Srce i krvni sudovi 2019; 38(4): 193-202

Current Opinion

The year in cardiology 2019

The year in cardiology: imaging

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Received 11 November 2019; revised 28 November 2019; editorial decision 10 December 2019; accepted 11 December 2019

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Introduction

Multimodality imaging and artificial intelligence applied to imaging techniques have been a major interest in this year. The pathophysiological insights that various imaging modalities have provided in numerous clinical scenarios (heart failure, coronary artery disease, and valvular heart disease) influence the way we evaluate and manage patients. Conventional imaging to assess cardiac structure and function is still the first approach to evaluate patients and decide the management. However, advanced echocardiography with strain imaging techniques, tissue characterization with cardiovascular magnetic resonance (CMR), and assessment of biological processes with nuclear imaging techniques have helped to understand that early intervention may be needed in order to prevent or halt the progression of the disease.By applying machine learning techniques to all these imaging modalities, we are able to generate algorithms that can identify certain patterns of disease or risk and develop decisions in a morepersonalized way. This Year in Cardiology review articles summarize the most relevant studies in the field of imaging published in the last year.

This year, artificial intelligence and machine learning applied to cardiac imaging has been one of the main novelties. Other advances innon-invasive cardiac imaging published in 2019 are summarized inthis Year in Cardiology review article (*Take home figure*).

Echocardiography

Early detection of left ventricular (LV) dysfunction in various populations has been the focus of numerous publications in 2019. Left ventricular diastolic function usually precedes LV systolic dysfunctionand is associated with cardiovascular morbidity and mortality. Fromthe Copenhagen City Heart Study, a population-based study including 6238 individuals, Lassen *et al.*[3] evaluated the association between LV filling pressures measured on tissue Doppler imaging (E/E^0)and speckle tracking echocardiography (E/E^0sr) with the occurrenceof cardiovascular death, admission for incident heart failure or myocardial infarction (MI). Of 1238 participants, 140 (11.3%) reached the primary endpoint during a median follow-up of 11 years. After adjusting for various clinical and echocardiographic parameters, E/E^0sr was independently associated with the endpoint [hazard ratio (HR) 1.08,95% confidence interval (CI) 1.02–1.13 per each 10 cm increase;$P = 0.003$] whereas E/E^0 was not. In addition, E/E^0sr provided incremental prognostic value over the SCORE risk chart, currently usedto evaluate the risk of cardiovascular morbidity and mortality in thegeneral population. Increased LV filling pressures may reflect the ageing process of the heart characterized by increased fibrosis. This fibrosis may lead to conduction abnormalities that influence the contractile function of the LV. Modin *et al.*[4] evaluated in 1138 participants of the Copenhagen City Heart Study the prognostic value ofLV mechanical dispersion which is measured as the standard deviation from time to peak longitudinal strain of the three LV apical views. The mean value of LV mechanical dispersion in the generalpopulation was 45 ± 38 ms and increased with age, hypertension, body mass index, and presence of MI. Large LV mechanical dispersion was associated with worse LV systolic and diastolic function. Each10 ms increase in LV mechanical dispersion was independently associated with increased risk of cardiovascular death (HR 1.04, 95% CI1.01–1.06; $P = 0.004$).

Despite the growing evidence on the diagnostic and prognostic
value of strain derived measures of LV systolic and diastolic function,LV ejection fraction (EF) remains the mainstay parameter for risk stratification in clinical practice. The association between physicianreported LVEF and sur-

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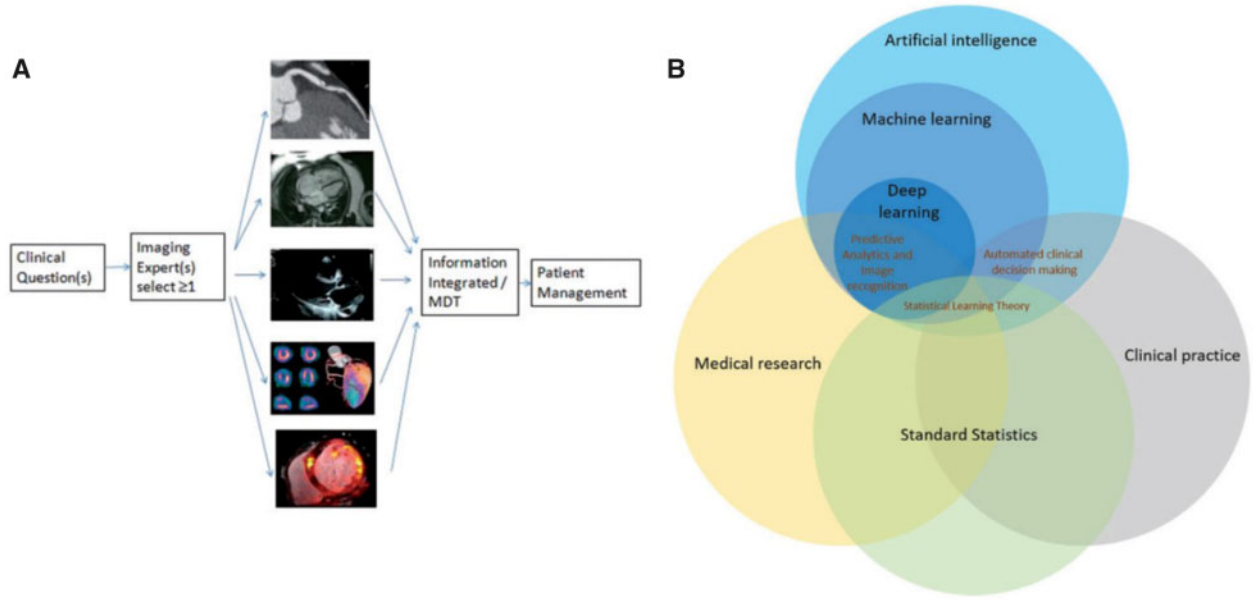

