Almanah 2014.: kardiovaskularna slikovna dijagnostika

Almanac 2014: Cardiovascular Imaging

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SAŽETAK: Almanah-izvješća pružaju pregled članaka o određenim temema koji su objavljeni u časopisu „Heart" tijekom posljednje 2 godine, u kontekstu napredaka unutar tog polja, uključujući publikacije iz nekoliko drugih časopisa. Ovaj je Almanah-članak usredotočen na kadiovaskularnu slikovnu dijagnostiku – kao u općem kardiološkom časopisu, istraživanje slikovne dijagnostike u časopisu „Heart" je uglavnom klinički orijentirano i često ima utjecaja na naše kliničko djelovanje.

SUMMARY: The 'Almanac' Reviews provide an overview of articles on a specific topic published in Heart over the past 2 years, put in the context of advances in the field, including publications from several other journals. The focus of this Almanac article is Cardiovascular imaging — as a general cardiology journal, the imaging research in Heart tends to be clinically oriented and often will impact our clinical practice.

NAPREZANJE MIOKARDA

Ehokardiografska mjerenja naprezanja miokarda pokazala su se kao obećavajući alati za procjenu kardiološke funkcije i predviđanja prognoza za više kardioloških stanja.[1-3] LVEF je trenutno najpopularniji čimbenik za opisivanje sistoličke funkcije lijeve klijetke te za predviđanje rezultata kod pacijenata s infarktom miokarda i zatajivanjem srca. Međutim, EF ima neka tehnička ograničenja, poput teškoća u praćenju granice endokarda i pretpostavke u geometriji LV-a. Uz to, u usporedbi sa EF, čini se da globalno longitudinalno naprezanje (GLS) izvedeno iz 2D ehokardiografije akustičnih refleksija (engl. *speckle tracking*) predstavlja pouzdanije parametre i pruža korisnije prognostičke podatke u pacijenata sa zatajivanjem srca (ZS).[1,3]

Prethodna istraživanja uglavnom su bila usredotočena na pacijente u sinusnom ritmu. Međutim, postoji mnogo pacijenata s fibrilacijom atrija (FA) i ZS,[4] pogotovo u onih sa ZS s očuvanom ejekcijskom frakcijom. Poznato je da FA pogoršava ishode ZS i obrnuto.[5] Stoga je procjena kardi-

MYOCARDIAL STRAIN

Echocardiographic measures of myocardial strain have emerged as a promising tool to assess cardiac function and predict prognosis in several cardiac conditions.[1-3] LVEF currently is the most popular parameter to describe left ventricular systolic function and to predict outcomes in patients with myocardial infarction and heart failure. However, there are some technical limitations to EF such as difficulty of endocardial border tracing and assumptions in the geometry of the LV. Additionally, compared with EF, global longitudinal strain (GLS) derived from 2D speckle-tracking echocardiography appears to be a more reliable functional parameter and provides more useful prognostic data in patients with heart failure.[1,3]

Previous studies have mostly focused on patients in sinus rhythm. However, there are many patients with atrial fibrillation and heart failure,[4] especially in those with heart failure with preserved EF. Atrial fibrillation worsens the outcome of heart failure and vice versa.[5]

ološke funkcije kod pacijenata sa FA također važna.[6] U nizu od 196 pacijenata s FA, Su et al[7] su koristili metodu „indeksa otkucaja" da bi eliminirali problem varirajućih R-R intervala.[8,9] Za indeks otkucaja se uzima otkucaj nakon dva gotovo ista kardiološka ciklusa. Dva intervala koja prethode indeks otkucaju moraju biti duljine barem 500 ms, a razlika između ta dva otkucaja mora biti manja od 60 ms. Su et al su pokazali da je GLS bolji od EF lijeve klijetke i od sistoličke mitralne anularne brzine za predviđanje kardiovaskularnih događaja. Pacijenti sa GLS u iznosu od −12,5% ili manje imaju bolju stopu preživljavanja bez kardiovaskularnih događaja nego oni sa GLS >−12,5%. Procjena kardiološke funkcije u pacijenata s FA često se temelji na prosjeku mjerenja iz više otkucaja, ali ovaj pristup iziskuje mnogo vremena i napora.[10] Metoda indeksa otkucaja alternativno je rješenje za pacijente s FA koje se može šire primijeniti, ako se potvrdi u drugim studijama.

Uz procjenu općenite funkcije, naprezanje miokarda može se koristiti za procjenu regionalne funkcije miokarda. Za razliku od brzine miokarda mjerene tkivnom dopler ehokardiografijom, naprezanje miokarda neovisno je o pomaku (engl. *tethering*) i translacijskom pokretu. Stoga mjerenje područnog naprezanja može biti od kliničke koristi, a postoje mnoge publikacije koje pokušavaju procijeniti područno funkcioniranje u pacijenata s različitim kardiološkim bolestima poput ishemijske bolesti srca, valvularne bolesti srca i kardiomiopatija.[11] Kardioamiloidoza progresivna je infiltrativna kardiomiopatija s lošom prognozom. Njena dijagnoza je ponekad izazovna jer zadebljanje stijenke klijetke s prominentnom dijastoličkom i kasnije sistoličkom disfunkcijom, procijenjena ehokardiografijom, može biti uslijed drugih prevladavajućih patoloških stanja.[12] Nedavne studije ukazuju na to da učestalost kardioamiloidoze može biti podcijenjena te se ponekad predvidi u kliničkom okruženju.[13] Phelan et al[14] pronašli su jedinstvenu tipičnu distribuciju naprezanja miokarda u kardioamiloidozi. Oni su proučili 55 konsekutivnih pacijenata s kardioamiloidozom, 15 pacijenata s hipertrofijskom kardiomiopatijom i 15 pacijenata sa stenozom aorte (AS). Uz longitudinalno naprezanje, izračunano je relativno apikalno longitudinalno naprezanje kao omjer apikalnog longitudinalnog naprezanja i prosječnog ili bazalnog i srednje-longitudinalnog naprezanja. Ovi autori su dosljedno pronalazili tzv. uzorak *apical sparing* longitudinalnog naprezanja u pacijenata s kardioamiloidozom i veće relativno apikalno longitudinalno naprezanje (>1,0), koje ukazuje na više vrijednosti vršnog naprezanja uspoređeno s vrijednostima za naprezanje bazalno ili u području sredine septuma **(slika 1)**. Pomoću multivarijabilne logističke regresivne analize u koju su uvršteni simptomi, standardne ehokardiografske varijable i nalazi elektrokardiograma, samo relativno vršno longitudinalno naprezanje značajno predviđa kardioamiloidozu. Mehanizam *apical sparing* još se uvijek ne razumije dovoljno dobro. Autori pretpostavljaju da je depozit amiloida manji na apeksu nego na bazi ili na sredini klijetke, što je vidljivo iz smanjene hipertrofije u apeksu. Ranija istraživanja koja su koristila naprezanje izračinano pomoću tkivnog doplera su također predložila gradijent longitudinalnog naprezanja.[15,16] U kardioamiloidozi zabilježene su i razlike po područjima u naprezanju opsega .[12] Međutim, i dalje je nejasno je li *apical sparing* dijagnostičan za kardioamiloidozu i potrebne su daljnje studije koje će proučavati osjetljivost i

Therefore, the assessment of cardiac function in patients with atrial fibrillation also is important.[6] In a series of 196 patients with atrial fibrillation, Su *et al*[7] used the 'index beat' method to eliminate the issue of varying R-R intervals.[8,9] The index beat is taken as the beat following two nearly equal preceding cardiac cycles. The two intervals preceding the index beat must be at least 500 ms duration and the difference between these two beats must be less than 60 ms. Su *et al* showed that GLS was better than left ventricular EF and systolic mitral annular velocity for predicting cardiovascular events. Patients with a GLS of −12.5% or less had a better cardiovascular event-free survival than in those with a GLS >−12.5%. Assessment of cardiac function in patients with atrial fibrillation often is based on the average of measurements from multiple beats, but this approach is time consuming and cumbersome.[10] The 'index beat' method is an alternate solution in patients with atrial fibrillation that may be more widely applied if validated in other studies.

