardiographic diagnosis (11). Importantly, these patients present rapid clinical deterioration requiring intervention within 6 months after the diagnosis. These findings question the recommendation of performing an echocardiogram during the first 5 years of valve implantation (12). Current European Society of Cardiology (ESC) guidelines on valvular heart disease recommend performing an echocardiogram after 1 year of implantation and yearly thereafter (13).

Cardiovascular magnetic resonance

Late gadolinium enhanced (LGE) cardiovascular magnetic resonance (CMR) imaging is well-established for tissue characterisation in ischaemic and non-ischaemic heart disease, with new applications still emerging. The prognostic value of LGE CMR in myocarditis was demonstrated in a study of 670 patients (14). Abnormalities on LGE imaging were associated with two-fold risk of major adverse cardiovascular events (MACE) during 4.7 years follow-up. The location and distribution of LGE findings appeared to be of relevance, with the septal and midwall enhancement and a patchy scar pattern most strongly associated with MACE.

In a retrospective study of 164 consecutive survivors of sudden cardiac arrest and no coronary artery disease (CAD), patients who presented with MACE had more frequently LGE than patients without MACE over a median of 32 months (51% vs. 30%, p=0.02) (15). In addition, CMR contributed to making a final diagnosis including dilated cardiomyopathy, myocarditis, sarcoi-

dosis, occult myocardial infarction, and hypertrophic cardiomyopathy in half of the patients, underlining the value of CMR in this patient cohort.

T1 mapping and extracellular volume (ECV) fraction continue to dominate the recent CMR literature. A study of 36 patients with LV non-compaction cardiomyopathy and 18 controls undergoing 1.5T CMR showed higher native T1 (1,024±43 ms vs. 995±22 ms, p=0.01) and higher ECV (28.0±4.5% vs. 23.5±2.2%, p<0.001) in patients with LV non-compaction cardiomyopathy (16) Of various clinical and imaging parameters, only ECV was associated with a lower LVEF and increased risk of ventricular arrhythmias.

Several investigations have explored T1 mapping and ECV in patients with aortic stenosis. In a study of 133 patients with severe aortic stenosis, CMR was compared with intra-operative myocardial biopsy during surgical aortic valve replacement (17). While LGE CMR correlated with the collagen volume fraction on biopsy, ECV surprisingly did not. A high ECV was however associated with worse LV remodelling, LVEF and functional capacity. Histology revealed three distinct patterns of endocardial, microscopic or diffuse interstitial fibrosis *(Figure 2)* which may explain the lack of sensitivity of ECV. The authors conclude that myocardial fibrosis in severe aortic stenosis is complex, requiring a multi-parametric assessment for optimal risk stratification.

In the assessment of CAD, myocardial perfusion CMR is becoming an increasingly available tool and recently described automated analysis methods will bring quantitative myocardial blood flow (MBF) estimation closer to clinical routine. A recent study of the prognostic value of MBF estimation by CMR, although not using automated analysis, is therefore timely. In 395 patients with clinically indicated adenosine-stress perfusion CMR, ischemic burden derived from quantitative MBF estimation improved the prognostic value of CMR compared with a baseline model including age, sex, and LGE (area under the curve 0.75 to 0.85) (18).

A potential alternative to contrast enhanced perfusion CMR using rest/stress T1 mapping has recently been proposed. In 60 patients with angina who underwent