Take home figure Multimodality imaging and artificial intelligence in cardiac imaging. The use of the different imaging modalities should be based on a clinical question. Selecting the most appropriate imaging techniques and integrate them to answer that specific question will be key to improve the outcomes of patients (A). In the future, many of the process the clinicians are used to do to integrate all the information gathered from the imaging modalitiesmay be automated by using artificial intelligence techniques. How artificial intelligence interacts with medical research, clinical practice and statistics will be the focus of ongoing research (B). Reproduced with permission from Fox et al.[1] and Krittanawong et al.[2]

vival was assessed in 403 977 echocardiograms performed in 203 135 patients from USA.[5] Fifty percent of the population had an LVEF between 55% and 65%. Over a median follow-up of 4 years, 23% of patients died. A U-shaped relationship between LVEF and all-cause mortality was observed with the nadir atthe 60–65% LVEF category. These results were reproduced in an independent dataset from New Zealand including 45 531 echocardiograms from 35 976 patients. The U-shaped relationship was also observed in men and women, inpatients and outpatients with heartfailure, and deviations from LVEF of 60–65% were associated withgreater multiplicative increase in risk for younger patients as compared to old patients.

Left ventricular ejection fraction is also the parameter to classifyheart failure patients. Ten to 20% of patients with heart failure withreduced LVEF (≤40%) may improve in LVEF. However, the evidence on the frequency and outcomes of patients with heart failure and recovered LVEF is based on selected cohort of patients or randomized clinical trials. Of 3124 heart failure patients with reduced LVEF atbaseline treated with contemporary heart failure medications, 37.6% presented improvement in LVEF from 26% to 46% over a medianfollow-up of 17 months.[6] Patients with heart failure and recovered LVEF had lower rates for all-cause mortality, all-cause hospitalizations, cardiac transplantation, or LV assist device implantation thanthe patients who remained with reduced LVEF. Not less important isthe characterization of the right ventricular (RV) remodelling in heartfailure patients. In 271 patients with heart failure and preserved LVEF(HFpEF), RV fractional area change reduced by 10% and RV diastolicarea increased by 21% over a median follow-up of 4 years.[7] These changes exceeded the corresponding changes in the LV. In addition,the prevalence of tricuspid regurgitation increased by 45%. Atrial fibrillation, higher body weight, coronary artery disease, higher pulmonary pressures and LV filling pressures and RV dilation were associatedwith development of RV dysfunction (*Figure 1*).[7] Patients with HFpEF developing RV dysfunction had two-fold increased risk of death. Inthis group of heart failure patients, assessment of left atrial functionhas provided important new insights. In 308 patients with HFpEF, Freed *et al.*[8] showed that impaired left atrial reservoir strain (stiff leftatrium) was associated with increased pulmonary vascular resistanceand decreased peak oxygen consumption and was independently associated with the composite outcome of cardiovascular hospitalization or death. It should be noted that the study did not correct the association between left atrial reservoir strain and the composite outcome for neuro-hormonal markers and as acknowledged by the authors, the studies stablishing the reference values of normal leftatrial strain values across the echocardiographic systems and analysisplatforms are scarce.

In patients with asymptomatic severe aortic stenosis and preserved LVEF, LV global longitudinal strain (GLS) on speckle trackingechocardiography is more sensitive than LVEF to identify early changes in LV systolic function during the follow-up. An LV GLS of >-18.2% (more impaired) is associated with higher risk of developing symptoms and needing aortic valve intervention as compared to more preserved values of LV GLS (≤-18.2%).[9] Echocardiography is the imaging technique of first choice to assess valvular heart disease.Secondary mitral regurgitation quantification remains challenging. In423 heart failure patients, Bartko *et al.*[10] developed a unifying algorithm combining effective regurgitant orifice area (EROA), regurgitant volume, and regurgitant fraction that had better discrimina-

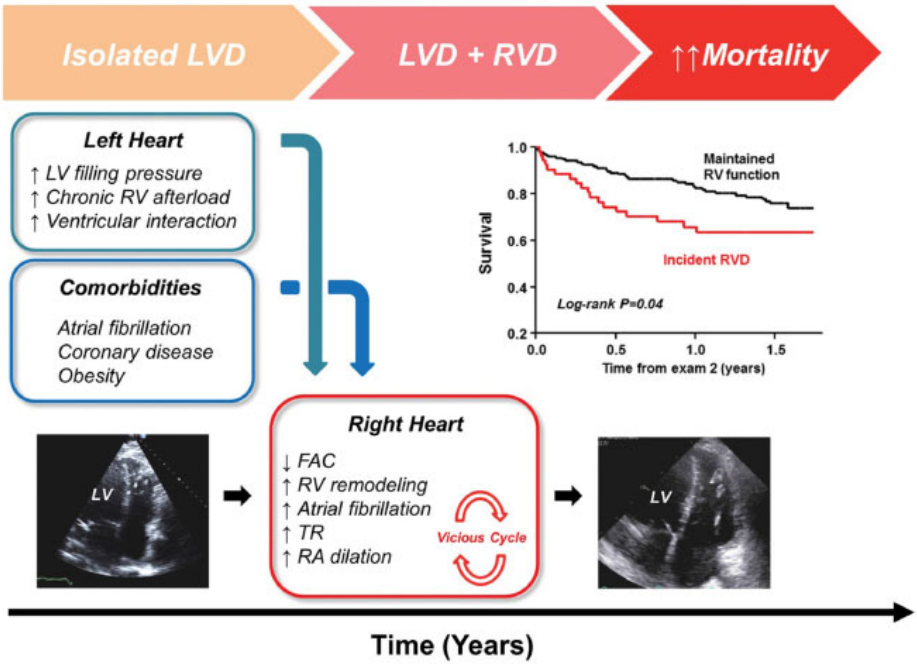

Figure 1 Development of right ventricular dysfunction (RVD) over time in patients with heart failure and preserved ejection fraction. Increased left ventricular (LV) filling pressures and associated comorbidities characterize the initial phase of isolated left ventricular dysfunction (LVD) and lead to right ventricular (RV) remodelling, right ventricular dysfunction. Patients with incident right ventricular dysfunction have worse outcome as compared to patients with preserved RV function. Reproduced with permission fromObokata et al.[7]

