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REVIEW

Role of cardiac magnetic resonance imaging in troponinemia syndromes

Nhung Nguyen Nguyen, Joseph George Assad, Giuseppe Femia, Andreas Schuster, James Otton, Tuan Le Nguyen

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Abstract

Cardiac magnetic resonance imaging (MRI) is an evolving technology, proving to be a highly accurate tool for quantitative assessment. Most recently, it has been increasingly used in the diagnostic and prognostic evaluation of conditions involving an elevation in troponin or troponinemia. Although an elevation in troponin is a nonspecific marker of myocardial tissue damage, it is a frequently ordered investigation leaving many patients without a specific diagnosis. Fortunately, the advent of newer cardiac MRI protocols can provide additional information. In this review, we discuss several conditions associated with an elevation in troponin such as myocardial infarction, myocarditis, Takotsubo cardiomyopathy, coronavirus disease 2019 related cardiac dysfunction and athlete's heart syndrome.

Key Words: Cardiac magnetic resonance imaging; Troponin; Myocardial infarction; Myocarditis; Takotsubo cardiomyopathy; COVID-19; Athlete's heart

Core tip: Cardiac magnetic resonance has excellent spatial resolution to assess ventricular volumes and function. It is also continuing to evolve to provide key diagnostic and prognostic information particularly through the use of gadolinium contrast agent for the conditions presented in this review.

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INTRODUCTION

Troponinemia describes an elevation in serum troponin levels that can result from a myriad of conditions such as acute myocardial infarction (AMI), takotsubo cardiomyopathy (TTS), myocarditis and athlete's heart syndrome (AHS). More recently, severe acute respiratory syndrome coronavirus 2 has been linked to cardiac disease and elevated troponin levels. Given that troponinemia is nonspecific, establishing a definitive diagnosis can be difficult. Fortunately, cardiac magnetic resonance imaging (CMRI) has the ability to characterise myocardial tissue and identify unique pathological features of cardiac disease. As a diagnostic tool for these conditions, CMRI imaging may be promising.

This narrative review gives an overview of the diagnostic features and potential role of CMRI in conditions associated with troponinemia such as myocardial infarction (MI), TTS, myocarditis, coronavirus disease 2019 (COVID-19) related cardiovascular disease and AHS (Table 1).

MI

AMI is one of the most common causes of elevated troponin levels. It is defined by the presence of acute myocardial injury in conjunction with dynamic changes in troponin levels, and evidence of myocardial ischaemia[1]. Electrocardiography (ECG), transthoracic echocardiography (TTE) and invasive coronary angiography are the standard of care in the evaluation of MI. Adjunctive use of CMRI can be useful to confirm the diagnosis, assess chronicity, guide management and aid prognosis. It can be utilised to distinguish the changes seen between an acute and an established, or also called chronic MI. CMRI is also highly accurate at assessing ventricular volumes and function with superior spatial resolution, contrast-to-noise ratio and tissue characterisation compared to TTE.

On CMRI, AMI can demonstrate ventricular regional wall motion abnormalities (RWMAs) corresponding with the affected vascular territory on cine images. Intramyocardial haemorrhage may occur, and is represented by a hypointense zone in the infarcted area on T2-imaging or mapping[2]. Following ischaemic insult from coronary artery obstruction, myocardial cellular injury begins in the subendocardial region, and continues to extend towards the subepicardium if there is ongoing oxygen deprivation. This process is known as the "wavefront phenomenon of myocardial death", named by Reimer *et al*[3]. Late gadolinium enhancement images characteristically demonstrate a hypodense core surrounded by an area of hyperenhancement (Figure 1), and is found in a subendocardial or transmural distribution depending on the extent of the MI[4-6]. In chronic MI (CMI), cine images will typically show wall thinning, RWMA, and a lack of oedema on T2-weighted images[7]. In a study by Rehwald *et al*[8], the authors used rabbit models to demonstrate that gadolinium contrast agent uptake was greater in infarcted myocardial tissue. In another study, Kim *et al*[9] demonstrated that the extent of transmural hyperenhancement reflected the degree of irreversible injury. Native T1-sequences have also been explored by Kali *et al*[10], who demonstrated CMRI may be useful in diagnosing CMI, and determining likely irreversible injury. It is particularly useful in some situations, such as in renal failure patients, where gadolinium contrast is contraindicated.

Besides determining left ventricular ejection fraction (LVEF) on cine imaging, a detailed assessment of LV deformation measurements can also take place using CMRI[11]. Left ventricular global radial strain, circumferential strain and global longitudinal strain (GLS) have all shown association with increased major adverse cardiac events (MACEs)[12], and GLS has been demonstrated to be an independent predictor of post-MI clinical outcome. Impairment of left atrial strain on CMRI post-MI has also been demonstrated to be an independent predictor for increase in MACEs, as well as improving prognostic value when combined with LVEF[13,14].

It has been demonstrated that in patients with coronary artery disease, those treated with revascularisation have a significantly lower annual mortality rate compared to those treated with medical therapy [15,16]. In these patients, CMRI can be used to assess the viability of a coronary artery territory. The most important parameters are LV end-diastolic wall thickness, quantitative LV systolic or diastolic performance during low-dose dobutamine stress testing, and late gadolinium enhancement (LGE)[17].

Table 1 Cardiac magnetic resonance imaging features

Condition	Cardiac magnetic resonance imaging features
Myocardial infarction	**< 1 mo**
	Myocardial oedema present on T2-weighted images, T2 mapping and T1 mapping
	Microvascular obstruction revealed as a hypointense core within hyperintense infarct zone in area of LGE
	Infarct size can be calculated using pre and post-contrast T1-weighted mapping and ECV assessment
	Myocardial necrosis/scar by LGE in a subendocardial or full-thickness pattern within a coronary artery territory
	Additionally at < 6 mo
	T2-weighted hyperintensity on double inversion recovery turbo spin echo
Takotsubo syndrome	Can help distinguish coexisting CAD or acute myocarditis LGE typically absent
	Myocardial oedema present on T2-weighted images, T2 mapping and T1 mapping
	Accurate assessment of WMAs on cine imaging
	Can be useful to identify ventricular thrombus
Myocarditis	Inflammatory hyperaemia demonstrated on T1-weighted images
	Myocardial oedema on T2-weighted images
	Myocardial necrosis/scar by LGE in a subepicardial or mid-wall pattern
	Greater T1 and T2 increases with acute inflammation
	Pericardial effusion
COVID-19 related cardiac dysfunction	Features similar to that of acute myocarditis
	Myocardial oedema on T2-weighted images
	Myocardial necrosis/scar by LGE in a subepicardial or mid-wall pattern
	Myocardial fibrosis using T1-weighted mapping and ECV assessment
	Can be useful to identify ventricular thrombus and pericardial effusion
Athlete's heart	LVH typically < 12 mm
	Lower ECV with LVH compared to HCM
	RV dilatation seen on cine imaging
	LGE focal and generally at the RV insertion points

LGE: Late gadolinium enhancement; ECV: Extra-cellular volume; CAD: Coronary artery disease; WMAs: Wall motion abnormalities; LVH: Left ventricular hypertrophy; HCM: Hypertrophic cardiomyopathy; RV: Right ventricular; COVID-19: Coronavirus disease 2019.

For example, in a LV segment with ≤ 50% transmural LGE, a normal dobutamine response is correlated with greater functional recovery after revascularisation[18,19]. In contrast, the presence of ≥ 50% transmural LGE indicates nonviable infarcted tissue[20,21]. This technique is comparable to fluorodeoxyglucose positron emission tomography, which is considered the gold standard in the assessment of myocardial viability[22]. Unfortunately, the role of CMRI can be limited in many healthcare settings, considering factors including machine access, availability of imaging experts, cost and time.

The use of CMRI in assessing prognosis following MI has shown promising results. Assessment for microvascular obstruction (MVO) through the use of first pass perfusion studies during and following gadolinium contrast administration is one of the prognostic features that has been studied. It is implicated in adverse ventricular remodelling, larger infarct size (IS) and poorer clinical outcome[23-25]. van Kranenburg *et al*[26] have also demonstrated that MVO is an independent predictor for major adverse clinical outcomes at 2 years. Infarct size on CMRI has also been shown to be strongly associated with heart failure hospitalisation and all-cause mortality[27]. More recently, postcontrast T1 mapping has been shown to accurately quantify IS in a small study[28]. CMRI has also demonstrated some correlation between IS and peak troponin I[29], however this has not been a consistent or reliable finding. Intramyocardial haemorrhage has been linked to adverse LV remodelling and increased MACEs, but heterogeneity in imaging techniques mean further study is required[23]. The presence of

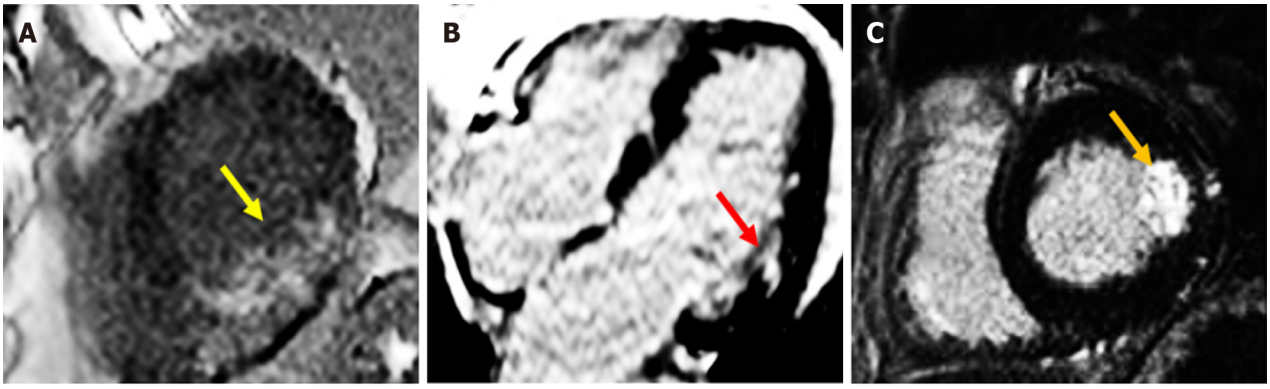

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Figure 1 Cardiac magnetic resonance imaging of acute myocardial infarction. A: Short axis mid-ventricular image demonstrating almost full-thickness transmural late gadolinium enhancement (LGE) in posterolateral wall (yellow arrow); B: Four-chamber image demonstrating focal LGE in lateral wall (red arrow); C: Short axis image demonstrating > 75% transmural LGE in lateral wall (orange arrow).

LGE in patients with symptoms suggestive of MI conferred worse MACEs compared to those without LGE[30]. The prognostic importance of LVEF has been demonstrated in a number of studies[31,32]. Study delay for at least 1 wk following AMI should be considered, to allow for myocardial functional recovery as found by Mather *et al*[33], and further imaging at up to 6 mo may be required to assess stabilised LVEF[34]. LVEF ≤ 35% and LGE were independently associated with MACEs, with better predictive value than TTE[35]. The extent of LV scarring has also been clearly associated with risk of spontaneous ventricular arrhythmias[36-38]. Assessment of the peri-infarct, or "grey-zone", surrounding the infarcted core may also play a role in risk stratifying post-MI patients, with increased size posing potential heightened ventricular arrhythmic risk[39]. Yan *et al*[40] used a semiautomatic software detection system to quantify percentage of abnormal myocardial delayed enhancement of tissue surrounding the infarct core, and noted that it was an independent predictor of post-MI all-cause and cardiovascular mortality.

Incorporation of artificial intelligence-based analyses will likely have a role to play in the future in cardiac outcome and prognosis prediction. It has already been demonstrated that fully automated volumetric and myocardial segmentation assessment are equally effective as manual efforts in predicting MACEs[41].

As it stands, without the availability of randomised controlled data or larger studies, the actions to be taken if high risk CMRI features are seen are not completely clear[42,43].

TTS

TTS, which is also known as Takotsubo cardiomyopathy, transient apical ballooning syndrome, broken heart syndrome and stress-induced cardiomyopathy, is a condition of transient LV dysfunction that is typically triggered by physical or emotional stress[44]. TTS mimics MI with often indistinguishable clinical presentation, ECG changes and cardiac enzyme elevation, but without angiographic evidence of acute obstructive coronary artery disease or plaque rupture[44,45]. Given the transient nature of TTS, traditionally it was thought of as a benign condition however more recent data suggests this is misguided, with complications comparable to those seen in patients with the acute coronary syndrome [46,47]. CMRI is increasingly used to diagnose and evaluate complications of TTS in both the acute and subacute setting, particularly in those with atypical features, or bystander coronary artery disease[48].

In the acute setting, CMRI can define TTS by excluding other aetiologies such as MI and myocarditis and identifying RWMAs that extend beyond a single coronary artery distribution[49] (Figure 2). One of the hallmarks is reversible myocardial inflammation corresponding to RWMA[31,44]. CMRI can assess myocardial inflammation and oedema with T2-weighted images[44,50-52].

In the subacute phase, its strength in identifying subtle RWMA makes it the ideal modality to accurately assess for resolution of regional dysfunction, with full recovery being a criteria confirmation of diagnosis[44].

Late gadolinium-enhanced imaging is a valuable adjunct in confirming a diagnosis of TTS when there is coexisting coronary artery disease or suspicion for myocarditis. It is widely believed that in TTS, there is an absence of LGE on CMRI[31], however, there are studies challenging this notion, having demonstrated LGE in patients with TTS in the acute phase[52-54]. It should be noted that LGE in this setting is transient, resolving on serial imaging to confirm the diagnosis of TTS, and has been associated with increased incidence cardiogenic shock and a longer timeframe for resolution of wall motion abnormalities[55,56]. In contrast, patients with myocardial infarction will have focal subendocardial or

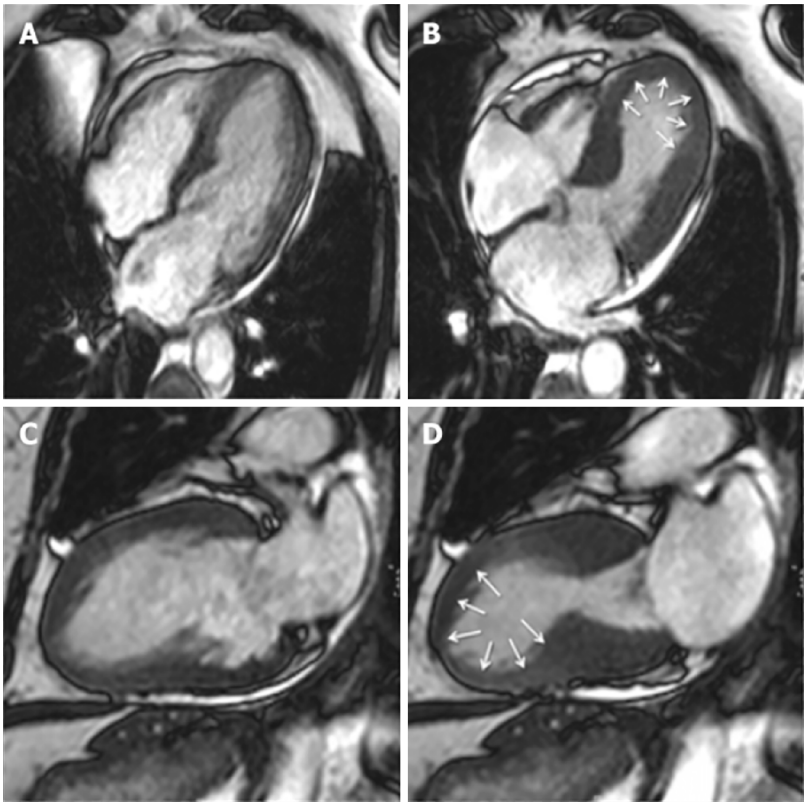

Figure 2 Cardiac magnetic resonance imaging of Takotsubo cardiomyopathy. Typical apical ballooning seen in takotsubo syndrome. A, B: Cine four-chamber in late diastole and systole respectively; C, D: Two-chamber view in late diastole and systole respectively. Modified from Plácido *et al*[123] and licensed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

transmural LGE evident, while those with myocarditis typically will have a mid-wall distribution of LGE[57].

In addition to confirming the diagnosis of TTS, CMRI is useful in identifying complications such as mitral regurgitation and LV outflow tract obstruction seen on blood flow imaging, pericardial effusion seen on black blood T1-weighted sequences, and ventricular (including apical) thrombi not visualised on TTE, during early gadolinium (EGE) sequences. Thrombi will appear as a low signal intensity without gadolinium uptake, in comparison to the high intensity signal from the blood pool[50,52].

It has been hypothesised that the elevated catecholamines observed in TTS have a role in the microvascular dysfunction noted in patients with TTS, correlating with improvement in myocardial function[58]. While not established in TTS, there is emerging evidence in the utility of quantitative perfusion CMRI to more objectively assess the role that microvascular dysfunction plays in this syndrome, and is subject to further research[59].

ACUTE MYOCARDITIS

Acute myocarditis is an inflammatory cardiomyopathy secondary to infectious and noninfectious conditions, sometimes associated with symptoms of heart failure developing over ≤ 3 mo. The clinical presentation can be nonspecific and may include chest pain, heart failure, cardiogenic shock, arrhythmias and/or sudden cardiac death. Early investigations may demonstrate elevated troponin levels, elevated acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate and eosinophil count. An ECG may be normal, show nonspecific abnormalities or be similar to the pattern of acute pericarditis and AMI. Most importantly, it is important to exclude alternative causes such as MI. Due to the variable clinical presentation, the gold standard for diagnosis remains an endomyocardial biopsy (EMB), which is an invasive procedure that carries risk of life-threatening complications. CMRI may provide a noninvasive alternative for the assessment of myocarditis[60].

CMRI has become an important tool in the assessment of myocardial inflammation in patients with suspected myocarditis. Assessment of gross abnormalities includes changes in ventricular size and geometry, regional and global wall motion abnormalities and identification of pericardial effusion. In addition, there are techniques to assess microscopic markers of myocardial inflammation such as T1-weighted sequences for detection of myocardial hyperaemia, LGE for myocardial necrosis, fibrosis or scars and T2-weighted imaging to identify oedema[61-63]. Following early CMRI data, consensus

diagnostic criteria were released and incorporated into the Lake Louise criteria[60] (LLC) (Table 2). The use of newer mapping techniques such as for native T1 and T2, and quantification of extracellular volume (ECV), in comparison to the LLC, appear superior in the diagnosis of acute myocarditis, with positive predictive value of 90% *versus* 71%[64].

LGE has been shown to be highly accurate in the diagnosis of myocarditis with a high correlation with EMB[65]. Acute myocarditis is associated with subepicardial or mid-wall late gadolinium enhancement most commonly in the lateral, inferolateral or inferior wall[66-68] (Figure 3). In particular, small studies have suggested specific patterns for certain viruses: parvovirus B19 is associated with the lateral wall while human herpes virus 6 is linked to the septal wall[69]. The presence of LGE on follow-up studies denotes areas of irreversible myocardial injury[62,65].

CMRI diagnostic accuracy in the workup for chronic myocarditis (> 14 d) is not as well established compared to acute myocarditis, with T2-mapping providing the only discernible additional diagnostic benefit together with the LLC[66,70].

Although CMRI has demonstrated prognostic guidance in acute myocarditis, cardiac enzyme markers do not reflect the degree of myocardial injury or permanent scarring as demonstrated on CMRI LGE[70]. There are insufficient data available to relate CMRI features to independent risk of ventricular arrhythmias, although this is clearly raised in the context of impaired LV function[67,71]. In a meta-analysis, the presence of LGE, particularly anteroseptal location, has been found to be an independent risk factors for adverse cardiac outcomes, including all-cause mortality, cardiac mortality including sudden cardiac death, and MACEs[72].

COVID-19 RELATED CARDIAC DYSFUNCTION

COVID-19 infection has variable presentations, most commonly involving respiratory symptoms. However, since the declaration of the pandemic in March 2020, there have been increasing reports of cardiovascular disease. The incidence has been reported to be ≥ 40%, depending on the definition or population sampled[73-76]. Postmortem studies of confirmed COVID-19 cases have demonstrated the presence of the virus in the myocardium, but not necessarily with consistent expression of cardiac sequelae[77]. There are numerous mechanisms involved in myocardial injury, which include direct viral invasion and host innate immunity response, hypoxia, micro- and macrovascular thrombosis, inflammatory injury and stress-induced cardiomyopathy[78].

Considering the multifaceted components of COVID-19-induced myocardial injury, it should not be expected that the imaging findings of this infection would duplicate that of a viral myocarditis syndrome alone. Cardiac involvement in COVID-19 infection may not be present with clinically severe cardiac symptoms[75,79], and even though echocardiography is a sensitive tool to identify gross cardiac dysfunction, LVEF may be normal[77]. There have been reports of primary cardiac involvement in COVID-19[80], where CMRI can be useful in identifying acute viral myocarditis features, as well as evidence of thrombosis such as LV apical thrombus.

Studies using CMRI have demonstrated the severity of cardiovascular involvement following acute infection. In a report by Huang *et al*[81], the authors noted that 57% of patients had myocardial oedema or LGE on CMRI performed > 1 mo after development of infection (Figure 4). This suggests an ongoing pathological process affecting the myocardium. Historically, the LGE distribution in acute viral myocarditis involved the lateral and inferior walls. However with COVID-19, LGE patterns have been reported as subepicardial, mid-wall or subendocardial mimicking AMI[75]. Of note, there are no studies available where participants have baseline cardiac MRI data prior to COVID-19 infection. In addition, T2-signal hyperintensity tended to favour the interventricular septum, anterior and anterolateral walls, as well as basal inferior and mid-chamber. T1-mapping and ECV also demonstrated increased values, suggestive of myocardial fibrosis[75,81].

A developing use for CMRI is in the diagnosis suspected COVID-19-vaccine-associated myocarditis. These events tend to occur more frequently in young male patients after the second dose of mRNA vaccine[82,83]. Patients typically present with chest pain, troponin elevations, and abnormal CMRI findings[84]. CMRI abnormalities include myocardial oedema, hyperaemia and LGE, which are expected findings in acute myocarditis[85-89]. To date, there are no specific features for COVID-19-vaccine-associated myocarditis.

Evidence for the outcome of COVID-19-induced myocardial injury continues to evolve. Studies have found that elevation in troponin T levels confer significantly increased risk of mortality[73,90,91]. However, whether this and other markers of myocardial injury are byproducts of disease severity, or directly contribute to morbidity and mortality, remains to be elucidated. Currently, there is no long-term data on COVID-19 effects on the cardiovascular system, but considering its global impact, the identification, monitoring and study of outcomes is critical, with CMRI likely to play an essential role [92,93].

Table 2 Lake Louise consensus criteria for myocarditis on cardiac magnetic resonance imaging

Two out of three criteria must be met to be consistent with myocardial inflammation:
Regional or global myocardial signal intensity increase in T2-weighted images
Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
At least one focal lesion with nonischaemic regional distribution in inversion recovery-prepared gadolinium enhanced T1-weighted images (late gadolinium enhancement)

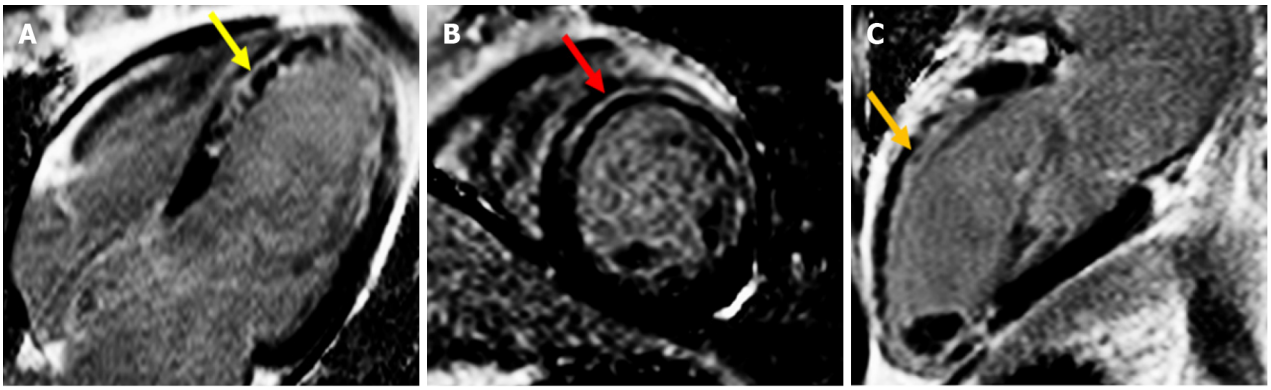

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Figure 3 Cardiac magnetic resonance imaging of acute myocarditis. A: Four-chamber image demonstrating LGE in septal wall in a mid-wall pattern (yellow arrow); B: Short axis mid-left ventricular image demonstrating LGE in anteroseptal wall in a mid-wall pattern (red arrow); C: Two-chamber image demonstrating LGE in the anterior wall in a mid-wall pattern (orange yellow).

HIGH-ENDURANCE ATHLETES AND AHS

Competitive sports level training can lead to a condition known as AHS, defined by complex cardiac chamber remodelling, ventricular systolic impairment and abnormalities involving the electrical conduction system. Electrocardiogram changes can include first-degree atrioventricular block, incomplete right bundle branch block, early repolarisation and isolated increased QRS voltages that may meet criteria for LV hypertrophy (LVH)[94]. Transient troponin elevation occurs with moderate-to-high intensity exercise[95,96]. The role of CMRI is also continuing to evolve in helping distinguish AHS from conditions such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM), which can have similar ECG and TTE features.

Although ventricular hypertrophy and dilatation can occur in both ventricles, impairment of systolic function following prolonged exercise tends to observed more frequently in the right ventricle (Figure 5A). In early forms of the disease, diastolic dysfunction is often observed, first defined by a reduction in mitral E:A ratio on echocardiographic Doppler imaging[97-100]. A hallmark of AHS is increased LV mass[101]. Unfortunately, this is not a discriminating feature and can overlap with other conditions such as HCM and ACM[102]. In particular, differentiating AHS from mild HCM, with LV wall thickness range 13–15 mm, is critical in preventing adverse outcomes for athletes. Despite early reports suggesting that different cardiac conditions can lead to particular patterns of LVH, this has not been demonstrated in subsequent studies[103,104]. Cessation of training usually leads to LVH regression and improvement in clinical outcomes.

The advancement of CMRI technology may help shed light on the potential long-term effects of competitive level exercise and help differentiate different cardiac conditions. LV cavity size (LV end-diastolic and end-systolic diameter) in AHS is usually larger than HCM, particularly if the end-diastolic diameter exceeds 54 mm[100]. CMRI can also provide accurate morphology assessment for excessive trabeculation and noncompaction cardiomyopathy, if it cannot be clearly delineated on echocardiography[105]. The use of more advanced CMRI tissue characterisation techniques such as T1 mapping and ECV assessment is also helpful. Athletes have been demonstrated to have lower ECV, likely as a result of myocyte enlargement, compared to nonathletes. Conversely, in HCM, there is increased ECV [106,107]. The role of LGE to distinguish AHS compared to HCM is not yet certain. Domenech-Ximenos *et al*[106] found that focal LGE was more prevalent in intensive endurance athletes compared to healthy subjects (37.6% *vs* 2.8%), with a typical pattern at the right ventricular (RV) insertion points. This may overlap with the LGE distribution in HCM[107].

Ventricular dilatation has been noted in athletes compared to healthy nonathletic individuals[108, 109]. LV dilatation is less severe as compared to the RV dilatation. Stress echocardiography observation

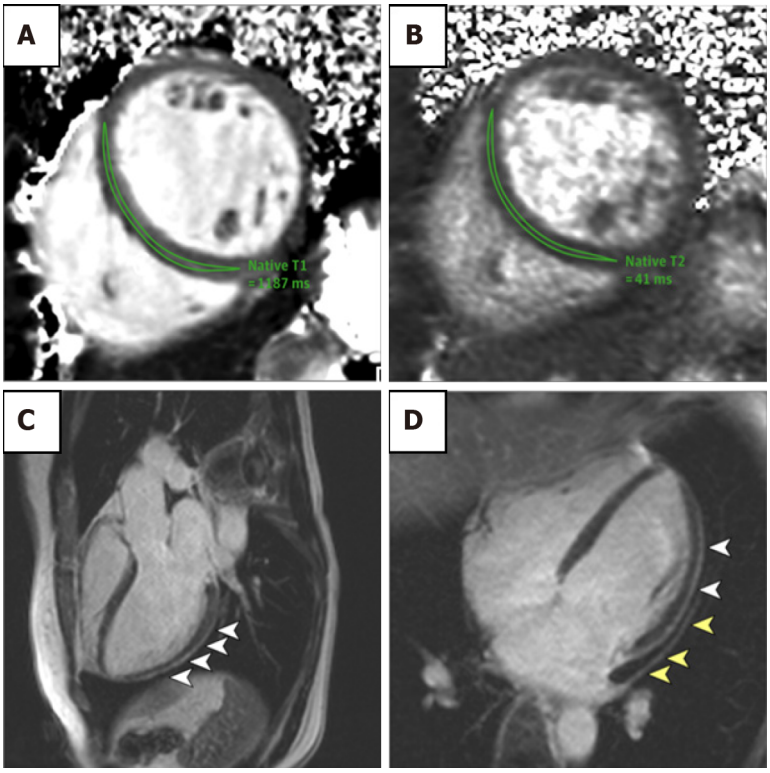

Figure 4 COVID-19 related cardiac dysfunction on cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging of an adult woman with COVID-19-related perimyocarditis. A, B: Significantly raised native T1 and native T2 in myocardial mapping acquisitions; C, D: Pericardial effusion and enhancement (yellow arrowheads) and epicardial and intramyocardial enhancement (white arrowheads) using LGE acquisition. Modified from Puntmann *et al*[75] and licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

of improvement in LVEF by > 11%, and presence of mid-wall LGE may help to discriminate between AHS and pathological dilated cardiomyopathy[95,96,110,111] but this has not yet been investigated in large studies. In a meta-analysis performed by D'Ascenzi *et al*[102], in high-performance athletes, RV end-diastolic volume (EDV) and end-systolic volume (ESV) exhibited the greatest relative increase in ventricular remodelling, compared to baseline parameters. This may be in response to increased venous return and other hemodynamic changes. The increase in RV size in athletes has led to situations where the dimensions meet part of the ACM criteria[112]. CMRI can be useful to improve spatial resolution in cases with poor echocardiographic windows. It can quantify function, identify RWMAs, and determine the presence of myocardial fibrosis and fibrofatty infiltration, to evaluate ACM versus AHS. In one study, Zaidi *et al*[113] found that the presence of RV ejection fraction < 45%, the ratio of RV EDV to LV EDV > 1.1/1, RV RWMA and LGE found together in athletes was highly indicative of ACM.

Exercise CMRI may provide addition diagnostic information by comparing the difference between adaptive responses and ventricular pathology in AHS, as well as potential prognostic information. The development of in-scanner CMRI exercise protocols with excellent reproducibility has been important in facilitating studies on the difference in physiological and pathological responses of athletes[114,115]. During exercise, elite athletes with evidence of ventricular arrhythmias had an increase in RV EDV, decrease in RV ESV, and, as a result, had reduced RV ejection fraction compared to athletes with no evidence of ventricular arrhythmia and healthy controls[116]. Of note, stress TTE yielded similar sensitivity in identifying exercise induced RV dysfunction.

The use of CMRI has been explored in AHS adverse outcome prognostication. In the context of excellent spatial and temporal resolution of CMRI, there appears to be no difference in resting in cardiac volumes of elite athletes with and without evidence of ventricular arrhythmias[116]. LGE at the junction of the right ventricle and interventricular septum has previously been noted in athletes, but is not related to any clinical sequelae. A pattern of myocardial wall fibrosis in AHS has otherwise not consistently been demonstrated, or has been affected by confounding factors such as veteran athletes with coronary artery atherosclerotic plaques[112,117-119] (Figure 5B–5D). Zorzi *et al*[120] did note that in athletes who presented with a history of ventricular arrhythmias and subsequently found to have LV LGE, a striae subepicardial – midmyocardial lateral LV wall distribution pattern was more prevalent. There are no long-term data on outcome of incidental finding of myocardial LGE[114,121-123]. The definitive role of CMRI for prognostication in AHS remains to be defined outside of its roles in excluding other important diagnoses such as HCM and ARC.

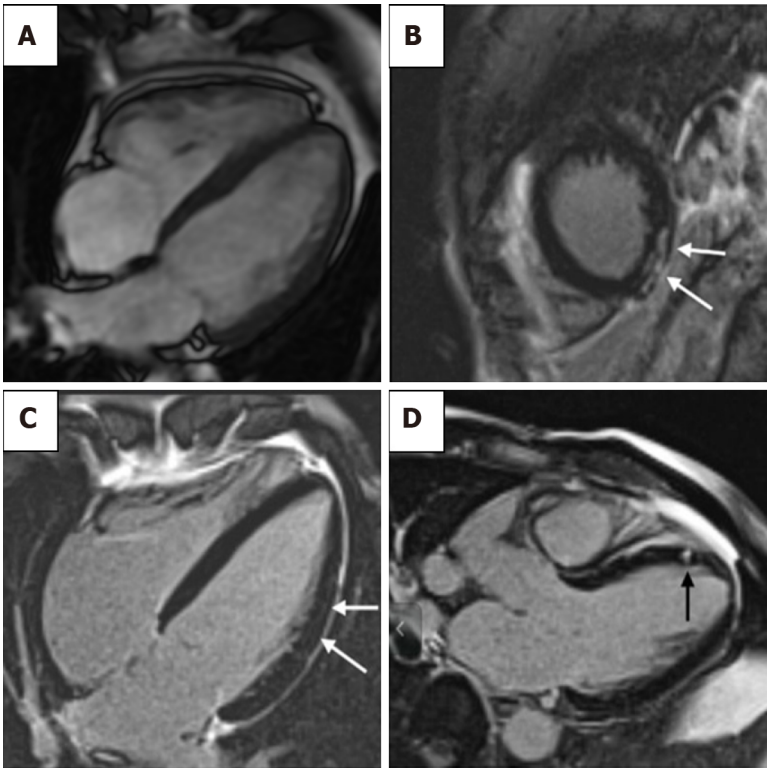

Figure 5 Cardiac magnetic resonance imaging of athlete's heart syndrome. A: Cardiac magnetic resonance imaging of an endurance athlete. Increased right and left ventricular volumes. Overall muscle mass may be increased although wall thickness remains within standard reference range[102]; B: A 51-year-old athlete training 7 h/wk in the last 30 years. The short-axis view shows subepicardial late gadolinium enhancement (LGE) in the inferior apical wall; C: A 55-year-old athlete training 8 h/wk in the last 30 years. Mild intramyocardial LGE is the lateral wall is shown in the four-chamber view; D: A 55-year-old athlete training 10 h/wk in the last 28 years. Mesocardial LGE in the apical-septal wall shown in three-chamber view image. Reproduced from Pujadas *et al*[122] and licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

COMMENTS AND LIMITATIONS

Traditionally, gross morphological cine scanning and determination of LGE location in the myocardial wall has formed key diagnostic features in the use of CMRI for many conditions. The advent of more advanced techniques such as T1 and T2 mapping has allowed a deeper understanding of the pathophysiological process involved.

The limitations for the use of CMRI include: (1) Access to CMR facilities with trained staff to perform the scan and process the images; (2) Standardised protocols; (3) Duration of procedure; (4) High cost; and (5) Lack of superiority to cheaper, faster and more accessible imaging modalities.

Moving forward, improving access to CMRI, increasing the number of skilled personnel and developing clear scanning guidelines are needed. Further research including large randomised trials are necessary to further define the role of CMRI in the assessment of MI, TTS, myocarditis, AHS and COVID-19-related cardiac conditions.

CONCLUSION

Troponinemia or an elevation in serum troponin levels can result from several different conditions making the diagnosis difficult. CMRI provides a powerful insight into the pathological mechanisms of disease, diagnostic features, as well as potential prognosis. With advancement in technology and research, this will only continue to improve.

FOOTNOTES

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REFERENCES

1 **Thygesen K**, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018; **138**: e618-e651 [PMID: 30571511 DOI: 10.1161/CIR.0000000000000617]
2 **Bulluck H**, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ. Cardiovascular Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction: Recent Advances, Controversies, and Future Directions. *Circulation* 2018; **137**: 1949-1964 [PMID: 29712696 DOI: 10.1161/CIRCULATIONAHA.117.030693]
3 **Reimer KA**, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977; **56**: 786-794 [PMID: 912839 DOI: 10.1161/01.cir.56.5.786]
4 **Ichikawa Y**, Sakuma H, Suzawa N, Kitagawa K, Makino K, Hirano T, Takeda K. Late gadolinium-enhanced magnetic resonance imaging in acute and chronic myocardial infarction. Improved prediction of regional myocardial contraction in the chronic state by measuring thickness of nonenhanced myocardium. *J Am Coll Cardiol* 2005; **45**: 901-909 [PMID: 15766827 DOI: 10.1016/j.jacc.2004.11.058]
5 **Thiele H**, Kappl MJ, Conradi S, Niebauer J, Hambrecht R, Schuler G. Reproducibility of chronic and acute infarct size measurement by delayed enhancement-magnetic resonance imaging. *J Am Coll Cardiol* 2006; **47**: 1641-1645 [PMID: 16631003 DOI: 10.1016/j.jacc.2005.11.065]
6 **Mahrholdt H**, Wagner A, Holly TA, Elliott MD, Bonow RO, Kim RJ, Judd RM. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. *Circulation* 2002; **106**: 2322-2327 [PMID: 12403661 DOI: 10.1161/01.CIR.0000036368.63317.1C]
7 **Rajiah P**, Desai MY, Kwon D, Flamm SD. MR imaging of myocardial infarction. *Radiographics* 2013; **33**: 1383-1412 [PMID: 24025931 DOI: 10.1148/rg.335125722]
8 **Rehwald WG**, Fieno DS, Chen EL, Kim RJ, Judd RM. Myocardial magnetic resonance imaging contrast agent concentrations after reversible and irreversible ischemic injury. *Circulation* 2002; **105**: 224-229 [PMID: 11790705 DOI: 10.1161/hc0202.102016]
9 **Kim HW**, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. *J Am Coll Cardiol* 2009; **55**: 1-16 [PMID: 20117357 DOI: 10.1016/j.jacc.2009.06.059]
10 **Kali A**, Choi EY, Sharif B, Kim YJ, Bi X, Spottiswoode B, Cokic I, Yang HJ, Tighiouart M, Conte AH, Li D, Berman DS, Choi BW, Chang HJ, Dharmakumar R. Native T1 Mapping by 3-T CMR Imaging for Characterization of Chronic Myocardial Infarctions. *JACC Cardiovasc Imaging* 2015; **8**: 1019-1030 [PMID: 26298071 DOI: 10.1016/j.jcmg.2015.04.018]
11 **Ersbøll M**, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, Hassager C, Søgaard P, Køber L. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2013; **61**: 2365-2373 [PMID: 23563128 DOI: 10.1016/j.jacc.2013.02.061]
12 **Eitel I**, Stiermaier T, Lange T, Rommel KP, Koschalka A, Kowallick JT, Lotz J, Kutty S, Gutberlet M, Hasenfuß G, Thiele H, Schuster A. Cardiac Magnetic Resonance Myocardial Feature Tracking for Optimized Prediction of Cardiovascular Events Following Myocardial Infarction. *JACC Cardiovasc Imaging* 2018; **11**: 1433-1444 [PMID: 29454776 DOI: 10.1016/j.jcmg.2017.11.034]
13 **Schuster A**, Backhaus SJ, Stiermaier T, Navarra JL, Uhlig J, Rommel KP, Koschalka A, Kowallick JT, Lotz J, Gutberlet M, Bigalke B, Kutty S, Hasenfuss G, Thiele H, Eitel I. Left Atrial Function with MRI Enables Prediction of Cardiovascular Events after Myocardial Infarction: Insights from the AIDA STEMI and TATORT NSTEMI Trials. *Radiology* 2019; **293**: 292-302 [PMID: 31526253 DOI: 10.1148/radiol.2019190559]
14 **Nayyar D**, Nguyen T, Pathan F, Vo G, Richards D, Thomas L, Dimitri H, Otton J. Cardiac magnetic resonance derived

left atrial strain after ST-elevation myocardial infarction: an independent prognostic indicator. *Cardiovasc Diagn Ther* 2021; **11**: 383-393 [PMID: 33968617 DOI: 10.21037/cdt-20-879]

15 **Allman KC**, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002; **39**: 1151-1158 [PMID: 11923039 DOI: 10.1016/s0735-1097(02)01726-6]

16 **Hachamovitch R**, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107**: 2900-2907 [PMID: 12771008 DOI: 10.1161/01.CIR.0000072790.23090.41]

17 **Charoenpanichkit C**, Hundley WG. The 20 year evolution of dobutamine stress cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010; **12**: 59 [PMID: 20977757 DOI: 10.1186/1532-429X-12-59]

18 **Bove CM**, DiMaria JM, Voros S, Conaway MR, Kramer CM. Dobutamine response and myocardial infarct transmurality: functional improvement after coronary artery bypass grafting--initial experience. *Radiology* 2006; **240**: 835-841 [PMID: 16926330 DOI: 10.1148/radiol.2403051150]

19 **Motoyasu M**, Sakuma H, Ichikawa Y, Ishida N, Uemura S, Okinaka T, Isaka N, Takeda K, Nakano T. Prediction of regional functional recovery after acute myocardial infarction with low dose dobutamine stress cine MR imaging and contrast enhanced MR imaging. *J Cardiovasc Magn Reson* 2003; **5**: 563-574 [PMID: 14664134 DOI: 10.1081/jcmr-120025233]

20 **Hillenbrand HB**, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. *Circulation* 2000; **102**: 1678-1683 [PMID: 11015347 DOI: 10.1161/01.cir.102.14.1678]

21 **Perazzolo Marra M**, Lima JA, Iliceto S. MRI in acute myocardial infarction. *Eur Heart J* 2011; **32**: 284-293 [PMID: 21112897 DOI: 10.1093/eurheartj/ehq409]

22 **Bax JJ**, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *J Am Coll Cardiol* 1997; **30**: 1451-1460 [PMID: 9362401 DOI: 10.1016/s0735-1097(97)00352-5]

23 **Hamirani YS**, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2014; **7**: 940-952 [PMID: 25212800 DOI: 10.1016/j.jcmg.2014.06.012]

24 **Eitel I**, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, Desch S, Schuler G, Thiele H. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2014; **64**: 1217-1226 [PMID: 25236513 DOI: 10.1016/j.jacc.2014.06.1194]

