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REVIEW ARTICLE

Echocardiographic assessment of cardiac structure and function in chronic renal disease

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Abstract
Chronic kidney disease (CKD) is a global health problem and is independently associated with increased risk for cardiovascular disease (CVD). The presence and severity of CKD is strongly related to the progression of coronary atherosclerosis, ventricular hypertrophy, myocardial fibrosis, valvular calcification, and cardiac conduction system abnormalities. Echocardiography plays a major role in the assessment of structural and functional cardiac abnormalities in CKD including abnormal left-ventricular (LV) geometry, LV diastolic dysfunction, valvular disease, and left atrial dilatation, which are very frequently present especially in patients with end-stage renal disease.

Keywords Chronic kidney disease · End-stage renal disease · Echocardiography · Cardiovascular disease

Introduction

About 13.3 million Japanese people are affected by chronic kidney disease (CKD), including one-eighth of the adult population [1]. CKD is associated with increased cardiovascular mortality and morbidity [2]. Although the etiology of the increased risk of cardiovascular disease (CVD) in CKD is in part due to shared CVD risk factors including diabetes, hypertension, obesity, and lipid abnormalities [3], multiple studies have shown that the association of CKD with cardiovascular mortality persists after adjustment for those CVD risk factors [4–6]. A collaborative meta-analysis of 10 cohorts with 266,975 patients revealed that adjusted hazard ratios (HRs) at estimated glomerular filtration rate (eGFR) of 60, 45, and 15 ml/min per 1.73 m^2 were 1.11 (0.93–1.32), 1.73 (1.49–2.00), and 3.08 (1.89–5.01) for cardiovascular mortality, respectively [7]. Albuminuria is also a significant risk factor for poor prognosis in patients with CKD. Current meta-analyses revealed that eGFR and albuminuria were found to be independently associated with increased risk of all-cause and cardiovascular mortality [8, 9].

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Conventional echocardiography is a reliable and accessible tool that can detect early changes in cardiac function, and, therefore, facilitates CVD risk profile management and understanding of the pathogenesis of heart disease in CKD. Although cardiac computed tomography and magnetic resonance imaging using contrast agents have revolutionized the diagnostic approach for heart disease during the last decade, patients with reduced renal function are at risk of developing contrast-induced nephrotoxicity. Meanwhile, echocardiography remains a common examination performed in almost all patients with CKD [10].

CKD and heart disease

CVD is one of the most serious complications of CKD, and heart disease is highly prevalent and leads to increased mortality. There is a graded increased risk in mortality following any cardiac event including myocardial infarction and heart failure (HF) across stages of CKD [11]. CKD-related (anemia and disorders of mineral metabolism) risk factors with the combination of non-traditional (inflammation and oxidative stress) and traditional risk factors for CVD accelerate the progression of coronary atherosclerosis, ventricular hypertrophy, myocardial fibrosis, valvular calcification, and cardiac conduction system abnormalities [12, 13]. With rare exceptions, patients with end-stage renal disease (ESRD) who do not receive renal replacement therapy (RRT) develop

signs and symptoms of HF including dyspnea and edema due to inability of the severely diseased kidneys to excrete not only sodium and water but also uremic toxins. The 11th Acute Dialysis Quality Initiative proposed a classification schema of HF based on patient-reported dyspnea assessed both pre- and post-RRT (Fig. 1) in conjunction with echocardiography [14]. The echocardiographic criteria that suggest or are supportive of cardiac disease are summarized in Table 1 [14]. Hickson et al. analyzed patients who underwent echocardiography examination ≤ 1 month prior to or ≤ 3 months following initiation of hemodialysis (HD)