tionpower to identify patients with increased mortality risk than currentguideline-based definitions. Low-risk patients were characterized byan EROA of <20 mm^2 and a regurgitant volume of <30mL whereashigh-risk patients were defined by an EROA of ≥30 mm^2 and a regurgitant volume of ≥45 mL. Intermediate-risk patients (with an EROA between 20 and 29 mm^2 and a regurgitant volume of 30– 44 mL) were reclassified as high risk if the regurgitant fraction was ≥50%. However, this algorithm had a rather modest discrimination power (area under the curve 0.63).

The use of transthoracic focused cardiac ultrasound (FoCUS) isgaining popularity at the emergency department and intensive careunits. Among 839 patients with suspected acute aortic syndrome, an aortic dissection detection risk score of ≤1 and a negative FoCUS could rule out an acute aortic syndrome with a sensitivity of 94% anda failure rate of 1.9%.[11]

Finally, elevated carotid artery wave intensity measured on DuplexDoppler ultrasound was independently associated with faster cognitive decline among 3191 individuals enrolled in the Whitehall II study,[12] highlighting the relevance of ultrasound imaging outside theheart.

Cardiovascular magnetic resonance

The ICELAND-MI study is providing significant new data in the understanding of MI and fibrosis in elderly adults. In the first report byShanbhag *et al.*,[13] 397 patients aged 72–81 years were studied using CMR incorporating late gadolinium enhancement (LGE) imaging which identifies myocardial fibrosis due to MI (subendocardial) andother causes (other patterns). During the follow-up of 5.8 years, 192events were recorded. The authors found that major non-ischaemicfibrosis was the only independent predictor of outcome (*Figure 2*).[13]

In the second report from the ICELAND-MI trial, Acharya *et al.*[14] report on the long-term predictive value of unrecognized MI (UMI) inan elderly cohort of 935 subjects aged 67–93 years. Previous reportshave suggested a poor short-term prognosis but this study extendsfollow-up to 13.3 years. The authors showed that all-cause mortality in UMI patents was lower than recognized MI for at least 5 years, butsimilar at 10 years. At all time-points UMI had a higher mortality thanpatients with no MI. It is not known whether secondary preventionwould be useful in UMI patients.

Cardiovascular magnetic resonance has made an enormous contribution to the diagnosis and management of the cardiomyopathies through the presence and patterns of myocardial fibrosis from LGE imaging, tissue characterization through T1, T2, and T2* mapping, and accurate measures of ventricular function and mass.Gutman *et al.*[15] studied 452 patients with non-ischaemic dilated cardiomyopathy (DCM) stratified by the presence or absence of non-ischaemic myocardial fibrosis by LGE. In patients with fibrosis, the mortality was reduced by an implantable cardioverter-defibrillator (ICD) with HR 0.45 (P = 0.003), but in patients without fibrosis there was no improvement in mortality with ICD (HR 1.22,P = 0.64). The authors conclude that in non-ischaemic DCM, the presence of fibrosis may allow for improved selection of patients requiring ICD. Galan-Arriola *et al.*[16] used serial CMR to identify the early stages of anthracycline-induced cardiotoxicity in a pig study. The earliest detectable abnormality was increased T2 relaxation which was correlated on histology with intramyocyte oedema, with-

