Review Article

Constrictive Pericarditis: An Update on Noninvasive Multimodal Diagnosis

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Abstract

Constrictive pericarditis (CP) is a rare condition that can affect the pericardium after every pericardial disease process and has been described even after SARS-CoV-2 infection or vaccine. In CP, the affected pericardium, usually the inner layer, is noncompliant, constraining the heart to a fixed maximum volume and impairing the diastolic function. This leads to several clinical features, that, however, can be pleomorphic. In its difficult diagnostic workup, noninvasive multimodal imaging plays a central role, providing important morphological and functional data, like the enhanced ventricular interdependence and the dissociation between intrathoracic and intracardiac pressures. An early and proper diagnosis is crucial to set an appropriate therapy, changing the prognosis of patients affected by CP. In this review, we cover in detail the main elements of each imaging technique, after a reminder of pathophysiology useful for understanding the diagnostic findings.

Keywords: Cardiac computed tomography, cardiac imaging, cardiac magnetic resonance, cardiac positron emission tomography, constrictive pericarditis, echocardiography, multimodal imaging, noninvasive imaging, noninvasive multimodal diagnosis

Introduction

Definition and etiology

Constrictive pericarditis (CP) is an increasingly recognized disease affecting the pericardium that can occur after every pericardial disease process. Idiopathic or viral pericarditis is the main cause of CP in Western countries (42%–49%), followed by postsurgical (11%–37%) and postradiotherapy (9%–31%) pericarditis. Rarer causes are connective tissue disorders (3%–7%) and infections (tuberculosis, bacterial; 3%–6%). In developing countries, tuberculosis is a leading cause of CP, even the most common. Variant forms of CP are described in the literature: effusive, occult, localized, and transient. In general, CP is divided into three syndromes: transient constriction, effusive–CP, and chronic constriction. All of them share a common pathophysiology, even with differences in medical history and clinical evolution.[1-6]

Epidemiology

The true prevalence of CP has not been clearly defined. It is known to occur in ~1% of cases after idiopathic pericarditis and in 0.2%–0.4%, or even more, of cases after cardiac surgery.[2,5]

Pathophysiology

The pericardium is a membrane composed of two layers, an outer fibrous and an inner serous, with a pericardial fluid, <50 mL, between them. This membrane envelops the whole heart except for a small portion of the left atrium (LA) and the pulmonary veins (PV). Normally, the pericardium is thin, elastic, and has little effect on hemodynamics. In fact, variations in intrathoracic pressure lead to analog changes in pericardial and intracardiac pressures, causing physiological changes of the ventricle's filling. In CP, the affected pericardium, usually the inner layer, is noncompliant, constraining the heart to a

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fixed maximum volume and impairing the diastolic function. In fact, the ventricles can fill up to a maximum volume allowed by the pericardial constriction, and beyond this point, the filling stops abruptly. This situation leads to the elevation of cardiac filling pressures and venous pressures, decreased stroke volume, and equalization of end-diastolic pressures, which is a hallmark feature of CP. Other hemodynamic features are the dissociation between intrathoracic and intracardiac pressures and the increased ventricular interdependence with magnified septal shifting during the respiratory cycle. During inspiration, intrathoracic pressure decreases together with pressure in PV, but not in LA. This reduces the PV–LA pressure gradient, affecting the left ventricle (LV) filling. Furthermore, during this phase, the right ventricle (RV) preload is augmented by negative intrathoracic pressure on systemic venous return. The opposite occurs during expirations, favoring LV filling. In this setting, in which the two ventricles alternatively fill affecting the other one's filling, a respirophasic interventricular septal shift (RISS) occurs, to the left during inspiration and to the right during expiration, expression of a respiration-dependent ventricular filling and of a ventricular interdependence. Consequently, during expiration, a blood flow reversal in the hepatic veins could occur. Understanding the pathophysiology behind CP is very helpful in getting the most out of imaging techniques to make a proper diagnosis.[1,2,4-7]

Clinical presentation

The classic clinical picture is mostly characterized by signs and symptoms of right heart failure; the most common of which are dyspnea on exertion, peripheral edema, and fatigue. Cardiac auscultation may detect an early diastolic sound called pericardial knock, due to the ventricular wall vibration during sudden and abrupt cessation of filling. Jugular venous pressure (JVP) is generally greater than normal and has rapid x- and y-descents (the latter known as Friedreich's sign), reflecting apical displacement of the tricuspid annulus and rapid early diastolic filling of RV that terminates abruptly. This is called the "W sign," a nonspecific physical finding of CP that can help in differentiating from restrictive cardiomyopathy (RCM), in which x-descent is reduced. In addition, due to impaired right ventricular filling, JVP may paradoxically rise with inspiration (Kussmaul's sign); however, this occurs only in ~20% of CP cases. Similarly, a paradoxical inspiratory drop of systemic blood pressure >10 mmHg (pulsus paradoxus) may occur. Despite the signs of heart failure, clinical presentation can be pleomorphic, and it is not uncommon that patients undergo extensive diagnostic workup in the suspicion of thoracic or gastrointestinal diseases before coming to the cardiologist's attention. It is, therefore, important to maintain a high level of suspicion in patients at risk of CP, because underdiagnosis or delayed diagnosis is frequent.[1,2,5,8]

