Constrictive pericarditis as late complication of cryoballoon pulmonary vein isolation

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Introduction

Constrictive pericarditis (CP) is a rare cause of heart failure and is characterized by impaired chamber filling owing to a fibrotic pericardium encasing the heart. The diagnosis is often challenged by nonspecific symptoms, discrepant investigation results, and a low level of suspicion. Nevertheless, timely recognition remains crucial, as it is a potentially curable condition. We present the intriguing case of a 78-year-old patient with CP 1 year after cryoballoon pulmonary vein isolation (PVI) for atrial fibrillation (AF). This is the first reported case of CP with this ablation technique. The timeline of this case report is summarized in Table 1.

Case report

A 78-year-old male patient was assessed in November 2017 for progressive exertional dyspnea, ascites, and diuretic refractory peripheral edema.

His past medical history included arterial hypertension, left ventricular outflow tract ablation for symptomatic premature ventricular complexes (June 2016), and cryoballoon PVI for AF (August 2016). Following PVI, he developed a chronic nonproductive cough with normal pulmonic evaluation. Pulmonary vein stenosis was excluded by chest computed tomography (CT) scan. Repeat transthoracic echocardiography showed a new mild circumferential pericardial effusion of 8 mm, establishing the diagnosis of exudative pericarditis (October 2016). The patient responded well to anti-inflammatory treatment with ibuprofen and colchicine, although this was continued for 6 months, as symptoms relapsed during initial tapering. Over the next months, the patient became progressively short of breath with both clinical and echocardiographic evidence of congestion. Therefore, the diagnosis of heart failure with preserved ejection fraction was made (March 2017).

At time of our assessment in November 2017, physical examination revealed a cachectic patient with decreased skin turgor and dry oral mucosa. Hemodynamic parameters were normal (blood pressure 103/62 mm Hg and heart rate 73 beats/min). Heart and lung auscultation were unremarkable. Despite prolonged treatment with highly dosed diuretics, overt right-sided congestion (high central venous pressure, ascites, and extensive peripheral pitting edema) remained present.

Biochemically, a slightly elevated C-reactive protein of 12.6 mg/L (<10 mg/L) with normal leukocyte count of 9.120 × 10E9/L (<9.760 × 10E9/L), a high brain natriuretic peptide of 1200 pg/mL (<100 pg/mL), and mildly deranged transaminases were noted. Note that previous hepatologic and renal reviews (June 2016) were reassuring (ie, no evidence of liver cirrhosis, nephrotic syndrome, or amyloidosis).

Electrocardiogram showed sinus rhythm with premature atrial complexes and microvoltages in precordial leads

KEY TEACHING POINTS

- Constrictive pericarditis (CP) should be part of the differential diagnosis of (predominantly) right-sided heart failure, especially if a precipitating event is identified.
- Cryoballoon pulmonary vein isolation has now been established as a potential cause of CP.
- A multimodality (noninvasive and invasive) approach is often necessary to make the correct diagnosis.
- Distinction with restrictive cardiomyopathy is challenging yet crucial, as constrictive pericarditis, if timely diagnosed, is a curable pathology.

KEYWORDS Case report; Constrictive pericarditis; CP; Cryoballoon; Pericardiectomy; Pulmonary vein isolation; PVI
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Table 1 Timeline

Timing	Event
June 2016	LVOT ablation for symptomatic PVC
August 2016	Cryoballoon PVI for AF
October 2016	Diagnosis: pericarditis; treatment: ibuprofen and colchicine
March–October 2017	Exercise intolerance, dyspnea, and edema; tentative diagnosis: HFpEF; treatment: diuretics (variable dosing over time)
November 2017	Diuretic refractory heart failure; diagnosis: constrictive pericarditis; treatment: surgical pericardiectomy
December 2017 – April 2019	Full recovery; no residual heart failure (off diuretics)

AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; LVOT = left ventricular outflow tract; PVC = premature ventricular complexes; PVI = pulmonary vein isolation.