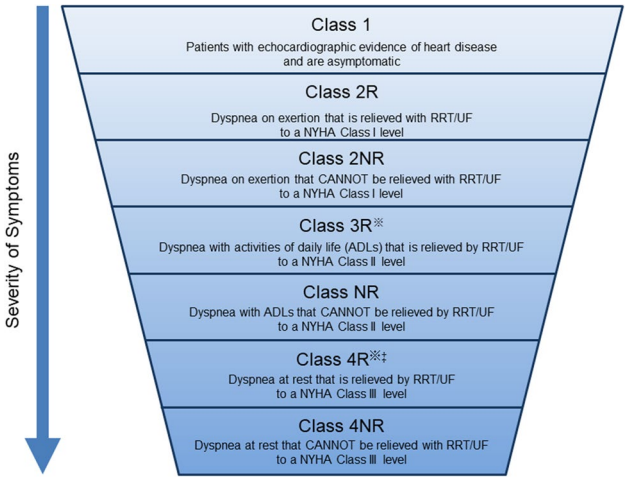

Fig. 1 ADQI Heart Failure in ESRD Classification System (modified from Chawla et al.). Classification is determined by a dyspnea assessment before and after renal replacement therapy (RRT)/ultrafiltration (UF). When patients have the same class assessment before and after RRT/UF, they are scored by their post-treatment assessment. The classification scheme assumes that the class assignment represents the patient's achievement of optimized UF and is representative of the patient's usual level of dyspnea before and after RRT/UF. *If dyspnea symptoms improve to class I levels, the patient would be classified as class 2R. ‡If dyspnea symptoms improve to class II levels, the patient would be classified as class 3R. *ADQI* acute dialysis quality initiative, *ESRD* end-stage renal disease, *NYHA* New York Heart Association

($n = 654$, 66 ± 16 years) [15], and revealed that echocardiography findings that met 1 or more and ≥ 3 of the new criteria were discovered in 87% and 54% of patients, respectively. In their study, age- and sex-adjusted echocardiography variables associated with death over a median follow-up period of 2.4 years were left-ventricular ejection fraction (LVEF) ≤ 45% and right-ventricular (RV) systolic dysfunction. They ultimately found that RV dysfunction was independently associated with death (HR 1.66; CI 1.34–2.06; $p < 0.001$) after adjustment for age, sex, race, diabetic kidney disease, and dialysis access.

Though RRT is a life-sustaining treatment and remains the most important tool for all patients with ESRD, RRT may inadvertently be contributing to the accelerated development of cardiac disease. Indeed, patients with ESRD requiring RRT have an extraordinarily high prevalence of structural and functional abnormalities of the heart including calcified valvular sclerosis, LV remodeling, and diastolic dysfunction [16]. Matsuo et al. examined 315 Japanese patients with ESRD (67.9 ± 10.6 years, 47.6% male) on chronic HD for ≥ 1 year using transthoracic echocardiography, and showed that only 11.5% and 3.4% of all patients had normal LV geometry and normal LV filling pattern, respectively. In addition, 76.5% and 58.4% of patients had aortic and mitral valvular calcification, and approximately 50% of patients had aortic valve narrowing with AVA < 2.0 cm^2 (Fig. 2) [16].

LV remodeling and hypertrophy

LV remodeling including LV hypertrophy (LVH) is highly prevalent in patients with CKD even in early stages, and is strongly associated with cardiovascular mortality. There are several methods that effectively calculate LV mass using M-mode echocardiography, two-dimensional echocardiography (2DE), and 3DE [17], and all measurements should be performed at the end of diastole. All methods convert

Table 1 Echocardiography criteria (modified from Chawla et al.)

LVH (LV mass index > 110 g/m^2 for women and > 130 g/m^2 for men or > 47 g/$m^{2.7}$ for women and > 50 g/$m^{2.7}$ for men). Latter measure is LV mass calculated by the area-length method and indexed to height
Increased LV volume index > 86 ml/m^2 diastolic or > 37 ml/m^2 systolic
Left atrial enlargement (left atrial volume index ≥ 34 ml/m^2)
Diastolic dysfunction (ASE grade ≥ 2)
Moderate-to-severe mitral or aortic valvular disease (stenosis or regurgitation)
RV systolic dysfunction by accepted criteria (e.g., TAPSE < 17 mm)
LV ejection fraction ≤ 45%
Regional wall motion abnormality of LV (> 10% of the myocardium)

At least 1 (of 8) listed criteria must be abnormal to fulfil the definition of echocardiographic evidence of heart disease

LV left ventricle, *LVH* left-ventricular hypertrophy, *RV* right ventricle, *TAPSE* tricuspid annular plane systolic excursion