25 **Symons R**, Pontone G, Schwitter J, Francone M, Iglesias JF, Barison A, Zalewski J, de Luca L, Degrauwe S, Claus P, Guglielmo M, Nessler J, Carbone I, Ferro G, Durak M, Magistrelli P, Lo Presti A, Aquaro GD, Eeckhout E, Roguelov C, Andreini D, Vogt P, Guaricci AI, Mushtaq S, Lorenzoni V, Muller O, Desmet W, Agati L, Janssens S, Bogaert J, Masci PG. Long-Term Incremental Prognostic Value of Cardiovascular Magnetic Resonance After ST-Segment Elevation Myocardial Infarction: A Study of the Collaborative Registry on CMR in STEMI. *JACC Cardiovasc Imaging* 2018; **11**: 813-825 [PMID: 28823746 DOI: 10.1016/j.jcmg.2017.05.023]

26 **van Kranenburg M**, Magro M, Thiele H, de Waha S, Eitel I, Cochet A, Cottin Y, Atar D, Buser P, Wu E, Lee D, Bodi V, Klug G, Metzler B, Delewi R, Bernhardt P, Rottbauer W, Boersma E, Zijlstra F, van Geuns RJ. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. *JACC Cardiovasc Imaging* 2014; **7**: 930-939 [PMID: 25212799 DOI: 10.1016/j.jcmg.2014.05.010]

27 **Stone GW**, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship Between Infarct Size and Outcomes Following Primary PCI: Patient-Level Analysis From 10 Randomized Trials. *J Am Coll Cardiol* 2016; **67**: 1674-1683 [PMID: 27056772 DOI: 10.1016/j.jacc.2016.01.069]

28 **Bulluck H**, Hammond-Haley M, Fontana M, Knight DS, Sirker A, Herrey AS, Manisty C, Kellman P, Moon JC, Hausenloy DJ. Quantification of both the area-at-risk and acute myocardial infarct size in ST-segment elevation myocardial infarction using T1-mapping. *J Cardiovasc Magn Reson* 2017; **19**: 57 [PMID: 28764773 DOI: 10.1186/s12968-017-0370-6]

29 **Ingkanisorn WP**, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol* 2004; **43**: 2253-2259 [PMID: 15193689 DOI: 10.1016/j.jacc.2004.02.046]

30 **Kwong RY**, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, Davis RB. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006; **113**: 2733-2743 [PMID: 16754804 DOI: 10.1161/CIRCULATIONAHA.105.570648]

31 **Eitel I**, Kubusch K, Strohm O, Desch S, Mikami Y, de Waha S, Gutberlet M, Schuler G, Friedrich MG, Thiele H. Prognostic value and determinants of a hypointense infarct core in T2-weighted cardiac magnetic resonance in acute reperfused ST-elevation-myocardial infarction. *Circ Cardiovasc Imaging* 2011; **4**: 354-362 [PMID: 21518773 DOI: 10.1161/CIRCIMAGING.110.960500]

32 **El Aidi H**, Adams A, Moons KG, Den Ruijter HM, Mali WP, Doevendans PA, Nagel E, Schalla S, Bots ML, Leiner T. Cardiac magnetic resonance imaging findings and the risk of cardiovascular events in patients with recent myocardial infarction or suspected or known coronary artery disease: a systematic review of prognostic studies. *J Am Coll Cardiol* 2014; **63**: 1031-1045 [PMID: 24486280 DOI: 10.1016/j.jacc.2013.11.048]

33 **Mather AN**, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Timing of cardiovascular MR imaging after acute myocardial infarction: effect on estimates of infarct characteristics and prediction of late ventricular remodeling. *Radiology* 2011; **261**: 116-126 [PMID: 21828188 DOI: 10.1148/radiol.11110228]

34 **Ripa RS**, Nilsson JC, Wang Y, Søndergaard L, Jørgensen E, Kastrup J. Short- and long-term changes in myocardial

function, morphology, edema, and infarct mass after ST-segment elevation myocardial infarction evaluated by serial magnetic resonance imaging. *Am Heart J* 2007; **154**: 929-936 [PMID: 17967600 DOI: 10.1016/j.ahj.2007.06.038]

35 **Pontone G**, Guaricci AI, Andreini D, Solbiati A, Guglielmo M, Mushtaq S, Baggiano A, Beltrama V, Fusini L, Rota C, Segurini C, Conte E, Gripari P, Dello Russo A, Moltrasio M, Tundo F, Lombardi F, Muscogiuri G, Lorenzoni V, Tondo C, Agostoni P, Bartorelli AL, Pepi M. Prognostic Benefit of Cardiac Magnetic Resonance Over Transthoracic Echocardiography for the Assessment of Ischemic and Nonischemic Dilated Cardiomyopathy Patients Referred for the Evaluation of Primary Prevention Implantable Cardioverter-Defibrillator Therapy. *Circ Cardiovasc Imaging* 2016; **9** [PMID: 27729359 DOI: 10.1161/CIRCIMAGING.115.004956]

36 **Scott PA**, Morgan JM, Carroll N, Murday DC, Roberts PR, Peebles CR, Harden SP, Curzen NP. The extent of left ventricular scar quantified by late gadolinium enhancement MRI is associated with spontaneous ventricular arrhythmias in patients with coronary artery disease and implantable cardioverter-defibrillators. *Circ Arrhythm Electrophysiol* 2011; **4**: 324-330 [PMID: 21493964 DOI: 10.1161/CIRCEP.110.959544]

37 **Scott PA**, Rosengarten JA, Curzen NP, Morgan JM. Late gadolinium enhancement cardiac magnetic resonance imaging for the prediction of ventricular tachyarrhythmic events: a meta-analysis. *Eur J Heart Fail* 2013; **15**: 1019-1027 [PMID: 23558217 DOI: 10.1093/eurjhf/hft053]

38 **Acosta J**, Fernández-Armenta J, Borràs R, Anguera I, Bisbal F, Martí-Almor J, Tolosana JM, Penela D, Andreu D, Soto-Iglesias D, Evertz R, Matiello M, Alonso C, Villuendas R, de Caralt TM, Perea RJ, Ortiz JT, Bosch X, Serra L, Planes X, Greiser A, Ekinci O, Lasalvia L, Mont L, Berruezo A. Scar Characterization to Predict Life-Threatening Arrhythmic Events and Sudden Cardiac Death in Patients With Cardiac Resynchronization Therapy: The GAUDI-CRT Study. *JACC Cardiovasc Imaging* 2018; **11**: 561-572 [PMID: 28780194 DOI: 10.1016/j.jcmg.2017.04.021]

39 **Roes SD**, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, Reiber JH, Zeppenfeld K, Lamb HJ, de Roos A, Schalij MJ, Bax JJ. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. *Circ Cardiovasc Imaging* 2009; **2**: 183-190 [PMID: 19808591 DOI: 10.1161/CIRCIMAGING.108.826529]

40 **Yan AT**, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, Di Carli MF, Reynolds HG, Stevenson WG, Kwong RY. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation* 2006; **114**: 32-39 [PMID: 16801462 DOI: 10.1161/CIRCULATIONAHA.106.613414]

41 **Schuster A**, Lange T, Backhaus SJ, Strohmeyer C, Boom PC, Matz J, Kowallick JT, Lotz J, Steinmetz M, Kutty S, Bigalke B, Gutberlet M, de Waha-Thiele S, Desch S, Hasenfuß G, Thiele H, Stiermaier T, Eitel I. Fully Automated Cardiac Assessment for Diagnostic and Prognostic Stratification Following Myocardial Infarction. *J Am Heart Assoc* 2020; **9**: e016612 [PMID: 32873121 DOI: 10.1161/JAHA.120.016612]

42 **Al-Khatib SM**, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2018; **138**: e272-e391 [PMID: 29084731 DOI: 10.1161/CIR.0000000000000549]

43 **Elayi CS**, Charnigo RJ, Heron PM, Lee BK, Olgin JE. Primary Prevention of Sudden Cardiac Death Early Post-Myocardial Infarction: Root Cause Analysis for Implantable Cardioverter-Defibrillator Failure and Currently Available Options. *Circ Arrhythm Electrophysiol* 2017; **10** [PMID: 28630173 DOI: 10.1161/CIRCEP.117.005194]

44 **Ghadri JR**, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J* 2018; **39**: 2032-2046 [PMID: 29850871 DOI: 10.1093/eurheartj/ehy076]

45 **Dote K**, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases]. *J Cardiol* 1991; **21**: 203-214 [PMID: 1841907]

46 **Barrera-Ramirez CF**, Jimenez-Mazuecos JM, Alfonso F. Apical thrombus associated with left ventricular apical ballooning. *Heart* 2003; **89**: 927 [PMID: 12860874 DOI: 10.1136/heart.89.8.927]

47 **Scally C**, Rudd A, Mezincescu A, Wilson H, Srivanasan J, Horgan G, Broadhurst P, Newby DE, Henning A, Dawson DK. Persistent Long-Term Structural, Functional, and Metabolic Changes After Stress-Induced (Takotsubo) Cardiomyopathy. *Circulation* 2018; **137**: 1039-1048 [PMID: 29128863 DOI: 10.1161/CIRCULATIONAHA.117.031841]

48 **Lyon AR**, Akashi YJ. Use of cardiac MRI to diagnose Takotsubo syndrome. *Nat Rev Cardiol* 2015; **12**: 669 [PMID: 26440986 DOI: 10.1038/nrcardio.2015.155]

49 **Eitel I**, Behrendt F, Schindler K, Kivelitz D, Gutberlet M, Schuler G, Thiele H. Differential diagnosis of suspected apical ballooning syndrome using contrast-enhanced magnetic resonance imaging. *Eur Heart J* 2008; **29**: 2651-2659 [PMID: 18820322 DOI: 10.1093/eurheartj/ehn433]

50 **Bratis K**. Cardiac Magnetic Resonance in Takotsubo Syndrome. *Eur Cardiol* 2017; **12**: 58-62 [PMID: 30416553 DOI: 10.15420/ecr.2017:7:2]

51 **Eitel I**, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, Francone M, Desch S, Gutberlet M, Strohm O, Schuler G, Schulz-Menger J, Thiele H, Friedrich MG. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011; **306**: 277-286 [PMID: 21771988 DOI: 10.1001/jama.2011.992]

52 **Gunasekara MY**, Mezincescu AM, Dawson DK. An Update on Cardiac Magnetic Resonance Imaging in Takotsubo Cardiomyopathy. *Curr Cardiovasc Imaging Rep* 2020; **13**: 1-8 [DOI: 10.1007/s12410-020-09536-0]

53 **Avegliano G**, Huguet M, Costabel JP, Ronderos R, Bijnens B, Kuschnir P, Thierer J, Tobón-Gomez C, Martinez GO, Frangi A. Morphologic pattern of late gadolinium enhancement in Takotsubo cardiomyopathy detected by early

cardiovascular magnetic resonance. *Clin Cardiol* 2011; **34**: 178-182 [PMID: 21400545 DOI: 10.1002/clc.20877]

54 **Rolf A**, Nef HM, Möllmann H, Troidl C, Voss S, Conradi G, Rixe J, Steiger H, Beiring K, Hamm CW, Dill T. Immunohistological basis of the late gadolinium enhancement phenomenon in tako-tsubo cardiomyopathy. *Eur Heart J* 2009; **30**: 1635-1642 [PMID: 19389788 DOI: 10.1093/eurheartj/ehp140]

55 **Nakamori S**, Matsuoka K, Onishi K, Kurita T, Ichikawa Y, Nakajima H, Ishida M, Kitagawa K, Tanigawa T, Nakamura T, Ito M, Sakuma H. Prevalence and signal characteristics of late gadolinium enhancement on contrast-enhanced magnetic resonance imaging in patients with takotsubo cardiomyopathy. *Circ J* 2012; **76**: 914-921 [PMID: 22293447 DOI: 10.1253/circj.cj-11-1043]

56 **Naruse Y**, Sato A, Kasahara K, Makino K, Sano M, Takeuchi Y, Nagasaka S, Wakabayashi Y, Katoh H, Satoh H, Hayashi H, Aonuma K. The clinical impact of late gadolinium enhancement in Takotsubo cardiomyopathy: serial analysis of cardiovascular magnetic resonance images. *J Cardiovasc Magn Reson* 2011; **13**: 67 [PMID: 22035445 DOI: 10.1186/1532-429X-13-67]

57 **Satoh H**, Sano M, Suwa K, Saitoh T, Nobuhara M, Saotome M, Urushida T, Katoh H, Hayashi H. Distribution of late gadolinium enhancement in various types of cardiomyopathies: Significance in differential diagnosis, clinical features and prognosis. *World J Cardiol* 2014; **6**: 585-601 [PMID: 25068019 DOI: 10.4330/wjc.v6.i7.585]

58 **Lyon AR**, Citro R, Schneider B, Morel O, Ghadri JR, Templin C, Omerovic E. Pathophysiology of Takotsubo Syndrome: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021; **77**: 902-921 [PMID: 33602474 DOI: 10.1016/j.jacc.2020.10.060]

59 **Ojha V**, Khurana R, Ganga KP, Kumar S. Advanced cardiac magnetic resonance imaging in takotsubo cardiomyopathy. *Br J Radiol* 2020; **93**: 20200514 [PMID: 32795180 DOI: 10.1259/bjr.20200514]

60 **Friedrich MG**, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol* 2009; **53**: 1475-1487 [PMID: 19389557 DOI: 10.1016/j.jacc.2009.02.007]

61 **Friedrich MG**, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. *Circulation* 1998; **97**: 1802-1809 [PMID: 9603535 DOI: 10.1161/01.cir.97.18.1802]

62 **Mahrholdt H**, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, Fritz P, Klingel K, Kandolf R, Sechtem U. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation* 2004; **109**: 1250-1258 [PMID: 14993139 DOI: 10.1161/01.CIR.0000118493.13323.81]

63 **Abdel-Aty H**, Boyé P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, Bock P, Dietz R, Friedrich MG, Schulz-Menger J. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. *J Am Coll Cardiol* 2005; **45**: 1815-1822 [PMID: 15936612 DOI: 10.1016/j.jacc.2004.11.069]

64 **Lurz P**, Luecke C, Eitel I, Föhrenbach F, Frank C, Grothoff M, de Waha S, Rommel KP, Lurz JA, Klingel K, Kandolf R, Schuler G, Thiele H, Gutberlet M. Comprehensive Cardiac Magnetic Resonance Imaging in Patients With Suspected Myocarditis: The MyoRacer-Trial. *J Am Coll Cardiol* 2016; **67**: 1800-1811 [PMID: 27081020 DOI: 10.1016/j.jacc.2016.02.013]

65 **Citro R**, Lyon AR, Meimoun P, Omerovic E, Redfors B, Buck T, Lerakis S, Parodi G, Silverio A, Eitel I, Schneider B, Prasad A, Bossone E. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: clinical and prognostic implications. *J Am Soc Echocardiogr* 2015; **28**: 57-74 [PMID: 25282664 DOI: 10.1016/j.echo.2014.08.020]

66 **Hunold P**, Schlosser T, Vogt FM, Eggebrecht H, Schmermund A, Bruder O, Schüler WO, Barkhausen J. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. *AJR Am J Roentgenol* 2005; **184**: 1420-1426 [PMID: 15855089 DOI: 10.2214/ajr.184.5.01841420]

67 **Grün S**, Schumm J, Greulich S, Wagner A, Schneider S, Bruder O, Kispert EM, Hill S, Ong P, Klingel K, Kandolf R, Sechtem U, Mahrholdt H. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 2012; **59**: 1604-1615 [PMID: 22365425 DOI: 10.1016/j.jacc.2012.01.007]

68 **Aquaro GD**, Perfetti M, Camastra G, Monti L, Dellegrottaglie S, Moro C, Pepe A, Todiere G, Lanzillo C, Scatteia A, Di Roma M, Pontone G, Perazzolo Marra M, Barison A, Di Bella G; Cardiac Magnetic Resonance Working Group of the Italian Society of Cardiology. Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function: ITAMY Study. *J Am Coll Cardiol* 2017; **70**: 1977-1987 [PMID: 29025554 DOI: 10.1016/j.jacc.2017.08.044]

69 **Mahrholdt H**, Wagner A, Deluigi CC, Kispert E, Hager S, Meinhardt G, Vogelsberg H, Fritz P, Dippon J, Bock CT, Klingel K, Kandolf R, Sechtem U. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. *Circulation* 2006; **114**: 1581-1590 [PMID: 17015795 DOI: 10.1161/CIRCULATIONAHA.105.606509]

70 **Berg J**, Kottwitz J, Baltensperger N, Kissel CK, Lovrinovic M, Mehra T, Scherff F, Schmied C, Templin C, Lüscher TF, Heidecker B, Manka R. Cardiac Magnetic Resonance Imaging in Myocarditis Reveals Persistent Disease Activity Despite Normalization of Cardiac Enzymes and Inflammatory Parameters at 3-Month Follow-Up. *Circ Heart Fail* 2017; **10** [PMID: 29158437 DOI: 10.1161/CIRCHEARTFAILURE.117.004262]

71 **Mavrogeni S**, Petrou E, Kolovou G, Theodorakis G, Iliodromitis E. Prediction of ventricular arrhythmias using cardiovascular magnetic resonance. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 518-525 [PMID: 23324829 DOI: 10.1093/ehjci/jes302]

72 **Georgiopoulos G**, Figliozzi S, Sanguineti F, Aquaro GD, di Bella G, Stamatelopoulos K, Chiribiri A, Garot J, Masci PG, Ismail TF. Prognostic Impact of Late Gadolinium Enhancement by Cardiovascular Magnetic Resonance in Myocarditis: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Imaging* 2021; **14**: e011492 [PMID: 33441003 DOI: 10.1161/CIRCIMAGING.120.011492]

73 **Guo T**, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 811-818 [PMID: 32219356 DOI: 10.1001/jamacardio.2020.1017]

74 **Lala A**, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Mancini DM, Fuster V; Mount Sinai COVID Informatics Center. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* 2020; **76**: 533-546 [PMID: 32517963 DOI: 10.1016/j.jacc.2020.06.007]

75 **Puntmann VO**, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265-1273 [PMID: 32730619 DOI: 10.1001/jamacardio.2020.3557]

76 **Shi S**, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802-810 [PMID: 32211816 DOI: 10.1001/jamacardio.2020.0950]

77 **Lindner D**, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Püschel K, Westermann D. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiol* 2020; **5**: 1281-1285 [PMID: 32730555 DOI: 10.1001/jamacardio.2020.3551]

78 **Giustino G**, Pinney SP, Lala A, Reddy VY, Johnston-Cox HA, Mechanick JI, Halperin JL, Fuster V. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. *J Am Coll Cardiol* 2020; **76**: 2011-2023 [PMID: 33092737 DOI: 10.1016/j.jacc.2020.08.059]

79 **Li X**, Wang H, Zhao R, Wang T, Zhu Y, Qian Y, Liu B, Yu Y, Han Y. Elevated Extracellular Volume Fraction and Reduced Global Longitudinal Strains in Participants Recovered from COVID-19 without Clinical Cardiac Findings. *Radiology* 2021; **299**: E230-E240 [PMID: 33434112 DOI: 10.1148/radiol.2021203998]

80 **Gravinay P**, Issa N, Girard D, Camou F, Cochet H. CMR and serology to diagnose COVID-19 infection with primary cardiac involvement. *Eur Heart J Cardiovasc Imaging* 2021; **22**: 133 [PMID: 32556106 DOI: 10.1093/ehjci/jeaa169]

81 **Huang L**, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020; **13**: 2330-2339 [PMID: 32763118 DOI: 10.1016/j.jcmg.2020.05.004]

82 **Jain SS**, Steele JM, Fonseca B, Huang S, Shah S, Maskatia SA, Buddhe S, Misra N, Ramachandran P, Gaur L, Eshtehardi P, Anwar S, Kaushik N, Han F, Chaudhuri NR, Grosse-Wortmann L. COVID-19 Vaccination-Associated Myocarditis in Adolescents. *Pediatrics* 2021; **148** [PMID: 34389692 DOI: 10.1542/peds.2021-053427]

83 **Tano E**, San Martin S, Girgis S, Martinez-Fernandez Y, Sanchez Vegas C. Perimyocarditis in Adolescents After Pfizer-BioNTech COVID-19 Vaccine. *J Pediatric Infect Dis Soc* 2021; **10**: 962-966 [PMID: 34319393 DOI: 10.1093/jpids/piab060]

84 **Bozkurt B**, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. *Circulation* 2021; **144**: 471-484 [PMID: 34281357 DOI: 10.1161/CIRCULATIONAHA.121.056135]

85 **Kim HW**, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, Parker MA, Kim RJ. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. *JAMA Cardiol* 2021; **6**: 1196-1201 [PMID: 34185046 DOI: 10.1001/jamacardio.2021.2828]

86 **Larson KF**, Ammirati E, Adler ED, Cooper LT Jr, Hong KN, Saponara G, Couri D, Cereda A, Procopio A, Cavalotti C, Oliva F, Sanna T, Ciconte VA, Onyango G, Holmes DR, Borgeson DD. Myocarditis After BNT162b2 and mRNA-1273 Vaccination. *Circulation* 2021; **144**: 506-508 [PMID: 34133884 DOI: 10.1161/CIRCULATIONAHA.121.055913]

87 **Montgomery J**, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, Loran D, Hrncir D, Herring K, Platzer M, Adams N, Sanou A, Cooper LT Jr. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. *JAMA Cardiol* 2021; **6**: 1202-1206 [PMID: 34185045 DOI: 10.1001/jamacardio.2021.2833]

88 **Marshall M**, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, Shaughnessy R, Caron R, Fuss C, Corbin KJE, Emuren L, Faherty E, Hall EK, Di Pentima C, Oster ME, Paintsil E, Siddiqui S, Timchak DM, Guzman-Cottrill JA. Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination. *Pediatrics* 2021; **148** [PMID: 34088762 DOI: 10.1542/peds.2021-052478]

89 **Vollmann D**, Eiffert H, Schuster A. Acute Perimyocarditis Following First Dose of mRNA Vaccine Against COVID-19. *Dtsch Arztebl Int* 2021; **118**: 546 [PMID: 34515024 DOI: 10.3238/arztebl.m2021.0288]

90 **Shi S**, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, Liu X, Xiang Y, Zhao Q, Huang H, Yang B, Huang C. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020; **41**: 2070-2079 [PMID: 32391877 DOI: 10.1093/eurheartj/ehaa408]

91 **Metkus TS**, Sokoll LJ, Barth AS, Czarny MJ, Hays AG, Lowenstein CJ, Michos ED, Nolley EP, Post WS, Resar JR, Thiemann DR, Trost JC, Hasan RK. Myocardial Injury in Severe COVID-19 Compared With Non-COVID-19 Acute Respiratory Distress Syndrome. *Circulation* 2021; **143**: 553-565 [PMID: 33186055 DOI: 10.1161/CIRCULATIONAHA.120.050543]

92 **Sanghvi SK**, Schwarzman LS, Nazir NT. Cardiac MRI and Myocardial Injury in COVID-19: Diagnosis, Risk Stratification and Prognosis. *Diagnostics (Basel)* 2021; **11** [PMID: 33467705 DOI: 10.3390/diagnostics11010130]

93 **Mitrani RD**, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. *Heart Rhythm* 2020; **17**: 1984-1990 [PMID: 32599178 DOI: 10.1016/j.hrthm.2020.06.026]

94 **Corrado D**, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, Biffi A, Buja G, Delise P, Gussac I, Anastasakis A, Borjesson M, Bjørnstad HH, Carrè F, Deligiannis A, Dugmore D, Fagard R, Hoogsteen J, Mellwig KP, Panhuyzen-Goedkoop N, Solberg E, Vanhees L, Drezner J, Estes NA 3rd, Iliceto S, Maron BJ, Peidro R, Schwartz PJ, Stein R, Thiene G, Zeppilli P, McKenna WJ; Section of Sports Cardiology, European Association of Cardiovascular Prevention and Rehabilitation. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J* 2010; **31**: 243-259 [PMID: 19933514 DOI: 10.1093/eurheartj/ehp473]

95 **Marshall L**, Lee KK, Stewart SD, Wild A, Fujisawa T, Ferry AV, Stables CL, Lithgow H, Chapman AR, Anand A, Shah ASV, Dhaun N, Strachan FE, Mills NL, Ross MD. Effect of Exercise Intensity and Duration on Cardiac Troponin Release. *Circulation* 2020; **141**: 83-85 [PMID: 31887079 DOI: 10.1161/CIRCULATIONAHA.119.041874]

96 **Shave R**, Oxborough D. Exercise-induced cardiac injury: evidence from novel imaging techniques and highly sensitive cardiac troponin assays. *Prog Cardiovasc Dis* 2012; **54**: 407-415 [PMID: 22386291 DOI: 10.1016/j.pcad.2012.01.007]

97 **Middleton N**, Shave R, George K, Whyte G, Hart E, Atkinson G. Left ventricular function immediately following prolonged exercise: A meta-analysis. *Med Sci Sports Exerc* 2006; **38**: 681-687 [PMID: 16679983 DOI: 10.1249/01.mss.0000210203.10200.12]

98 **Carrió I**, Serra-Grima R, Berná L, Estorch M, Martinez-Duncker C, Ordoñez J. Transient alterations in cardiac performance after a six-hour race. *Am J Cardiol* 1990; **65**: 1471-1474 [PMID: 2353653 DOI: 10.1016/0002-9149(90)91357-c]

99 **La Gerche A**, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart* 2008; **94**: 860-866 [PMID: 17483127 DOI: 10.1136/hrt.2006.101063]

100 **Caselli S**, Maron MS, Urbano-Moral JA, Pandian NG, Maron BJ, Pelliccia A. Differentiating left ventricular hypertrophy in athletes from that in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2014; **114**: 1383-1389 [PMID: 25217454 DOI: 10.1016/j.amjcard.2014.07.070]

101 **Morganroth J**, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med* 1975; **82**: 521-524 [PMID: 1119766 DOI: 10.7326/0003-4819-82-4-521]

102 **D'Ascenzi F**, Anselmi F, Piu P, Fiorentini C, Carbone SF, Volterrani L, Focardi M, Bonifazi M, Mondillo S. Cardiac Magnetic Resonance Normal Reference Values of Biventricular Size and Function in Male Athlete's Heart. *JACC Cardiovasc Imaging* 2019; **12**: 1755-1765 [PMID: 30553678 DOI: 10.1016/j.jcmg.2018.09.021]

103 **Pluim BM**, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation* 2000; **101**: 336-344 [PMID: 10645932 DOI: 10.1161/01.cir.101.3.336]

104 **Galanti G**, Stefani L, Mascherini G, Di Tante V, Toncelli L. Left ventricular remodeling and the athlete's heart, irrespective of quality load training. *Cardiovasc Ultrasound* 2016; **14**: 46 [PMID: 27855701 DOI: 10.1186/s12947-016-0088-x]

105 **Swoboda PP**, McDiarmid AK, Erhayiem B, Broadbent DA, Dobson LE, Garg P, Ferguson C, Page SP, Greenwood JP, Plein S. Assessing Myocardial Extracellular Volume by T1 Mapping to Distinguish Hypertrophic Cardiomyopathy From Athlete's Heart. *J Am Coll Cardiol* 2016; **67**: 2189-2190 [PMID: 27151352 DOI: 10.1016/j.jacc.2016.02.054]

106 **Domenech-Ximenos B**, Sanz-de la Garza M, Prat-González S, Sepúlveda-Martínez A, Crispi F, Duran-Fernandez K, Perea RJ, Bijnens B, Sitges M. Prevalence and pattern of cardiovascular magnetic resonance late gadolinium enhancement in highly trained endurance athletes. *J Cardiovasc Magn Reson* 2020; **22**: 62 [PMID: 32878630 DOI: 10.1186/s12968-020-00660-w]

107 **Rubinshtein R**, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, Bos JM, Tajik AJ, Valeti US, Nishimura RA, Gersh BJ. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail* 2010; **3**: 51-58 [PMID: 19850699 DOI: 10.1161/CIRCHEARTFAILURE.109.854026]

108 **Prakken NH**, Velthuis BK, Teske AJ, Mosterd A, Mali WP, Cramer MJ. Cardiac MRI reference values for athletes and nonathletes corrected for body surface area, training hours/week and sex. *Eur J Cardiovasc Prev Rehabil* 2010; **17**: 198-203 [PMID: 20042862 DOI: 10.1097/HJR.0b013e3283347fdb]

109 **Pelliccia A**, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med* 1999; **130**: 23-31 [PMID: 9890846 DOI: 10.7326/0003-4819-130-1-199901050-00005]

110 **Gati S**, Sharma S. Determinants of the athlete's heart: a cardiovascular magnetic resonance imaging study. *Eur J Prev Cardiol* 2020; **27**: 536-539 [PMID: 31403882 DOI: 10.1177/2047487319870339]

111 **Gati S**, Sharma S, Pennell D. The Role of Cardiovascular Magnetic Resonance Imaging in the Assessment of Highly Trained Athletes. *JACC Cardiovasc Imaging* 2018; **11**: 247-259 [PMID: 29413645 DOI: 10.1016/j.jcmg.2017.11.016]

112 **Heidbüchel H**, Hoogsteen J, Fagard R, Vanhees L, Ector H, Willems R, Van Lierde J. High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. *Eur Heart J* 2003; **24**: 1473-1480 [PMID: 12919770 DOI: 10.1016/s0195-668x(03)00282-3]

113 **Zaidi A**, Sheikh N, Jongman JK, Gati S, Panoulas VF, Carr-White G, Papadakis M, Sharma R, Behr ER, Sharma S. Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies. *J Am Coll Cardiol* 2015; **65**: 2702-2711 [PMID: 26112193 DOI: 10.1016/j.jacc.2015.04.035]

114 **La Gerche A**, Claessen G, Van de Bruaene A, Pattyn N, Van Cleemput J, Gewillig M, Bogaert J, Dymarkowski S, Claus P, Heidbuchel H. Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging* 2013; **6**: 329-338 [PMID: 23258478 DOI: 10.1161/CIRCIMAGING.112.980037]

115 **Le TT**, Bryant JA, Ting AE, Ho PY, Su B, Teo RC, Gan JS, Chung YC, O'Regan DP, Cook SA, Chin CW. Assessing exercise cardiac reserve using real-time cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2017; **19**: 7 [PMID: 28110638 DOI: 10.1186/s12968-017-0322-1]

116 **La Gerche A**, Claessen G, Dymarkowski S, Voigt JU, De Buck F, Vanhees L, Droogne W, Van Cleemput J, Claus P, Heidbuchel H. Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes. *Eur Heart J* 2015; **36**: 1998-2010 [PMID: 26038590 DOI: 10.1093/eurheartj/ehv202]

117 **Maestrini V**, Merghani A, Rosmini S, Cox A, Bulluck H, Culotta V, Cheang M, Fontana M, Treibel TA, Abdel-Gadir A, Sharma S, Moon J. CMR findings in high endurance veteran athletes - a 247 subject study. *J Cardiovasc Magn Reson* 2016; **18**: O38 [DOI: 10.1186/1532-429X-18-S1-O38]

118 **La Gerche A**, Burns AT, Mooney DJ, Inder WJ, Taylor AJ, Bogaert J, Macisaac AI, Heidbüchel H, Prior DL. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* 2012; **33**: 998-1006 [PMID: 22160404 DOI: 10.1093/eurheartj/ehr397]

119 **Breuckmann F**, Möhlenkamp S, Nassenstein K, Lehmann N, Ladd S, Schmermund A, Sievers B, Schlosser T, Jöckel KH, Heusch G, Erbel R, Barkhausen J. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic

relevance in marathon runners. *Radiology* 2009; **251**: 50-57 [PMID: 19332846 DOI: 10.1148/radiol.2511081118]

120 **Zorzi A**, Perazzolo Marra M, Rigato I, De Lazzari M, Susana A, Niero A, Pilichou K, Migliore F, Rizzo S, Giorgi B, De Conti G, Sarto P, Serratosa L, Patrizi G, De Maria E, Pelliccia A, Basso C, Schiavon M, Bauce B, Iliceto S, Thiene G, Corrado D. Nonischemic Left Ventricular Scar as a Substrate of Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death in Competitive Athletes. *Circ Arrhythm Electrophysiol* 2016; **9** [PMID: 27390211 DOI: 10.1161/CIRCEP.116.004229]

121 **Androulakis E**, Swoboda PP. The Role of Cardiovascular Magnetic Resonance in Sports Cardiology; Current Utility and Future Perspectives. *Curr Treat Options Cardiovasc Med* 2018; **20**: 86 [PMID: 30167977 DOI: 10.1007/s11936-018-0679-y]

122 **Pujadas S**, Doñate M, Li CH, Merchan S, Cabanillas A, Alomar X, Pons-Llado G, Serra-Grima R, Carreras F. Myocardial remodelling and tissue characterisation by cardiovascular magnetic resonance (CMR) in endurance athletes. *BMJ Open Sport Exerc Med* 2018; **4**: e000422 [PMID: 30498573 DOI: 10.1136/bmjsem-2018-000422]

123 **Plácido R**, Cunha Lopes B, Almeida AG, Rochitte CE. The role of cardiovascular magnetic resonance in takotsubo syndrome. *J Cardiovasc Magn Reson* 2016; **18**: 68 [PMID: 27729054 DOI: 10.1186/s12968-016-0279-5]

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REVIEW

Cardiac myxomas: A narrative review

A K M Monwarul Islam

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Abstract

Cardiac myxomas are common primary neoplasms of the heart. They are biologically benign but "functionally malignant" because of the potential for embolization. They arise most commonly from the left atrium, but no chambers of the heart are immune. They may be sporadic in the majority but also familial as a part of the Carney complex. Two morphological forms exist: polypoid and papillary. Polypoid myxomas often present with obstructive features, while the papillary forms are more prone to embolization. Histogenesis is still controversial; the current view centres around origin from the primitive pluripotent mesenchymal cells. They may be of giant proportion, be calcified or get infected. Clinical presentation typically involves the triad of intracardiac obstruction, embolic events and constitutional symptoms. Precordial examination findings may simulate those of mitral or tricuspid stenosis. The presence of tumour plop and change of the physical findings with changing position may help differentiation between the two. Echocardiography is the investigation of choice. Echogenic polypoid or papillary mobile mass within the atrial cavity remaining attached to the interatrial septum through a stalk are the tell-tale echocardiographic features. Cardiac magnetic resonance and computed tomographic scanning may have incremental diagnostic value. Histopathological examination reveals abundant loose myxoid stroma with scattered round, polygonal or stellate cells with dense irregular nuclei. Genetic testing may detect mutations in the *PRKAR1A* gene in the familial form of cardiac myxoma, *i.e.* the Carney complex. Surgical excision is the mainstay of treatment with low operative mortality, excellent postoperative survival and low recurrence rate. The current trend favours minimal-access surgery with or without robotic assistance. Physicians should have appropriate preparedness to make a timely diagnosis and enthusiastic treatment to avoid potentially fatal complications.

Key Words: Myxoma; Cardiac; Neoplasm; Carney Complex; Echocardiography; Embolism

Core Tip: Cardiac myxomas are biologically benign but "functionally malignant". They can cause life-threatening embolic events. Associated constitutional symptoms may mimic those of inflammatory or connective tissue disorders. Timely diagnosis is of utmost importance because it offers a scope for definitive treatment, *i.e.* surgical excision. Cardiac myxoma is a relatively rare diagnosis, so physicians should have appropriate preparedness to deal with this entity. This review article has summarised the available information, offered practical tips and highlighted the recent advances.

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INTRODUCTION

Cardiac myxomas are primary neoplasms of the heart. Despite a preference for the left atrium, it can involve any of the cardiac chambers. The unusual feature of cardiac myxoma is that it has the biological potential to embolise and grow at the site of embolization[1], causing organ infarction. Timely diagnosis and treatment are essential for the prevention of sometimes life-threatening complications. Though a well-known entity, some aspects of cardiac myxoma are still evolving.

Epidemiology

Cardiac myxoma is a rare disease; however, the exact prevalence is unknown. The reported prevalence is 0.03% in the general population[2]. Annual incidence of cardiac myxoma may be 0.5 to 1 case per million individuals[3,4]. A recently published Spanish study revealed a higher incidence; age-adjusted incidence was 1.6 per million population adjusting to the world population as a reference and 2.1 per million adjusting to the European population[5]. Myxomas are the commonest primary cardiac tumour constituting 50% to 85% of benign ones[6-8]. Middle-aged persons are commonly affected, but no age is immune. The tumour has a female preponderance with a female-to-male ratio of approximately 3:1[3, 4]. Two epidemiological forms of cardiac myxoma exist: sporadic and familial. The former is far more common than the latter, constituting about 95% of cases[6].

Anatomy

Cardiac myxomas can affect any chamber of the heart, but the left atrium is most commonly affected. Sites affected include the following: left atrium (75%); right atrium (15%-20%); left ventricle (3%-4%); and right ventricle (3%-4%)[9-12]. Regarding origin, myxoma has a predilection for limbus fossa ovalis of the interatrial septum. However, it can arise from the posterior atrial wall, anterior atrial wall and atrial appendage (Figure 1). The sporadic myxomas are usually single and bear these characteristics. On the other hand, familial myxomas may be multiple, multicentric and arising from atypical sites[13]. Less commonly, myxomas may be bi-atrial or multi-chamber; the latter may be part of the Carney complex [14-18] (Figures 2 and 3). Only rarely, myxomas affect the heart valves[7,19-21].

Myxomas may be 'more solid' polypoid in approximately two-thirds of cases or 'softer' papillary in one-third of cases[22] (Figure 4). The polypoid myxomas are generally pedunculated, more compact and have less tendency to undergo fragmentation and consequent embolisation[6]. On the other hand, papillary or villous myxomas are gelatinous, less compact, fragile and have a high potential for spontaneous fragmentation and embolisation to the central nervous system, kidney, spleen, extremities and coronary vessels (Figure 5).

Myxomas are considered biologically benign but "functionally malignant" tumours. They usually remain localised to the site of origin. They have a well-documented potential for fragmentation and embolisation. Besides this, metastasis to different locations, including the brain, sternum, spine and pelvis, has been described[23-29].

Myxomas may be enormous, occupying significant parts of the concerned cavity, sometimes termed "giant myxoma" (Figure 6). Rarely, they undergo calcification or osseous metaplasia[30-32] (Figure 7). Occasionally, they get infected[33-35] (Figure 8).

Histology

Histologically cardiac myxomas are mainly composed of stellated fusiform and polygonal cells immersed in an amorphous myxoid stroma[36] (Figure 9). Multinucleated cells are also observed. The cells are shaped and structured in chained rings or nests around the capillaries[37]. The surface of the tumour is often layered by flattened endothelium, while the tumour mass is infused liberally by thin-walled vessels lacking pericytes.

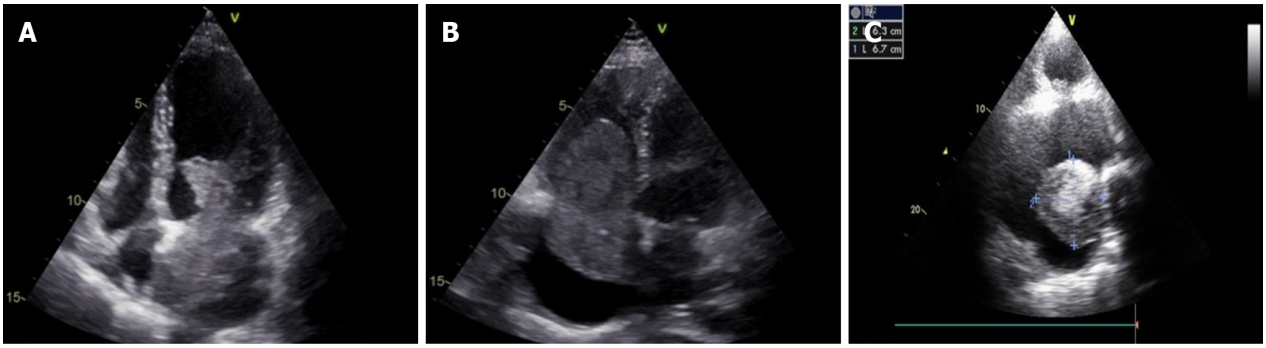

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Figure 1 Different locations of myxoma. A-C: Cardiac myxoma involving the left atrium (A and C) and the right atrium (B); A, B: The myxoma mass is attached to the atrial septum; C: The tumour is related to the lateral wall of left atrium.

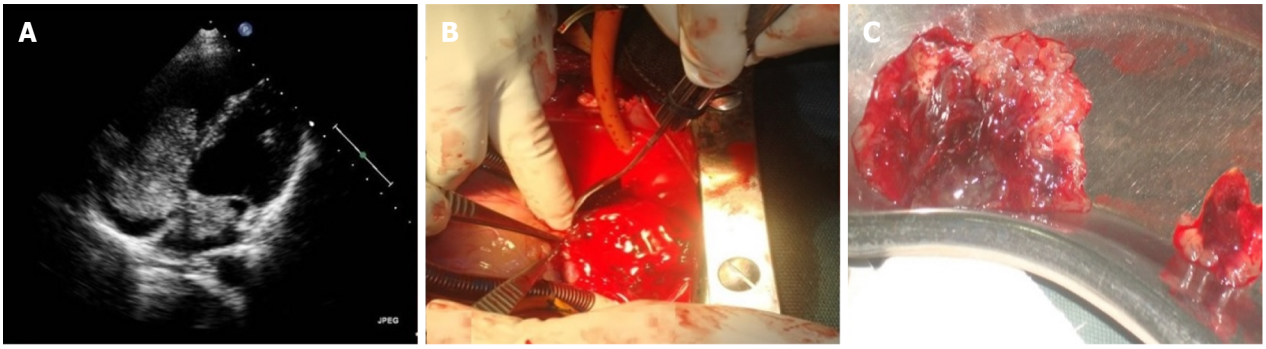

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Figure 2 Biatrial myxoma in a 22-yr-old Bangladeshi male. A: 2-D transthoracic echocardiography shows biatrial myxoma arising from the midinteratrial septum; B, C: Tumour mass during and after surgery.

