Utility of multimodality cardiac imaging in disorders of the pericardium

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Abstract

Disorders of the pericardium represent a diverse range of conditions that traditionally may not have received the same level of attention by cardiologists and physicians, owing partly to a lack of research into advanced diagnostic modalities, and limited, evidence-based treatment options. In recent years, there has been a timely resurgence of interest in pericardial diseases, in particular pericarditis. This is attributable to advances in multimodality cardiovascular imaging, in particular cardiac magnetic resonance (CMR), which may help guide treatment decisions for patients with pericardial syndromes. Additionally, increased research and understanding of the pathophysiological basis of pericarditis have shed light on the role of inflammation in pericarditis. This knowledge may help identify potential specific treatment targets. This article aims to provide a practical review of the role of multimodality cardiovascular imaging (echocardiography, multi-detector cardiac computed tomography (MDCT), CMR) in pericardial conditions, focusing on the strengths and potential limitations of each imaging modality.

Introduction

Disorders of the pericardium include a diverse spectrum of clinical conditions, ranging from common conditions such as acute pericarditis, to rare entities, such as congenital absence of the pericardium (1, 2). Multimodality cardiovascular imaging plays vital roles in the diagnosis and management of these pericardial conditions, providing structural, functional and hemodynamic characteristics (3, 4).

This article aims to provide a practical review of the role of multimodality cardiovascular imaging (echocardiography, multi-detector cardiac computed tomography (MDCT), CMR) in pericardial conditions, focusing on the strengths and potential limitations of each imaging modality.

Echocardiography

Echocardiography is the mainstay first-line imaging investigation for the investigation of patients with suspected pericardial disorders (Table 1). The strengths of transthoracic echocardiography (TTE) include its wide availability, portability and relative low cost. In patients with good imaging windows, TTE can be performed with good spatial resolution. TTE should be the first cardiac imaging investigation for patients with suspected acute pericarditis, although it should be emphasized that the diagnosis of acute pericarditis is mainly based on clinical criteria, including the presence of two or more of the following: pleuritic chest pain, pericardial friction rub and classic electrocardiographic changes including diffuse, concave upward ST-segment elevation and PR depression (3, 4, 5, 6).
Table 1  The strengths and limitations of the mainstay cardiovascular imaging investigations used for the investigation of patients with suspected pericardial disorders.

<table>
<thead>
<tr>
<th>Cardiac imaging modality</th>
<th>Transthoracic echocardiography</th>
<th>Multi-detector cardiac computed tomography</th>
<th>Cardiac magnetic resonance imaging</th>
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TTE, in the setting of suspected acute pericarditis, provides confirmatory evidence of the diagnosis, when a new or increasing pericardial effusion is detected in the appropriate clinical situation (2, 5). Most commonly, in acute pericarditis, no significant abnormalities are noted on TTE (1, 7). However, for patients presenting with an acute chest pain syndrome, of which acute pericarditis is a possible differential diagnosis, the assessment of regional wall motion can help differentiate and exclude ST-segment elevation myocardial infarction (8). This may translate into a reduction in unnecessary invasive coronary angiography (9). In addition, TTE may play a role in detecting impaired systolic function in cases of perimyocarditis with the involvement of the myocardium (2).

Hemodynamic assessment obtained by TTE can help stratify patients with acute pericarditis into those with, and those without high-risk features, including the presence of tamponade physiology, which has been reported in 3% of patients presenting with acute pericarditis (Table 2) (3). Additionally, there may be clues on TTE that point toward early features of constrictive pathophysiology, such as an abnormal diastolic septal bounce.

Recurrent pericarditis refers to subsequent further episodes of pericarditis, after a documented initial episode of acute pericarditis, with a symptom-free period of 4–6 weeks or longer between the episodes (4). Up to as many as one-third of patients may develop recurrence after an initial episode of acute pericarditis (6, 7, 10, 11). Depending on the clinical context, TTE can be performed in recurrent pericarditis to assess for the presence of a new pericardial effusion or features of constrictive pathophysiology.

Echocardiography is also the first-line imaging investigation for patients with suspected constrictive...
pericarditis, having a class I recommendation in the European Society of Cardiology guidelines for the diagnosis and management of pericardial diseases (4). Accurate diagnosis can be difficult, although it is very important to make an accurate diagnosis. Patients with end-stage calcific pericardial constriction may be treated with surgical pericardiectomy, while subsets of patients with transient pericardial constriction, as well as early stages of pericardial constriction, can be treated medically. In the developed world, common etiologies for constrictive pericarditis include idiopathic or viral, post cardiac injury or radiation (12, 13). In the developing world, tuberculosis is the most common cause for the constrictive pericarditis (14).

