The year 2020 in the European Heart Journal - cardiovascular imaging: part I

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REVIEW

The year 2020 in the *European Heart Journal – Cardiovascular Imaging*: part I

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The *European Heart Journal – Cardiovascular Imaging* was launched in 2012 and has during these 9 years become one of the leading multimodality cardiovascular imaging journals. The journal is currently ranked as number 20 among all cardiovascular journals. Our journal is well established as one of the top cardiovascular journals and is the most important cardiovascular imaging journal in Europe. The most important studies published in our Journal in 2020 will be highlighted in two reports. Part I of the review will focus on studies about myocardial function and risk prediction, myocardial ischaemia, and emerging techniques in cardiovascular imaging, while Part II will focus on valvular heart disease, heart failure, cardiomyopathies, and congenital heart disease.

Keywords multimodality imaging • echocardiography • cardiovascular magnetic resonance • nuclear imaging

Introduction

European Heart Journal – Cardiovascular Imaging has successfully consolidated as a multimodality journal and is currently rated as number 20 out of 141 cardiovascular journals in the World with an impressive impact factor of 6.875. It 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 published each last year is here continued.[1,2] In two articles, we will summarize the most important papers from the journal in 2019. Part I will focus on myocardial function and risk prediction, myocardial ischaemia, and emerging techniques in cardiovascular imaging.

Recommendations and expert consensus documents from the European Association of Cardiovascular Imaging

One important assignment of *European Heart Journal – Cardiovascular Imaging* is to publish position papers, recommendations and expert consensus papers from the European Association of Cardiovascular Imaging (EACVI). The journal published important recommendations and expert consensus papers in the field of cardiac imaging.[3–6] These papers are commented on in more detail elsewhere in the two documents. The EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel

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during the ongoing pandemic was published together with advice on the role of cardiovascular imaging for myocardial injury in hospitalized COVID-19, and how to use lung ultrasound.[7–9]

The EACVI scientific initiatives committee published four interesting surveys in 2020, including a global survey of the echocardiographic findings in 1216 patients hospitalized with COVID-19.[10–13] A new section on how to do different imaging measures was created, with the first manuscripts focusing on left atrial (LA) and right ventricular (RV) strain imaging.[14,15] The best research presented at our conferences in 2019 was also published.[16–18]

Myocardial function and risk prediction

Two echocardiographic studies showed the importance of RV function assessment in risk stratification. Muraru *et al.*[19] included a large population of patients with various cardiac diseases, and identified the partition values for RV ejection fraction (EF) by 3D echocardiography to define mild (RVEF > 45%), moderate (RVEF ≤ 45% and >40%), and severe (RVEF ≤40%) RV dysfunction based on the associated risk of mortality. 3D RVEF confirmed its prognostic value in an external validation cohort and with higher predictive value as compared to standard measures of RV function. RV free wall strain, as another sensitive measure of RV function, was found by Gavazzoni *et al.*[20] to be independently associated with all-cause mortality and heart failure hospitalization in 458 patients with asymptomatic left-sided structural heart disease, and with an optimal cut-off value of -22%.

Echocardiographic measures of left ventricular (LV) function were also proposed to improve risk stratification. The mid-wall fractional shortening (MWFS), a simple and geometry-independent measure derived from the M-mode, demonstrated an independent association with the risk of heart failure and death in the DAVID-Berg study, which included a large primary care population at high cardiovascular risk.[21] Of interest, MWFS showed an additional prognostic value on top of patient clinical characteristics and elevated proBNP, and with a complementary role to LVEF. Reduced contractility in myocardial fibres can appear as a paradoxical stretch at the beginning of systole, the so-called early systolic lengthening (DESL), which can be assessed by speckle tracking imaging. In more than 1200 individuals from a low-risk general population, DESL showed an independent association with heart failure and myocardial infarction (MI), but not with cardiovascular death in a study by Brainin *et al.*[22] Braunauer *et al.*[23] proposed the left atrium filling index as a novel accurate measure to estimate LV filling pressure using speckle tracking imaging. In patients with cardiovascular risk, but with preserved LVEF, this index was associated with the risk of heart failure hospitalization even after correction for important clinical and echocardiographic confounders. Hwang *et al.*[24] developed a risk model which included LV global longitudinal strain alongside other clinical factors, and showed accurate prediction of mortality across the different ranges of LVEF in patients with acute heart failure ($n = 3248$).