Diagnosis

Diagnosis of CP is challenging and consists of many steps; the first is the clinical evaluation. CP is not generally evident on standard testing and mimics other causes of heart failure and lung and liver diseases. No gold-standard diagnostic test can provide a definitive diagnosis or firm evidence of CP. Laboratory tests are not specifically altered, except for the possibility of increased inflammation biomarkers in case of acute transient constriction or effusive–CP. Electrocardiogram is often unremarkable: 25% of patients show low voltage, and atrial fibrillation is possible. Chest radiography, which is recommended (class I, level C) in all suspected cases of CP by the 2015 European Society of Cardiology (ESC) Guidelines for diagnosis and management of pericardial diseases,[1] might show pleural effusion, pulmonary vascular congestion, cardiomegaly, and pericardial calcification (<50% of cases). The major help comes from multimodal cardiac imaging techniques, as explained below: echocardiography, cardiac magnetic resonance (CMR), computed tomography (CT), and cardiac catheterization. If the diagnosis still remains uncertain, endomyocardial biopsy and surgical exploration could be considered. Differentiating CP from RCM, which is the main differential diagnosis, is crucial due to markedly different therapeutic options and prognosis, and is based on the demonstration of dissociation between intrathoracic and intracardiac pressures and enhanced ventricular interdependence, both typical of CP. Other differential diagnoses could be a mixed disease (CP and RCM together) and severe tricuspid regurgitation (TR). In conclusion, the diagnostic workup of CP may be very difficult, also because of a large amount of data coming from different imaging techniques. In the future, a cognitive machine-learning approach may be considered, to help in the differentiation of CP from other diagnoses.[1,2,5,6]

Therapy and prognosis

The treatment of choice for CP, especially for the chronic form, is surgical pericardiectomy with the removal of both layers of the pericardium (class I, level C).[1] Medical management is difficult. A drug therapy for specific pericarditis, i.e., tubercular, is recommended to prevent the progression of constriction (class I, level C).[1] Empiric anti-inflammatory therapy with nonsteroidal anti-inflammatory drugs, colchicine, and steroids may be considered in transient or new diagnoses of CP if evidence of pericardial inflammation is found at laboratory tests or cardiac imaging (class IIb, level C).[1] Finally, supportive medical therapy with diuretics and others can control symptoms of congestion in all stages of the disease; however, supportive therapy should never delay surgery, if feasible. In this framework, the importance of multimodal imaging appears not only for diagnostic purposes but also for the choice of appropriate therapy and prognostic stratification, as seen for example in heart failure. The main features explained in the introduction are summarized in Table 1.[1,3,6,9-12]

Noninvasive Diagnosis of Constrictive Pericarditis

According to the latest 2015 ESC Guidelines for the diagnosis and management of pericardial diseases[1] and to the most recent literature,[13] the role of integrated multimodal imaging is crucial for the diagnosis of CP. A definite diagnosis is difficult to be made

only on clinical features. As a first-choice technique, transthoracic echocardiography is recommended in all patients with suspected CP (class I, level C), as well as chest X-ray (class I, level C), as mentioned above. In selected cases, CT and/or CMR are indicated as second-level imaging techniques (class I, level C). According to many recent studies,[4,5,7,14] CMR might be preferred over CT for the possibility to obtain not only morphological but also functional data. Finally, invasive cardiac catheterization is indicated when imaging does not provide sufficiently supportive data to make a diagnosis (class I, level C). It is important to remark that morphologic alterations are not always present and are not equivalent to CP; even if the more extensive they are, the more likely it is a constrictive mechanism. Based on different studies, in up to 20% of cases of CP, the thickness of the pericardium was found normal.[4,5,7,14] Findings of pericardial inflammation, also, can suggest a constrictive pathophysiology. Main elements of multimodal diagnosis of constrictive pericarditis are provided in Table 2.

Echocardiography

Standard two-dimensional echocardiography

Pericardial morphologic features

Transthoracic echocardiography, and still more transesophageal although less applicable in this setting, can assess the thickness and calcifications of the pericardium, as shown in Figure 1. Normal thickness is 2 mm or less, and when found of 4 mm or more is considered very suggestive of CP, especially if >5–6 mm. However, the reliability of echocardiography for this evaluation is uncertain, due to the technical limitations and the possible regionalization of CP alterations. Moreover, anatomical alterations do not always reflect constrictive pathophysiology, especially in patients with a history of thoracic radiation therapy or open surgery.[4,5,7,14-16]

Pericardial tethering

In normal conditions, the two layers of the pericardium slide over each other during the cardiac cycle. When pericardial adherence is present, due to fibrosis or calcifications, the independent motion of the visceral and parietal pericardium is lost. This is called pericardial tethering and can be seen in two-dimensional (2D) echocardiography, even if is more easily assessed with Doppler or speckle-tracking studies.