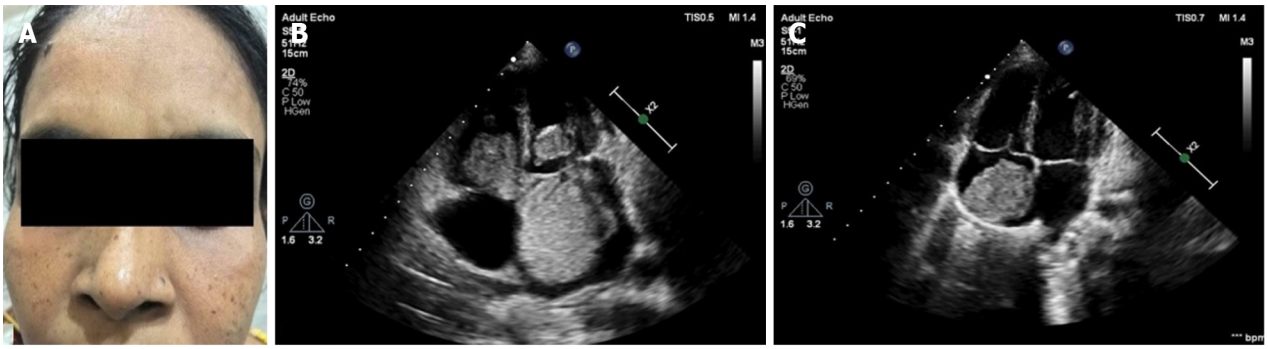

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Figure 3 Carney complex in a middle-aged Bangladeshi female. A: Multiple pigmented lentigines distributed symmetrically on the face of the patient; B: 2-D transthoracic echocardiography shows multichamber myxoma involving the left atrium, left ventricle and the right atrium; C: 2-D transthoracic echocardiography of the son of the lady shows myxoma in the right atrium.

Immunohistochemically, a wide array of biological molecules has been found to be related to the cardiac myxomas, including CD31, CD34, CD56, FVIIIAg, S-100 protein, calretinin, vimentin, desmin, smooth muscle myosin, α1 antitrypsin and alpha 1-antichymotrypsin[38].

The histogenesis of myxoma is poorly understood; however, the current opinion favours origin from primitive pluripotent mesenchymal cells. Genes encoding heart precursor markers may get reactivated and expressed in cardiac myxoma cells leading to differentiation along endothelial/endocardial lines [39]. Previously, myxomas were thought to arise from Prichard structures, the microscopic endocardial/endothelial structures lined by plump endothelial cells, located in the fossa ovalis[40,41]. Origin from neuroendocrine tissue was also proposed.

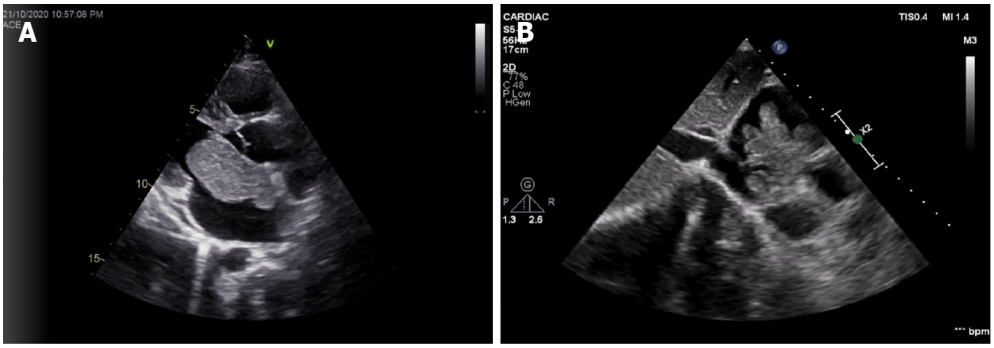

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Figure 4 Polypoid and papillary myxoma in 2D echocardiography. A: Parasternal long axis view shows a polypoid left atrial myxoma; B: Subcostal view shows a papillary right atrial myxoma with multiple projections.

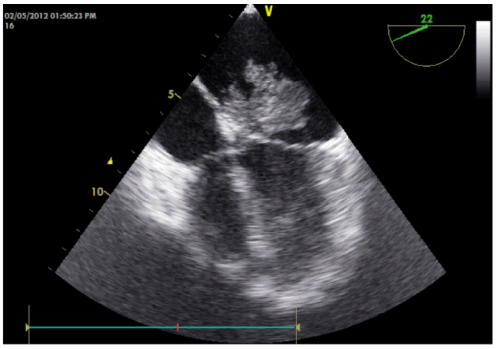

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Figure 5 Papillary myxoma presenting with ischemic stroke. Transesophageal echocardiography shows a fragile papillary myxoma. The young patient presented with acute ischemic stroke.

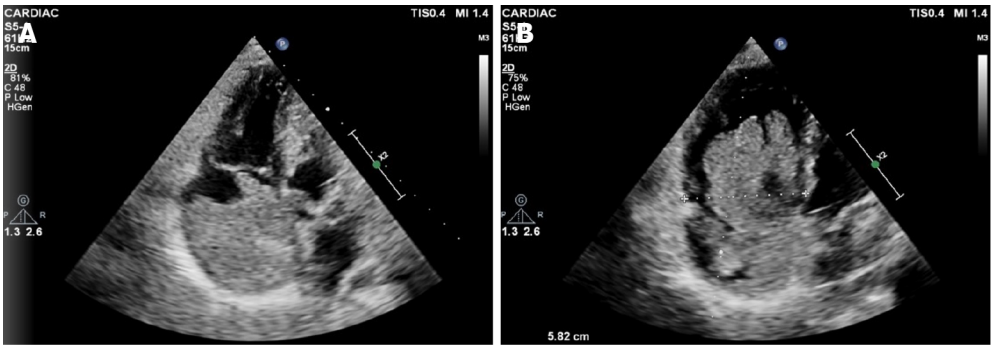

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Figure 6 Giant myxoma in right atrium. A, B: 2D transthoracic echocardiography shows a giant myxoma occupying the major parts of the right atrial cavity. Note the multiple papillary projections evident in (B).

Clinical presentation

The clinical presentation of cardiac myxoma depends on their location, size and mobility and is typified by the triad of intracardiac obstruction, embolisation and constitutional symptoms[6]. In a French series of 112 cases of cardiac myxoma, intracardiac obstruction in the form of mitral valve obstruction was the commonest manifestation (67%), followed by embolisation (29%) and constitutional symptoms (34%) [22].

Intracardiac obstruction: Intracardiac obstruction is common in polypoid myxoma. Because of preferential location, mitral valve pseudo-obstruction is the typical presentation[42-48]. Pulmonary hypertension may be present[43,47]. Valvular obstruction may even lead to syncope[46,49].

Right atrial myxomas may obstruct the tricuspid valve, the manifestation of which may be heart failure[50,51] or even collapse[52].

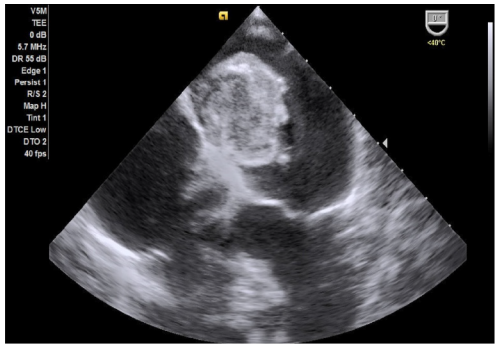

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Figure 7 Calcified myxoma in the left atrium. Transesophageal echocardiography shows a large calcified myxoma occupying the left atrial cavity.

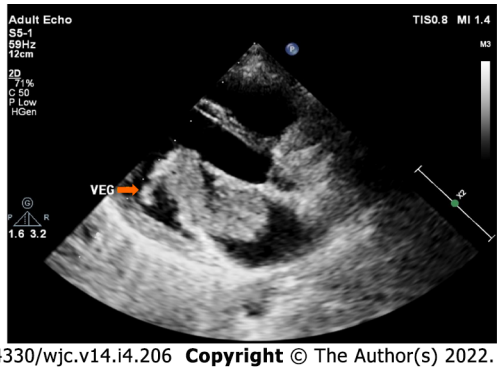

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Figure 8 Infected myxoma in the left atrium. Transthoracic echocardiography shows a large left atrial myxoma protruding into the left ventricular cavity across the mitral valve. A vegetation with independent mobility is attached to the tumour. The patient presented with prolonged fever with positive blood culture.

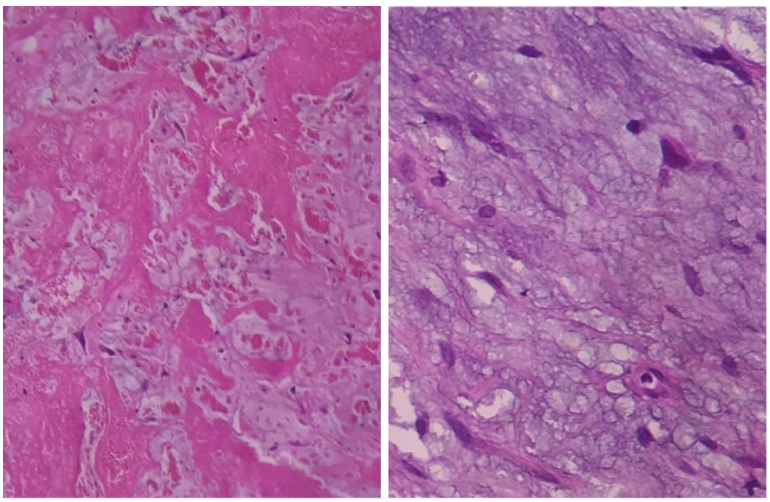

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Figure 9 Histopathology of myxoma. Histopathological examination shows abundant loose myxoid stroma with scattered round, polygonal or stellate cells with dense irregular nuclei.

Embolisation: Embolisation is typically a feature of papillary-type myxomas because of their loose consistency and fragility. Overall, embolism occurs in 30% to 40% of patients with myxomas[6]. The site of embolisation depends on the location of the tumours. Left atrial myxomas commonly embolise to the brain, causing ischaemic stroke and occasionally visual loss. Coronary, renal and limb arteries may also be affected. In a retrospective study of 162 patients with cardiac myxomas surgically treated between 1998 and 2014 in China, the embolic event was observed in 33 patients (20.4%), in the brain (15.43%), limb (3.70%), pulmonary (0.62%) and coronary (0.62%)[53]. Tumour location (atypical), macroscopic

appearance (irregular surface), mean platelet volume and high platelet count were strong risk factors for embolic events in patients with cardiac myxomas in this study. Cerebral embolisation is relatively common, leading to ischaemic stroke[54,55] and cerebral aneurysm formation[56]. Retinal artery occlusion and consequent visual loss have also been reported[57-60]. Coronary embolisation is a rare but well-documented and potentially fatal complication of cardiac myxomas[61-64]. Systemic embolisation may affect multiple sites, *e.g.*, coronaries, viscera and limbs[65-67]. Right-sided myxomas are less prone to embolisation. However, right atrial myxoma, when present, may cause a pulmonary embolism[68-73].

Cardiac myxomas may even embolise peroperatively, leading to complications. Right atrial myxoma was reported to embolise during surgical excision, causing pulmonary embolism and cardiogenic shock and subsequent recovery after removal of the tumour embolus from the pulmonary artery[74].

Constitutional symptoms: Cardiac myxomas are commonly associated with constitutional symptoms mimicking inflammatory or connective tissue disorders[75-77]. These symptoms are more common in women than in men, in right-sided myxomas than in left-sided ones and in large and multicentric myxomas[78]. Malaise, anorexia, fever, arthralgia and weight loss are common. The underlying pathophysiology may be releasing cytokines from the tumour, especially interleukin-6 (IL-6)[79]. In fact, IL-6 may be a more sensitive biomarker than C-reactive protein in predicting the inflammatory status of patients with cardiac myxomas. Sessile, irregular and voluminous tumours tend to be associated with higher circulating IL-6 levels[80]. Myxomas occasionally present with pyrexia of unknown origin[79, 81]. They may mimic bronchial asthma[82] or pulmonary tuberculosis[14]. Rarely, myxomas are associated with pleural effusion[14,83,84].

Infected myxoma: Occasionally, myxomas get infected, presenting with high fever and multiple embolic events[85-88] (Figure 8).

Cardiac myxoma in pregnancy: Occasionally, cardiac myxomas are diagnosed for the first time in pregnancy, mostly by echocardiography. Favourable maternal and foeto-neonatal outcomes with surgical management of cardiac myxoma in the pregnant patients have been reported in a recent review of 44 articles with 51 patients[89].

PHYSICAL EXAMINATION

Cardiac myxomas are typified by the triad of intracardiac obstruction, embolic manifestations and constitutional symptoms. However, because of heterogeneity in location, size, morphology and histopathology, they may remain entirely asymptomatic, present with classical manifestations or produce life-threatening emergency of systemic embolisation or even sudden cardiac death[90]. As little as 10% to as high as 50% of the myxomas may be diagnosed incidentally during clinical evaluation[91, 92]. General examination may reveal cachexia, fever, cyanosis, clubbing or rash. Neck veins may be engorged, and there may be a prominent A wave in the jugular venous pulse. Precordial findings may mimic mitral stenosis. The first heart sound (S1) may be loud and widely split because of the delay in the closure of the mitral valve due to the prolapse of the tumour into the mitral valve orifice. The pulmonary component of the second heart sound (P2) may be normal or loud depending on the presence of pulmonary hypertension. The characteristic "tumour plop" is a low-pitched early diastolic sound just after the S2. It may be confused with the opening snap of rheumatic mitral stenosis; however, the latter is high-pitched. It may be followed by a low-pitched diastolic murmur. The tumour plop is produced by the impact of the myxoma against the endocardial wall or when its excursion is halted. Also, a third heart sound (S3), fourth heart sound (S4) or a diastolic murmur of functional mitral or tricuspid stenosis may be audible. Occasionally, a systolic murmur of mitral or tricuspid regurgitation may be present. The auscultatory findings of cardiac myxomas characteristically change with changes in the position of the patient.

INVESTIGATIONS

Echocardiography is the critical investigation for the diagnosis of cardiac myxomas. Other imaging modalities like computed tomography (CT) scanning and magnetic resonance imaging play an ancillary role. Chest X-ray and electrocardiography are of limited value. Haematological investigations are also routinely done. Histopathology confirms the diagnosis. Genetic testing plays a vital role in familial cases of myxomas.

Echocardiography

Transthoracic echocardiography is the most practical investigation and often yields adequate information necessary for surgical resection. It makes the diagnosis and determines the location, size

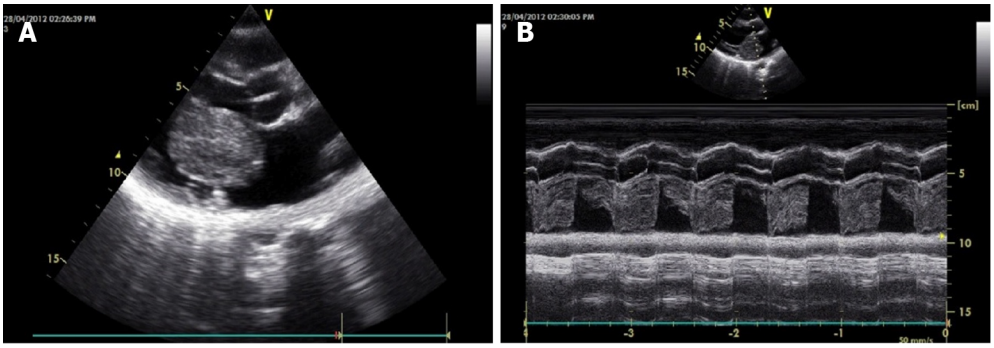

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Figure 10 Echocardiographic features of myxoma. A, B: Transthoracic echocardiography 2D (A) and M-mode (B) shows a large polypoid mass in the left atrial cavity attached to the interatrial septum by means of a stalk (not visualized here) and protruding into the left ventricular cavity across the mitral valve in diastole.

and shape of the tumour and its connections. Transesophageal echocardiography has a higher sensitivity and specificity and can detect small tumours, tumours located at atypical locations and possible multichamber myxomas[93-97].

Three-dimensional transthoracic echocardiography and transoesophageal echocardiography have also been used[98]. In a European study, transoesophageal echocardiography was superior to transthoracic echocardiography for myxoma detection (100% *vs* 95%) and attachment point identification (95.2% *vs* 64.5%)[99].

The classical features of an atrial myxoma in echocardiography include polypoid or papillary mass attached to the interatrial septum through a stalk and moving to and fro into the cavity, sometimes protruding into the corresponding ventricular cavity across the atrioventricular valve (Figure 10). Occasionally, the tumour mass may get areas of liquefaction or calcification. Doppler echocardiography shows the hemodynamic consequences of atrial myxoma.

During echocardiography, differentiation between myxoma and thrombus is of crucial importance. Myxomas typically have a stalk, a preference for limbus fossa ovalis of the atrial septum for stalk attachment and characteristic mobility. On the other hand, the thrombus is usually situated in the posterior portion of the atrium, has a preference for the atrial appendage, has a layered appearance and is most commonly seen in the presence of valvular mitral stenosis, atrial fibrillation and spontaneous echo contrast.

Contrast echocardiography can aid in the differential diagnosis of intracardiac masses based on perfusion of the mass. Malignant tumours are frequently highly vascular and present greater contrast enhancement than the adjacent myocardium, whereas myxomas demonstrate partial perfusion with lesser contrast enhancement than the adjoining myocardium. Thrombi, being avascular, show a complete absence of perfusion[100-102].

Despite the invaluable role of echocardiography and other imaging modalities, histopathological examination is the gold standard test for confirmation of the diagnosis of cardiac myxomas. A recently published study from Korea shows that out of 265 cases with an echocardiographic diagnosis of cardiac myxomas, 174 (65.7%) were surgically confirmed as myxomas. Compared with cardiac myxomas, other tumours were smaller and more frequently found in non-atrial sites[103].

ECG

ECG findings are nonspecific. Atrial enlargement or ventricular hypertrophy may be present. In contrast to the findings in mitral valve disease, atrial fibrillation is uncommon[6].

Other imaging modalities

Chest skiagram has a limited role. Occasionally, it can present features of mitral stenosis, *e.g.*, straightening of the left cardiac border and double contour of the right cardiac border and only rarely tumour calcification. Signs of pulmonary hypertension may be present.

Magnetic resonance imaging provides helpful information about the myxoma size, shape, surface characteristics and even its mobility on cine magnetic resonance gradient echo. The most frequent presentation is a mass isointense at T1-weighted and hyperintense at T2-weighted imaging with foci of hypointensity at one or two of these sequences[104]. Also, tissue characteristics can be used to differentiate a tumour from a thrombus.

CT scanning, generally, is not useful for the diagnosis of cardiac myxomas because it cannot reliably differentiate between myxomas and thrombi[105]. Typically, myxomas appear homogenous and isodense or as a slightly hypodense mass on non-contrast CT scanning, which does not show enhancement after iodinated contrast injection[106]. However, CT is the preferred technique to detect calcification, which is encountered in 10%–30% of cases[106,107].

Fluorodeoxyglucose positron emission tomography scanning is not typically indicated in the evaluation for myxoma[108].

Angiocardiography

Angiocardiography is seldom used for diagnosis of cardiac myxomas because of availability of non-invasive investigation modalities especially echocardiography. Also, manipulation of a catheter during angiocardiography carries a high risk of embolisation of tumour fragments[109,110]. In angiocardiography, cardiac myxomas typically appear as filling defects. In cases of left atrial myxoma, the levophase of a pulmonary angiogram may outline a radiolucent mass within the left atrium.

Genetic testing

Genetic testing for mutations in the *PRKAR1A* gene is increasingly used for diagnostic certainty of Carney complex.

Haematological tests

Erythrocyte sedimentation rate and C-reactive protein are generally elevated. Anaemia may be present. IL-6 rises especially when constitutional symptoms dominate.

TREATMENT

Cardiac myxoma needs surgical excision often on an emergency basis. This is to reduce the risk of embolisation of the tumour. Surgery is otherwise simple. The root of the stalk and the full thickness of the adjacent interatrial septum is excised, and the consequent atrial septal defect is closed accordingly. Data published over the past decades show excellent overall outcomes in operative mortality, short- and long-term survival and tumour recurrence[4,101-118]. Surgical excision of 23 myxomas in Turkey between 2010 and 2017 showed excellent outcomes with no early or late mortality[112]. A 16-year single centre study from China reported no need for secondary surgery in 97.4% ± 2.5% of cases after 10 years. Overall, the actuarial survival was 98.4% ± 1.6% at 5 years and 96.0% ± 2.8% at 10 years[113].

A similar encouraging outcome was observed in Italy; surgical excision of 98 cardiac myxomas between 1990 and 2007 showed 3% operative mortality. Actuarial survival was 98%, 98% and 89% at 5, 10 and 15 years, respectively. There was only one recurrence 68 mo after the first surgery[115].

In a smaller series of 18 patients treated surgically over 5 years in the United Kingdom, no death occurred within 30 d post-procedure[116]. Follow-up of surgical treatment of cardiac myxomas in Germany showed no in-hospital deaths. Out of 57 patients, 52 were alive at a median follow-up of 7.5 years[117]. Between 2002 and 2008, 34 cardiac myxomas were operated on in a single centre in Pakistan; 32 patients survived the surgery, 2 patients died over a median follow-up of 34 mo, and 1 patient had recurrence after 27 mo[118]. Twenty-four years of experience in 49 patients from Austria revealed relatively low early mortality of 2.0% and late mortality of 6.1%. The long-term prognosis was excellent, with an actuarial survival rate of 0.74. The rate of reoperations was low, with 2.0% after 24 years[4]. In a recently published small study from Bangladesh, all 20 patients with cardiac myxoma survived the surgery, and 1 patient presented with recurrence 28 mo after the surgery[111]. In recent years, cardiac myxomas have been excised successfully by minimally invasive surgery with or without robotic assistance[119-122]. Robotic surgery has been associated with early restoration of normal quality of life and early return to employment[121].

Utmost caution is warranted during surgical excision of cardiac myxomas because of their potential for embolisation peroperatively[74].

FAMILIAL CARDIAC MYXOMAS

Familial cardiac myxoma is rare and tend to form a syndrome, *e.g.*, Carney complex. They can usually be distinguished from the sporadic forms by the presentation at a younger age, the unusual location and multicentricity of the lesions and the presence of rare pathological conditions. In addition, a higher rate of recurrent lesions is usually associated with the familial forms of this disease. Carney complex is a rare multiple neoplasia syndrome, characterised by pigmented lesions of the skin and mucosa, cardiac and extra-cardiac myxomatous tumours and multiple endocrine and non-endocrine neoplasms (Figure 3) [123,124]. It is inherited as an autosomal-dominant disorder in three-fourths of the cases. In the remaining one-fourth, it occurs sporadically as a result of a de novo genetic mutation[125]. The disease is caused by inactivating mutations or large deletions of the *PRKAR1A* gene located at 17q22–24 coding for the regulatory subunit type I alpha of protein kinase A (*PKA*) gene[126]. Myxomatous tumours also occur in the skin and breast. Lentigines, blue nevus and cutaneous myxoma are the common skin manifestations (Figure 3). Primary pigmented nodular adrenocortical disease and thyroid nodules are examples of endocrinopathies[127,128].

Table 1 Diagnostic criteria for Carney complex

Diagnostic criteria
Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
Myxoma (cutaneous and mucosal)[1]
Cardiac myxoma[1]
Breast myxomatosis[1] or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
Primary pigmented nodular adrenocortical disease[1] or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test
Acromegaly due to growth hormone-producing adenoma[1]
Large cell calcifying Sertoli cell tumour[1] or characteristic calcification on testicular ultrasonography
Thyroid carcinoma[1] or multiple, hypoechoic nodules on thyroid ultrasonography, in a young patient
Psammomatous melanotic schwannoma[1]
Blue nevus, epithelioid blue nevus (multiple)[1]
Breast ductal adenoma (multiple)[1]
Osteochondromyxoma[1]
Supplemental criteria:
Affected first-degree relative
Inactivating mutation of the*PRKAR1A* gene

[1]With histologic confirmation.

The Carney complex is diagnosed by the diagnostic criteria defined by Stratakis *et al*[124] (Table 1). Making the diagnosis, required either: (1) Two of the twelve manifestations of the disease listed; or (2) One of the twelve manifestations and one of the supplemental criteria. Genetic testing for mutations in the *PRKAR1A* gene confirms the diagnosis. For management, cardiac myxoma needs surgical excision. Primary pigmented nodular adrenocortical disease and pituitary adenomas are managed surgically, or the latter can be managed with somatostatin analogues[129,130]. Prognosis is good at present; however, lifelong follow-up is indicated[126].

CONCLUSION

Cardiac myxomas are the commonest neoplasm of the heart. They are primarily sporadic but may be familial as Carney complex. Though histologically benign, myxomas are prone to cause intracardiac obstruction and embolisation. Associated constitutional features may mimic inflammatory and connective tissue disorders creating diagnostic dilemmas. Echocardiography is a versatile tool for making the diagnosis and choosing the optimum management strategy. Surgery is the mainstay of treatment with an excellent prognosis. Long-term follow-up is often needed to look for recurrence. Physicians should have appropriate preparedness to diagnose this uncommon entity. Only timely diagnosis and prompt surgery can reduce the morbidity and mortality of cardiac myxoma patients.

FOOTNOTES

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REFERENCES

1 **Velez Torres JM**, Martinez Duarte E, Diaz-Perez JA, Rosenberg AE. Cardiac Myxoma: Review and Update of Contemporary Immunohistochemical Markers and Molecular Pathology. *Adv Anat Pathol* 2020; **27**: 380-384 [PMID: 32732585 DOI: 10.1097/PAP.0000000000000275]
2 **Grebenc ML**, Rosado de Christenson ML, Burke AP, Green CE, Galvin JR. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. *Radiographics* 2000; **20**: 1073-103; quiz 1110 [PMID: 10903697 DOI: 10.1148/radiographics.20.4.g00jl081073]
3 **Yoon DH**, Roberts W. Sex distribution in cardiac myxomas. *Am J Cardiol* 2002; **90**: 563-565 [PMID: 12208428 DOI: 10.1016/s0002-9149(02)02540-7]
4 **Keeling IM**, Oberwalder P, Anelli-Monti M, Schuchlenz H, Demel U, Tilz GP, Rehak P, Rigler B. Cardiac myxomas: 24 years of experience in 49 patients. *Eur J Cardiothorac Surg* 2002; **22**: 971-977 [PMID: 12467822 DOI: 10.1016/s1010-7940(02)00592-4]
5 **Pérez-Andreu J**, Arribas Leal JM, Gervase G, Rivera-Caravaca JM, Cánovas López S, Marín F. Epidemiology of Cardiac Myxoma in a Spanish Population. A 30-year Surgical Series. *Rev Esp Cardiol (Engl Ed)* 2019; **72**: 685-686 [PMID: 30316755 DOI: 10.1016/j.rec.2018.08.021]
6 **Reynen K**. Cardiac myxomas. *N Engl J Med* 1995; **333**: 1610-1617 [PMID: 7477198 DOI: 10.1056/NEJM199512143332407]
7 **Wold LE**, Lie JT. Cardiac myxomas: a clinicopathologic profile. *Am J Pathol* 1980; **101**: 219-240 [PMID: 7446701 DOI: 10.1097/00000433-198012000-00019]
8 **GOLDBERG HP**, GLENN F, DOTTER CT, STEINBERG I. Myxoma of the left atrium; diagnosis made during life with operative and post-mortem findings. *Circulation* 1952; **6**: 762-767 [PMID: 12988355 DOI: 10.1161/01.cir.6.5.762]
9 **Hall RJ**, Cooley DA, McAllister HA Jr, Frazier OH. Neoplastic heart disease. In: Hurst JW, ed. The heart, arteries and veins. 7th ed. New York: McGraw-Hill, 1990:1382-403
10 **Silverman NA**. Primary cardiac tumors. *Ann Surg* 1980; **191**: 127-138 [PMID: 7362282 DOI: 10.1097/00000658-198002000-00001]
11 **McAllister HA**, Fenoglio JJ. Tumors of the cardiovascular system. Atlas of tumor pathology. 2nd Series. Fascicle 15. Washington, DC: Armed Forces Institute of Pathology, 1978:1-20
12 **Meller J**, Teichholz LE, Pichard AD, Matta R, Litwak R, Herman MV, Massie KF. Left ventricular myxoma: echocardiographic diagnosis and review of the literature. *Am J Med* 1977; **63**: 816-823 [PMID: 930952 DOI: 10.1016/0002-9343(77)90168-1]
13 **McCarthy PM**, Piehler JM, Schaff HV, Pluth JR, Orszulak TA, Vidaillet HJ Jr, Carney JA. The significance of multiple, recurrent, and "complex" cardiac myxomas. *J Thorac Cardiovasc Surg* 1986; **91**: 389-396 [PMID: 3951243 DOI: 10.1016/S0022-2828(86)80415-1]
14 **Islam AKMM**, Islam KS, Ananya KF, Uddin MJ. A Tuberculosis Case Is Discovered to Be Carney Complex Instead! *CASE (Phila)* 2020; **4**: 369-373 [PMID: 33117931 DOI: 10.1016/j.case.2020.05.010]
15 **Islam AM**, Rahman MT, Paul TK. Biatrial myxoma in a young male patient. *Korean Circ J* 2011; **41**: 770-771 [PMID: 22259612 DOI: 10.4070/kcj.2011.41.12.770]
16 **Dittmann H**, Voelker W, Karsch KR, Seipel L. Bilateral atrial myxomas detected by transesophageal two-dimensional echocardiography. *Am Heart J* 1989; **118**: 172-173 [PMID: 2741784 DOI: 10.1016/0002-8703(89)90088-4]
17 **Tway KP**, Shah AA, Rahimtoola SH. Multiple bilateral myxomas demonstrated by two-dimensional echocardiography. *Am J Med* 1981; **71**: 896-899 [PMID: 7304662 DOI: 10.1016/0002-9343(81)90394-6]
18 **Balk AH**, Wagenaar SS, Bruschke AV. Bilateral cardiac myxomas and peripheral myxomas in a patient with recent myocardial infarction. *Am J Cardiol* 1979; **44**: 767-770 [PMID: 484504 DOI: 10.1016/0002-9149(79)90300-x]
19 **Sharma SC**, Kulkarni A, Bhargava V, Modak A, Lashkare DV. Myxoma of tricuspid valve. *J Thorac Cardiovasc Surg* 1991; **101**: 938-940 [PMID: 2023454]
20 **Blondeau P**. Primary cardiac tumors--French studies of 533 cases. *Thorac Cardiovasc Surg* 1990; **38** Suppl 2: 192-195 [PMID: 2237901 DOI: 10.1055/s-2007-1014065]
21 **Sandrasagra FA**, Oliver WA, English TA. Myxoma of the mitral valve. *Br Heart J* 1979; **42**: 221-223 [PMID: 486284 DOI: 10.1136/hrt.42.2.221]
22 **Pinede L**, Duhaut P, Loire R. Clinical presentation of left atrial cardiac myxoma. A series of 112 consecutive cases. *Medicine (Baltimore)* 2001; **80**: 159-172 [PMID: 11388092 DOI: 10.1097/00005792-200105000-00002]
23 **Wan Y**, Du H, Zhang L, Guo S, Xu L, Li Y, He H, Zhou L, Chen Y, Mao L, Jin H, Hu B. Multiple cerebral metastases and metastatic aneurysms in patients with left atrial Myxoma: a case report. *BMC Neurol* 2019; **19**: 249 [PMID: 31646971 DOI: 10.1186/s12883-019-1474-4]
24 **Brinjikji W**, Morris JM, Brown RD, Thielen KR, Wald JT, Giannini C, Cloft HJ, Wood CP. Neuroimaging Findings in Cardiac Myxoma Patients: A Single-Center Case Series of 47 Patients. *Cerebrovasc Dis* 2015; **40**: 35-44 [PMID: 26068450 DOI: 10.1159/000381833]
25 **Zhan R**, Ji T, Fan Z, Pan D. Perplexing imaging manifestations of multiple metastatic intracranial lesions associated with atrial myxoma. *J Craniofac Surg* 2013; **24**: 651-652 [PMID: 23524767 DOI: 10.1097/SCS.0b013e318264690f]

26 **Raza E**, Kamal AK. Recurrent non-aneurysmal, metastatic intraparenchymal haemorrhages following resection of atrial myxoma - case report and literature review. *BMJ Case Rep* 2012; **2012** [PMID: 23104629 DOI: 10.1136/bcr.02.2012.5772]

27 **Moiyadi AV**, Moiyadi AA, Sampath S, Kalpana SR, Mahadevan A, Shankar SK, Srikanth SG. Intracranial metastasis from a glandular variant of atrial myxoma. *Acta Neurochir (Wien)* 2007; **149**: 1157-1162 [PMID: 17906966 DOI: 10.1007/s00701-007-1291-1]

28 **Hirsch BE**, Sehkar L, Kamerer DB. Metastatic atrial myxoma to the temporal bone: case report. *Am J Otol* 1991; **12**: 207-209 [PMID: 1882971]

29 **Okada N**, Yamamura T, Kitano Y, Nakamura T, Kamido H, Matsuzawa Y, Katayama S, Ohara K. Metastasizing atrial myxoma: a case with multiple subcutaneous tumours. *Br J Dermatol* 1986; **115**: 239-242 [PMID: 3741787 DOI: 10.1111/j.1365-2133.1986.tb05724.x]

30 **Cervetti MR**, Camporrotondo M, Clusa NM, Navia D. Advanced calcification of a left atrial myxoma. *Eur J Cardiothorac Surg* 2020; **57**: 196 [PMID: 31168588 DOI: 10.1093/ejcts/ezz175]

31 **Singh SK**, Kumar A, Tewarson V, Rani AK, Chandra S, Puri A. Calcified left atrial myxoma with osseous metaplasia. *Indian J Chest Dis Allied Sci* 2012; **54**: 201-203 [PMID: 23008931]

32 **Weiss SL**, Russell HM, Lay A, Backer CL. Calcified right atrial myxoma in an adolescent. *World J Pediatr Congenit Heart Surg* 2011; **2**: 523-525 [PMID: 23804011 DOI: 10.1177/2150135111405857]

33 **Patel N**, Arkonac D, Aoi S, Finkielstein D. Infective Endocarditis of a Left Ventricular Myxoma in a Heroin User. *Tex Heart Inst J* 2019; **46**: 215-218 [PMID: 31708707 DOI: 10.14503/THIJ-17-6235]

34 **Yuan SM**. Infected Cardiac Myxoma: an Updated Review. *Braz J Cardiovasc Surg* 2015; **30**: 571-578 [PMID: 26735605 DOI: 10.5935/1678-9741.20140112]

35 **Revankar SG**, Clark RA. Infected cardiac myxoma. Case report and literature review. *Medicine (Baltimore)* 1998; **77**: 337-344 [PMID: 9772922 DOI: 10.1097/00005792-199809000-00003]

36 **Burke AP**, Tazeelar H, Gomez-Roman J, Loire R, Araoz PA. Benign tumours of pluripotent mesenchyme. In: Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, eds. World Health Organization tumours of the lung, pleura, thymus and heart. Lyon: IARC Press, 2004; 260-265

37 **Altundag MB**, Ertas G, Ucer AR, Durmus S, Abanuz H, Calikoğlu T, Ozbagi K, Demirkasimoglu A, Kaya B, Bakkal BH, Altundag K. Brain metastasis of cardiac myxoma: case report and review of the literature. *J Neurooncol* 2005; **75**: 181-184 [PMID: 16132507 DOI: 10.1007/s11060-005-1859-7]

38 **Hernández-Bringas O**, Ortiz-Hidalgo C. [Histopathological and immunohistochemical features of cardiac myxomas]. *Arch Cardiol Mex* 2013; **83**: 199-208 [PMID: 23663893 DOI: 10.1016/j.acmx.2013.02.002]

39 **Di Vito A**, Mignogna C, Donato G. The mysterious pathways of cardiac myxomas: a review of histogenesis, pathogenesis and pathology. *Histopathology* 2015; **66**: 321-332 [PMID: 25297937 DOI: 10.1111/his.12531]

40 **PRICHARD RW**. Tumors of the heart; review of the subject and report of 150 cases. *AMA Arch Pathol* 1951; **51**: 98-128 [PMID: 14789340]

41 **Krikler DM**, Rode J, Davies MJ, Woolf N, Moss E. Atrial myxoma: a tumour in search of its origins. *Br Heart J* 1992; **67**: 89-91 [PMID: 1531423 DOI: 10.1136/hrt.67.1.89]

42 **Theodoropoulos KC**, Masoero G, Pagnano G, Walker N, Papachristidis A, Monaghan MJ. Mitral pseudostenosis due to a large left atrial myxoma. *J Geriatr Cardiol* 2018; **15**: 244-245 [PMID: 29721006 DOI: 10.11909/j.issn.1671-5411.2018.03.009]

43 **Shimizu Y**, Itoda Y, Higashikuni Y, Kadowaki Y, Saito A, Fujita H, Yamashita H, Watanabe M, Ono M, Komuro I. Giant left atrial myxoma that caused mitral valve obstruction and pulmonary hypertension. *Int J Cardiol* 2015; **199**: 38-39 [PMID: 26186627 DOI: 10.1016/j.ijcard.2015.06.158]

44 **Avakian SD**, Takada JY, Mansur Ade P. Giant obstructive left atrial myxoma resembling mitral valve stenosis. *Clinics (Sao Paulo)* 2012; **67**: 853-854 [PMID: 22892935 DOI: 10.6061/clinics/2012(07)25]

45 **Baztarrica GP**, Salvaggio F, Porcile R. [Severe mitral valve stenosis caused by giant left atrial myxoma]. *G Ital Cardiol (Rome)* 2012; **13**: 71-72 [PMID: 22690391]

46 **Strecker T**, Agaimy A. Giant left atrial myxoma causing drop attacks by prolapsing into the mitral valve. *Int J Clin Exp Pathol* 2012; **5**: 996-999 [PMID: 23119119]

47 **Buyukates M**, Aktunc E. Giant left atrial myxoma causing mitral valve obstruction and pulmonary hypertension. *Can J Surg* 2008; **51**: E97-E98 [PMID: 18815642]

48 **Thangaroopan M**, Chiu B, Thangaroopan N, Mullen J, Kasa L. Large left atrial myxoma causing mitral valve obstruction: diagnosis by computed tomography. *J Card Surg* 2006; **21**: 508-510 [PMID: 16948774 DOI: 10.1111/j.1540-8191.2006.00287.x]

49 **Rajani AR**, Muaz RN, Govindaswamy PR, Mian MH. Arrhythmias are not to blame for all cardiac syncope patients: left atrial myxoma causing syncope in a middle-aged man. *BMJ Case Rep* 2015; **2015** [PMID: 25878232 DOI: 10.1136/bcr-2014-209119]

50 **Agstam S**, Kumar B, Dahiya N, Guleria VS. Giant right atrial myxoma presenting as right heart failure: a rare manifestation. *BMJ Case Rep* 2020; **13** [PMID: 32193186 DOI: 10.1136/bcr-2019-230461]

51 **Alamri Y**, Lau YY, Lainchbury J. Large right atrial myxoma presenting with heart failure. *ANZ J Surg* 2019; **89**: 1341-1342 [PMID: 29984482 DOI: 10.1111/ans.14720]

52 **Agrawal R**, Sharma A, Nath RK, Pandit BN. Massive right atrial myxoma presenting as congestive heart failure: an unusual presentation of a rare tumour. *BMJ Case Rep* 2018; **2018** [PMID: 29666089 DOI: 10.1136/bcr-2017-223903]

53 **He DK**, Zhang YF, Liang Y, Ye SX, Wang C, Kang B, Wang ZN. Risk factors for embolism in cardiac myxoma: a retrospective analysis. *Med Sci Monit* 2015; **21**: 1146-1154 [PMID: 25900256 DOI: 10.12659/MSM.893855]

54 **Ihsen Z**, Hela M, Khadija M, Zouhayer J. Cerebral embolism complicating left atrial myxoma: a case report. *Pan Afr Med J* 2016; **24**: 140 [PMID: 27642478 DOI: 10.11604/pamj.2016.24.140.9778]

55 **Al-Mateen M**, Hood M, Trippel D, Insalaco SJ, Otto RK, Vitikainen KJ. Cerebral embolism from atrial myxoma in pediatric patients. *Pediatrics* 2003; **112**: e162-e167 [PMID: 12897323 DOI: 10.1542/peds.112.2.e162]

56 **Alrohimi A**, Putko BN, Jeffery D, Van Dijk R, Chow M, McCombe JA. Cerebral Aneurysm in Association with Left Atrial Myxoma. *Can J Neurol Sci* 2019; **46**: 637-639 [PMID: 31203822 DOI: 10.1017/cjn.2019.59]

57 **Galvez-Ruiz A**, Galindo-Ferreiro A, Lehner AJ, Kozac I. Clinical presentation of multiple cerebral emboli and central retinal artery occlusion (CRAO) as signs of cardiac myxoma. *Saudi J Ophthalmol* 2018; **32**: 151-155 [PMID: 29942186 DOI: 10.1016/j.sjopt.2017.09.001]

58 **Shin YT**, Kim JH, Park DH, Shin JP, Kim IT. Central Retinal Artery Occlusion by Left Atrial Myxoma. *Korean J Ophthalmol* 2017; **31**: 88-89 [PMID: 28243029 DOI: 10.3341/kjo.2017.31.1.88]

59 **Kim JH**, Youn HJ, Jung MH, Oh CY, Ahn SH, Cho WH, Lee JH, Lee YS, Hyun HJ. Retinal artery occlusion by left atrial myxoma misdiagnosed as thrombus. *Springerplus* 2016; **5**: 352 [PMID: 27064439 DOI: 10.1186/s40064-016-1990-2]

60 **Yu Y**, Zhu Y, Dong A, Su Z. Retinal artery occlusion as the manifestation of left atrial myxoma: a case report. *BMC Ophthalmol* 2014; **14**: 164 [PMID: 25539990 DOI: 10.1186/1471-2415-14-164]

61 **Peters MJ**, Tuwairqi KW, Farah MG. A Case of Infected Left Atrial Myxoma Presenting as ST-Elevation Myocardial Infarction (STEMI). *Am J Case Rep* 2019; **20**: 1930-1935 [PMID: 31871313 DOI: 10.12659/AJCR.918192]

62 **Chaudhuri AA**, Simmons C Jr, Ellison D, Hemp J, Chung K. Atrial Myxoma Presenting as Myocardial Infarction Diagnosed by Echocardiography, Managed Endoscopically with Robot-Assisted Surgery. *Cureus* 2016; **8**: e484 [PMID: 27014518 DOI: 10.7759/cureus.484]

63 **Marta L**, Peres M, Alves M, Ferreira da Silva G. [Giant left atrial myxoma presenting as acute myocardial infarction]. *Rev Port Cardiol* 2012; **31**: 815-819 [PMID: 23138051 DOI: 10.1016/j.repc.2012.04.013]

