Constrictive Pericarditis Versus Restrictive Cardiomyopathy?

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ABSTRACT

About one-half of the patients with congestive heart failure have preserved left ventricular ejection fraction (HFpEF). Although the etiology of HFpEF is most commonly related to long-standing hypertension and atherosclerosis, a significant number of suspected HFpEF patients have a restrictive cardiomyopathy or chronic pericardial disease. Recognizing these syndromes is important because early diagnosis may lead to instituting specific therapy that may prolong survival, improve quality of life, and/or recognize and treat an underlying systemic disorder. Advances in diagnostic imaging, biomarkers, and genetic testing today allow identification of the specific etiology in most cases. Novel pharmacological, immunologic, and surgical therapies are leading to improved quality of life and survival. (J Am Coll Cardiol 2016;67:2061–76) © 2016 by the American College of Cardiology Foundation.

Approximately one-half of all patients with heart failure (HF) have preserved ejection fraction (HFpEF) (1). Whereas hypertension, coronary artery disease, and/or abnormal vascular compliance are identified as the cause in most patients with HFpEF (2), as many as 10% to 15% have a restrictive cardiomyopathy, a group of conditions with diverse etiologies characterized by intrinsic abnormalities of the myocyte and/or the intercellular matrix that result in impaired left ventricular (LV) relaxation and/or increased LV stiffness (3). The differential diagnosis of the restrictive cardiomyopathies includes constrictive pericarditis, a syndrome that has a similar insidious clinical presentation and shares many common features in diagnostic imaging tests (4). Patients with restrictive cardiomyopathies and constrictive pericarditis are often excluded or under-represented in large randomized clinical trials (2,5,6), making it difficult to make inferences from the prognostic and treatment features that apply to other HFpEF patients. Untreated, patients with restrictive cardiomyopathies have, in general, poor outcomes (7). However, early diagnosis can lead to improved symptoms, prevent end-organ damage, and improve survival. Table 1 summarizes general and specific diagnostic features of these syndromes.

RESTRICTIVE CARDIOMYOPATHIES

The restrictive cardiomyopathies have been traditionally classified as primary or secondary to other diseases, such as storage or infiltrative disorders (3). The definition of restrictive cardiomyopathies is on the basis of anatomic, histological, and physiological criteria, namely the presence of abnormal LV diastolic filling associated with intracellular or interstitial infiltration and/or fibrosis in the absence of LV dilation. Many infiltrative myocardial disorders (e.g., hemochromatosis) may manifest as either restrictive or dilated cardiomyopathy. Others, such as cardiac sarcoidosis, present almost exclusively with a dilated phenotype, whereas some forms of hypertrophic cardiomyopathy present with a restrictive phenotype (8). This review is limited to only those conditions that may present with a restrictive phenotype.

COMMON FEATURES. Patients with restrictive cardiomyopathy typically exhibit HF symptoms, such as dyspnea and fatigue. Findings on physical
examination include elevated jugular venous pressure, presence of a third or fourth heart sound, pulmonary rales, ascites, and peripheral edema. Atrial fibrillation and electrocardiographic (ECG) conduction abnormalities are common.

Patients with restrictive cardiomyopathies have normal or increased LV wall thickness and normal or reduced LV cavity size. Impaired LV relaxation may be detected by Doppler echocardiography before the onset of symptoms. Decreased LV chamber compliance is often a late manifestation (9). The resulting steep increase in LV pressure with small changes in LV volume causes a chronic increase in diastolic filling pressures that leads to atrial enlargement. The Central Illustration compares the morphological and hemodynamic features of normal, restrictive, and constrictive hearts.

Echocardiography and cardiac magnetic resonance (CMR) imaging detect the typical, albeit nonspecific morphological alterations that characterize the restrictive cardiomyopathies. LV ejection fraction is usually preserved, but may be decreased in advanced stages. Left and right ventricular (RV) wall thickness is normal or mildly increased in primary restrictive cardiomyopathy, but more commonly increased in the secondary forms. Severe atrial enlargement is a classic, albeit nonspecific feature. Advanced impairment of LV diastolic filling is invariably present. On echocardiography studies, tissue Doppler typically demonstrates reduced early diastolic myocardial velocity (e'). LV filling pulsed Doppler may show impaired relaxation (E/A ratio <1), pseudonormalization, or a restrictive filling pattern (short E deceleration time), which correlate with stage of progression, symptoms, and prognosis. B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide are typically elevated in patients with HF secondary to restrictive cardiomyopathy. Table 2 summarizes general and specific treatments for restrictive cardiomyopathies.