On echocardiography, a restrictive pattern of transmural filling profile is classic, characterized by very rapid early diastolic filling of the left ventricle, before the pericardial constraint limits further left ventricular filling from mid-diastole onwards (Fig. 1) (1, 2, 15, 16). TTE also plays a vital role in the assessment of ventricular interdependence, a hallmark of constrictive pericarditis, with M-mode, two-dimensional and Doppler imaging, as well as respirometry. Movement of the ventricular septum toward the left ventricle on inspiration, and movement of the ventricular septum toward the right ventricle on expiration can point toward ventricular interdependence on M-mode echocardiography (12). On two-dimensional imaging, diastolic septal bounce and respirophasic septal shift over several respiratory cycles support the diagnosis of ventricular interdependence.

The key strengths of echocardiography in the assessment of suspected constrictive pericarditis lie in its ability to provide detailed hemodynamic assessment. In fact, the echocardiographic laboratory has taken over from cardiac catheterization laboratory for demonstrating the key hemodynamic effects of constriction. In constrictive pericarditis, significant respiratory variation is evident in the inflow profiles across the mitral and tricuspid valves: on inspiration, the peak mitral E wave velocity decreases by ≥25% at the onset of inspiration using pulsed-wave Doppler analysis; at the onset of expiration, the peak tricuspid E wave velocity decreases by ≥40% (17, 18) (Fig. 1). Important clues to underlying constrictive pathophysiology can be obtained by analyzing the pattern of hepatic venous Doppler flow. In constrictive pericarditis, there is prominent expiratory diastolic flow reversal compared to diastolic forward flow. In contrast, in restrictive cardiomyopathy, the exaggerated flow reversal in the hepatic venous Doppler profile occurs on inspiration as well as expiration (3). Tissue Doppler imaging can be helpful in the diagnosis of constrictive pericarditis, with the demonstration of the so-called ‘annulus reversus’, with a normal or elevated medial early mitral annular diastolic velocity (medial e’), which
features were found to be independently associated with constrictive pericarditis: (1) Respirophasic interventricular septal shift; (2) Increased medial early diastolic mitral annular velocity (medial e') and (3) Increased hepatic venous expiratory diastolic reversal ratio on pulsed-wave Doppler analysis (21). The combination of respirophasic interventricular septal shift and a medial early diastolic mitral annular velocity (medial e') $\geq 9$ cm/s or a hepatic vein expiratory diastolic reversal to forward velocity ratio of $\geq 0.79$ yielded the highest diagnostic sensitivity (87%) and specificity (91%) (21).

Additional diagnostic clues to constrictive pathophysiology can be derived from advanced echocardiographic imaging, including strain imaging. In constrictive pericarditis, global longitudinal strain is generally preserved, whereas circumferential strain, torsion and early diastolic twisting are reduced (22, 23). Pericardial tethering could result in the reduction of left ventricular anterolateral wall and right ventricular free wall strain, while septal strain is relatively preserved (23). This pattern of findings on strain imaging ‘strain reversus’ is analogous to ‘annulus reversus’ on tissue Doppler imaging (Fig. 2) and has been shown to be reversible following pericardiectomy (23). The systolic component of the superior vena caval inflow Doppler profile in constrictive pericarditis is relatively flat, due to impaired cardiac filling in constrictive pathophysiology. Clinically, Kussmaul’s sign, a paradoxical elevation of jugular venous pressure on inspiration, also relates to impaired superior vena caval flow into the right atrium in constrictive pathophysiology.

In contrast to constrictive pericarditis, pericardial effusions generally present more acutely. Due to the potentially life-threatening nature of rapidly accumulating, acute pericardial effusions, early diagnosis is the key. Pericardial effusions result from multiple etiologies, including acute pericarditis, end-stage renal disease, hypothyroidism and malignancy (3, 4).