In addition to assessment of global function, myocardial strain can be used to assess regional myocardial function. Unlike myocardial velocity measured by tissue Doppler echocardiography, myocardial strain is independent of tethering and translational motion. Thus, regional strain measures may be clinically useful and there have been numerous publications attempting to evaluate regional function in patients with various cardiac diseases such as ischaemic heart disease, valvular heart disease and cardiomyopathy.[11] Cardiac amyloidosis is a progressive infiltrative cardiomyopathy with a poor prognosis. Its diagnosis is sometimes challenging because a thickened ventricular wall with prominent diastolic and later systolic dysfunction, as assessed with echocardiography, can be due to other prevalent pathologies.[12] In fact, a recent study suggests the prevalence of cardiac amyloidosis may be underestimated and is sometimes overlooked in the clinical setting.[13] Phelan *et al*[14] found a unique feature of myocardial strain distribution in cardiac amyloidosis. They studied 55 consecutive patients with cardiac amyloidosis, 15 patients with hypertrophic cardiomyopathy and 15 patients with aortic stenosis (AS). In addition to longitudinal strain, relative apical longitudinal strain was calculated as the ratio of apical longitudinal strain to the average of basal and midlongitudinal strain. These authors consistently found an 'apical sparing' pattern of longitudinal strain in patients with cardiac amyloidosis, and a higher relative apical longitudinal strain (>1.0), indicating a larger apical strain value compared with basal and mid-ventricular strain values **(Figure 1)**. By multivariable logistic regression analysis, when symptoms, standard echocardiographic parameters and ECG findings were included in the analysis, only relative apical longitudinal strain was significantly predictive of cardiac amyloidosis. The mechanism of 'apical sparing' is not well understood. The authors speculated that amyloid deposition was less in the apex than the base and mid-ventricle as evidenced by less hypertrophy in the apex. Previous investigators using tissue Doppler-derived strain also suggested an apex-to-base gradient of longitudinal strain.[15,16] Regional differences in circumferential strain also have been reported in cardiac amyloidosis.[12] However, it remains unclear whether 'apical sparing' is diagnostic for cardiac amyloidosis, and further studies look-

specifičnost tih pronalazaka. Nadalje, učinak stupnja bolesti ovog tipa (amiloidni laki lanac (AL) primarna amiloidoza ili transtiretin (TTR)) na ovaj fenomen još uvijek nije procijenjen. Međutim, prisutnost pojave *apical sparing* trebala bi potaknuti promišljanje o dijagnozi kardioamiloidoze kod pacijenata s hipertrofijom lijeve klijetke nepoznata podrijetla te se može pokazati kao korisno za izbjegavanje nedostatka dijagnoze kardioamiloidoze.[13]

KORONARNA KOMPJUTORIZIRANA TOMOGRAFIJA

Koronarna angiografija kompjutoriziranom tomografijom s primjenom kontrasta (CCTA) omogućuje oslikavanje koronarnih arterija u visokoj rezoluciji da bi se utvrdila veličina i mjesto značajne stenoze i karakteristika aterosklerotskog plaka. Zbog visokih dijagnostičkih performansi, CCTA se učestalo koristi za isključenje prisutnosti koronarne stenoze **(tablica 1)**.[17-20] Međutim, postoji manjak podataka vezanih za učestalost i karakteristike koronarne ateroskleroze kod asimptomatskih pacijenata koji imaju nizak rizik za koronarnu bolest srca (KBS).

Kim et al[21] izvršili su CCTA na 2133 asimptomatska pacijenta srednje dobi koji su klasificirani niskorizičnima prema smjernicama Programa za nacionalnu edukaciju o kolesterolu (NCEP).[22] Kod 243 osobe (11,4%) uočen je aterosklerotski plak. Kod njih 28 (1,3%) postojala je značajna koronarna stenoza, a 18 (0,8%) imalo je značajnu koronarnu stenozu uzrokovanu nekalcificiranim plakom (NCP). Većina pacijenata sa značajnom stenozom imala je bolest jedne žile i većina lezija bile su

ing at the sensitivity and specific of this finding are needed. Moreover, the effect of disease stage or the type (amyloid light chain (AL) primary amyloidosis or transthyretin (TTR)) on this phenomenon has not been evaluated. However, the presence of 'apical sparing' should prompt consideration of the diagnosis of cardiac amyloidosis in patients with unknown origin of left ventricular hypertrophy, and may prove useful in avoiding underdiagnosis of cardiac amyloidosis.[13]

CORONARY CT

Contrast-enhanced coronary CT angiography (CCTA) provides high-resolution images of the coronary arteries showing the severity and the location of significant stenosis and characteristics of atherosclerotic plaque. Because of its high diagnostic performance, CCTA has been increasingly used to exclude the presence of coronary stenosis **(Table 1)**.[17–20] However, there is a paucity of data regarding the prevalence and characteristics of coronary atherosclerosis in asymptomatic patients with few risk factors for coronary disease.

Kim *et al*[21] performed CCTA imaging in 2133 middle-aged asymptomatic patients who were classified as low risk by National Cholesterol Education Program (NCEP) guidelines.[22] There were 243 persons (11.4%) with atherosclerosis plaques. Twenty-eight of them (1.3%) had a significant coronary stenosis, and 18 (0.8%) of them had significant coronary stenosis caused by non-calcified plaque (NCP). Most patients with significant stenosis had single-vessel disease and most of the significant lesions were located in the left anterior de-

