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CME

Pericardial Delayed Hyperenhancement With CMR Imaging in Patients With Constrictive Pericarditis Undergoing Surgical Pericardiectomy

A Case Series With Histopathological Correlation

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JACC: CARDIOVASCULAR IMAGING CME

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CME Objective for This Article: After reading the CME feature article, the reader will be able to: identify and describe the utility of cardiac magnetic resonance imaging in patients with constrictive pericarditis; identify and describe the significance of pericardial delayed hyperenhancement; understand and determine pericardial delayed hyperenhancement score and thickness score; and analyze and correlate pathologic, and cardiac magnetic resonance findings for constrictive pericarditis.

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Pericardial Delayed Hyperenhancement With CMR Imaging in Patients With Constrictive Pericarditis Undergoing Surgical Pericardiectomy

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OBJECTIVES The purpose of this study was to examine the prevalence and histopathologic correlates of pericardial delayed hyperenhancement (DHE) seen with cardiac magnetic resonance imaging (CMR) among patients with constrictive pericarditis (CP) undergoing pericardiectomy.

BACKGROUND Constrictive pericarditis patients studied by CMR will occasionally demonstrate pericardial DHE following gadolinium contrast administration.

METHODS We identified 25 CP patients who underwent pericardiectomy following CMR-gadolinium study. We also assessed 10 control subjects with no evidence of pericardial disease referred for cardiac viability imaging. A novel 14-segment pericardial model was used to determine pericardial DHE score and thickness score. Histopathology of pericardial specimens was reviewed and evaluated semiquantitatively on a 4-point scale for the extent of calcification, fibrosis, inflammation, and neovascularization.

RESULTS DHE was present in 12 (48%) CP patients (DHE+ group), and absent in 13 CP patients (DHE– group) and all control patients. The DHE+ group had greater fibroblastic proliferation and neovascularization, as well as more prominent chronic inflammation and granulation tissue. Fibroblastic proliferation and chronic inflammation correlated with DHE presence quantitated by DHE score (Spearman $r = 0.578$, $p < 0.002$, and $r = 0.590$, $p < 0.002$, respectively), but not with pericardial thickness. Segmental analysis demonstrated no significant difference in the percentage of patients with different pericardial segmental thickness; however, overall, in each segment, the DHE+ group tended to have greater pericardial thickness.

CONCLUSIONS The presence of pericardial DHE on CMR is common in patients with CP, and its presence is associated with histological features of organizing pericarditis, which may be a target for future focused pharmacological interventions. Patients with CP without pericardial DHE had more pericardial fibrosis and calcification, as well as lesser degrees of pericardial thickening. (J Am Coll Cardiol Img 2011;4:1180–91)

Constrictive pericarditis (CP) has long posed a diagnostic challenge to the clinician. Whereas the normal pericardium is a thin, avascular sac enveloping the heart in the anterior mediastinum, its relative inelasticity provides constraint during diastolic filling that limits chamber dilation, particularly the thin-walled right atrium and ventricle (1). Classically, CP is defined as an impedance to diastolic filling caused by a fibrotic pericardium (2), with pericardiectomy, involving partial or complete decortication, being the treatment of choice in experienced centers.

In the past decade, with the rapid development of several complimentary, noninvasive, cardiovascular imaging modalities, constrictive physiology can be more readily identified. Cardiac magnetic resonance (CMR) represents one of the most versatile noninvasive imaging modalities available, offering high spatial resolution and image contrast, along with tissue characterization, and basic hemodynamic assessment. Further, CMR does not impose ionizing radiation exposure, which is generating greater concern among both physicians and the lay public (3).

Delayed hyperenhancement (DHE) CMR has emerged as the gold standard in the detection and characterization of myocardial infarction and fibrosis in recent years (4). DHE CMR images are acquired with an inversion recovery–prepared gradient-echo or steady-state free-precession, imaging pulse sequence, with images acquired 10 to 15 min following gadolinium (Gd) chelate contrast administration. The most commonly used Gd

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agents are extracellular and excluded by intact myocardial cell membranes, but they accumulate in areas of abnormal myocardium resulting in T_1 (the recovery of longitudinal magnetization) shortening. This T_1 shortening, in combination with an inversion time set to null normal myocardium, results in higher signal intensity on T_1-weighted imaging and improved contrast between normal and abnormal myocardium, such as in acute myocardial infarction, or chronic infarction.

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Previous studies have demonstrated the diagnostic and prognostic roles of myocardial DHE in patients with ischemic heart disease (5–7), hypertrophic cardiomyopathy (8), inflammatory or infiltrative cardiomyopathy (9), and dilated cardiomyopathy (10). Myocardial DHE has also been identified in patients suspected of having acute myocarditis (11). Prior case reports and small case series have shown that pericardial DHE correlates with pericardial inflammation (12–16). However, there is a paucity of data in CP patients correlating DHE CMR and surgical histopathology. In the present study, we tested the hypothesis that pericardial DHE is present in patients with CP and correlates with histopathologic findings of active inflammation.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CP = constrictive pericarditis

DHE = delayed hyperenhancement

Gd = gadolinium

hpf = high power field(s)

MRI = magnetic resonance imaging

T_1 = recovery of longitudinal magnetization

TE = echo time

TR = recovery time

METHODS

Study population. Sixty-eight CP patients were retrospectively identified who underwent surgical pericardiectomy at the Cleveland Clinic between August 2006 and April 2010. Of these, 25 patients were identified who, due to physician referral, underwent pre-operative CMR examination following Gd contrast administration and had available surgical pathology specimen for review (23 men, 2 women; mean age: 59 ± 16 years, range 18 to 80 years). A control group of 10 consecutive patients (2 men, 8 women; mean age: 56 ± 11 years, range 41 to 68 years) with no clinical evidence of pericardial disease was referred for myocardial viability imaging and also imaged. Clinical, laboratory, and demographic data were obtained from electronic medical records, and the protocol was approved by the local Institutional Review Board.