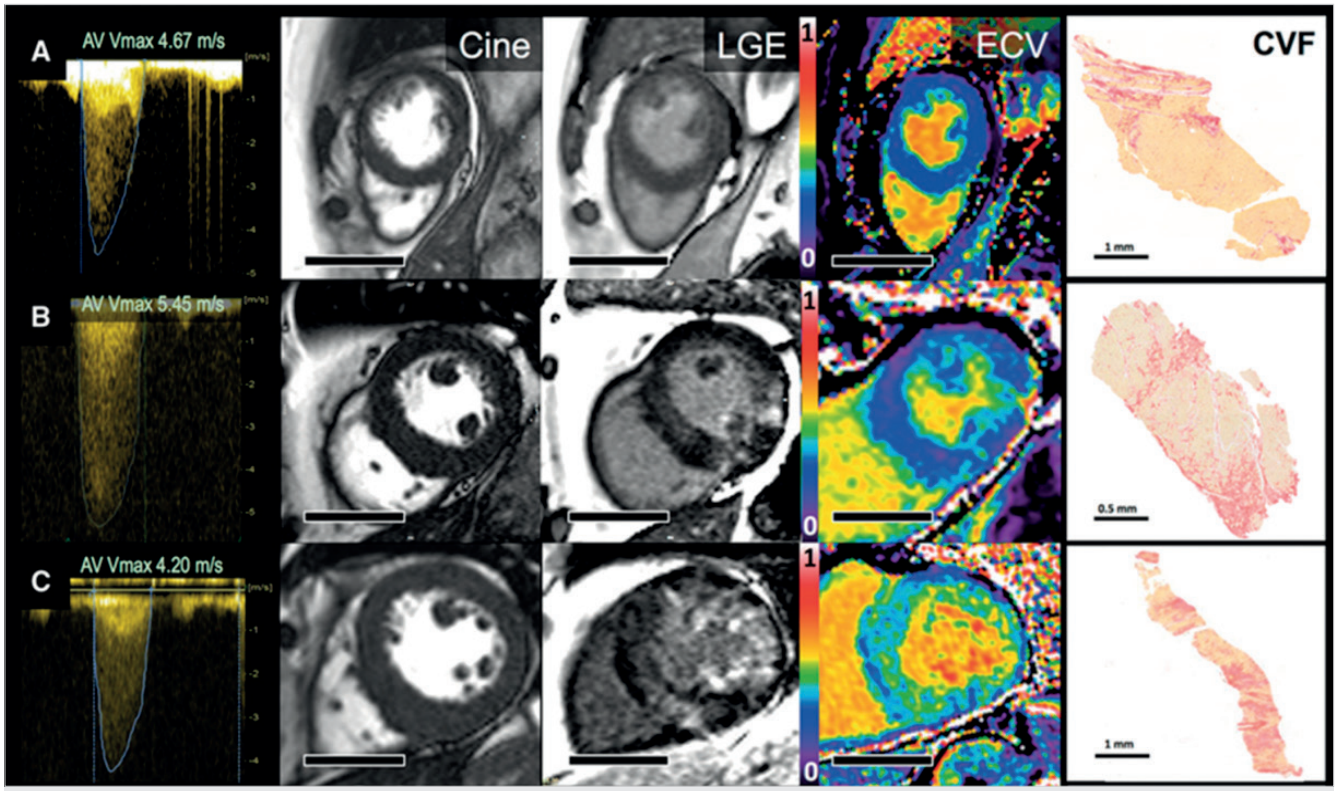

FIGURE 2. Hemodynamic assessment, tissue characterization and histology evaluation in severe aortic stenosis. The peak aortic flow velocity (AV V_{max}) measured on continuous wave Doppler echocardiography, the left ventricular hypertrophy, late gadolinium enhancement (LGE) and extracellular volume (ECV) measured on cardiac magnetic resonance and the collagen volume fraction (CVF) assessed on myocardial biopsies are shown for 3 different patients. Patient A has severe aortic stenosis, with no left ventricular hypertrophy or LGE, minimal ECV (28.4%) and minimal subendocardial fibrosis on biopsy (CVF 4.6%). In contrast, patient B, shows higher peak jet velocity, moderate left ventricular hypertrophy, patchy LGE and increased ECV (29.9%) which is concordant with moderate fibrosis based on CVF measures (19.3%). Patient C has concentric left ventricular hypertrophy, larger extent of non-infarct LGE, higher ECV (36.5%) and severe fibrosis on biopsy (CVF 24.5%). Adapted with permission from Treibel et al. (17)

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rest and adenosine stress CMR, T1 mapping using a short Modified Look Locker method was assessed, whereas fractional flow reserve (FFR) and index of microcirculatory resistance were measured on invasive coronary angiography (19). While native T1 increased between rest and adenosine stress by 6.2% in 30 normal controls, it showed no change between baseline and stress (ΔT1=0.7±0.7%) in ischemic viable myocardium (FFR<0.8). Rest/stress T1 mapping was more accurate than first-pass contrast enhanced perfusion for detecting significant coronary artery stenosis (area under the curve 0.97±0.02 vs. 0.91±0.03, respectively; p<0.001). This study may mark a new era of non-contrast stress testing in CMR if the findings can be reproduced in multiple, non-expert centres.

