The contemporary role of cardiac computed tomography and cardiac magnetic resonance imaging in the diagnosis and management of pericardial diseases

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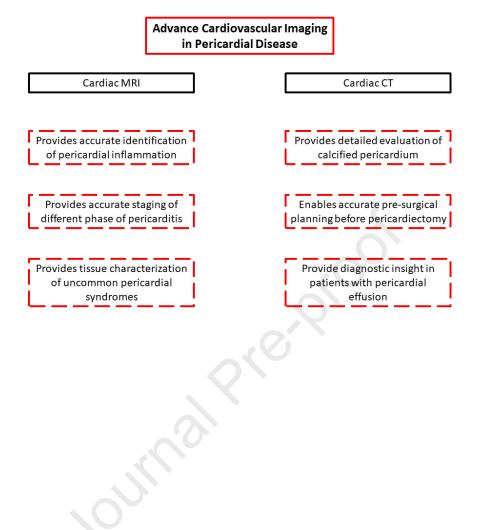
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The contemporary role of cardiac computed tomography and cardiac magnetic resonance

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Short Title: Advance Imaging for pericardial diseases

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ABSTRACT

Pericardial syndromes encompass different clinical conditions from acute pericarditis to idiopathic chronic pericardial effusion. Transthoracic echocardiogram is the first and most important initial diagnostic imaging modality in most patients affected by pericardial disease. However, cardiac computed tomography and cardiac magnetic resonance (CMR) have recently gained a pivotal role in cardiology and recent reports supported the role of both these advanced techniques in the evaluation and guiding therapy of pericardial disease. The most promising tool is the capability of CMR to identify the presence of pericardial inflammation carrying both diagnostic and prognostic value in the setting of recurrent and chronic pericardial. On the other side cardiac CT permits accurate evaluation of the presence and extension of pericardial calcification providing important information in confirming the diagnosis of constrictive pericarditis and during the preprocedural planning for patients undergoing pericardiectomy. Both cardiac CT and CMR correct indication and proper evaluation need specific expertise, especially for the evaluation of pericardial disease, thus the aim of the present review is to provide physicians an updated overview on the CCT and CMR role in pericardial disease focusing on technical issues, recent research findings and potential clinical applications.

Introduction

Pericardial syndromes encompass different clinical conditions from acute pericarditis to idiopathic chronic pericardial effusion (1). Clinical presentation, diagnostic workflow and prognosis significatively differ among pericardial diseases and an accurate clinical evaluation is of fundamental importance for the appropriate management of patients. Beyond electrocardiogram and biochemical analysis, transthoracic echocardiogram is the first and most important diagnostic tool in most cases. It is widely available, even in the emergency setting, enabling immediate identification of pericardial effusion and its hemodynamic impact; of note, early signs of cardiac tamponade could be detected before the onset of clinically pericardial tamponade. In the absence of pericardial effusion, constrictive physiology could be evaluated both in the setting of acute and chronic pericarditis. For these reasons, transthoracic echocardiography is a pivotal tool in the evaluation of patients with pericardial disease both during the early phases of patient management and during the strict clinical follow-up that is often needed in this clinical setting.(2)

During the last two decades, cardiac computed tomography (CCT) and cardiac magnetic resonance (CMR) have been introduced in the clinical setting gaining a pivotal role in most fields of cardiology (i.e. ischemic heart disease and myocardial disease). Of interest, recent studies suggested the potential role of both CMR and CCT in the evaluation of patients with pericardial diseases (3-4-5); the use of advanced cardiovascular imaging, if correctly indicated and interpreted, may provide important insights for the management of patients on top of the comprehensive information already available at transthoracic echocardiography. In this narrative review, we are going to provide an updated overview on the CCT and CMR role in pericardial disease focusing on technical issues, recent research findings and potential clinical applications (Table 1).