In valvular heart disease, several studies confirmed the value of assessing myocardial function by echocardiography to better risk stratify these patients. Vollema *et al.*[25] showed that LV GLS was independently associated with all-cause mortality in 616 patients with symptomatic severe aortic stenosis (AS). They were able to refine the prognostic value of the recently proposed staging classification based on cardiac damage, from LV damage, to left atrium damage and to pulmonary vasculature and RV damage (*Figure 1*). A layer-specific assessment of longitudinal strain was also proposed by Ilardi *et al.*[26] in 211 patients with severe AS and preserved LVEF. The authors found that endocardial longitudinal strain was the most sensitive in detecting the presence of symptoms and was independently associated with cardiovascular outcomes. Anand *et al.*[27] reconstructed from echocardiographic measures the pre-operative LV end-diastolic pressure-volume curves and derived a measure of LV stiffness in a large cohort ($n = 1893$) of patients undergoing aortic valve replacement for AS. The authors showed that this estimate was associated with long-term mortality across different grades of LV diastolic function and both in patients with preserved and reduced LVEF.

Finally, other advanced echocardiographic measures demonstrated their use in the risk stratification of patients with different cardiovascular disease. The myocardial performance index (MPI) by Tissue Doppler Imaging was independently associated with adverse cardiovascular events in 210 atrial fibrillation patients with ongoing arrhythmia during examination by Dons *et al.*[28] with an increased risk of 20% per 0.1 increase in MPI.

In the long-term follow-up of the EVINCI study, Neglia *et al.*[29] evaluated the prognostic relevance of coronary anatomy, ischaemia, and early revascularization in patients with stable coronary artery disease (CAD). The EVINCI-Outcome study population consisted of 430 patients who underwent anatomical imaging by coronary computed tomography angiography (CTA) and non-invasive myocardial ischaemia imaging followed by invasive coronary angiography (ICA) if at least one non-invasive test was abnormal. Obstructive CAD at coronary CTA was the only independent imaging predictor of adverse events during 4.4 years of follow-up. The study demonstrated that the early management of CAD guided by combined anatomical and functional imaging improves clinical outcome.

Multiple studies have investigated the prognostic value of adverse plaque characteristics and atherosclerotic plaque burden as depicted by coronary CTA. In the long-term coronary CTA CONFIRM registry, van Rosendael *et al.*[30] examined the prognostic value of risk factors and atherosclerotic extent in patients with normal coronary CTA or non-obstructive CAD ($N = 3547$). Adjusted for segment involvement score, hypertension, and diabetes predicted major adverse cardiac event (MACE) risk in non-obstructive CAD, while diabetes did not increase risk in the absence of CAD. Another long-term follow-up study published by Finck *et al.*[31] evaluated the incremental prognostic value of morphological plaque features beyond clinical risk and coronary stenosis. A total of 1615 patients with suspected CAD underwent coronary CTA and morphological plaque features were assessed, follow-up was 10.5 years. In addition to plaque extent, morphologic plaque features such as a spotty calcification pattern and napkin-ring sign were predictive for events. Ferraro *et al.*[32] sought to determine the association between high-risk plaque (HRP) and future acute coronary syndrome (ACS) events on a lesion level within the ICONIC study. ACS patients with culprit lesions confirmed by ICA and co-registered to baseline coronary CTA were included in the study. Compared to non-obstructive HRP lesions, obstructive lesions without HRP exhibited a non-significant HR for ACS. While HRP was more prevalent among obstructive lesions, non-obstructive HRP lesions outnumbered those that were