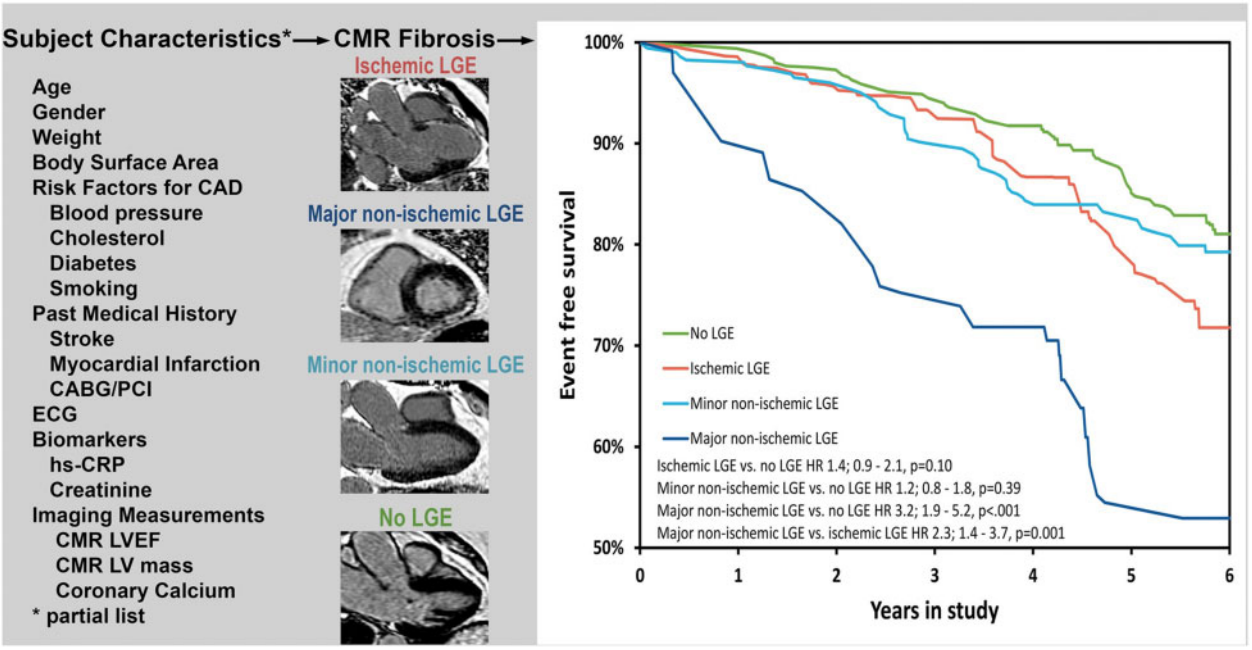

Figure 2 Inverse propensity adjusted prognosis of ischaemic and non-ischaemic myocardial fibrosis. Reproduced with permission from Shanbhag et al.[13]

out change in the extracellular space. Changes in T1 and the extracellular volume on T1 mapping occurred much laterand coincided with wall motion abnormalities. Stopping doxorubicin upon detection of T2 abnormality resolved intramyocyte vacuolization, indicating that the early T2 findings are at a stage when reversibility is still possible. These findings have important clinical implications for cancer therapy. Scally *et al.*[17]studied 55 patients with takotsubo cardiomyopathy using CMR including ultrasmall paramagnetic particles of iron oxide (USPIO) which localize in inflammatory macrophages. During the acute presentation, USPIO signal was reduced in the ballooning zone by27% ($P < 0.001$) as compared to non-ballooning zone (19%$P = 0.02$). No enhancement was visible in either zone at 5 months. The authors conclude that takotsubo cardiomyopathy is characterized by an acute myocardial macrophage inflammatory infiltrate, most marked in the ballooning zone. Aung *et al.*[18] report on3920 subjects from the UK Biobank study who were free of overtcardiovascular disease but had chronic exposure to ambient air pollutants including particulates and nitrogen dioxide. There was an incremental increase in LV and RV end-diastolic and LV endsystolic volumes with increasing exposure to particulates with a diameter of <2.5 lm. Likewise, biventricular volumes were increased with higher nitrogen dioxide exposure. The authors conclude that air pollution is an under-recognized cardiac risk factor that may contribute to heart failure.

Diffusion tensor (DT) CMR is a new technique that images the asymmetry of water diffusion to define tissue architecture. Tissuessuch as neurons and the myocardium can be interrogated because oftheir longitudinal grain. The technique has recently become possible*in vivo* in humans and has been well validated. The three-dimensional(3D) architecture of the layers of the heart is now well described and is preserved across mammalian species suggesting that the observedstructure has functional importance. Khalique *et al.*[19] report the firstseries of patients in whom the 3D architecture is deranged, thesebeing those with situs inversus totalis (SIT, dextrocardia). The normalepicardial left-handed myocyte helix was switched to right handed at the base with a return to left handed at the apex. The endocardiumwas likewise inverted at the base, with variable derangement moreapically. There was reduced strain in the SIT hearts. The long-termconsequences of these findings are not yet known, but it could behypothesized that SIT patients may be more susceptible to heart failure from a second insult such as hypertension or infarction. Ariga*et al.*[20] used DT-CMR to examine 50 patients with hypertrophic cardiomyopathy and report a reduction in the diffusion parameter calledfractional anisotropy (FA) in patients with ventricular arrhythmias[odds ratio (OR) 2.5, $P = 0.015$]. Fractional anisotropy reflects packing of the myocytes and could therefore be reduced in myocardialdisarray. Whilst there is no direct evidence of this from histology, theauthors conclude that connection of reduced FA with arrhythmiasmight reflect disarray. Further work is needed to validate this intriguing study.

Cardiovascular magnetic resonance has been used for decades toimage the aorta and the aortic valve. Musa *et al.*[21] report on 674 patients with severe aortic stenosis who also underwent LGE CMRat six UK centres. The presence and extent of myocardial fibrosis independently predicted mortality with a two-fold increase in late mortality. Guala *et al.*[22] report on 117 Marfan patients in a multicentrestudy of outcome. During 86 months of follow-up, the growth rate ofthe aortic diameter was 0.62mm/year, and events were independently predicted by the proximal aorta longitudinal strain.The authors suggest that this simple measure could be included inrisk assessment of Marfan patients.