Cardiac Computed Tomography

CCT has recently gained a wide clinical application in patients with suspected coronary artery disease. This is due to the fast technological innovations that have been introduced in the clinical field during the last two decades. Above all, the possibility of obtaining ECG-gated images enabled physician to accurately visualize and evaluate heart anatomy. Consequently even thin structures such as the pericardium are

nowadays visible and evaluable at CT whose spatial resolution is far below 1 mm. In order to obtain an appropriate evaluation of the pericardium, a contrast-enhanced and ECG gated-CT should be performed given only the presence or absence of pericardial effusion could be described at traditional non-gated thorax CT. As a general rule, pericardial effusion density>10 HU suggests a high protein content, while >30 HU suggests a hemorrhagic effusion. Pericardial calcifications are evident on a CCT and a three-dimensional reconstruction of the site and extension of calcified pericardial plaques could be provided. Of interest, delayed CT scan acquisitions after contrast medium i.v. administration has been described during acute pericardial fibrosis identification at CCT (7). This technique is widely available and could be easily performed even in an emergency setting. , It should, however, be underlined that radiation dose is not negligible, especially in younger patients and if an older generation CT scanner is used. Moreover, a dedicated advanced imager in cardiovascular imaging is needed for an appropriate assessment.

Cardiac Magnetic Resonance

CMR is considered the gold standard for biventricular volumes and function evaluation and for the noninvasive myocardial tissue characterization (8). Even if black-blood T1-weighted spin-echo MR imaging performed with a fast segmented sequence is the best approach for morphologic study of the pericardium, commonly used cine images (bSSFP) could provide a detailed anatomical evaluation of pericardium. In addition , both T2-weighted images and late-gadolinium enhancement (LGE) sequences could be used to identify pericardial inflammation. In this regard, it should be emphasized that while a hyperintense signal within the myocardium when using LGE sequences represents myocardial fibrosis, the hyperintensity signal within the pericardial layers represents an active inflammatory state related to pericardial neovascularization. The hyperintense signal due to pericardial edema on T2-weighted imaged and LGE could be difficult to differentiate from epicardial fat, prompting the use of fat suppression sequences to differentiate inflammation from epicardial fat. Of interest, cine-images during forced inspiration could be performed to identify the presence of exaggerated biventricular interdependence, a sign of pericardial constrictive physiology. CMR clinical application is often limited because this technique is not widely

available and could be of difficult management in acute setting. Moreover, some patients may have specific contraindications (i.e. claustrophobia or in the presence of CMR unsafe medical devices) further limiting the wide applicability of this technique.

Normal findings

Pericardium is a double-layered sac surrounding heart and roots of great vessels. Two distinct layers are recognizable: the fibrous pericardium (outer layer) and the serous pericardium (inner layer) The serous layer is a closed sac with the visceral component lining the heart (called epicardium) and the parietal component adhering the fibrous outer layer (9). A small amount of fluid, usually below 50 ml, is physiologically present between the visceral and the parietal component of the serous layer, but it should be noted that an even higher amount of fluid could be detected in normal subjects (10). According to most recent consensus documents, the normal pericardial thickness is between 1 and 2 mm when assessed withhigh-resolutionn CT, while pericardium visualized in CMR is considered normal when below 2 mm. In summary, even if no clear consensus exists, a pericardium thickness above 3 mm should be considered as pathological at both CT and CMR (2-11). It should be underlined that a discrete amount of pericardial fluid could be obtained and the "thickness" of pericardial fluid should be then measured and reported, ideally in diastolic phase if an ECG-gated CT has been performed. On the other hand, dimensions of pericardial fluid "thickness" should not be measured on the axial views as this may lead to overestimating the amount of pericardial fluid.

Acute or recurrent pericarditis

Acute pericarditis is characterized by active inflammation of the pericardium, with or without pericardial effusion. At least two of four diagnostic criteria should be fulfilled to reach a diagnosis according to ESC guidelines, as follows: pericarditic chest pain, pericardial rubs, new widespread ST-elevation or PR depression on ECG and pericardial effusion (new or worsening). Additional supporting findings are the elevation of serum inflammatory markers and/or the evidence of inflammation at CCT or CMR. (1). In this