CMR protocol. Digitally archived CMR studies were retrospectively reviewed by 2 experienced readers (M.A.B., D.H.K.), who were blinded to original clinical data, initial CMR study interpretation, and histological findings. CMR studies were performed on a 1.5-T magnetic resonance imaging (MRI) scanner—Achieva XR (Philips Medical Systems, Best, the Netherlands) (n = 12) or an Avanto (Siemens Healthcare, Berlin, Germany) (n = 12)—or a 3.0-T MRI scanner (Trio, Siemens Healthcare) (n = 1). All imaging was performed using commercially available software, electrocardiographic triggering, and dedicated phased-array receiver coils.

Phase sensitive inversion recovery DHE imaging, for comprehensive assessment of both pericardium and myocardium, was performed following the intravenous injection of Gd-diethylenetriamine penta-acetic acid (0.1 to 0.2 mmol/kg body weight), using an inversion recovery–spoiled gradient-echo technique in the cardiac short-axis, vertical long-axis, as well as 3- and 4-chamber long-axis planes. (Typical imaging parameters: 1.5-T Philips Achieva: recovery time [TR]: 6.5 ms, echo time [TE]: 3.2 ms, flip angle: 15°, matrix: 128 × 144, field of view: 250 to 300 × 310 to 340, echo train length: 15; 1.5-T Siemens Avanto: TR: 8.7 ms, TE: 3.4 ms, flip angle: 25°, matrix: 156 × 256, field of view: 276 × 340, 25 lines per segment; 3.0-T Siemens Trio: TR: 3.1 ms, TE: 1.8 ms, flip angle: 55°, matrix: 340 × 255, field of view: 192 × 163, 15 lines per segment). Inversion time was selected for optimal nulling of viable myocardium based on evaluation of images obtained from an ultrafast gradient-echo pulse sequence (Look-Locker technique), using a single short-axis slice with progressively increasing inversion time (typical inversion times were in the range of 225 to 300 ms). Post-Gd images were obtained 8 to 15 min following injection of contrast agent. Morphologic pericardial assessment and thickness measurements were made using breath-hold, segmented k-space, turbo spin-echo pulse sequences. (Typical imaging parameters: 1.5-T Philips Achieva: TR: 1500 ms, TE: 80 ms, echo train length: 32, number of signal averages: 2, matrix: 192 × 240, field of view: 330 × 330; 1.5-T Siemens Avanto: TR: 2 R-R intervals, TE: 56 ms, echo spacing: 7 ms, 15 lines per segment, number of signal averages: 1, typical matrix: 166 × 256, field of view: 293 × 360; 3.0-T Siemens Trio: TR: 2000 ms, TE: 60 ms, echo train length: 20, number of signal averages: 1, matrix: 236 × 165, field of view: 320 × 320).

Continuous and categorical MRI variables included Gd contrast volume (ml), left ventricular

ejection fraction (%), left ventricular end-diastolic volume and end-systolic volume, cardiac output (l/min), pericardial effusion, increased pericardial thickness (≥4 mm), epicardial tethering/diastolic restraint, interventricular septal bounce, and tubular ventricular morphology. For each study, only the presence or absence of pericardial DHE and overall pericardial thickness (<4 mm or ≥4 mm) were based on the impression of the clinical reader at the time of the clinical study. Using a novel, 14-segment model (developed in-house) of the pericardium, 2 experienced readers reviewed the CMRs, determined the presence or absence of DHE in each pericardial segment, and performed representative pericardial thickness measurements in each segment (categorized as: <2 mm, 2 to <5 mm, 5 to <10 mm, >10 mm). DHE was defined as a subjective increase in signal intensity of the pericardium relative to that of chest wall soft tissue. Presence of DHE by blinded reader review was defined by having at least 2 segments positive for DHE. A DHE score was calculated as the sum of the pericardial segments thought to contain any DHE, with a total possible score of 14, with 1 point being given to each of the 14 segments we included in our model.

Surgical pathology. The organization of pericardial inflammation is a dynamic process. Organizing pericarditis with fibroplasia (i.e., abundant proliferating fibroblast present) results in thickening of the pericardium as a result of the presence of granulation tissue and fibrinous exudates, in addition to fibrosis (Fig. 1). The granulation tissue comprises a proliferation of plump fibroblasts and capillaries (neovascularization) in an edematous stroma infiltrated by variable amounts of lymphoplasmacytic cells. As the inflammatory process subsides, the organizing pericarditis evolves to increased fibrosis with marked decrease of fibroblasts and inflammatory cells as well as decreased vascularity. The end-stage result is an organized pericarditis that exhibits densely fibrotic pericardium with varying degrees of calcification.

Pericardial specimens were routinely formalin-fixed, paraffin-embedded, and sectioned for