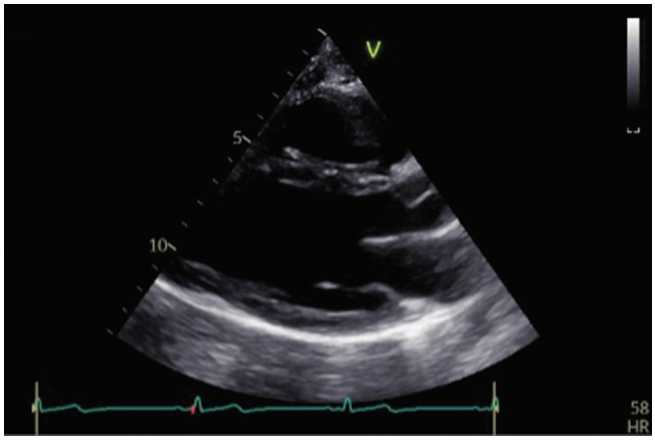

Figure 1: Thickening of the pericardium seen in a parasternal long-axis section. Image obtained with transthoracic echocardiography

Ventricles morphology and function

A RISS is typical of CP and is due to abrupt ventricular volume changes as a reflection of enhanced interventricular dependence. As explained above, during inspiration, a minor LV filling occurs, causing a left-side septal shift, as shown in Figure 2. During expiration, conversely, the septum returns to a normal position or moves into RV. RISS can be seen on M-mode or 2D, even better combining the use of a respirometer, and has a sensitivity for CP of 93%.[17] This phenomenon could be observed also in patients with chronic obstructive pulmonary disease (COPD) due to increased respiratory swings in intrathoracic pressure: However, as explained below, other parameters can differentiate these two conditions. Furthermore, a septal shudder or bounce is common in CP, although not specific: it is characterized by an abrupt displacement of the interventricular septum in early diastole independently of breathing, and it is due to the different filling of both ventricles [Figure 3 and Video 1]. This phenomenon is possible because the movement of the interventricular septum, unlike those of the free wall of ventricles, is not anatomically limited by a constrictive pericardium. Septal shudder should not be confused with RISS, which is more specific of CP. LV function, assessed with ejection fraction, is preserved except in the case of other cardiac comorbidities. Finally, a hyperdynamic mitral annulus with exaggerated motion of the septal side is frequent, but better evaluated with Doppler analysis.[4,5,7,14]

Other findings

It is common to find bi-atrial enlargement (61% of cases[14]) and systemic venous congestion, like inferior vena cava (IVC) plethora; however, these signs are not very specific of CP because shared with RCM. However, the presence of IVC plethora is generally required for the diagnosis of CP. Some authors reported a dense spontaneous echo contrast in IVC.[18] The presence of pericardial effusion together with findings typical of CP suggests the diagnosis of effusive–CP.[4,5,7]

Doppler analyses

Doppler findings are crucial for the diagnosis of CP, reflecting closely the typical hemodynamic alterations.

Mitral and tricuspid flows

Due to the etiopathogenetic mechanism, almost all LV filling occurs in the first phase of diastole, with elevated filling pressure. This results in increased E-wave velocity with shortened deceleration time, small or absent A-wave, E/A >0.8, and usually resembling a restrictive inflow pattern, like in RCM. However, the variations during respiration help differentiate this pattern from those in RCM. In fact, due to the dissociation of intrathoracic and intracardiac pressures, during inspiration, the filling pressure of LV decreases, causing a decrease in peak mitral E-wave velocity ≥25% and a prolongation of the isovolumic relaxation time (usually >20%),

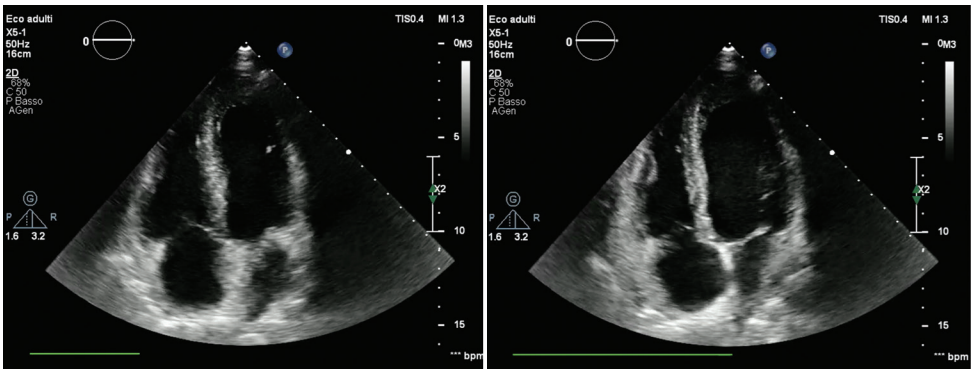

Figure 2: Respirophasic interventricular septal shift seen in a four-chamber section, obtained with transthoracic echocardiography, at end-diastole. Left: image obtained during inspiration, with left-side septal shift. Right: image obtained during expiration, with normal position of the interventricular septum. More information in the text