FIGURE 1.
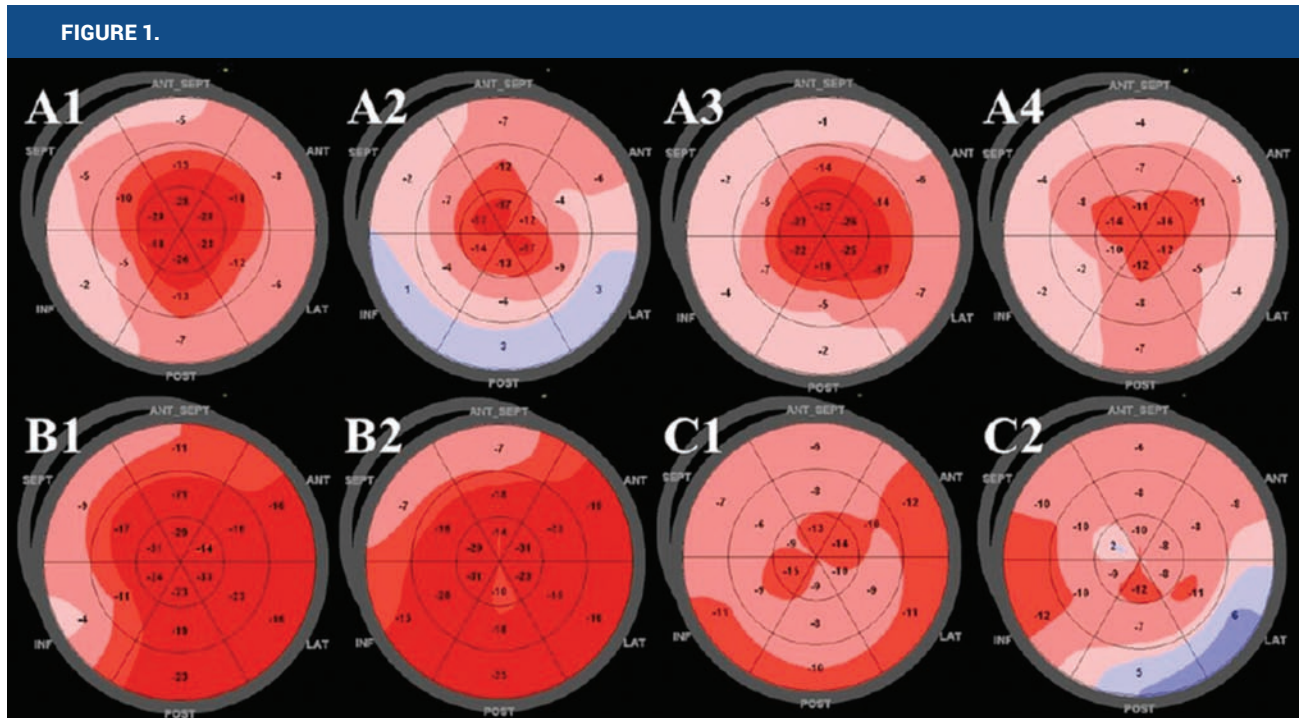
Representative two-dimensional speckle-tracking longitudinal strain patterns ('bull's eye plots') for each subgroup. (A1−4) Apical sparing pattern in patients with cardiac amyloidosis. (B1,2) Isolated impairment of septal longitudinal strain in septal hypertrophic cardiomyopathy. (C1,2) Patchy reduction in longitudinal strain in left ventricular hypertrophy related to aortic stenosis. (Cited from ref. 14).

TABLE 1. Diagnostic performance of CT for anatomically obstructive stenosis in individuals without known CAD.

	Sensitivity	Specificity	PPV	NPV
ACCURACY	94	83	48	99
N=230, stable chest pain; no known CAD; no exclusion (CACS, HR, BMI); CAD prevalence 13%				
Meijboom *et al*	99	64	85	97
N=360, acute and stable chest pain; CAD prevalence 68%				
CorE64	85	90	91	83
N=291, stable chest pain; no known and known CAD; exclusion CACS >600; CAD prevalence 56%				
Meijboom *et al*	95	91	71	99
N=415 (83), 20−80% pretest LK of CAD				

BMI, Body Mass Index; CACS, Coronary Artery Calcification Score; CAD, coronary artery disease; HR, heart late; LK, likelihood; N, number; NPV, negative predictive value; PPV, positive predictive value (Cited from ref. 18).

smještene na lijevoj prednjoj silaznoj koronarnoj arteriji. Veći-na osoba sa značajnom stenozom uzrokovanom NCP-om bile su mlade odrasle osobe. Multivarijatna analiza je razjasnila da su muški spol i razine LDL-kolesterola neovisni predika-tori značajne stenoze uzrokovane NCP. Kardiološki događaji su se zbili kod 4 osobe tijekom srednje dugog promatranja (29,3 ± 14,9 mjeseci). Sva četiri pacijenta imala su aterosklerotski plak, a tri su imala značajnu NCP stenozu. Iz ovog istraživanja možemo prepoznati da učestalost subkliničke ateroskleroze nije zanemariva, čak i kod asimptomatskih niskorizičnih bo-lesnika, pogotovo kod mladih odraslih osoba. Iako trenutne smjernice ne opravdavaju CCTA kao sredstvo za testiranje kod asimptomatskih pacijenata, potrebno je daljnje istraživa-nje da bi se pojasnilo ima li CCTA potencijala za identificiranje visokorizičnih pacijenata koji bi inače bili klasificirani kao ni-skorizični prema NCEP smjernicama.

Postoji mnogo istraživanja koja pokazuju da CCTA može pružiti važne prognostičke informacije i stratifikaciju rizika u pacijenata kod kojih se sumnja na KBS.[23,24] Međutim, većina prethodnih istraživanja usredotočila su se na širu populaciju, a samo su ograničeni podatci dostupni za razlike s obzirom na dob i spol. S ciljem procjene razlika u pojavnosti KBS, CCTA je obavljen na 2432 pacijenta u kojih se sumnjalo na KBS u multicentričnoj prospektivnoj studiji s podatcima iz Regi-stra.[25] Obavljena je analiza na četiri podskupine razdijeljene prema spolu (muškarci i žene) i dobi (dobi <60 ili ≥60 godina). Kod 991 (41%) pacijenta uočen je normalan CCTA rezultat, kod 761 (31%) uočena je nesignifikantna KBS, a kod njih 680 (28%) utvrđene su značajne promjene na koronarnim arterijama. Ti-jekom praćenja (srednja duljina od 819 dana) kardiovaskular-ni događaj se zbio kod 59 (2,4%) pacijenata bez razlike u dobi ili spolu. CCTA nalazi su bili prediktivni za zajednički ciljni ishod (nesmrtonosni infarkt miokarda i kardiološka smrt) kod muških pacijenata, dobi i <60 i ≥60 godina i kod ženskih pacijenata ≥60 godina. Međutim, kod ženskih pacijenata <60 godina, CCTA nalazi nisu bili prediktivni za neželjene kardi-ovaskularne događaje. Stoga, dok CCTA može biti koristan pri

scending coronary artery. Notably, the majority of subjects with significant stenosis caused by NCP were young adults. Multivariate analysis clarified that male gender and LDL-cholesterol level were independent predictors of significant stenosis caused by NCP. Cardiac events occurred in four in-dividuals during mid-term follow-up (29.3 ±14.9 months). All four of these patients had atherosclerotic plaques, and three had significant NCP stenosis. From this study, we recognise that the prevalence of subclinical atherosclerosis is not negli-gible even in asymptomatic patients with low risk, especially in young adults. Although CCTA is not justified as a screening tool for asymptomatic patients by current guidelines, further research is needed to clarify if CCTA has the potential to iden-tify high-risk patients who would otherwise be classified as low risk by NECP guidelines.