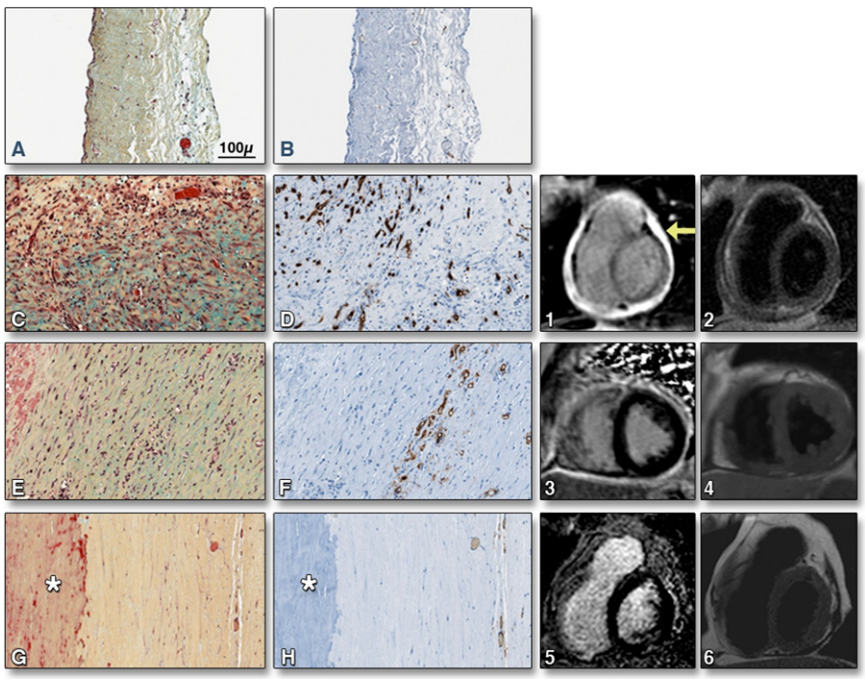


Figure 1. Imaging the Pericardium

First column is Movat pentachrome stain of pericardium. **Second column** is a section of pericardium with immunostaining with CD34, which highlights the endothelial lining of the capillaries. Panels **(A)** and **(B)** represent normal pericardium; **(C)** and **(D)** represent organizing pericarditis with fibroplasias; **(E)** and **(F)** represent organizing pericarditis demonstrating fibrosis with organizing fibrinous exudate; and **(G)** and **(H)** represent organized fibrous pericarditis showing dense fibrosis with calcification **(asterisk). Third column (1, 3, 5)** are phase sensitive inversion recovery images, and **fourth column (2, 4, 6)** is breath-hold, turbo spin-echo black-blood image. Pericardial delayed hyperenhancement **(arrow)** is represented in **third column, second row, image 1**.

hematoxylin-eosin and Movat pentachrome staining. All specimens from the 25 surgical patients were reviewed by 2 experienced cardiovascular pathologists (C.D.T., E.R.R.). For the purpose of this study, pathological diagnoses were categorized as organizing pericarditis with fibroplasia, organizing pericarditis, and organized fibrous pericarditis. In addition, a more detailed histological assessment included measurement of the maximal thickness (mm) and recording for the presence or absence of granulation tissue, fibrinous exudate, acute inflammation, granulomatous inflammation, hemosiderin deposition, and mesothelial hyperplasia. Calcification and chronic inflammation were semiquantitatively graded on a 4-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Fibroblastic proliferation was semiquantitatively and semiqualitatively graded per 10 high power fields (hpf) as follows: 0 = absent; 1 = few spindly fibroblasts; 2 = many spindly fibroblasts; 3 = many plump reactive fibroblasts. Immunohistochemical staining with CD34 (Cell Marque, Rocklin, California) was performed to better assess the extent of neovascularization, which was assessed as follows: 0 = <5 capillary profiles/hpf; 1 = 5 to 10 capillaries/hpf; 2 = 11 to 20 capillaries/hpf; 3 = >20 capillaries/hpf.

Invasive hemodynamics and echocardiography. Invasive cardiac hemodynamics were obtained by review of the electronic medical record. Continuous variables included right atrial mean pressure (mm Hg), pulmonary capillary wedge pressure (mm Hg), left ventricular end-diastolic pressure (mm Hg), and pulmonary artery mean pressure (mm Hg).

Digitally archived, echocardiographic recordings were sequentially reviewed by a single, experienced cardiologist (A.O.Z.). Categorical variables included pericardial effusion (present or absent), inferior vena cava plethora (defined as >2 cm in diameter) and interventricular diastolic septal bounce. Continuous variables included percentage respiratory change in mitral pulse-wave Doppler early (E) inflow (% from expiration) and septal and lateral annular early (e′) velocities and E/e′.

Statistical analysis. Continuous variables are presented as mean ± SD and as 25th, 50th (median), and 75th percentiles, when the variable is skewed. Comparisons were made using Wilcoxon rank sum tests and Kruskal-Wallis test if more than 2 groups existed. Categorical data are described using frequencies and percentages. Comparisons were made using Fisher exact tests. All analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc., Cary, North Carolina). Uncertainty is expressed by 95% confidence limits. Spearman correlation was used to measure relation of DHE severity quantitated by DHE score and pericardial thickness with histopathologic variables. Agreement between the readers for the segmental pericardial DHE was assessed with Cohen kappa and with Spearman rho for the DHE index. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient characteristics. Of 25 patients who underwent pericardiectomy with pre-operative CMR examination with intravenous Gd contrast (surgical group), pericardial DHE was present in 12 (48%). DHE was absent in 13 CP patients (DHE− group) and in all control patients. Patients were well matched by age: DHE+ (58 ± 18 years), DHE− (60 ± 15 years), control (56 ± 11) ($p > 0.36$) (Table 1). However, there were significantly more women in the control group (8 of 10 [80%]) than in the surgical group (2 of 25 [8%], $p < 0.0001$ for both) and more Caucasians in the surgical group (24 of 25 [92%]) than in the control group (8 of 10 [80%], $p = 0.08$ for both). In addition, more patients in the DHE− group were New York Heart Association functional class III (DHE+: 7 of 12 [58%]; DHE−: 9 of 13 [69%]; control group: 1 of 10 [10%]; $p = 0.0079$). The most common etiology of CP was idiopathic (67% DHE+, 62% DHE−). Four patients (33%) in the DHE+ group and 3 patients (23%) in the DHE− group had undergone prior cardiac surgery (coronary revascularization, valve repair/replacement). Univariate unadjusted comparisons of all surgical patients showed that there were no statistically significant differences in demography and medical history between these 2 groups. Compared with the control group, there was a significantly greater number of patients with prior episodes of clinical pericarditis among the surgical group (15 of 25 [60%] vs. 0 of 10 [0%], $p = 0.005$). Although there was a trend toward greater nonsteriodal anti-inflammatory drug use among DHE+ patients, overall medication use at time of CMR (within 1 week) was not significantly different between groups.