The safety of magnetic resonance imaging and CMR has been the subject of several important publications in 2018. *Nazarian et al.* (20) showed in 1,509 patients that 1.5T magnetic resonance imaging can be safe in patients who have conventional cardiac devices that are not designated as magnetic resonance-conditional. Only minor changes in device mode and P-wave amplitude were observed during magnetic resonance imaging, but no significant immediate or long-term adverse clinical events occurred.

The recent debate over the potential of magnetic resonance imaging to induce genotoxic effects was the subject of an in vitro and in vivo study published by *Critchley and colleagues* (21). Isolated peripheral blood mononuclear cells from healthy volunteers showed no change in cell integrity measures such as histone H2AX phosphorylation (c-H2AX) expression after exposure to a standard magnetic resonance imaging scan. In vivo, blood samples obtained from 64 consecutive patients before and after a CMR scan, also showed no change in cell integrity measures with wide variability between subjects, but there was a reduction in circulating T-cells. The authors conclude that previous small studies using γ-H2AX as a marker of DNA damage should be interpreted with caution.

Computed tomography

The main clinical application of cardiac CT remains coronary artery imaging and the analysis of coronary atherosclerotic disease. Despite the advent of coronary CT angiography (CTA), coronary calcium quantification by CT continues to be an option to quantify coronary atherosclerosis for risk stratification, which in certain patient populations is endorsed by the European Society of Cardiology guidelines (22). The prognostic value of coronary artery calcium (CAC) persists over a long period of time, as demonstrated by *Budoff et al.* (23) in 6,814 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) study aged between 45-84 years (51% women) and free of cardiovascular disease at baseline. During a median follow-up of 11.1 years, 500 atherosclerotic disease events occurred. Event rates in individuals without CAC ranged from 1.3% to 5.6%, depending on age, gender, and racial subgroups. On the other hand, individuals with CAC score >300 had 10-year event rates from 13.1% to 25.6%, highlighting the strong and long-term, prognostic power of CAC. Whether the progression of CAC has prognostic implications in healthy individuals was evaluated by the Heinz Nixdorff Recall Study (24) where 3,281 individuals randomly selected from the population underwent repeated CAC scans at a mean interval of 5.1 years, and were followed for 8 years after the second scan. A total of 241 cardiovascular events occurred and CAC progression was significantly larger in individuals with events as compared to those without events (115 vs. 8 Agatston units). While progression of CAC was associated with the occurrence of cardiovascular events, it only added minimally to the risk prediction beyond the last CAC scan that was performed.

Coronary CTA has been associated with relatively high radiation exposure in the past. In the Prospective Multicenter Registry on RadiaTion Dose Estimates of Cardiac CT AngIOgraphy IN Daily Practice (PROTECTION IV) survey, an analysis of contemporary radiation exposure of coronary CTA across 61 hospitals in 31 countries was performed. Among 4,502 patients enrolled, the median dose length product of coronary CTA was 195 mGy*cm (IQR 110-338), corresponding to effective doses between 2.7 and 5.1 mSv, depending on the conversion factor used (25). Overall, radiation dose was 78% lower than in a similar survey performed in 2007 (26). Importantly, only 1.9% of coronary CTA examinations were classified as “unevaluable“ indicating the improvement in technology and acquisition protocols to minimize radiation dose without significant impact on image quality.