clinical setting, echocardiography is the first line test and when pericarditis is uncomplicated, often, no further imaging evaluation is needed. On the contrary, in case of complicated or high-risk pericarditis as reported in ESC guidelines (i.e. suspected myocarditis, refractory to NSAID therapy, etc), CMR could be of added clinical value providing accurate information about the pericardial anatomy, hemodynamic significance and regarding the presence and extent of myocardial involvement (12). More recently, emerging is the capability of this technique to identify the presence of pericardial inflammation whose quantification appeared to be correlated with the incidence of recurrent pericarditis (13-14). More precisely, the presence of hyperintense signals both at pre-contrast T2 weighted images and at LGE sequences, performed after 10-15 minutes after i.v. contrast injection, (Figure 1) has been associated with active pericardial inflammation (2). It should be underlined that for identification of pericardial hyperintensity an expert reader is needed because often is not easily distinguished from epicardial fat; however dedicated fat suppression techniques should be performed to better distinguish epicardial fat from the inflamed pericardium (Figure 2). The possibility to demonstrate active pericardial inflammation is of clinical interest especially among patients with new appearance of symptoms during medical therapy tapering after the first episode of pericarditis (14). A previous study reported that in a cohort of 275 patients with a history of idiopathic pericarditis, 10% of subjects had a recurrence of chest pain without any other evidence of active pericarditis (15); in this setting, CMR may help physicians to correctly identify those patients with pericarditis recurrences. Moreover, in 2017 a retrospective cohort study including 159 patients with recurrent pericarditis by Kumar et al reported that quantitative pericardial LGE had incremental prognostic value over baseline clinical and laboratory variables, with higher values being associated with higher recurrence rate at 6 months (odds ratio: 1.14; 95% CI: 1.02 to 1.29; p = 0.026) (16). In 2020 a study including 128 patients with acute pericarditis who underwent CMR, confirmed the capability of CMR to identify patients at higher risk of pericardial events at follow-up; of interest, in that study, CMR findings were blunted in those patients who underwent CMR after 4 weeks from the first occurrence of symptoms (17). These data suggest that CMR for the identification of pericardial inflammation should be performed early in the course of disease, otherwise imaging findings could be blunted and some prognostic information could be missed. More recently, a pilot study including a small

group of patients who underwent CMR early after the first episode of pericarditis needing hospitalization confirmed the prognostic values of positive pericardial LGE even in the setting of first episode of acute pericarditis (18). Overall these studies suggested that CMR analysis and especially LGE sequences may help physicians correctly identify patients at higher risk of pericarditis recurrences and that may merit more aggressive medical therapy, even after the first episode of pericarditis (Table 2). Of interest, most of these patients do not present pericardial effusion and pericardial inflammation could be missed at traditional transthoracic echocardiography. From a pathophysiological point of view, the relatively avascular healthy pericardium will not retain gadolinium resulting in a null signal when capturing delayed images. On the other hand, the injured pericardium will undergo neovascularization, fibroblast proliferation, and an expanded extracellular space, attracting gadolinium and delaying its washout, resulting in increased signal on LGE sequences (2). In the future, an imaging-based approach in a selected subgroup of patients may help to better identify patients at higher risk of complicated pericarditis/recurrent pericarditis, leading to potentially overcoming the actual one-fits-all approach in pericarditis medical therapy. More precisely, the use of third line therapy, such as anakinra or rilonacept could be anticipated in a selected group of patients, potentially reducing the disabling symptoms of recurrent pericarditis; on the contrary patients without pericardial LGE, in the absence of symptoms and with normal serum CPR values, may benefit of a shortduration anti-inflammatory therapy. However, further studies are needed before this approach could be applied on a routine clinical basis (19-20-21)

CCT use in acute pericarditis is limited to those cases in which echocardiography results to be inconclusive and CMR is contraindicated. In this regard, Andreini et al recently demonstrated the capability of CCT to correctly identify myocardial fibrosis when compared to CMR supporting the potential role of CCT as an appropriate alternative to CMR for myocardial tissue characterization (7) (Figure 3). The presence of pericardial effusion is easily evaluated by CCT and quantification could be performed even in term of pericardial fluid volume. Moreover, pericardial effusion nature could be determined and more specifically a density >10 HU suggests a high protein content, while >30 HU suggests a hemorrhagic effusion. Of interest, CCT may exclude or confirm the presence of acute aortic syndrome as the cause of pericardial

effusion/inflammation and a CCT must be always performed when this life-threatening diagnosis is suspected. Similarly, CCT including mediastinum and lung parenchyma evaluation could provide important insight if an oncological or other comorbidity is suspected. . However, it should be underlined that the CTassociated cumulative radiation dose could not be negligible; accordingly serial CT images for follow-up is discouraged.