CMR with inter-rater agreement. The median time from pre-operative CMR to surgery in the DHE+ group was 42 days (range 1 to 150 days), and in the DHE− group, it was 27 days (range 2 to 157 days,

Table 1. Patient Characteristics at Baseline

	Surgical Group				
	DHE+ (n = 12)	DHE– (n = 13)	p Value*	Control Group (n = 10)	p Value†
Demographics					
Age, yrs	58 ± 18	60 ± 15	0.74	56 ± 11	0.36
Female sex	2 (17)	0 (0)	0.22	8 (80)	**<0.0001**
Race					
Caucasian	11 (100)	13 (100)	1.0	8 (80)	0.08
African American	0 (0)	0 (0)	1.0	1 (10)	0.29
Other	0 (0)	0 (0)	1.0	1 (10)	0.29
NYHA functional class			0.61		**0.0079**
I	4 (33)	2 (15)		4 (40)	
II	1 (8)	2 (15)		5 (50)	
III	7 (58)	9 (69)		1 (10)	
BNP,‡ 25th/median/75th	148/198/237	96/115/138	**0.0065**	—	—
Comorbidities					
CKD, GFR <60	1 (8.3)	3 (23)	0.59	0 (0)	0.30
History of chest trauma	0 (0)	2 (15)	0.48	0 (0)	>0.9
Prior cardiac surgery	4 (33)	3 (23)	0.67	1 (10)	0.39
Neoplasia	0 (0)	1 (7.7)	>0.9	0 (0)	>0.9
Pericarditis	7 (58)	8 (62)	>0.9	0 (0)	**0.0016**
Immunologic condition	2 (17)	1 (7.7)	0.59	1 (10)	>0.9
MRI outcomes/characteristics					
MRI pericardial effusion	6 (50)	3 (23)	0.23	2 (20)	0.45
MRI pericardial thickness, ≥4 mm	9 (75)	12 (92)	0.32	0 (0)	**<0.0001**
MRI epicardial tethering/diastolic restraint	11 (92)	11 (85)	>0.9	0 (0)	**<0.0001**
MRI septal bounce	12 (100)	13 (100)	1.0	0 (0)	**<0.0001**
MRI tubular ventricle	11 (92)	11 (85)	>0.9	0 (0)	**<0.0001**
CMR IVC size, mm	33 ± 6	31 ± 5	0.48	—	—
CMR LVEF, %	58 ± 8.6	53 ± 6.8	0.15	33 ± 16	**0.0005**
CMR EDV, cc	121 ± 32	142 ± 25	0.19	202 ± 51	**0.0007**
CMR ESV, cc	53 ± 22	67 ± 17	0.07	138 ± 56	**0.0003**
CMR cardiac output, l/min	5.3 ± 1.0	5.3 ± 1.1	>0.9	4.8 ± 1.8	0.44
Medication at time of MRI					
None	4 (33)	6 (46)	0.69	4 (40)	>0.9
ASA	7 (58)	5 (38)	0.43	5 (50)	>0.9
DMARD	1 (8.3)	1 (7.7)	>0.9	0 (0)	>0.9
NSAID	3 (25)	1 (7.7)	0.32	0 (0)	0.30
Steroid	1 (8.3)	2 (15)	>0.9	1 (10)	>0.9

Values are presented as n (%) or mean ± SD unless otherwise indicated. Boldface values are statistically significant, and dashes indicate data are not available. *Comparison between DHE+ group (n = 12) and DHE– group (n = 13). †Comparison between surgical group (n = 25) and nonsurgical group (n = 10). ‡BNP values are missing for 4 patients in the DHE+ group and 6 patients in the DHE– group.

ASA = aspirin; BNP = brain natriuretic peptide; CKD = chronic kidney disease; CMR = cardiac magnetic resonance; DHE+ = with pericardial delayed hyperenhancement; DHE– = without pericardial delayed hyperenhancement; DMARD = disease-modifying antirheumatic drug; EDV = end-diastolic volume; ESV = end-systolic volume; GFR = glomerular filtration rate; IVC = inferior vena cava; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; NYHA = New York Heart Association.

p = 0.4 for both) (Table 2). Pericardial thickness ≥4 mm, epicardial tethering/diastolic restraint, interventricular septal bounce, and tubular-shaped ventricles were more common among surgical patients compared with controls (Table 1). Inferior vena cava size by CMR in DHE+ and DHE– patients was 33 ± 6 and 31 ± 5 (p = 0.48), respectively. None of the patients in the surgical (DHE+ and DHE–) group had concomitant myocardial disease. There was a trend toward more common pericardial effusion among the DHE+ group (6 of 12, 50%) compared with the DHE– group (3 of 13, 23%); however, this did not reach statistical significance (p = 0.23). The left ventricular ejection fraction and cardiac output were both significantly lower, and the end-diastolic and end-systolic volumes were both significantly higher among control patients, as would be expected in this patient popula-

Table 2. Surgical Patient Invasive Hemodynamic Characteristics

	Surgical				
	DHE+ (n = 12)		DHE- (n = 13)		
	n*	Mean ± SD	n*	Mean ± SD	p Value
Interval (catheterization to surgery), months	9	1.1 (0–6.1)	9	3.1 (7 days–15 months)	0.13
RA mean pressure, mm Hg	9	17 ± 4	9	21 ± 3	0.09
PCW mean pressure, mm Hg	8	20 ± 4	9	25 ± 6	0.075
LVED pressure, mm Hg	8	21 ± 4	8	25 ± 5	0.11
PA mean pressure, mm Hg	8	28 ± 5	9	33 ± 7	0.11