**PRIMARY RESTRICTIVE CARDIOMYOPATHY.** Primary (idiopathic) restrictive cardiomyopathy is a rare condition that may present in both children and adults (10,11). Increased myofilament sensitivity to calcium, as well as increased accumulation of desmin and collagen type III, has been implicated in the pathophysiology of this condition (12-15). Both familial and sporadic cases have been described (16,17). Familial cases are usually characterized by autosomal dominant inheritance with incomplete penetrance. Mutations in genes encoding the sarcomeric proteins troponin I, troponin T, alpha cardiac actin, and beta-myosin heavy chain, which are similar to those associated with hypertrophic cardiomyopathy, are implicated (18,19). Skeletal myopathy may also be present. Heart transplantation is an effective therapy for patients with end-stage primary restrictive cardiomyopathy (20,21), but is contraindicated in the presence of severe pulmonary hypertension, which is commonly present in this condition.

**SECONDARY RESTRICTIVE CARDIOMYOPATHIES.** Secondary restrictive cardiomyopathies are subclassified as infiltrative, noninfiltrative, and storage disorders. In infiltrative disorders, abnormal deposits occur in the interstitial space, whereas in storage disorders, deposits occur within the cell.

**Endomyocardial fibrosis (EMF).** EMF is probably the most common cause of restrictive cardiomyopathy, affecting an estimated 12 million people worldwide (22). EMF is endemic in tropical and subtropical Africa, Asia, and South America, but is also occasionally encountered outside the tropics (23-25). Parasitic infections, autoimmune disorders, and hematologic malignancies lead to an initial, acute inflammatory phase with fever and pancarditis, frequently associated with eosinophilia, facial and periorbital swelling, and urticaria, also known as Loeffler endocarditis (26,27). This is followed by an intermediate phase associated with LV and RV thrombus formation. The final stage occurs months to years later with endocardial fibrosis. Mitral and tricuspid regurgitation are common due to tethering of the leaflets. Echocardiography may show endomyocardial thickening, ventricular apical obliteration, and involvement of the posterior mitral leaflet (28). CMR often provides additional diagnostic information due to its ability to detect subendocardial fibrosis and its greater sensitivity for ventricular thrombus detection (Figure 1) (29,30).

**Cardiac amyloidosis.** Cardiac amyloidosis is an infiltrative disorder caused by deposition of insoluble fibrillar protein in the interstitial space, which classically displays as apple-green birefringence under polarized light microscopy with Congo Red staining (31). It typically presents as a systemic disorder, with infiltration also occurring in the liver, kidney, bowel, nerves, skin, and tongue. Five major clinical types of cardiac amyloidosis are recognized, each associated with a different precursor protein. Primary or systemic amyloid light-chain (AL) amyloidosis is the most common form of amyloidosis and is associated with monoclonal gammapathy of undetermined significance or plasma cell dyscrasias, such as multiple

**ABBREVIATIONS AND ACRONYMS**

AL = amyloid light-chain
CMR = cardiac magnetic resonance
CT = computed tomography
E = pulsed Doppler early left ventricular filling velocity
e' = tissue Doppler early myocardial velocity
ECG = electrocardiographic/electrocardiogram
EMF = endomyocardial fibrosis
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
LV = left ventricle/ventricular
LVH = left ventricular hypertrophy
m-TTR = mutant transthyretin
RV = right ventricle/ventricular
SCD = sudden cardiac death
wt-TTR = wild-type transthyretin
### TABLE 1 Diagnostic Features of Restrictive Cardiomyopathies and Constrictive Pericarditis

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*Highly sensitive findings with low specificity. †Highly specific findings with low sensitivity. ‡Findings that are both highly sensitive and specific.