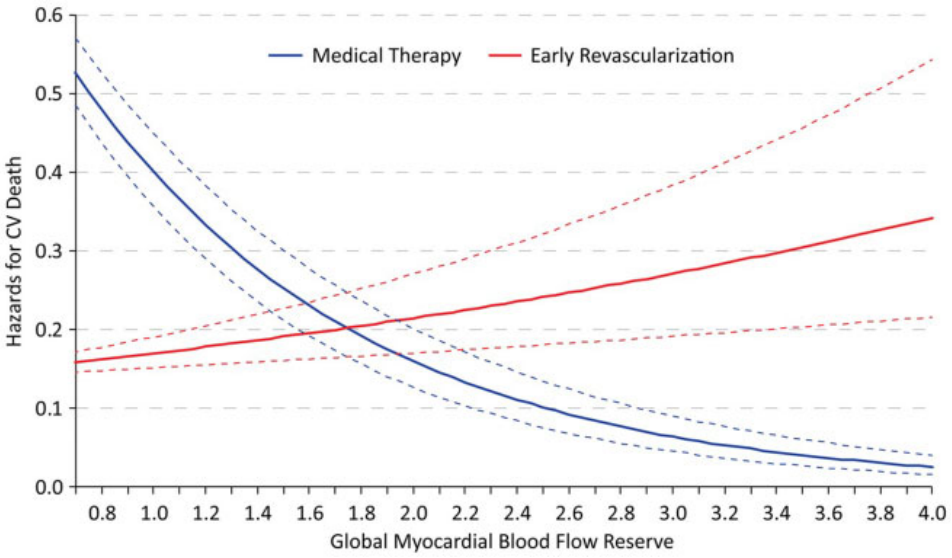

Figure 3 Hazards for cardiac death with early revascularization compared to medical therapy based on global myocardial blood flow reserve by positron emission tomography myocardial perfusion imaging. Reproduced with permission fromPatel et al.[26]

Nuclear imaging

The current limitation of coronary computed tomography angiography (CCTA) is its suboptimal positive predictive value for the identification of myocardial ischaemia. Myocardial perfusion imaging (MPI)using CT could solve that limitation. Alessio *et al.*[23] performed a dynamic contrast-enhanced cardiac CT and ^{82}rubidium positron emission tomography (PET) imaging in 34 high-risk patients. The CTderived global myocardial blood flow values correlated highly withthose measured on PET (r = 0.92; P < 0.001). In addition, the mean global myocardial blood flow values estimated on CT vs. PET werecomparable (0.9 ± 0.3 vs. 1.0 ± 0.2 mL/min/g at rest and 2.1 ± 0.7 vs. 2.0 ± 0.8 mL/min/g during stress, respectively). However, myocardialblood flow estimates on CT contained substantial individual variance with a standard error of the estimate of 0.44 mL/min/g. The results are promising but further development is needed to improve reliability of the methodology at individual level as well. Furthermore, thestudy measured only global perfusion, while regional values would bemore clinically meaningful. Another novel method to determine whether a coronary lesion is functionally significant is transluminal attenuation gradient (TAG) that can be measured using standard CCTA data. In the presence of significant coronary stenosis, luminalattenuation will decrease rapidly on CCTA and can be measured with TAG. In the study by Bom *et al.*[24] Transluminal attenuation gradient was compared against quantitative PET perfusion imaging andinvasive fractional flow reserve (FFR) and demonstrated that TAGdid not discriminate between vessels with or without ischaemia as defined by either PET or FFR. The lack of diagnostic value of TAGwas related to the large variability of coronary luminal dimensions.

Artificial intelligence is currently a hot topic in medical image analysis. Machine learning, especially deep learning has been shown to bepromising in disease detection and classification using image data. Betancur *et al.*[25] explored deep learning for automatic prediction ofobstructive CAD from the polar plots of single photon emission CT(SPECT) MPI in 1638 patients with suspected CAD. The area under the receiver operating characteristic curve for disease prediction bydeep learning was higher than that of the standard analysis (per patient: 0.80 vs. 0.78; per vessel: 0.76 vs. 0.73; P < 0.01). The results demonstrate that deep learning has the potential to perform automatic interpretation of MPI images with at least the same accuracy than the standard analysis.

While the diagnostic and prognostic power of MPI has been wellcharacterized, there is little evidence on how this information shouldguide patient management. Patel *et al.*[26] examined a cohort of 12 594patients with suspected or known CAD undergoing PET MPI. Thepatients were followed-up for 3.2 years. As expected, the low global perfusion reserve was associated with greater hazard of all-cause death. More interestingly, the patients with global perfusion reserve ≤1.8 had a survival benefit with early revascularization, regardless of the level of regional ischaemia. However, the patients with preservedperfusion reserve had no benefit of revascularization over medicaltherapy (*Figure 3*).[26] The results are concordant with earlier findingsshowing that large ischaemia justifies revascularization[27,28] and extend this notion also to global myocardial perfusion reserve.

^{18}F-fluoride PET imaging is gaining increasing interest in variousconditions as an indicator of tissue microcalcification, which is occurring in atherosclerosis. Creager *et al.*[29] investigated in an *ex vivo* studyif ^{18}F-fluoride accumulation on atherosclerotic plaques are related tothe development of microcalcifications that are not visible on CT. Inthis complex study, ^{18}F-fluoride signal in tissue analysis of human andmouse specimens was found to be clearly linked with small microcalcifications, which were not detected on CT. These results confirmthat plaque mineralization is an active process and that ^{18}F-fluoride PET imaging detects coronary and carotid plaques with high-risk features.