Echocardiographic assessment with TTE imaging is the principal investigation for the assessment of pericardial effusions. Echocardiography not only provides semi-quantitative assessment of the size of the pericardial effusion, but more importantly, echocardiography assesses the physiological significance of pericardial effusions, including the presence of tamponade physiology. On M-mode echocardiography, separation between the parietal pericardium and epicardium throughout the cardiac cycle has been reported to correlate with pericardial effusions larger than 50mL (24). A large pericardial

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Figure 1
Doppler assessment in constrictive pericarditis. Classically, a restrictive pattern of transmitral inflow profile is seen in constrictive pericarditis (A). Respirophasic variation in transmitral inflow, with a decrease in peak E wave velocity on the first heart beat following inspiration (B). Respirophasic variation in tricuspid inflow, with an increase in peak E wave velocity on the first heart beat following inspiration (C). Exp, expiration; Insp, inspiration; MV, transmitral inflow; TV, tricuspid inflow.
effusion is categorized by an end-diastolic measurement greater than 2 cm, while a very large pericardial effusion is categorized by an end-diastolic measurement greater than 2.5 cm on two-dimensional echocardiography (25). Physical characteristics of pericardial effusions, such as the presence of fibrinous stranding, or clots, as well as loculation, may be detected by TTE imaging. Pericardial effusions associated with end-stage kidney disease can also be effectively assessed by TTE imaging (26).

When a hemodynamically significant pericardial effusion significantly restricts cardiac chamber filling, with resultant elevated and equal intra-cardiac diastolic...
pressures, cardiac tamponade occurs with compromised cardiac output (27). This is a potentially life-threatening situation, and TTE imaging should be performed urgently. The diagnostic accuracy of echocardiography for the presence of a pericardial effusion is excellent (3). Cardiac tamponade is diagnosed clinically (tachycardia, elevated jugular venous pressure, pulsus paradoxus), with important complementary clues provided by echocardiography. In the context of a pericardial effusion, the following TTE imaging lend support to the presence of tamponade physiology: (1) dilated, and fixed inferior vena cava, which does not collapse significantly on inspiration; (2) reduced left ventricular forward stroke volume on Doppler assessment; (3) right ventricular compression, or collapse in severe cases, during diastole and (4) right atrial systolic collapse (28). It must be noted that certain echocardiographic features of tamponade physiology, such as right ventricular compression, may not be present in certain conditions, such as severe pulmonary hypertension and right ventricular hypertrophy (Fig. 3) (29, 30). Therefore, the echocardiographic assessment of tamponade physiology should not be based on the absence of a single imaging feature. Classically, in tamponade physiology, significant respiratory variations in mitral and tricuspid inflows are observed. During the first heart beat on inspiration, the peak mitral E wave velocity decreases >30%, while the peak tricuspid E velocity decreases >60% during the first heart beat on expiration (31).

Effusive-constrictive pericarditis represents a unique condition, in which a tense pericardial effusion co-exists with pericardial constriction by the visceral pericardium. In a recent single-center study of 205 patients undergoing pericardiocentesis, 33 patients (16%) were found to have effusive-constrictive pericarditis after pericardiocentesis (32). Echocardiography is the first-line imaging modality in this condition, and certain echocardiographic features at baseline, prior to pericardiocentesis, might identify and predict, which patients would be at higher risk of developing effusive-constrictive pericarditis. These features included higher early diastolic septal mitral annular velocity, increased transmitral respiratory variation, increased hepatic venous diastolic flow reversal and increased respirophasic septal shift (32).

Echocardiography is also useful for the assessment of rare pericardial conditions, such as congenital absence of the pericardium (CAP). CAP is often detected as an incidental finding during cardiac imaging. Patients may be asymptomatic, or may have a diverse range of atypical symptoms, such as atypical chest pain and palpitations (3, 50, 51).

Figure 3
Echocardiographic assessment of pericardial effusion in pulmonary hypertension. Significant elevation of estimated right ventricular systolic pressure is consistent with pulmonary hypertension (A). Transthoracic echocardiographic imaging (parasternal long-axis imaging (B); parasternal short-axis imaging (C)) demonstrates a significant pericardial effusion. However, in the presence of right ventricular hypertrophy and pulmonary hypertension, there are no echocardiographic features of tamponade physiology, such as significant chamber compression (B and C). The inferior vena cava is also normal in caliber, collapsing more than 50% on forced inspiration, suggesting normal estimated right atrial pressure (D).
TTE imaging should be the first-line imaging investigation for patients with suspected CAP. A proposed systematic algorithm to the diagnosis and management of patients with CAP has been published (33, 34). TTE imaging features that raise the suspicion for CAP include (1) presence of unusual imaging windows; (2) the appearance of right ventricular dilatation and (3) excessive cardiac motion.