64 **Braun S**, Schrötter H, Reynen K, Schwencke C, Strasser RH. Myocardial infarction as complication of left atrial myxoma. *Int J Cardiol* 2005; **101**: 115-121 [PMID: 15860393 DOI: 10.1016/j.ijcard.2004.08.047]

65 **Latifi AN**, Ibe U, Gnanaraj J. A case report of atrial myxoma presenting with systemic embolization and myocardial infarction. *Eur Heart J Case Rep* 2019; **3**: ytz104 [PMID: 31660480 DOI: 10.1093/ehjcr/ytz104]

66 **Wu Y**, Fu XM, Liao XB, Zhou X. Stroke and peripheral embolisms in a pediatric patient with giant atrial myxoma: Case report and review of current literature. *Medicine (Baltimore)* 2018; **97**: e11653 [PMID: 30045317 DOI: 10.1097/MD.0000000000011653]

67 **Bernatchez J**, Gaudreault V, Vincent G, Rheaume P. Left Atrial Myxoma Presenting as an Embolic Shower: A Case Report and Review of Literature. *Ann Vasc Surg* 2018; **53**: 266.e13-266.e20 [PMID: 30012450 DOI: 10.1016/j.avsg.2018.04.024]

68 **Ma G**, Wang D, He Y, Zhang R, Zhou Y, Ying K. Pulmonary embolism as the initial manifestation of right atrial myxoma: A case report and review of the literature. *Medicine (Baltimore)* 2019; **98**: e18386 [PMID: 31861001 DOI: 10.1097/MD.0000000000018386]

69 **Pandey AC**, Carey JJ, Thompson JL. Right atrial myxoma presenting as a pulmonary embolism in a 32-year-old female. *JRSM Cardiovasc Dis* 2019; **8**: 2048004018817606 [PMID: 31019681 DOI: 10.1177/2048004018817606]

70 **Kurnicka K**, Domienik-Karłowicz J, Ciurzyński M, Biederman A, Pruszczyk P. Right atrial myxoma with pulmonary embolism. *Kardiol Pol* 2015; **73**: 298 [PMID: 25892262 DOI: 10.5603/KP.2015.0058]

71 **Aydın C**, Taşal A, Ay Y, Vatankulu MA, Inan B, Bacaksız A. A giant right atrial villous myxoma with simultaneous pulmonary embolism. *Int J Surg Case Rep* 2014; **5**: 206-208 [PMID: 24657800 DOI: 10.1016/j.ijscr.2013.11.014]

72 **Subban V**, Lakshmanan A, Sethurathinam R, Ajit MS. Right atrial myxoma--an unusual cause of pulmonary embolism. *J Card Surg* 2012; **27**: 604 [PMID: 22372852 DOI: 10.1111/j.1540-8191.2011.01414.x]

73 **Cheema U**, Thomas J. A giant right atrial myxoma presenting as acute pulmonary emboli. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 799 [PMID: 22514010 DOI: 10.1093/ehjci/jes080]

74 **Papadopoulos K**, Alexiou C, Ozden Tok O, Vannan MA. Intraoperative embolism of a right atrial myxoma: a case report. *Eur Heart J Case Rep* 2020; **4**: 1-4 [PMID: 33442600 DOI: 10.1093/ehjcr/ytaa476]

75 **Garcia-Carretero R**, Naranjo-Mansilla G, Luna-Heredia E, Arias-Baldo P, Beamonte-Vela BN. Incidental Finding of a Left Atrial Myxoma While Characterising an Autoimmune Disease. *J Crit Care Med (Targu Mures)* 2018; **4**: 64-67 [PMID: 30581997 DOI: 10.2478/jccm-2018-0009]

76 **Moreno-Ariño M**, Ortiz-Santamaria V, Deudero Infante A, Ayats Delgado M, Novell Teixidó F. A classic mimicker of systemic vasculitis. *Reumatol Clin* 2016; **12**: 103-106 [PMID: 25935820 DOI: 10.1016/j.reuma.2015.03.006]

77 **Lazaros G**, Masoura C, Brili S, Stavropoulos G, Kafiri G, Stefanadis C. Large left atrial myxoma in an oligosymptomatic young woman. *Hellenic J Cardiol* 2013; **54**: 60-63 [PMID: 23340131]

78 **Endo A**, Ohtahara A, Kinugawa T, Ogino K, Hisatome I, Shigemasa C. Characteristics of cardiac myxoma with constitutional signs: a multicenter study in Japan. *Clin Cardiol* 2002; **25**: 367-370 [PMID: 12173903 DOI: 10.1002/clc.4950250805]

79 **Gavrielatos G**, Letsas KP, Pappas LK, Dedeilias P, Sioras E, Kardaras F. Large left atrial myxoma presented as fever of unknown origin: a challenging diagnosis and a review of the literature. *Cardiovasc Pathol* 2007; **16**: 365-367 [PMID: 18005878 DOI: 10.1016/j.carpath.2007.01.001]

80 **Yuan SM**, Lin HZ. Predictors of Normalization of Circulating Interleukin-6 after Cardiac Myxoma Resection. *Braz J Cardiovasc Surg* 2019; **34**: 22-27 [PMID: 30810670 DOI: 10.21470/1678-9741-2018-0161]

81 **Lin JN**, Lai CH, Lu LF, Lin HH. Fever of unknown origin from a left atrial myxoma: an immunologic basis and cytokine association. *South Med J* 2011; **104**: 360-362 [PMID: 21606720 DOI: 10.1097/SMJ.0b013e3182142bbd]

82 **Zuwasti U**, Quarrie R, Allen E, Haas C. Severe functional mitral stenosis due to a left atrial myxoma masquerading as asthma. *BMJ Case Rep* 2020; **13** [PMID: 33334748 DOI: 10.1136/bcr-2020-236876]

83 **Cakar MA**, Arslan C, Yildiz A, Vatan MB, Gunduz H. Left atrial myxoma with pleural effusion. *J Clin Med Res* 2009; **1**: 297-299 [PMID: 22481994 DOI: 10.4021/jocmr2009.11.1269]

84 **Strâmbu I**, Ilieşiu A, Creţul R, Stoicescu IP. [Recurrent pleural effusion revealing a left atrial myxoma]. *Pneumologia* 2002; **51**: 54-58 [PMID: 12043278]

85 **Yalta K**, Ozturk C, Yalta T, Yetkin E. Systemic Inflammation in the Setting of Cardiac Myxomas: an Overview of Clinical and Practical Considerations. *Korean Circ J* 2021; **51**: 784-786 [PMID: 34494408 DOI: 10.4070/kcj.2021.0241]

86 **Nagata T**, Totsugawa T, Katayama K, Kuinose M, Yoshitaka H, Uesugi T. Infected cardiac myxoma. *J Card Surg* 2013; **28**: 682-684 [PMID: 23931763 DOI: 10.1111/jocs.12184]

87 **Leone S**, dell'aquila G, Giglio S, Magliocca M, Maio P, Nigro FS, Pacifico P, De Chiara G, Acone N. Infected atrial myxoma: case report and literature review. *Infez Med* 2007; **15**: 256-261 [PMID: 18162737]

88 **Uchino K**, Mochida Y, Ebina T, Tobe M, Kobayashi S, Yano Y, Kobayashi T, Nakazawa I, Ishikawa T, Kimura K, Takanashi Y, Umemura S. Infected left atrial myxoma. *Intern Med* 2002; **41**: 957-960 [PMID: 12487167 DOI: 10.2169/internalmedicine.41.957]

89 **Yuan SM**. Cardiac myxoma in pregnancy: a comprehensive review. *Rev Bras Cir Cardiovasc* 2015; **30**: 386-394 [PMID: 26313731 DOI: 10.5935/1678-9741.20150012]

90 **Rios RE**, Burmeister DB, Bean EW. Complications of atrial myxoma. *Am J Emerg Med* 2016; **34**: 2465.e1-2465.e2 [PMID: 27324853 DOI: 10.1016/j.ajem.2016.05.079]

91 **Gošev I**, Paić F, Durić Z, Gošev M, Ivčević S, Jakuš FB, Biočina B. Cardiac myxoma the great imitators: comprehensive histopathological and molecular approach. *Int J Cardiol* 2013; **164**: 7-20 [PMID: 22243936 DOI: 10.1016/j.ijcard.2011.12.052]

92 **Beghetti M**, Gow RM, Haney I, Mawson J, Williams WG, Freedom RM. Pediatric primary benign cardiac tumors: a 15-year review. *Am Heart J* 1997; **134**: 1107-1114 [PMID: 9424072 DOI: 10.1016/s0002-8703(97)70032-2]

93 **Obeid AI**, Marvasti M, Parker F, Rosenberg J. Comparison of transthoracic and transesophageal echocardiography in diagnosis of left atrial myxoma. *Am J Cardiol* 1989; **63**: 1006-1008 [PMID: 2929455 DOI: 10.1016/0002-9149(89)90162-8]

94 **Gadhinglajkar S**, Sreedhar R. Intraoperative evaluation of left atrial myxoma using real-time 3D transesophageal echocardiography. *Ann Card Anaesth* 2010; **13**: 180-181 [PMID: 20442555 DOI: 10.4103/0971-9784.62937]

95 **Gadhinglajkar S**, Sreedhar R. Utility of transoesophageal echocardiography during surgery on left atrial myxoma. *Ann Card Anaesth* 2008; **11**: 142-143 [PMID: 18603766 DOI: 10.4103/0971-9784.41599]

96 **Srivastava R**, Hsiung MC, Fadel A, Nanda NC. Transesophageal echocardiographic demonstration of biatrial myxoma. *Echocardiography* 2004; **21**: 187-188 [PMID: 14961801 DOI: 10.1111/j.0742-2822.2004.03090.x]

97 **Pérez de Isla L**, de Castro R, Zamorano JL, Almería C, Moreno R, Moreno M, Lima P, García Fernández MA. Diagnosis and treatment of cardiac myxomas by transesophageal echocardiography. *Am J Cardiol* 2002; **90**: 1419-1421 [PMID: 12480063 DOI: 10.1016/s0002-9149(02)02891-6]

98 **Tolstrup K**, Shiota T, Gurudevan S, Luthringer D, Luo H, Siegel RJ. Left atrial myxomas: correlation of two-dimensional and live three-dimensional transesophageal echocardiography with the clinical and pathologic findings. *J Am Soc Echocardiogr* 2011; **24**: 618-624 [PMID: 21367578 DOI: 10.1016/j.echo.2011.01.007]

99 **Engberding R**, Daniel WG, Erbel R, Kasper W, Lestuzzi C, Curtius JM, Sutherland GR, Lambertz H, von Hehn A, Lesbre JP. Diagnosis of heart tumours by transoesophageal echocardiography: a multicentre study in 154 patients. European Cooperative Study Group. *Eur Heart J* 1993; **14**: 1223-1228 [PMID: 8223737 DOI: 10.1093/eurheartj/14.9.1223]

100 **Bhattacharyya S**, Khattar R, Senior R. Characterisation of intra-cardiac masses by myocardial contrast echocardiography. *Int J Cardiol* 2013; **163**: e11-e13 [PMID: 22805540 DOI: 10.1016/j.ijcard.2012.06.098]

101 **Uenishi EK**, Caldas MA, Saroute AN, Tsutsui JM, Piotto GH, Falcão SN, Mathias W Jr. Contrast echocardiography for the evaluation of tumors and thrombi. *Arq Bras Cardiol* 2008; **91**: e48-e52 [PMID: 19142370 DOI: 10.1590/s0066-782x2008001700015]

102 **Kirkpatrick JN**, Wong T, Bednarz JE, Spencer KT, Sugeng L, Ward RP, DeCara JM, Weinert L, Krausz T, Lang RM. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. *J Am Coll Cardiol* 2004; **43**: 1412-1419 [PMID: 15093876 DOI: 10.1016/j.jacc.2003.09.065]

103 **Lee SH**, Park JS, Park JH, Chin JY, Yoon WS, Kim HY, Cho JY, Kim KH, Kim WH. Comparison of Clinical and Echocardiographic Characteristics between Cardiac Myxomas and Masses Mimicking Myxoma. *Korean Circ J* 2020; **50**: 822-832 [PMID: 32725996 DOI: 10.4070/kcj.2020.0024]

104 **Colin GC**, Dymarkowski S, Gerber B, Michoux N, Bogaert J. Cardiac myxoma imaging features and tissue characteristics at cardiovascular magnetic resonance. *Int J Cardiol* 2016; **202**: 950-951 [PMID: 26493410 DOI: 10.1016/j.ijcard.2015.10.111]

105 **Scheffel H**, Baumueller S, Stolzmann P, Leschka S, Plass A, Alkadhi H, Schertler T. Atrial myxomas and thrombi: comparison of imaging features on CT. *AJR Am J Roentgenol* 2009; **192**: 639-645 [PMID: 19234259 DOI: 10.2214/AJR.08.1694]

106 **Shin W**, Choe YH, Kim SM, Song IY, Kim SS. Detection of cardiac myxomas with non-contrast chest CT. *Acta Radiol* 2014; **55**: 273-278 [PMID: 23926237 DOI: 10.1177/0284185113496561]

107 **Grebenc ML**, Rosado-de-Christenson ML, Green CE, Burke AP, Galvin JR. Cardiac myxoma: imaging features in 83 patients. *Radiographics* 2002; **22**: 673-689 [PMID: 12006696 DOI: 10.1148/radiographics.22.3.g02ma02673]

108 **Colin GC**, Gerber BL, Amzulescu M, Bogaert J. Cardiac myxoma: a contemporary multimodality imaging review. *Int J Cardiovasc Imaging* 2018; **34**: 1789-1808 [PMID: 29974293 DOI: 10.1007/s10554-018-1396-z]

109 **Wagner WL**, Manz M, Steudel A, Kirchhoff PG, Lüderitz B. [Noninvasive diagnosis of bilocular left atrial and right ventricular myxoma of the heart]. *Z Kardiol* 1988; **77**: 251-255 [PMID: 3388940]

110 **Pindyck F**, Peirce EC 2nd, Baron MG, Lukban SB. Embolization of left atrial myxoma after transseptal cardiac cathertization. *Am J Cardiol* 1972; **30**: 569-571 [PMID: 5073672 DOI: 10.1016/0002-9149(72)90052-5]

111 **Hosain N**, Quaium Chowdhury MA, Maruf MF, Chowdhury MR, Barua S, Rahman M. Surgical Treatment of Atrial Myxomas: Outstanding Outcome of a Treacherous Tumor. *CJC Open* 2021; **3**: 354-360 [PMID: 33778452 DOI: 10.1016/j.cjco.2020.10.021]

112 **Gür AK**, Aykaç MC. Surgical Treatment of Cardiac Myxomas: A 23-Case Experience. *Heart Surg Forum* 2018; **21**: E370-E374 [PMID: 30311887 DOI: 10.1532/hsf.1987]

113 **Lin Y**, Xiao J, Chen J, Hong J, Peng H, Kang B, Wu L, Wang Z. Treating cardiac myxomas: a 16-year Chinese single-center study. *J Cardiovasc Med (Hagerstown)* 2016; **17**: 44-53 [PMID: 24933197 DOI:

10.2459/JCM.0000000000000114]
114 **Vroomen M**, Houthuizen P, Khamooshian A, Soliman Hamad MA, van Straten AH. Long-term follow-up of 82 patients after surgical excision of atrial myxomas. *Interact Cardiovasc Thorac Surg* 2015; **21**: 183-188 [PMID: 25972592 DOI: 10.1093/icvts/ivv125]
115 **Garatti A**, Nano G, Canziani A, Gagliardotto P, Mossuto E, Frigiola A, Menicanti L. Surgical excision of cardiac myxomas: twenty years experience at a single institution. *Ann Thorac Surg* 2012; **93**: 825-831 [PMID: 22296980 DOI: 10.1016/j.athoracsur.2011.11.009]
116 **Owers CE**, Vaughan P, Braidley PC, Wilkinson GA, Locke TJ, Cooper GJ, Briffa NP, Hopkinson DN, Sarkar PK. Atrial myxomas: a single unit's experience in the modern era. *Heart Surg Forum* 2011; **14**: E105-E109 [PMID: 21521672 DOI: 10.1532/HSF98.20101163]
117 **Kuroczyński W**, Peivandi AA, Ewald P, Pruefer D, Heinemann M, Vahl CF. Cardiac myxomas: short- and long-term follow-up. *Cardiol J* 2009; **16**: 447-454 [PMID: 19753524]
118 **Khan MA**, Khan AA, Waseem M. Surgical experience with cardiac myxomas. *J Ayub Med Coll Abbottabad* 2008; **20**: 76-79 [PMID: 19385463]
119 **Dang QH**, Le NT, Tran DD, Ngo TH. Totally Endoscopic Resection of Giant Left Atrial Myxoma Without Robotic Assistance. *Innovations (Phila)* 2018; **13**: 136-139 [PMID: 29688943 DOI: 10.1097/IMI.0000000000000487]
120 **Onan B**, Kahraman Z, Erturk M, Erkanli K. Robotic resection of giant left ventricular myxoma causing outflow tract obstruction. *J Card Surg* 2017; **32**: 281-284 [PMID: 28417503 DOI: 10.1111/jocs.13128]
121 **Yang M**, Yao M, Wang G, Xiao C, Wu Y, Zhang H, Gao C. Comparison of postoperative quality of life for patients who undergo atrial myxoma excision with robotically assisted versus conventional surgery. *J Thorac Cardiovasc Surg* 2015; **150**: 152-157 [PMID: 25769777 DOI: 10.1016/j.jtcvs.2015.01.056]
122 **Schilling J**, Engel AM, Hassan M, Smith JM. Robotic excision of atrial myxoma. *J Card Surg* 2012; **27**: 423-426 [PMID: 22640373 DOI: 10.1111/j.1540-8191.2012.01478.x]
123 **Sandrini F**, Stratakis C. Clinical and molecular genetics of Carney complex. *Mol Genet Metab* 2003; **78**: 83-92 [PMID: 12666684 DOI: 10.1016/s1096-7192(03)00006-4]
124 **Stratakis CA**, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J Clin Endocrinol Metab* 2001; **86**: 4041-4046 [PMID: 11549623 DOI: 10.1210/jcem.86.9.7903]
125 **Kirschner LS**, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nat Genet* 2000; **26**: 89-92 [PMID: 10973256 DOI: 10.1038/79238]
126 **Correa R**, Salpea P, Stratakis CA. Carney complex: an update. *Eur J Endocrinol* 2015; **173**: M85-M97 [PMID: 26130139 DOI: 10.1530/EJE-15-0209]
127 **Stratakis CA**, Raygada M. Carney Complex. 2003 Feb 5. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993– [PMID: 20301463]
128 **Stratakis CA**. Hereditary syndromes predisposing to endocrine tumors and their skin manifestations. *Rev Endocr Metab Disord* 2016; **17**: 381-388 [PMID: 27943006 DOI: 10.1007/s11154-016-9401-0]
129 **Stratakis CA**. Genetics of Carney complex and related familial lentiginoses, and other multiple tumor syndromes. *Front Biosci* 2000; **5**: D353-D366 [PMID: 10704431 DOI: 10.2741/stratakis]
130 **Watson JC**, Stratakis CA, Bryant-Greenwood PK, Koch CA, Kirschner LS, Nguyen T, Carney JA, Oldfield EH. Neurosurgical implications of Carney complex. *J Neurosurg* 2000; **92**: 413-418 [PMID: 10701527 DOI: 10.3171/jns.2000.92.3.0413]

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ORIGINAL ARTICLE

Basic Study

GRK5 is an essential co-repressor of the cardiac mineralocorticoid receptor and is selectively induced by finerenone

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Abstract

BACKGROUND

In the heart, aldosterone (Aldo) binds the mineralocorticoid receptor (MR) to exert damaging, adverse remodeling-promoting effects. We recently showed that G protein-coupled receptor-kinase (GRK)-5 blocks the cardiac MR by directly phosphorylating it, thereby repressing its transcriptional activity. MR antagonist (MRA) drugs block the cardiac MR reducing morbidity and mortality of advanced human heart failure. Non-steroidal MRAs, such as finerenone, may provide better cardio-protection against Aldo than classic, steroidal MRAs, like spironolactone and eplerenone.

AIM

To investigate potential differences between finerenone and eplerenone at engaging GRK5-dependent cardiac MR phosphorylation and subsequent blockade.

METHODS

We used H9c2 cardiomyocytes, which endogenously express the MR and GRK5.

RESULTS

GRK5 phosphorylates the MR in H9c2 cardiomyocytes in response to finerenone but not to eplerenone. Unlike eplerenone, finerenone alone potently and efficiently suppresses cardiac MR transcriptional activity, thus displaying inverse agonism. GRK5 is necessary for finerenone's inverse agonism, since GRK5 genetic deletion renders finerenone incapable of blocking cardiac MR transcriptional activity. Eplerenone alone does not fully suppress cardiac MR basal activity regardless of GRK5 expression levels. Finally, GRK5 is necessary for the anti-

apoptotic, anti-oxidative, and anti-fibrotic effects of both finerenone and eplerenone against Aldo, as well as for the higher efficacy and potency of finerenone at blocking Aldo-induced apoptosis, oxidative stress, and fibrosis.

CONCLUSION

Finerenone, but not eplerenone, induces GRK5-dependent cardiac MR inhibition, which underlies, at least in part, its higher potency and efficacy, compared to eplerenone, as an MRA in the heart. GRK5 acts as a co-repressor of the cardiac MR and is essential for efficient MR antagonism in the myocardium

Key Words: Aldosterone; Cardiac myocyte; Finerenone; G protein-coupled receptor kinase-5; Mineralocorticoid receptor antagonist; Signal transduction

Core Tip: G protein-coupled receptor-kinase (GRK)-5 blocks the cardiac actions of aldosterone *via* phosphorylation of the mineralocorticoid receptor (MR). We show here that the non-steroidal MR antagonist (MRA) finerenone may provide better cardio-protection against aldosterone than classic, steroidal MRAs, like eplerenone, thanks to induction of GRK5's phosphorylation and subsequent blockade of cardiac MR. GRK5 is necessary for the anti-apoptotic, anti-oxidative, and anti-fibrotic effects of both finerenone and eplerenone against aldosterone but also for the higher efficacy/potency of the former drug at producing all these effects in cardiomyocytes. Thus, GRK5 acts as a co-repressor of the cardiac MR and is essential for efficient MR antagonism in the myocardium.

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INTRODUCTION

Aldosterone (Aldo) is one of several cardio-toxic hormones, whose elevated circulating levels significantly confound and aggravate heart disease, including hypertension and chronic heart failure (CHF)[1-4]. The mineralocorticoid receptor (MR), a cytosolic transcription factor that, upon activation, translocates to the nucleus to activate gene transcription, is the main receptor mediating Aldo's adverse remodeling effects in the failing heart[1-5]. GRK2 and GRK5 are the most abundant cardiac G protein-coupled receptor (GPCR)-kinase (GRK) isoforms. Both phosphorylate GPCRs but also non-GPCR substrates[6-10]. We recently showed that GRK5 blocks the cardio-toxic MR-dependent effects of aldosterone in the heart by directly phosphorylating the cardiac MR and inhibiting its transcriptional activity[11].

MR antagonist (MRA) drugs are beneficial in human advanced CHF thanks to their blockade of the MR in various cardiovascular tissues, including in cardiomyocytes and cardiac fibroblasts[3,12]. Novel, non-steroidal MRAs, such as finerenone, may provide better cardio-protection against aldosterone's cardio-toxic actions than the classic steroidal MRAs, such as sprironolactone and eplerenone[13,14]. Indeed, finerenone was recently shown to be a more potent and efficacious inverse agonist at the MR, compared to eplerenone, in terms of cardiac fibrosis/adverse remodeling attenuation[15]. This prompted us to investigate the effects of these two MRAs on GRK5-dependent cardiac MR phosphorylation and subsequent suppression, in an effort to delineate potential molecular mechanisms underlying their differences in cardiac MR blocking efficacy. Indeed, we found that finerenone, but not eplerenone, promotes the inhibitory action of GRK5 on cardiac MR, which may underlie finerenone's significantly greater efficacy/potency as an inverse agonist at this receptor. Moreover, GRK5 is necessary for both MRA drugs' cardioprotective actions against Aldo in cardiac myocytes.

MATERIALS AND METHODS

All methods were carried out in accordance with the relevant guidelines and regulations.

Materials

All drugs/chemicals were from Sigma-Aldrich (St. Louis, MO, United States), except for finerenone (BAY94-8862) which was purchased from MedKoo Biosciences, Inc. (Cat. #319698, Morrisville, NC, United States).

Cell culture, viruses, and transfections

The H9c2 rat cardiomyoblast cell line was purchased from American Type Culture Collection (Manassas, VA, United States) and cultured as previously described[11,16-18]. Recombinant lentiviruses encoding for wild-type full-length GRK5 or for empty vector (control) (OriGene Technologies, Rockville, MD, United States) were propagated and purified *via* CsCl density gradient ultracentrifugation, as described previously[11,19]. For CRISPR/Cas9-mediated *GRK5* gene deletion, a gRNA sequence was custom-synthesized by Sigma-Aldrich (target ID: RN0000391809, target sequence: 5′-GTGGTT-TGAATTTATGCGG-3′) and incorporated into a lentiviral vector (Sigma-Aldrich). Along with negative control CRISPR lentiviral particles (CNCV, Cat #CRISPR12V-1EA, Sigma-Aldrich), this lentivirus was also propagated and purified through cesium chloride density gradient ultracentrifugation.

Immunoprecipitation/western blotting

Cell extracts were prepared, as described previously[11,20], in a 20-mmol/L Tris pH 7.4 buffer containing 137 mmol/L NaCl, 1% Nonidet P-40, 20% glycerol, 10 mmol/L phenylmethylsulfonyl-fluoride (PMSF), 1 mmol/L Na_3VO_4, 10 mmol/L NaF, 2.5 μg/mL aprotinin, and 2.5 μg/mL leupeptin. Protein concentration was determined (Pierce BCA Protein Assay Kit, Thermo Scientific, Waltham, MA, United States), and equal amounts of protein per sample were used for Immunoprecipitation (IP) or western blotting. MR was immunoprecipitated by overnight incubation of extracts with an anti-MR antibody (#ab62532; Abcam, Cambridge, MA, United States), attached to Protein A/G-Sepharose beads (Sigma-Aldrich). The IPs were then subjected to immunoblotting for GRK5 (#sc-565; Santa Cruz Biotechnology, Santa Cruz, CA, United States) or for phosphoserine (#AB1603; Millipore-Sigma, Burlington, MA, United States) to measure the pSer content of the immunoprecipitated MR. Finally, an anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH) antibody (#sc-25778; Santa Cruz Biotechnology) was used to control for protein loading. All immunoblots were revealed by enhanced chemiluminescence (ECL, Life Technologies, Grand Island, NY, United States) and visualized in the FluorChem E Digital Darkroom (Protein Simple, San Jose, CA, United States), as described previously[21].

Luciferase reporter activity assay

Luciferase reporter activity assay was performed, as described previously, by transfecting the cells with the LightSwitch™ luciferase reporter gene vector under the influence of the MR promoter (Active Motif, Inc., Carlsbad, CA, United States)[11]. The measurements were done the next day with the manufacturer's assay kit and according to the manufacturer's instructions.

TUNEL

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay to measure apoptotic cell death was done as described[22]. Briefly, cells were fixed with 10% neutral buffered formalin, embedded in paraffin, and sectioned at 5-μm thickness. DNA fragmentation was detected in situ in deparaffinized sections using the ApopTag peroxidase *in situ* apoptosis detection Kit (Millipore-Sigma) and according to the manufacturer's instructions. The total number of nuclei was determined by manual counting of 4′,6′-diamidino-2-phenylindole (DAPI)-stained nuclei in six random fields per section. All terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL)-positive nuclei were counted in each section.

Real-time PCR

Real-time PCR for rat plasminogen activator inhibitor (PAI)-1 and rat fibronectin mRNA levels in total RNA isolated from cells was done as described previously[16]. Briefly, quantitative real-time PCR was performed using a MyIQ Single-Color Real-Time PCR detection system (Bio-Rad Laboratories, Hercules, CA, United States) using SYBR Green Supermix (Bio-Rad) and 100 nmol/L of gene-specific oligonucleotides. Quantification of mRNA included normalization to 18s rRNA levels. No bands were seen in control reactions in the absence of reverse transcriptase. Primer pairs used were: 5′-TTCCTCCACAGC-CATTCTAGTCT-3′ and 5′-GAAAGGATCGGTCTAAAACCATCTC-3′ for PAI-1; 5′-CGAGGTGACA-GAGACCACAA-3′ and 5′-CTGGAGTCAAGCCAGACACA-3′ for fibronectin; and 5′-TCGATGCTCT-TAGCTGAGTG-3′ and 5′-TGATCGTCTTCGAACCTCC-3′ for 18S rRNA.

Oxidative stress assay

To determine reactive oxygen species (ROS) production, the 2′,7′-dichlorofluorescein diacetate (DCFDA) dye-based assay kit from Molecular Probes (Cat. #C13293; Eugene, OR, United States) was used and the measurements were done according to manufacturer's instructions and as previously described[11]. Briefly, cell extracts were incubated with 2 μmol/L DCFDA for 20 min and ROS production was

monitored by determining the fluorescence intensity using a fluorescent plate reader in which excitation and emission wavelengths were set at 495 and 520 nm, respectively. The fluorescence OD values obtained were normalized with protein determination and expressed as % of the values obtained upon 100 nmol/L Aldo treatment (1 mmol/L DMSO was used as vehicle treatment).

Statistical analysis

Student's *t* test and one- or two-way ANOVA with Bonferroni test were used for statistical comparisons, unless otherwise indicated. For multiple group analyses, Dunnett's test with SAS version 9 software (Cary, NC, United States) was also used. A P value of < 0.05 indicated statistical significance.

RESULTS

Finerenone, but not eplerenone, induces GRK5-dependent cardiac MR phosphorylation

We recently reported that GRK5 selectively phosphorylates and inhibits the cardiac MR[11]. Based also on recent evidence suggesting greater potency for finerenone, compared to eplerenone, at inhibiting the cardiac MR and its downstream fibrosis[15], we hypothesized, in the present study, that the higher efficacy/potency of finerenone over eplerenone might be due (at least in part) to differences in modulation of the GRK5 inhibitory action on the cardiac MR. Thus, in a first series of experiments, we overexpressed or knocked out (*via* CRISPR) GRK5 in H9c2 cardiac myocytes (Figure 1A), which endogenously express both GRK5 and MR[11,23], and checked for the effects of the two MRA drugs on MR serine phosphorylation. GRK5, being a Ser/Thr kinase, likely phosphorylates multiple Ser and Thr residues of the MR protein, with phosphorylations of Ser601 and Ser843 (in the human orthologue sequence), in particular, resulting in significant functional inhibition of the MR, courtesy of cytosolic retention and transcriptional activity suppression, respectively[24,25]. After preliminary concentration-response experiments (not shown), and based on the associated literature, we chose a 10 mmol/L concentration for both drugs throughout the experiments of our study, as this concentration (10 mmol/L) is quite close to both drugs' effective IC_{50} values[12,15]. As shown in Figure 1B and C, finerenone led to much higher phosphorylation (pSer content) of the MR than eplerenone did in control H9c2 cardiomyocytes (mock virus-EV lanes). This finerenone-induced MR phosphorylation was significantly enhanced upon GRK5 overexpression but essentially abrogated in GRK5-depleted H9c2 cardiomyocytes (Figure 1B and C). Notably, eplerenone essentially failed to elicit any appreciable MR Ser phosphorylation in H9c2 cardiomyocytes (Figure 1B and C), irrespective of GRK5 expression levels [eplerenone-induced phosphorylation: 1.2 ± 0.25-fold of vehicle in EV cells; 1.23 ± 0.27-fold of vehicle in GRK5-OE cells; 0.6 ± 0.55-fold of vehicle in GRK5-KO cells; *i.e.*, non-significant *vs* vehicle, in all three clones at $P = 0.05$ ($n = 3$); Figure 1C]. Although we cannot account for the potential of some extent of Thr phosphorylation of the MR induced by the two drugs, these results strongly suggest that only finerenone (not eplerenone) induces GRK5-mediated phosphorylation of the MR in H9c2 cardiac myocytes.

GRK5 is essential for finerenone's inverse agonism at the cardiac MR

Since GRK5-induced phosphorylation translates into transcriptional repression of the cardiac MR[11], we next examined the impact of the finerenone-induced, GRK5-mediated MR phosphorylation on the transcriptional activity of the receptor. In contrast with eplerenone, finerenone lacks agonist activity at the MR in control (CNCV) H9c2 cardiomyocytes, *i.e.*, no increase in MR basal transcriptional activity (in the absence of Aldo) is observed with finerenone (Figure 2). In the absence of GRK5 however, finerenone loses the ability to keep the MR transcriptionally inactive, *i.e.*, the MR displays significant basal activity in GRK5-KO H9c2 cardiomyocytes (Figure 2). Upon GRK5 overexpression, this picture is reversed, *i.e.*, finerenone acts as potent inverse agonist at the MR, markedly suppressing MR basal transcriptional activity in GRK5-overexpressing (GRK5-OE) cardiomyocytes (Figure 2). In contrast, eplerenone allows for substantial MR basal transcriptional activity, regardless of GRK5 expression levels (Figure 2). Taken together, these results indicate that GRK5 is essential for finerenone's inverse agonism at the cardiac MR, while eplerenone is essentially a partial agonist (mixed agonist/antagonist) at this receptor in the heart, a finding consistent with the literature[12,15]. GRK5 is unable to affect eplerenone's actions on the cardiac MR, probably because this MRA agent cannot induce the inhibitory phosphorylation of this receptor by GRK5 in cardiac myocytes (see above, Figure 1).

GRK5 is essential for MRA-dependent antagonism of Aldo-induced cardiac apoptosis and oxidative stress and underlies finerenone's advantage over eplerenone toward these effects

Next, we compared the cardio-protective efficacies of the two MRA drugs against the deleterious actions of Aldo. Finerenone was much more effective than eplerenone at suppressing Aldo-induced apoptosis (Figure 3A) and oxidative stress (Figure 3B), in control myocytes. However, upon GRK5 genetic deletion, both MRAs failed completely to block these two cardiac adverse remodeling-promoting Aldo effects (Figures 3A and B). This strongly suggests that GRK5 is essential for the anti-

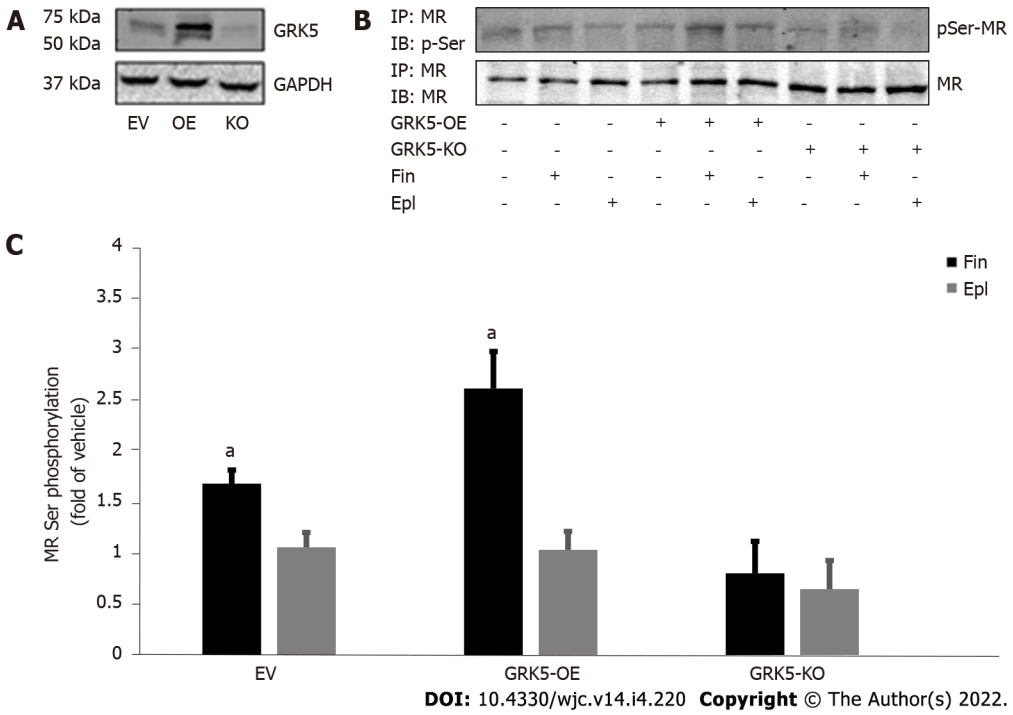

Figure 1 G protein-coupled receptor-kinase 5 phosphorylates the cardiac mineralocorticoid receptor in response to finerenone but not to eplerenone. A: Western blotting to confirm G protein-coupled receptor-kinase (GRK)-5 overexpression (OE) with a wild type GRK5-encoding lentivirus or deletion (KO) *via* a GRK5-targeting CRISPR lentivirus in H9c2 cardiomyocytes. GAPDH blotting is also shown as loading control; B, C: Western blotting for the phosphoserine content of the mineralocorticoid receptor in response to 10 mmol/L finerenone (Fin) or 10 mmol/L eplerenone (Epl) in GRK5-overexpressing (GRK5-OE) or in GRK5-KO or in control, empty virus (EV)-infected H9c2 cells. Representative blots are shown in (B) and the densitometric quantitation of three independent experiments in (C). $^{a}P < 0.05$, *vs* Epl; $n = 3$ independent experiments performed in duplicate per cell clone/treatment. EV: Empty vector mock virus-transfected (control) cells; IP: Immunoprecipitation; IB: Immunoblotting.

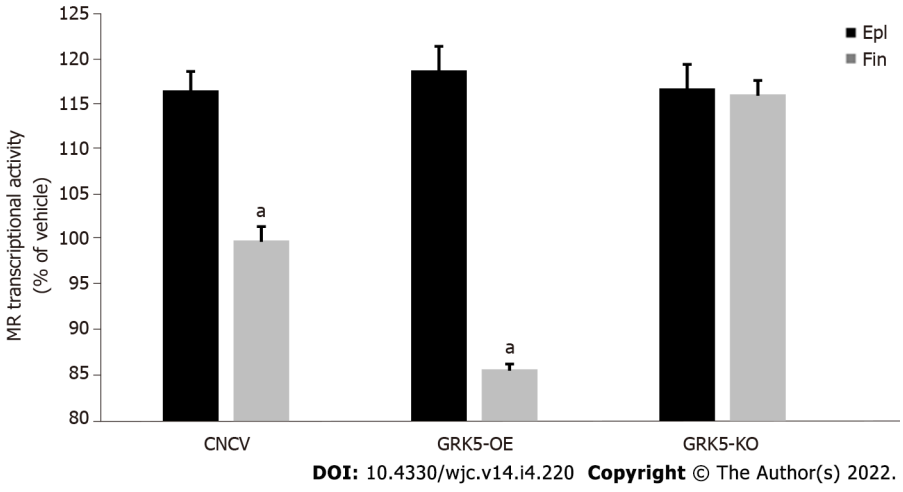

Figure 2 G protein-coupled receptor-kinase 5 inhibits the cardiac mineralocorticoid receptor in response to finerenone but not to eplerenone. Transcriptional activity of the mineralocorticoid receptor (MR) in response to either 10 mmol/L eplerenone or 10 mmol/L finerenone in H9c2 cardiomyocytes overexpressing G protein-coupled receptor-kinase (GRK)-5 or having GRK5 genetically deleted *via* CRISPR (GRK5-KO). Neither agent was able to suppress MR basal transcriptional activity in GRK5-KO cells. $^{a}P < 0.05$, *vs* eplerenone; $n = 5$ independent measurements per cell clone/treatment performed in triplicate. CNCV: CRISPR negative control virus-infected control cells; GRK5-OE: G protein-coupled receptor-kinase 5-overexpressing.

apoptotic and anti-oxidative effects of MRAs against Aldo in the heart, as well as for the better cardioprotective efficacy of finerenone *vs* eplerenone against Aldo.

GRK5 is essential for MRA-dependent anti-fibrotic effects in the heart and for finerenone's advantage over eplerenone towards this effect

In addition to apoptosis and oxidative stress, we compared the two MRAs in terms of Aldo-induced

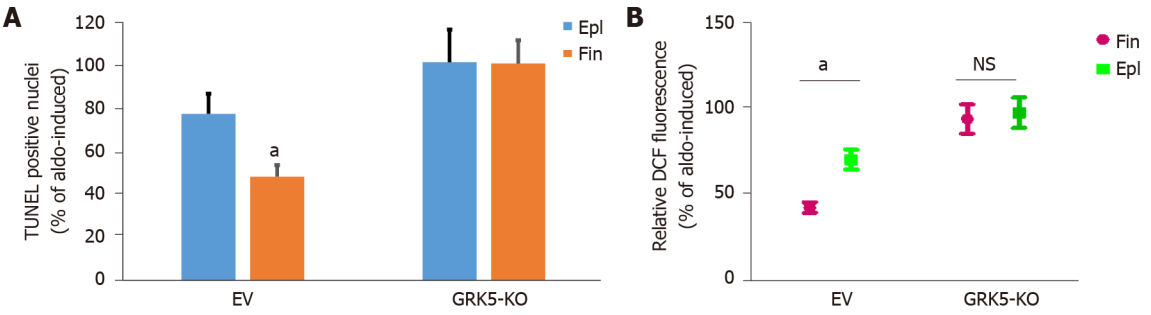

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Figure 3 Comparison of anti-apoptotic and anti-oxidative efficacies of finerenone *vs* eplerenone in aldosterone-treated cardiomyocytes in the presence or absence of G protein-coupled receptor-kinase 5. A: Apoptotic cell death in control, empty vector (mock) virus-infected (EV) cells or in cells having G protein-coupled receptor-kinase (GRK)-5 genetically (CRISPR lentivirus-mediated) deleted (GRK5-KO) and treated with 100 nmol/L aldosterone (Aldo) alone or in the presence of 10 mmol/L eplerenone (Epl) or 10 mmol/L finerenone for 24 h. $^{a}P < 0.05$, *vs* Epl; $n = 4$ independent experiments per transfection/treatment. Essentially no inhibition of Aldo-induced apoptosis could be detected with either drug in GRK5-KO cells; B: ROS generation in these cells, as measured *via* the DCF assay. $^{a}P < 0.05$. Not significant at $P = 0.05$; $n = 4$ independent experiments per transfection/treatment. EV: Empty virus; Epl: Eplerenone; Fin: Finerenone; NS: Not significant.

fibrosis inhibition in cardiac myocytes. Assessment of Aldo-dependent mRNA induction of two major pro-fibrotic stimuli, PAI-1 and fibronectin, both of which are immediate/early MR-responsive genes[1,3,16], revealed that finerenone was more effective than eplerenone at suppressing both PAI-1 (Figure 4A) and fibronectin (Figure 4B) mRNA inductions by Aldo in control cells. Again however, neither drug was effective at all when GRK5 was absent (Figure 4A and B, compare with GRK5-KO bars). Thus, GRK5 is essential also for the anti-fibrotic effects of MRAs in cardiac myocytes.