Constrictive pericarditis

Constrictive pericarditis physiology is characterized by impaired diastolic filling of the ventricles due to reduced pericardial compliance leading to a clinical syndrome dominated by peripheral venous congestion and low cardiac output leading patients to complain about fatigue, peripheral oedema, breathlessness and abdominal swelling (2)

The capability of CMR to identify pericardial inflammation is of utmost clinical importance in this setting enabling the clinician to identify patients in which anti-inflammatory therapy may lead to partial resolution of constrictive pericarditis, potentially avoiding pericardiectomy which is often associated with elevated rates of complications (transient constrictive pericarditis) (22). In this regard, Feng et al. (15), in 29 patients with constrictive pericarditis, demonstrated that thickened pericardium(>3 mm) and little or no imaging or biochemical evidence of inflammation was not associated with clinical improvement after antiinflammatory therapy, while those with thickened pericardium and signs of inflammation showed a reduction in pericardial thickness and an increase in pericardial compliance after medical therapy. These data support the use of CMR in all patients with possible clinical indication to pericardiectomy to correctly identify those with active pericardial inflammation in which medical therapy should be optimized, deferring pericardiectomy (23).

The main clinical value of CCT in patients with constrictive pericarditis is the possibility to accurately evaluate the presence and extension of pericardial calcification (Figure 4). This is of utmost importance in confirming the clinical diagnosis of constrictive pericarditis and provides important information during pericardiectomy pre-procedural planning. More specifically, it provides an accurate three-dimensional

description of pericardial calcification location and distribution especially related to coronary arteries course, informing surgeons of potentially life-threatening conditions during pericardiectomy. As an example, the coronary artery course is well evident and the distance between coronary vessels and calcified pericardium could be accurately defined informing surgeons during pre-procedural planning. It should be underlined that the need for contrast medium and radiation dose issues limit the use of serial CT scans during follow-up.

Pericardial Effusion

Pericardial effusion without active inflammation often represents a clinical dilemma. In this setting transthoracic echocardiography is of utmost importance as it provides an extensive hemodynamical evaluation that is not feasible neither with CMR nor with CCT. In this regard, dedicated real time cine images during forced inspiration should be always performed in patients with pericardial effusion undergoing CMR in order to identify the presence of paradoxical septal movement during inspiration that is the most commonly used sign of biventricular interdependence evaluable at CMR and reflects the hemodynamic importance of pericardial effusion. Advanced cardiac imaging with both CCT and CMR could be of help in selected cases providing important insight and potentially leading to specific clinical diagnoses. Moreover, the nature of the effusion could be determined at CCT; more specifically a density >10 HU suggests a high protein content, while >30 HU suggests a hemorrhagic effusion. On the contrary, isolated evidence of pericardial effusion without any signs of pericardial inflammation or pathological findings at CMR is associated with good prognosis (2) (Figure 5). Similarly, at CMR both T1 and T2 weighted images may provide information regarding the pericardial effusion nature; more specifically a transudate fluid usually presents with a hyperintense signal on T2w images and with low signal in T1w images while a proteinaceous fluid is characterized by an elevated signal on T1w images and a hypointense signal on T2w images (24). Thus, both CCT and CMR may help physicians better elucidate the etiology of pericardial effusion, information that has been traditionally associated to prognosis. In this regard, a recent study on a consecutive cohort of patients with occasional identification of pericardial effusion at CCT performed for suspected CAD demonstrated that the presence of pectus excavatum is associated with higher prevalence

of even moderate pericardial effusion; at follow-up, none of these patients had any pericardial events (pericardial tamponade or need for pericardiocentesis) suggesting that even large pericardial effusion could be associated with good prognosis in specific clinical setting (10) (Figure 6). Recent data support to extend these recommendations of watchful waiting to most of the patients with asymptomatic or oligosymptomatic idiopathic, chronic, large pericardial effusion, without hemodynamic relevance (25-26). On the contrary, the presence of pericardial masses could be missed at transthoracic echocardiography but are easily identified and well characterized both at CCT and CMR. It should be underlined even if both CMR and CCT should be considered during the initial diagnostic evaluation of idiopathic pericardial effusion, these techniques are of limited value during patients' follow-up when transthoracic echocardiography should be preferred.