There are many studies showing that CCTA can provide important prognostic information and risk stratification in patients with suspected coronary artery disease.[23,24] Howev-er, most of the previous studies have focused on the general population, and limited data are available for age and gender-specific differences. To evaluate these differences in the in-cidence of coronary artery disease, CCTA was performed in 2432 patients with suspected coronary artery disease in the multicentre prospective registry study.[25] Analysis was done in four subgroups stratified according to gender (male or fe-male) and age (aged <60 or ≥60 years). There were 991 patients (41%) with normal CCTA results, 761 (31%) with non-significant coronary artery disease and 680 (28%) with significant coro-nary artery disease. During the follow-up (median 819 days), a cardiovascular event occurred in 59 (2.4%) with no gender-specific and age-specific difference. CCTA results were pre-dictive of the composite end point (non-fatal myocardial inf-arction and cardiac death) in male patients, both aged <60 and ≥60 years, and in female patients aged ≥60 years. However, in female patients aged <60 years, CCTA results were not predic-tive of adverse cardiovascular events. Thus, while CCTA may be a valuable tool to rule out coronary artery disease, its prog-nostic value appears to be limited in women aged <60 years.

isključivanju KBS, čini se da je njegova prognostička vrijednost ograničena na žene u dobi od <60 godina.

OPTIČKA KOHERENTNA TOMOGRAFIJA

Optička koherentna tomografija (OCT) ekstenzivno se primjenjuje jednako dugo kao i intrakoronarna slikovna dijagnostika, zbog svoje visoke aksijalne rezolucije koja ima raspon od 12 do 18 μm, u usporedbi sa 150-200 μm za intravaskularni ultrazvuk.[26] OCT je koristan da bi se vizualizirale mikrostrukture plaka, mikrožile unutar koronarnog plaka, premosnice i neointimalne promjene unutar stentova.[26,27]

Neovaskularizacija unutar plaka (NV) koja većinom proizlazi iz prethodno postojećeg u pridruženih krvnih žila (*vasa vasorum*), prepoznata je kao važan proces za progresiju ateroskleroze u većim žilama.[28] Međutim, istraživanje na NV koronarnog plaka je bilo ograničeno. Tian et al[29] proučavali su važnost NV unutar plaka u koronarnom plaku pomoću OCT. Oni su analizirali kritične plakove i 203 nekritičnih plakova od 92 pacijenta s nestabilnom anginom pektoris i 61 plak kod 25 pacijenata sa stabilnom anginom pektoris. NV je definiran kao mala crna rupa unutar plaka s dijametrom od 50-300 μm koja je bila prisutna u barem tri konsekutivna sloja dobivenih slika. Učestalost NV unutar plaka je bila oko 30% i nije bila različita za kritične i nekritične promjene kod pacijenata s nestabilnom i stabilnom anginom pektoris. Međutim, među kritičnim lezijama pacijenata s nestabilnom anginom pektoris, plak sa NV imao je tanju fibroznu kapu, veću lipidnu jezgru i učestaliji fibroateromi tanke kape nego onaj bez NV. Nije bilo značajne razlike u karakteristikama plaka između nekritičnih lezija od nestabilnih angina pektoris i lezija od stabilnih angina pektoris. Kritični plak sa NV ima ranjivije karakteristike u usporedbit sa onima bez NV u pacijenata sa nestabilnom anginom pektoris **(slika 2)**. NV unutar plaka ima dvostruki učinak na plak ovisno o stadiju bolesti.[30] U ranoj fazi on potpomaže opskrbljivanje stijenki žila hranjivim tvarima i kisikom te štiti plak od ishemijskog oštećenja. Međutim, u kasnoj fazi, s razvojem nejednakosti između antiangiogenskih i proangiogenskih čimbenika, NV unutar plaka postaje nezreliji i počinje propuštati te tako potiče konverziju stabilnog plaka u nestabilni plak.[30] Stoga, NV unutar plaka može pooštriti destabilizaciju plaka u pacijenata s nestabilnom anginom pektoris.

PERFUZIJA MIOKARDA

Perfuzija miokarda procjenjuje se pomoću jednofotonske emisijske CT (SPECT), pozitronske emisijske tomografije, MRI perfuzije i kontrastne ehokardiografije. SPECT je bio najpopularniji te je zabilježena zadovoljavajuća dijagnostička sposobnost za identificiranje pacijenata kojima je koristila revaskularizacija.[31,32] Međutim, rezultat dijagnostičkog testa može utjecati na daljnje upućivanje na precizniji test. Kada se uzme u obzir odstupanje zbog daljnjeg upućivanja, stres SPECT ima samo 65% osjetljivost i 67% specifičnost pri identifikaciji pacijenata sa značajnom stenozom.[33] Štoviše, postoji i problem ograničene prostorne rezolucije i manjak kvantifikacije.

Višeredni detektorski CT (*multirow detector* CT, MDCT) ima bolju vremensku i prostornu rezoluciju. Zabilježeno je da MDCT može mjeriti krvotok miokarda (MBF) primjenjujući dekonvolucijsku metodu zasnovanu na modelima unutar koronarne

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) has been extensively used recently as an intracoronary imaging method because of its high axial resolution ranging from 12 to 18 μm, compared with 150−200 μm for intravascular ultrasound.[26] OCT is useful to visualise plaque microstructure, microvessels within coronary plaques, stents and neointimal changes inside stents.[26,27]

Intraplaque neovascularisation (NV), derived mainly from pre-existing vasa vasorum, has been recognised as an important process for the progression of atherosclerosis of larger vessels.[28] However, investigation on coronary plaque NV has been limited. Tian *et al*[29] studied the significance of intraplaque NV in the coronary plaques using OCT. They analysed 92 culprit plaques and 203 non-culprit plaques from 92 patients with unstable angina pectoris and 61 plaques from 25 patients with stable angina pectoris. A NV was defined as a small black hole within a plaque with a diameter of 50−300 μm that was present on at least three consecutive frames in pull-back images. The incidence of intraplaque NV was around 30% and not different among culprit and non-culprit lesions in patients with unstable and stable angina pectoris. However, among culprit lesions obtained from patients with unstable angina pectoris, plaques with NV had thinner fibrous cap, larger lipid core and higher incidence of thin cap fibroatheroma than those without NV. There was no significant difference in plaque characteristics between non-culprit lesions from unstable angina pectoris and lesions from stable angina pectoris. They found that the culprit plaques with NV had vulnerable features compared with those without NV in patients with unstable angina pectoris **(Figure 2)**. Intraplaque NV has dual effects on the plaque depending on the stage of the disease.[30] At the early stage, it helps to supply nutrients and oxygen to the vessel wall and protects the plaque from ischaemic damage. However, at the late stage, with development of an imbalance between antiangiogenic and proangiogenic factors, the intraplaque NV becomes more immature and leaky, promoting the conversion of a stable plaque to an unstable plaque.[30] Thus, intraplaque NV might aggravate destabilisation of plaques in patients with unstable angina pectoris.