The clinical role of coronary CTA was strengthened in outcome trials that demonstrated the value of integrating CT imaging into clinical decision making. In the Scottish COmputed Tomography of the Heart (SCOT-Heart) trial (27), 4,146 patients who had been referred to outpatient clinic for stable angina were randomized to receive standard workup (consisting mainly of exercise electrocardiogram) or standard workup plus coronary CTA. After 5 years of follow-up, the rate of the primary endpoint (death from coronary heart disease or nonfatal myocardial infarction) was significantly lower in the coronary CTA group (2.3%) as compared to standard of care (3.9%, HR 0.59; 95% CI 0.41–0.84, p=0.004). This difference was driven by a reduction in non-fatal myocardial infarction, whereas there was no difference in cardiac mortality. Interestingly, there were more revascularisations in the CTA arm in the early phase of follow-up, but after 5 years, revascularization rates were equal in both patient groups (491 patients in the coronary CTA group and 502 in the standard of care group).

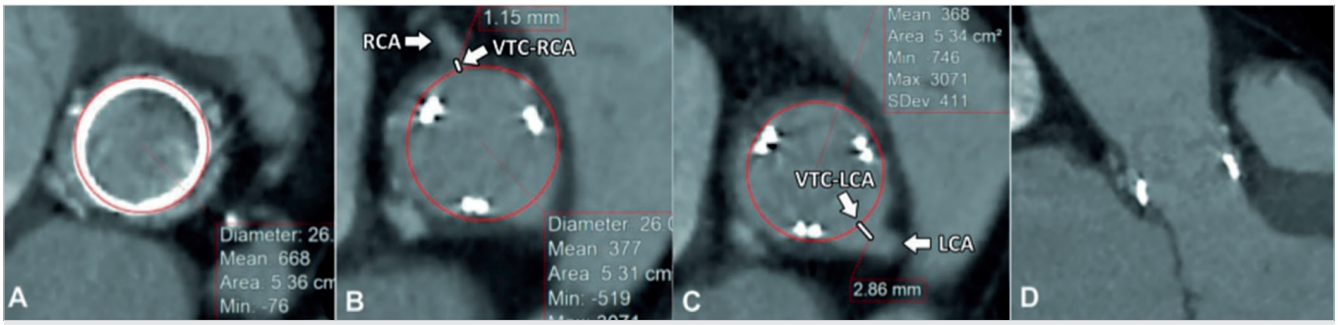

FIGURE 3. Computed tomography evaluation of the distance between a virtual "transcatheter ring" and the ostium of the left and right coronary artery. A ring with the same diameter as the valve to be implanted is virtually placed at the height of each coronary ostium and the distance is measured. Distances < 4.0 mm are the best predictor of obstruction. Reproduced with permission from *Ribeiro et al.* (34)