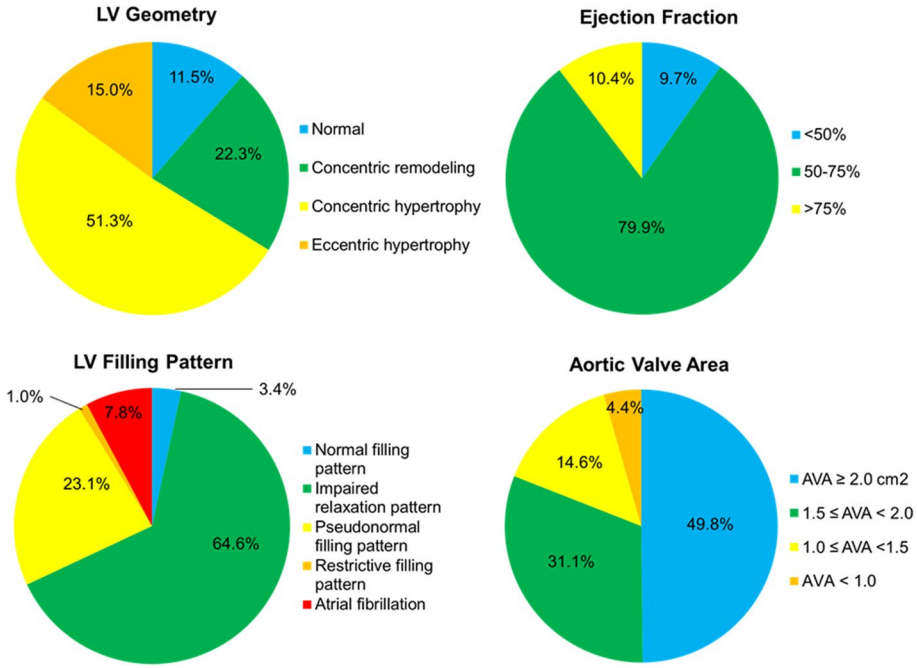

Fig. 2 Distribution of LV geometry patterns (Left top), left-ventricular ejection fraction (Right Top), LV filling pattern (Left bottom), and aortic valve area (Right bottom) (modified from Matsuo et al.)

the volume to mass by multiplying the volume of myocardium by the myocardial density (approximately 1.05 g/mL) [17]. To measure LV mass in an individual patient over time, especially those with cardiac disease, the 2D echocardiographic methods have advantages compared with the linear dimension technique [17]. When the entire ventricle is measured from 2DE images, either the area length or truncated ellipsoid technique is used [17]. Because 3DE is the only echocardiographic method that directly measures myocardial volume, it is an appropriate approach. However, to date, there have been few studies assessing its practical use, feasibility, variability, or prognostic value in large-scale clinical environments [17]. LV geometries were classified into four types according to relative wall thickness (RWT) and LV mass index: (1) normal, 2 × posterior wall thickness/LV diastolic diameter < 0.42 and LV mass index < 88 g/m^2 for female subjects and < 102 g/m^2 for male subjects; (2) concentric remodeling, PWT > 0.42 and LVMI < 88 g/m^2 for female subjects and < 102 g/m^2 for male subjects; (3) eccentric hypertrophy, PWT < 0.42 and LVMI > 88 g/m^2 for female and > 102 g/m^2 for male subjects; and (4) concentric hypertrophy, PWT > 0.42 and LVMI > 88 g/m^2 for female subject and > 102 g/m^2 for male subjects [16, 17].

LV remodeling can develop already during the milder CKD stages. Pluta et al. recently showed that about 60% of CKD stages' 1–3 patients have any form of abnormalities including LV concentric remodeling (20.0%), concentric hypertrophy (22.2%), or eccentric hypertrophy (18.9%) in a single-center study [18]. In patients with ESRD, the prevalence of LVH increases up to 65–85% on echocardiography or cardiac MRI [16, 19–23]. A recent cross-sectional study in 3,487 CKD patients showed that the prevalence of LVH was 32%, 48%, 57%, and 75% in patients with eGFRs of ≥ 60, 45–59, 30–44, and < 30 mL/min/1.73 m^2, respectively [24]. LV mass index (LVMI) increases substantially in the majority of HD patients treated according to the usual standard of care. The presence of either baseline or progressive LVH is considered an important risk factor for adverse cardiovascular outcomes in HD patients [25]. Key principles in the treatment of LVH in CKD patients are mainly based on anemia and blood pressure control, together with the management of secondary hyperparathyroidism and sudden cardiac death prevention [26].