MYOCARDIAL PERFUSION

Myocardial perfusion has been assessed by single photon emission CT (SPECT), positron emission tomography, perfusion MRI and contrast echocardiography. SPECT has been most popular, and an acceptable diagnostic capability to identify patients who have benefitted from revascularisation has been reported.[31,32] However, the result of a diagnostic test may affect the subsequent referral for a more definitive test. When adjusted for referral bias, stress SPECT provided only 65% of sensitivity and 67% of specificity to identify patients with severe stenosis.[33] Moreover, there is a problem of limited spatial resolution and a lack of quantification.

Multirow detector CT (MDCT) has better temporal and spatial resolution. It has been reported that MDCT can measure myocardial blood flow (MBF) using a model-based deconvolution method in a canine model of coronary stenosis.[34] Nakauchi *et al*[35] assessed the feasibility of this method to quantify myocardial perfusion in patients with acute myocardial

stenoze psećeg modela.[34] Nakauchi et al[35] procijenili su provedivost ove metode za kvantificiranje perfuzija miokarda kod pacijenata s akutnim infarktom miokarda. Zamijetili su da su krvotok u tkivu i volumen krvotoka znatno reducirani u infarktom zahvaćenom miokardu u usporedbi s istima u miokardu koji nije doživio infarkt. Oštećeno područje mjereno na bojama kodiranoj mapi volumena krvi tkiva je pokazivalo korelaciju s najvišim razinama kreatinin-kinaze i SPECT stupanj oštećenja. Kod pacijenata koji su podvrgnuti MDCT i MRI unutar nekoliko dana, volumen krvotoka u tkivu mjeren MDCT-om slagao se s onim mjerenim MRI-om. Ovo je istraživanje pokazalo provedivost evaluacije perfuzije miokarda u jednom CT-u koji se izvodi u kliničkoj praksi. S obzirom na to da se protokol skeniranja podudara s osnovnim slikama CCTA, moguće je istovremeno procijeniti perfuziju miokarda i stenozu koronarnih arterija tijekom jednog pregleda.
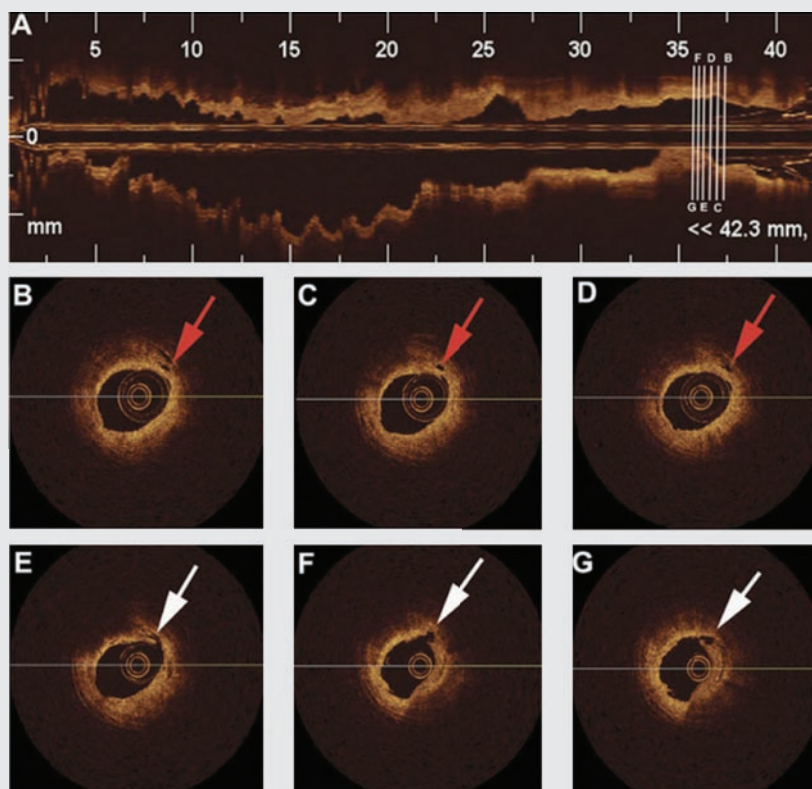
CCTA se koristi kako bi se vizualizirala koronarna morfologija. Međutim, hemodinamska važnost otkrivenih koronarnih stenoza ne može biti procijenjena pomoću CT-a tako da je potreban dodatni SPECT ili MRI perfuzije miokarda. SPECT i MRI perfuzije miokarda, međutim, ne pomažu pri procjeni koronarne morfologije. To su klinički značajni problemi jer je važno identificirati lokaciju koronarnih stenoza koje opskrbljuju miokard demonstriranim ishemijama, dok revaskularizacija vodi ka redukciji smrtnosti i poboljšava prognozu.[36] Greif et al[37] iznose istraživanje o slikovnoj dijagnostici perfuzije miokarda putem CT-a. Protokol slikavanja koristio je CT sistem s dva izvo-

infarction. They found tissue blood flow and tissue blood volume were significantly reduced in the infarcted myocardium compared with those in the non-infarcted myocardium. The defect area measured on the colour-coded tissue blood volume map correlated well with peak creatinine kinase level and SPECT defect score. In patients undergoing MDCT and MRI within a few days, the tissue blood flow measured with MDCT agreed well with that measured with MRI. This study demonstrated the feasibility of evaluating myocardial perfusion in a single CT as performed in clinical practice. Because the scan protocol is congruent with the baseline images for CCTA, it is possible to assess myocardial perfusion and coronary artery stenosis simultaneously in a single examination.

CCTA is used to visualise coronary morphology. However, the haemodynamic significance of detected coronary stenosis cannot be evaluated by CT so that additional SPECT or myocardial perfusion MRI is needed. SPECT and myocardial perfusion MRI, however, are not helpful to assess coronary morphology. Clinically, these are relevant issues because it is important to identify the location of coronary stenoses that supply myocardium with demonstrated ischaemia as revascularisation leads to reduction of mortality and improved prognosis.[36] Greif et al[37] report a study on myocardial perfusion imaging using CT imaging. The imaging protocol used a fast dual-source CT system, and evaluated coronary artery and myocardial perfusion with an adenosine stress test. Briefly, a dedicated parametric deconvolution technique was

FIGURE 2.

Representative optical coherence tomography images of ruptured plaque with neovascularisation (red arrows). The longitudinal pull-back image (A) of the vessel with the locations of five cross-sectional images (B−G). Neovascularisation (red arrows) were located at the shoulder region of plaque (B−D). Plaque rupture (white arrows) was visualised at the 7-o'clock position (E−G). Minimum lumen area site (G). (Cited from ref. 30).