In the study by Cartlidge *et al.*,[30] the degeneration of bio-

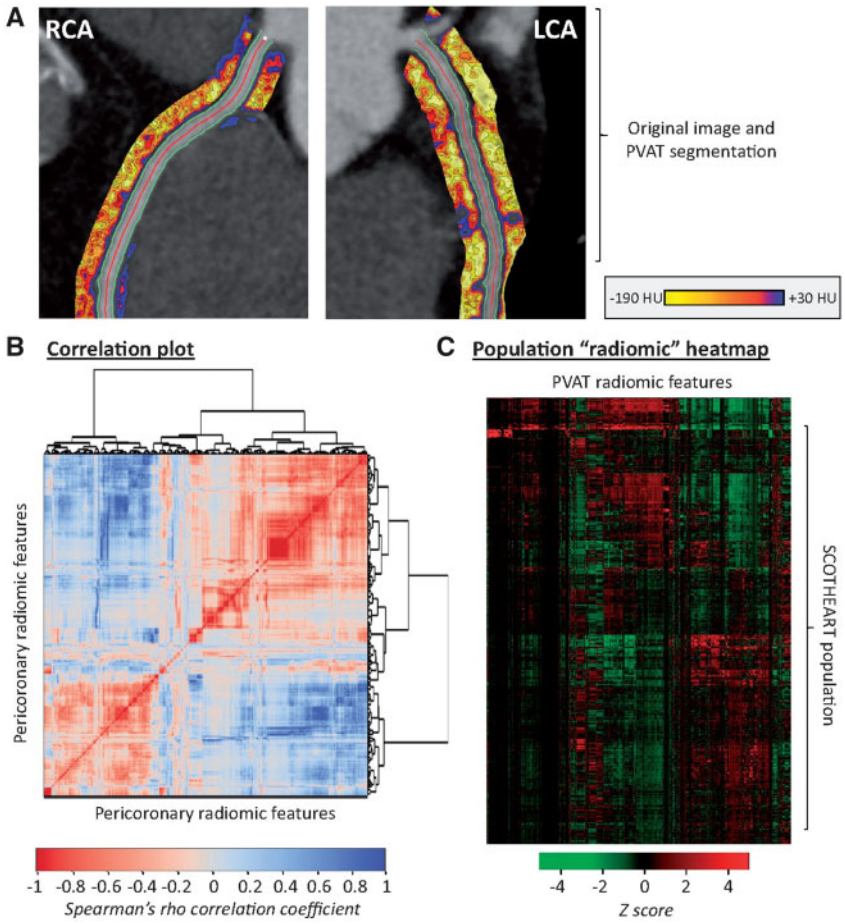

Figure 4 Radiomic phenotyping of coronary perivascular adipose tissue. (A) The perivascular adipose tissue (PVAT) of the right (RCA) and left (LCA) coronary was segmented and used to calculate a number of shape-, attenuation-, and texture-related statistics. (B) Correlation plot of all 1391 stable radiomic features in the SCOT-HEART population (n= 1575 patients), with hierarchical clustering revealing distinct clusters of radiomic variance. (C) Heatmap of scaled radiomic features in the SCOT-HEART population revealing between-patient variance across the cohort. Reproduced with permission from Oikonomou et al.[44]

prostheticaortic valve was investigated using ^{18}F-fluoride PET. In *ex vivo* analyses,the ^{18}F-fluoride uptake colocalized with tissue degeneration on histology. In patients with aortic bioprostheses, increased valve ^{18}F-fluoride uptake in PET imaging was associated with more rapid deterioration in valve function at 2-year follow-up. Aortic bioprosthesis dysfunction was detected in 10 patients and all of them showed^{18}F-fluoride uptake at baseline when still the valve haemodynamicswere normal. On multivariable analysis, ^{18}F-fluoride uptake was theonly independent predictor of future bioprosthetic dysfunction. Although a larger patient cohort is needed, ^{18}F-fluoride PET imaging appears promising method in predicting dysfunction of bioprostheticvalves.

Infection and inflammation imaging using molecular imaging methods is an established technique in prosthetic valve endocarditis and device infections. Swart *et al.*[31] investigated the possible confoundersthat may impact on the accuracy of ^{18}F-fluoro-deoxyglucose (FDG)PET/CT. In a multicentre study, 160 patients with suspected prosthetic valve endocarditis and 77 control patients were scanned. Theauthors found that low inflammatory activity (C-reactive protein <40 mg/L)—possibly linked with prolonged antibiotic therapy at the time of imaging—and use of surgical adhesives during prosthetic heart valve implantation were significant confounders, whereas recent valve implantation was not.

Another challenging population is patients with suspected infectionof cardiac implantable electronic devices. In a study by Calais *et al.*,[32]the diagnostic positive and negative predictive values were 80% and91% for FDG PET and 100% and 85% for white blood cell SPECT, respectively. A prolonged antibiotic therapy before imaging tended todecrease the sensitivity for both techniques. As FDG is not specificfor inflammation but for glucose uptake, more specific imaging agentsfor infection are being developed.

Computed tomography

Cardiac computed tomography has evolved into a one-stop-shop imaging tool that can provide valuable diagnostic and prognostic information in patients with suspected or known CAD. Assessment of coronary artery calcium (CAC) score on CT can be used as a riskmodifier and may guide statin therapy. Mitchel *et al.*[33] assessed therelative impact of statins on adverse cardiovascular events stratifiedby CAC scores in 13 644 patients (mean age 50 years; 71% men)who were followed-up for a median of 9.4 years. Patients without CAC had an excellent prognosis irrespective of statin therapy whereas in patients

with CAC > 0 statin therapy was associated withreduced risk of major adverse cardiovascular events (adjusted subHR 0.76; 95% CI 0.60–0.95; *P* = 0.015). The effect of statin use on major adverse cardiovascular events was significantly related to theseverity of CAC (*P* < 0.0001 for interaction), with a number needed to treat to prevent 1 initial major adverse cardiovascular events over10 years ranging from 100 (when CAC was 1–100) to 12 (if CAC >100). A recent *post hoc* analysis of the SCOT-HEART trial demonstrated that coronary heart disease death or non-fatal MI was threetimes more frequent in patients with high-risk plaque features (positive remodelling or low attenuation plaque) and was twice as frequent in those with obstructive CAD.[34] However, these associationswere not independent of CAC score, a surrogate measure of atherosclerosis burden.