LV systolic function and strain-assessment

LVEF has been widely used to define systolic function, assess prognosis, and select patients for therapeutic interventions. However, it gives limited insight into direction-based myocardial systolic function. Indeed, subclinical systolic dysfunction can be observed in patients with CKD despite normal LVEF. LV longitudinal dysfunction reflects early CKD-related myocardial changes such as myocardial ischemia, fibrosis, and hypertrophy, because subendocardial longitudinal myocardial fibers are more sensitive to reduced coronary perfusion and increased wall stress [27, 28]. Global longitudinal strain (GLS) using two-dimensional (2D) speckle-tracking echocardiography (STE) has emerged as a more sensitive index of myocardial systolic function than LVEF in heart disease [17]. Lui et al. showed that GLS deteriorated along with the decline of renal function among

153 patients (56 without CKD, 37 with stages 3–5 CKD and 60 with ESRD undergoing HD) [29]. In ESRD patients receiving chronic HD, the presence and severity of LV longitudinal systolic dysfunction is strongly associated with LV geometric patterns. Wang et al. assessed LV systolic function in a cohort of 98 chronic HD patients with preserved LVEF ($\geq 50\%$), no wall motion abnormalities, and no severe valvular heart disease using 2D-STE [30]. They revealed that LV GLS was lower in HD patients with LVH compared with healthy controls and non-hypertrophic HD patients, and that it was even lower in the concentric hypertrophy group than the eccentric hypertrophy group ($-15.5 \pm 2.2\%$ versus $-17.8 \pm 2.6\%$, $p = 0.001$). Recent clinical studies also have demonstrated that GLS is a more sensitive predictor of all-cause and cardiovascular mortality compared to LVEF [28, 29]. Krishnasamy et al. assessed LV function including GLS and LVEF in 183 patients (57% male, 63% on dialysis) with CKD stage 4, 5 including those receiving HD, and 112 (61%) patients died in a follow-up of 7.8 ± 4.4 years and 41% of deaths were due to CVD [28]. In this cohort, GLS was a significant predictor of all-cause [HR 1.09, 95%; confidence interval (CI) 1.02–1.16; $p = 0.01$] and cardiovascular mortality (HR 1.16 95%; CI 1.04–1.30; $p = 0.008$) following adjustment for relevant clinical variables including LVMI and LVEF [28].

LV dyssynchrony

LV mechanical dyssynchrony is generally caused by electrical abnormalities in the ventricular myocardium, typically with left bundle branch block (LBBB). On the other hand, LV mechanical dyssynchrony can also be caused by inhomogeneous myocardial tissue damage, inhomogeneous ventricular wall structures, and abnormal loading conditions. Many studies have shown that LV mechanical dyssynchrony is highly present in patients with ESRD [31–33]. Shi et al. very recently reported that young and middle-aged uremic peritoneal dialysis patients developed LV mechanical dyssynchrony in the longitudinal direction despite preserved LVEF using 2D-STE [32].

Time-to-peak strain especially in the anterior, the anterior septum, and the posterior wall from basal segments, and the inferior wall from apical segments was delayed due to post-systolic shortening, which resulted in LV mechanical dyssynchrony [32]. Delayed myocardial contraction may occur in myocardial ischemia, stunning, or hibernation [34]. Long-term high afterload, renal toxicity, and volume imbalance can cause myocardial insults including myocyte hypertrophy, fibroblast overgrowth, changes in extracellular matrix substance, and thereby intra- and intercellular electrical transmission delay. HD can ameliorate LV mechanical dyssynchrony at least partially by correcting volume over load. Murata et al. first revealed that ESRD was associated with longitudinal and radial LV dyssynchronies and single session of HD therapy dramatically improved radial LV dyssynchrony using 2D-STE in a total of 23 patients with ESRD who receiving chronic HD therapy three times a week [34]. They found that improvement of the radial LV dyssynchrony modestly correlated with the reduction of the LV end-diastolic volume index and the reduction of the delayed segments [34]. Takahashi et al. performed phase analysis using gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography before the start of long-term HD (baseline) and 3 months later in 12 patients with ESRD, and revealed that 3-month HD decreased LV volume, mass, and mechanical dyssynchrony [33].

Diastolic function and LA function

The term "diastolic dysfunction" includes the issues of both LV relaxation and compliance, and also increased LV filling pressure. Partially due to a strong coupling between LV systolic contraction and relaxation sequentially from normal to failing myocardium [35, 36], diastolic dysfunction nearly always coexists with systolic dysfunction in a spectrum of different severity in the pathophysiological process of LV remodeling. LV diastolic dysfunction is common in patients with CKD, and a previous population-based epidemiological research study has demonstrated that the presence and the severity of CKD is associated with the progression of LV diastolic dysfunction (i.e., from preclinical stage B to symptomatic stage C HF) independently of age, sex, hypertension, coronary disease, and ejection fraction [37]. Farshid et al. showed that some degree of diastolic dysfunction was present in 86% of patients on HD with a mean age of 58.7 ± 15.0 years, and 35% had grade ≥ 2 diastolic dysfunction, which was a powerful independent predictor of mortality [38]. Matuso et al. showed that almost all patients had some degree of abnormal LV filling pattern or AF (impaired relaxation: 64.6%, pseudo-normal filling pattern: 23.1%, restrictive filling pattern 1.0%, and AF 7.8%) in 315 Japanese patients with mean age of 67.9 ± 10.6 years (Fig. 2) [16].