	Advantages	Disadvantages
TABLE 2. Methods of physiologic assessment by CT.		
Transluminal contrast opacification gradients	Able to be performed on rest CCTA scans Surrogate measure of coronary blood flow	Questionable significance of rest coronary contrast opacification Labour intensive
Adverse plaque characteristics	May represent endothelial injury Associated with worsened prognosis and ischaemia	Does not directly measure coronary or myocardial ischaemia Labour intensive No assessment of stress-induced state CT perfusion
CT perfusion	General familiarity with performance of stress testing Measures of subendocardial and transmural myocardial ischaemia FFRCT	Requires additional radiation Requires additional contrast Optimal method not yet determined
FFR$_{CT}$	Diagnostic of lesion-specific inschaemia Can be performed on typically acquired CCTA, thus, no extra radiation or contrast Validated in prospective multicentre studies	Requires sending of CCTA data to external laboratory

CCTA, coronary CT angiography; FFRCT, fractional flow reserve CT technique. (Cited from ref. 18).

ra i evaluirao perfuziju koronarne arterije i miokarda pomoću adenozin stres testa. Ukratko, primijenjena je tehnika parametrijske dekonvolucije, i MBF je izračunan iz maksimalnog nagiba krivulje tkivnog vremenskog prigušenja (engl. *tissue time-attenuation*).[38] Za hemodinamski značajnu koronarnu stenozu uzimala se vrijednosti ispitivanja koronarne cirkulacije (*pressure wire*) mjerenjem frakcijske rezerve protoka (FFR) od ≤0,80 ili suženje lumena >90%. CCTA je otkrio sve hemodinamski relevantne stenoze (osjetljivost 100%) dok je specifičnost bila 43,8%, a dijagnostička preciznost 72%. Prosječni MBF reduciran je u segmentima miokarda koji pripadaju hemodinamski značajnim koronarnim stenozama. Osjetljivost, specifičnost i dijagnostička preciznost prikaza CT-a perfuzije miokarda bile su 97%, 65,6% i 81,5%. Kombinacija prikaza CCTA i CT-a perfuzije miokarda nije pokazala nikakvo dodatno poboljšanje pri otkrivanju hemodinamski značajnih stenoza uspoređeno sa samo CT slikovnim prikazom perfuzije miokarda. Dakle, CT slikovni prikaz perfuzije miokarda pomoću CT-a s dva izvora omogućava otkrivanje hemodinamskih stenoza koronarnih arterija s umjerenom dijagnostičkom preciznošću. Ova metoda dopušta istovremenu procjenu i koronarne morfologije i djeluje neinvazivno.

Postoji nekoliko novijih metoda fiziološke procjene KBS pomoću CT-a **(tablica 2)**.[17] Prisutno je postupno smanjivanje zamućenosti kontrasta od proksimalnog ka distalnom dijelu koronarne arterije. Zamijećeno je da se gradijenti zamućenosti transluminalnog kontrasta (TAG) smanjuju u skladu s procjenom protoka TIMI ljestvicom.[39] Međutim, ova metoda ovisi o više čimbenika poput EF lijeve klijetke, stopa bolus kontrasta, brzina koronarnog toka i koncentracija i volumen kontrasta. Zbog nedavnih napredaka u računalnoj dinamici toka, predviđanje koronarnog toka i pritiska, i po tome izračunavanje FFR specifičnih za lezije (FFRCT, FFR CT *technique*) su mo-

used, and from the maximum slope of the tissue time-attenuation curve, MBF was calculated.[38] Fractional flow reserve (FFR) ≤0.80 measured by a pressure wire or lumen narrowing >90% was considered as haemodynamically significant coronary stenosis. CCTA detected all haemodynamically relevant stenosis (sensitivity 100%) while the specificity was 43.8% and diagnostic accuracy was 72%. Mean MBF was reduced in the myocardial segments pertaining to haemodynamically significant coronary stenosis. Sensitivity, specificity and diagnostic accuracy of CT myocardial perfusion imaging were 97%, 65.6% and 81.5%, respectively. The combination of CCTA and CT myocardial perfusion imaging demonstrated no significant further improvement in detection of haemodynamically significant stenosis compared with CT myocardial perfusion imaging alone. Thus, CT myocardial perfusion imaging using a dual-source CT permits the detection of haemodynamically coronary artery stenosis with a moderate diagnostic accuracy. This method allows the simultaneous assessment of both coronary morphology and function non-invasively.

There are several other novel methods for physiologic assessment of coronary artery disease using CT **(Table 2)**.[17] There is a gradual diminution of contrast opacification from the proximal portion to the distal portion in the coronary artery. Transluminal contrast attenuation gradients (TAG) have been reported to decrease in accordance with Thrombolysis in Myocardial Infarction (TIMI) flow grade.[39] However, this technique is dependent on a multiple factors such as left ventricular EF, contrast bolus rates, coronary flow velocity and contrast concentration and volumes. Owing to recent advances in computational flow dynamics, prediction of coronary flow and pressure, and thereby calculation of lesion-specific FFR (FFRCT, FFR CT technique) have been possible from typically acquired static CT images.[40] In a multicentre study with

guće iz tipičnih statičnih CT slika.[40] U multicentričnoj studiji s uključenih 252 pacijenta sa 150 žila s umjernim stenozama, FFRCT bio je bolji od CCTA za dijagnoze ishemija specifičnih za lezije.[41] Stoga ova metoda obećava neinvazivno isključivanje pacijenata s ishemijom miokarda.

Hibridni SPECT/CCTA pokazao se uspješnim pri dijagnozi značajne KBS **(slika 3)**.[42] Međutim, nije poznato postoji li razlika u učinku na odabir strategija liječenja između hibridne dijagnostike primjenom SPECT/CCTA i SPECT s dodatnom koronarnom angiografijom. U prospektivnom istraživanju izvedenom na 107 pacijenata sa stabilnom anginom pektoris i prijelaznom do visokom predtestnom vjerojatnošću KBS,[42] pacijenti su podvrgnuti SPECT-u s ergometrijskim ili farmakološkim opterećenjem, nakon kojih je uslijedio CCTA. Koronarna angiografija obavljena je u roku od 14 dana nakon SPECT/CCTA. Nalazi hibridnih pretraga kategorizirani su kao usklađeni, neusklađeni i normalni. Usklađeni nalaz definiran je kao ishemijsko SPECT oštećenje u području miokarda kojeg opskrbljuje stenozirana koronarna arterija. Neusklađeni nalaz definiran je kao ishemijsko SPECT oštećenje bez značajne koronarne lezije ili kao neishemijski SPECT nalaz sa značajnom koronarnom lezijom. Normalan nalaz definiran je kao normalna SPECT perfuzija, bez značajne koronarne stenoze. Odbor koji se sastojao od dva intervencijska kardiologa i jednog kardiototrakalnog kirurga, odlučio je o postotku slaganja odluka o liječenju (bez revaskularizacije, perkutane koronarne intervencije ili operacije premosnice koronarne arterije) za hibridnu dijagnostiku primjenom SPECT/CCTA i SPECT s dodatnom koronarnom angiografijom. Postotak slaganja u odlukama o liječenju kod svih pacijenata kojima je bila potrebna revaskularizacija je iznosio 92%, a u pacijenata s usklađenim, neusklađenim i normalnim nalazima hibridne dijagnostike primjenom SPECT/CCTA iznosio je 95%, 84% i 100%. Postotak slaganja stratificiran metodom revaskularizacije (perkutana intervencija ili ugradnja premosnice) bio je 72% za usklađene pacijente i 79% za neusklađene pacijente. Ovo je istraživanje pokazalo da novi pregled koji uključuje slikovni prikaz dobiven hibridnom dijagnostikom primjenom SPECT/CCTA i tradicionalni koji uključuje invazivnu koronarnu angiografiju mogu dovesti do sličnih odluka o liječenju. Prema tome, pacijentima sa srednje visokom do visokom predtestnom vjerojatnošću može biti odgođena ili indicirana revaskularizacija s obzirom na hibridnu dijagnostiku primjenom SPECT/CCTA, iako moramo obratiti pozornost na razinu zračenja.[43]