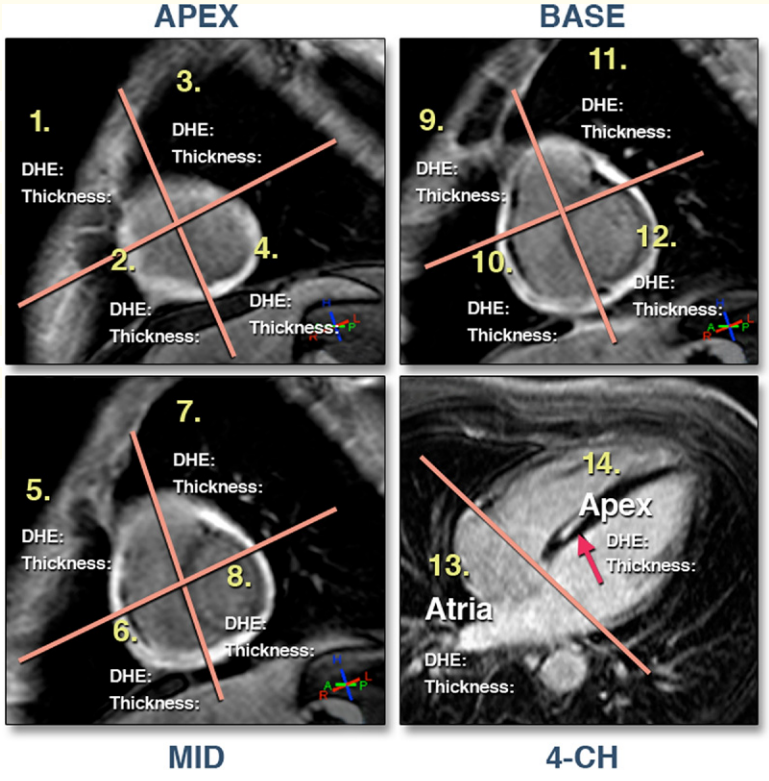
*Data available.
LVED = left ventricular end-diastolic; PA = pulmonary artery; PCW = pulmonary capillary wedge; RA = right atrial; other abbreviations as in Table 1.

tion with predominantly ischemic cardiomyopathy referred for viability assessment.

Segmental CMR analysis showed that for each segment, both blinded readers agreed with the initial reader regarding determined groups (DHE+ and DHE–) (Table 3). Segmental analysis demonstrated no significant difference in the percentage of patients with different pericardial segmental thickness; however, overall, in each segment, the DHE+ group tended to have greater pericardial thickness.

Table 3. Inter-Rater Agreement (Cohen Kappa) Between Reader #1 and Reader #2, by Segment

Segment	Inter-Rater Agreement (Kappa) Overall (n = 35)
1	0.68
2	0.85
3	0.62
4	0.82
5	0.60
6	0.67
7	0.61
8	0.66
9	0.82
10	0.71
11	0.71
12	0.52
13	–0.04
14	0.25
Overall	0.66
Segments 1–12 only	0.69



Inter-rater agreement (Cohen kappa) between Reader #1 and Reader #2, by segment **(left)**. Using a 14-segment model (developed in-house) of the pericardium (right), two experienced, blinded readers rereviewed CMRs and determined presence or absence of DHE in each pericardial segment. Each segment was assessed for DHE and assigned a binary score (0 = DHE–, 1 = DHE+). Total scores for all 14 segments were summed to arrive at total DHE score. In addition, representative pericardial thickness measurements in each segment (categorized as: <2 mm, 2 to <5 mm, 5 to <10 mm, >10 mm) were performed by each reader using corresponding views on T_2-weighed turbo spin-echo images without fat-saturation. Abbreviations as in Table 1.

Of note, compared with the original MRI interpretation, both blinded readers noted a few patients in the DHE− group as having some segments with DHE. Overall, there was moderate inter-rater agreement using Cohen kappa (k = 0.66) (Table 3) between Reader #1 and Reader #2. However, segmental analysis demonstrated a moderate to strong agreement between readers (k = 0.69, range 0.52 to 0.85) when only segments 1 through 12 (short-axis views) were included. DHE score showed a strong agreement between readers (Spearman rho = 0.82, $p < 0.001$).

Surgical pathology. Pathological evaluation of the pericardium in 25 surgical patients revealed organizing pericarditis with fibroplasia being far more common among the DHE+ group (9 of 12 [75%] vs. 2 of 13 [15%], p = 0.005) and organized fibrous pericarditis being the predominant diagnosis among the DHE− group (8 of 13 [62%], p = 0.041) (Table 4). Accordingly, significant neovascularization (>20 capillaries/hpf) was notably more common among patients in the DHE+ group (4 of 12 [33%] vs. 0 of 13 [0%], p = 0.039) (Figs. 1 and 2). There was a trend toward absence of pericardial calcification (9 of 12 [75%] vs. 5 of 13 [38%], p = 0.11) and mild to severe chronic inflammation (moderate: 3 of 12 [25%] vs. 1 of 13 [7.7%], p = 0.32; severe: 3 of 12 [25%] vs. 0 of 13 [0%], p = 0.096) among DHE+ group. No cases were diagnosed as normal pericardium, nor were there cases of neoplastic or infectious etiology. Fibroblastic proliferation and chronic inflammation correlated with DHE quantitated by DHE score (Spearman r = 0.578, $p < 0.05$, and r = 0.590, $p < 0.05$, respectively), but not with pericardial thickness.

Invasive hemodynamics and echocardiography. Invasive hemodynamic data were available in 69% of DHE− patients and 75% of DHE+ patients. There was a trend toward higher right atrial mean pressure, pulmonary capillary wedge mean pressure, and left ventricular end-diastolic and pulmonary artery mean pressure in the DHE+ patient group compared with mean pressures in the DHE− group, though this did not reach statistical significance (Table 2). The average time from catheterization to surgery was 1.1 months (range 0 to 6.1 months) among the DHE+ patient group and 3.1 months (range 7 days to 15 months) among the DHE− patient group.