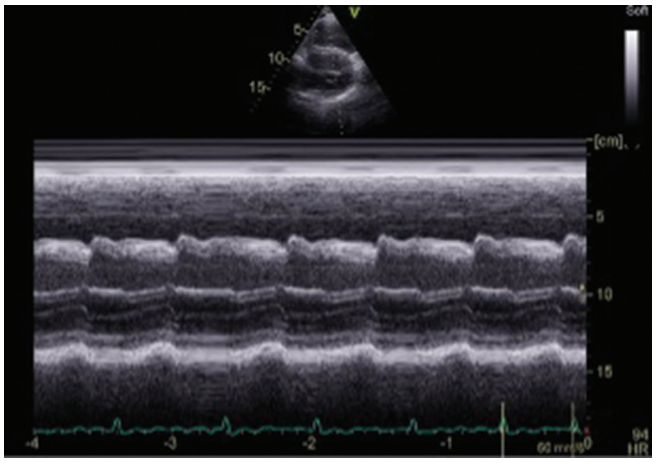

Figure 3: Septal shudder seen with M-mode. Image obtained with transthoracic echocardiography

compared to expiration. The opposite happens in RV, as an expression of interventricular dependence, causing an increase of tricuspid flow velocities ≥40%. The reverse mechanism occurs during expiration. Similar findings can be seen with the Doppler analysis of flow in the pulmonary and hepatic veins. These characteristic variations are much less frequent in RCM or TR. However, since almost 30% of patients with proven CP lack respiratory mitral flow variations, these are not required for the diagnosis. Moreover, these variations could be absent or confused in patients with very high LA pressure or with atrial arrhythmias (even if unmasked with maneuvers decreasing preload), and instead, they can be present in the case of COPD or TR. In patients with COPD, however, the E/A ratio is lower, deceleration time is longer, and there is an increase of inspiratory systolic forward flow in the superior vena cava, absent or mild in CP. This Doppler finding may be equivalent to Kussmaul's sign. Finally, the E/e' ratio cannot be used to estimate the filling pressure in patients with CP, since it does not correlate with elevated pulmonary wedge pressure. This may be due to an exaggerated longitudinal motion of the mitral annulus despite high filling pressures. As a secondary measure, the color M-mode flow of LV filling may be helpful to differentiate CP from RCM, resulting in normal or increased inflow velocity of first aliasing (>100 cm/s) in CP while reduced in RCM.[4,5,7,14,17]

Hepatic veins flow

Flow in hepatic veins is influenced by the typical hemodynamic alterations. In fact, during expiration, an important reversal of flow during late diastole occurs, and this has a specificity of 88% for the diagnosis of CP.[17] In RCM and severe TR, the filling of the right chambers is not as impaired during expiration. More, in TR, the possible flow reversal occurs during systole.

Tissue Doppler imaging

As mentioned above, a hyperdynamic mitral annulus with exaggerated motion is typical in patients with CP. In fact, as compensation for pericardium-based diastolic dysfunction, myocardial relaxation is improved, in the absence of other causes of diastolic dysfunction. In patients with heart failure and normal mitral annulus movement, CP should be strongly considered. This phenomenon can be well studied considering e' velocities by tissue Doppler imaging (TDI). An average mitral annular velocity of 8 cm/s or a medial e' velocity ≥9 cm/s is considered the optimal cut point to differentiate CP from RCM, in which e' velocities are generally reduced. However, it is important to remember that e' velocity could be low in case of mitral calcification or myocardial diseases. Moreover, since the lateral mitral annular translocation is affected by the tethering of adjacent fibrotic and scarred pericardium (pericardial tethering), the lateral e' velocity is reduced and lower than the medial e' velocity. This phenomenon is called "annulus reversus;" it is present in 75% of cases of confirmed CP, and it is highly specific for CP.[19] Furthermore, the assessment of systolic mitral annular velocity (S') could be useful to differentiate CP from RCM, in which usually S' is reduced: in fact, an average septal and lateral S' velocity <8 cm/s, together with an e' velocity <8 cm/s, has been described to have high sensitivity (93%) and specificity (88%) in excluding CP.[14] Finally, TDI allows to better study the movement of the interventricular septum, with characteristic early diastolic high velocity and abnormal fluttering motions.[4,5,7,17,20]

Speckle-tracking imaging

The use of speckle-tracking analysis has been established as helpful to diagnose CP, which is generally associated with a preserved global longitudinal strain (GLS) and a typical regional pattern of reduced lateral strain with preserved medial, likely due to the effect of pericardial tethering on the free wall of the LV and RV (strain reversus). The epicardial dysfunction in CP impairs the circumferential strain and the twist movement. Conversely, in RCM, which mostly affects subendocardial fibers oriented in a longitudinal direction, GLS is usually reduced. These different patterns of ventricles' movement could be easily assessed using speckle-tracking imaging, whose potential incremental value in the diagnosis workup of CP, however, has not yet been validated. The reduction in the regional longitudinal strain of the left ventricular lateral wall and the sparing of the septal one create an easily recognizable bull's-eye plot pattern called "hot septum."[21] It is crucial to consider other diseases that could affect the myocardium and so the pattern of GLS in a similar way to CP, like ischemic heart disease. Recently, the strain imaging analysis of LA has been evaluated to diagnose CP, showing a characteristic pattern of impaired early diastolic strain of the superior and lateral walls compared to the septal wall.[4,5,7,17,22]