The MR has long been established as an important molecular culprit in heart disease progression[1-5], including a recent study in transgenic mice showing that, unlike its closely related glucocorticoid receptor, the MR promotes cardiac dysfunction even in the absence of a cardiac insult or injury[26]. Indeed, the well-documented deleterious effects of the cardiac MR have provided the pharmacological basis for the use of MRA drugs in advanced stage human CHF and other heart diseases[1-5,27,28]. The MRA drug class, which began with the approval and marketing of spironolactone more than 60 years ago, now encompasses several agents, with some already in clinical use and some in clinical trials. The MRAs are broadly divided to traditional, steroidal MRAs, like spironolactone and eplerenone currently in clinical use, and later generation, non-steroidal agents. Among the latter is finerenone (formerly BAY 94-8862), a third generation, non-steroidal, dihydropyridine-derived MRA currently in phase III clinical trials[3,12].

Despite being very potent and effective aldosterone antagonists with salutary effects in the heart and kidneys, the currently available steroidal MRAs are hampered by several limiting side effects, most prominent of which are hyperkalemia, renal function deterioration, and gynecomastia. These are generally thought to be due to their binding to other types of steroid receptors (*e.g.*, estrogen receptor, glucocorticoid receptor, *etc.*) exactly because of their steroidal structure[3,12,29]. Thus, non-steroidal MRAs have been developed, currently headlined by finerenone. Finerenone has shown advantageous pharmacological and therapeutic profiles, compared to the steroidal MRAs. It has demonstrated improved therapeutic properties in heart failure animal models in head-to-head comparisons with eplerenone[12,15] and leads to bigger improvements in HFrEF (heart failure with reduced ejection fraction) confounded by diabetes or chronic kidney disease[12,14]. In addition to its much higher selectivity for the MR over other steroid receptors, finerenone is also at least one log scale more potent at MR antagonism than eplerenone and spironolactone, both of which are competitive MR antagonists[3]. Furthermore, finerenone displays inverse agonist activity at the MR, whereas the steroidal MRAs are only partial MR antagonists[3,12]. This means that, depending on the activity status of the MR, spironolactone and eplerenone may actually promote the activity of the MR rather than inhibiting it[12,14,15]. In other words, eplerenone inhibits the MR when the receptor is activated by Aldo but it may actually promote the activity of the MR when bound alone to the receptor (in the absence of Aldo). Finerenone, thanks to the non-steroidal nature of its structure, appears to be devoid of any agonist activity at the MR and thus, has strong potential to provide better cardiovascular and renal outcomes, especially in diseases severely affected by hyperaldosteronism.

One of the most important parameters affecting the selectivity of a particular MRA for the MR *vs* other steroid receptors, as well as tissue specificity for MR antagonism (inhibition of the cardiac MR *vs* inhibition of the MR in other tissues), is the identity/identities of the receptor's co-factors activated or repressed by the MRA agent, which ultimately affects the MRA drug's potency and efficacy[1,3,15,25]. In other words, how good a particular MRA is at blocking the cardiac MR depends strongly on which co-activators of the MR the drug inhibits and/or which co-repressors of the MR it activates inside the cardiac myocyte[3]. Indeed, a recent study in mice reported much higher potency and inverse agonism

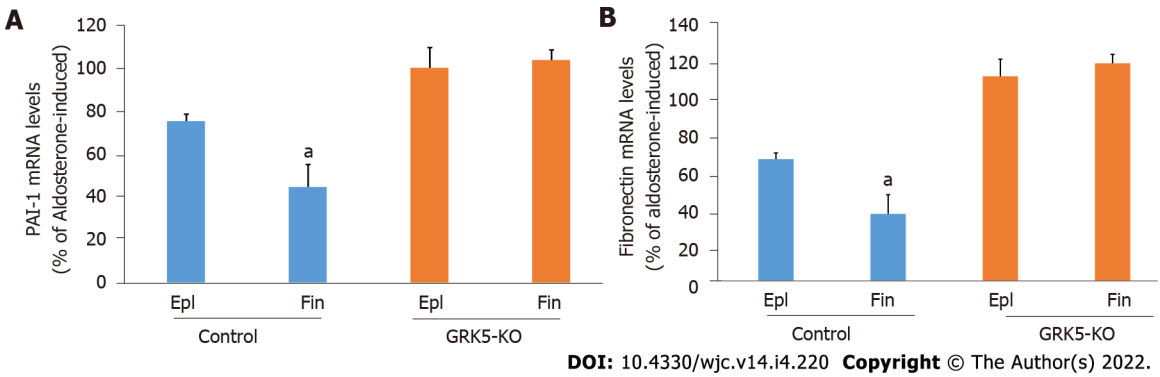

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Figure 4 Comparison of the anti-fibrotic efficacies of finerenone *vs* eplerenone in aldosterone-treated cardiomyocytes in the presence or absence of G protein-coupled receptor-kinase 5. mRNA levels of PAI-1 (A) and fibronectin (B), in response to a 2-h-long treatment of 100 nmol/L aldosterone in the presence of either 10 mmol/L eplerenone (Epl) or 10 mmol/L finerenone in control (mock, empty vector CRISPR lentivirus-infected) or in G protein-coupled receptor-kinase (GRK)-5-KO (rat GRK5-targeting CRISPR lentivirus-infected) cells. 18S rRNA levels were used for normalization of the results. [a]$P < 0.05$, *vs* Epl; $n = 3$ independent measurements per cell clone/treatment performed in triplicate. Epl: Eplerenone; Fin: Finerenone.

of finerenone, relative to eplerenone, in terms of cardiac fibrosis suppression and suggested that the pharmacological difference between these two MRAs was probably due to differential cardiac MR co-factor regulation/engagement[15]. We recently uncovered that GRK5 is an important co-repressor of the cardiac MR, *via* its direct binding to, and phosphorylation of the MR that results in cytosolic retention of the phosphorylated receptor and thus, MR transcriptional repression[11]. Our present data strongly suggest that finerenone selectively activates this kinase in cardiac myocytes to potently inhibit/repress the cardiac MR. In contrast, eplerenone is incapable of this action (GRK5 activation) and thus, is a much weaker MR antagonist in the myocardium.

There are a few very important questions emanating from our present work that await delineation in future studies. First, does finerenone activate GRK5 to suppress MR activity only in the heart or in other tissues, as well (*e.g.*, kidneys)? Another critical question is whether this property is shared by other non-steroidal MRAs or it is specific to finerenone. Finally, there is also the obvious mechanistic question of how exactly finerenone, not known to be a GPCR agonist, induces GRK5, normally activated by a GPCR, such as the b_2-adrenergic receptor (Figure 5)[8,11], to phosphorylate and inhibit the MR in the cytosol of a cardiac myocyte. Nevertheless, these salient questions will be the focus of our future investigations, along with our already ongoing efforts to map the specific phosphorylation sites of GRK5 on the human MR protein and to characterize the functional impact for the receptor of each one of them.

In summary, our present study reinforces the emerging and therapeutically very intriguing notion that GRK5, acting as a cardiac MR co-repressor in this instance, may actually be beneficial in the myocardium[11,31-33], contrary to its counterpart GRK2 that is generally considered deleterious in the heart[7,10]. Importantly, we have identified GRK5 as a potential co-factor of the cardiac MR that is differentially regulated by finerenone and eplerenone, which may underlie the higher potency/efficacy (and inverse agonism) of finerenone at the MR. To our knowledge, cardiac GRK5 is the first such MR co-factor to be shown as differentially modulated/stimulated among different individual MRA drugs. Finally, from the therapeutic standpoint, we provide evidence that GRK5 is indispensable for MRAs' cardioprotective actions against Aldo (*e.g.*, anti-apoptosis, anti-oxidant action, anti-fibrosis) and, importantly, this applies to both steroidal (eplerenone) and non-steroidal (finerenone) MRA agents alike.

DISCUSSION

In the present study, we report that finerenone is a more potent and efficacious cardiac MR blocker than eplerenone, thanks, at least in part, to stimulation of GRK5-dependent cardiac MR phosphorylation, which eplerenone is incapable of inducing (Figure 5). This non-canonical effect of GRK5 on the cardiac MR is essential for efficient blockade of Aldo's deleterious actions in the heart, such as apoptosis, oxidative stress, fibrosis, and probably other adverse remodeling-associated effects (Figure 5). Therefore, GRK5-dependent inhibitory phosphorylation is a key molecular mechanism for cardiac MR inverse agonism and needs to be considered in the design and development of novel, more effective MRA drugs for heart disease (*e.g.*, CHF, hypertension, renal insufficiency, *etc.*) treatment.

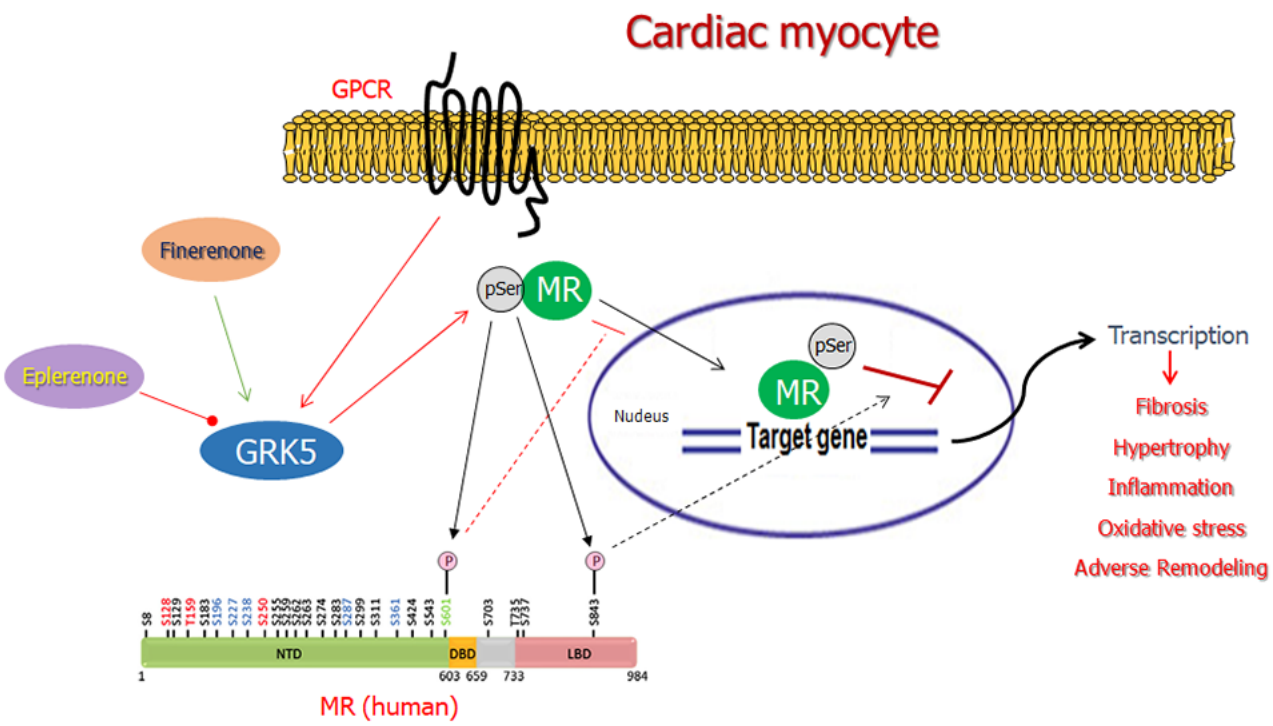

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Figure 5 Schematic illustration of the differential effects of finerenone *vs* eplerenone on G protein-coupled receptor-kinase 5-dependent repression of the cardiac mineralocorticoid receptor. Finerenone, unlike eplerenone, stimulates G protein-coupled receptor-kinase (GRK)-5 to phosphorylate the mineralocorticoid receptor (MR). The two main (putative) GRK5 phosphorylation sites on the human MR protein, Ser601 and Ser843, are highlighted, along with their functional impacts for the MR (pSer601 blocks nuclear translocation; pSer843 suppresses Aldo-induced transcriptional activity)[24,30]. GPCR: G protein-coupled receptor; NTD: N-terminal domain; DBD: DNA-binding domain; LBD: Ligand-binding domain; pSer: Phosphoserine. See text for more details and for all other molecular acronyms' descriptions.

CONCLUSION

Cardiac GRK5 is an essential mediator of the general cardio-protection afforded by MRA drugs against the cardio-toxic effects of excess Aldo, *e.g.*, during CHF and other chronic cardiac diseases. This is due to the inhibitory phosphorylation GRK5 performs on the cardiac MR. This non-canonical (given the substrate is not a GPCR), co-repressor effect of GRK5 on cardiac MR is also (at least partly) responsible for the inverse agonism properties of finerenone at this receptor that bestow this non-steroidal MRA with superior potency and efficacy, compared to eplerenone, at protecting the heart against the damaging effects of Aldo. Finally, since GRK5 is a co-repressor of the MR, at least in the myocardium, its stimulation (or potentiation) should be a desired property of every novel MRA drug designed and developed for improved cardiovascular pharmacotherapy.

ARTICLE HIGHLIGHTS

Research background

Different mineralocorticoid receptor (MR) antagonists (MRAs) have different potencies at the cardiac MR blockade. G protein-coupled receptor kinase (GRK)-5 phosphorylates the MR in the heart and inhibits its transcriptional activity.

Research motivation

The authors wanted to compare two different MRAs, eplerenone and finerenone, in their ability to stimulate GRK5-dependent MR inhibition in cardiac myocytes.

Research objectives

The authors sought to identify a mechanism for the increased effectiveness of finerenone over eplerenone at blocking cardiac MR.

Research methods

The authors studied MR phosphorylation and activity in cardiomyocytes in response to eplerenone or finerenone treatments.

Research results

GRK5 is necessary for the anti-apoptotic, anti-oxidative, and anti-fibrotic effects of both finerenone and eplerenone against Aldo, as well as for the higher efficacy and potency of finerenone at blocking Aldo-induced apoptosis, oxidative stress, and fibrosis.

Research conclusions

Finerenone, but not eplerenone, induces GRK5-dependent cardiac MR inhibition, which underlies, at least in part, its higher potency and efficacy, compared to eplerenone, as an MRA in the heart.

Research perspectives

GRK5 is an essential mediator of finerenone's effects on cardiac aldosterone antagonism.

FOOTNOTES

Author contributions: Pollard CM, Suster MS, Cora N, and Carbone AM performed all experiments and assisted with data analysis; Lymperopoulos A supervised the project, performed data analysis, provided funding for the study, and wrote the manuscript; and All authors have read and approved the manuscript.

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REFERENCES

1 **Parker BM**, Wertz SL, Pollard CM, Desimine VL, Maning J, McCrink KA, Lymperopoulos A. Novel Insights into the Crosstalk between Mineralocorticoid Receptor and G Protein-Coupled Receptors in Heart Adverse Remodeling and Disease. *Int J Mol Sci* 2018; **19** [PMID: 30486399 DOI: 10.3390/ijms19123764]

2 **Luther JM**. Is there a new dawn for selective mineralocorticoid receptor antagonism? *Curr Opin Nephrol Hypertens* 2014; **23**: 456-461 [PMID: 24992570 DOI: 10.1097/MNH.0000000000000051]

3 **Lother A**, Moser M, Bode C, Feldman RD, Hein L. Mineralocorticoids in the heart and vasculature: new insights for old hormones. *Annu Rev Pharmacol Toxicol* 2015; **55**: 289-312 [PMID: 25251996 DOI: 10.1146/annurev-pharmtox-010814-124302]

4 **Weber KT**. Aldosterone in congestive heart failure. *N Engl J Med* 2001; **345**: 1689-1697 [PMID: 11759649 DOI:

10.1056/NEJMra000050]
5 **Mihailidou AS**, Funder JW. Nongenomic effects of mineralocorticoid receptor activation in the cardiovascular system. *Steroids* 2005; **70**: 347-351 [PMID: 15862816 DOI: 10.1016/j.steroids.2005.02.004]
6 **Lymperopoulos A**, Bathgate A. Pharmacogenomics of the heptahelical receptor regulators G-protein-coupled receptor kinases and arrestins: the known and the unknown. *Pharmacogenomics* 2012; **13**: 323-341 [PMID: 22304582 DOI: 10.2217/pgs.11.178]
7 **Sato PY**, Chuprun JK, Schwartz M, Koch WJ. The evolving impact of g protein-coupled receptor kinases in cardiac health and disease. *Physiol Rev* 2015; **95**: 377-404 [PMID: 25834229 DOI: 10.1152/physrev.00015.2014]
8 **Komolov KE**, Benovic JL. G protein-coupled receptor kinases: Past, present and future. *Cell Signal* 2018; **41**: 17-24 [PMID: 28711719 DOI: 10.1016/j.cellsig.2017.07.004]
9 **McCrink KA**, Brill A, Lymperopoulos A. Adrenal G protein-coupled receptor kinase-2 in regulation of sympathetic nervous system activity in heart failure. *World J Cardiol* 2015; **7**: 539-543 [PMID: 26413230 DOI: 10.4330/wjc.v7.i9.539]
10 **Siryk-Bathgate A**, Dabul S, Lymperopoulos A. Current and future G protein-coupled receptor signaling targets for heart failure therapy. *Drug Des Devel Ther* 2013; **7**: 1209-1222 [PMID: 24143078 DOI: 10.2147/DDDT.S35905]
11 **Maning J**, McCrink KA, Pollard CM, Desimine VL, Ghandour J, Perez A, Cora N, Ferraino KE, Parker BM, Brill AR, Aukszi B, Lymperopoulos A. Antagonistic Roles of GRK2 and GRK5 in Cardiac Aldosterone Signaling Reveal GRK5-Mediated Cardioprotection *via* Mineralocorticoid Receptor Inhibition. *Int J Mol Sci* 2020; **21** [PMID: 32326036 DOI: 10.3390/ijms21082868]
12 **Kolkhof P**, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and Novel Non-steroidal Mineralocorticoid Receptor Antagonists in Heart Failure and Cardiorenal Diseases: Comparison at Bench and Bedside. *Handb Exp Pharmacol* 2017; **243**: 271-305 [PMID: 27830348 DOI: 10.1007/164_2016_76]
13 **Sueta D**, Yamamoto E, Tsujita K. Mineralocorticoid Receptor Blockers: Novel Selective Nonsteroidal Mineralocorticoid Receptor Antagonists. *Curr Hypertens Rep* 2020; **22**: 21 [PMID: 32114686 DOI: 10.1007/s11906-020-1023-y]
14 **Rico-Mesa JS**, White A, Ahmadian-Tehrani A, Anderson AS. Mineralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone. *Curr Cardiol Rep* 2020; **22**: 140 [PMID: 32910349 DOI: 10.1007/s11886-020-01399-7]
15 **Grune J**, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, Brix S, Betz IR, Schupp M, Foryst-Ludwig A, Klopfleisch R, Stawowy P, Houtman R, Kolkhof P, Kintscher U. Selective Mineralocorticoid Receptor Cofactor Modulation as Molecular Basis for Finerenone's Antifibrotic Activity. *Hypertension* 2018; **71**: 599-608 [PMID: 29437893 DOI: 10.1161/HYPERTENSIONAHA.117.10360]
16 **Pollard CM**, Desimine VL, Wertz SL, Perez A, Parker BM, Maning J, McCrink KA, Shehadeh LA, Lymperopoulos A. Deletion of Osteopontin Enhances β_2-Adrenergic Receptor-Dependent Anti-Fibrotic Signaling in Cardiomyocytes. *Int J Mol Sci* 2019; **20** [PMID: 30897705 DOI: 10.3390/ijms20061396]
17 **McCrink KA**, Maning J, Vu A, Jafferjee M, Marrero C, Brill A, Bathgate-Siryk A, Dabul S, Koch WJ, Lymperopoulos A. β-Arrestin2 Improves Post-Myocardial Infarction Heart Failure *via* Sarco(endo)plasmic Reticulum Ca^{2+}-ATPase-Dependent Positive Inotropy in Cardiomyocytes. *Hypertension* 2017; **70**: 972-981 [PMID: 28874462 DOI: 10.1161/HYPERTENSIONAHA.117.09817]
18 **McCrink KA**, Brill A, Jafferjee M, Valero TR, Marrero C, Rodriguez MM, Hale GM, Lymperopoulos A. β_1-adrenoceptor Arg389Gly polymorphism confers differential β-arrestin-binding tropism in cardiac myocytes. *Pharmacogenomics* 2016; **17**: 1611-1620 [PMID: 27643874 DOI: 10.2217/pgs-2016-0094]
19 **Pollard CM**, Ghandour J, Cora N, Perez A, Parker BM, Desimine VL, Wertz SL, Pereyra JM, Ferraino KE, Patel JJ, Lymperopoulos A. GRK2-Mediated Crosstalk Between β-Adrenergic and Angiotensin II Receptors Enhances Adrenocortical Aldosterone Production In Vitro and In Vivo. *Int J Mol Sci* 2020; **21** [PMID: 31963151 DOI: 10.3390/ijms21020574]
20 **Nguyen K**, Kassimatis T, Lymperopoulos A. Impaired desensitization of a human polymorphic α2B-adrenergic receptor variant enhances its sympatho-inhibitory activity in chromaffin cells. *Cell Commun Signal* 2011; **9**: 5 [PMID: 21299895 DOI: 10.1186/1478-811X-9-5]
21 **Salazar NC**, Vallejos X, Siryk A, Rengo G, Cannavo A, Liccardo D, De Lucia C, Gao E, Leosco D, Koch WJ, Lymperopoulos A. GRK2 blockade with βARKct is essential for cardiac β2-adrenergic receptor signaling towards increased contractility. *Cell Commun Signal* 2013; **11**: 64 [PMID: 23984976 DOI: 10.1186/1478-811X-11-64]
22 **Lymperopoulos A**, Rengo G, Zincarelli C, Kim J, Koch WJ. Adrenal beta-arrestin 1 inhibition in vivo attenuates post-myocardial infarction progression to heart failure and adverse remodeling *via* reduction of circulating aldosterone levels. *J Am Coll Cardiol* 2011; **57**: 356-365 [PMID: 21232674 DOI: 10.1016/j.jacc.2010.08.635]
23 **Ashton AW**, Le TY, Gomez-Sanchez CE, Morel-Kopp MC, McWhinney B, Hudson A, Mihailidou AS. Role of Nongenomic Signaling Pathways Activated by Aldosterone During Cardiac Reperfusion Injury. *Mol Endocrinol* 2015; **29**: 1144-1155 [PMID: 26121234 DOI: 10.1210/ME.2014-1410]
24 **Faresse N**. Post-translational modifications of the mineralocorticoid receptor: How to dress the receptor according to the circumstances? *J Steroid Biochem Mol Biol* 2014; **143**: 334-342 [PMID: 24820770 DOI: 10.1016/j.jsbmb.2014.04.015]
25 **Fuller PJ**. Novel interactions of the mineralocorticoid receptor. *Mol Cell Endocrinol* 2015; **408**: 33-37 [PMID: 25662276 DOI: 10.1016/j.mce.2015.01.027]
26 **Oakley RH**, Cruz-Topete D, He B, Foley JF, Myers PH, Xu X, Gomez-Sanchez CE, Chambon P, Willis MS, Cidlowski JA. Cardiomyocyte glucocorticoid and mineralocorticoid receptors directly and antagonistically regulate heart disease in mice. *Sci Signal* 2019; **12** [PMID: 30992401 DOI: 10.1126/scisignal.aau9685]
27 **Markan U**, Pasupuleti S, Pollard CM, Perez A, Aukszi B, Lymperopoulos A. The place of ARBs in heart failure therapy: is aldosterone suppression the key? *Ther Adv Cardiovasc Dis* 2019; **13**: 1753944719868134 [PMID: 31401939 DOI: 10.1177/1753944719868134]
28 **Lymperopoulos A**, Aukszi B. Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy. *World J Cardiol* 2017; **9**: 200-206 [PMID: 28400916 DOI: 10.4330/wjc.v9.i3.200]
29 **Juurlink DN**, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after

publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351**: 543-551 [PMID: 15295047 DOI: 10.1056/NEJMoa040135]

30 **Shibata S**, Rinehart J, Zhang J, Moeckel G, Castañeda-Bueno M, Stiegler AL, Boggon TJ, Gamba G, Lifton RP. Mineralocorticoid receptor phosphorylation regulates ligand binding and renal response to volume depletion and hyperkalemia. *Cell Metab* 2013; **18**: 660-671 [PMID: 24206662 DOI: 10.1016/j.cmet.2013.10.005]

31 **Eijgelsheim M**, Visser LE, Uitterlinden AG, Stricker BH. Protective effect of a GRK5 polymorphism on heart failure and its interaction with beta-adrenergic receptor antagonists. *Pharmacogenomics* 2008; **9**: 1551-1555 [PMID: 18855542 DOI: 10.2217/14622416.9.10.1551]

32 **Wu JH**, Zhang L, Fanaroff AC, Cai X, Sharma KC, Brian L, Exum ST, Shenoy SK, Peppel K, Freedman NJ. G protein-coupled receptor kinase-5 attenuates atherosclerosis by regulating receptor tyrosine kinases and 7-transmembrane receptors. *Arterioscler Thromb Vasc Biol* 2012; **32**: 308-316 [PMID: 22095977 DOI: 10.1161/ATVBAHA.111.239608]

33 **Montó F**, Oliver E, Vicente D, Rueda J, Agüero J, Almenar L, Ivorra MD, Barettino D, D'Ocon P. Different expression of adrenoceptors and GRKs in the human myocardium depends on heart failure etiology and correlates to clinical variables. *Am J Physiol Heart Circ Physiol* 2012; **303**: H368-H376 [PMID: 22685168 DOI: 10.1152/ajpheart.01061.2011]

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ORIGINAL ARTICLE

Observational Study

Association of dissected ascending aorta diameter with preoperative adverse events in patients with acute type A aortic dissection

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Abstract

BACKGROUND

Acute type A aortic dissection (ATAAD) is a life-threatening disease associated with high morbidity and mortality.

AIM

To evaluate the diameter of dissected ascending aorta in patients diagnosed with ATAAD and whether the aortic diameter is associated with preoperative adverse events.

METHODS

A total of 108 patients diagnosed with ATAAD who underwent emergency operation under hypothermic circulatory arrest were enrolled in this study. Demographic characteristics and perioperative data were recorded. In all patients, preoperative chest and abdomen computed tomography (CT) scans were performed.

RESULTS

Median age of the patients was 61.5 (52.5-70.5) years and median body mass index (BMI) was 28.2 (25.1-32.6) cm^2. The number of female patients was 37 (25%). Median diameter of the ascending aorta was 5.0 (4.5-6) cm and 53.8% of the patients had an aortic diameter < 5.0 cm, while 32.3% of the patients had an aortic diameter of 4.5cm and 72.0% had an ascending aorta diameter < 5.5 cm. The diameter of the ascending aorta did not differ in patients with *vs* without preoperative adverse events: Preoperative neurological dysfunction (P = 0.53) and hemodynamic instability (P = 0.43). Median age of patients with preoperative hemodynamic instability was 65 (57.5-74) years, while it was 60 (51-68) years in patients without (P = 0.04)

CONCLUSION
Although current guidelines suggest replacing the ascending aorta with a diameter > 5.5 cm, most of the patients with ATAAD had an aortic diameter of less than 5.5 cm. The diameter of the ascending aorta in patients diagnose with ATAAD is not associated with preoperative adverse events.

Key Words: Acute; Aortic dissection; Type A; Ascending aorta; Diameter

Core Tip: Do patients with an ascending aorta diameter < 5.5 cm undergo more aggressive surgery for prevention of acute type A aortic dissection (ATAAD)? Most of the patients (72.0%) with ATAAD had an ascending aorta diameter < 5.5 cm. An international taskforce should adapt the new data extracted from the most recent scientific evidence in the surgical treatment of the ascending aortic aneurysm.

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INTRODUCTION

Acute type A aortic dissection (ATAAD) is a life-threatening condition with excessive mortality and morbidity if not operated, reaching approximately 50% during the first 24 h and 70%-90% days and weeks after diagnosis[1-3]. Emergency surgical correction with replacement of the ascending aorta with or without aortic arch, despite being the treatment of choice, also carries a significant mortality and morbidity burden. Nowadays, emergency surgical correction of ATAAD under hypothermic circulatory arrest remains the treatment of choice[4-6]. On the other hand, the mortality rate of patients who underwent ATAAD repair is high at approximately 15%-25%[7-9].

The most common clinical manifestation of thoracic aorta dissection is acute chest pain. Due to the much commoner incidence of acute coronary syndrome (ACS), pulmonary embolism (PE), and other thoracic pathology, accurate diagnosis is frequently hindered or delayed. The sudden and insidious onset of symptoms, the delay in diagnosis, and the time required to transport of patients to cardiac surgery centers for treatment negatively affect the outcomes of these patients[10-12]. Replacement of the ascending aorta in patients with an enlarged aortic diameter is considered as an option for preventing acute aortic dissection. Existing and current guidelines recommend replacing the ascending aorta if the size reaches 5.5 cm in patients without Marfan syndrome[6,13]. On the other hand, the exact threshold of aortic size (< 5.5 cm) for early (preventive) operation remains a grey zone in current indications and guidelines, because in most patients with acute aortic dissection, the maximum aortic diameter is approximately 5 cm or less[14-17].

The present study evaluated the diameter of dissected ascending aorta in patients diagnosed with ATAAD and whether the aortic diameter is associated with preoperative adverse events.

MATERIALS AND METHODS

Study population

The study period was 2010-2017. This retrospective study included 108 patients with ATAAD who underwent an emergency operation under hypothermic circulatory arrest with antegrade or retrograde cerebral perfusion. Patients with a known diagnosis of connective tissue disorder or Marfan syndrome or iatrogenic dissection were excluded. All demographic characteristics and perioperative data were recorded. In all patients, preoperative chest and abdomen computed tomography (CT) scans were performed. The ascending aorta diameter was calculated based on preoperative chest CT or CT angiography. The maximum diameter of the ascending aorta was defined as the diameter which included the true and false lumen of the ascending aorta. The method for measuring the maximum aortic diameter was double oblique short axis. All preoperative neurological dysfunctions (including temporary and permanent neurological dysfunctions) on admission were included in our database. Temporary neurological dysfunctions (TND) were defined if the patients had transient ischemic attack (TIA) or delirium or disorientation, while permanent neurological dysfunctions (PND) if the patients

were admitted to hospital with hemiplegia or paraplegia or coma. Preoperative hemodynamic instability was defined as preoperative cardiac arrest or systolic blood pressure (< 80 mmHg) despite inotropic support or preoperatively diagnosed cardiac tamponade with hemodynamic consequences. The study was approved by the hospital's institutional review board (546/30-04-2015).

Statistical analysis

Continuous variables are presented as the median (interquartile range), while categorical variables are presented as *n* (%). Normality of continuous variables was examined by Shapiro-Wilk test and Q-Q plot. Continuous variables were compared by Student's *t*-test for the normally distributed, while Mann-Whitney and Kruskal-Wallis tests for the non-normally distributed variables. Chi-square or Fisher's exact test was implemented for the rest variables (categorical variables). Correlation of ascending aorta diameter with continuous variables was evaluated by Spearman (r_s) or Pearson (r) correlation coefficient. Univariable linear regression model was used to identify the association of demographics and other factors with diameter of the ascending aorta. The effect size was expressed by linear regression coefficient ''β''. Binary univariable and multivariable logistic regression modeling was used to estimate the association of ascending aorta diameter with preoperative adverse events (neurological dysfunction and hemodynamic instability). Predictive ability is presented as odds ratio (OR). The Hosmer-Lemeshow goodness of fit test was performed for logistic regression analysis model. Confidence interval (CI) was set at 95% in all tests. Statistical significance was considered at $P < 0.05$. IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, United States) was used in analysis.

RESULTS

Median age of the patients was 61.5 (52.5-70.5) years and median body mass index (BMI) was 28.2 (25.1-32.6) cm^2. Thirty-seven (25%) were female patients. Median diameter of the ascending aorta was 5.0 (4.5-6) cm and 53.8% of patients had an aortic diameter < 5.0 cm, while 32.3% of the patients had an aortic diameter of 4.5 cm. In addition, 72.0% of the patients had an ascending aorta diameter < 5.5 cm. Coexisting aortic regurgitation was recorded in 26.8% of the patients, while history of hypertension was observed in 86.1%. Other demographic characteristics and preoperative details are listed in Table 1.

We tested the correlation of aortic diameter with age, BMI, LVEF, D-dimer, and NT-proBNP. No correlation was detected between aortic diameter and age ($r = 0.13$, $P = 0.20$), BMI ($r = 0.05$, $P = 0.67$), LVEF ($r = 0.08$, $P = 0.47$), D-dimer ($r_s = -0.14$, $P = 0.31$), or NT-proBNP ($r_s = 0.19$, $P = 0.14$). No difference in ascending aorta diameters was observed between males *vs* females ($P = 0.83$), as well as between patients with *vs* without history of hypertension ($P = 0.87$) and smoking *vs* no smoking ($P = 0.90$). The BMI did not predict the diameter of the ascending aorta [β = 0.01, 95%CI: -0.05 to 0.08, $P = 0.68$]. Preoperative plasma creatinine was not associated with the diameter of the ascending aorta (β = 0.09, 95%CI: -0.19-0.36, $P = 0.53$).

The diameter of the ascending aorta did not differ in patients with *vs* without preoperative adverse events: Preoperative neurological dysfunction ($P = 0.53$) and hemodynamic instability ($P = 0.43$). In addition, univariable logistic regression analysis showed that aortic diameter did not predict the preoperative hemodynamic instability (OR = 1.2, 95%CI: 0.87-1.60, $P = 0.29$) or preoperative neurological dysfunction (OR = 1.0, 95%CI: 0.72-1.51, $P = 0.81$). Multivariable logistic regression analysis (adjusted for age, gender, and BMI) showed that aortic diameter did not predict preoperative neurological dysfunction (OR = 1.1, 95%CI: 0.68-1.74, $P = 0.70$) (Table 2). Furthermore, multivariable logistic regression analysis (adjusted for age, gender, BMI, and aortic diameter) revealed that only age predicted the preoperative hemodynamic instability (OR = 1.05, 95%CI: 1.01-1.11, $P = 0.02$), while diameter of the aorta did not (OR=1.1, 95%CI: 0.68-1.57, $P = 0.86$) (Table 3). Median age of the patients with preoperative hemodynamic instability was 65 (57.5-74) years, while it was 60 (51-68) years in those without ($P = 0.04$) (Figure 1). In conclusion, our analysis showed that no difference in dissected ascending aorta diameter was observed between patients who died in hospital *vs* who did not ($P = 0.75$). In addition, the diameter of dissected ascending aorta was not correlated with postoperative ICU or hospital stay ($r_s = -0.08$, $P = 0.45$ and $r_s = -0.02$, $P = 0.85$, respectively).

DISCUSSION

Currently, American and European guidelines are in agreement regarding the main criterion for elective surgical aneurysm resection in the thoracic aorta: The size of the aortic diameter[6,13]. For non-syndromic, asymptomatic aortic aneurysmal disease, the indicative diameter threshold for elective replacement of the ascending aorta is 5.5 cm. However, these guidelines are relying on post-dissection diameter measurements, which are much larger than diameter size prior to dissection[6,13].

Table 1 Demographic characteristics and preoperative details of patients

Variable	Total number of patients (*N* = 108)
Age, yr, median (IQR)	61.5 (52.5-70.5)
Body mass index, cm^2, median (IQR)	28.2 (25.1-32.6)
Female, *n* (%)	37 (25)
History of hypertension, *n* (%)	93 (86.1)
History of smoking, *n* (%)	65 (60.2)
Aortic regurgitation, *n* (%)	29 (26.8)
Left ventricle ejection fraction, %, median (IQR)	45 (40-50)
Diabetes mellitus, *n* (%)	11 (10.2)
Preoperative neurological dysfunction, *n* (%)	22 (16.1)
Temporary neurological dysfunction	14 (13.0)
Permanent neurological dysfunction	3 (2.7)
Preoperative hemodynamic instability, *n* (%)	35 (32.4)
Maximum diameter of ascending aorta, cm, median (IQR)	5.0 (4.5-6)
NT-proBNP, pg/mL, median (IQR)	377.5 (180-928)
D-Dimers, μg/L, median (IQR)	5256.5 (2477-10000)

NT-proBNP: N-terminal pro-brain natriuretic peptide; IQR: Interquartile range.

Table 2 Multivariable logistic regression analysis of risk factors for preoperative neurological dysfunction

Variable	*P* value	OR	95%CI
Age	0.28	1.1	0.97-1.09
Gender	0.46	1.7	0.38-8.12
Body mass index	0.42	1.1	0.92-1.19
Diameter of ascending aorta	0.70	1.1	0.68-1.74

OR: Odds ratio; CI: Confidence interval.

Table 3 Multivariable logistic regression analysis of risk factors for preoperative hemodynamic instability

Variable	*P* value	OR	95%CI
Age	0.02[1]	1.05	1.01-1.11
Gender	0.76	0.81	0.21-3.11
Body mass index	0.56	0.97	0.86-1.08
Diameter of ascending aorta	0.86	1.1	0.68-1.57

[1]Statistical significance ($P < 0.05$).
OR: Odds ratio; CI: Confidence interval.

There is evidence to suggest that the size of the aorta significantly increases post-dissection[18]. Mansour *et al*[18] from the Aortic Institute at Yale-New Haven Hospital demonstrated that the mean aortic diameter at ATAAD was 54.2 mm, whereas the mean aortic diameter prior to dissection was only 45.1 mm[18]. Wu *et al*[19] described an 18% increase in aortic diameter after an ATAAD. Therefore, the pre-dissection aortic diameter falls in several studies well below the current threshold for elective surgical replacement of the ascending aorta. Saade *et al*[20] introduced the term aortic size index in order to stratify patients into risk groups. It was calculated by dividing the aortic diameter by the body

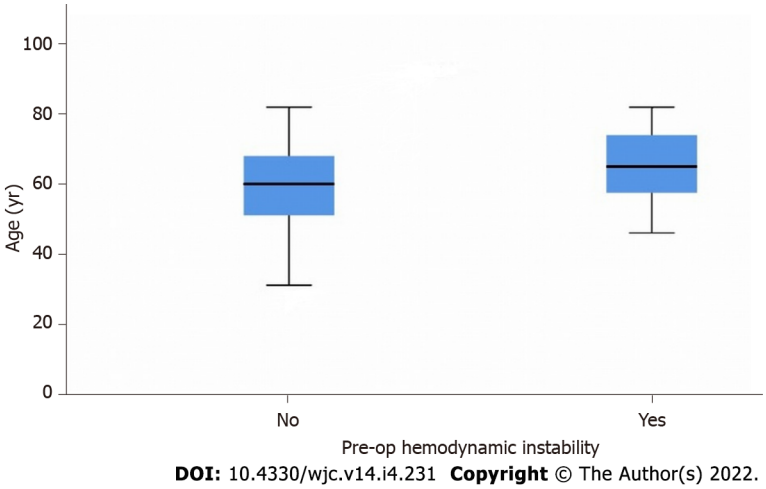

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Figure 1 Boxplot graph for the age of patients with and without preoperative hemodynamic instability (*P* = 0.04).

surface area. However, 10 years later, researchers from the same institution argued against that theory and concluded that body surface area should not be taken into consideration[21]. The same researchers focused on the importance of aortic height index, which is calculated by dividing the aortic diameter by the patient's height. An increased index is associated with an increased annual risk of aortic aneurysm complications[21]. Eliathamby *et al*[22] concluded that the aortic length (distance between the aortic valve and the innominate artery) was strongly correlated with the diameter of the ascending aorta. Wu *et al*[19] suggested the length-height index, which is calculated by dividing the aortic length by the patient's height. An index > 7.5 cm/m was found to have an annual fivefold increased risk of aortic adverse events compared with patients with an index < 5.5 cm/m. However, genetic susceptibility should always be taken into account as it plays an important role in identifying high risk patients[19,23].

ATAAD continues to carry a high peri-operative mortality risk with rates reaching as high as 25%[23,24]. Many authors highlight the safety of preventive surgical replacement of the ascending aorta as published data on elective replacement of the ascending aorta is associated with mortality rates less than 3%[23,24]. For elective operations, postoperative stroke rates are also low with no more than 1.0% strokes noted when the operation takes place in a large volume aortic centre[25]. Moreover, emergency surgical operations show a 5-year survival rate of 37%, rather poorer than the rate (> 85%) related to elective surgical repair of the ascending aorta[25].

CONCLUSION

Although current guidelines suggest replacing the ascending aorta with a diameter ≥ 5.5 cm, many of the patients with ATAAD have an aortic diameter of less than 5.5 cm. The diameter of the ascending aorta in patients diagnosed with ATAAD is not associated with preoperative adverse events. An international taskforce should adapt the new data extracted from the most recent scientific evidence for the surgical treatment of the ascending aortic aneurysm.

ARTICLE HIGHLIGHTS

Research background

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular disease. Current guidelines recommend that ascending aortic replacement be performed when the ascending aorta is 5.5 cm in non-syndromic patients, while in syndormic patients, it should be replaced if the diameter reaches 4.5 cm in the sinus of Valsalva and 5.0 cm in the ascending aorta.

Research motivation

New approach for ascending aorta aneurysm management should be considered for prevention of ATAAD.

Research objectives

The objective of our study was to evaluate the correlation of the diameter of dissected ascending aorta in patients with ATAAD with preoperative adverse events, such as neurological dysfunctions and

hemodynamic instability.

Research methods
A retrospective analysis was performed on patients who were admitted to our hospital for ATAAD treatment. In all patients, the diameter of dissected ascending aorta was measured and its association with adverse events was analyzed.

Research results
The diameter of dissected ascending aorta was not associated with adverse events. Also, the diameter of the ascending aorta was not associated with 30-d mortality and ICU and hospital stay postoperatively.

Research conclusions
Maybe the threshold of ascending aorta aneurysm should be revised for lower limits regarding the risk for late acute dissection

Research perspectives
Randomized controlled studies including more patients should be performed to confirm our results and preventive ascending aorta replacement may be considered for prevention of ATAAD.