CMR = cardiac magnetic resonance; CPK = creatine phosphokinase; CT = computed tomography; e′ = tissue Doppler early myocardial velocity; ECG = electrocardiogram; Echo = echocardiography; EMF = endomyocardial fibrosis; H/O = history of; LV = left ventricle/ventricular; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; PRKAG2 = protein kinase AMP-activated noncatalytic subunit gamma 2; RCM = restrictive cardiomyopathy.
Normal (A), restrictive (B), and constrictive (C) hearts. In both restriction and constriction, LV chamber compliance is reduced. LV relaxation, seen as the rate of LV pressure decay in early diastole, is abnormal only in restriction. LA = left atrial; LV = left ventricular.
myeloma. Cardiac involvement is associated with a poor prognosis, with a median survival from diagnosis of 1 year (32).

Wild-type transthyretin (wt-TTR) amyloidosis (previously referred to as senile amyloidosis) is seen in 25% to 36% of patients above 80 years of age (33,34) and is caused by the interstitial deposition of normal, wt-TTR. The prognosis is better than with primary amyloidosis, with a median survival of 6 years (35). Cardiac involvement is rare in amyloid A amyloidosis, seen in chronic inflammatory conditions, such as rheumatoid arthritis (36). Mutant TTR amyloidosis (m-TTR) is a systemic autosomal dominant disorder due to tissue deposition of various proteins, including TTR and apolipoproteins A-I and A-II (37), and is often associated with peripheral or autonomic neuropathy. The most common mutation (Val122Ile) associated with m-TTR is present in 3% to 4% of African Americans, who often have the disease misdiagnosed as hypertensive cardiomyopathy (38). The clinical presentation of m-TTR varies according to the specific associated mutation. As of today, more than 80 mutations have been described. Cardiac involvement leading to HF is common, but is less aggressive than in AL amyloidosis. A comprehensive review of TTR amyloidosis was recently published in the Journal (39).

Cardiac amyloid deposition also occurs in isolated atrial and dialysis-related (β2 microglobulin) amyloidosis. HF is uncommon, although isolated atrial amyloidosis is associated with development of atrial fibrillation (40). About 90% of patients with primary amyloidosis have a monoclonal gammopathy. Troponin may also be increased, and elevated serum levels of troponin and B-type natriuretic peptide are associated with a worse prognosis (41).

An ECG finding of low voltage in a HFP EF patient with increased LV wall thickness by echocardiography should raise the suspicion of cardiac amyloidosis. However, low voltage and a pseudoinfarct pattern are detected in <50% of patients with biopsy-proven cardiac involvement (42). Echocardiography commonly demonstrates increased thickening of the ventricular wall, mitral and tricuspid leaflets, and interatrial septum. Nevertheless, LV

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AA = amyloid A; AL = amyloid light-chain; ICD = implantable cardioverter-defibrillator; m-TTR = mutant transthyretin; wt-TTR = wild-type transthyretin; other abbreviations as in Table 1.

**FIGURE 1** CMR Obtained in a Patient With HFP EF Secondary to EMF

On standard cine sequences (A), a large mass is seen in the basal posterolateral wall of the LV, involving the mitral valve apparatus. After gadolinium contrast injection (B), a thin area of endocardial late enhancement is evident between the normal myocardium and the amorphous, avascular mass composed by thrombus and necrotic material. CMR = cardiac magnetic resonance; EMF = endomyocardial fibrosis; HFP EF = heart failure with preserved ejection fraction; LV = left ventricle.
wall thickness may be normal in 5% of patients with histologically confirmed cardiac involvement (43). LV wall thickness (≥15 mm) (44), restrictive filling on Doppler echocardiography with an early mitral inflow (E) deceleration time <150 ms (45), and reduced LV ejection fraction have been associated with poor prognosis. More recently, decreased global longitudinal strain has also been shown to be a strong predictor of reduced survival (46,47). CMR is very useful to establish the presence and determine the severity of amyloid infiltration. Cardiac amyloidosis is associated with short subendocardial T1 times and a distinctive pattern of diffuse, predominantly subendocardial and mid-myocardial delayed gadolinium late enhancement (Figure 2) (48). The radiotracer 99mTc-pyrophosphate localizes to TTR cardiac amyloid deposits and can distinguish between the AL and wt-TTR types (50). However, the sensitivity is much lower for detecting m-TTR amyloid. A positive noncardiac biopsy supports the diagnosis of cardiac amyloidosis if cardiac imaging diagnostic criteria are present. Direct endomyocardial biopsy can achieve nearly 100% sensitivity if a minimum of 4 samples are obtained during the biopsy procedure (51). Immunohistochemical staining using specific antibodies can discriminate between the different types of amyloidosis (52). Mass spectrometry is superior to immunohistochemistry in identifying amyloid type, with sensitivity and specificity more than 98% (53).