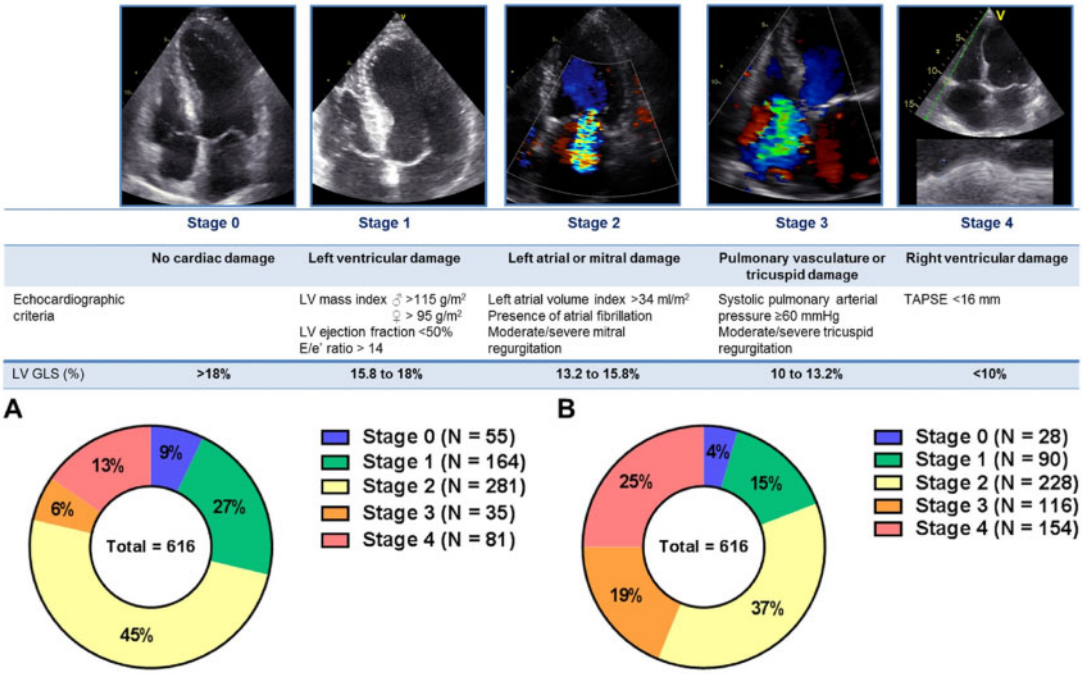

Figure 1 Proposed staging classification according to the presence and extent of cardiac damage on echocardiography with addition of LV GLS quintiles for reclassification. Distribution of stages of cardiac damage in study population according to the proposed staging classification (*A*) and after reclassification by incorporating LV GLS (*B*). Modified from ref.[25] GLS, global longitudinal strain; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion.

obstructive and conferred risk clinically approaching that of obstructive lesions without HRP. All these investigations provide solid evidence that coronary CTA allows for reliable anatomic evaluation of CAD, which is associated with strong prognostic information.

Building on these and other previous findings a position paper from EACVI has addressed the current concepts regarding the relationship between adverse plaque characteristics as assessed by non-invasive imaging techniques and MI.[4] The position paper underlines the fact that whilst individual adverse atherosclerotic plaques may cause acute MI, much more commonly they will heal without causing an event. The predictive value of individual adverse plaque therefore remains too low to warrant plaque level risk prediction or treatment. The concept however works better at the level of the patient, whereby patients that develop adverse plaques are more likely to suffer MI than those that do not and the higher burden of adverse plaques the worse the prognosis. Further work is required to assess how this information can be best incorporated in to clinical practice and used to govern treatment decisions.

Compelling evidence has been further accumulated regarding the role of coronary artery calcium (CAC) scoring in risk assessment in various asymptomatic patient populations. Miname *et al.*[33] demonstrated that vascular age derived from CAC score can improve atherosclerosis cardiovascular disease (CVD) risk discrimination in primary prevention asymptomatic heterozygous familial hypercholesterolaemia patients undergoing standard lipid-lowering therapy. A study from the Multi-Ethnic Study of Atherosclerosis investigated the associations of recreational and non-recreational physical activity (PA) with CAC density vs. volume and cardiovascular disease events ($n = 3393$) over 13.7 years of follow-up with 520 CVD events.[34] Recreational PA was associated with lower CVD risk. The study showed that recreational PA may be associated with a higher density, but not a higher volume of CAC. On the other hand, non-recreational PA may be associated with lower CAC density, suggesting these forms of PA may not have equivalent associations with CAC. Importantly, while PA may affect the composition of CAC, the associations of PA with CVD risk appear to be independent of CAC.