(Figure 1). These microvoltages were discrepant with body habitus and left ventricular hypertrophy and were not present on electrocardiograms prior to PVI. Moreover, in retrospect, an abrupt decrease in voltages was seen 10 months after PVI.

Transthoracic echocardiography revealed a mild hypertrophic left ventricle with global borderline systolic function and septal bounce (Supplemental Video). Diastolic assessment was conflicting with normal average E/E′ 6, high E′ values without annulus reversus, and normal pulmonary vein inflow pattern despite diastolic dysfunction with restrictive E/A ratio >2 (note the present premature atrial complexes) and severe biatrial enlargement (note already present pre-PVI) (Figure 2A–E). No significant respiratory variation in mitral valve or tricuspid valve inflow pattern was present. Hepatic vein pulsed-wave Doppler signal showed increased inspiratory forward systolic velocities as well as an increased expiratory diastolic flow reversal (Figure 2F). The inferior vena cava was severely dilated without any respiratory variation and the pericardium was mildly thickened (4 mm) on subcostal view (Figure 2G and H).

Interval differential diagnosis of this severe diuretic refractory and predominantly right-sided heart failure with preserved ejection fraction included CP and restrictive cardiomyopathy (RCM) (Table 2).

Additional noninvasive work-up showed a normal left ventricular global longitudinal strain (-17%), therefore arguing against restrictive pathology; no evidence of intracardiac shunting on transesophageal echocardiography; and a diffusely thickened noncalcified pericardium on chest CT scan (Supplemental Figures S1 and S2).

Subsequently, a thorough left and right heart catheterization was performed, showing normal coronary arteries and elevated filling pressures and mild postcapillary pulmonary hypertension (mean pulmonary capillary wedge pressure of 20 mm Hg, mean central venous pressure of 23 mm Hg, and mean pulmonary artery pressure of 29 mm Hg) (Supplemental Figure S3). Oximetry run confirmed the absence of shunting. Specific hemodynamic waveform analysis favored constrictive pathology. Firstly, the right atrial and left ventricular pressure tracings displayed a prominent y-descent with preserved x-descent (Figure 3A). Secondly, the right and left ventricular pressure waveforms revealed a "square root sign" with complete diastolic pressure equalization (Figure 3B). Finally, interventricular dependence was

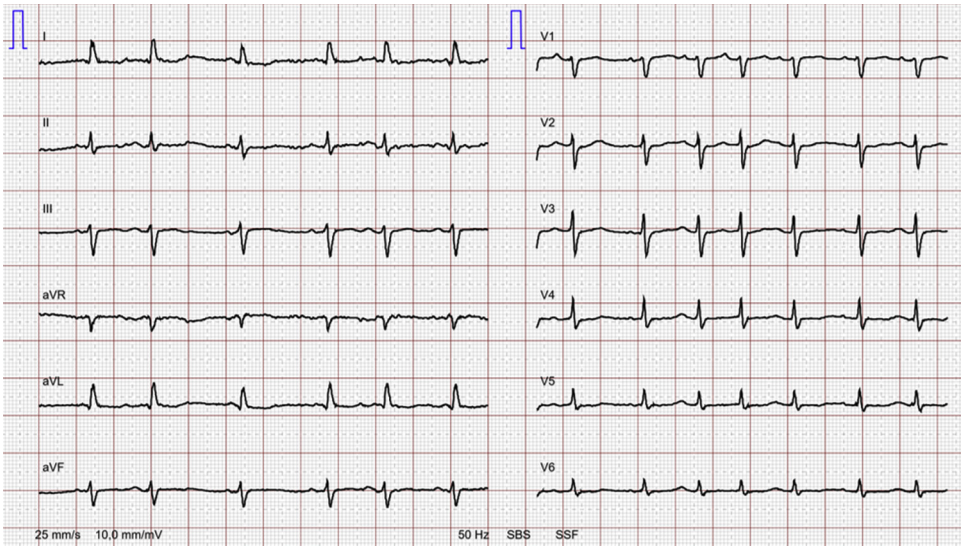

Figure 1 Electrocardiogram shows sinus rhythm with premature atrial contractions and microvoltages in precordial leads. Note the new onset of these microvoltages 10 months after pulmonary vein isolation and the discrepancy with body habitus (cachexia) and left ventricular hypertrophy.