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The trial therefore does not support the frequent notion that the use of coronary CTA leads to an excess in invasive angiograms and revascularizations. The difference in myocardial infarction rates is likely due to optimization of secondary prevention treatments. Substantial clinical data have become available for CT-derived Fractional Flow Reserve (FFR_{CT}). *Jensen et al.* (28) published a series of 774 patients who underwent coronary CTA with calculation of FFR_{CT}. Patients in whom invasive angiography had been cancelled because of a negative FFR_{CT}, did not experience MACE during a mean follow-up period of 157 ± 50 days. Similarly, the Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care (ADVANCE) registry enrolled 5,083 patients who underwent coronary CTA at 38 sites because of suspected CAD between 2015 and 2017 (29). On one hand, change in core laboratory management plans was reported: the availability of FFR_{CT} led to a change in the management plan (as compared to core laboratory coronary CTA alone) in 67% of patients. This, however, was somewhat "virtual" since patients were not treated according to the core laboratory management plan but according to local decision. However, the authors report that no deaths/myocardial infarctions occurred within 90 days in 1592 patients with FFR_{CT} >0.80, while 14 events occurred in 3145 patients with FFR_{CT}≤0.80. Furthermore, *Collet et al.* (30) showed the role of coronary CTA on the management of patients with coronary artery disease. The coronary CTA or invasive coronary angiography of 223 patients with de novo diagnosis of left main or 3-vessel CAD were evaluated by separate heart teams composed of an interventional cardiologist, a cardiac surgeon and a radiologist. Each heart team, blinded for the other imaging modality, quantified the anatomical complexity of the CAD according to the SYNTAX score and integrated clinical information using the SYNTAX score II to recommend treatment. The agreement concerning the treatment decision between coronary CTA and invasive coronary angiography (primary endpoint) was very high (kappa 0.82) and the heart teams agreed on which segments should be revascularised in 80% of cases. The use of FFR_{CT} changed the treatment decision in 7% of patients. *Ferencik et al.* (31) studied the relationship between high-risk plaque on coronary CTA and downstream events based on 4,415 patients from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, of which 676 had high-risk plaque. During 25 months follow-up, 131 events occurred. The presence of high-risk plaque was associated with a higher event rate, (6.4% vs. 2.4%; HR, 2.73; 95% CI, 1.89–3.93), but the authors draw careful conclusions about potential clinical value of high-risk plaque detection because of the low positive predictive value of high-risk plaque. *Oikonomou et al.* (32) defined a "Fat Attenuation Index" (FAI) to describe the gradient of CT attenuation within pericoronary fat surrounding coronary lesions. Both in a derivation cohort of 1,872 patients, and a validation cohort of 2,040 patients, a HR of approximately 2.1 was found for the FAI around the right coronary artery to predict cardiac mortality. This completely novel approach to the identification of high-risk plaque – to analyze changes in pericoronary fat attenuation under the assumption that plaque inflammation changes fat composition – has also been used by *Göller et al.* (33) in a similar fashion but on a much smaller scale, and will certainly benefit from further validation.

The evidence underlining the value of cardiac CT in the workup of patients scheduled for transcatheter aortic valve-in-valve implantation is rapidly growing. From 1,612 transcatheter aortic valve-in-valve procedures, *Ribeiro et al.* (34) reported a frequency of clinically relevant obstruction of the coronary ostia of 2.3%. The authors showed that a short distance between a virtual transcatheter ring and the respective coronary ostium measured on CT was the strongest predictor of coronary obstruction, highlighting the ability of cardiac CT to provide very exact, complex spatial measurements *(Figure 3)*.

Nuclear imaging

Quantitative coronary flow measurement with positron emission tomography (PET) and its prognostic implications attracted much attention in the last year. *Gupta et al.* (35) collected 5,6 year follow-up data in a large cohort of 4,029 patients with known or suspected CAD who underwent quantitative PET. Patients with concordant impairment of global LV coronary flow reserve (CFR) and stress MBF had significantly higher cardiovascular mortality as compared to patients with impaired CFR but preserved stress MBF (3.3% vs. 1.7% per year). Patients with preserved CFR but impaired stress MBF and patients with concordantly preserved CFR and stress MBF had cardiovascular mortality of 0.9% and 0.4% per year, respectively. At multivariable analysis, global CFR was a stronger independent predictor of cardiovascular mortality (HR, 1.83; 95% CI 1.47–2.27; p<0.001 per unit decrease in CFR) than stress MBF (HR 1.35; 95% CI 1.47–2.27; p<0.001 per unit decrease in stress MBF). The stronger independent prognostic value of CFR compared to maximal MBF can be partly explained by the fact that CFR better reflects vasodilator capacity and reduces systematic errors in the measurement of MBF. This integrated non-invasive physiological assessment of coronary circulatory function identifies phenotypes of stable CAD with varying prognosis and provides risk-based guidance for decision of referral for invasive coronary angiography. Patients with concordantly reduced CFR and stress MBF have a higher likelihood of multi-vessel disease and further evaluation with invasive coronary angiography maybe needed whereas patients with preserved CFR and MBF are unlikely to have significant coronary artery stenosis and can be treated conservatively. Interestingly, patients with reduced CFR but preserved stress MBF have increased risk of cardiovascular death despite the lack of myocardial ischemia in whom intensification of preventive therapies may be beneficial.