In the ROBINSCA (Risk Or Benefit IN Screening for CArdiovascular disease) trial, asymptomatic individuals were randomized into screening arm A [$n = 14478$; Systematic COronary Risk Evaluation (SCORE), 10-year fatal and non-fatal risk] or screening arm B ($n = 14450$; CAC scoring).[35] The authors demonstrated that compared to risk stratification based on SCORE, CAC scoring classified significantly fewer men and women at increased risk, and less preventive treatment was indicated.

Van der Ven *et al.*[36] contributed an important paper detailing reference ranges for left and RV volumes and mass for the paediatric population (0–18 years). Data were stratified by age range including non-indexed and indexed to body surface area values with participants coming from three European centres. Truong *et al.*[37] also proposed reference ranges for LA strain and strain rate using cardiac magnetic resonance (CMR) feature tracking.

Several groups considered the prognostic value of CMR in ACS. Feistritzer *et al.*[38] prospectively investigated nearly 300 patients presenting with a non-ST-elevation myocardial infarction (NSTEMI) with all patients undergoing CMR three days after admission. They found that, in contrast to patients presenting with ST-elevation myocardial infarction (STEMI), there was no additional long-term prognostic value of CMR-derived infarct characteristics above and beyond LV ejection fraction. Masci *et al.*[39] examined the optimal timing of CMR examination in patients with STEMI. They found that early, deferred or paired CMR studies were equivalent stratification strategies for outcome prediction. Linhares-Filho *et al.*[40] investigated the clinically challenging diagnosis of periprocedural MI. They found that new late gadolinium enhancement (LGE) was a better prognostic predictor than a biomarker-only definition of periprocedural MI after uncomplicated revascularization. In patients who suffered an out-of-hospital cardiac arrest, Baritussio *et al.*[41] showed that LGE presence and extent showed a significant association with recurrent adverse events whilst ejection fraction did not identify those with an unfavourable outcome.

In dilated cardiomyopathy, Xu *et al.*[42] described an LV remodelling index and showed that it was an independent predictor of all-cause mortality, heart transplantation and heart failure readmission. In arrhythmogenic RV cardiomyopathy (ARVC), Segura-Rodriguez *et al.*[43] showed that desmin (*DES*) mutation carriers could be identified by a specific and extensive LV subepicardial circumferential LGE pattern (31702781). In a similar study by Augusto *et al.*[44] considering arrhythmogenic LV cardiomyopathies, they showed that in patients with mutations associated with desmoplakin (*DSP*) and filamin C (*FLNC*), there was a characteristic subepicardial ring-like scar pattern. Interestingly, in work examining the important question of screening of relatives in ARVC Jurlander *et al.*[45] found that focusing on electrical abnormalities with 12 lead electrocardiogram (ECG), signal-averaged ECG, and Holter monitoring was more sensitive than imaging modalities in detecting cases. In hypertrophic cardiomyopathy (HCM), a prospective study by Chen *et al.*[46] showed that those with sarcomeric mutations had a greater extent of myocardial fibrosis and more severe ventricular diastolic dysfunction than those without. In the apical phenotype, Yang *et al.*[47] describe the prevalence of LV apical aneurysm which is often missed by echocardiography and confirm that it is associated with higher risk of MACE compared to apical HCM without aneurysm. Hooks *et al.*[48] published on the use of CMR for LV thrombus detection in non-ischaemic cardiomyopathy. They found that the 12-month incidence of embolism associated with LV thrombus was not different compared with LV thrombus in ischaemic cardiomyopathy and could be independently predicated by lower LV ejection fraction and LGE extent.