Uncommon pericardial syndromes

Less common pericardial diseases include pericardial cysts, pericardial diverticula, congenital pericardial defects and pericardial masses. In these rare entities, CMR is the gold standard for evaluation and characterization of the rare disease as it provides wide field of view on the entire thorax and enables tissues characterization (27). CT could be of support in selected cases. Pericardial cysts are rare, mostly benign, fluid-filled sometimes loculated masses with well-defined borders that are usually located at the right costophrenic border; cardiac MRI is the most appropriate technique to characterize this rare finding that usually presents fluid hyperintensity in T2w weighted images without contrast enhancement. Pericardial diverticular are focal outpouching arising from the pericardium that could be differentiated from cyst because direct communication with the pericardium is usually well evident. Complete agenesia of pericardium is usually characterized by a leftward and posterior rotation of the heart with lung parenchyma well evident between aorta and pulmonary artery. While these congenital entities are of benign nature most of pericardial tumors are metastasis from lung, breast, lymphoma and melanoma tumors with mesothelioma representing the most common primary malignant pericardial tumor.

Conclusion and future perspective

Transthoracic echocardiography remains the main diagnostic tool in patients with pericardial diseases. However, advanced cardiac imaging with both CMR and CCT, is gaining a growing role in this setting. The prognostic value of pericardial inflammation identified at T2w and LGE images should be considered as the most promising data (28), providing important insight regarding the specific stage of pericarditis (from acute pericarditis to burned-out constrictive pericarditis) (Figure 7). More specifically, the use of these modalities may enable the identification of subgroups of patients at higher risk of recurrent pericarditis potentially leading to different therapeutical approaches and improving the prognosis of patients that nowadays suffer of disabling symptoms from severe episodes of recurrent pericarditis and could potentially take advantage of early and more aggressive medical therapy (29-30-31). Further studies are needed before a personalized approach to pericarditis could be part of the clinical routine and advanced cardiac imaging, especially with CMR, seems to be a promising tool for the appropriate identification of patients at higher risk.

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TABLES

Clinical scenario Recommendations Acute pericarditis with small or no effusion Neither CT or CMR is routinely • and no suspected myocarditis suggested and echocardiography is enough in most of patients Acute pericarditis with small or no effusion CMR is recommended to confirm • but with suspected/diagnosed myocarditis clinical diagnosis Acute pericarditis with complicated course Recommendations should be and/or moderate-to-severe effusion and no considered CMR to determine tamponade presence/extent of pericardial LGE and for identification of specific causes of pericardial effusion. Acute pericarditis with complicated course CTA is generally recommended as and/or moderate-to-severe effusion and no CMR may be technically difficult. tamponade associated with trauma, aortic dissection or inconclusive.

Table 1. Recommendations for CT or CMR in pericardial disease

Cardiac tamponade and pericardiocentesis Cardiac tamponade and pericardiocentesis, in case of trauma or high suspicion of aortic dissection	 CMR is reasonable only in very selected cases for follow-up after pericardiocentesis to determine the presence/extent of pericardial LGE CTA is generally recommended as CMR may be technically difficult.
Chronic constrictive pericarditis	 CMR is recommended to exclude transient forms of pericardial constriction In case of inconclusive echocardiography, CT is reasonable to confirm clinical diagnosis CT is reasonable for planning a pericardiotomy CMR is recommended before pericardiotomy to evaluate the presence of pericardium inflammation CMR is reasonable for follow-up
Effusive-constrictive pericarditis	 In case of inconclusive echocardiography, CT/CMR is reasonable to confirm clinical diagnosis CMR with contrast is reasonable to evaluate presence of pericardium inflammation CMR is reasonable for follow-up

CTA, computed tomography angiography; CMR, cardiovascular magnetic resonance.