Mayo Clinic criteria

In 2014, several echocardiographic parameters were evaluated by the Mayo Clinic experts' team to define some diagnostic criteria for CP.[17] Five parameters were evaluated [Table 3]: RISS, variation in mitral inflow E velocity, medial mitral annular e' velocity, the ratio of medial mitral annular e' to lateral e', and the hepatic veins expiratory diastolic reversal ratio. Three out of five resulted independently associated with CP, even in patients with atrial fibrillation or flutter, and they are (1) RISS, (2) medial mitral e' ≥9 cm/s, and (3) prominent hepatic veins expiratory diastolic reversal. The presence of (1) in combination with (2) or (3) had a desirable combination of sensitivity (87%) and specificity (91%). If all three factors were present, specificity increased to 97% but sensitivity decreased to 64%. Given the almost constant presence of IVC plethora, this might be considered a prerequisite. Then, RISS is a highly sensitive starting point for the suspicion of CP. Evaluating these three criteria along with the other typical features, as in the diagnostic algorithm proposed by Welch in 2018,[5] the echocardiogram mostly allows the differentiation of CP from other conditions such as RCM and severe TR,[4] even if in case of mixed constriction and restriction disease diagnosis can be still incomplete. It should be remembered that both false-positive and false-negative results exist and that no single echocardiographic parameter could be diagnostic alone: a multiparameter approach is needed to increase the accuracy of cardiac echography. When transthoracic echocardiography is diagnostic for CP, no further investigations are necessary. In case of discordant data, CT and/or CMR are indicated as second-level imaging techniques (class I, level C).[1]

Cardiac computed tomography

Considering that the diagnosis of CP is above all a hemodynamic assessment, cardiac CT, which mainly provides anatomical data about the pericardium, could not be the most indicated imaging technique, even if from the last ESC Guidelines, it is indicated at the same level as CMR (class I, level C).[1] CT is, in fact, the most accurate method to study pericardial thickness and calcifications [Figure 4]. however, these findings are not always present in CT study of patients with CP (70%–80% and 25%–50% of cases, respectively).[7] The localization of pericardial calcifications is variable too, with no recurrent patterns described as well. Pericardial calcifications and thickening could also be present in other pathological or iatrogenic conditions. Moreover, contrast-enhanced cardiac CT could provide information about the atrial and ventricular morphology, the interventricular septal deviation, the septal bounce, and the dilation of IVC, but with much lower accuracy than echocardiography and CMR, due to the limited temporal resolution and the restriction of breathing during exam. A respirophasic assessment may be performed using four-dimensional gated imaging; however, its value in the diagnostic workup for CP has not yet been evaluated. However, cardiac CT is useful in the preoperative evaluation for pericardiectomy, assessing the location of cardiac and vascular structures as well as other pathological changes, also permitting an estimate of the surgical risk. We must not forget the possibility to assess other concomitant findings like variations of anatomical relationships between heart and lungs during the cardiac cycle, pleural effusion, dilated hepatic veins, hepatosplenomegaly, and ascites. Radiation exposure risk related to this imaging technique should be considered as well.[5,6,14,15,23]

Cardiac magnetic resonance

CMR, like cardiac CT, is a second-line imaging modality for the evaluation of CP (class I, level C)[1] useful to evaluate structural and hemodynamic aspects, especially when using gadolinium as a contrast agent and when performed in real-time mode during free breathing. Since CMR provides more information compared to cardiac CT, it has recently been considered by some authors as a superior imaging modality in the diagnostic workup for CP. According to several studies,[11,16] CMR should be reserved to particular situations: (1) when

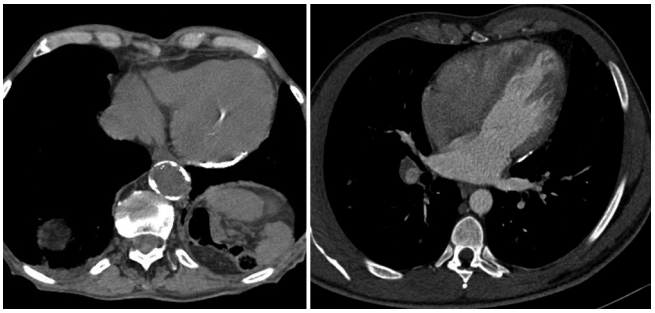

Figure 4: Pericardial calcifications. Images obtained with cardiac computed tomography

diagnosis remains uncertain by other noninvasive techniques or even invasive catheterization; (2) in patients with increased inflammatory biomarkers and/or short durations of constrictive symptoms; (3) when concomitant myocardial disease is suspected; and (4) when pericardial and cardiovascular anatomical assessment is required for management decisions. A recent Italian study[24] proposed to use CMR early during acute pericarditis to detect parameters, such as late gadolinium enhancement (LGE) and pericardial thickness, that along with clinical and anamnestic data would allow to identify the patients at higher risk of complications, including CP.

Structural evaluation

CMR offers information about cardiac chamber morphology, myocardial structure, pericardial structure, pericardial–myocardial adherence, vascular dilation, and pericardial tissue characterization. Furthermore, CMR can contribute to preoperative planning, providing anatomical and tissue information, like active inflammation of pericardium.[4,7,14] Elements not specifically treated below are considered comparable to those obtained with other imaging methods.