In valvular heart disease, Postigo *et al.*[49] compared the clinical efficacy of echocardiography and CMR for chronic aortic regurgitation. Hwang *et al.*[50] examined native T1 values after surgical aortic valve replacement for severe AS. They found that changes in native T1 values were associated with changes in LV systolic function as well as prognosis. Bhuva *et al.*[51] utilized a machine learning approach to examine differences in myocardial plasticity in patients with AS by anatomical location and sex.

In a heart failure with preserved EF (HFpEF) cohort, Nitsche *et al.*[52] suggest that higher T1 values at the anterior RV insertion point are independently associated with prognosis in these patients, whilst Miller *et al.*[53] demonstrated sex-specific differences in patterns of LV remodelling. Simon *et al.*[54] showed that regular alcohol consumption only minimally affects LV, RV and LA structure and function as measured by CMR in the UK Biobank cohort. From the same dataset, van Hout *et al.*[55] compared general vs. visceral obesity and their effect on LV parameters and suggest that visceral obesity is more important in LV remodelling.

Ischaemic heart disease

Authors are to be applauded for the diversity of their achievements in the studies published in 2020. The field of CAD is a typical field requiring multimodality imaging, but also important single imaging modality studies were launched during 2020. A prospective study enrolled 2149 consecutive patients who underwent both coronary angiography and carotid ultrasonography. Ultrasound max-carotid plaque length provided independent and incremental predictive information for the clinical severity of CAD over traditional risk factors. It appeared to be a rapid and simple tool for CAD risk stratification. The best cut-off value for the max-carotid plaque length was 6.3 mm with good sensitivity (84.6%) and negative predictive values (89.1%).[56]

Mechanical dispersion (MD) is a speckle tracking-derived echocardiographic parameter gaining interest as a marker of ventricular arrhythmias in a wide range of cardiac conditions, including CAD and cardiomyopathies.[57] The physiological determinants for MD are not fully elucidated, but LV MD seems to be the result of heterogeneous electrical conduction. Increased MD was associated with the prevalence of CAD, hypertension, obesity, and diabetes ($P < 0.01$ for all) in a study of 2529 subjects (general population).[58] A retrospective, observational study of 96 patients demonstrated the association between LV MD and the extent of LV scar as assessed with contrast-enhanced CMR after STEMI.[59] Abou *et al.* demonstrated that higher LV MD was an independent risk marker of subsequent cardiovascular event. Electro-mechanical coupling is also important to understand the electromechanical interactions after myocardial infarct. This was elegantly demonstrated in a study conducted in the STANISLAS cohort.[60] Longer QTc was related to increased MD. However, the QRS duration was not associated with MD, suggesting that the simple measurement of MD will have incremental value as compared to clinical, biological, LV ejection fraction, and ECG characteristics.

The diagnostic and prognostic value of dobutamine stress echocardiography (DSE) has been well-documented for years, and DSE has similar sensitivity and higher specificity compared with nuclear perfusion imaging for the detection of CAD.[61] Up to 33% of the patients referred for DSE have suboptimal image quality despite harmonic and improvement in ultrasound imaging, and the value of LV-opacification and the combination of 3D, tri-plan to 2D images was explored in 718 patients with indication for DSE.[62] The authors demonstrated the high feasibility and the improved quality of DSE when 3D was used in addition to 2D, both combined with contrast LV-opacification.

Basic and advanced quantification skills are important to secure high-quality care for our patients. Learning and developing new proficiencies in echocardiography is key and new learning opportunities are provided by different simulation tools.[6]