The prognostic implications of sequential hybrid imaging strategy, using PET perfusion imaging when obstructive CAD on coronary computed tomography angiography (CTA) is suspected, were evaluated in 864 consecutive symptomatic patients with intermediate probability of CAD (36). Suspected obstructive coronary artery lesions on coronary CTA were observed in 402 (47%) patients. Of those, 207 patients had abnormal myocardial perfusion on PET. The annual MACE rate was significantly higher in these patients than in patients with normal myocardial perfusion on PET (2.5% vs. 0.5%, p=0.004). There were no differences in the annual MACE rate of patients with normal myocardial perfusion on PET and patients without obstructive CAD on coronary CTA. The study emphasizes that, myocardial ischemia has major role in outcome and beyond the anatomical findings in CTA. The selective perfusion imaging after CTA appears a feasible strategy to diagnose and risk-stratify patients with suspected CAD.

The effect of myocardial revascularization to restore absolute myocardial perfusion was investigated in 53 patients who underwent serial [^{15}O]H_2O PET perfusion imaging at baseline and after revascularization (37). After revascularization, regional rest and stress MBF improved from 0.77±0.16 to 0.86±0.25 mL/min/g and from 1.57±0.59 to 2.48±0.91 mL/min/g, respectively (p<0.01 for both). After percutaneous coronary intervention, an increase in FFR paralleled the improvement in myocardial perfusion. The study confirmed that successful coronary revascularization had a significant and positive impact on absolute myocardial perfusion and the improvement of FFR after revascularization is directly related to the increase in hyperemic MBF.

Psychological stress may precipitate myocardial ischemia and this has been associated with adverse cardiovascular outcomes in patients with CAD, although the mechanisms of this increased risk remain unknown. On the other hand, cardiac troponin is a recognized marker of myocardial injury but also can be released in the setting of myocardial ischemia, even in the absence of necrosis. *Hammadah et al.* (38) investigated whether patients with mental stress–induced myocardial ischemia will have high resting and post-stress high-sensitivity cardiac troponin I (hs-cTnI). In this study, 587 patients with stable CAD underwent single photon emission computed tomography (SPECT) myocardial perfusion imaging during mental stress testing and during conventional exercise stress testing. Ischemia was detected during mental stress in 16% (n=94) and during physical exercise in 34.8% (n=204) patients. Most patients who developed exercise-induced ischemia also developed ischemia during mental stress (74.5%), but the groups were not completely overlapping. Interestingly, the baseline hs-cTnI levels were similarly elevated in all groups with ischemia, either mental or physical, as compared to those without ischemia. Furthermore, the patients with high hs-cTnI had greater odds of developing mental (odds ratio: 2.4; p<0.001) and physical (odds ratio: 2.4; p<0.001) ischemia. However, the increase in hs-cTnI levels after stress occurred only in the patients with ischemia during physical stress. The findings suggest that hs-cTnI elevation is an indicator of chronic ischemic burden experienced during everyday life.

Refractory angina is a clinical challenge as the therapeutic options are limited. In a randomized study of 30 patients the effects of angiogenic and lymphangiogenic AdVEGF-DDNDC gene therapy were investigated (39) Electromechanical NOGA mapping and [^{15}O]H_2O PET were used to identify hibernating viable myocardium where treatment was targeted. Myocardial perfusion was assessed at baseline and after 3- and 12-months of follow-up. The gene therapy increased perfusion reserve significantly in the treated area in the active the-