Cardiac chamber morphology

The assessment of cardiac chambers' areas and volumes using CMR revealed to be useful in the diagnostic workup of CP. RV has often a reduced volume and a narrow tubular shape. An RV volume <133 ml had a sensitivity of 77% and a specificity of 90% for the diagnosis of CP.[25] An LV area change of ~18% reaches a desirable accuracy for the diagnosis of CP, while RV area changes are not so accurate.[14,26] In addition, a recent study[27] demonstrated how quantification of biatrial enlargement could differentiate CP from RCM: the ratio between LA volume and right atrium volume was significantly higher in patients with CP compared to those with RCM. This fact is based on an anatomical feature: the posterior wall of LA is separated from the pericardial space, and hence, it can enlarge greater than the right atrium walls. This causes a greater volume of LA compared to those of the right atrium in CP. In RCM instead, both atria expand equally.[14]

Myocardial structure and motion

Contrast-enhanced CMR provides useful information about myocardial infiltrative diseases or other conditions, suggesting an alternate diagnosis of RCM in the absence of CP. In addition, the myocardial strain assessed with CMR allows to detect the abnormal myocardial motion, like previously described in echocardiography: in fact, a ratio of LV (or RV) lateral wall (or free wall) strain to septal wall strain <0.96 for LV and <0.97 for RV reaches a good grade of accuracy for the diagnosis of CP.[7,14]

Pericardial structure and motion

From the literature results, a pericardial thickness >3–4 mm yields a sensitivity of ~85% and a specificity of almost 100% to diagnose CP. The assessment of pericardial thickness by CMR showed a 100% concordance with surgical findings. On the other hand, CMR does not permit to study calcifications with an acceptable grade of accuracy. It is known from the literature that pericardial radiofrequency (RF) tissue tagging by CMR is highly sensitive and specific to assess the pericardial tethering, that is the absence of slipping between the visceral and parietal layers of the pericardium.[28] Recently, RF tissue tagging in this setting showed a 100% agreement with surgical findings of CP,[29] and hence, it may become a new gold standard highly helpful in the diagnostic workup of CP.[4,7,14,16]

Vascular dilation

Due to the high sensitivity of CMR to detect IVC dilation, its absence can almost exclude CP.[7,14]

Pericardial tissue characterization

Contrast-enhanced CMR allows a tissue characterization of the pericardium. Pericardial edema is detectable using a T2 short-tau inversion recovery sequence with edema-weighted imaging [Figure 5], while active inflammation is demonstrated by LGE, which indicates vascular permeability, increased fibroblast proliferation, and neovascularization [Figures 6 and 7].[23] When edema and inflammation are found together with findings suggesting CP, an acute or subacute process is likely, defining a probable transient constriction reversible with anti-inflammatory therapy. Moreover, the degree of LGE seems to be directly correlated with the response to anti-inflammatory therapy and so inversely with the need for pericardiectomy. A setting in which edema is absent (negative T2 STIR imaging) and inflammation is present (LGE present), along with pericardial effusion, suggests a transitional or subacute stage like effusive–CP.[9] The absence of both LGE and T2 signal is suggestive of no active inflammation and so of a chronic constriction. These findings have pivotal prognostic value and should be related to clinical and biochemical data for individualized therapeutic plans and follow-up. Furthermore, new pathophysiology concepts could be derived from CMR performed at different stages of CP.[4,7,11]

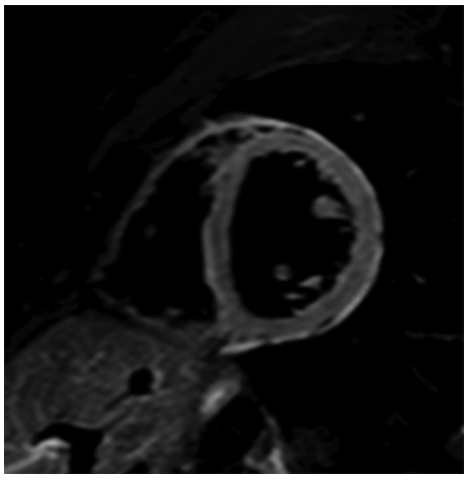

Figure 5: Short-axis section showing diffuse edema of the pericardium. Image obtained with cardiac magnetic resonance using a T2-weighted short-tau inversion recovery sequence

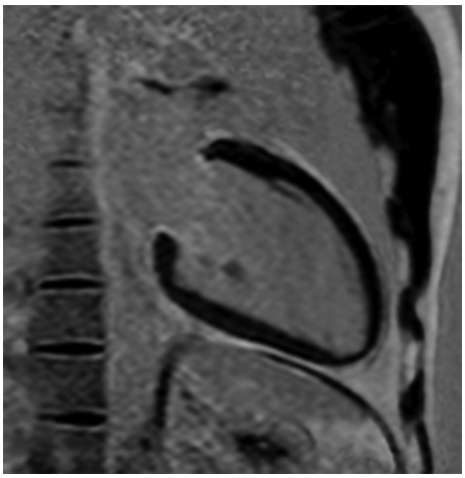

Figure 6: Hyperenhancement of the pericardium seen in a dual-chamber section. Image obtained with cardiac magnetic resonance using late sequences to detect late gadolinium enhancement