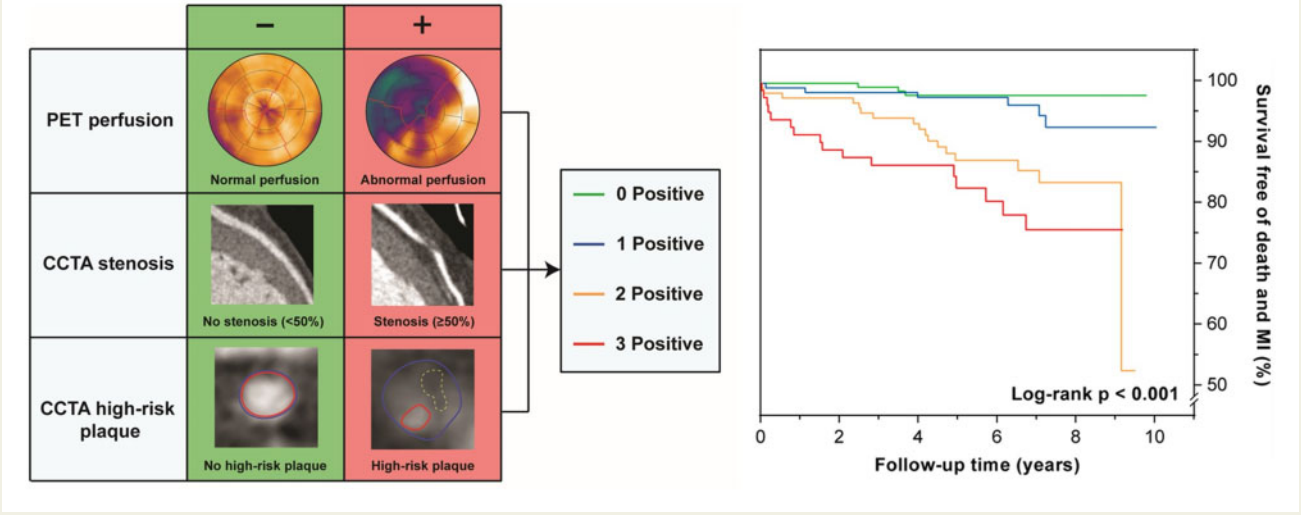

Figure 2 Prognostic values of PET perfusion imaging, CCTA-derived stenosis and HRPs for the occurrence of death or MI.[67]

Kinnel *et al.*[64] examined the utility of stress perfusion CMR in patients who have undergone coronary artery bypass grafting. They described the discriminative prognostic value of the technique with a higher incidence of MACE and cardiovascular death in patients with inducible ischaemia and/or LGE. A similarly underrepresented group in clinical trials is the elderly population. Pezel *et al.* show that stress perfusion CMR is safe and has discriminative prognostic value in those over the age of 75 years.[63] De Knegt *et al.*[65] showed that visual CMR perfusion and computed tomography (CT) quantitative relative myocardial blood flow (MBF) outperformed visual CT perfusion and provided incremental discrimination compared with coronary CTA alone for the diagnosis of haemodynamically significant CAD.

The decline in the prevalence of myocardial ischaemia observed on single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been well described. Al Badarin *et al.*[66] sought to determine if similar trends exist with positron emission tomography (PET). The authors have analysed a total of 156 244 MPI studies [30% (PET) and 70% SPECT)]. Between 2003 and 2017, the number of PET studies increased from 18 to 61 studies/1000 patient encounters, while SPECT volumes declined from 169 to 34/1000 patient encounters ($P < 0.001$). The prevalence of any ischaemia in SPECT-tested patients declined from 53.9% to 28.3%, whereas ischaemia prevalence in PET-tested patients declined from 57.2% to 38.2% ($P < 0.001$). The utilization of PET MPI at a large-volume referral centre increased significantly, however the prevalence of ischaemia with SPECT and PET during the same period both have decreased.

Driessen *et al.*[67] sought to determine the prognostic value of combined functional testing using PET perfusion imaging and anatomical testing using coronary CTA. In 539 patients referred for hybrid [^{15}O]H_2O PET-CT imaging due to suspected CAD, PET was used to determine MBF, whereas coronary CTA images were evaluated for obstructive stenoses and HRP morphology. Patients were followed up for the occurrence of MACE for 6.8 years and 42 (7.8%) patients experienced events. The authors demonstrated that PET-derived MBF, coronary CTA-derived stenosis severity, and HRP morphology were univariably associated with death and MI, whereas only stenosis severity and HRP morphology provided independent prognostic value (*Figure 2*).