The investigators of the PROMISE Trial assessed the prevalenceand clinical predictors of high-risk CAD (defined as left main stenosisor either ≥50% stenosis or ≥70% stenosis of 3 vessels or 2-vessel CAD involving the proximal left anterior descending artery).[35] Highrisk CAD was identified in 6.6% (≥50% stenosis) and 2.4% (≥70% stenosis) of patients. Variables predictive of high-risk CAD included family history of premature CAD, age, male sex, lower glomerular filtration rate, diabetes mellitus, elevated systolic blood pressure, andangina. High-risk CAD was associated with more frequent invasiveinterventions and adverse events as compared to non-high-risk CAD.

An intriguing study has investigated the prognostic value of combined information of lesion-specific ischaemia (FFR) and adverse plaque features by CCTA.[36] The authors evaluated 772 vessels (299 patients) by both CCTA and invasive FFR measurement.Interestingly, the presence of ≥3 high-risk plaque features was independently associated with clinical events in the FFR > 0.80 group, butnot in the FFR ≤0.80 group. It seems that the integration of both lesion-specific ischaemia and CT plaque features may provide betterprognostic stratification than either individual component alone, especially in patients with *n* FFR >0.80.

Using computational fluid dynamics simulations CT is now capable to provide non-invasive FFR measurements. A study by Norgaard *et al.*[37] assessed real-world clinical outcomes following a diagnostic strategy including first-line coronary CTA with selective FFR_{CT} testing. The study reviewed the results of 3674 consecutive patients with stable chest pain evaluated with CTA and FFR_{CT} testing. The presence of intermediate-range CAD and FFR_{CT} >0.80 was associated with favourable clinical outcomes similar to the prognosis in patients without or with minimal evidence of CAD. Beyond FFR_{CT} simulation stress CT perfusion has emerged as a potential strategy to acquire anatomic and functional evaluation of CAD. Whole heart coverage CT scanners have become readily available, which allow a more robust stress CT MPI (CTP). The diagnostic accuracy of latest scanner generation was tested by Pontone *et al.*[38] in 100 intermediateto high-risk symptomatic patients with suspected CAD. CCTA alone demonstrated a sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 98%, 76%, 99%, 63%, and 83%, respectively. Combining CCTA with stress CTP, these values were 91%, 94%, 96%, 86%, and 93%, respectively, with a significant improvement in specificity, positive predictive value, and accuracy. The mean effective radiation dose for CCTA and stress CTP were 2.8 ± 1.4 mSv and 2.5 ± 1.1 mSv. Patients with diabetes are a high-risk patient cohort for adversecardiovascular outcomes. The PROMISE Trial investigators assessedwhether a diagnostic strategy based on CCTA is superior to functional stress testing in reducing cardiovascular death or MI amongsymptomatic patients with diabetes [*n* = 1908 (21%)] vs. patients without diabetes [*n* = 7058 (79%)].[39] Patients with diabetes who underwent CCTA had a lower risk of cardiovascular death or MI compared with functional stress testing [CCTA: 1.1% (10 of 936) vs.stress testing: 2.6% (25 of 972); adjusted HR 0.38; 95% CI 0.18–0.79; *P* = 0.01]. Another study including also individuals with diabetes,investigated the rate and extent of plaque progression, changes in plaque features, and clinical predictors of plaque progression.[40] A totalof 1602 patients who underwent serial CCTA (median scan interval 3.8 years) were enrolled and analysed from the PARADIGM (Progression of Atherosclerotic Plaque Determined by ComputedTomographic Angiography Imaging) trial.[41] Diabetes was an independent risk factor for plaque progression (OR 1.526, 95% CI 1.100–2.118; *P*=0.011).

A more precise risk assessment that incorporates the detection ofcoronary inflammation would allow personalized medical interventions. Novel analytical techniques such perivascular fat attenuationindex or plaque-based radiomics may facilitate the detection and quantification of pericoronary inflammation and atherosclerotic plaque activity.[42,43] An innovative study by Oikonomou *et al.*[44] demonstrated that artificial intelligence powered pericoronary fat radiomicprofile (FRP) analysis significantly improved major adverse cardiovascular events prediction beyond traditional risk stratification that included risk factors, CAC, coronary stenosis, and high-risk plaquefeatures on CCTA in the SCOT-HEART trial (*Figure 4*). The authors conclude that FRP leads to a significant improvement of cardiac riskprediction over and above the current state-of-the-art, which mighthelp to identify patients with elevated residual risk for cardiovascularevents.

Advanced imaging, fusion imaging, and applied artificial intelligence in imaging

Cardiovascular (invasive and non-invasive) imaging is developing atultrafast pace and the clinician of today gets daily confronted with different imaging modalities, with major technological developments,but also fusion imaging and introduction of artificial intelligence andmachine learning. From a clinical perspective, the cardiovascular imager of tomorrow needs to be familiar with the different modalities, when to apply which technique in which clinical scenario.A dedicated task force of The European Association ofCardiovascular Imaging (part of the ESC) has published a statementon the organization of multimodality imaging services in cardiology,the use of the different modalities as well as training and research inthe multimodality era.[1]

Ramos *et al.*[45] used an animal (mice) model to study myocardialhealing after infarction using serial imaging (7