Rectal biopsy has been largely replaced by abdominal fat aspiration, which carries a lower risk of serious complications and appears more sensitive (84% to 88%) for AL and wt-TTR types (50). However, the sensitivity is much lower for detecting m-TTR amyloid. The primary goal of treatment in cardiac amyloidosis remains relief of symptoms. Diuretic therapy relieves congestion, but needs to be monitored closely due to the risk of hypotension and renal failure. Parasternal long-axis (A), short-axis (B), and 4-chamber (C) views. The CMR obtained in the same patient (D) shows diffuse subendocardial and atrial late enhancement. AL = amyloid light-chain; LA = left atrial; LV = left ventricular.
Digoxin and calcium channel blockers are contraindicated due to the high risk of heart block (54,55). Beta-blockers and angiotensin-converting enzyme inhibitors are poorly tolerated. Chemotherapy and stem cell transplantation for AL amyloid may prolong survival and increase quality of life if started early. Stem cell transplantation has shown some promise for treatment of primary amyloidosis. However, compared with other hematologic malignancies, the early post-procedural mortality is significantly higher in patients with amyloidosis (56,57). Bortezomib-based regimens have shown near complete remission of plasma cell dyscrasias and are now considered to be the preferred treatment option (58). Clinical trials of several drugs that seek to reduce amyloid protein production in m-TTR are currently in progress (59). Recent data support the benefit of implantable cardioverter-defibrillators for primary prevention of sudden cardiac death (SCD) (60). Cardiac transplantation may be effective in patients with m-TTR amyloid if there is limited hepatic and nerve involvement. Liver and combined liver-cardiac transplantation may improve survival in these patients when there is significant liver involvement. Drug-induced restrictive cardiomyopathy. Drug-induced restrictive cardiomyopathy is a rare disorder that has been described with the long-term use of the antimalarial medications chloroquine and hydroxychloroquine. Endomyocardial biopsy shows disruption of normal muscle fiber architecture, with loss of z-lines and myosin filaments, and abundant curvilinear bodies, lysosomes, myeloid bodies, and glycogen granules located between myofibrils and perinuclear areas (61). Conduction abnormalities and valvular thickening are common findings. Echocardiography demonstrates increased wall thickening and restrictive LV filling that may improve after cessation of therapy (62). Post-radiation heart disease. Post-radiation heart disease is a noninfiltrative disorder that occurs as a result of endothelial cell damage and subsequent microvascular dysfunction due to fibrosis. In the ventricular tissue of irradiated hearts, there is a significant increase in total tissue collagen concentration (63), leading to decreased distensibility. Radiation affects all tissues, including the coronary vessels, heart valves, and pericardium (Figure 3). Echocardiographic findings typically demonstrate normal LV wall thickness, abnormal LV filling, valvular calcification, and, in many patients, features of pericardial constriction (64). Glycogen storage disorders. Glycogen storage disorders, including Anderson-Fabry disease, Pompe disease, Danon disease (lysosome-associated membrane protein 2 [LAMP2]), and protein kinase AMP-activated noncatalytic subunit gamma 2 (PRKAG2)-deficient cardiomyopathy, are systemic diseases associated with variable degrees of cardiac involvement. The ECG and echocardiographic features are similar to those seen in hypertrophic cardiomyopathy (65,66). Anderson-Fabry disease is the most common glycogen storage disorder, affecting approximately 1 in 50,000 people. It is an X-linked recessive disorder that results in reduced or absent activity of alpha-galactosidase and progressive lysosomal accumulation of glycosphingolipids in kidneys, nerves, and cardiac tissue. The disease presents during childhood or adulthood with varying degrees of mental retardation, proteinuria, and/or unexplained left ventricular hypertrophy (LVH) and HFpEF (67). Other glycogen...
Storage disorders are also associated with skeletal myopathy and elevation of skeletal muscle enzymes (65,66). ECG changes associated with Anderson-Fabry disease include a short PR interval (<0.12 ms), widened QRS interval with right bundle branch block pattern, LVH, and giant negative T waves (68,69). Ventricular pre-excitation and Wolff-Parkinson-White syndrome are common in patients with Danon disease and PRKAG2-deficient cardiomyopathy (65). In patients with Anderson-Fabry disease, tissue Doppler echocardiography shows a decrease in systolic and diastolic myocardial velocities, even before development of LVH (70). CMR may show a mid-myocardial pattern of late enhancement of the basal inferolateral wall, or a more diffuse pattern in patients with severe LVH (71). Anderson-Fabry disease was also reported to be associated with a prolonged myocardial T2 relaxation time (72). Nevertheless, none of these findings are sufficiently sensitive or specific. Demonstration of decreased or absent levels of serum α-galactosidase is required to establish the diagnosis. Endomyocardial biopsy reveals concentric lamellar bodies in the sarcoplasm of myocardial cells on electron microscopy (72). Cardiac biopsy in Danon disease and PRKAG2-deficient cardiomyopathy shows the characteristic histological changes of myocyte enlargement with pronounced vacuole formation within the cells (65,74). Enzyme replacement therapy with agalsidase beta in patients with Fabry disease reduces globothriaosylceramide levels in infiltrated tissues throughout the body (75). Enzyme replacement therapy with agalsidase beta has been reported to decrease LV wall thickness, decrease LV mass, and result in improved LV systolic and diastolic function (76–79). The use of this drug is restricted by its limited availability and elevated cost.