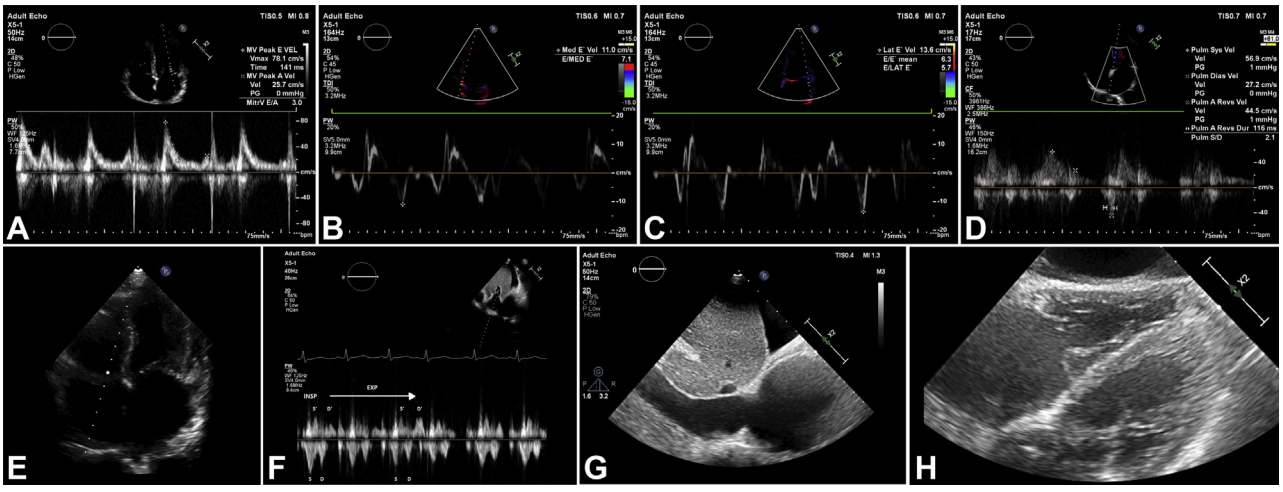

Figure 2 Conflicting findings on transthoracic echocardiography. **A:** Restrictive pulsed-wave Doppler mitral valve inflow pattern suggestive of grade 3 diastolic dysfunction. Note very frequent premature atrial complexes may contribute to the small A waves. **B, C:** Supranormal tissue Doppler E′ waves despite high left ventricular end-diastolic pressure, a phenomenon known as "annulus paradoxus." Note the absence of "annulus reversus" (medial E′ higher than lateral E′). **D:** Normal pulsed-wave Doppler pulmonary venous flow velocity pattern suggestive of normal left ventricular end-diastolic pressure. **E:** Severe biatrial dilatation (note history of atrial fibrillation). **F:** HV pulsed-wave Doppler showing increased inspiratory S wave (forward velocity) and increased expiratory D′ wave (flow reversal). The HV diastolic reversal ratio (ie, diastolic reversal velocity divided by forward velocity ratio) was 0.98. **G:** Widely dilated inferior vena cava without respiratory variation. **H:** Thickened pericardium (4 mm) without residual effusion.

demonstrated by an increased systolic area index during inspiration, yet without discordance (Figure 3B).

After multidisciplinary heart team discussion, the tentative diagnosis of CP was withheld and the patient was referred for pericardiectomy.