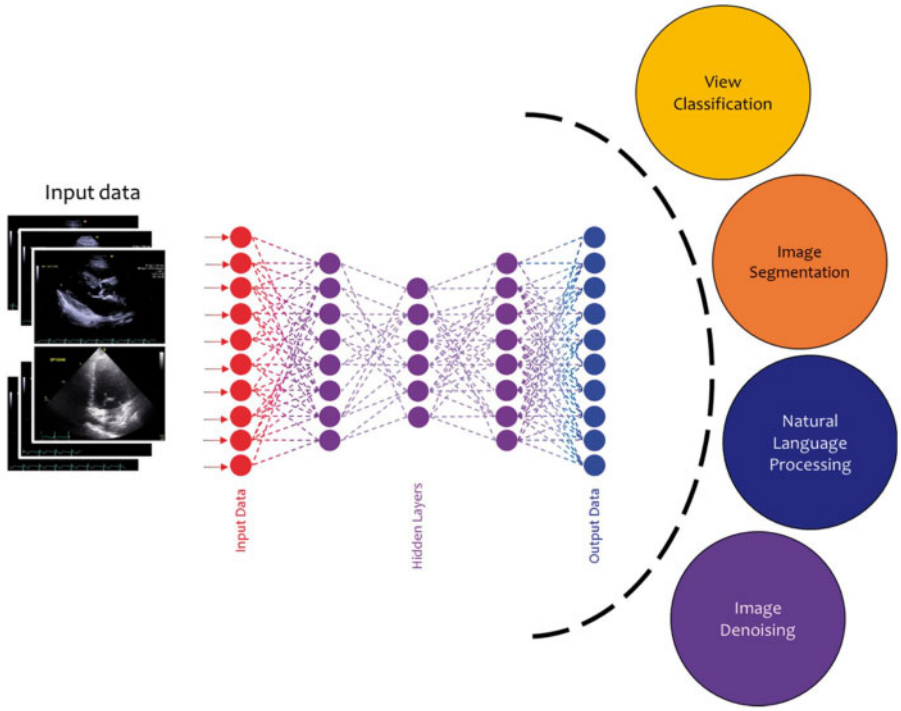

Figure 5 Machine learning algorithms applied to echocardiography. Echocardiographic data are post-processed to automate many processes performed in clinical practice by cardiologists and sonographers such as view classification and image segmentation that will lead to the interpretation of the data and the diagnosis. Reproduced with permission from Al'Aref et al.[49]

days and 21 days postinfarction) with 3 T magnetic resonance imaging (MRI) and a 19F/1Hsurface coil. Injected 19F-perfluorocarbon nanoparticles were usedto evaluate recruitment of inflammatory cells (e.g. macrophages), and an injected gadolinium-based elastin-binding contrast agent was usedto assess elastin content. The combination of these imaging techniques enabled assessing the time course of the remodelling and healing process, as well as scar development.

Engel *et al.*[46] evaluated 25 patients with either stable CAD or presenting with suspected ACS using a non-invasive albumin-binding probe gadofosveset-enhanced CMR, as well invasive coronary angiography and optical coherence tomography (OCT). CMR was performed twice: prior to baseline examination and 24 h aftergadofosveset-trisodium administration. The patients with suspectedACS revealed significantly higher signal enhancement on CMR following gadofosveset-trisodium application on the segments containing aculprit lesion as compared to patients with stable CAD. On OCT,these patients presented with thin-cap fibroatheroma. The novel CMRapproach may enable early detection of patients with potential ACS.

Several articles in the field of multimodality and fusion imaging are worth to highlight. Mitral annular calcification is observed in patients with mitral regurgitation/stenosis and is important when transcatheter valve replacement is considered. To better understand pathophysiology, Massera *et al.*[47] performed CT calcium score of the mitral annulus, as well as PET with ^{18}F-fluoride (calcification activity) and ^{18}F-FDG (inflammation activity) in 104 patients. Mitral annular calcification was noted in 35 patients who exhibited increased ^{18}F-fluoride uptake and FDG uptake, suggesting increased local calcification and inflammation. Fernandez-Friera *et al.*[48] used hybrid FDG PET/MRI to assess arterial vascular plaques in middle-aged individuals (n = 755). With this sophisticated imaging technology, the authors evaluated multiterritorial atherosclerosis (carotid, aortic, and ilio-femoral arteries);plaques were present on MRI in 90.1% (73.9% femorals, 55.8% iliacs,and 53.1% carotids), whereas inflammation was observed on PET in48.2% of individuals (24.4% femorals, 19.3% aorta, 15.8% carotids,and 9.3% iliacs). The authors concluded that arterial inflammation isnoted in 50% of arterial plaques in middle-aged individuals.

The current status of artificial intelligence and machine learning was elegantly reviewed by Al'Aref *et al.*[49] With the increasing digitization of data making big datasets available and easier to process, machine learning has enabled to autonomously acquire knowledge by the extraction of patterns from these large datasets. Particularly in cardiology machine learning has been rapidly adopted in various fields, to permit automated analysis of electrocardiograms and imaging (echocardiography, nuclear perfusion imaging, and CCTA) (*Figure 5*).

Another excellent review was published by Krittanawong *et al.*[2]providing further insight in deep learning. This is a branch of artificialintelligence, which combines computer science, statistics and decision theory to discover patterns in complex and big data. CasaclangVerzosa *et al.*[50] applied machine learning to advanced network analysis to demonstrate automated assessment of LV (hypertrophy) inresponse to aortic valve stenosis from echocardiographic images. Finally, Zhang *et al.*[51] published original research on the use of deeplearning to analyse echocardiographic data (n = 14 035 echocardiograms), in a fully automated fashion, including (i) view identifica-

tion, (ii) image segmentation, (iii) quantification of structure and function,and (iv) disease detection. Specifically, convolutional neural networkswere trained to detect hypertrophic cardiomyopathy, cardiac amyloidosis, and pulmonary arterial hypertension with respective C statistics of 0.93, 0.87, and 0.85.

Conflict of interest: The Department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Biotronik, Bioventrix, Boston Scientific, Edwards Lifesciences, Medtronic and GE Healthcare. J.J.B. received speaker fees from Abbott Vascular. V.D. received speaker fees from Abbott Vascular and Medtronic. D.P. reports research support from Siemens, grants from La Jolla, grants from Bayer, grants and personal fees from ApoPharma. The remaining authors have nothing to disclose.

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