Table 2: Prognostic value of CMR in pericarditis: main studies

Authors/Year of publication	Study design	N of patients	Inclusion criteria	Endpoints	Main results
M Chadi Alraies et al 2015	Retrospective	507	Recurrent pericarditis Two Groups : CMR guided vs no CMR	 Incidence of constrictive pericarditis, pericardial window, or pericardiectomy Total dose of steroids administered 	There was no significant difference in the incidence of pericardial events between groups with or without CMR No CMR group had higher overall total milligrams of steroid administered vs CMR group
Kumar et al 2017	Retrospective	159	Recurrent pericarditis underwent CMR	 Clinical remission prevalence Time to recurrence 	Quantitative analysis of pericardial LGE was associated with outcome
Kumar et al 2018	Retrospective	200	History of previous recurrent pericarditis	 Prevalence of active pericarditis at CMR 	Pericardial LGE provided incremental information to diagnose

					recurrences over conventional clinical criteria			
lmazio et al 2020	Prospective	128	Recurrent pericarditis	 diagnostic accuracy of CMR for active pericarditis Incidence of additional recurrences, cardiac tamponade, and constrictive pericarditis at follow-up 	CMR findings show high diagnostic accuracy and may help identifying patients at higher risk of complications.			
Conte et al 2022	Retrospective	26	First episode of acute pericarditis	 Incidence of recurrent pericarditis, chronic constrictive pericarditis, surgery for pericardial disease. 	Pericardial inflammation identified by CMR, with LGE images, has a prognostic value independently from clinical and bio-humoral variables.			

FIGURES

Figure 1: Recurrent pericarditis at CMR

A case of recurrent pericarditis in a young male of 29 y/o with chest pain, normal ECG and mild increase of CRP serum values. CMR confirmed the presence of an early recurrence of pericarditis. In panel A, B and C long axis view on LGE sequence in which hyperintense signal of pericardium is well evident (red arrows in all panels). In panel C mild hyperintensity on T2 weighted images and in panel D LGE sequences in short axis

view (red arrows in all panels). Of note, in the absence of pericardial effusion transthoracic echocardiography resulted to be normal.

Figure 2: Dedicated sequence to distinguish pericardial fat from pericardial inflammation.

A case example of dedicated sequences for correctly distinguishing pericardial fat from pericardium with active inflammation. In panel A, balance steady state free precession (bSSFP) images are presented where pericardial fat is hyperintense (white arrows) while pericardium is hypointense (white arrowhead); in panel B and D T2 weighed and LGE images where pericardial inflammation is well evident as a hyperintense signal (blue arrows); in panel C T1 weighted images well demonstrated pericardial fat with an hyperintense signal while pericardium resulted to be hypointense (red arrows)

Figure 3: Acute pericardial inflammation at CCT

A case of contrast CT dedicated to liver parenchyma evaluation revealed future potential applications of CT to evaluate pericardial inflammation. In panel A the early post-contrast phase where pericardial thickening is evident (red arrows). In panel B, from the same patients, a late angiographic phase were hyperdense pericardium is well evident suggesting active pericarditis diagnosis that was subsequently confirmed. In both panel a 2 mm pericardial thickening is well evident (yellow bar).

Figure 4: Chronic constrictive pericarditis at CCT

A case of constrictive pericarditis in which CCT enables detailed evaluation of pericardial calcification (red arrows in all panels) that completely encircled heart leading to hemodynamic impairment (D-shape septum is well evident in panel C and Supplemental Video S1). Three-dimensional images could be provided for a comprehensive visualization of pericardial calcifications (panel E).

Figure 5: Idiopathic pericardial effusion at CMR.

A case example of pericardial effusion without any sign of pericardial inflammation. In panel A left ventricular short axis view at bSSFP sequences (red arrow) and in panel B left ventricle short-axis view at

LGE sequences. Yellow line in panel A demonstrates how to measure pericardial effusion (32 mm is reported in this cases), while in panel B a red line demonstrates normal myocardial wall thickness (9 mm).