Nomura *et al.*[68] investigated the association between pericoronary inflammation as assessed by pericoronary adipose tissue (PCAT) CT attenuation and coronary flow reserve (CFR) by PET in patients with suspected CAD. They demonstrated that coronary perivascular inflammation by coronary CTA was independently associated with downstream myocardial perfusion by PET and that CFR was lower in the presence of higher perivascular inflammation. They concluded that PCAT CT attenuation might help in identifying patients likely to have myocardial ischaemia.

Emerging techniques

Raisi-Estabragh *et al.*[69] contributed a timely review on the novel image analysis technique of radiomics with its potential to radically alter the depth of image phenotyping beyond routinely measured parameters (*Figure 3*). A study by Hu *et al.*[70] utilized a machine learning (ML) technique to optimize per-vessel prediction of early coronary revascularization (ECR) within 90 days after fast SPECT MPI. A total of 1980 patients with suspected CAD who underwent stress/rest 99mTc-sestamibi/tetrofosmin MPI with new-generation SPECT scanners were included in the analysis. ML utilized 18 clinical, 9 stress test, and 28 imaging variables to predict per-vessel and per-patient ECR with 10-fold cross-validation. Per-vessel and per-patient, the area under the curve of ECR prediction by ML was higher than that of standard quantitative analysis and expert interpretation. Kumamaru *et al.*[71] developed the first fully automated (i.e. free from human input) method to calculate fractional flow reserve (FFR) from coronary CTA. They used deep learning to develop the model from a cohort of 1052 patients with both coronary CTA and invasive FFR measurements available and then applied it to a cohort of 921