**Multi-detector cardiac computed tomography**

In general, MDCT should not be used as the first imaging investigation for most pericardial conditions. With a high level of use of computed tomography (CT) for investigation of patients presenting to the emergency department, even though investigation of suspected pericardial conditions may not be the primary reason for a CT examination, incidental pericardial findings may be detected at the time of the CT examination, that point toward an underlying pericardial condition. For instance, a thickened pericardium may be occasionally detected on CT, and may be a supportive feature of acute pericarditis (35). Pericardial effusions can also be incidentally detected by CT (36). A small pericardial effusion may lend support to the diagnosis of acute pericarditis, whereas a large pericardial effusion detected by CT should always be investigated further with correlation of the clinical findings, as well as echocardiographic assessment. Data from MDCT reconstructions may help treatment planning for pericardial effusions, including the need for surgical vs percutaneous drainage. A further strength of MDCT in the assessment of pericardial effusion lies in its ability to provide information about the type of pericardial effusion, based on attenuation values. Attenuation values <10 Hounsfield units point to the presence of a transudate; attenuation values between 20 and 60 Hounsfield units point to the presence of exudates; attenuation values >60 Hounsfield units suggest the presence of haemorrhagic pericardial effusion (37, 38).

In the context of chronic, end-stage calcific pericardial constriction, MDCT is essential in the evaluation of the location, as well as extent of pericardial calcification (Fig. 4) (39). Pericardial calcification results from chronic, persistent pericardial inflammation with associated irreversible fibrosis and calcific changes (40). MDCT is also critical in the assessment of patients with prior cardiac surgery and radiation heart disease. It not only provides assessment of cardiac structures, but also provides information about parenchymal lung disease, and the proximity of cardiovascular structures to the sternum.

It should be emphasized that generally, the hemodynamic assessment for patients with suspected constrictive pericarditis is primarily performed by echocardiography, complemented by cardiac magnetic resonance (CMR) imaging. Occasionally, in select cases, retrospective four-dimensional (4D) MDCT data set may be acquired for the assessment of respirophasic interventricular septal shift as a marker of constrictive physiology.

Although MDCT can detect thickening of the pericardium, it should also be noted that absence of pericardial thickening does not exclude constrictive pericarditis. Out of 143 patients with constrictive pericarditis confirmed surgically, pericardial thickness was not increased on MDCT for 28% of the study cohort (41).

**Cardiac magnetic resonance imaging**

CMR imaging has unique niche roles in the assessment of pericardial disorders, beyond conventional imaging with echocardiography and MDCT. CMR is highly sensitive for the diagnosis of active pericarditis, although it is not routinely used for the initial diagnosis of most cases of uncomplicated acute pericarditis. Anatomical findings such as pericardial thickness and pericardial effusion can be evaluated on T1-weighted black-blood imaging (15, 42). T2-weighted short tau inversion recovery (STIR) is a dedicated CMR sequence, which can be used to assess for edema. An increased pericardial signal on T2-STIR
imaging suggests active pericardial edema, consistent with an acute/subacute inflammatory process (Fig. 5) (43).

For a small proportion of patients, the course of pericarditis may become prolonged, and there may be uncertainties regarding the effectiveness and duration of treatment. In this clinical context, CMR imaging is a very useful imaging investigation for the assessment of ongoing pericardial inflammation. Delayed gadolinium enhancement (DHE) imaging is a unique strength of contrast-enhanced CMR imaging. The histological correlates of pericardial DHE have been characterized: the presence of DHE correlates with increased vascular permeability, neovascularization and fibroblast proliferation in the pericardium (40). The reported sensitivity of pericardial DHE for the detection of pericardial inflammation is excellent (94–100%) (43, 44).

These findings help guide patient management decisions. In a recent retrospective study of 159 patients
with recurrent pericarditis, quantitative assessment of pericardial DHE had incremental prognostic value over baseline clinical and laboratory variables (integrated discrimination improvement: 8%; net reclassification improvement: 36%), with patients having a higher quantitative DHE developing recurrence at shorter time intervals ($P=0.012$) and a higher recurrence rate at 6 months ($P=0.026$) (45). A quantitative approach to evaluation of pericardial delayed enhancement may be superior to visual assessment (46). Patients without pericardial delayed enhancement are unlikely to respond to anti-inflammatory therapy. Although TTE is usually performed in patients with suspected recurrent pericarditis, the most useful diagnostic imaging test is CMR. The presence and extent pericardial DHE could help guide the institution of anti-inflammatory therapy (46) (Fig. 5). It has been shown that patients with significant pericardial DHE were more likely to respond to anti-inflammatory therapy and achieved resolution of constrictive pericarditis (47). CMR is also helpful in excluding recurrent pericarditis by documenting the absence of pericardial inflammation. For instance, if recurrent chest pain for a patient with prior acute pericarditis is associated with increased pericardial DHE, the clinician may integrate this finding, and prolong or intensify the duration of anti-inflammatory therapy. In contrast, if the same patient did not have evidence of pericardial edema or pericardial DHE on CMR imaging, the clinician may be guided toward tapering or discontinuation of medication treatment. In a cohort of 507 patients with recurrent pericarditis, approximately half of these patients were investigated with CMR (48). Patients without significant pericardial enhancement on CMR subsequently received less glucocorticoids (48). Similarly, in patients with constrictive pathophysiology, evidence of pericardial delayed enhancement may guide clinicians toward enhanced and/or increased duration of anti-inflammatory treatment (46).

