Almanac 2014: cardiovascular imaging*
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Abstract: 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.

MYOCARDIAL STRAIN

Echocardiographic measures of myocardial strain have emerged as a promising tool to assess cardiac function and predict prognosis in several cardiac conditions¹-³. 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 failure¹³.

Previous studies have mostly focused on patients in sinus rhythm. However, there are many patients with atrial fibrillation and heart failure⁴, especially in those with heart failure with preserved EF. Atrial fibrillation worsens the outcome of heart failure and vice versa⁵. Therefore, the assessment of cardiac function in patients with atrial fibrillation also is important⁶. In a series of 196 patients with atrial fibrillation, Su et al⁷ used the ‘index beat’ method to eliminate the issue of varying R-R intervals⁸,⁹. 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 cumbersome¹⁰. 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 cardiomyopathy¹¹. 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 pathologies¹². In fact, a recent study suggests the prevalence of cardiac amyloidosis may be underestimated and is sometimes overlooked in the clinical setting¹³. Phelan et al¹⁴ 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 mid-longitudinal strain. These authors consistently found an ‘apical sparing’ pattern with a GLS >−12.5%.

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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 looking at the sensitivity and specificity 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 descending 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 individuals during midterm follow-up (29.3±14.9 months). All four of these

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**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).
patients had atherosclerotic plaques, and three had significant NCP stenosis. From this study, we recognise that the prevalence of subclinical atherosclerosis is not negligible 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 identify 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. However, 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 incidence of coronary artery disease, CCTA was performed in 2432 patients with suspected coronary artery disease in the multicentre prospective registry study. Analysis was done in four subgroups stratified according to gender (male or female) 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 coronary 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 predictive of the composite end point (non-fatal myocardial infarction 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 predictive of adverse cardiovascular events. Thus, while CCTA may be a valuable tool to rule out coronary artery disease, its prognostic value appears to be limited in women aged <60 years.

**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. OCT is useful to visualise plaque microstructure, microvessels within coronary plaques, stents and neointimal changes inside stents. 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.

However, investigation on coronary plaque NV has been limited. Tian et al. 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. Intraplaque NV has dual effects on the plaque depending on the stage of the disease. 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 angiogenic and proangiogenic factors, the intraplaque NV becomes more immature and leaky, promoting the conversion of a stable plaque to an unstable plaque. 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\(^3\)\(^,\)\(^2\). 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\(^3\).

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\(^4\). Nakauchi et al\(^5\) assessed the feasibility of this method to quantify myocardial perfusion in patients with acute myocardial 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. Greif et al. 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 used, and from the maximum slope of the tissue time-attenuation curve, MBF was calculated. 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). 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. However, this technique is dependent on 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 (FFR_CT, FFR CT technique) have been possible from typically acquired static CT images. In a multicentre study with 150 vessels of intermediate stenosis from 252 patients, FFR_CT was better than CCTA for the diagnosis of lesion-specific ischaemia. 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). 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, 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

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of two interventional cardiologists and one cardiotho-
racic surgeon, decided the percentage agreement of
treatment decisions (no revascularisation, percutane-
ous 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 per-
cent agreement stratified by method of revascularisation
(percutaneous intervention or bypass surgery) was
72% for matched patients and 79% for unmatched pa-
tients. This study showed that a new work-up including
hybrid SPECT/CCTA imaging, and a traditional work-
up including invasive coronary angiography, could re-
ach similar treatment decisions. Thus, patients with an
intermediate to high pretest likelihood could be accu-
ратely deferred from, or indicated for revascularisation
based on hybrid SPECT/CCTA, although we have to
care about the radiation dose43.

OTHERS

Myocardial fibrosis is found in various conditions,
such as hypertension, ischaemic heart disease and car-
diomyopathy. 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 extensi-
vely used to assess local fibrosis44. 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 al45 demonstrated that CMR measured
myocardial fibrosis, decreased after 6 months in pati-
ents undergoing TAVI, although no effect was seen in
patients undergoing surgical aortic valve replacement.
Thus, CMR with postcontrast late gadolinium en-
han cement is useful, but it is time consuming, deman-
ds complex processing, and cannot be used in patients
with severe renal impairment46. Myocardial T1 values
change with tissue composition47. Bull et al48 found that
non-contrast CMR T1 mapping could identify myo-
cardial fibrosis in patients with AS (Figure 4). They
showed a significant correlation between T1 values and
biopsy-quantified fibrosis. This method could be appli-
ced as a simple, non-invasive, non-contrast assessment
of diffuse myocardial fibrosis in other cardiac diseases.

Last, one article is taken up from nuclear cardio-
logy49. 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 metiodobenzylguanidine (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. 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.

Competing interests: None.

Ethics approval.

Provenance and peer review Commissioned; externally peer reviewed.

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