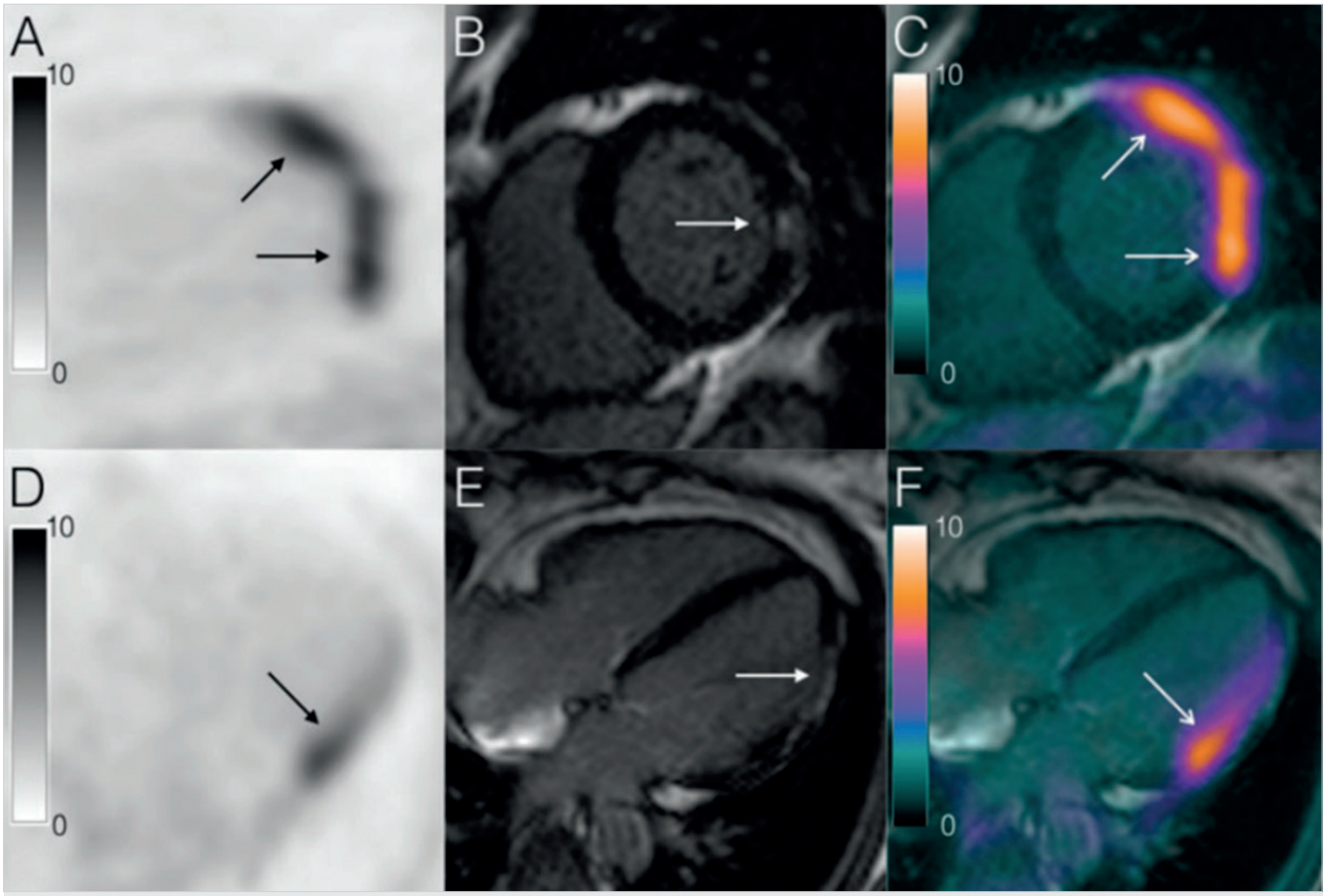

FIGURE 4. Hybrid imaging assessment of biopsy-proven cardiac sarcoidosis. On maximum intensity projection positron emission tomography (PET) images (A and D) of the short- and long-axis of the left ventricle, uptake of ^{18}F-fluorodeoxyglucose (FDG) of the lateral wall indicating inflammation is shown (arrows). On late gadolinium contrast enhanced cardiac magnetic resonance, patchy epicardial and mid-myocardial fibrosis can be visualized (B and E, arrows). Fusing PET-MR images, the activity of the disease can be assessed showing areas of inflammation that exceed the areas of fibrosis (panels C and F). Reproduced with permission from *Wicks et al.* (42)

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rapy group as compared to baseline (baseline 1.00±0.3, at 3 months 1.31±0.46 and 12 months 1.44±0.48 mL/g/min) and as compared to placebo group. The study demonstrated that AdVEGF-DDNDC gene therapy is safe and can improve myocardial perfusion in patients with refractory angina.