In cases of ambiguity about the diagnosis of constrictive pathophysiology after thorough echocardiographic assessment, CMR may provide useful complementary assessment. Early diastolic septal flattening is a feature of constrictive pathophysiology, which could be effectively assessed by CMR (49). During real-time cine imaging with free-breathing, an increased relative septal excursion is also a specific finding for constrictive pathophysiology (49, 50, 51). An additional supportive feature of pericardial constriction on CMR is markedly thickened pericardium (43, 51) (Fig. 6). Although less frequently performed, CMR utilizing real-time phase contrast imaging, has been previously reported, in a similar fashion to echocardiographic hemodynamic assessment, to be valuable for the diagnosis of constrictive pathophysiology, when ≥25% variation in transmitral flow was demonstrated during respiration (52).

For patients with end-stage, calcific constrictive pericarditis, or recalcitrant treatment-resistant cases of recurrent pericarditis, published observational data support pericardiectomy as a treatment option. In a retrospective study of 58 patients undergoing pericardiectomy after failed medical therapy for recurrent pericarditis, patients in the surgical group had a decreased relapse rate, compared to patients who were medically treated (53).

In the investigation of pericardial effusions, CMR can provide helpful additional information for the evaluation of complex, loculated pericardial effusions (Fig. 7). For the rare condition of CAP, advanced cardiovascular imaging with CMR and/or MDCT could be considered for symptomatic patients. These imaging investigations may help guide potential surgical planning, evaluation of high-risk anatomy features, which may predispose to strangulation, and further risk stratification. Displacement of the heart into the left hemithorax (levorotation), with posterolateral displacement of the left ventricular apex, is a key diagnostic feature of CAP on CMR and MDCT.
Transient constrictive pericarditis

A unique entity known as transient constrictive pericarditis affects an important subset of patients with constrictive pathophysiology. Accurate identification of this entity is important. The predominant pathophysiological process involved in transient constrictive pericarditis is ongoing pericardial inflammation. Therefore, transient constrictive pericarditis is usually post pericarditis, and could be viewed as a ‘temporary’ form of pericardial constriction, which can resolve with anti-inflammatory therapy (4, 54).

TTE and CMR imaging can be used to assess for anatomical features of pericardial thickening and pericardial effusion, as well as hemodynamic features of constrictive pathophysiology, in a similar fashion to the workup of patients with constrictive pericarditis.

Positron emission tomography

The novel application of [18F] fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for transient constriction deserves special mention (55). Recently, it was demonstrated in patients with tuberculosis constrictive pericarditis that [18F] FDG PET/CT could successfully predict the response to steroid therapy with a high accuracy (55). Data are limited regarding the utility of PET/CT imaging in constrictive pericarditis, although results of the early study suggest that this imaging modality may become more widely used in the future, adding to the existing armamentarium of multimodality cardiovascular imaging for cardiologists in the investigation of patients with suspected pericardial disorders. Additionally, [18F] Fluorodeoxyglucose (FDG) positron emission tomography/cardiac magnetic resonance (PET/CMR) has been described in the diagnosis of active pericarditis (56).

Conclusion

While disorders of the pericardium are heterogeneous, with a good understanding of the strengths and relative limitations of existing mainstay cardiovascular imaging investigations (echocardiography, MDCT, CMR), appropriate selection and interpretation of the results of these imaging investigations can help clinicians achieve timely and accurate diagnosis, and appropriate management of most patients with these diverse conditions. Echocardiography is the first-line imaging investigation for patients with most pericardial conditions, due to its proven safety, availability, portability, excellent temporal resolution and ability to provide anatomical as well as hemodynamic assessment. MDCT provides excellent anatomical assessment of the pericardium, as well as extra-cardiac structures. CMR is a powerful adjuvant imaging modality, which provides valuable information about the presence of active pericardial inflammation and edema, allowing clinicians to integrate results of imaging investigations into treatment decisions for patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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