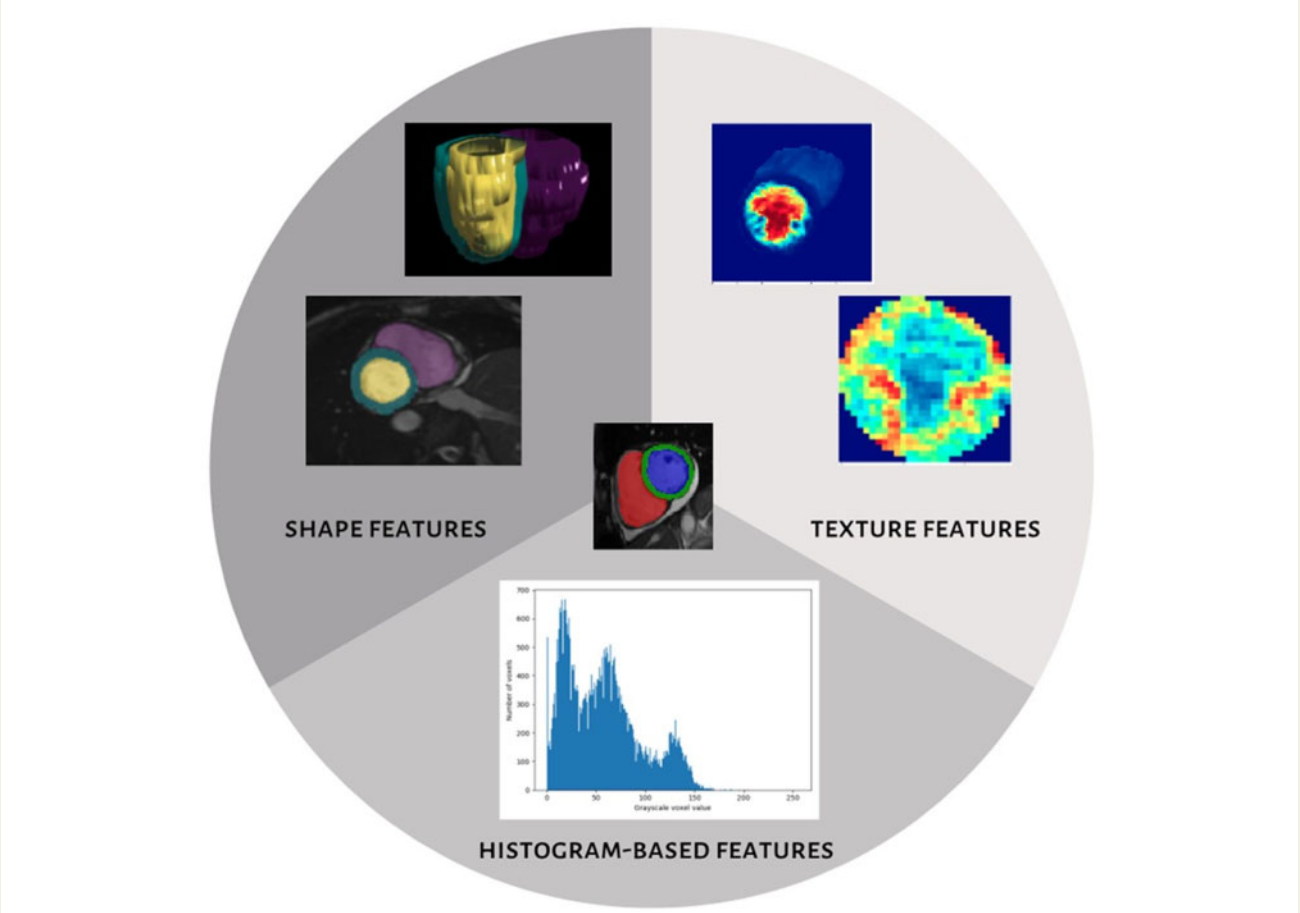

Figure 3 Summary of the types of radiomics features. *Shape features*: An image mask is an approximation of the 3D shape of the region of interest, in this case, it is derived from the ventricular contours. The radiomics shape features are derived from this image mask and include conventional and more advanced geometric quantifiers. *Texture features*: Texture features are derived by assigning a signal intensity level to each voxel in the region of interest and considering the pattern and relationships between different voxel signal intensities through application of various mathematical processes. *Histogram-based features*: The signal intensities observed in the analysed region of interest may be described by plotting a histogram with voxel signal intensity value on the *x* axis and frequency on the *y* axis. Summary statistics derived from the histogram such as mean, median, and standard deviation may be used to describe the global signal intensity distribution.[69]

patients who had a coronary CTA but no invasive FFR. The model-derived FFR demonstrated good diagnostic accuracy versus invasive measurements achieving 76% accuracy with a sensitivity of 85% and specificity of 63%.

Several novel imaging approaches were described. Spath *et al.*[72] performed CMR using manganese contrast in patients with hypertrophic and dilated cardiomyopathy; they found differential uptake between different clinical phenotypes suggesting that it may provide a measure of altered myocyte function and sensitive marker of cardiomyopathic disease states.

Hubert *et al.*[73] proposed a semi-automatic method for deriving strain-volume loops, thereby developing a novel assessment of diastolic function. These strain-volume loops demonstrated good diagnostic accuracy for differentiation between controls and patients with amyloid and HFpEF. It is often challenging to get good transthoracic echocardiographic images in patients with LV assist devices. Based on computer modelling, Strachinaru *et al.*[74] proposed that a right intercostal transhepatic approach would be optimal. They then demonstrated that this approach was feasible in all patients and provided diagnostic images in 93%, allowing precise quantification of LV and RV volumes more often than standard echocardiographic approaches.

Other papers described novel molecular imaging approaches. Kwiecinski *et al.*[75] investigated the relationship between 18F-fluoride PET as a marker of atherosclerotic disease activity (calcification activity) and coronary CTA assessments of plaque characteristics in patients with stable CAD. Low attenuation plaque, a marker of necrotic core, demonstrated excellent specificity (98%) for increased coronary 18F-fluoride PET, however sensitivity was relatively low (39%) indicating that increased disease activity can be observed in the absence of low attenuation plaque. Andrews *et al.*[76] described a novel PET tracer, ENC2015 targeting Factor XIIIA, to detect active cardiovascular thrombus formation. The tracer demonstrated favourable characteristics in both an *ex vivo* human translational model

and an *in vivo* rodent model of arterial thrombosis. This probe holds promise for the non-invasive identification of thrombus formation in cardiovascular disease.

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