FOOTNOTES

Author contributions: All authors contributed equally in carrying out the research and writing the manuscript.

Institutional review board statement: The study was approved by our hospital's institutional review board (No. 546/30-04-2015).

Conflict-of-interest statement: All authors declare that there are no any conflicts of interest to disclose.

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REFERENCES

1 **Khan H**, Hussain A, Chaubey S, Sameh M, Salter I, Deshpande R, Baghai M, Wendler O. Acute aortic dissection type A: Impact of aortic specialists on short and long term outcomes. *J Card Surg* 2021; **36**: 952-958 [PMID: 33415734 DOI: 10.1111/jocs.15292]
2 **Luehr M**, Merkle-Storms J, Gerfer S, Li Y, Krasivskyi I, Vehrenberg J, Rahmanian P, Kuhn-Régnier F, Mader N, Wahlers T. Evaluation of the GERAADA score for prediction of 30-day mortality in patients with acute type A aortic dissection. *Eur J Cardiothorac Surg* 2021; **59**: 1109-1114 [PMID: 33374014 DOI: 10.1093/ejcts/ezaa455]
3 **Helgason D**, Helgadottir S, Ahlsson A, Gunn J, Hjortdal V, Hansson EC, Jeppsson A, Mennander A, Nozohoor S, Zindovic I, Olsson C, Ragnarsson SO, Sigurdsson MI, Geirsson A, Gudbjartsson T. Acute Kidney Injury After Acute Repair of Type A Aortic Dissection. *Ann Thorac Surg* 2021; **111**: 1292-1298 [PMID: 32961133 DOI: 10.1016/j.athoracsur.2020.07.019]
4 **Pupovac SS**, Hemli JM, Bavaria JE, Patel HJ, Trimarchi S, Pacini D, Bekeredjian R, Chen EP, Myrmel T, Ouzounian M, Fanola C, Korach A, Montgomery DG, Eagle KA, Brinster DR. Moderate Versus Deep Hypothermia in Type A Acute Aortic Dissection Repair: Insights from the International Registry of Acute Aortic Dissection. *Ann Thorac Surg* 2021; **112**: 1893-1899 [PMID: 33515541 DOI: 10.1016/j.athoracsur.2021.01.027]
5 **Li L**, Zhou J, Hao X, Zhang W, Yu D, Xie Y, Gu J, Zhu T. The Incidence, Risk Factors and In-Hospital Mortality of Acute Kidney Injury in Patients After Surgery for Acute Type A Aortic Dissection: A Single-Center Retrospective Analysis of 335 Patients. *Front Med (Lausanne)* 2020; **7**: 557044 [PMID: 33178711 DOI: 10.3389/fmed.2020.557044]

6 **Erbel R**, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**: 2873-2926 [PMID: 25173340 DOI: 10.1093/eurheartj/ehu281]

7 **Rylski B**, Hoffmann I, Beyersdorf F, Suedkamp M, Siepe M, Nitsch B, Blettner M, Borger MA, Weigang E; Multicenter Prospective Observational Study. Acute aortic dissection type A: age-related management and outcomes reported in the German Registry for Acute Aortic Dissection Type A (GERAADA) of over 2000 patients. *Ann Surg* 2014; **259**: 598-604 [PMID: 23657079 DOI: 10.1097/SLA.0b013e3182902cca]

8 **Jassar AS**, Sundt TM 3rd. How should we manage type A aortic dissection? *Gen Thorac Cardiovasc Surg* 2019; **67**: 137-145 [PMID: 29926291 DOI: 10.1007/s11748-018-0957-3]

9 **Gudbjartsson T**, Ahlsson A, Geirsson A, Gunn J, Hjortdal V, Jeppsson A, Mennander A, Zindovic I, Olsson C. Acute type A aortic dissection - a review. *Scand Cardiovasc J* 2020; **54**: 1-13 [PMID: 31542960 DOI: 10.1080/14017431.2019.1660401]

10 **Matthews CR**, Madison M, Timsina LR, Namburi N, Faiza Z, Lee LS. Impact of time between diagnosis to treatment in Acute Type A Aortic Dissection. *Sci Rep* 2021; **11**: 3519 [PMID: 33568755 DOI: 10.1038/s41598-021-83180-6]

11 **Pan E**, Wallinder A, Peterström E, Geirsson A, Olsson C, Ahlsson A, Fuglsang S, Gunn J, Hansson EC, Hjortdal V, Mennander A, Nozohoor S, Wickbom A, Zindovic I, Gudbjartsson T, Jeppsson A. Outcome after type A aortic dissection repair in patients with preoperative cardiac arrest. *Resuscitation* 2019; **144**: 1-5 [PMID: 31505231 DOI: 10.1016/j.resuscitation.2019.08.039]

12 **Teman NR**, Peterson MD, Russo MJ, Ehrlich MP, Myrmel T, Upchurch GR Jr, Greason K, Fillinger M, Forteza A, Deeb GM, Montgomery DG, Eagle KA, Isselbacher EM, Nienaber CA, Patel HJ. Outcomes of patients presenting with acute type A aortic dissection in the setting of prior cardiac surgery: an analysis from the International Registry of Acute Aortic Dissection. *Circulation* 2013; **128**: S180-S185 [PMID: 24030404 DOI: 10.1161/CIRCULATIONAHA.112.000342]

13 **Hiratzka LF**, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American College of Radiology; American Stroke Association; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of Thoracic Surgeons; Society for Vascular Medicine. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. *J Am Coll Cardiol* 2010; **55**: e27-e129 [PMID: 20359588 DOI: 10.1016/j.jacc.2010.02.015]

14 **Heuts S**, Adriaans BP, Rylski B, Mihl C, Bekkers SCAM, Olsthoorn JR, Natour E, Bouman H, Berezowski M, Kosiorowska K, Crijns HJGM, Maessen JG, Wildberger J, Schalla S, Sardari Nia P. Evaluating the diagnostic accuracy of maximal aortic diameter, length and volume for prediction of aortic dissection. *Heart* 2020; **106**: 892-897 [PMID: 32152004 DOI: 10.1136/heartjnl-2019-316251]

15 **Yamauchi T**, Takano H, Takahashi T, Masai T, Sakaki M, Shirakawa Y, Kitabayashi K, Asano N, Toda K, Sawa Y; Osaka Cardiovascular Surgery Research Group (OSCAR). Equations Estimating the Predissected Diameter of the Ascending Aorta for Acute Type A Aortic Dissection. *Ann Thorac Surg* 2019; **108**: 481-490 [PMID: 30914284 DOI: 10.1016/j.athoracsur.2019.02.046]

16 **Wang D**, Wang ZY, Wang JF, Zhang LL, Zhu JM, Yuan ZX, Wang Y. Values of aortic dissection detection risk score combined with ascending aorta diameter >40 mm for the early identification of type A acute aortic dissection. *J Thorac Dis* 2018; **10**: 1815-1824 [PMID: 29707336 DOI: 10.21037/jtd.2018.02.42]

17 **Tozzi P**, Gunga Z, Niclauss L, Delay D, Roumy A, Pfister R, Colombier S, Patella F, Qanadli SD, Kirsch M. Type A aortic dissection in aneurysms having modelled pre-dissection maximum diameter below 45 mm: should we implement current guidelines to improve the survival benefit of prophylactic surgery? *Eur J Cardiothorac Surg* 2021; **59**: 473-478 [PMID: 33006606 DOI: 10.1093/ejcts/ezaa351]

18 **Mansour AM**, Peterss S, Zafar MA, Rizzo JA, Fang H, Charilaou P, Ziganshin BA, Darr UM, Elefteriades JA. Prevention of Aortic Dissection Suggests a Diameter Shift to a Lower Aortic Size Threshold for Intervention. *Cardiology* 2018; **139**: 139-146 [PMID: 29346780 DOI: 10.1159/000481930]

19 **Wu J**, Zafar MA, Li Y, Saeyeldin A, Huang Y, Zhao R, Qiu J, Tanweer M, Abdelbaky M, Gryaznov A, Buntin J, Ziganshin BA, Mukherjee SK, Rizzo JA, Yu C, Elefteriades JA. Ascending Aortic Length and Risk of Aortic Adverse Events: The Neglected Dimension. *J Am Coll Cardiol* 2019; **74**: 1883-1894 [PMID: 31526537 DOI: 10.1016/j.jacc.2019.07.078]

20 **Saade W**, Vinciguerra M, Romiti S, Macrina F, Frati G, Miraldi F, Greco E. 3D morphometric analysis of ascending aorta as an adjunctive tool to predict type A acute aortic dissection. *J Thorac Dis* 2021; **13**: 3443-3457 [PMID: 34277040 DOI: 10.21037/jtd-21-119]

21 **Zafar MA**, Li Y, Rizzo JA, Charilaou P, Saeyeldin A, Velasquez CA, Mansour AM, Bin Mahmood SU, Ma WG, Brownstein AJ, Tranquilli M, Dumfarth J, Theodoropoulos P, Thombre K, Tanweer M, Erben Y, Peterss S, Ziganshin BA, Elefteriades JA. Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. *J Thorac Cardiovasc Surg* 2018; **155**: 1938-1950 [PMID: 29395211 DOI: 10.1016/j.jtcvs.2017.10.140]

22 **Eliathamby D**, Gutierrez M, Liu A, Ouzounian M, Forbes TL, Tan KT, Chung J. Ascending Aortic Length and Its Association With Type A Aortic Dissection. *J Am Heart Assoc* 2021; **10**: e020140 [PMID: 34121418 DOI: 10.1161/JAHA.120.020140]

23 **Rylski B**, Branchetti E, Bavaria JE, Vallabhajosyula P, Szeto WY, Milewski RK, Desai ND. Modeling of predissection aortic size in acute type A dissection: More than 90% fail to meet the guidelines for elective ascending replacement. *J Thorac Cardiovasc Surg* 2014; **148**: 944-8.e1 [PMID: 24998700 DOI: 10.1016/j.jtcvs.2014.05.050]

24 **Ziganshin BA**, Zafar MA, Elefteriades JA. Descending threshold for ascending aortic aneurysmectomy: Is it time for a "left-shift" in guidelines? *J Thorac Cardiovasc Surg* 2019; **157**: 37-42 [PMID: 30557953 DOI: 10.1016/j.jtcvs.2018.07.114]

25 **Kuzmik GA**, Sang AX, Elefteriades JA. Natural history of thoracic aortic aneurysms. *J Vasc Surg* 2012; **56**: 565-571 [PMID: 22840907 DOI: 10.1016/j.jvs.2012.04.053]

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ORIGINAL ARTICLE

Retrospective Study

Global longitudinal strain is superior to ejection fraction for detecting myocardial dysfunction in end-stage renal disease with hyperparathyroidism

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Abstract

BACKGROUND

The estimation of left ventricular ejection fraction (LVEF) by 2D echocardiography (2D-ECHO) is the most used tool to assess LV systolic function (LVSF). Global longitudinal strain (GLS) has recently been suggested as a superior method for

several evaluations. This study explored the association and prevalence of LV systolic dysfunction (LVSD) by using these methods in patients with end-stage renal disease (ESRD) and severe hyperparathyroidism (SHPTH); both associated with cardiovascular events (CEs).

AIM

To evaluate the myocardial function in patients with ESRD and SHPTH by using the GLS and LVEF measured through conventional 2D-ECHO.

METHODS

In 62 patients with ESRD and SHPTH, asymptomatic, and without a history of CEs, LVSF was evaluated by 2D-ECHO, obtaining the EF, by the Simpson biplane method, and GLS by speckle tracking.

RESULTS

The total patients with ESRD had a preserved LVEF (> 50%) but abnormal GLS (< 13.55%). Additionally, multivariate analysis showed an independent association of GLS and serum parathyroid hormone (PTH), LV mass index, and hemoglobin. Also, PTH was independently associated with lateral e' wave and tricuspid regurgitation velocity.

CONCLUSION

In patients with SHPTH linked to ESRD, the use of GLS by 2D-ECHO is a more sensitive tool than LVEF for detecting LVSD.

Key Words: Left ventricular hypertrophy; Systolic dysfunction; Global longitudinal strain; End-stage renal disease; Parathormone

Core Tip: This study compared global longitudinal strain (GLS) with the often-used left ventricular ejection fraction to estimate ventricular dysfunction in patients with end-stage renal disease. GLS had an advantage to detect dysfunction, but also, it was found that the parathyroid hormone levels were attractive as a complementary tool to predict patient status.

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INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Heart failure (HF) is a cardiovascular event (CE) that may occur simultaneously in these patients[1-3]. Chronic elevated pressure, volume overload and nonhemodynamic factors including inappropriate activation of the renin–angiotensin–aldosterone system (RAAS) and alterations in calcium–phosphorus mineral metabolism by an excess of parathyroid hormone[4,5] are involved in left ventricular hypertrophy (LVH)[6,7], then, in the myocardial dysfunction in ESRD[3,8].

LV ejection fraction (LVEF) calculated by 2D echocardiography (2D-ECHO) is the most widely used echocardiographic parameter that provides objective information on LV systolic function (LVSF), and it has been used as a prognostic and treatment indicator for CVD[9-11]. However, in some studies involving patients with ESRD, LVEF fails as a sensitive parameter for detecting subclinical data of LV systolic dysfunction (LVSD). In this sense, research groups have explored new variables and methods to increase the early and efficient diagnosis and prognosis of patients with LVSD[12]. Thus, for example, determination of left atrial volume[13], natriuretic peptides (NPs)[14] and catecholamines metabolites in serum (related to sympathetic overactivity)[15] have been proposed as advantageous tools.

Special attraction is on alternative 2D-ECHO methods, specifically, predialysis and peritoneal dialysis patients with preserved LVEF (> 50%) showed reduced GLS (15%), which was associated with an increased risk of HF hospitalization and increased mortality[3]. Thus, GLS may be a better tool to assess

subclinical changes in LVSD in particular cases, for example, where the LVEF is preserved as in those patients subject to volume or pressure overload, or both[3,16]. Additionally, studies have mentioned that the variables used to define a preserved LVEF and a reduced GLS are associated with differences between the characteristics of the population studied (race, stage of ESRD, risk factors, and comorbidities). However, despite this variability, GLS is an important echocardiographic tool that might be used in patients with ESRD to identify those with a high-risk prognosis for developing HF or other CEs.

In the present study, a comparison was made from echocardiographic changes in patients with ESRD and hyperparathyroidism, the degree of LV remodeling, LVSF using 2D-ECHO, EF (by Simpson's method), and GLS (by Speckle tracking). Additionally, plasma parathyroid hormone (PTH) concentration was considered to increase ability to detect LVSD in patients with ESRD and hyperparathyroidism (a common hormone elevated in ESRD, but poorly explored or linked to CEs in these patients).

MATERIALS AND METHODS

This study was done in patients with asymptomatic ESRD with renal replacement therapy (RRT; dialysis and hemodialysis) and with no history of CEs. The degree of LVDD (I, II or III) was assigned by applying the Nagueh SF, 2020 recommendations[17], and the measurement of plasma PTH in relation to the LVSF and LV diastolic function (LVDF) was explored.

This retrospective and observational study included a total of 77 individuals divided into three groups: healthy individuals with no known disease (Control; n = 15), age > 18 years, both genders; patients with ESRD on hemodialysis (ESRD-HD; n = 31) and patients with ESRD on peritoneal dialysis (ESRD-PD; n = 31). The ESRD groups came from the Nephrology service of Centro Médico SXXI, IMSS. This study was carried out from February 2019 to October 2020.

All patients with ESRD maintained their RRT and were supplemented with calcium and calcitriol following clinical practice guidelines[18]. Those individuals with hemodynamic alterations increasing risk on their physical integrity were excluded. A complete medical history was taken. Demographic, clinical and comorbid characteristics were collected. A blood sample was collected in the morning before the RRT, and 4 h later, echocardiography was performed.

Echocardiography

Transthoracic echocardiography images were obtained using a commercially available ultrasound system (Ecocardiograph iE33; Philips). Standard 2D Doppler, color, pulsed and continuous wave echocardiographic acquisitions were made. LV dimensions were obtained from images in a long axis parasternal view, and LV mass and body surface area-corrected indexed LV mass were calculated. In addition, the relative wall thickness was obtained as a ratio of (2 × RWTd) / LVIDd, where RWTd is the back-wall thickness, and LVIDd is the internal diameter of the LV at the end of diastole. The LV end-diastolic and systolic volumes were then measured from the apical views (two and four chambers) using the Simpson biplane method[19]. Mitral annulus early diastolic velocity (E') was identified by tissue Doppler imaging in a four-chamber view. Mitral inflow velocities, such as transmitral peak early passive filling velocity (E), late diastolic filling velocity caused by atrial contraction (A), and deceleration time, were determined using Pw-Doppler over the mitral valve in four-chamber views. The degree of diastolic dysfunction of each patient was assessed[17].

GLS was evaluated by obtaining LV grayscale scatter images from all three apical views. From the 2D images, the endocardial border was manually drawn during the end of the systole, and the thickness of the myocardial region of interest was adjusted to include the entire thickness of the myocardial wall. In each echocardiographic view, the myocardium was automatically divided into six segments. Therefore, the overall maximum systolic longitudinal pressure was calculated by averaging the maximum systolic values of all 18 segments, derived from the three apical views (six segments in each apical view) adjusted to the heart rate.

Biostatistics

Continuous variables are expressed as the mean ± SD. Continuous variables were compared between groups using ANOVA and then a χ^2 test. A multivariate logistic regression analysis was used, which included the clinical and echocardiographic parameters associated with the univariate analysis as independent variables. $P < 0.05$ was considered statistically significant. The statistical analysis was performed with SPSS version 20.

RESULTS

The characteristics were as follows from the total population: 48 participants were female (62%) and 29

Table 1 Demographic and clinical variables in the study groups

Demographic variables	Control, *n* = 15	ESRD-HD, *n* = 15	ESRD-PD, *n* = 15	Total, *n* = 15
Age (yr)	34 ± 13	36 ± 2	34 ± 10	34.6 ±
Gender, *n* (%)	F = 10 (67), M = 5 (33)	F = 26 (84), M = 5 (16)	F = 12 (39), M = 19 (61)	F = 48 (62), M = 29 (38)
BMI (kg/m^2)	23.4	23.3	22.4	23 ±
Hypertension, *n* (%)	N/A	28 (90)	31 (100)	59 (77)
DMT2, *n* (%)	N/A	2 (6.45)	5 (16)	7 (9.09)

ESRD: End-stage renal disease; ESRD-HD: ESRD on hemodialysis; ESRD-PD: ESRD on peritoneal dialysis; F: Female; M: Male; BMI: Body mass index; N/A: Not available.

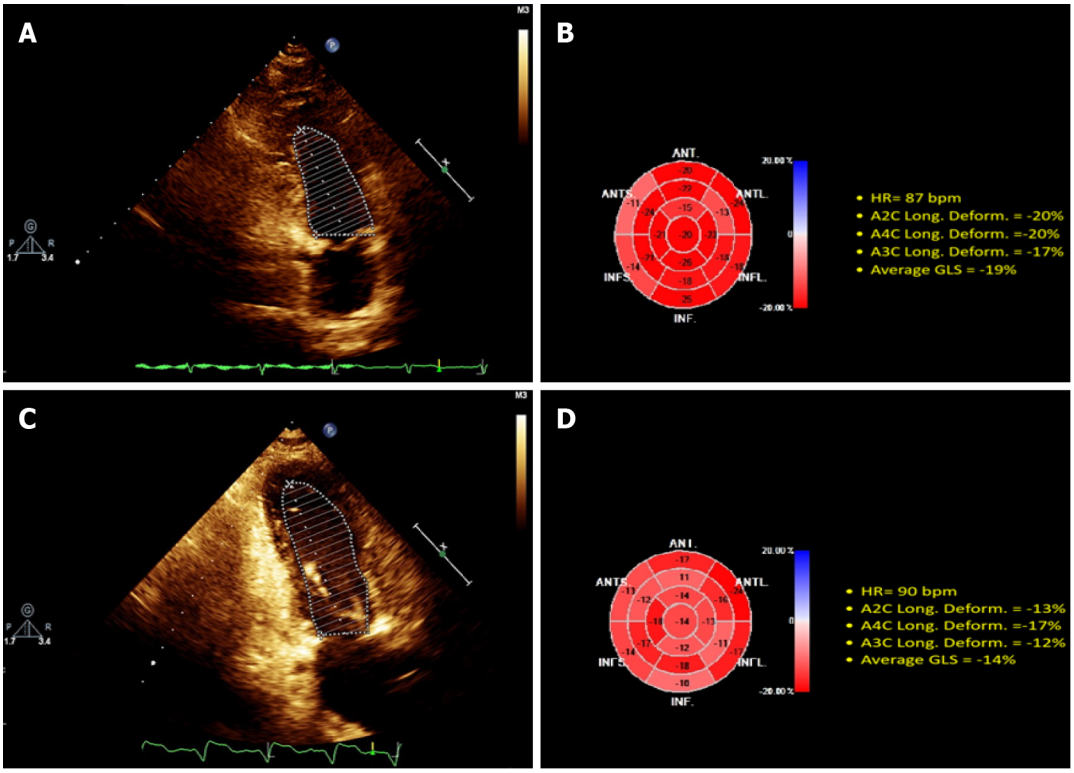

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Figure 1 Illustrative 2D echocardiography. Top: control patient; Bottom: patient with end-stage renal disease (ESRD) and severe hyperparathyroidism (SHPTH). The ejection fraction (EF) by the Simpson method was calculated as a function of the endocardial borders at end-diastole and end-systole in the apical projection of two cavities. A and C (left): in the control patient, left ventricular EF (LVEF) was 56% (A), and 61% in the patient with ESRD and SHPTH (C). 2D ECHO ST real-time showed longitudinal deformation (B and D, right). The deformation pattern in the control patient (B) was normal, with global longitudinal strain (GLS) = 19%, and GLS was abnormal (14%) in the patient with ESRD and SHPTH (D).

(38%) male. According to the division, in the control group, the age was 34 ± 13 years, body mass index (BMI) 23.4 kg/m^2, 67% female and 33% male, without relevant comorbidities. The ESRD-HD group age was 36 ± 2 years, BMI 23.3 kg/m^2, 84% female and 16% male, 90% presented with hypertension and 6.45% with type 2 diabetes mellitus (T2DM). In the ESRD-PD group, age was 34 ± 10 years, BMI 22.4 kg/m^2, 39% female and 61% male, all presented with hypertension, and 16% with T2DM (Table 1).

Patients with ESRD had severe refractory hyperparathyroidism (PTH > 650 pg/mL), but calcium (Ca^{2+}), phosphorus (P), and calcium/phosphorus (Ca_{2+}/P) ratio levels were within normal ranges. There was no significant difference from the control group, suggesting an average plasma calcitriol level. All of our population with ESRD showed LVH. LV mass and LV mass index (LVMI) were substantially increased; LVH concentric type was predominant (ESRD-HD = 80.65% and ESRD-PD = 93.35%) (Table 2).

The 2D-ECHO variables of the population studied are shown (illustrative case in Figure 1), demonstrating that by Simpson's method, LVEF was preserved, while the GLS was substantially reduced compared to the control group (21% ± 0.58% *vs* 13.93% and 13.18%; $P < 0.0001$; control *vs* ESRD-HD and ESRD-PD). The average GLS was 13.55% in all populations with ESRD. This shows that LVEF

Table 2 Biochemical and left ventricular remodeling variables in the study groups: Control, end-stage renal disease on hemodialysis and end-stage renal disease on peritoneal dialysis

Variables	Control	ESRD-HD	ESRD-PD	*P* value
Biochemical				
PTH (pg/mL)	50 ± 4.55[a,c]	1188 ± 203.9	1188 ± 203.9	< 0.0001
Ca^{2+} (mg/dL)	8.55 ± 2.34	8.47 ± 0.14	8.38 ± 0.09	NS
P (mg/dL)	4.56 ± 2.28	4.75 ± 0.24	4.75 ± 0.28	NS
Ca^{2+}/P (mg^2/dL^2)	45.32 ± 1.05	42.31 ± 2.35	39.87 ± 2.5	NS
Albumin (mg/dL)	4.47 ± 0.10[a,c]	4.13 ± 0.12	3.94 ± 0.06	< 0.0284
Hemoglobin (g/dL)	15.3 ± 0.12[a,c]	8.73 ± 0.24	8.91 ± 0.22	< 0.0001
LV remodeling				
LV mass (g)	133.8 ± 3[a,c]	182.7 ± 12.2	186.6 ± 15	< 0.0001
LVMI (g/m^2)	70.65 ± 2.11[a,c]	130.2 ± 6.24	127.5 ± 6.55	< 0.0001
RWT	0.39 ± 0.016[a,c]	0.51 ± 0.01	0.51 ± 0.02	< 0.0001

[a]*P* < 0.05, control *vs* ESRD-HD.
[c]*P* < 0.05, control *vs* ESRD-PD.
The data represent the mean SD. ANOVA followed by a Tukey test was performed and was considered significant. ESRD: End-stage renal disease; ESRD-HD: ESRD on hemodialysis; ESRD-PD: ESRD on peritoneal dialysis; PTH: Plasma parathyroid hormone; LV: Left ventricular; LVMI: LV mass index; NS: Not significant.

Table 3 Echocardiographic population variables control, end-stage renal disease on hemodialysis and end-stage renal disease on peritoneal dialysis

Variables	Control	ESRD-HD	ESRD-PD	*P* value
LVEF	60.75 ± 1.30	63.5 ± 10.36	61.8 ± 11.19	NS
GLS (%)	21 ± 0.58[a,c]	13 ± 0.72	12 ± 1.83	< 0.0001
LAV (mL/m^2)	33.07 ± 0.22[a,c]	26.49 ± 1.4	25.73 ± 1.57	< 0.0001
E/A ratio	1.25 ± 0.03[a,c]	1.05 ± 0.06	0.91 ± 0.05	< 0.0001
E/é ratio	5.38 ± 0.18[a,c]	11.62 ± 0.96	12.22 ± 1.13	< 0.0001
E (cm/s)	60.39 ± 1.71[a,c]	80.19 ± 6.26	81.29 ± 6.97	< 0.0001
Lateral e' (cm/s)	13.44 ± 0.36[a,c]	8.33 ± 0.43	7.49 ± 0.16	< 0.0001
Septal é (cm/s)	10.85 ± 0.35[a,c]	6.18 ± 0.24	6.49 ± 0.23	< 0.0001
TRV (m/s)	2.21 ± 0.02[a,c]	2.94 ± 0.08	2.80 ± 0.07	< 0.0001
LVMI (g/m^2)	70.65 ± 2.11[a,c]	130.2 ± 6.24	127.5 ± 6.55	< 0.0001
RWT	0.39 ± 0.016[a,c]	0.51 ± 0.01	0.51 ± 0.02	< 0.0001

[a]*P* < 0.05, control *vs* ESRD-HD.
[c]*P* < 0.05, control *vs* ESRD-PD.
The data represents mean SD. ANOVA followed by Tukey test was performed and was considered significant. ESRD: End-stage renal disease; ESRD-HD: ESRD on hemodialysis; ESRD-PD: ESRD on peritoneal dialysis; LVEF: Left ventricular ejection fraction; GLS: Global longitudinal strain; LAV: Left atrial volume; TRV: Tricuspid regurgitation velocity; LVMI: LV mass index; NS: Not significant; RWT: Relative wall thickness.

does not establish systolic dysfunction in patients diagnosed with ESRD, even though they have systolic dysfunction by GLS evaluation (Table 3).

In the bivariate analysis, an association of GLS with hemoglobin, hypertension, PTH, LVH and LVMI was shown. In comparison, the multivariate analysis showed an independent association of GLS and hemoglobin, PTH and LVMI (Table 4).

This study analyzed the LVDF by obtaining the pattern of transmitral flow rates and their relationship with the tissue velocities at the mitral ring level. The above is related to the fact that the increase in LV filling pressures is the primary physiological consequence of LVDD. These variables

Table 4 Global longitudinal strain and variables association

Variables	Univariate					Multivariate using significant variables					Multivariate by step method				
	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value
			Lower limit	Upper limit				Lower limit	Upper limit				Lower limit	Upperlimit	
Association with GLS (%)															
Hemoglobin	-1.09	-0.61	-1.42	-0.77	0.00	-0.58	-0.32	-1.12	-0.05	0.03	-0.62	-0.35	-0.99	-0.26	0.00
Hypertension	5.60	0.54	3.58	7.61	0.00	1.52	0.15	-1.44	4.49	0.31					
PTH	0.00	0.50	0.00	0.00	0.00	0.00	0.27	0.00	0.00	0.01	0.00	0.29	0.00	0.00	0.00
LVEF	-0.04	-0.08	-0.15	0.07	0.50										
LVH	6.40	0.57	4.27	8.53	0.00	-1.82	-0.16	-7.75	4.12	0.54					
LVMI	0.06	0.51	0.04	0.08	0.00	0.03	0.28	0.01	0.05	0.01	0.03	0.29	0.01	0.05	0.00
RWT	11.36	0.25	1.27	21.46	0.03	-1.21	-0.03	-10.14	7.73	0.79					

95%CI: 95% confidence interval; GLS: Global longitudinal strain; PTH: Plasma parathormone; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; RWT: Relative wall thickness.

Table 5 Association between parathyroidism levels and left ventricular diastolic dysfunction variables

Variables	Univariate					Multivariate using significant variables					Multivariate by step method				
	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value	B	β	95%CI for B		*P* value
			Lower limit	Upper limit				Lower limit	Upper limit				Lower limit	Upper limit	
Association with PTH															
E/é ratio	54.22	0.33	18.34	90.09	0.00	28.19	0.17	-11.55	67.93	0.16					
é lateral	-124.,51	-0.36	-199.34	-49.69	0.00	-81.10	-0.23	-177.06	14.87	0.10	-89.72	-0.26	-169.01	-10.44	0.03
é septal	-121.78	-0.28	-215.64	-27.91	0.01	-0.63	0.00	-121.22	119.97	0.99					
TRV	698.98	0.35	276.86	1121.10	0.00	360.73	0.18	-141.53	862.99	0.16	500.88	0.25	53.87	947.89	0.03

95%CI: 95% confidence interval; PTH: Plasma parathormone; TRV: Tricuspid regurgitation velocity.

were significantly altered in the ESRD population compared to the controls (Table 3).

The tricuspid regurgitation velocity (TRV) and E/e' ratio associated with the decrease in the E/A ratio and the e' septal lateral waves reflect the pattern of altered relaxation and myocardial distensibility during the diastolic phase. Previously reported recommendations were applied[17], and it was found that among individuals with ESRD-HD, 67.74% (n = 21) had grade I, 22.58% (n = 7) grade II, and 9.67% (n = 3) grade III LVDD. Among individuals with ESRD-PD, 84.37% (n = 27) had grade I and 15.63% (n = 4) had grade II LVDD. The univariate and multivariate analyses (Table 5) showed the associations between the variables studied and PTH. An independent association of serum PTH and lateral e' wave and TRV was shown.

DISCUSSION

Despite the extended use of EF to evaluate myocardial dysfunction, recent proposals promise to improve detection of cardiovascular dysfunction. As an example, 2D-ECHO for measuring left atrial volume is useful to predict diastolic dysfunction in ESRD patients[13]. Measuring plasma biomarkers has been suggested to extend diagnostic advantages. Thus, plasma NP levels are reported to be linked to cardiac remodeling[18], survival[19] and volume expansion-related LV disorders[20] in patients with ESRD[14].

Currently, 2D-ECHO methods remain core in diagnosis and evaluation of patients with CEs. The identification of LV strain changes is crucial for early cardiac damage detection in ESRD[21-24]. This study showed that increased LVMI, low hemoglobin levels but high PTH are independent factors associated with GLS alterations. The overall average GLS was 13.55%, with LVEF > 50% in the patient population, which according to the literature, is related to poor prognosis[25-29]. In this case, it was suggested that in the population with ESRD, the determination of GLS by 2D-ECHO is highly recommended for the assessment of LVSF; being a more powerful tool than LVEF, which can identify systolic myocardial damage[3,18,19] during follow-up of patients[29].

In patients with ESRD, bone mineral disorder is correlated with adverse outcomes from cardiovascular causes[25,30,31]. Recently, the mineral disorders in the early stages of ESRD have been associated with myocardial remodeling, which is a crucial point for LVH development[31-33]. In our study population, the presence of LVH was 100%, with a predominance of the concentric type. In this regard, some studies have directly implicated hyperphosphatemia and hypercalcemia in developing LVH[7,30] by regulating several factors[31,34-36]. However, it must be considered that the kidney is an essential target organ for PTH, and the interaction with its receptor activates multiple signaling pathways[37-39], triggering numerous changes in the kidney and some other systems[40]. As strong evidence of the PTH role in cardioremodeling, studies have shown that patients undergoing parathyroidectomy (PTX) have a substantial reduction in LV mass[41]; in contrast, patients with severe hyperparathyroidism and PTX showed a significant decrease in the risk of death from all causes[42]. Patients in the current study were supplemented with calcium or analogs; plasma values of Ca, P and Ca/P ratio were within normal ranges, while PTH levels were higher than reference values (PTH > 650 pg/mL). Multivariate analysis showed an independent association of GLS and PTH, suggesting a putative role of PTH in LVSF by diverse mechanisms, including those related to remodeling of subendocardial fibers[43].

Additional research is required to elucidate the mechanisms involved in the PTH modulation of the structure and function of the cardiomyocytes, as the pleiotropic effects are attributed to the interaction of PTH with its receptor [33,40].

PTH serum levels showed an independent association with some diastolic function parameters (Table 5): Particularly e' lateral wave and TRV. The alterations in diastolic function primarily involve the mechanisms of myocardial relaxation and compliance. The signaling pathways involving remodeling and cardiac fibrosis in patients with ESRD are complex and multifactorial, involving alterations in the extracellular matrix proteins, type I collagen, elastin, fibroblasts, and myofibroblasts[9,44-46], which reduce myocardial compliance. These effector pathways involve PTH and 25-hydroxy vitamin D3 and several other factors[34-39,46-51]. Elevated levels of catecholamine by sympathetic overactivity are reported to be linked to LV disorders and volume excess in ESRD patients[15].

Finally, our results are in line with recent reports supporting that conventional speckle-tracking echocardiography[52-54] might help identify LVSD in patients with ESRD and preserved LVEF. Early detection of myocardial morphological and functional changes in the routine evaluation of patients with ESRD can tackle the early stages of disease-independent modifiable risk factors that are associated with adverse CEs.

CONCLUSION

An accurate diagnosis is increasingly important in this type of patient with ESRD with systolic and diastolic myocardial function evaluation, offering integrated, lower cost, and noninvasive information. The use of new diagnostic tools is essential to provide the population with new targeted therapies for

defined subsets of patients who may be at risk of developing potential complications. The use of GLS by 2D-ECHO is a more sensitive tool than LVEF to detect of LVSD. For individuals with ESRD and severe hyperparathyroidism refractory to hormone replacement but with normal Ca/P levels, it is essential to recommend the use of GLS as a diagnostic and prognostic tool for systolic myocardial dysfunction; albeit if patients have preserved LVEF.

ARTICLE HIGHLIGHTS

Research background

Echocardiography is the most-used tool for diagnosis of myocardial dysfunction. Among 2D-ecocardiography (2D-ECHO) methods, ejection fraction (EF) is the most used. In patients with myocardial dysfunction and end-stage renal disease (ESRD) parathyroid hormone (PTH) is often altered.

Research motivation

Recent echocardiography methods are being compared with ejection fraction. Global longitudinal strain (GLS) is among the most explored. Additional serum biomarkers could help to increase sensibility of tests.

Research objectives

To compare the EF and global strain methods for detecting myocardial dysfunction. To measure the potential role of some biomarkers as complementary tools in patient evaluation.

Research methods

Left ventricular systolic function (LVSF) was evaluated in 62 patients with ESRD with altered levels of PTH. LVSF was evaluated by performing 2D-ECHO, obtaining the EF, by the Simpson biplane method, and GLS by speckle tracking.

Research results

All patients with ESRD had preserved LVEF (> 50%) but abnormal GLS (< 13.55%). PTH was independently associated with lateral e' wave and tricuspid regurgitation velocity.

Research conclusions

In patients with elevated PTH and ESRD, the use of GLS by 2D-ECHO is a more-sensitive tool than LVEF for detecting myocardial dysfunction.

Research perspectives

GLS and serum PTH should be widely explored as potential sensitive tools to detect myocardial dysfunction in patients with ESRD. The mechanisms linked to this disrupted condition should be analyzed. Alternative echocardiography methods and biomarkers should be compared to select the most-sensitive and accurate tools.

FOOTNOTES

Author contributions: Carrasco-Ruiz MF, Ruiz-Rivera A, and Perez-Capistran T conceptualized the study; Ruiz-Rivera A, Martinez-Hernandez CM and Manuel-Apolinar L done data collection; Carrasco-Ruiz MF, Ruiz-Rivera A, Mejia-Ruiz A, Soriano-Ursúa MA and Martinez-Hernandez C carried out data analysis and interpretation; Carrasco-Ruiz MF, Soriano-Ursúa MA, and Perez-Capistran T drafting article; and All authors revised and approved the final version of this manuscript.