Imaging vascular processes with 18F–Sodium Fluoride (^{18}F-NaF) PET has provided new insights. *Lee et al.* evaluated the clinical relevance of coronary ^{18}F-NaF uptake using optical coherence tomography (OCT), intravascular ultrasound (IVUS), and coronary CTA in 51 patients with CAD.40 Coronary plaques with ^{18}F-NaF uptake showed significantly higher plaque burden, more frequent posterior attenuation and positive remodelling on IVUS, and significantly higher maximum lipid arc and more frequent microvessels on OCT (all $p<0.05$). There were no differences in minimum lumen area and area of calcium between ^{18}F-NaF–positive and –negative lesions. Among the 15 lesions that met both IVUS- and OCT-defined criteria for high-risk plaque, 14 showed ^{18}F-NaF–positive uptake. The study confirms the earlier results that accumulation of ^{18}F-NaF in the coronary plaques is a sign of plaques with high-risk characteristics.

Cardiac PET and CMR are the mainstay of non-invasive imaging for the detection of cardiac sarcoidosis and ongoing inflammation. However, whether the extent and severity of perfusion and ^{18}F-fluorodeoxyglucose (FDG) metabolism abnormalities have prognostic implications is yet undefined. *Sperry et al.* (41) observed in 203 patients with suspected cardiac sarcoidosis that the summed score in segments with a perfusion–metabolism mismatch and the heterogeneity of metabolism quantified by the coefficient of variation were independently associated with adverse events (death, heart transplant and ventricular arrhythmia requiring defibrillation). The results suggest that quantitative measures of FDG PET images provide incremental prognostic advantage over conventional scoring.

Fusion imaging

Fusion imaging with PET/CT and PET/CMR is used in the clinical and pre-clinical setting to relate anatomical tissue changes with functional alterations. *Wicks et al.* (42) evaluated the diagnostic and prognostic value of positron emission tomography (PET) with F18-fluorodeoxyglucose (FDG) and cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) in 51 patients with suspected cardiac sarcoidosis *(Figure 4).* The prevalence was 65%. The sensitivity of PET and CMR were 85% versus 82% respectively, which improved to 94% when both modalities were integrated (hybrid imaging). Specificity however was low (44%). Over the median follow-up of 2.2 years, events occurred in 18 (35%) patients (death, arrhythmias, heart failure). Predictors of events were cardiac PET abnormalities, and the presence of LGE on CMR; the presence of abnormalities of both imaging modalities was the strongest predictor of outcome. In addition, Vita and colleagues (43) used PET/CMR in 107 patients with suspected sarcoidosis. Cardiac LGE on CMR was detected in 91 (85%) patients, of which 60 had abnormal PET FDG uptake (active inflammation). The addition of the PET data to the CMR data significantly reclassified patients as having a higher or lower likelihood of cardiac sarcoidosis.

Calcagno et al. (44) used PET/CMR in a rabbit model of atherosclerosis, to quantify plaque inflammation and to assess the efficacy of a leukotriene A4 hydrolase (LTA4H) inhibitor. Plaque inflammation was assessed with FDG, and the arterial vessel wall was evaluated with LGE CMR to quantify plaque inflammation, neovasculature, permeability, and burden. The results showed a modest reduction in plaque inflammation (by FDG PET) in the animals treated with low dose of the LTA4H inhibitor, while no changes in the vessel wall (by LGE CMR) were noted.

Rivers and colleagues (45) used (FDG) PET/CT to evaluate the relation between abdominal visceral adipose tissue (on CT) and vascular inflammation (on FDG PET) in 77 patients with psoriasis. Importantly, psoriatic plaques are not limited to the skin, but systemic effects may lead to visceral obesity and inflammatory atherogenesis with increased risk of myocardial infarction, stroke and cardiovascular death. The results showed that visceral adiposity on CT was associated with vascular inflammation on FDG PET. Moreover, 13 patients underwent repeat PET/CT after 1 year psoriasis treatment; the results showed a reduction in psoriasis severity and visceral obesity, with an improvement in vascular inflammation.

Disclosures

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