Perioperatively, the definite diagnosis of CP was established by the presence of a tense fibrous pericardium and a clear "jump" of the heart after wide incision with immediate hemodynamic normalization (Supplemental Figure S4). Total pericardiectomy was performed. Hospital stay was uncomplicated and the patient was discharged within 1 week. During 16 months of follow-up, the patient regained full functional capacity and remains off diuretics.

Discussion

CP is an uncommon cause of heart failure and is characterized by encasement of the heart by a thickened, rigid, and fibrous pericardium.[1] This noncompliant armor impairs ventricular diastolic filling and causes ventricular interdependence, resulting in a low cardiac output state.[2]

Over the last decades, postsurgical and postinterventional pericardites are increasingly recognized as CP etiology in the developed world, whilst tuberculosis—often in the setting of human immunodeficiency virus—and radiotherapy remain the major causes of CP worldwide.[3]

In the reported case, the patient underwent 2 ablations in a narrow time frame of 2 months: specifically, catheter ablation of left ventricular outflow tract ventricular ectopy and cryoballoon PVI for AF. Although both ablations could have induced pericardial inflammation leading to constriction, we strongly believe that the cryoballoon PVI was the main trigger in this patient. Firstly, clinical symptoms arose only after the PVI and exudative pericarditis was firmly diagnosed. Secondly, as inflammatory markers (CRP and leukocyte count) were normal on the day before the PVI and CRP remained mildly elevated over time since, this indicates that the global inflammatory process (resulting in CP) started with the PVI (Supplemental Table S1). Thirdly, the prior ventricular ectopy ablation was a limited procedure with only 4 radiofrequency energy applications, there was no pericardial effusion on follow-up echocardiogram afterwards, and a normal nonthickened pericardium was seen on chest CT scan prior to PVI. Finally, other causes of pericarditis were excluded (ie, normal autoimmune/virology/tuberculosis screening and no malignancy on positron emission tomography–CT scan).

Three cases of CP in the context of ablation have previously been described, all of them with the use of radiofrequency energy: 1 after epicardial ventricular tachycardia ablation, 1 after catheter ablation for AF, and 1 after inappropriate sinus tachycardia ablation.[4–6] Our case report is unique, as it shows that CP also can occur after cryoenergy ablation.

Over the past decade, cryoballoon ablation has emerged as a safe and effective technique for PVI in the treatment of AF. In particular, the beneficial safety profile with low risk of severe complications such as cardiac tamponade or atrioesophageal fistula is well substantiated.[7] This case report, however, establishes CP as a potential complication and, therefore, CP must be considered in the differential diagnosis of dyspnea or new-onset heart failure after cryoballoon PVI.

Table 2 Differential diagnostic dilemma of constrictive pericarditis vs restrictive cardiomyopathy

Investigations	Favoring CP	Favoring RCM	Comment
1. Medical history			
Precipitating event	x		Cryoballoon PVI complicated with pericarditis
2. Clinical examination			
Right-sided heart failure	x	x	High CVP, peripheral edema, ascites
3. ECG			
Microvoltages		x	Discordance with cachexia and left ventricular hypertrophy
4. Biochemistry			
Strongly elevated BNP >600 pg/mL		x	BNP 1200 pg/mL
Deranged liver function tests	x	x	
5. Chest radiograph / CT scan			
Noncalcified pericardium		x	Note calcified pericardium only present in 25% of CP
Thickened pericardium	x		
6. Transthoracic echocardiography			
2D			
Left ventricular hypertrophy		x	Mild; note arterial hypertension
Thickened pericardium	x		4 mm on subcostal view
No LV or RV free wall tethering		x	
Septal bounce	x		
Dilated IVC and hepatic veins	x	x	
Biatrial dilatation		x	Note previous atrial fibrillation
Doppler			
Restrictive mitral valve inflow		x	
No annulus reversus		x	
Annulus paradoxus / high E′ values	x		
No respiratory variation ≥25% mitral valve inflow		x	
No respiratory variation ≥40% tricuspid valve inflow		x	
Exaggerated expiratory diastolic flow reversal in HV	x		
Strain imaging			
Normal GLS		x	Note absence of typical CP pattern of reduced lateral strain
7. Invasive hemodynamics			
Elevated PCW and CVP	x	x	
Systolic PAP <55 mm Hg	x		PAPs 39 mm Hg
Square root sign ("dip and plateau") >7 mm Hg	x		
RV end-diastolic pressure / systolic pressure >1/3	x		20 mm Hg / 34 mm Hg
LV-RV end-diastolic pressure difference ≤5 mm Hg	x		
Elevated systolic area index during inspiration	x		
No respiratory discordance LV/RV pressure waves		x	