**Hemochromatosis.** Hemochromatosis is a storage disorder that results from increased iron deposition in the sarcoplasmic reticulum of cells in a variety of organs, including the liver, pancreas, heart, and gonads. Primary, or hereditary, hemochromatosis is a relatively common autosomal recessive disorder, affecting up to 0.8% of Caucasians, and results in increased intestinal absorption of iron (80). Secondary hemochromatosis results from receiving multiple blood transfusions in conditions where there is ineffective erythropoiesis, such as thalassemia major, sideroblastic anemia, and myelodysplastic syndrome. Approximately 15% of patients with hemochromatosis present with cardiac symptoms (81). Early in the course of the disease, iron overload may cause diastolic dysfunction, including restrictive physiology (82). Most patients with clinical HF, however, exhibit a dilated cardiomyopathy phenotype. Cardiac involvement may result in supraventricular arrhythmias, such as atrial fibrillation (83). CMR has high accuracy in the diagnosis of myocardial iron overload. Myocardial iron deposition results in lower T2 times, with decreased myocardial signals on T2-weighted images (Figure 4) (84). A T2* time <20 ms has been associated with reduced LV function (85). CMR is superior to serum ferritin levels for determination of the extent of cardiac involvement. In addition, serial assessment of T2* times may be used to evaluate the response to

![Figure 4 CMR T2-Weighted Images Obtained From a Normal Subject and a Patient With Hemochromatosis](image-url)
therapy (86). Cardiac biopsy shows abnormal deposits of granular, yellow-gray material within the sarcoplasm of the myocytes under light microscopy and Prussian blue stains positive for iron, which is diagnostic of iron overload (87). Phlebotomy is the first-line treatment for primary hemochromatosis. In patients who are anemic, iron chelation therapy with either deferoxamine, deferasirox, or deferiprone is the treatment of choice. Cardiac transplantation in patients who have advanced HF refractory to medical therapy has been reported to achieve a 10-year survival of 40% (88).

**Friedreich’s ataxia.** Friedreich’s ataxia is an autosomal recessive neurodegenerative disorder caused
by a mutation of the frataxin gene that manifests in the second to third decade of life with diabetes mellitus, ataxia, and HF (89). The disease is almost exclusively seen in Caucasians, with an estimated prevalence of 1 in 50,000. Ventricular arrhythmias and SCD are common. Early in the course of the disease, ECG and echocardiographic findings resemble those of hypertrophic cardiomyopathy, including symmetric LV hypertrophy, abnormal myocardial relaxation, and LV outflow obstruction (90). CMR shows nonspecific patchy late enhancement, which correlates with the extent of cardiac fibrosis. Over time, the restrictive phenotype evolves into a dilated phenotype. Myocardial biopsy shows enlarged cardiomyocytes with iron-reactive inclusions surrounded by increased interstitial fibrosis and reduced frataxin (91). There is no specific treatment for this condition other than standard HF drugs. Implantable cardioverter-defibrillators are used for prevention of SCD, but a survival benefit has not been demonstrated. A proposed algorithm to identify the probable etiology of HFP EF is shown in Figure 5.