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REFERENCES

1 **Gansevoort RT**, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013; **382**: 339-352 [PMID: 23727170 DOI: 10.1016/S0140-6736(13)60595-4]
2 **Shah S**, Meganathan K, Christianson AL, Leonard AC, Thakar CV. Pre-dialysis acute care hospitalizations and clinical outcomes in dialysis patients. *PLoS One* 2019; **14**: e0209578 [PMID: 30650094 DOI: 10.1371/journal.pone.0209578]
3 **Hensen LCR**, Goossens K, Delgado V, Abou R, Rotmans JI, Jukema JW, Bax JJ. Prevalence of left ventricular systolic dysfunction in pre-dialysis and dialysis patients with preserved left ventricular ejection fraction. *Eur J Heart Fail* 2018; **20**: 560-568 [PMID: 29164753 DOI: 10.1002/ejhf.1077]
4 **Tonelli M**, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; **17**: 2034-2047 [PMID: 16738019 DOI: 10.1681/ASN.2005101085]
5 **Tamulėnaitė E**, Žvirblytė R, Ereminienė R, Žiginskienė E, Ereminienė E. Changes of Left and Right Ventricle Mechanics and Function in Patients with End-Stage Renal Disease Undergoing Haemodialysis. *Medicina (Kaunas)* 2018; **54** [PMID: 30428607 DOI: 10.3390/medicina54050087]
6 **Kim IY**, Kim JH, Kim MJ, Lee DW, Hwang CG, Han M, Rhee H, Song SH, Seong EY, Lee SB. Plasma neutrophil gelatinase-associated lipocalin is independently associated with left ventricular hypertrophy and diastolic dysfunction in patients with chronic kidney disease. *PLoS One* 2018; **13**: e0205848 [PMID: 30325973 DOI: 10.1371/journal.pone.0205848]
7 **Di Lullo L**, Gorini A, Russo D, Santoboni A, Ronco C. Left Ventricular Hypertrophy in Chronic Kidney Disease Patients: From Pathophysiology to Treatment. *Cardiorenal Med* 2015; **5**: 254-266 [PMID: 26648942 DOI: 10.1159/000435838]
8 **Herzog CA**. Kidney disease in cardiology. *Nephrol Dial Transplant* 2009; **24**: 34-37 [PMID: 19028753 DOI: 10.1093/ndt/gfn637]
9 **Ponikowski P**, Jankowska EA. Pathogenesis and clinical presentation of acute heart failure. *Rev Esp Cardiol (Engl Ed)* 2015; **68**: 331-337 [PMID: 25743769 DOI: 10.1016/j.rec.2015.02.001]
10 **McGuire DK**, Alexander JH, Johansen OE, Perkovic V, Rosenstock J, Cooper ME, Wanner C, Kahn SE, Toto RD, Zinman B, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, Marx N; CARMELINA Investigators. Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA. *Circulation* 2019; **139**: 351-361 [PMID: 30586723 DOI: 10.1161/CIRCULATIONAHA.118.038352]
11 **Kümler T**, Gislason GH, Køber L, Torp-Pedersen C. Persistence of the prognostic importance of left ventricular systolic function and heart failure after myocardial infarction: 17-year follow-up of the TRACE register. *Eur J Heart Fail* 2010; **12**: 805-811 [PMID: 20494923 DOI: 10.1093/eurjhf/hfq071]
12 **Halliday BP**, Senior R, Pennell DJ. Assessing left ventricular systolic function: from ejection fraction to strain analysis. *Eur Heart J* 2021; **42**: 789-797 [PMID: 32974648 DOI: 10.1093/eurheartj/ehaa587]
13 **Tripepi G**, Mattace-Raso F, Mallamaci F, Benedetto FA, Witteman J, Malatino L, Zoccali C. Biomarkers of left atrial volume: a longitudinal study in patients with end stage renal disease. *Hypertension* 2009; **54**: 818-824 [PMID: 19635983 DOI: 10.1161/HYPERTENSIONAHA.109.136804]
14 **Mallamaci F**, Zoccali C, Tripepi G, Benedetto FA, Parlongo S, Cataliotti A, Cutrupi S, Giacone G, Bellanuova I, Stancanelli B, Malatino LS; CREED Investigstors. The Cardiovascular Risk Extended Evaluation. Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 2001; **59**: 1559-1566 [PMID: 11260421 DOI: 10.1046/j.1523-1755.2001.0590041559.x]
15 **Abd ElHafeez S**, Tripepi G, Stancanelli B, Dounousi E, Malatino L, Mallamaci F, Zoccali C. Norepinephrine, left ventricular disorders and volume excess in ESRD. *J Nephrol* 2015; **28**: 729-737 [PMID: 25708914 DOI: 10.1007/s40620-015-0182-4]
16 **Kamperidis V**, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral

regurgitation: left ventricular ejection fraction *vs* speckle tracking global longitudinal strain. *Eur Heart J* 2016; **37**: 811-816 [PMID: 26685140 DOI: 10.1093/eurheartj/ehv680]

17 **Nagueh SF**. Diastology: 2020-A practical guide. *Echocardiography* 2020; **37**: 1919-1925 [PMID: 32476157 DOI: 10.1111/echo.14742]

18 **Cataliotti A**, Malatino LS, Jougasaki M, Zoccali C, Castellino P, Giacone G, Bellanuova I, Tripepi R, Seminara G, Parlongo S, Stancanelli B, Bonanno G, Fatuzzo P, Rapisarda F, Belluardo P, Signorelli SS, Heublein DM, Lainchbury JG, Leskinen HK, Bailey KR, Redfield MM, Burnett JC Jr. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin Proc* 2001; **76**: 1111-1119 [PMID: 11702899 DOI: 10.4065/76.11.1111]

19 **Zoccali C**, Mallamaci F, Benedetto FA, Tripepi G, Parlongo S, Cataliotti A, Cutrupi S, Giacone G, Bellanuova I, Cottini E, Malatino LS. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol* 2001; **12**: 1508-1515 [PMID: 11423580 DOI: 10.1681/ASN.V1271508]

20 **Enia G**, Mallamaci F, Benedetto FA, Panuccio V, Parlongo S, Cutrupi S, Giacone G, Cottini E, Tripepi G, Malatino LS, Zoccali C. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant* 2001; **16**: 1459-1464 [PMID: 11427641 DOI: 10.1093/ndt/16.7.1459]

21 **Khwaja A**. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179-c184 [PMID: 22890468 DOI: 10.1159/000339789]

22 **Ewe SH**, Haeck ML, Ng AC, Witkowski TG, Auger D, Leong DP, Abate E, Ajmone Marsan N, Holman ER, Schalij MJ, Bax JJ, Delgado V. Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 992-999 [PMID: 25733208 DOI: 10.1093/ehjci/jev019]

23 **de Brito Galvao JF**, Nagode LA, Schenck PA, Chew DJ. Calcitriol, calcidiol, parathyroid hormone, and fibroblast growth factor-23 interactions in chronic kidney disease. *J Vet Emerg Crit Care (San Antonio)* 2013; **23**: 134-162 [PMID: 23566108 DOI: 10.1111/vec.12036]

24 **Drüeke TB**. Hyperparathyroidism in Chronic Kidney Disease. 2021 Oct 18. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [PMID: 25905209]

25 **Ke QQ**, Xu HB, Bai J, Xiong L, Li MM. Evaluation of global and regional left ventricular myocardial work by echocardiography in patients with chronic kidney disease. *Echocardiography* 2020; **37**: 1784-1791 [PMID: 33084159 DOI: 10.1111/echo.14864]

26 **Panoulas VF**, Sulemane S, Konstantinou K, Bratsas A, Elliott SJ, Dawson D, Frankel AH, Nihoyannopoulos P. Early detection of subclinical left ventricular myocardial dysfunction in patients with chronic kidney disease. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 539-548 [PMID: 25428945 DOI: 10.1093/ehjci/jeu229]

27 **Tadic M**, Cuspidi C. Left ventricular strain and arterial hypertension: Is longitudinal strain ready for primetime? *J Clin Hypertens (Greenwich)* 2020; **22**: 683-685 [PMID: 32073217 DOI: 10.1111/jch.13833]

28 **Park JH**, Park JJ, Park JB, Cho GY. Prognostic Value of Biventricular Strain in Risk Stratifying in Patients With Acute Heart Failure. *J Am Heart Assoc* 2018; **7**: e009331 [PMID: 30371332 DOI: 10.1161/JAHA.118.009331]

29 **Park JJ**, Mebazaa A, Hwang IC, Park JB, Park JH, Cho GY. Phenotyping Heart Failure According to the Longitudinal Ejection Fraction Change: Myocardial Strain, Predictors, and Outcomes. *J Am Heart Assoc* 2020; **9**: e015009 [PMID: 32519555 DOI: 10.1161/JAHA.119.015009]

30 **de Albuquerque Suassuna PG**, Sanders-Pinheiro H, de Paula RB. Uremic Cardiomyopathy: A New Piece in the Chronic Kidney Disease-Mineral and Bone Disorder Puzzle. *Front Med (Lausanne)* 2018; **5**: 206 [PMID: 30087898 DOI: 10.3389/fmed.2018.00206]

31 **Kaesler N**, Babler A, Floege J, Kramann R. Cardiac Remodeling in Chronic Kidney Disease. *Toxins (Basel)* 2020; **12** [PMID: 32150864 DOI: 10.3390/toxins12030161]

32 **Fujii H**, Joki N. Mineral metabolism and cardiovascular disease in CKD. *Clin Exp Nephrol* 2017; **21**: 53-63 [PMID: 28062938 DOI: 10.1007/s10157-016-1363-8]

33 **Iseri K**, Dai L, Chen Z, Qureshi AR, Brismar TB, Stenvinkel P, Lindholm B. Bone mineral density and mortality in end-stage renal disease patients. *Clin Kidney J* 2020; **13**: 307-321 [PMID: 32699616 DOI: 10.1093/ckj/sfaa089]

34 **Faul C**, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121**: 4393-4408 [PMID: 21985788 DOI: 10.1172/JCI46122]

35 **Tanaka S**, Fujita S, Kizawa S, Morita H, Ishizaka N. Association between FGF23, α-Klotho, and Cardiac Abnormalities among Patients with Various Chronic Kidney Disease Stages. *PLoS One* 2016; **11**: e0156860 [PMID: 27400031 DOI: 10.1371/journal.pone.0156860]

36 **Custódio MR**, Koike MK, Neves KR, dos Reis LM, Graciolli FG, Neves CL, Batista DG, Magalhães AO, Hawlitschek P, Oliveira IB, Dominguez WV, Moysés RM, Jorgetti V. Parathyroid hormone and phosphorus overload in uremia: impact on cardiovascular system. *Nephrol Dial Transplant* 2012; **27**: 1437-1445 [PMID: 21825304 DOI: 10.1093/ndt/gfr447]

37 **Verdelli C**, Corbetta S. MECHANISMS IN ENDOCRINOLOGY: Kidney involvement in patients with primary hyperparathyroidism: an update on clinical and molecular aspects. *Eur J Endocrinol* 2017; **176**: R39-R52 [PMID: 27601015 DOI: 10.1530/EJE-16-0430]

38 **Vilardaga JP**, Romero G, Friedman PA, Gardella TJ. Molecular basis of parathyroid hormone receptor signaling and trafficking: a family B GPCR paradigm. *Cell Mol Life Sci* 2011; **68**: 1-13 [PMID: 20703892 DOI: 10.1007/s00018-010-0465-9]

39 **Vilardaga JP**, Gardella TJ, Wehbi VL, Feinstein TN. Non-canonical signaling of the PTH receptor. *Trends Pharmacol Sci* 2012; **33**: 423-431 [PMID: 22709554 DOI: 10.1016/j.tips.2012.05.004]

40 **Fujii H**. Association between Parathyroid Hormone and Cardiovascular Disease. *Ther Apher Dial* 2018; **22**: 236-241 [PMID: 29707916 DOI: 10.1111/1744-9987.12679]

41 **McMahon DJ**, Carrelli A, Palmeri N, Zhang C, DiTullio M, Silverberg SJ, Walker MD. Effect of Parathyroidectomy Upon Left Ventricular Mass in Primary Hyperparathyroidism: A Meta-Analysis. *J Clin Endocrinol Metab* 2015; **100**: 4399-4407 [PMID: 26445115 DOI: 10.1210/jc.2015-3202]

42 **Li W**, Zhang M, Du S, Yu Y, Liu J, Zhang L, Yao L. Impact of parathyroidectomy on survival among haemodialysis patients: A prospective cohort study. *Nephrology (Carlton)* 2016; **21**: 133-138 [PMID: 26199009 DOI: 10.1111/nep.12564]

43 **Sanchis L**, Andrea R, Falces C, Poyatos S, Vidal B, Sitges M. Differential Clinical Implications of Current Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. *J Am Soc Echocardiogr* 2018; **31**: 1203-1208 [PMID: 30241926 DOI: 10.1016/j.echo.2018.08.011]

44 **Lan HY**. Diverse roles of TGF-β/Smads in renal fibrosis and inflammation. *Int J Biol Sci* 2011; **7**: 1056-1067 [PMID: 21927575 DOI: 10.7150/ijbs.7.1056]

45 **Chen L**, Yang T, Lu DW, Zhao H, Feng YL, Chen H, Chen DQ, Vaziri ND, Zhao YY. Central role of dysregulation of TGF-β/Smad in CKD progression and potential targets of its treatment. *Biomed Pharmacother* 2018; **101**: 670-681 [PMID: 29518614 DOI: 10.1016/j.biopha.2018.02.090]

46 **van Ballegooijen AJ**, Visser M, Kestenbaum B, Siscovick DS, de Boer IH, Gottdiener JS, deFilippi CR, Brouwer IA. Relation of vitamin D and parathyroid hormone to cardiac biomarkers and to left ventricular mass (from the Cardiovascular Health Study). *Am J Cardiol* 2013; **111**: 418-424 [PMID: 23168286 DOI: 10.1016/j.amjcard.2012.10.021]

47 **Almahmoud MF**, Soliman EZ, Bertoni AG, Kestenbaum B, Katz R, Lima JAC, Ouyang P, Miller PE, Michos ED, Herrington DM. Fibroblast Growth Factor-23 and Heart Failure With Reduced Versus Preserved Ejection Fraction: MESA. *J Am Heart Assoc* 2018; **7**: e008334 [PMID: 30371180 DOI: 10.1161/JAHA.117.008334]

48 **Dobaczewski M**, Chen W, Frangogiannis NG. Transforming growth factor (TGF)-β signaling in cardiac remodeling. *J Mol Cell Cardiol* 2011; **51**: 600-606 [PMID: 21059352 DOI: 10.1016/j.yjmcc.2010.10.033]

49 **Biernacka A**, Dobaczewski M, Frangogiannis NG. TGF-β signaling in fibrosis. *Growth Factors* 2011; **29**: 196-202 [PMID: 21740331 DOI: 10.3109/08977194.2011.595714]

50 **Falcón D**, Galeano-Otero I, Calderón-Sánchez E, Del Toro R, Martín-Bórnez M, Rosado JA, Hmadcha A, Smani T. TRP Channels: Current Perspectives in the Adverse Cardiac Remodeling. *Front Physiol* 2019; **10**: 159 [PMID: 30881310 DOI: 10.3389/fphys.2019.00159]

51 **Raggi P**, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002; **39**: 695-701 [PMID: 11849871 DOI: 10.1016/s0735-1097(01)01781-8]

52 **Geyer H**, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, Nesser HJ, Khandheria B, Narula J, Sengupta PP. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr* 2010; **23**: 351-69; quiz 453 [PMID: 20362924 DOI: 10.1016/j.echo.2010.02.015]

53 **Kizilca O**, Ozmen D, Demircan T, Yilmaz N, Kir M, Soylu A, Unal N, Kavukcu S. Evaluation of left ventricular systolic functions in two-dimensional speckle-tracking echocardiography in children with chronic renal failure. *Cardiol Young* 2021; **31**: 421-428 [PMID: 33308338 DOI: 10.1017/S1047951120004205]

54 **Wang X**, Hong J, Zhang T, Xu D. Changes in left ventricular and atrial mechanics and function after dialysis in patients with end-stage renal disease. *Quant Imaging Med Surg* 2021; **11**: 1899-1908 [PMID: 33936973 DOI: 10.21037/qims-20-961]

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META-ANALYSIS

Effect of preoperative renin-angiotensin system blockade on vasoplegia after cardiac surgery: A systematic review with meta-analysis

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Abstract

BACKGROUND

Vasoplegia is a common complication of cardiac surgery but its causal relationship with preoperative use of renin angiotensin system (RAS) blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB)] is still debated.

AIM

To update and summarize data on the effect of preoperative use of RAS blockers on incident vasoplegia.

METHODS

All published studies from MEDLINE, EMBASE, and Web of Science providing relevant data through January 13, 2021 were identified. A random-effects meta-analysis method was used to pool estimates, and post-cardiac surgery shock was differentiated from vasoplegia.

RESULTS

Ten studies reporting on a pooled population of 15672 patients (none looking at ARBs exclusively) were included in the meta-analysis. All were case-control studies. Use of ACEIs was associated with an increased risk of vasoplegia [pooled

adjusted odds ratio (Aor) of 2.06, 95%CI: 1.45-2.93] and increased inotropic/vasopressor support requirement (pooled aOR 1.19, 95%CI: 1.10-1.29). Post-cardiac surgery shock was increased in the presence of left ventricular dysfunction (pooled aOR 2.32, 95%CI: 1.60-3.36; I^2 49%) but not increased by the use of beta blockers (pooled aOR 0.78, 95%CI: 0.36-1.69; I^2 77%). Two randomized control trials (RCTs), not eligible for the meta-analysis, did not show an association between continuation of RAS blockers and vasoplegia.

CONCLUSION

Preoperative continuation of ACEIs is associated with an increased need for inotropic support postoperatively and with an increased risk of vasoplegia in observational studies but not in RCTs. The absence of a consensus definition of vasoplegia should lead to the use of perioperative cardiovascular monitoring when designing RCTs to better understand this discrepancy.

Key Words: Vasoplegia; Cardiac surgery; Coronary artery bypass graft; Angiotensin converting enzyme inhibitors

Core Tip: Vasoplegia is a common complication of cardiac surgery but its causal relationship with preoperative use of renin angiotensin system blockers, mainly angiotensin converting enzyme inhibitors (ACEIs), is still debated. The meta-analysis of observational studies suggests that preoperative continuation of ACEIs is associated with an increased risk of vasoplegia and of the use of inotropic support postoperatively. However, these associations were not observed in two included randomized controlled trials with limited power. These findings support the potential benefit of holding ACEIs prior to cardiac surgery to reduce the risk of vasoplegia and associated adverse outcomes. However, well-powered randomized controlled trials using a consensus definition of vasoplegia are still needed to properly assess management strategies of RAS blockers in the perioperative setting.

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INTRODUCTION

Shock is a frequent complication of major cardiac surgery, occurring in approximately a quarter of procedures, especially those with cardiopulmonary bypass (CPB)[1-3]. Vasoplegia is a form of distributive shock characterized by persistent hypotension, reduced systemic vascular resistance (SVR) with normal or elevated cardiac output[1]. It is due to reduced vascular smooth cell contraction resulting from several mechanisms including the alteration of the endothelial glycocalyx, impaired receptor signaling, changes in endothelial cell metabolism, and depletion and decreased response to endogenous vasopressors[1,4]. This impairment of vascular reactivity is worsened by a systemic inflammatory response to surgical trauma, ischemia-reperfusion syndrome, and exposure of blood to the foreign surfaces during extracorporeal circulation[1,4]. The use of some medications prior to surgery is also thought to contribute to inappropriate vasodilatation in vasoplegia[1,4].

The association of continuation of renin angiotensin system (RAS) blockers and vasoplegia following cardiac surgery is still a matter of debate[2,5-7]. Preoperative administration of ACEIs has been associated with poor outcomes including acute kidney injury and increased mortality[8]. This systematic review and meta-analysis aimed to comprehensively summarize data on the effect of preoperative use of RAS blockers on vasoplegia in patients undergoing cardiac surgery.

MATERIALS AND METHODS

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines[9]. It was registered with PROSPERO (CRD42017072923).

Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science were searched to identify all cohort studies, case-control studies or randomized controlled trials (RCTs) reporting primary data on the association between ACEIs or ARBs and the incidence of vasoplegia after cardiac surgery, published by January 13, 2021 (date of the last search), without language restriction. The search strategy used a combination of terms or their synonyms related to vasoplegia, a detailed list of cardiac surgical procedures, and names of ACEIs or ARBs (Supplementary Table 1). The reference lists of relevant research and review articles were also screened to identify potential additional data sources.

Study selection

We included: (1) Cohort studies, case-control studies or RCTs; (2) With 30 participants or more; and (3) Reporting on risk of vasoplegia associated with ACEIs or ARBs, or studies with enough data to compute these estimates. We excluded studies: (1) Which included patients undergoing non-cardiac surgery; (2) Lacking explicit description of the perioperative follow-up of patients; and (3) Not reporting primary data (reviews, commentaries, editorials). For duplicate publication of the same group/cohort of patients, we included the single most comprehensive report with the largest sample size. Two investigators (JJN and BN) independently selected records from bibliographic searches based on titles and abstracts screening. Full texts of articles deemed potentially eligible were retrieved and screened independently by the same investigators for final inclusion. Disagreements were resolved *via* discussion and consensus.

Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by a second investigator (BN). We collected data on study characteristics, type of cardiac surgery, definition of vasoplegia, sample size, mean or median age, sex proportion, proportion of patients with co-morbidities such as hypertension, diabetes, heart failure, or previous cardiac surgery, proportion of patients taking relevant medications (ACEIs, ARBs, beta blockers, calcium channel blockers, nitrates, number of participants with vasoplegia, and risk estimate [odds ratio (OR) or relative risk (RR)] with the 95% confidence interval (95%CI) for the association between vasoplegia and ACEIs or ARBs. We also extracted adjusted risk estimates (from multivariable regression analysis) for other risk factors for vasoplegia as complementary information. We assessed the risk of bias using the tools for case-control studies and randomized controlled trial developed by the CLARITY group at McMaster University[10,11]. We separated studies with or without perioperative cardiac index monitoring in an attempt to further differentiate post-cardiac surgery shock from vasoplegia.

Statistical analysis

Analyses were conducted with R statistical software (version 3.6.2, The R Foundation for statistical computing, Vienna, Austria). The generic inverse variance method was used to pool adjusted risk estimates (OR or RR) and their standard errors with the random-effects meta-analysis model using the *metagen* function. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic, which was quantified by I^2 values, assuming I^2 values of 25%, 50% and 75% respectively representing low, moderate and high heterogeneity[12]. We assessed the presence of publication bias related to small study effect by funnel plot inspection and by linear regression test of funnel plot asymmetry (Egger's test)[13]. All statistical tests were two-tailed and statistical significance defined as P value ≤ 0.05.

RESULTS

Study selection and characteristics

Bibliographic searches retrieved 8076 records and 12 articles were finally included[2,5-7,14-21]. Ten studies were included in the meta-analysis[2,5-7,14-19] and 2 were summarized narratively[20,21]. The study selection is summarized in Figure 1. The observational studies included in the meta-analysis reported data from a pooled sample of 15672 patients undergoing a cardiac surgery. Half of them focused on patients undergoing coronary artery bypass (CABG)[6,7,15,18,19], while the other studies included patients undergoing various procedures including CABG or valvular surgery[2,5,14,16,17]. All observational studies were case-control studies, with data collection done prospectively in most of them [5-7,14-17,19]. The two studies summarized narratively were RCTs[20,21]. The characteristics of the included studies are presented in the appendix (Supplementary Table 2). Most of the studies had a low risk of bias in the majority of assessment items (Supplementary Tables 3 and 4).

The definition of vasoplegia varied across studies (Table 1). Nine studies were considered having acceptable definitions of vasoplegia[2,5-7,14-17,20]. In the remaining three studies, the need for inotropic support was the outcome variable and the definition of vasoplegia seemed to encompass other causes of shock[18,19,21]. We therefore separated studies reporting on vasoplegia and those reporting on post-cardiac surgery shock. The proportions of patients who developed post-cardiac surgery shock

Table 1 General characteristics of included studies

Ref.	Design	Procedure	Definition of vasoplegia	Total sample	Vasoplegia (%)	ACEI (%)
Tuman *et al*[14]	Case-control	Coronary artery and/or valve surgery requiring CPB	Post-CPB ≥ 2 vasoconstrictors with adequate cardiac output	4301	4.5	12.1
Bruce *et al*[16]	Case-control	Cardiac surgery requiring CPB	MAP ≤ 50 mmHg, indexed SVR ≤ 1400 dynes s/cm^5/m^2, cardiac index ≥ 2.2 L/min/m^2, requiring norepinephrine infusion	188	34.0	42.0
Carrel *et al*[17]	Case-control	CABG or AVR	SVR < 600 dynes s/cm^5 with adequate cardiac output	800	7.5	43.1
Mekontso-Dessap *et al*[7]	Case-control	CABG	MAP < 70 mmHg, indexed SVR ≤ 1400 dynes s/cm^5/m^2, normal cardiac output, requiring vasoconstrictor	108	33.3	31.5
Sun *et al*[15]	Case-control	CABG	MAP ≤ 70 mmHg, indexed SVR ≤ 1400 dynes s/cm^5/m^2, cardiac index ≥ 2.5 L/min/m^2, and central venous pressure ≥ 10 mmHg	696	4.7	38.5
Levin *et al*[2]	Case-control	Cardiac surgery	Epinephrine/norepinephrine (≥ 150 ng/kg/min), dopamine (≥ 10 μg/kg/min) or vasopressin (≥ 4 U/h)	2823	20.4	19.7
Shahzamani *et al*[6]	Case-control	CABG	MAP < 65 mmHg, normal cardiac output, requiring vasoconstrictor	300	17.0	64.0
Radaelli *et al*[19]	Case-control	Cardiac surgery	3 of these 4: MAP < 65 mmHg, indexed SVR ≤ 1600 dynes s/cm^5/m^2, cardiac index ≥ 2.5/min/m^2, and requirement of norepinephrine (> 0.03 μg/kg/min) or vasopressin	3139	32.5	52.1
Suga *et al*[5]	Case-control	CABG	Inotropic support post-CABG	562	11.7	9.1
Miceli *et al*[18]	Case-control	CABG	Inotropic support post-CABG	2655	43.5	51.0
Pigot *et al*[21]	RCT	CABG	Inotropic support post-CABG	40	15.0	100
van Diepen *et al*[20]	RCT	CABG or valve surgery	MAP < 60 mmHg requiring vasopressor administration for at least 4 h and a central venous pressure ≥ 8 mmHg	121	29.8	76.9

ACEI: Angiotensin; AVR: Aortic valve replacement; CABG: Coronary artery bypass graft; CPB: Cardiopulmonary bypass; MAP: Mean arterial blood pressure; RCT: Randomized controlled trial; SVR: Systematic vascular resistance.

varied from 4.5% to 34.0% (Table 1). The proportion of patients who used ACEIs preoperatively varied from 9.1% to 64.0% in observational studies. Data on the use of other medications such as ARBs, beta blockers, calcium channel blockers, and nitrates are reported in the appendix (Supplementary Table 2), along with the distribution of co-morbidities across study populations. One of the 2 RCTs reported on an aggregated use of ACEIs and ARBs[20].

Association between angiotensin converting enzyme inhibitors and vasoplegia

From the 10 observational studies selected, 1076 out of 9778 patients had post-cardiac surgery shock (Figure 2A). In the 6 studies with perioperative cardiac monitoring, 755 patients (12.0%) developed vasoplegia and the risk was increased by preoperative continuation of ACEIs [pooled adjusted odds ratio (aOR) 2.06, 95%CI: 1.45-2.93] (Figure 2B). Considering the high heterogeneity (I^2 = 80%), we performed influencer analysis using a leave-one-out approach. Omission of the study by Carrel *et al*[17] resulted in a pooled aOR that changed to 1.61 (95%CI: 1.41-1.85) (Supplementary Figure 1). There was no evidence of small study effect on funnel plot inspection (Supplementary Figure 2), and according to the Egger's test (P = 0.906).

Association between angiotensin converting enzyme inhibitors and inotropic support

Three studies reported data on the association of omitting ACEIs with the need of inotropic support (use of at least one inotropic drug). A total of 4226 (31.1%) patients required inotropic support from a pooled population of 13595 patients undergoing cardiac surgery. Preoperative continuation of ACEI was associated with an increased risk of inotropic support requirement (pooled aOR 1.19, 95%CI: 1.10-1.29) (Figure 3). There was no heterogeneity (I^2 = 0), and no evidence of publication bias both on funnel plot inspection (Supplementary Figure 3) and based on the Egger's test (P = 0.2).

Risk factors for post-cardiac surgery shock

There was no association between beta-blockers and post-cardiac surgery shock (pooled aOR 0.78, 95%CI: 0.36-1.69; I^2 77%) (Figure 4A). The presence of left ventricular dysfunction (ejection fraction <

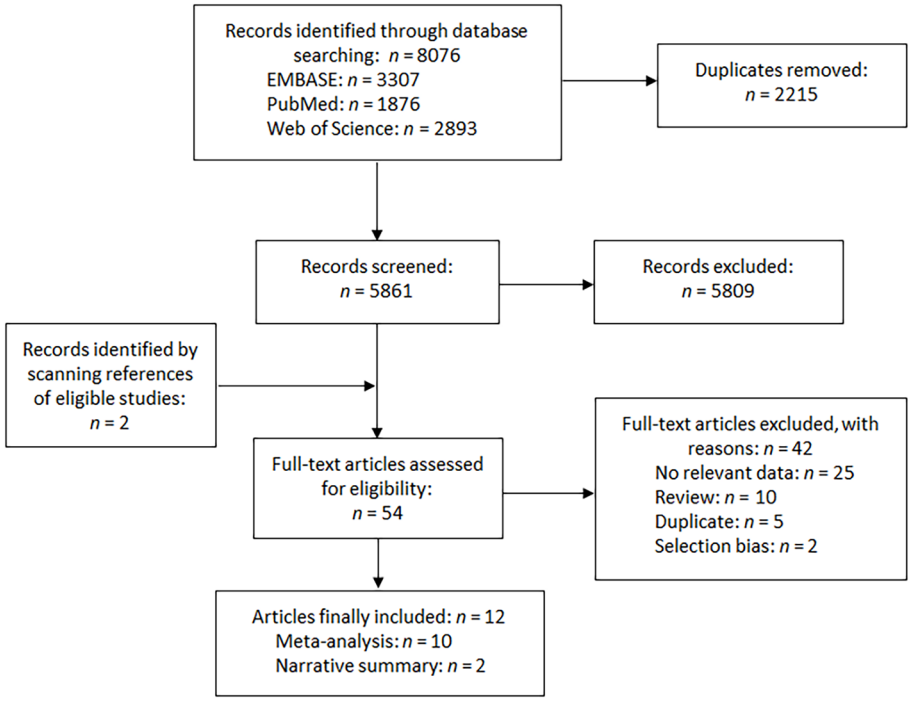

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Figure 1 PRISMA flow chart of study selection.

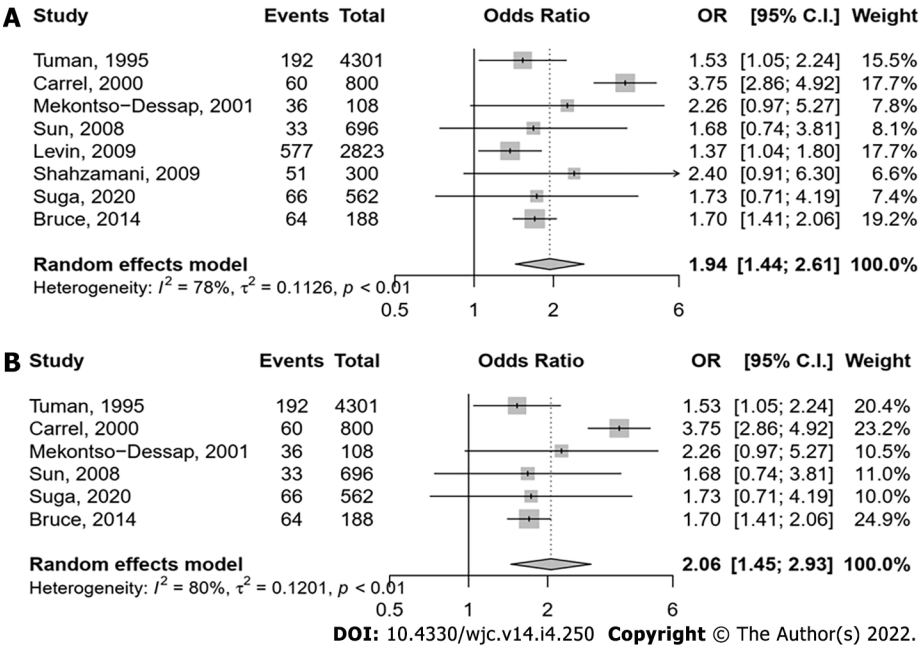

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Figure 2 Association between angiotensin converting enzyme inhibitors adverse vascular outcomes. A: Post cardiac surgery shock; B: Vasoplegia.

40%) increased the risk of post-cardiac surgery shock (pooled aOR 2.32, 95%CI: 1.60-3.36; I^2 49%) (Figure 4B). The risk of post-cardiac surgery shock increased with CPB time (pooled aOR 1.012 per 1 min increase, 95%CI: 1.003-1.021, P = 0.008; I^2 0%) (Figure 4C). There was no significant association between age and post-cardiac surgery shock (pooled aOR 1.02 per 1 year increase, 95%CI: 1.00-1.04, P = 0.052; I^2 0%) (Supplementary Figure 4). There was no evidence of publication bias on funnel plot inspection (Supplementary Figures 5 and 6), and according to the Egger's test for studies reporting on the association between beta blockers and vasoplegia (P = 0.906), and between left ventricular dysfunction and vasoplegia (P = 0.193).

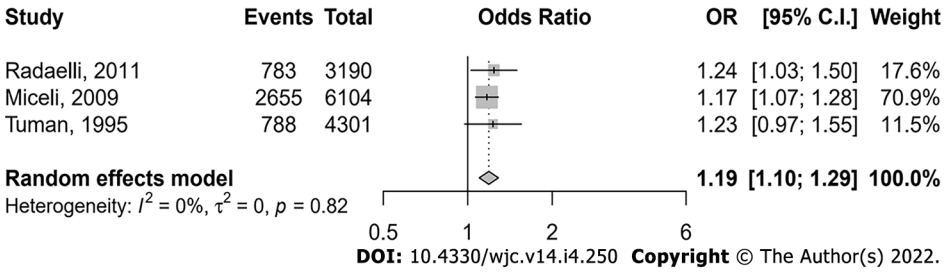

Figure 3 Association between angiotensin converting enzyme inhibitors and need for inotropic support.

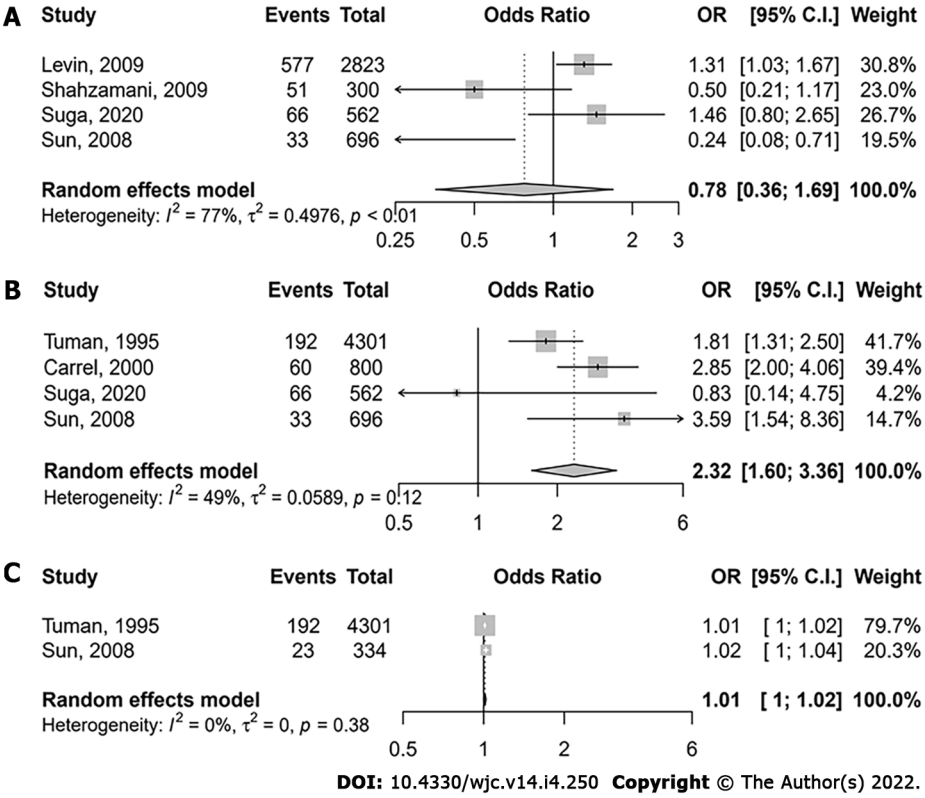

Figure 4 Association between other variables and post cardiac surgery shock. A: Beta blockers; B: Left ventricular dysfunction (EF < 40%); C: Cardiopulmonary bypass time (in minute).

Clinical trials on continuation of ACEIs and vasoplegia

Two RCTs reported on the risk of refractory hypotension with preoperative use of ACEIs[20,21]. The study by van Diepen *et al*[20] included perioperative cardiac monitoring in their definition of vasoplegia and had a larger sample size (61 patients taking RAS blockers)[21]. Incidence of post-cardiac surgery shock was 5%-15% in the study by Pigott *et al*[21] and in the RCT by van Diepen *et al*[20], vasoplegia was found in 29.8% of patients. Preoperative continuation of ACEIs (RAS blockers) was not associated with an increased risk of vasoplegia.

DISCUSSION

This study aimed to summarize data on the effect of preoperative use of ACEIs on incident vasoplegia in patients undergoing cardiac surgery using all relevant studies. Higher odds of vasoplegia (even when defined using perioperative cardiac monitoring) and more frequent use of inotropic support postoperatively were observed in patients who did not discontinue ACEIs. Other factors associated with the risk of post-cardiac surgery hypotension included left ventricular dysfunction and longer duration of CPB, whereas beta blockers use preoperatively was not. Interestingly, the 2 RCTs which evaluated the risk of vasoplegia and continuation of ACEIs (RAS blockers) before cardiac surgery did not show any association.

Hypotension is very common in cardiac surgery, especially with CPB. In response to reduced systemic blood pressure, the kidneys release renin that cleaves angiotensinogen to yield angiotensin I, further converted into angiotensin II by the angiotensin–converting enzyme which causes systemic vasoconstriction. It also increases the secretion of arginine vasopressin and aldosterone, and potentiates the release of norepinephrine by direct action on postganglionic sympathetic fibers. The increased risk of vasoplegia attributable to preoperative ACEI use reported in our study is also consistent with the evidence supporting a hemodynamic benefit of treatment with angiotensin II in patients undergoing cardiac surgery. For instance, a post-hoc analysis of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) multinational, randomized, double-blind trial showed that patients with vasoplegia after cardiac surgery with CPB rapidly responded to angiotensin II, reducing significantly vasopressor use[22].

Whether RAS blockers and specifically ACEIs should be held or not before cardiac surgery has been a matter of debate for more than two decades. The benefits of ACEIs and ARBs in patients with cardiovascular disease are well-established[23]. These positive effects are particularly prominent in the long-term management of patients with ischemic heart disease, especially those undergoing CABG, as evidenced in the QUinapril On Vascular Ace and Determinants of Ischemia (QUO VADIS) RCT[24]. A meta-analysis of 29 studies, mostly retrospective, showed that preoperative use of RAS blockers was associated with increased odds of postoperative acute kidney injury and mortality in patients undergoing cardiovascular surgery[25]. Despite the theoretical favorable mechanisms for RAS blockers in reducing post-operative atrial fibrillation, an increased incidence of post-operative atrial fibrillation has been shown in patients on preoperative RAS blockers, with an adverse effect on survival[26]. These data have motivated the recommendation to omit ACEIs or ARBs before cardiac surgery as a rational strategy to reduce the risk of postoperative vasoplegia and other adverse outcomes[27]. The two RCTs included in this review did not confirm an increased risk of vasoplegia, increased inotropic use or acute kidney injury when ACEIs (RAS blockers) were not discontinued before cardiac surgery[20,21]. However, these trials were not well-powered to be conclusive. They highlight the importance of conducting large multicenter randomized trials to examine the impact of preoperative RAS blockers discontinuation and of its timing on postoperative hemodynamic and clinical outcomes. A previous review already mentioned the weakness of the association between ACEIs and post-cardiac surgery vasoplegia, but a causal relationship has been widely accepted in some cardiovascular anesthesiology communities[28].

This study has some limitations. The definition of vasoplegia was not exactly the same across studies, thereby introducing a potential bias. This is probably due to the fact that there is still no consensus definition of vasoplegia. To address this issue, we pooled together data from studies that used similar definitions and as a result, the level of heterogeneity was low in most analyses. Next, it is possible that the effect of RAS blockers on vasoplegia and inotrope use were confounded by LVEF. Patients receiving RAS blockers are more likely to have low LVEF as these drugs are guideline-recommended in this population. As patients with low LVEF are more likely to have a more complicated post-operative course, it is possible that it is the low LVEF that drove the results, rather than the use of RAS blockers. Unfortunately, stratified analyses by LVEF were not available in the included studies. Moreover, there was no standardized perioperative medication management across studies. It is unclear whether patients reportedly not on ACEI ever took one, or whether some of them were chronically on ACEI but stopped few days before surgery. Another limitation is the relatively low number of eligible studies, which makes some of our estimates less robust. Furthermore, the association between vasoplegia and other factors such as age, CPB time, left ventricular dysfunction or preoperative beta blockers were not preplanned. These variables were not specifically included in the search strategy. Therefore, it is possible that some studies reporting on their attributable risk of vasoplegia were missed. Our findings related to these variables should therefore be interpreted with caution. Despite these limitations, our study is the first to systematically present the discrepancy between observational studies and RCT's on the effect of preoperative RAS blockage and the risk of vasoplegia.

CONCLUSION

Our meta-analysis shows that preoperative continuation of ACEIs is associated with an increased risk of vasoplegia and of the use of inotropic support postoperatively. These findings support the potential benefit of holding ACEIs prior to cardiac surgery to reduce the risk of vasoplegia and associated adverse outcomes. A consensus definition of vasoplegia may help future RCTs properly assess management strategies of RAS blockers in the perioperative setting.

ARTICLE HIGHLIGHTS

Research background

Vasoplegia is a common complication of cardiac surgery. The use of some medications prior to surgery is thought to contribute to inappropriate vasodilatation in vasoplegia. The causal relationship between preoperative use of renin angiotensin system (RAS) blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB)] between vasoplegia is unclear.

Research motivation

If perioperative use of RAS blockers is associated with vasoplegia, withholding these medications in patients undergoing cardiac surgery might help preventing vasoplegia after cardiac surgery.

Research objectives

To update and summarize data on the effect of preoperative use of RAS blockers on incident vasoplegia.

Research methods

The authors performed a systematic review of the literature, and summarized available data using a random-effects meta-analysis.

Research results

Ten studies reported on a pooled population of 15672 patients were included in the meta-analysis. Use of ACEIs was associated with an increased risk of vasoplegia and increased inotropic/vasopressor support requirement. Left ventricular dysfunuction increased the risk of post-cardiac surgery shock. There was no association between continuation of RAS blockers and vasoplegia in the two included randomized control trials (RCTs) .

Research conclusions

Preoperative continuation of ACEIs is associated with an increased risk of the use of inotropic support postoperatively and vasoplegia in observational studies but not in RCTs.

Research perspectives

Further studies are needed to clarify the relationship between perioperative use of RAS blockers and vasoplegia after cardiac surgery. Such studies should use a consensus definition of vasoplegia and conduct appropriate perioperative cardiovascular monitoring.

FOOTNOTES

Author contributions: Nouthe B, Noubiap JJ, Spaziano M and Sia YT contributed to the conception and design; Nouthe B, Noubiap JJ, and Spaziano M contributed to the search strategy; Nouthe B and Noubiap JJ contributed to the studies selection, data analysis and synthesis, data interpretation; Noubiap JJ contributed to the manuscript drafting; Nouthe B, Noubiap JJ, Spaziano M and Sia YT contributed to the manuscript revision, and approval of the final manuscript.