The DHE+ patients had a significantly higher rate of pericardial effusion on pre-operative transthoracic echocardiography (DHE+: n = 8 [67%]; DHE−: n = 3 [23%], $p < 0.05$). The median time from pre-operative echocardiogram to surgery in the DHE+ group was 13 days (range 2 to 70 days), and in the DHE− group was 10 days (range 2 to 68 days). Percentage respiratory change in pulse-wave Doppler early mitral inflow was increased in DHE+ patients (26 ± 30%) versus DHE− patients (17 ± 17%, p = 0.39). Average inferior vena cava size was increased among nearly all surgical patients (2.58 ± 0.38 cm DHE+ patients; 2.75 ± 0.52 cm DHE− patients, p = 0.42) and interventricular septal bounce was noted frequently (8 of 12 [67%] DHE+ patients; 12 of 13 [92%] DHE− patients, p = 0.11). The average E/e′ was not different between groups. There was no difference in the

Table 4. Histopathologic Difference Between DHE and Non-DHE Surgical Groups

	Surgical		
	DHE+ (n = 12)	DHE− (n = 13)	p Value
Normal	0 (0)	0 (0)	0.011
Organizing pericarditis with fibroplasia	9 (75)	2 (15)	0.0048
Organizing pericarditis	1 (8.3)	3 (23)	0.59
Organized fibrous pericarditis	2 (17)	8 (62)	0.041
Calcification			
Absent	9 (75)	5 (38)	0.11
Mild	1 (8.3)	2 (15)	>0.9
Moderate	0 (0)	1 (7.7)	>0.9
Severe	2 (17)	5 (38)	0.34
Neovascularization			
<5 capillary lumina/hpf	2 (17)	6 (46)	0.20
5 to 10 capillary lumina/hpf	1 (8.3)	3 (23)	0.59
11 to 20 capillary lumina/hpf	5 (42)	4 (31)	0.69
>20 capillary lumina/hpf	4 (33)	0 (0)	0.039
Fibroblasts Movat			
Absent	2 (17)	8 (62)	0.041
Few spindly	1 (8.3)	3 (23)	0.59
Many spindly	3 (25)	2 (15)	0.64
Many plump	6 (50)	0 (0)	0.0052
Chronic inflammation			
Absent	3 (25)	8 (62)	0.11
Mild	3 (25)	4 (31)	>0.9
Moderate	3 (25)	1 (7.7)	0.32
Severe	3 (25)	0 (0)	0.096
Acute inflammation	1 (8.3)	0 (0)	0.48
Granulation tissue	9 (75)	4 (31)	0.047
Fibrinous exudate	7 (58)	4 (31)	0.24
Hemosiderin deposition	6 (50)	2 (15)	0.097
Mesothelial hyperplasia	0 (0)	1 (7.7)	>0.9
Thickness	4.6 ± 1.4	3.1 ± 1.7	0.021

Values are n (%) or mean ± SD.
hpf = high powered field; other abbreviations as in Table 1.

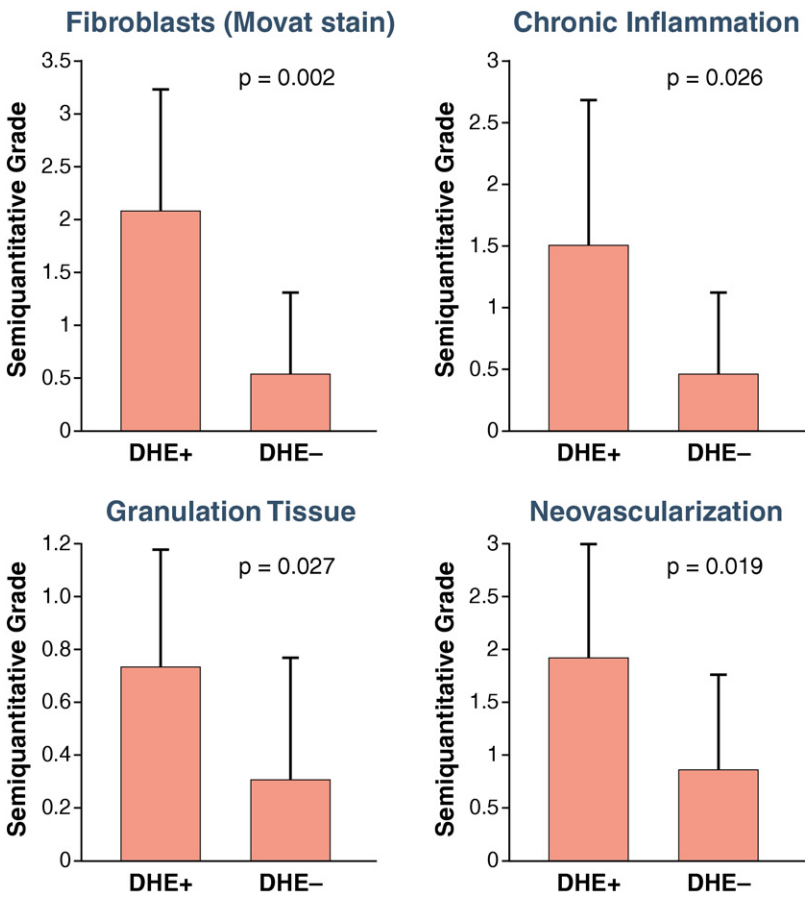


Figure 2. Surgical Pathology Semiquantitative Comparison Between DHE+ and DHE– Groups

Statistically significant increase in fibroblasts, chronic inflammation, neovascularization, and more prominent granulation tissue among patients with pericardial delayed hyperenhancement (DHE+) compared with those without DHE (DHE–).

mean septal E/e′ between the DHE+ and DHE– groups (8 ± 3 vs. 7 ± 3; p = 0.41) and mean lateral E/e′ (8 ± 3 vs. 7 ± 4; p = 0.27).

DISCUSSION

Our study is the largest cohort to date demonstrating that the presence of pericardial DHE on CMR occurs commonly in patients with CP and that presence is associated with histological markers of chronic inflammation and increased neovascularization.