BNP = brain natriuretic peptide; CP = constrictive pericarditis; CT = computed tomography; CVP = central venous pressure; ECG = electrocardiogram; GLS = global longitudinal strain; HV = hepatic vein; IVC = inferior vena cava; LV = left ventricle; PAP = pulmonary artery pressure; PCW = pulmonary wedge pressure; PVI = pulmonary vein isolation; RCM = restrictive cardiomyopathy; RV = right ventricle.

Note that, in the reported case, the cryoballoon freeze characteristics were within normal limits (Supplemental Table S2).

The diagnosis of CP is often complex in the setting of nonspecific symptoms, conflicting test results, and an insidious course.[8] Especially the differential diagnosis with RCM remains challenging, as both pathologies share the common features of predominantly right-sided heart failure in the setting of preserved left ventricular systolic function.[9] This (differential) diagnostic dilemma was clearly noted in our case, illustrated by various inconclusive test results despite the clinically impressive diuretic refractory heart failure (summary in Table 2). Additionally, the severity and chronicity of the heart failure could be appreciated by the overt cachexia of the patient.

Interestingly, initial echocardiographic features were conflicting and a dedicated CP-focused echocardiogram was necessary. The presence of septal bounce, suggestive hepatic vein pulsed-wave Doppler pattern, and striking annulus paradoxus (in retrospect, after invasively documented elevated pulmonary wedge pressure) clearly favored CP, with—according to the Mayo diagnostic criteria for CP—a combined specificity of 97%.[10] On the contrary, other typical echocardiographic CP features, such as annulus reversus or increased respiratory variation of mitral and tricuspid valve inflow pattern, were absent in this patient, and severe biatrial dilatation suggested other etiology. Nevertheless, normal global longitudinal strain was a strong argument against restrictive pathology.[8] In our opinion, a more prominent role of global longitudinal strain in the diagnostic approach of CP should be considered.

Despite recent literature promoting noninvasive multimodality imaging as the cornerstone in CP diagnosis, in our