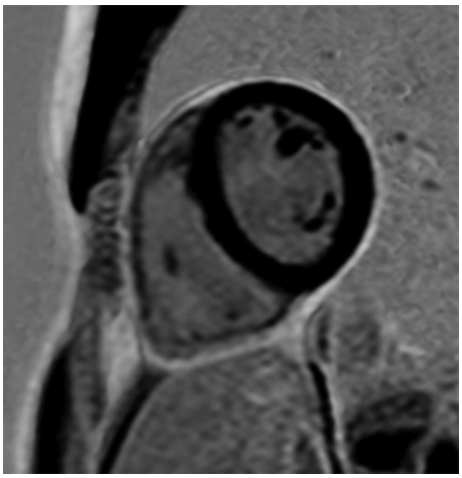

Figure 7: Hyperenhancement of the pericardium seen in a short-axis section. Image obtained with cardiac magnetic resonance using late sequences to detect late gadolinium enhancement

Hemodynamic evaluation

Cine CMR both during free breathing and with breath-held provides pivotal information reflecting the pathophysiological mechanisms of CP, especially the interventricular interdependence and the dissociation between intrathoracic and intracardiac pressures, representing a good alternative to Doppler echocardiography.[16] Ventricular interdependence can be assessed with good sensitivity and specificity both visually, studying the typical RISS, and quantitatively. The first parameter can be the ratio between the LV end-inspiration area and LV end-expiration area, described as significantly lower in patients with CP (100% specificity, 100% positive predictive value, and 83% negative predictive value).[14] Moreover, the ratio of RV free wall-septum distance to that of the biventricular distance ≥11.8% was reported to suggest the diagnosis of CP and to help differentiating from RCM and normal subjects.[14] Finally, the presence of septal bounce is nearly constant in patients with CP. A study described the usefulness of these parameters, assessed during free breathing, in differentiating CP from RCM and other diseases causing a septal shift, such as cor pulmonale and pericardial effusion.[30] Moreover, the use of velocity-encoded phase contrast CMR allows the assessment of mitral and tricuspid flow velocities: an increased early ventricular filling together with a reduced or absent late filling and variations of mitral and tricuspid inflow with respiration were reported as helpful to differentiate CP from RCM, as expression of dissociation between intrathoracic and intracardiac pressures too.[7]

Positron emission tomography

Even if, according to the 2015 ESC Guidelines,[1] its use is not indicated in the diagnostic workup of CP, 18F-fluorodeoxyglucose positron emission tomography (PET) can be useful to detect pericardial inflammation with high sensitivity, and thus to make a diagnosis of transient inflammatory constriction, and to predict response to steroid therapy. Furthermore, PET can help in identifying the cause of pericardial inflammation, and in particular, tuberculosis pericarditis shows greater uptake of 18F-fluorodeoxyglucose than idiopathic forms. We remember that tuberculosis is a major cause of CP in developing countries. However, the experience of PET in CP is limited and most of the data come from a single-center study with a little cohort of patients, most of whom were suffering from tuberculosis pericarditis.[31] In addition, the low spatial resolution is a big limitation to study pathological pericardium. A recent case report[10] suggested a combined approach (PET/CMR) to reduce the limitations of a single method and to improve the efficacy of noninvasive cardiac imaging.[7,15]

Differentiation between constrictive pericarditis and restrictive cardiomyopathy and other morbidities

Differentiating CP from RCM, the main differential diagnosis is fundamental due to radical different treatment options and prognosis. According to 2016 guidelines for the evaluation of diastolic function from the American Society of Echocardiography and the European Association of Cardiovascular Imaging,[32] the presence of mitral annular medial e' velocity >8 cm/s, annulus reversus, and expiratory reversal flow in the hepatic vein excludes RCM, thus permitting to make diagnosis of CP. These data were mainly derived by a validated algorithm from Mayo Clinic comparing CP and RCM.[17] The use of multimodality noninvasive imaging generates plenty of data,[7] helpful for differential diagnosis. However, many diseases, such as mitral annular calcification, mitral valve prosthesis, TR, RV systolic dysfunction, and myocardial infiltrative diseases, could cripple the TDI, by providing a reduced medial e' velocity even if LV systolic function is normal and RCM is absent too. In these cases, the study of GLS, significantly higher in CP than in RCM, is extremely helpful, with both echocardiography and CMR. A promising Doppler parameter from echocardiography is a lower degree of early velocity reduction on pulmonary regurgitation in RCM compared to CP, reflecting different

Table 1: Main features of constrictive pericarditis; more information in the text