OSTALO

Fibroza miokarda pronalazi se u raznim stanjima, poput hipertenzije, ishemijske bolesti srca i kardiomiopatije. Neinvazivna procjena stupnja fibroze miokarda potrebna je jer je izravno povezana s prognozom. Prikaz kontrastne magnetske rezonancije s primjenom kontrasta (CMR) učestalo se koristi za procjenu lokalne fibroze.[44] Od razvitka transkateterske implantacije aortnog zalistka (TAVI) postoji povećano zanimanje za aortnu stenozu (AS). Očekuje se da je jedna od odrednica prognoze AS-a fibroza miokarda koja nastaje uslijed dugoročnog preopterećenja pritiska. Fairbairn et al[45] pokazali su da se fibroza miokarda mjerena CMR-om smanjila u razdoblju od 6 mjeseci nakon podvrgnuća TAVI, iako nije primijećen nikakav učinak kod pacijenata koji su bili podvrgnuti kirurškoj zamjeni aortnog zalistka.

150 vessels of intermediate stenosis from 252 patients, FFRCT was better than CCTA for the diagnosis of lesion-specific ischaemia.[41] Thus, this method is promising to exclude patients with myocardial ischaemia non-invasively.

Hybrid SPECT/CCTA has been shown to have good performance in the diagnosis of significant coronary artery disease **(Figure 3)**.[42] However, it has not been known whether there is a difference in the effect on the choice of treatment strategy between hybrid SPECT/CCTA and SPECT plus coronary angiography. In a prospective study of 107 patients with stable angina pectoris, and an intermediate to high pretest likelihood of coronary artery disease,[42] patients underwent an exercise or pharmacological stress SPECT study followed by CCTA. Coronary angiography was performed within 14 days of the SPECT/CCTA. The hybrid findings were categorised as matched, unmatched or normal. A matched finding was defined as an ischaemic SPECT defect in a myocardial territory subtended by a stenotic coronary artery. An unmatched finding was defined as an ischaemic SPECT defect without significant coronary lesion or a non-ischaemic SPECT finding with significant coronary lesion. A normal finding was defined as normal SPECT perfusion, with no significant coronary stenosis. The panel, consisting of two interventional cardiologists and one cardiothoracic surgeon, decided the percentage agreement of treatment decisions (no revascularisation, percutaneous coronary intervention or coronary artery bypass grafting) between hybrid SPECT/CCTA and SPECT and coronary angiography. The percentage agreement of treatment decisions in all patients on the necessity of revascularisation was 92%, and that in patients with matched, unmatched and normal hybrid SPECT/CCTA findings was 95%, 84% and 100%, respectively. The percent agreement stratified by method of revascularisation (percutaneous intervention or bypass surgery) was 72% for matched patients and 79% for unmatched patients. This study showed that a new work-up including hybrid SPECT/CCTA imaging, and a traditional work-up including invasive coronary angiography, could reach similar treatment decisions. Thus, patients with an intermediate to high pretest likelihood could be accurately deferred from, or indicated for revascularisation based on hybrid SPECT/CCTA, although we have to care about the radiation dose.[43]

OTHERS

Myocardial fibrosis is found in various conditions, such as hypertension, ischaemic heart disease and cardiomyopathy. Because it directly relates to prognosis, non-invasive assessment of the degree of myocardial fibrosis is needed. Contrast-enhanced cardiovascular magnetic resonance (CMR) imaging has been extensively used to assess local fibrosis.[44] Since the advent of transcatheter aortic valve implantation (TAVI), there is an increasing interest in AS. One of the determinants of prognosis of AS is expected to be myocardial fibrosis which occurs due to a long-standing pressure overload. Fairbairn et al[45] demonstrated that CMR measured myocardial fibrosis, decreased after 6 months in patients undergoing TAVI, although no effect was seen in patients undergoing surgical aortic valve replacement.

Thus, CMR with postcontrast late gadolinium enhancement is useful, but it is time consuming, demands complex processing, and cannot be used in patients with severe renal

Prema tome, CMR s postkontrastnim kasnim pojačanjem gadolinija jest koristan, ali iziskuje mnogo vremena, zahtijeva složeno procesiranje i ne može se koristiti kod pacijenata sa značajnim bubrežnim oštećenjem.[46] T1 vrijednosti miokarda mijenjaju se sa sastavom tkiva.[47] Bull et al[48] pronašli su da nekontrastno CMR mapiranje T1 može otkriti fibrozu miokarda kod pacijenata sa AS **(slika 4)**. Pokazali su značajnu korelaciju između vrijednosti T1 i fibroza kvantificiranih biopsijom. Ova se metoda može primijeniti kao jednostavna, neinvazivna, nekontrastna procjena difuzne fibroze miokarda kod drugih kardioloških bolesti.

Na posljetku, jedan je članak uzet iz nuklearne kardiologije.[49] Funkcija kardiološkog simpatičkog živca igra važnu ulogu u patofiziologiji, progresiji i stratifikaciji rizika i predviđanju kliničkih ishoda kroničnog zatajivanja rada srca. Jod-123 metaiodobenzilgvanidin (123I-IMBG) analog je norepinefrina, a kardiološka 123I-IMBG scintigrafija se koristi za procjenu simpatičke aktivnosti miokarda. Nekoliko publikacija je pokazalo kliničku efikasnost kardioloških 123I-IMBG slikovnih prikaza kod pacijenata sa zatajivanjem srca. Abnormalna aktivnost 123I-IMBG i povećanje stope ispiranja usko su povezane s opadanjem funkcionalnog statusa, redukcijom EF lijeve klijetke te preživljavanjem.[50,51] Da bi se procijenila prognostička vrijednost 123I-IMBG kardiološke scintigrafije pri predviđanju aritmija klijetke, Marshall et al su proveli prospektivnu studiju na 27 pacijenata sa ZS koji su bili upućeni na implantaciju ugradljivog kardioverter-defibrilatora (ICD). Deset pacijenata doživjelo je značajne aritmijske događaje tijekom 16 mjeseci srednjeg praćenja. Ovi su pacijenti imali nizak rani i kasni omjer srca naspram medijastinuma (H:M) i viši 123I-IMBG SPECT rezultate oštećenja nego oni bez aritmijskih događaja. Rani H:M omjer, kasni H:M omjer i rezultati oštećenja su pokazali 60-78% osjetljivost i 77-88% specifičnosti za predviđanje aritmije. Stoga, u pacijenata sa ZS, slikovni prikaz kardiološkog 123I-IMBG pruža dodatne prognostičke podatke po pitanju rizika od budućih aritmija koje mogu biti korisne u informiranju procesa odabira slučajeva za liječenje ICD.

impairment.[46] Myocardial T1 values change with tissue composition.[47] Bull et al[48] found that non-contrast CMR T1 mapping could identify myocardial fibrosis in patients with AS **(Figure 4)**. They showed a significant correlation between T1 values and biopsy-quantified fibrosis. This method could be applied as a simple, non-invasive, non-contrast assessment of diffuse myocardial fibrosis in other cardiac diseases.