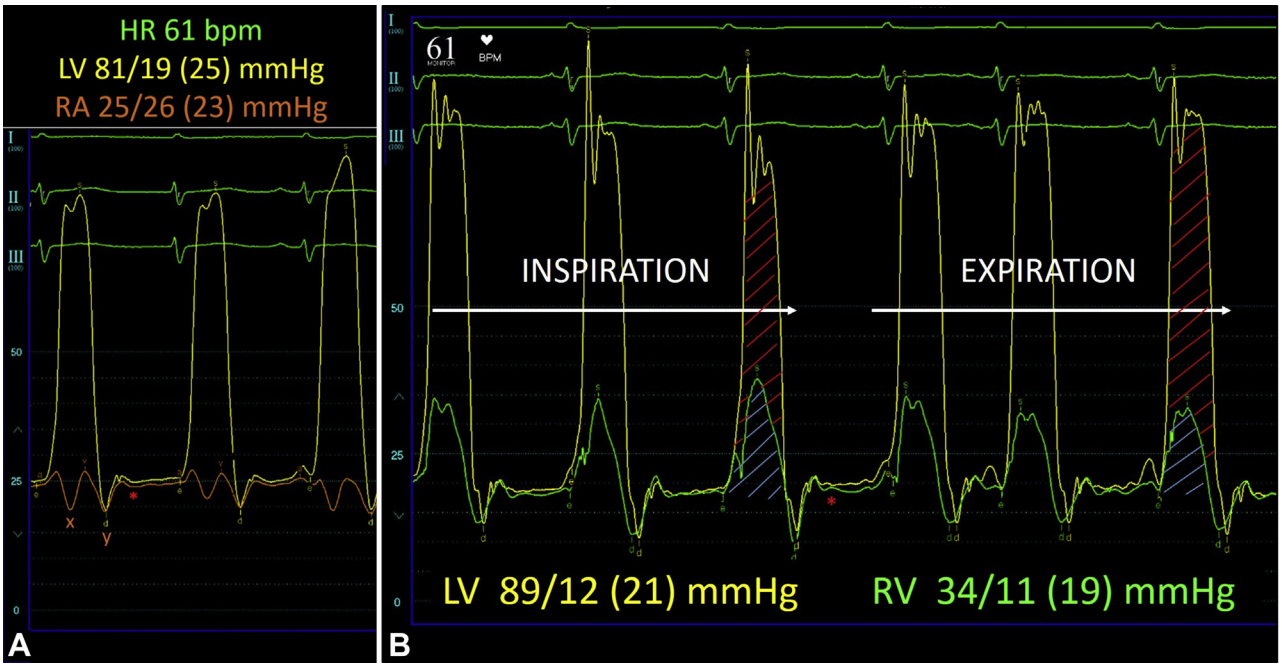

Figure 3 Invasive hemodynamic profile (gold standard) favoring constrictive physiology. Note the complete equalization of diastolic filling pressures (*asterisks*) and a "square root sign" (*arrow*). This square root sign (also referred to as "dip and plateau") is a marker of fast early diastolic filling (driven by high atrial pressures) followed by a rapid rise of ventricular pressures (due to the noncompliant pericardium). **A:** Right atrial pressure tracing showing prominent x- and y-descents. The preserved x-descent favors constrictive pericarditis (CP) and results from unimpaired atrial relaxation and supranormal ventricular longitudinal contraction. **B:** Respirophasic left ventricular (LV) and right ventricular (RV) pressure waveforms display enhanced interventricular dependence (*shading*) as the result of a fixed total pericardial volume in CP. This results in an increased systolic area index (ie, [RV area during inspiration × LV area during expiration] / [LV area during inspiration × RV area during expiration]). Furthermore, square root height >7 mm Hg and diastolic ventricular filling equalization <5 mm Hg further favor CP. Nevertheless, the pathognomonic ventricular pressure waveform discordance (ie, increase of RV pressure with decrease of LV pressure during inspiration and vice versa) is not present.

experience this is often inconclusive in challenging cases.[11] Therefore, work-up should be complemented with invasive hemodynamic profiling by a thorough left and right heart catheterization, still the gold standard. In the reported case, the pressure waveform traces favored constrictive pathology with overt square root sign, complete diastolic pressure equalization, and ventricular interdependence. However, pathognomonic respiratory discordance of left ventricular and right ventricular pressure waves was absent.[9]

Finally, the definite diagnosis was made in the operating theatre on direct surgical view. Total pericardiectomy was performed and the patient has regained full functional capacity.

Conclusion

CP is a rare complication of interventional cardiac procedures, and this case report establishes cryoballoon PVI as a potential trigger. Diagnosis remains challenging, and especially the differential diagnosis with RCM often necessitates a multimodality (combined noninvasive and invasive) approach. A high index of suspicion, especially if a potential precipitating event is identified, and adequate understanding of complex CP hemodynamics are paramount to establish the correct diagnosis. Furthermore, as CP (if timely recognized) is a potentially curable cause of heart failure, the importance of risen awareness among cardiologists needs to be emphasized.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2019.10.012.

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