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REFERENCES

1 **Lambden S**, Creagh-Brown BC, Hunt J, Summers C, Forni LG. Definitions and pathophysiology of vasoplegic shock. *Crit Care* 2018; **22**: 174 [PMID: 29980217 DOI: 10.1186/s13054-018-2102-1]

2 **Levin MA**, Lin HM, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. *Circulation* 2009; **120**: 1664-1671 [PMID: 19822810 DOI: 10.1161/CIRCULATIONAHA.108.814533]

3 **Weis F**, Kilger E, Beiras-Fernandez A, Nassau K, Reuter D, Goetz A, Lamm P, Reindl L, Briegel J. Association between vasopressor dependence and early outcome in patients after cardiac surgery. *Anaesthesia* 2006; **61**: 938-942 [PMID: 16978306 DOI: 10.1111/j.1365-2044.2006.04779.x]

4 **Barnes TJ**, Hockstein MA, Jabaley CS. Vasoplegia after cardiopulmonary bypass: A narrative review of pathophysiology and emerging targeted therapies. *SAGE Open Med* 2020; **8**: 2050312120935466 [PMID: 32647575 DOI: 10.1177/2050312120935466]

5 **Suga M**, Kawakami D, Ueta H, Shimozono T, Ito J, Seo R, Nakamori Y, Korenaga A, Morimoto T, Mima H. Longer term hemodialysis-dependent chronic renal failure increases the risk of post-cardiac surgery vasoplegic syndrome. *J Anesth* 2020; **34**: 243-249 [PMID: 31900585 DOI: 10.1007/s00540-019-02727-0]

6 **Shahzamani M**, Yousefi Z, Frootaghe AN, Jafarimehr E, Froughi M, Tofighi F, Azadani AN, Pourhoseingholi MA, Azadani PN. The effect of angiotensin-converting enzyme inhibitor on hemodynamic instability in patients undergoing cardiopulmonary bypass: results of a dose-comparison study. *J Cardiovasc Pharmacol Ther* 2009; **14**: 185-191 [PMID: 19721131 DOI: 10.1177/1074248409341879]

7 **Mekontso-Dessap A**, Houël R, Soustelle C, Kirsch M, Thébert D, Loisance DY. Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function. *Ann Thorac Surg* 2001; **71**: 1428-1432 [PMID: 11383777 DOI: 10.1016/S0003-4975(01)02486-9]

8 **Disque A**, Neelankavil J. Con: ACE Inhibitors Should Be Stopped Prior to Cardiovascular Surgery. *J Cardiothorac Vasc Anesth* 2016; **30**: 820-822 [PMID: 27321797 DOI: 10.1053/j.jvca.2016.01.016]

9 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]

10 **CLARITY Group**. Tool to Assess Risk of Bias in Case Control Studies. Available from: https://www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-case-control-studies-distillersr

11 **CLARITY Group**. Tool to Assess Risk of Bias in Randomized Controlled Trials. Available from: https://www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-randomized-controlled-trials-distillersr

12 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

13 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563 DOI: 10.1136/bmj.315.7109.629]

14 **Tuman KJ**, McCarthy RJ, O'Connor CJ, Holm WE, Ivankovich AD. Angiotensin-converting enzyme inhibitors increase vasoconstrictor requirements after cardiopulmonary bypass. *Anesth Analg* 1995; **80**: 473-479 [PMID: 7864410 DOI: 10.1097/00000539-199503000-00007]

15 **Sun X**, Zhang L, Hill PC, Lowery R, Lee AT, Molyneaux RE, Corso PJ, Boyce SW. Is incidence of postoperative vasoplegic syndrome different between off-pump and on-pump coronary artery bypass grafting surgery? *Eur J Cardiothorac Surg* 2008; **34**: 820-825 [PMID: 18715792 DOI: 10.1016/j.ejcts.2008.07.012]

16 **Durán Bruce M**, Gomar Sancho C, Holguera JC, Muliterno Español E. [Factors involved in the development of vasoplegia after cardiac surgery with extracorporeal circulation. A prospective observational study]. *Rev Esp Anestesiol Reanim* 2014; **61**: 246-253 [PMID: 24507583 DOI: 10.1016/j.redar.2013.11.015]

17 **Carrel T**, Englberger L, Mohacsi P, Neidhart P, Schmidli J. Low systemic vascular resistance after cardiopulmonary bypass: incidence, etiology, and clinical importance. *J Card Surg* 2000; **15**: 347-353 [PMID: 11599828 DOI: 10.1111/j.1540-8191.2000.tb00470.x]

18 **Miceli A**, Capoun R, Fino C, Narayan P, Bryan AJ, Angelini GD, Caputo M. Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol* 2009; **54**: 1778-1784 [PMID: 19682819 DOI: 10.1016/j.jacc.2009.07.008]

19 **Radaelli G**, Bodanese LC, Guaragna JC, Borges AP, Goldani MA, Petracco JB, Piccoli Jda C, Albuquerque LC. The use of inhibitors of angiotensin-converting enzyme and its relation to events in the postoperative period of CABG. *Rev Bras Cir Cardiovasc* 2011; **26**: 373-379 [PMID: 22086573 DOI: 10.5935/1678-9741.20110011]

20 **van Diepen S**, Norris CM, Zheng Y, Nagendran J, Graham MM, Gaete Ortega D, Townsend DR, Ezekowitz JA, Bagshaw SM. Comparison of Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Management Strategies Before Cardiac Surgery: A Pilot Randomized Controlled Registry Trial. *J Am Heart Assoc* 2018; **7**: e009917 [PMID: 30371293 DOI: 10.1161/JAHA.118.009917]

21 **Pigott DW**, Nagle C, Allman K, Westaby S, Evans RD. Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements. *Br J Anaesth* 1999; **83**: 715-720 [PMID: 10690132 DOI: 10.1093/bja/83.5.715]

22 **Klijian A**, Khanna AK, Reddy VS, Friedman B, Ortoleva J, Evans AS, Panwar R, Kroll S, Greenfeld CR, Chatterjee S. Treatment With Angiotensin II Is Associated With Rapid Blood Pressure Response and Vasopressor Sparing in Patients With Vasoplegia After Cardiac Surgery: A Post-Hoc Analysis of Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) Study. *J Cardiothorac Vasc Anesth* 2021; **35**: 51-58 [PMID: 32868152 DOI: 10.1053/j.jvca.2020.08.001]

23 **López-Sendón J**, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C; Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus

document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. *Eur Heart J* 2004; **25**: 1454-1470 [PMID: 15302105 DOI: 10.1016/j.ehj.2004.06.003]

24 **Oosterga M**, Voors AA, Pinto YM, Buikema H, Grandjean JG, Kingma JH, Crijns HJ, van Gilst WH. Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study). QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol* 2001; **87**: 542-546 [PMID: 11230836 DOI: 10.1016/s0002-9149(00)01428-4]

25 **Yacoub R**, Patel N, Lohr JW, Rajagopalan S, Nader N, Arora P. Acute kidney injury and death associated with renin angiotensin system blockade in cardiothoracic surgery: a meta-analysis of observational studies. *Am J Kidney Dis* 2013; **62**: 1077-1086 [PMID: 23791246 DOI: 10.1053/j.ajkd.2013.04.018]

26 **Bandeali SJ**, Kayani WT, Lee VV, Pan W, Elayda MA, Nambi V, Jneid HM, Alam M, Wilson JM, Birnbaum Y, Ballantyne CM, Virani SS. Outcomes of preoperative angiotensin-converting enzyme inhibitor therapy in patients undergoing isolated coronary artery bypass grafting. *Am J Cardiol* 2012; **110**: 919-923 [PMID: 22727178 DOI: 10.1016/j.amjcard.2012.05.021]

27 **Sousa-Uva M**, Head SJ, Milojevic M, Collet JP, Landoni G, Castella M, Dunning J, Gudbjartsson T, Linker NJ, Sandoval E, Thielmann M, Jeppsson A, Landmesser U. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg* 2018; **53**: 5-33 [PMID: 29029110 DOI: 10.1093/ejcts/ezx314]

28 **Raja SG**, Fida N. Should angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists be omitted before cardiac surgery to avoid postoperative vasodilation? *Interact Cardiovasc Thorac Surg* 2008; **7**: 470-475 [PMID: 18272542 DOI: 10.1510/icvts.2007.174698]

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CASE REPORT

Uncommon post-infarction pseudoaneurysms: A case report

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Abstract

BACKGROUND

Mechanical complications are a rare presentation in chronic coronary syndromes, which have significantly decreased in the primary coronary intervention era. Incomplete rupture may occur, resulting in pseudoaneurysms (PANs). Early reperfusion decreases the risk of this complication. Echocardiography is the method of choice for diagnosis.

CASE SUMMARY

A 54-year-old female hypertensive patient, with a history of non-revascularized inferior and anterior ST-segment elevation myocardial infarction (MI) 4 years prior, was admitted to the cardiac unit of the hospital with complaints of abdominal pain and dyspnea lasting 2 mo. The patient was hemodynamically stable, and 12-lead electrocardiogram showed persistent ST elevation and Q wave in the inferior and apical regions. Transthoracic echocardiogram in the two-chamber view showed a narrow neck of a wide PAN in the distal apical left ventricular inferior wall. In addition, the apical four-chamber and subcostal views revealed a second bulky PAN of the apical wall separated from the first by a common organizing thrombus. Cardiac magnetic resonance imaging confirmed the coexistence of more than one PAN. The patient received conservative medical treatment, and surgery was scheduled for outside the country. The patient had worsening multiple organ failure and died 4 wk after presentation.

CONCLUSION

Multifocal PANs rarely occur in chronic MI. Attention should be paid to patients with pain and cardiovascular risk factors.

Key Words: Cardiac rupture; Myocardial infarction; Pseudoaneurysm; Echocardiogram;

Case report

Core Tip: Multiple left ventricular pseudoaneurysms are a rare complication following myocardial infarction (MI), which can be diagnosed years after the infarction. This case highlights the ultimate importance of appropriate early reperfusion of MI and the role of echocardiography and multimodal imaging for the diagnostic assessment of this lethal condition.

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INTRODUCTION

Left ventricular (LV) pseudoaneurysms (PANs) are rare mechanical complications of acute myocardial infarction (MI). They are caused by rupture of the free wall, are composed of organizing thrombus due to hemorrhage into the pericardial space after cardiac rupture (CR), and involve various amounts of epicardium and parietal pericardium. As stated by Hung *et al*[1], "PAN following transmural infarction has a high mortality rate of up to 20%". There have been few reports of LV PAN during the chronic phase of MI, and among them all have had a single localization. Although surgical repair is the treatment of choice, transcatheter intervention for PAN repair is feasible in selected cases.

Herein, we present the first case of uncommon CR manifested as multiple adjacent LV PANs, which occurred in a female patient with a history of MI.

CASE PRESENTATION

Chief complaints

A 54-year-old female patient presented to the emergency department with complaints of abdominal pain and dyspnea.

History of present illness

The patient presented with recurrent episodes of epigastric pain and dyspnea, which began 2 mo prior and worsened 48 h before hospital admission.

History of past illness

The patient had a long history of untreated and advanced hypertension, as well as a history of inferior and anterior ST-segment elevation MI without revascularization, which had occurred 4 years prior.

Personal and family history

The patient had no relevant family history.

Physical examination

The patient presented with hemodynamic stability, a heart rate of 96 beats/min, respiratory rate of 16 breaths/min, blood pressure of 130/80 mmHg, and oxygen saturation in room air of 98%. Symptoms of acute heart failure were excluded by clinical cardiological examination. A painful and hard epigastric mass was detected upon abdominal examination.

Laboratory examinations

Blood analysis revealed mild leukocytosis (12 × 10^9/L), with neutrophil predominance (80%) and normal hematocrit and platelet levels. Prothrombin and partial thromboplastin times were normal, and troponin T was slightly increased at 1.2 ng/mL. Blood creatinine was increased at 435 mmol/L. The 12-lead electrocardiogram showed persistent ST elevation and Q wave in the inferior and apical territory. Chest X-ray revealed increased cardiothoracic ratio with rounded opacity along the left cardiac silhouette.

Imaging examinations

Echocardiography is the first test performed after admission because of its availability. In the four-chamber view, initial imaging evaluation with transthoracic echocardiogram (TTE) showed the narrow neck of a large PAN in the LV apical wall (arrow) (Figure 1A), in the apical two-chamber view (Figure 1B) and modified short axis view (Figure 2A). TTE revealed a second PAN of the distal apical inferior wall, separated from the first PAN by a common organizing fibrous tissue, as detected in the subcostal view (Figure 3A) and apex view (Figure 3B), without pericardial effusion. Color Doppler imaging in the four-chamber view (Figure 2B) demonstrated flow in and out of the pericardial cavity at the site of the tear, as well as abnormal flow into the PAN without any shunt through the organizing thrombus. The LV communicated with the PAN *via* a narrow neck formed by the ruptured apical and inferior myocardium. The dimensions of the cavity (68/15 mm; Figure 2A) and imaging findings were indicative of a PAN; however, it is of great clinical importance to differentiate PANs, which have a high likelihood of spontaneous rupture, from a true aneurysm, which seldom ruptures.

Further diagnostic work-up

The patient was further evaluated with transesophageal echocardiogram, despite the difficulty in assessing the apical wall by this approach; however, the left ventricle communicated with the PANs *via* a narrow neck formed by the ruptured apical and inferior myocardium (Figure 4). To better characterize this finding, a cardiac magnetic resonance (CMR) scan was performed since the severe chronic renal failure precluded evaluation by thoracic computed tomography angiography and to take advantage of the good non-invasive tissue characterization offered by CMR; the cine sequence images confirmed severe LV dysfunction and showed an apical PAN without an intracavitary thrombus in the two-chamber view (Figure 5A). Curiously, a larger and a small outpouching, separated by fibrous tissue, was revealed in the inferior apical wall (Figure 5B); the outpouchings were seen to be associated with disrupted myocardial wall, and they were surrounded only by pericardium.

FINAL DIAGNOSIS

Multiple adjacent LV PANs following chronic MI.

TREATMENT

The patient was immediately started on conservative medical treatment, including a curative anticoagulant (acenocoumarolum at 4 mg/d), diuretic (furosemide at 40 mg/d), heart failure therapeutics (bisoprolol at 5 mg and ramipril 5 mg, both one pill per day) and coronary heart disease therapeutics (aspirin at 75 mg/d and atorvastatin at 20 mg/d). After collegial discussion among the care team, the decision was made to proceed with surgical repairs outside the country due to the lack of a cardiac surgery center.

OUTCOME AND FOLLOW-UP

The patient had an uneventful clinical course with medical treatment; surgery was delayed considering the suspension of air travel due to the coronavirus disease 2019 pandemic. The patient had multiple organ failure caused by acute free intrapericardial rupture, which usually causes cardiac tamponade and death, and died 4 wk after presentation.

DISCUSSION

PAN is a contained progressive rupture of the LV free wall. It is commonly caused by MI but may also occur after cardiac surgery, chest trauma or infection, and endocardial electrophysiologic procedures; "although in some cases the etiology may be unknown[2]". Typically, LV PANs can also be identified by echocardiography and are typified by a PAN cavity that communicates with the LV chamber *via* a very narrow neck and frequently contains a thrombus. The characteristic to-and-fro blood flow through the site of rupture can be detected with Doppler and color flow imaging; however, "magnetic resonance imaging is necessary to establish the diagnosis if echocardiography findings are atypical[3]". While most PANs are located in the inferoposterior or inferolateral region, "some studies have concluded that the most typical location is the anterior or lateral wall[4].

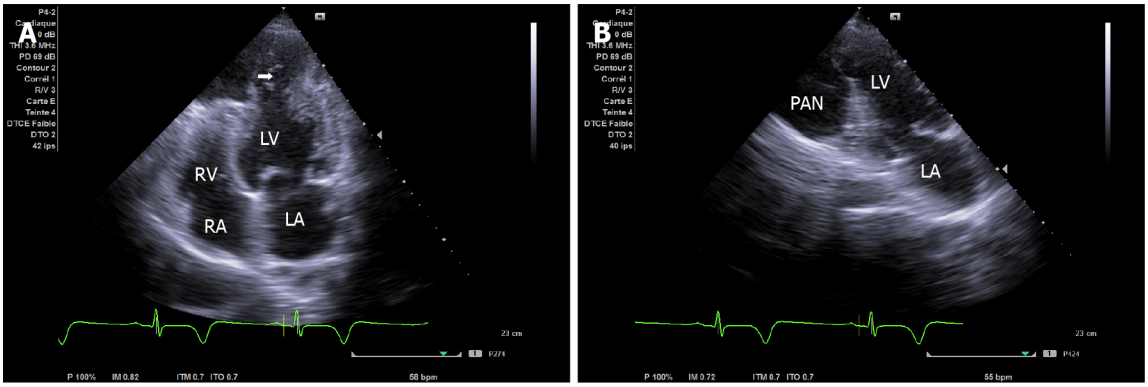

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Figure 1 Apical chamber view on transthoracic echocardiogram. A: Apical four-chamber view demonstrating the narrow neck of a pseudoaneurysm (PAN) in the apical wall (arrow indicates the site of free wall rupture); B: Apical two-chamber view demonstrating a second PAN of the infero-apical wall. LA: Left atrium; LV: Left ventricular; RA: Right atrium; RV: Right ventricular.

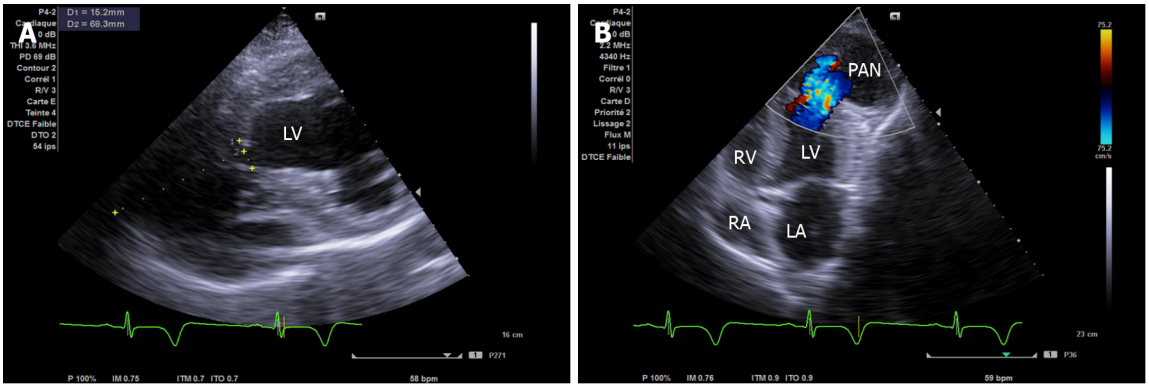

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Figure 2 Transthoracic echocardiogram. A: Modified short axis view with the pseudoaneurysm dimensions (width of the neck was 15 mm and the maximal internal diameter of the aneurysmal sac was 68 mm with a neck to sac ratio of less than 0.5); B: Apical modified 4/5 chamber view showing bidirectional shunt through the left ventricular wall.

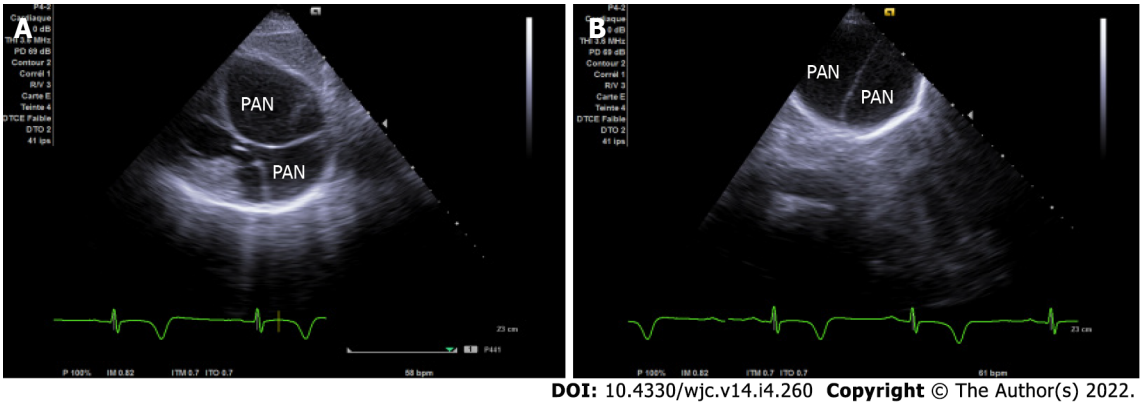

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Figure 3 Subcostal and apical views on transthoracic echocardiogram. A: Subcostal view illustrating two wide pseudoaneurysms isolated by organizing fibrous tissue; B: Apical view with inclination of the probe at a right angle to the skin showing two non-communicant adjacent cavities separated by fibrous tissue.

In the last several years, the incidence of CR has decreased with the development of "primary percutaneous coronary intervention (PPCI), which has been an important protective factor[5]". Risk factors include advanced age, female sex, first infarction, large infarction, and delivery of fibrinolytic therapy more than 14 h after the onset of symptoms. Our patient was in the 5th decade of life, female sex, and hypertensive, with an untreated large anterior MI. Hence, our patient was at high risk of developing CR. "Early reperfusion and the presence of collateral circulation, which limit the extent of

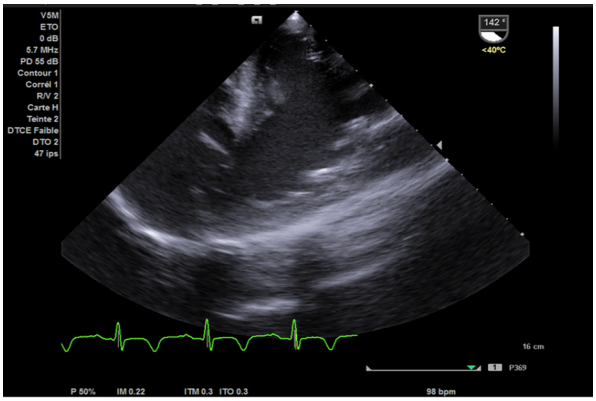

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Figure 4 Two-chamber view on transesophageal echocardiogram. Two-chamber view confirming the pseudoaneurysm and flow through the left ventricle.

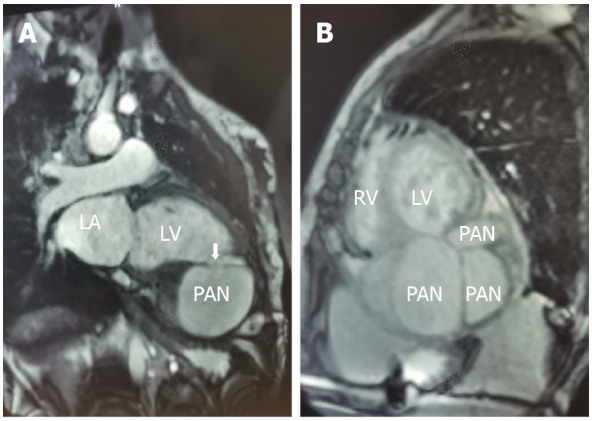

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Figure 5 Cardiac magnetic resonance imaging. A: Two-chamber view showing the connection between the left ventricular (LV) cavity and the LV pseudoaneurysm (PAN) (arrow); B: Short axis view showing multiple cavities corresponding to the PANs isolated by fibrous tissue. LA: Left atrium; RV: Right ventricular.

myocardial tissue damage, decrease the risk of free wall rupture[6]".

To the best of our knowledge, the presented case is the first in the literature to show more than one PAN caused by MI with long-term evolution. In this case, the onset and progression were possibly influenced by the large extension of non-revascularized MI, and the severity of hypertension explained by the advanced stage of chronic kidney failure. The first evaluation by echocardiography in the early phase of acute MI did not show the development of dyskinesia or aneurysm. In acute LV PAN, once the diagnosis is confirmed, surgical repair is the preferred treatment, although conservative medical treatment for certain high-risk patients may be associated with a good outcome, "as has been described in some retrospective studies showing that patients with an incidental finding of chronic small LV PAN, less than 3 cm in size, and patients with increased surgical risk can be managed conservatively[7]". However, the preferred approach remains surgical management. Our patient was primarily treated by medical treatment and was scheduled for surgery after discussion with the surgical team, but she died after 4 wk from acute free intrapericardial rupture, in accordance with the literature showing that "PANs have a high risk of rupture, occurring in 30% to 45% of cases[8]". In patients treated conservatively, some complications may occur, such as thromboembolism, compression of adjacent structures, and infection.

CONCLUSION

PANs are caused by rupture of the myocardial wall and are an infrequent complication of acute MI that rapidly leads to death. However, some cases may take a subacute or chronic course when a small rupture is temporarily sealed by fibrinous pericardial adhesions or thrombus. No cases of multiple PANs of LV have been reported. The best weapon against this lethal complication is timely pharma-

cologic or mechanical reperfusion.

FOOTNOTES

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REFERENCES

1 **Hung MJ**, Wang CH, Cherng WJ. Unruptured left ventricular pseudoaneurysm following myocardial infarction. *Heart* 1998; **80**: 94-97 [PMID: 9764070 DOI: 10.1136/hrt.80.1.94]
2 **Ashraf T**, Aziz R, Khuwaja AM. Left ventricular aneurysmectomy in a young female with pseudoaneurysm of unknown etiology. *J Saudi Heart Assoc* 2020; 32: 110-113 [DOI: 10.37616/2212-5043.1019]
3 **Caldeira A**, Albuquerque D, Coelho M, Côrte-Real H. Left Ventricular Pseudoaneurysm: Imagiologic and Intraoperative Images. *Circ Cardiovasc Imaging* 2019; **12**: e009500 [PMID: 31766861 DOI: 10.1161/CIRCIMAGING.119.009500]
4 **Abdelnaby M**, Al-Maghraby A, Saleh Y, El-Amin A, Hammad B. Post-Myocardial Infarction Left Ventricular Free Wall Rupture: A Review. *Ann Med Health Sci Res* 2017
5 **Honda S**, Asaumi Y, Yamane T, Nagai T, Miyagi T, Noguchi T, Anzai T, Goto Y, Ishihara M, Nishimura K, Ogawa H, Ishibashi-Ueda H, Yasuda S. Trends in the clinical and pathological characteristics of cardiac rupture in patients with acute myocardial infarction over 35 years. *J Am Heart Assoc* 2014; **3**: e000984 [PMID: 25332178 DOI: 10.1161/JAHA.114.000984]
6 **Sulzgruber P**, El-Hamid F, Koller L, Forster S, Goliasch G, Wojta J, Niessner A. Long-term outcome and risk prediction in patients suffering acute myocardial infarction complicated by post-infarction cardiac rupture. *Int J Cardiol* 2017; **227**: 399-403 [PMID: 27847155 DOI: 10.1016/j.ijcard.2016.11.037]
7 **Yeo TC**, Malouf JF, Oh JK, Seward JB. Clinical profile and outcome in 52 patients with cardiac pseudoaneurysm. *Ann Intern Med* 1998; **128**: 299-305 [PMID: 9471934 DOI: 10.7326/0003-4819-128-4-199802150-00010]
8 **Frances C**, Romero A, Grady D. Left ventricular pseudoaneurysm. *J Am Coll Cardiol* 1998; **32**: 557-561 [PMID: 9741493 DOI: 10.1016/s0735-1097(98)00290-3]

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LETTER TO THE EDITOR

Glucose lowering does not necessarily reduce cardiovascular risk in type 2 diabetes

Angeliki Bourazana, Grigorios Giamouzis, John Skoularigis, Filippos Triposkiadis, Andrew Xanthopoulos

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Abstract

Diabetes mellitus (DM) is a health condition characterized by glucose dysregulation and affects millions of people worldwide. The presentation of heart failure in diabetic cardiomyopathy extends over a wide phenotypic spectrum, commencing from asymptomatic, subclinical structural abnormalities to severely symptomatic biventricular dysfunction with increased mortality risk. Similarly, the spectrum of systolic dysfunction in diabetic-induced heart failure is diverse. DM leads also to cardiac electrical remodeling reacting on various targets. Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce glucagon and blood glucose levels by raising levels of the endogenous hormones glucagon-like-peptide 1 and glucose-dependent insulinotropic peptide and constitute a safe and effective glucose lowering treatment option in patients with type 2 DM. Despite DPP-4 inhibitors' efficacy regarding glycemic control, their effect on cardiovascular outcomes (myocardial infarction, stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization, and cardiovascular death) in diabetic patients has been neutral. The potential correlation between atrial flutter and DPP-4 inhibitors administration needs further investigation.

Key Words: Dipeptidyl peptidase-4 inhibitors; Diabetes mellitus; Outcomes; Meta-analysis; Heart failure; Atrial flutter

Core Tip: Dipeptidyl peptidase-4 inhibitors are a safe and effective glucose lowering treatment option in patients with type 2 diabetes mellitus. However, their effect on cardiovascular outcomes in diabetic patients has been neutral. The potential correlation between atrial flutter and dipeptidyl peptidase-4 inhibitors administration is an interesting finding, but since currently there is no sheer underlying pathophysiologic mechanism to justify it, more evidence is required.

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TO THE EDITOR

Diabetes mellitus (DM) is a health condition characterized by glucose dysregulation and affects 237.9 million males and 222 million females worldwide[1]. It is an established risk factor of cardiovascular disease, atrial and ventricular arrhythmias, as well as sudden cardiac death[2,3]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a safe and effective glucose lowering treatment option in patients with type 2 DM (T2DM). Nevertheless, pooled recent data on the effect of DPP-4 inhibitors on cardiovascular outcomes and major cardiac arrhythmias are lacking.

We read with great interest the paper by Patoulias *et al*[4], who attempted to close the abovementioned knowledge gap by performing a meta-analysis of six randomized controlled trials (52520 patients) concerning the impact of dipeptidyl peptidase-4 (DPP-4) inhibitors on "hard" cardiovascular outcomes and major cardiac arrhythmias. The authors concluded that DPP-4 inhibitors, compared to placebo, had no effect on fatal or non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization, and cardiovascular death and did not seem to confer any significant risk for major cardiac arrhythmias, with the exception of atrial flutter, which was associated with an increased risk equal to 52% (relative risk = 1.52, 95% confidence interval: 1.03-2.24, I^2 = 0%).

We agree with the authors' insight that the presence of DM per se increases the risk of adverse cardiovascular outcomes and arrhythmias and results in cellular destabilization of myocardial tissue altogether. For example, it has been demonstrated that diabetic patients present an increased propensity for developing heart failure[5]. Diabetic cardiomyopathy, defined as ventricular dysfunction in the absence of hypertension or coronary artery disease, has been attributed to the deregulated immune response in type-1 DM (T1DM) and to the background of obesity in the majority of T2DM patients. The amplified immune response of T1DM patients to myocardial injury, leads to the expansion of proinflammatory CD4+ T cells specific to myosin and the development of autoantibodies to MYH6 and other cardiac antigens. On the other hand, obesity that predominates over T2DM patients reduces the palliative actions of circulating natriuretic peptides on ventricular stress, pressure overload, and sympathetic activation. In the absence of natriuretic peptides' favorable actions, left ventricle hypertrophy, fibrosis, and insulin desensitization in skeletal muscles are more frequently observed in obese patients[5]. The presentation of heart failure in diabetic cardiomyopathy extends over a wide phenotypic spectrum, commencing from asymptomatic, subclinical structural abnormalities, developing progressively to severely symptomatic biventricular dysfunction with advanced mortality risk. Similarly, the spectrum of systolic dysfunction in diabetic-induced heart failure is diverse, originating in the heterogeneous risk factors that diabetes comes along, such as hypertension, hyperlipidemia, cardiovascular disease, and chronic kidney disease[6].

Except for the morphological implications on ventricular myocardium that account for the wide spectrum of left ventricular dysfunction, DM leads to cardiac electrical remodeling reacting on various targets. Among the diabetes-induced electrical disturbances, reduced conduction velocity, prolonged repolarization, and increased QT dispersion have been recognized, all predisposing to ventricular arrhythmias[7,8]. T1DM and T2DM lead to action potential duration prolongation, which becomes prominent on electrocardiography with a QRS prolongation in some diabetic patients[9]. QT duration prolongation subsequently predisposes to early after depolarizations development and an enhanced risk of torsade de pointes[10]. The proposed mechanisms are diabetes-exerted alterations in the function of several proteins involved in ion handling. More specifically, DM modifies ion channels responsible for depolarization as well as repolarization and resting phase[11]. Therefore, DM affects essentially all phases of action potential and correlates strongly to ventricular arrhythmias emergence.

The culprit pathophysiological mechanisms for the occurrence of atrial arrhythmias in DM substrate are not yet in depth elucidated. In atrial myocardium, DM favors the phenotypic switch of fibroblasts to myofibroblasts[12]. Mighty it is that diabetes induced atrial neuropathy as well as diabetes generated advanced myofibroblast differentiation promote atrial remodeling and lead to atrial cardiomyopathy

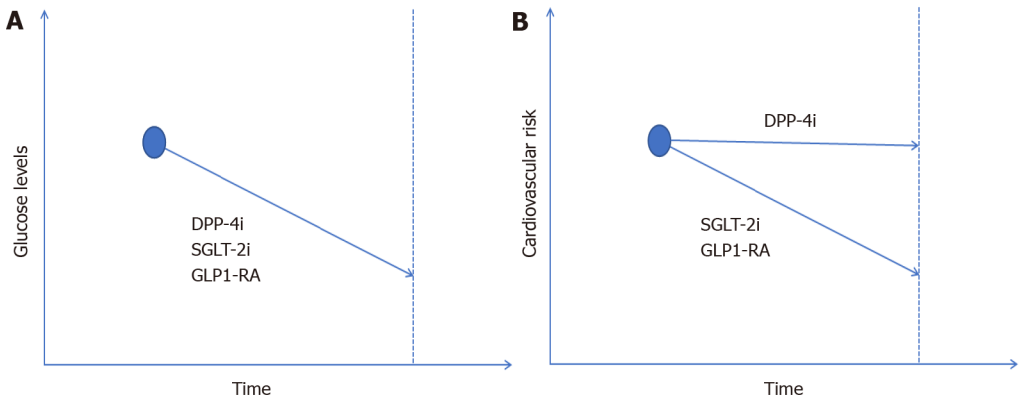

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Figure 1 Newer oral antidiabetic drugs, glucose levels, and cardiovascular risk. A: Dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 inhibitors (SGLT-2i), and glucagon-like peptide-1 receptor agonists (GLP1-RA) are effective glucose lowering agents in patients with type 2 DM; B SGLT-2i and GLP1-RA have shown significant decreases in adverse cardiovascular events, whereas the effect of DPP-4 inhibitors on cardiovascular outcomes in diabetic patients has been neutral. DPP-4i: DPP-4 inhibitors; SGLT-2i: Sodium-glucose cotransporter 2 inhibitors; GLP1-RA: glucagon-like peptide-1 receptor agonists.

overall[13]. Nonetheless, on epidemiological basis, DM is a strong independent risk factor for atrial fibrillation (AF) and atrial flutter occurrence.

Several studies have demonstrated that antidiabetic drugs may have differing effects on the risk of new-onset AF[14]. Metformin has been associated with anti-atrial arrhythmic benefits[15]. A case control study revealed no association between sulfonylurea and incident AF, whereas the use of insulin was associated with increased risk of new-onset AF[16]. A recent meta-analysis showed that DPP-4 inhibitor treatment resulted in a non-significant decrease in the risk for AF, whereas both glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2-i) were associated with a significant decrease in the risk for AF, equal to 14% and 19%, respectively[17]. Liraglutide (a GLP1-RA) demonstrated favorable effects on electrophysiological changes regarding AF inducibility and conduction velocity decrease[18].

DPP-4 inhibitors reduce glucagon and blood glucose levels by raising levels of the endogenous hormones glucagon-like-peptide 1 and glucose-dependent insulinotropic peptide, which are called incretins. Subsequently incretins inhibit glucagon release and increase insulin secretion. Despite DPP-4 inhibitors' indisputable efficacy regarding glycemic control, their effect on cardiovascular outcomes in diabetic patients, as denoted in the aforementioned and previous studies, has been neutral[19,20]. Furthermore, the risk of hypoglycemia is admitted to be increased compared to SGLT2-i. SGLT2-i reduce hyperglycemia through inhibition of glucose reabsorption in the renal proximal tubules. Acting on glucose/Na co-transporter they promote natriuresis and display not solely hypoglycemic effects but also reduce major adverse cardiovascular events (cardiovascular and total mortality, fatal or nonfatal myocardial infarction, or stroke) and hospitalization for heart failure and improve outcome in chronic kidney disease in diabetic and non-diabetic patients[21]. GLP1-RA are oral hypoglycemic drugs that mimic the effects of the incretin hormone glucagon-like-peptide 1. GLP-RA stimulate insulin release, inhibit glucagon secretion, and slow gastric emptying. Liraglutide, albiglutide, and dualiglutide have all shown significant decreases in adverse cardiovascular events[22]. In line with this evidence, the European Society of Cardiology guidelines recommend the administration of SGLT-2i or GLP1-RA as a first option in the presence of high or remarkably high cardiovascular risk or of cardiovascular disease [23].

The potential correlation between atrial flutter and DPP-4 inhibitors administration is an interesting finding, but since there is no sheer underlying pathophysiologic mechanism to justify it, more evidence is required to establish this thesis as a widely accepted knowledge admissible in clinical practice. The authors speculated that the abovementioned correlation may stem from the inherent higher risk of atrial flutter that patients with DM carry[24]. However, it is also well known that DM per se is a risk factor of AF[24], which in the current meta-analysis was not associated with DPP-4 inhibitor use.

In conclusion, the authors should be congratulated on their attempt to provide state of the art data on the association between DPP-4 inhibitors and cardiovascular outcomes as well as major cardiac arrhythmias. The reported increased risk of atrial flutter in patients receiving DPP-4 inhibitors needs further investigation (Figure 1).

FOOTNOTES

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REFERENCES

1 **Virani SS**, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MSV, Evenson KR, Ferguson JF, Gupta DK, Khan SS, Kissela BM, Knutson KL, Lee CD, Lewis TT, Liu J, Loop MS, Lutsey PL, Ma J, Mackey J, Martin SS, Matchar DB, Mussolino ME, Navaneethan SD, Perak AM, Roth GA, Samad Z, Satou GM, Schroeder EB, Shah SH, Shay CM, Stokes A, VanWagner LB, Wang NY, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* 2021; **143**: e254-e743 [PMID: 33501848 DOI: 10.1161/CIR.0000000000000950]

2 **Bell DSH**, Goncalves E. Atrial fibrillation and type 2 diabetes: Prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes Obes Metab* 2019; **21**: 210-217 [PMID: 30144274 DOI: 10.1111/dom.13512]

3 **Lynge TH**, Svane J, Pedersen-Bjergaard U, Gislason G, Torp-Pedersen C, Banner J, Risgaard B, Winkel BG, Tfelt-Hansen J. Sudden cardiac death among persons with diabetes aged 1-49 years: a 10-year nationwide study of 14 294 deaths in Denmark. *Eur Heart J* 2020; **41**: 2699-2706 [PMID: 31848583 DOI: 10.1093/eurheartj/ehz891]

4 **Patoulias DI**, Boulmpou A, Teperikidis E, Katsimardou A, Siskos F, Doumas M, Papadopoulos CE, Vassilikos V. Cardiovascular efficacy and safety of dipeptidyl peptidase-4 inhibitors: A meta-analysis of cardiovascular outcome trials. *World J Cardiol* 2021; **13**: 585-592 [PMID: 34754403 DOI: 10.4330/wjc.v13.i10.585]

5 **Triposkiadis F**, Xanthopoulos A, Bargiota A, Kitai T, Katsiki N, Farmakis D, Skoularigis J, Starling RC, Iliodromitis E. Diabetes Mellitus and Heart Failure. *J Clin Med* 2021; **10** [PMID: 34441977 DOI: 10.3390/jcm10163682]

6 **Triposkiadis F**, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, Backs J, Bauersachs J, Burkhoff D, Bonow RO, Chopra VK, de Boer RA, de Windt L, Hamdani N, Hasenfuss G, Heymans S, Hulot JS, Konstam M, Lee RT, Linke WA, Lunde IG, Lyon AR, Maack C, Mann DL, Mebazaa A, Mentz RJ, Nihoyannopoulos P, Papp Z, Parissis J, Pedrazzini T, Rosano G, Rouleau J, Seferovic PM, Shah AM, Starling RC, Tocchetti CG, Trochu JN, Thum T, Zannad F, Brutsaert DL, Segers VF, De Keulenaer GW. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J* 2019; **40**: 2155-2163 [PMID: 30957868 DOI: 10.1093/eurheartj/ehz158]

7 **Ninkovic VM**, Ninkovic SM, Miloradovic V, Stanojevic D, Babic M, Giga V, Dobric M, Trenell MI, Lalic N, Seferovic PM, Jakovljevic DG. Prevalence and risk factors for prolonged QT interval and QT dispersion in patients with type 2 diabetes. *Acta Diabetol* 2016; **53**: 737-744 [PMID: 27107571 DOI: 10.1007/s00592-016-0864-y]

8 **Gallego M**, Zayas-Arrabal J, Alquiza A, Apellaniz B, Casis O. Electrical Features of the Diabetic Myocardium. Arrhythmic and Cardiovascular Safety Considerations in Diabetes. *Front Pharmacol* 2021; **12**: 687256 [PMID: 34305599 DOI: 10.3389/fphar.2021.687256]

9 **Singleton MJ**, German C, Hari KJ, Saylor G, Herrington DM, Soliman EZ, Freedman BI, Bowden DW, Bhave PD, Yeboah J. QRS duration is associated with all-cause mortality in type 2 diabetes: The diabetes heart study. *J Electrocardiol* 2020; **58**: 150-154 [PMID: 31895990 DOI: 10.1016/j.jelectrocard.2019.11.053]

10 **Maruyama M**, Lin SF, Xie Y, Chua SK, Joung B, Han S, Shinohara T, Shen MJ, Qu Z, Weiss JN, Chen PS. Genesis of phase 3 early afterdepolarizations and triggered activity in acquired long-QT syndrome. *Circ Arrhythm Electrophysiol* 2011; **4**: 103-111 [PMID: 21078812 DOI: 10.1161/CIRCEP.110.959064]

11 **Yu P**, Hu L, Xie J, Chen S, Huang L, Xu Z, Liu X, Zhou Q, Yuan P, Yan X, Jin J, Shen Y, Zhu W, Fu L, Chen Q, Yu J, Hu J, Cao Q, Wan R, Hong K. O-GlcNAcylation of cardiac Nav1.5 contributes to the development of arrhythmias in diabetic hearts. *Int J Cardiol* 2018; **260**: 74-81 [PMID: 29530619 DOI: 10.1016/j.ijcard.2018.02.099]

12 **Fowlkes V**, Clark J, Fix C, Law BA, Morales MO, Qiao X, Ako-Asare K, Goldsmith JG, Carver W, Murray DB, Goldsmith EC. Type II diabetes promotes a myofibroblast phenotype in cardiac fibroblasts. *Life Sci* 2013; **92**: 669-676 [PMID: 23333820 DOI: 10.1016/j.lfs.2013.01.003]

13 **Wang A**, Green JB, Halperin JL, Piccini JP Sr. Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019; **74**: 1107-1115 [PMID: 31439220 DOI: 10.1016/j.jacc.2019.07.020]

14 **Lee TW**, Lee TI, Lin YK, Chen YC, Kao YH, Chen YJ. Effect of antidiabetic drugs on the risk of atrial fibrillation: mechanistic insights from clinical evidence and translational studies. *Cell Mol Life Sci* 2021; **78**: 923-934 [PMID: 32965513 DOI: 10.1007/s00018-020-03648-y]

15 **Nantsupawat T**, Wongcharoen W, Chattipakorn SC, Chattipakorn N. Effects of metformin on atrial and ventricular arrhythmias: evidence from cell to patient. *Cardiovasc Diabetol* 2020; **19**: 198 [PMID: 33234131 DOI: 10.1186/s12933-020-01176-4]

16 **Liou YS**, Yang FY, Chen HY, Jong GP. Antihyperglycemic drugs use and new-onset atrial fibrillation: A population-based nested case control study. *PLoS One* 2018; **13**: e0197245 [PMID: 30161122 DOI: 10.1371/journal.pone.0197245]

17 **Patoulias D**, Toumpourleka M, Papadopoulos C, Doumas M. Meta-analysis Evaluating the Risk of Atrial Fibrillation With Newer Antidiabetics Across the Cardiovascular and Renal Outcome Trials. *Am J Cardiol* 2021; **139**: 139-141 [PMID: 33080212 DOI: 10.1016/j.amjcard.2020.10.030]

18 **Nakamura H**, Niwano S, Niwano H, Fukaya H, Murakami M, Kishihara J, Satoh A, Yoshizawa T, Ishizue N, Igarashi T, Fujiishi T, Ako J. Liraglutide suppresses atrial electrophysiological changes. *Heart Vessels* 2019; **34**: 1389-1393 [PMID: 30762094 DOI: 10.1007/s00380-018-01327-4]

19 **Sinha B**, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. *Diabetes Res Clin Pract* 2019; **150**: 8-16 [PMID: 30794833 DOI: 10.1016/j.diabres.2019.02.014]

20 **Liu D**, Jin B, Chen W, Yun P. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. *BMC Pharmacol Toxicol* 2019; **20**: 15 [PMID: 30832701 DOI: 10.1186/s40360-019-0293-y]

21 **Xiao L**, Nie X, Cheng Y, Wang N. Sodium-Glucose Cotransporter-2 Inhibitors in Vascular Biology: Cellular and Molecular Mechanisms. *Cardiovasc Drugs Ther* 2021; **35**: 1253-1267 [PMID: 34273091 DOI: 10.1007/s10557-021-07216-9]

22 **Sheahan KH**, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J* 2020; **96**: 156-161 [PMID: 31801807 DOI: 10.1136/postgradmedj-2019-137186]

23 **Cosentino F**, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**: 255-323 [PMID: 31497854 DOI: 10.1093/eurheartj/ehz486]

24 **Movahed MR**, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol* 2005; **105**: 315-318 [PMID: 16274775 DOI: 10.1016/j.ijcard.2005.02.050]

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