**CONstrictive pericarditis.** This syndrome often presents as long-term sequelae of acute and chronic pericarditis and post-pericardiotomy, although an identifiable cause is not found in a significant proportion of cases (92). Tuberculous pericarditis is relatively common in Africa and in Latin American countries. The clinical presentation of constrictive pericarditis may be acute, subacute, or chronic and insidious, with typical symptoms of exertional dyspnea, fatigue, lower extremity edema, or abdominal distension (4), or with atypical presentation masquerading as primary liver disease. Physical findings may vary, including manifestations of predominantly right HF with elevated jugular venous distension and a prominent “x” and rapid “y” descent, hepatomegaly and splenomegaly, ascites, and edema (93). Kussmaul’s sign, described as a failure to decrease or a paradoxical increase in jugular venous pressure during inspiration, is relatively specific when present. Heart sounds may be reduced. When present, a pericardial knock occurring at the trough of the y descent in early diastole is often confused with an S3 (94). Bibasilar rales and dullness more commonly represent pleural effusions than lung edema, because right HF is predominant. Pulsus paradoxus is rare and usually indicates effusive-constrictive disease.

The ECG is more often normal, but may show low QRS voltage, nonspecific ST-segment changes, biatrial enlargement, sinus tachycardia, or atrial fibrillation. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide levels are normal or mildly elevated (95). Chest x-ray in patients with constrictive pericarditis may show pleural effusions without significant alveolar edema and biatrial enlargement. LV and RV and pulmonary vessels are normal in size. Pericardial calcifications are rare, occurring in 20% to 40% of constrictive cases and, more commonly, in tuberculous pericarditis (96,97).
Sodium restriction and diuretic agents are useful to reduce edema and hepatic congestion in patients with mild pericardial constriction (98), although pericardiectomy may eventually be required to normalize cardiac output (92,99–102). Pericardiectomy can be performed with low mortality and result in significant improvement in survival and quality of life. Failure to improve or recurrence of symptoms is often due to incomplete pericardiectomy, thus warranting referral to experienced cardiac surgeons. Long-term outcomes depend on the etiology, with worse outcomes seen in patients post-irradiation because they often have concomitant myocardial, coronary, and valvular injury. Transient constrictive pericarditis due to post-pericardiectomy syndrome, tuberculous, or viral pericarditis may respond to anti-inflammatory therapy (103). A recent study reported that response to anti-inflammatory therapy is more likely to occur in patients with evidence of significant pericardial late enhancement and increased C-reactive protein and erythrosedimentation rate (104). The relative utility of contrast CMR or positron emission tomography with 18F-fluorodeoxyglucose versus serum biomarkers of inflammation in guiding therapy, however, remains to be determined.

It is important to recognize the less common effusive-constrictive pericarditis syndrome. About 10% of patients who are initially recognized as having cardiac tamponade present with signs and symptoms of constriction following pericardiocentesis (105). The causes of effusive-constrictive pericarditis are similar to those of typical constriction, although patients with this syndrome may have a more acute presentation and are more likely to respond to anti-inflammatory therapy.

**DIFFERENTIATING CONSTRINGTION FROM RESTRICTION**

Even though the clinical presentation of constrictive pericarditis and restrictive cardiomyopathies is
similar, their pathophysiological and hemodynamic alterations differ. Both conditions may have reduced LV chamber compliance. In restrictive cardiomyopathy, reduced compliance is caused by abnormal elastic properties of the myocardium and/or intercellular matrix, whereas in constrictive pericarditis, reduced chamber compliance is imposed by the external pericardial constraint. Myocardial relaxation is impaired in restrictive cardiomyopathies, but is typically normal in constrictive pericarditis (106–108).