Figure 6: Pericardial effusion at CCT

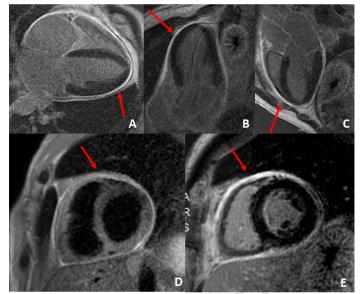
A case of pectus excavatum and pericardial effusion occasionally identified at CCT (red asterix). At CCT a transudate nature could be suspected (HU value of 6).

Figure 7: CMR evaluation of pericarditis at different stages

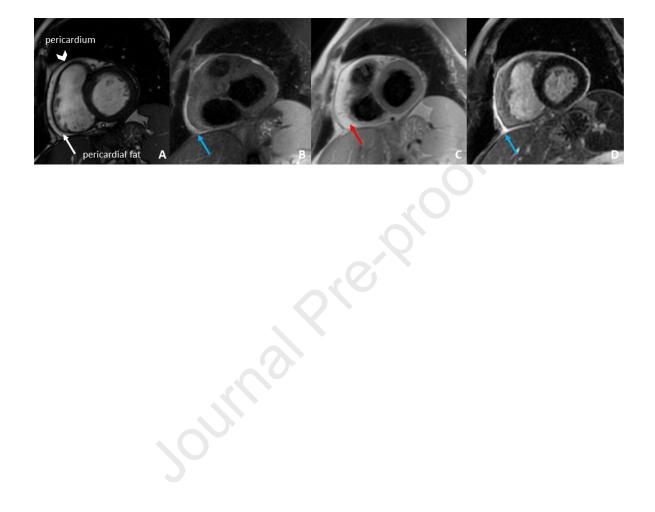
CMR evaluation enables differentiation of different stages of pericarditis from acute pericarditis (pericardium hyperintensity both at T2w images and at LGE images, panel A and D), sub-acute pericarditis (mild pericardial hyperintensity only at LGE images, panel B and E) and burned out pericarditis (absence of pericardial hyperintensity both at T2 weighted images and LGE images, with well evident thickening of pericardium, panel C and F).

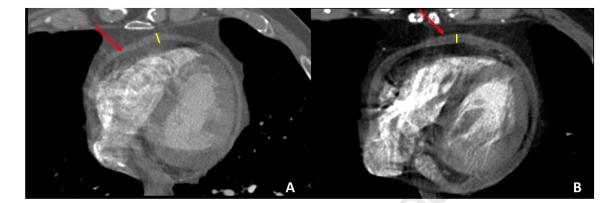
Supplemental Video S1

Exaggerated intraventricular interdependence is well evident in the Video. More precisely a paradoxical septal movement is elicited by deep inspiration. This is the only sign of constriction evaluable at CMR

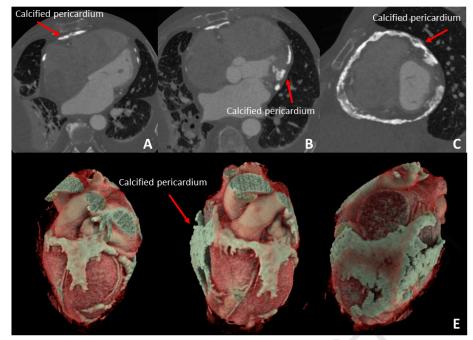


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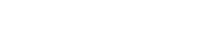


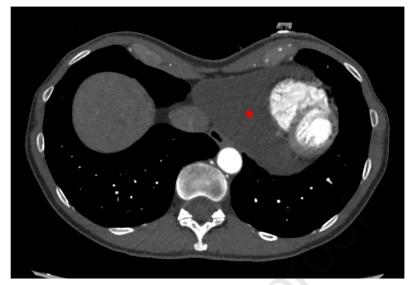
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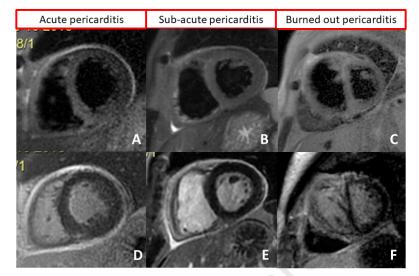
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