Among various echocardiography-derived parameters, ratio of early mitral flow velocity (E) to early mitral annulus velocity (E') (E/E') is an easy and reproducible parameter for the estimation of LV filling pressure, while it may be an unreliable in certain cardiac disorders including constrictive pericarditis, mitral stenosis or insufficiency, mitral or aortic valve replacement, mitral annular calcification, and hypertrophic cardiomyopathy. The previous study demonstrated that E/E' ratio > 15 was found to be the most accurate estimate of LV end-diastolic pressure ≥ 15 mmHg in ESRD [39]. More importantly, E/E' is one of the very useful

parameters in predicting prognosis of CKD patients [39]. Wang et al. demonstrated that *E*/*E*′ ratio > 15 was an independent predictor of general and cardiovascular mortality during the median follow-up of 48 months in 220 patients with ESRD [40].

The progression of LV diastolic dysfunction lead to pressure and volume overload of the left atrium, which results in left atrial (LA) enlargement [41]. LA volume (LAV) has recently emerged as a useful biomarker for risk stratification and risk monitoring in patients with ESRD [42–44]. A recent study has shown that diastolic dysfunction, defined as the *E*/*E*′ ratio > 15 and LAV index (LAVI) > 32 ml/m^2, are independent predictors of cardiovascular events in chronic HD patients [45]. 2D-STE can assess LA function, and a recent clinical study demonstrated that the presence of early CKD (eGFR 30–59 mL/min/1.73m^2) was an independent predictor of both enlarged LAVI and impaired LA strain despite normal LVMI and LVEF [10].

Valvular heart disease

CKD accelerates and amplifies the process of valvular calcification via multiple pathways including altered mineral metabolism, inflammation, oxidative stress, and pressure and volume overload. A series of population-based studies have demonstrated a high prevalence of aortic valve calcification in patients on chronic HD [46–48]. Recently, Matsuo et al. demonstrated that 76.5% and 58.4% of ESRD patients receiving HD had aortic and mitral valvular calcification, respectively. They also showed that approximately half of the patients had aortic valve narrowing < 2.0 cm^2 (Fig. 2) [16]. Importantly, valvular stenosis progresses more rapidly in ESRD patients receiving HD than those with earlier stages CKD [49]. Mitral annular calcification (MAC) is a common finding in patients with CKD especially those on HD. MAC-related calcium accumulation in the subvalvular region can limit mitral annular longitudinal excursion and, thus, can impair LV longitudinal systolic and diastolic function. Caseous calcification of the mitral annulus (CCMA) is a rare variant of MAC which occurs particularly in patients with ESRD [50]. On echocardiography, the calcification is a round mass with a central echolucent area, typically located at the base of the posterior leaflet, and can be mistaken for cardiac tumors or abscesses [50, 51]. MAC-related calcified amorphous tumor (CAT) is also a rare non-neoplastic intracavitary cardiac mass, which is strongly related to ESRD and HD (Fig. 3) [52]. MAC-related CAT has high mobility on echocardiography and resembles vegetation in clinical diagnosis. Several case reports highlighted that CCMA and MAC-related CAT share similar risk factors and potentially a common pathological link [52, 53].