CMR. Segmental analysis demonstrated no significant difference in the percentage of patients with different pericardial segmental thickness; however, overall in each segment, the DHE+ group tended to have greater pericardial thickness, suggesting that, though associated with DHE, increased pericardial thickness is not necessarily confined or localized to any particular segment. Histological findings suggest that the presence of pericardial DHE is an indicator of chronic pericardial inflammation. Additionally, the presence of increased neovascularization and fibroblast proliferation associated with pericardial DHE, as well as the trend toward greater granulation tissue, might provide insight into the etiology of Gd contrast agent accumulation within the pericardium, as both abnormal regional vascular permeability and expanded extracellular space can lead to pericardial DHE.

Common CMR metrics suggesting constrictive physiology, including pericardial thickness (>4 mm), epicardial tethering/diastolic restraint, interventricular septal bounce, and ventricular deformation were all statistically more frequent among surgical patients compared with control patients, which might support their usefulness in identification of patients with CP. However, clinicians and surgeons were not blinded to

this information prior to treatment, and this may alternatively reflect the incorporation of CMR data into clinical management.

Overall, there was moderate inter-rater agreement between readers #1 and #2 (k = 0.66), which improved mildly when only segments 1 through 12 were included (k = 0.69). This finding is likely a reflection of the current subjective nature of diagnosing pericardial DHE. Additionally, with regard to inter-rater agreement on segmental DHE, the moderate agreement noted at the segmental level, but overall strong agreement with DHE score, could be due to different classification of segmental location of DHE between the readers. A quantitative approach toward defining DHE was considered, though ultimately not pursued, as there is insufficient statistical validity to the approach. Specifically, the combination of a relatively thin structure (pericardium) and limited spatial resolution ensures that regions-of-interest drawn will have a small number of pixels, and be affected by volume averaging of edge pixels, thereby diminishing accuracy, particularly in cases of normal to only mildly thickened pericardium.

Surgical pathology. The phenomenon of pericardial DHE seen in patients with pericardial disease with histopathologic correlation has only rarely been described in the medical literature (11–15). Ha et al. (12) reported a case of tuberculous pericarditis in which DHE CMR imaging demonstrated prominent DHE localized at the visceral and parietal pericardium. Subsequent pathology revealed severe inflammation with granuloma and caseous necrosis. Yelgec et al. (11) reported pericardial enhancement in 9 patients among a group of 20 patients examined with CMR, all of whom had clinically suspected acute myocarditis, suggesting that myopericarditis is a common presentation. Whereas 5 patients in their study underwent endomyocardial biopsy, all with normal findings, none of these patients had pericardial tissue obtained for histological assessment. Thus, direct correlation with histology was lacking. Our DHE protocol was directed toward a comprehensive assessment of both myocardium and pericardium on post-contrast DHE images, and we had no cases where there was suspected myopericarditis.

Taylor et al. (13) published the sole case series looking at DHE in patients with possible pericardial disease. In their cohort, 16 patients with clinical suspicion of pericardial disease underwent CMR with DHE imaging, along with a control group of 12 patients with no clinical evidence of pericardial disease. Only 5 of 16 patients (31%) demonstrated pericardial DHE on MRI and were diagnosed with inflammatory pericarditis by 1 of 3 experienced cardiovascular MR imagers who were blinded to the histological findings. Of these 5 patients, histological diagnosis was subsequently reported to be acute bacterial pericarditis in 1, tubercular pericarditis in 2, and chronic inflammatory pericarditis in 2. All 5 patients with DHE were also shown to have thickened pericardial layers (>4 mm). Sensitivity and specificity of 100% for detection of pericardial inflammation using DHE CMR was reported when compared with pericardial histology. In addition, 6 patients with histological diagnosis of chronic fibrosing pericarditis demonstrated evidence of thickened pericardium, but neither DHE nor pericardial effusion were indicated on MRI.

Invasive hemodynamics and echocardiography. Invasive hemodynamics demonstrated that both groups had elevated filling pressures that were not statistically different (Table 2). Further, similar to CMR findings, echocardiography showed evidence of annulus paradoxus (17) with relatively decreased E/e′ and that pericardial effusion was more common among DHE+ patients, which is likely a consequence of increased vascular permeability associated with statistically increased neovascularization in this group.

Study limitations. A primary limitation of our study is the modest number of patients. Selection bias is also a potential. Whereas medication use at the time of MRI was known, use between MRI and surgery is not known and might have had an impact. Additionally, control patients were not matched for sex.

Pericardial enhancement intensity, as analyzed in this investigation, is a subjective metric dependent on several factors including timing of imaging after Gd contrast administration, dose of Gd, inversion time chosen for imaging, and coil separation distance. Magnetic field heterogeneities and incomplete tissue nulling can lead to variation in image interpretation as well. Further, differences in renal function can alter the uptake of Gd contrast agent in the interstitial space and elimination from the intravascular space, both of which will influence the contrast and signal intensity values measured in DHE-CMR.

CMR has excellent spatial resolution; however, measurement of pericardial thickness remains a challenge, given the relatively small dimensions associated with measuring a structure as thin as the pericardium. The slice thickness used might

result in significant volume averaging as well; however, imaging planes were selected such that the pericardium was perpendicular to the plane whenever possible. In the future, higher resolution scans may be advantageous to more accurately assess a structure as thin as the pericardium to limit the potential for partial volume averaging artifacts. Additionally, although our evaluation did not routinely include short tau inversion recovery images, which have been previously reported to demonstrate "edema-weighted" images (18), routine use of this imaging modality in the future might be useful during evaluation for pericardial inflammation. Nonetheless, despite several technical challenges, inter-rater agreement was moderate in this study for pericardial DHE and thickness measurements.