Last, one article is taken up from nuclear cardiology.[49] Cardiac sympathetic nerve function plays an important role in the pathophysiology, progression and the risk stratification and prediction of clinical outcomes in chronic heart failure. Iodine-123 metaiodobenzylguanidine (123I-MIBG) is an analogue of norepinephrine, and cardiac 123I-MIBG scintigraphy has been used to assess myocardial sympathetic activity. Several publications have demonstrated clinical efficacy for cardiac 123I-MIBG imaging in heart failure patients. Abnormal 123I-MIBG activity and augmentation of washout rate are closely related to deterioration of functional status, reduction of left ventricular EF and survival.[50,51] To assess the prognostic value of cardiac 123I-MIBG scintigraphy to predict ventricular arrhythmias, Marshall et al conducted a prospective study in 27 patients with heart failure referred for implantable cardioverter defibrillator (ICD) implantation. There were 10 patients who experienced significant arrhythmic events at 16 months of median follow-up. These patients had lower early and late heart-to-mediastinum (H:M) ratio and higher 123I-MIBG SPECT defect scores than those without arrhythmic events. Early H:M ratio, late H:M ratio and defect score provided 60–78% of sensitivity, and 77–88% of specificity to predict arrhythmia. Thus, in patients with heart failure, cardiac 123I-MIBG imaging provides incremental prognostic information regarding the risk of future arrhythmia which may be helpful in informing the process of case selection for ICD therapy.

FIGURE 3.
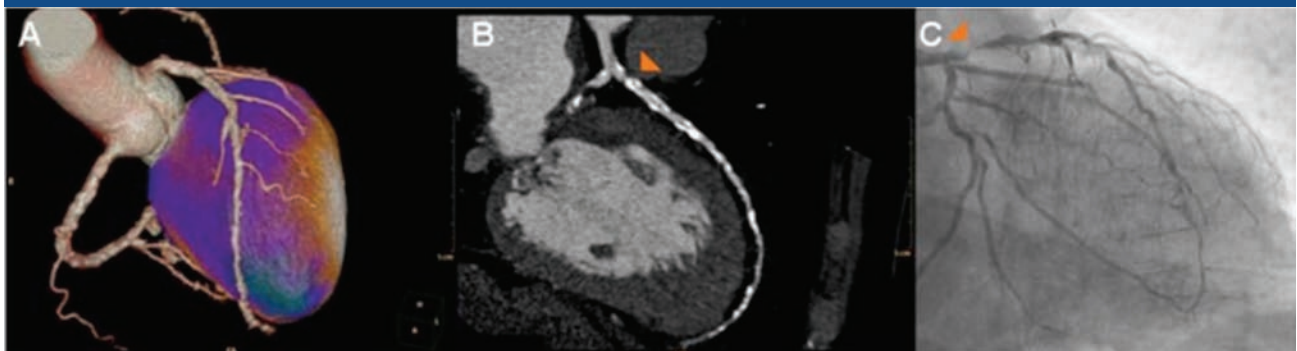
A 71-year-old male patient with typical anginal complaints, and a severe reversible perfusion defect anterior and apical on single photon emission CT (SPECT) (A, stress SPECT). Coronary CT angiography (CCTA) with evaluation was largely not possible due to severe coronary calcifications (coronary calcium score of 2279), although a severe stenosis in the proximal left anterior descending (LAD) artery was suspected (B). The presence of a significant stenosis in the proximal LAD was confirmed by invasive coronary angiogram (CA) (C). Based on evaluation of both hybrid SPECT/CCTA and SPECT and CA, the panel decided on percutaneous coronary intervention. (Cited from ref. 43).

FIGURE 4.
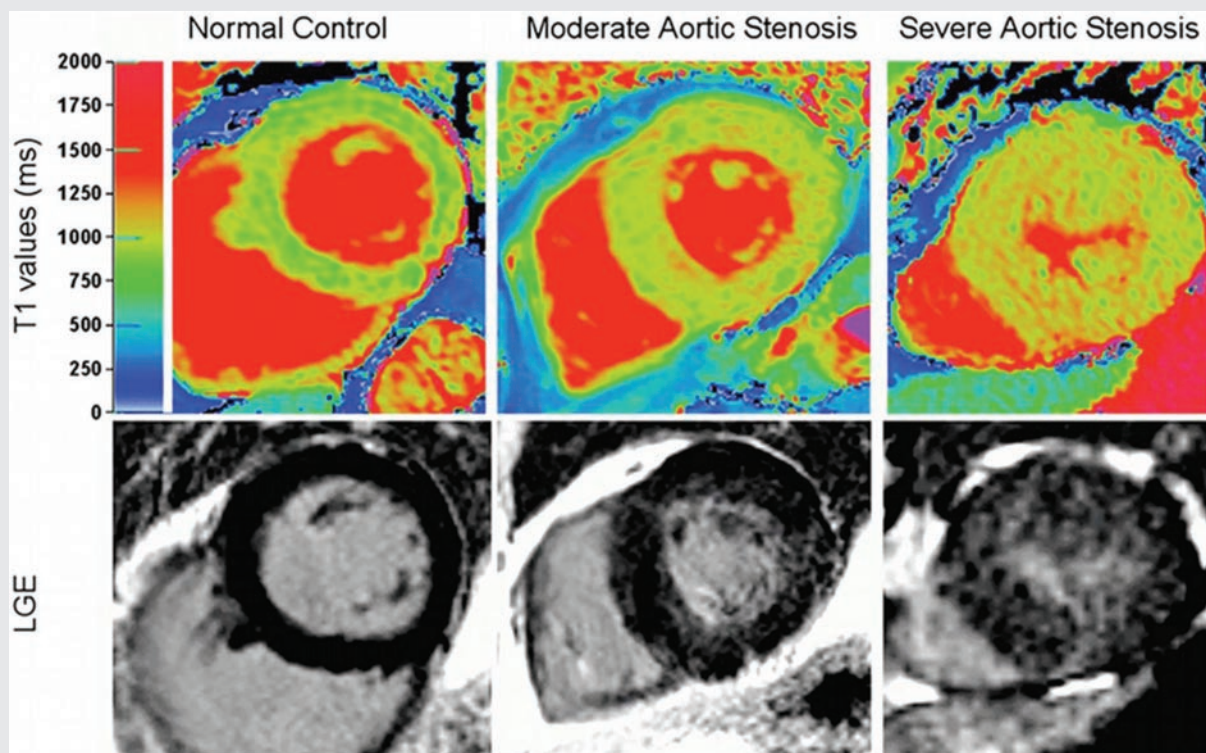
Top panel: colour maps of T1 values using shortened modified Look-Locker inversion in a mid-ventricular short-axis slice; bottom panel: the corresponding slice with late gadolinium enhancement imaging. The left-hand panel shows a normal volunteer (T1=944 ms). The middle panels show moderate aortic stenosis (AS) with moderate left ventricular hypertrophy (T1=951 ms). The right-hand panel shows severe AS with severe left ventricular hypertrophy (T1=1020 ms). (Cited from ref. 49).

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