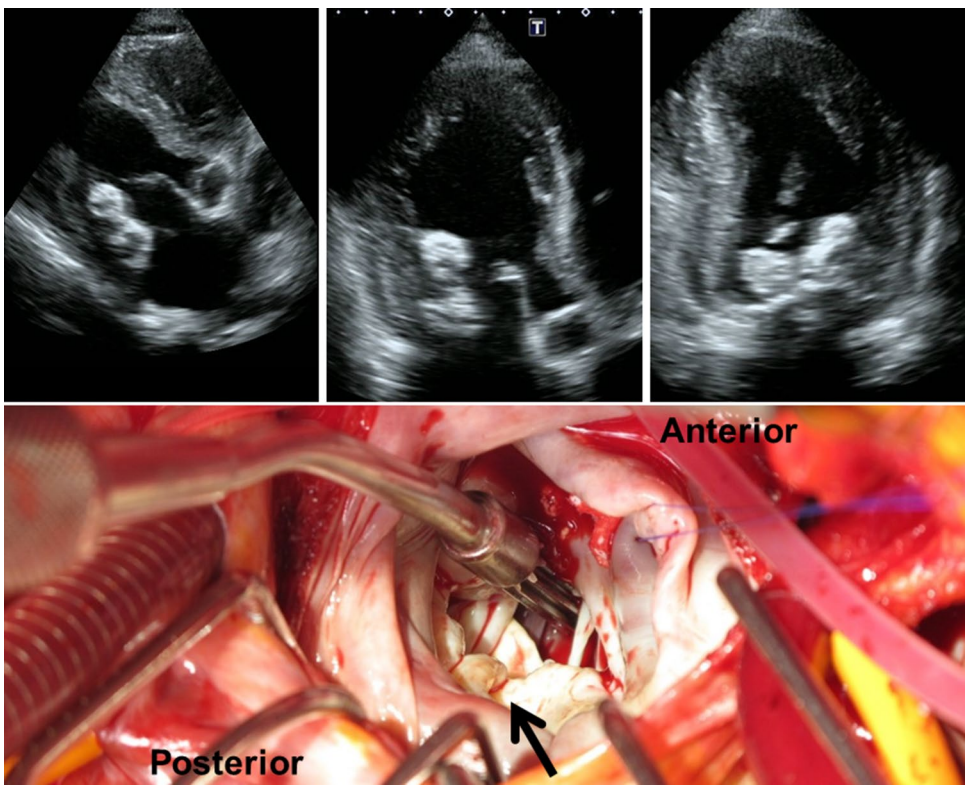

Fig. 3 Echocardiography examples (top) and operative findings (bottom) of mitral annular calcification-related calcified tumor (modified from Takeuchi et al.). Left top: parasternal long-axis view, middle top, apical long-axis view, and right top: apical two-chamber view

Role of echocardiography for fluid control

Fluid balance control using RRT is considered as an important component of the treatment for patients with ESRD. However, there is no simple and easy method to determine the dry weight. Echocardiography is one of the well-known methods for the assessment of the volume status in RRT patients. It has been shown that inferior vena cava diameter (IVCD) and blood volume are reduced proportionally during dialysis and are increased 2 h after dialysis through refilling intravascular space. As a result, IVCD changes are supposed to reflect the volume changes [54, 55]. On the other hand, LAV is a potential surrogate marker for chronic volume overload in HD patients. Cristina Di Gioia et al. recently elucidated that LAVI determined by echocardiographic area-length method had a significant relationship with hydration status based on bioimpedance-measured time-averaged fluid overload [56].

Right-ventricular function

CKD is associated with the progression of RV structural and functional abnormalities, which can lead to worse patient outcomes. Mavrakanas et al. showed that patients with worse renal function had higher prevalence of structural and functional LV and RV abnormalities including RV systolic impairment, RV hypertrophy, or dilated RV than those with preserved renal function in a recent retrospective cohort study including 29,219 patients [57]. As described in the "CKD and Heart disease" section, Hickson et al. demonstrated that RV dysfunction was independently associated with death (HR: 1.66; CI 1.34–2.06; $p < 0.001$) over a median follow-up period of 2.4 years in patients ($n = 654$) who began chronic HD who underwent ECHO ≤ 1 month prior to or ≤ 3 months following initiation of HD [15]. Unfortunately, the vast majority of the clinical studies including those by Mavrakanas et al. and Hickson et al. visually evaluated the RV structure and function among patients with CKD. Echocardiographic quantitative evaluation of RV function is still challenging due to the complex anatomy of the right ventricle. STE can be applied to analyzing RV myocardial deformation and GLS in the RV four-chamber view has recently been used as a surrogate for global RV function and as a predictor of the clinical outcomes of patients with various heart diseases [58]. More recently, 3DE technique including 3D-STE has been introduced as a method to measure RV volume and RV kinetics [59]. Implementation of this new technique might lead to a better understanding of the pathophysiological mechanisms of CKD-associated RV structural and functional abnormalities.

Conclusions

Echocardiographic abnormalities are frequent even in early CKD and echocardiographic assessment particularly of the left ventricle and left atrium may provide useful information for the care of patients in the whole spectrum of CKD.

Compliance with ethical standards

Conflict of interest K.D. received lecture fees of equal to or more than 500,000 yen from Otsuka Pharma Inc. and Takeda Pharmaceutical Co. Ltd. in 2018.

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