As a result of pericardial encasement, patients with constrictive pericarditis exhibit exaggerated interventricular dependence and dissociation between intracardiac and intrathoracic pressures during respiration (Figure 6). Echocardiography, CMR, and/or invasive catheterization can assess these pathophysiological changes (109,110). With inspiration, lower intrathoracic pressure is transmitted to the pulmonary veins, but not to the encased left atrium, therefore reducing the pressure gradient and venous return to the left heart. As the intracardiac volume is fixed by the encased pericardium, venous return increases to the right heart through the inferior vena cava because this vessel enters the right atrium directly from the abdomen and is not exposed to the intrathoracic pressure changes. Decreased venous return from the superior vena cava, which is exposed, is the hemodynamic alteration that produces Kussmaul’s sign (111).

Echocardiography may detect the presence of a thickened (>4 mm) pericardium, but is less useful than computed tomography (CT) and CMR to define the pericardial anatomy. Moreover, up to 20% of constrictive pericarditis cases occur with normal pericardial wall thickness (112). Doppler echocardiography is very useful for evaluating the altered physiology. The presence of atrial dilation with normal ventricular chambers and a dilated inferior vena cava and hepatic veins, although nonspecific, support the diagnosis of constrictive pericarditis. The most specific sign of constrictive pericarditis by 2-dimensional imaging is
shifting of the septum during the respiratory cycle, caused by the variability in venous return and exaggerated interventricular dependence (113). The Doppler examination, utilizing mitral and tricuspid inflow, hepatic vein flow, and tissue Doppler are fundamental (Figure 7) (110,114–116). In both constrictive pericarditis and in advanced restrictive cardiomyopathy, the deceleration time of the LV early filling pulsed Doppler is short, consistent with a restrictive filling pattern. However, significant respiratory variation of mitral, tricuspid, pulmonary, and hepatic flows occurs only with constriction. The magnitude of their variability will depend, however, on the severity of constriction, the volume status of the patient, and the inspiratory effort during the study acquisition. A normal tissue Doppler e’ velocity (>8 cm/s) indicates normal LV relaxation and virtually excludes restrictive cardiomyopathy (106,108). In constrictive pericarditis, e’ is invariably increased and, unlike normal subjects, patients with constriction have septal >lateral wall e’ (117). Invasive hemodynamic evaluation of patients with suspected constrictive pericarditis and inconclusive noninvasive test results may be required in a small proportion of patients. Criteria for the diagnosis of constriction and differentiation from restriction include equalization of diastolic RV and LV pressure, and absence of elevated RV systolic pressure (118). In addition, during respiration, changes in LV and RV systolic pressure are discordant. Contrast-enhanced cardiac CT can identify pericardial thickening with or without calcifications in the appropriate clinical scenario. Cardiac CT is also a useful tool for defining the location and extent of the focal thickening and pericardial calcification in the pre-surgical planning stages. ECG-gated cine images can demonstrate a septal bounce (119,120), although unlike echocardiography and CMR, cardiac CT is acquired over 1 to 4 cardiac cycles and cannot be used to evaluate respiratory-induced changes. In contrast to CT, even significant foci of calcification can be missed on CMR. However, CMR has superior ability to evaluate pericardial distensibility (119). Real-time low-resolution cine sequences during free breathing can demonstrate ventricular interdependence (Figure 8) (121). Pericardial late enhancement may be seen in the presence of inflammation or extensive fibrosis (Figure 9).

Despite clinical, noninvasive, and hemodynamic assessment, the differentiation of restrictive cardiomyopathy from constrictive pericarditis remains difficult in a small subset of patients that present with mixed constrictive/restrictive physiology. This condition is more frequently encountered in patients with radiation heart disease. Endomyocardial biopsy may be useful to avoid unnecessary thoracotomy in patients with significant myocardial involvement who may not respond to pericardectomy (122).

**FIGURE 9 CMR Images Demonstrating Late Enhancement of the Pericardium in a Patient With Constriction**

(A) Short axis and (B) 4-chamber views. CMR = cardiac magnetic resonance.
REFERENCES


KEY WORDS amyloidosis, echocardiography, endomyocardial fibrosis, heart failure, magnetic resonance imaging