	CP
Feature	**Elements**
Subtypes	Transient
	Effusive–constrictive
	Chronic
Etiology	Idiopathic or viral (42%–49%)
	Postcardiac surgery (11%–37%)
	Postradiation therapy (9%–31%)
	Connective tissue disorders (3%–7%)
	Infections (tuberculosis, bacterial; 3%–6%)
Symptoms	Fatigue/dyspnea at exertion
	Peripheral edema
	Ascites
Signs	Pericardial knock
	Friedrich's sign
	W sign
	Kussmaul's sign
	Pulsus paradoxus
Diagnosis	Laboratory tests
	Electrocardiogram
	Multimodal imaging
	Cardiac catheterization
Therapy	Surgical pericardiectomy (Class I, Level C)
	Specific drug therapy (i.e., antitubercular) (Class I, Level C)
	Empiric anti-inflammatory therapy (Class IIb, Level C)
	Supportive medical therapy (i.e., diuretics)

Table 2: Multimodal diagnosis of constrictive pericarditis; more information in the text

Multimodal diagnosis of CP
Transthoracic echocardiography, as a first-level technique (Class I, Level C)
CT/CMR, in selected cases, as a second-level technique (Class I, Level C)
PET
Cardiac catheterization (Class I, Level C)

CT=Computed tomography, CMR=Cardiac magnetic resonance, PET=Positron emission tomography, CP=Constrictive pericarditis

Table 3: Echocardiographic key features of constrictive pericarditis[4,5,17]

Echocardiographic key features of CP
RISS
Preserved or exaggerated medial mitral annulus early diastolic (e') velocity (≥9 cm/s)
Prominent expiratory diastolic flow reversal in hepatic veins
Increased mitral E-wave velocity and E/A ratio >1.6 (in expiration)
Respiratory variation of peak mitral E-wave velocity (at least >15%)
IVC plethora

The Mayo Clinic criteria are in bold. RISS=Respirophasic interventricular septal shift, CP=Constrictive pericarditis, IVC=Inferior vena cava

pressure gradients between RV and pulmonary artery. CMR also can provide useful data about myocardial thickening, and abnormal contrast enhancement pattern, suggestive of RCM or other diseases. Finally, when noninvasive imaging techniques does not allow a firm diagnosis, invasive catheterization should be considered: the ratio between RV and LV systolic pressure-time area during inspiration (systolic area index) >1.1 reaches the best accuracy for differentiating CP from RCM, reflecting the typical enhanced ventricular interdependence.[7]

Future directions

Actual cardiac imaging techniques produce a big amount of structural and functional data that are arduous to be fully used by the clinician to diagnose CP, a rare disease, and to differentiate it from other diseases, primarily RCM. Some authors suggest applying a cognitive machine learning model to identify the parameters most strongly associated with CP. From several studies, a four-variable model (end-diastolic ventricular septal and posterior wall thickness, mitral medial e' velocity, mitral E/e'), eventually along with speckle-tracking parameters, seemed to obtain satisfying results to diagnose CP and RCM. This approach, if validated, could be helpful, especially for clinicians with poor experience or working in peripheral centers, that rarely encounter CP.[4,7]

Constrictive pericarditis and COVID-19

With the spread of the pandemic COVID-19 and SARS-CoV-2 vaccines, cardiovascular involvement, even long-term, has been reported.[33-43] The pericardial disease primarily associated with these situations is known to be acute pericarditis.[44,45] However, we found >10 case reports of CP following the diagnosis of COVID-19 or the administration of mRNA-vaccine,[46-60] with a temporal relationship ranging from 4 days to 7 months, and without predilection for age groups. All cases reported an effusive–CP, suggesting an acute-on-chronic or subacute mechanism, except for two cases,[56,57] in which a transient constriction was described. In more than half of cases,[46-48,53,55-57] a cardiac comorbidity was present, with a predominance of arterial hypertension. Preexistent pulmonary fibrosis, alone or consequent to systemic sclerosis and present in two cases,[49,53] seems to be a predisposing factor; however, no statistical data are available. In most of these cases, CP represented a critical element of aggravation of clinical status and hospitalization time or need, sometimes by requesting pericardiectomy or being fatal. Especially in this category of patients, diagnosis of CP using multimodal imaging is crucial, not being able to perform invasive tests due to the fragility and the infectiveness. In conclusion, in patients with a recent diagnosis of COVID-19 or mRNA-vaccine administration presenting with *de novo* or rapidly worsened heart failure symptoms, effusive–CP should be considered, and a proper diagnostic workup should be followed. In this setting, the collection of cases in a single register and statistical analysis to identify possible predisposing factors and a short diagnostic workup could be desirable.

Conclusions

CP is a rare condition, difficult to identify and treat early, and poorly known by most specialists. Given these features,

it is not surprising that experiences on this disease come mainly from studies single-centered. Recently, an association with SARS-CoV-2 infection or vaccine has also been described. A careful differentiation of CP from RCM, its main differential diagnosis, is important, since CP has some effective therapeutic options, while the prognosis of RCM is considered poor due to limited therapies available. The imaging evaluation is focused on morphologic alterations, that are pericardial thickening and calcification, and on hemodynamic data, especially the enhanced ventricular interdependence and the dissociation between intrathoracic and intracardiac pressures. In this setting, multimodal imaging is crucial to make a proper diagnosis, with a remarkable impact on the prognosis.

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Conflicts of interest

There are no conflicts of interest.

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