Lastly, although pericardial segmentation for purposes of our analysis was standardized, we were unable to directly correlate imaging segmentation to the precise locations of surgical specimens in this analysis.

Clinical implications. Constrictive pericarditis remains a challenging diagnosis for the clinician. Through the implementation of CMR, and specifically DHE imaging, we are now better able to delineate the histopathology associated with this not uncommon CMR finding in patients with CP. Whereas this investigation is hypothesis generating, it also may help to provide insight into the medical and surgical management of this difficult patient population. Further, the correlation between DHE and histopathologic inflammation demonstrated in our study might prove useful in the management of patients with symptomatic inflammatory pericarditis (19,20). Studies evaluating interleukin-1 receptor antagonist, tumor necrosis factor receptor, matrix metalloproteinase activation, transforming growth factor beta, and possibly direct intrapericardial steroid deposition might help elucidate the role that termination of the inflammatory response has on patient outcomes with constrictive pericarditis. In the future, trials evaluating the interval change in pericardial DHE among patients with recurrent or transient CP with correlation to clinical symptoms might better elucidate the precise timing of changes in medication dosing.

CONCLUSIONS

The presence of pericardial DHE on CMR is common in patients with CP. Our data suggest that pericardial DHE is correlated with greater fibroblastic proliferation, chronic inflammation, and neovascularization, which is indicative of an ongoing, dynamic active inflammatory reaction. Patients with CP without pericardial DHE had more pericardial fibrosis and calcification, and lesser degrees of pericardial thickening. Further, progressively more chronic forms of organized fibrous pericarditis, though statistically more common among patients without pericardial DHE, were not unique to this patient population. This finding reflects that pericardial inflammation is a dynamic process and might be a target for focused pharmacological interventions. Additionally, although ours is a proof-of-concept study, larger, prospective studies, potentially incorporating T_2-weighted spin-echo imaging sequences with fat-saturation and serum markers of inflammation (ultrasensitive C-reactive protein, Westergren sedimentation rate) are necessary to confirm and expand the current study findings.

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REFERENCES

1. Troughton RW, Asher CR, Klein AL. Pericarditis. Lancet 2004;363:717–27.
2. Schwefer M, Aschenbach R, Heidemann J, Mey C, Lapp H. Constrictive pericarditis, still a diagnostic challenge: comprehensive review of clinical management. Eur J Cardiothorac Surg 2009;36:502–10.
3. Stein EG, Haramati LB, Bellin E, et al. Radiation exposure from medical imaging in patients with chronic and recurrent conditions. J Am Coll Radiol 2010;7:351–9.
4. Choi KM, Kim RJ, Gubernikoff G, Vargas JD, Parker M, Judd RM. Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. Circulation 2001;104:1101–7.
5. Ishida M, Kato S, Sakuma H. Cardiac MRI in ischemic heart disease. Circ J 2009;73:1577–88.
6. Kwon DH, Halley CM, Carrigan TP, et al. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study. J Am Coll Cardiol Img 2009;2:34–44.
7. Cheong BY, Muthupillai R, Wilson JM, et al. Prognostic significance of delayed-enhancement magnetic resonance imaging: survival of 857 patients with and without left ventricular dysfunction. Circulation 2009;120:2069–76.
8. Rubinshtein R, Glockner JF, Ommen SR, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail 2010;3:51–8.

9. Vohringer M, Mahrholdt H, Yilmaz A, Sechtem U. Significance of late gadolinium enhancement in cardiovascular magnetic resonance imaging (CMR). Herz 2007;32:129–37.
10. Hombach V, Merkle N, Torzewski J, et al. Electrocardiographic and cardiac magnetic resonance imaging parameters as predictors of a worse outcome in patients with idiopathic dilated cardiomyopathy. Eur Heart J 2009;30: 2011–8.
11. Yelgec NS, Dymarkowski S, Ganame J, Bogaert J. Value of MRI in patients with a clinical suspicion of acute myocarditis. Eur Radiol 2007; 17:2211–7.
12. Ha JW, Ko YG, Choi BW. Images in cardiology. Delayed hyperenhancement of the pericardium by magnetic resonance imaging as a marker of pericardial inflammation in a patient with tuberculous effusive constrictive pericarditis. Heart 2006; 92:494.
13. Taylor AM, Dymarkowski S, Verbeken EK, Bogaert J. Detection of pericardial inflammation with late-enhancement cardiac magnetic resonance imaging: initial results. Eur Radiol 2006;16:569–74.
14. Dawson D, Rubens M, Mohiaddin R. Comtemporary imaging of the pericardium. J Am Coll Cardiol Img 2011;4: 680–4.
15. Miller CA, Dormand H, Clark D, Jones M, Bishop P, Schmitt M. Comprehensive characterization of constrictive pericarditis using multiparametric CMR. J Am Coll Cardiol Img 2011;4:917–20.
16. Sa MI, Kiesewetter CH, Jagathesan R, Prasad SK. Images in cardiovascular medicine. Acute pericarditis assessed with magnetic resonance imaging: a new approach. Circulation 2009;119:e183–6.
17. Ha JW, Oh JK, Ling LH, Nishimura RA, Seward JB, Tajik AJ. Annulus paradoxus: transmitral flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. Circulation 2001;104:976–8.
18. Flamm SD, White RD, Hoffman GS. The clinical application of "edema-weighted" magnetic resonance imaging in the assessment of Takayasu's arteritis. Int J Cardiol 1998; 66 Suppl 1:S151–9.
19. Zurick AO 3rd, Klein AL. Effusive-constrictive pericarditis. J Am Coll Cardiol 2010;56:86.
20. Verhaert D, Gabriel RS, Johnston D, Lytle BW, Desai MY, Klein AL. The role of multimodality imaging in the management of pericardial disease. Circ Cardiovasc Imaging 2010;3: 333–43.

Key Words: cardiac magnetic resonance imaging ■ delayed hyperenhancement ■ pericardial disease ■ pericardiectomy.

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