16 Pericardial Disease, Constrictive Pericarditis and Restrictive Cardiomyopathy in Patients with Cancer

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Abstract

Pericardial disease, specifically acute pericarditis, constrictive pericarditis, and pericardial tamponade, are seen in cancer patients due to the malignant process or from radiation therapy. In this chapter we present an overview of acute pericarditis, constrictive pericarditis and pericardial tamponade. We also discuss restrictive cardiomyopathy and its differences from constrictive pericarditis.

Keywords

Pericardial disease • Cardiac tamponade • Constrictive heart disease • Restrictive heart disease

Acute Pericarditis

Acute pericarditis presents as chest pain, electrocardiogram (ECG) changes, and pericardial friction rub in patients with an acute inflammation of their pericardium. Acute pericarditis can occur in up to 4% of patients with chest pain [1]. There are many cause of acute pericarditis as shown in Table 16.1 and they include infectious, autoimmune, metabolic, malignant, drug-induced, and idiopathic etiologies [2]. To make the diagnosis of acute pericarditis patients need to have two of the following four criteria: typical chest pain, audible pericardial friction rub, diffuse ST-segment elevation, and new or worsening pericardial effusion [3].

Figure 16.1 shows an ECG of a patient who presented with sudden, sharp chest pain which was worse with inspiration and improved with sitting. On physical exam the patient had a pericardial rub. The ECG in patients with acute pericarditis generally shows wide spread ST-segment elevation and diffuse PR depression, except in lead AVR where there is ST depression and PR segment elevation. The ECG changes in pericarditis evolve over four stages. Stage 1 ECG changes last for hours to days and are comprised of ST segment elevation and PR depression. Stage 2 has normalization of the PR and ST segment to baseline. Stage 3 shows diffuse T-wave inversions. Stage 4 shows normalization of the T-wave inversions to baseline.

Echocardiograms in patients with acute pericarditis may show a pericardial effusion which is typically small in 60% of cases [4]. CT and MRI show inflammation-related pericardial enhancement.

Table 16.1 Etiology of pericarditis

Type	Causes
Infectious	Viral, bacterial, mycobacterial, fungal, Q fever
Noninfectious	Metastatic cancer, idiopathic, uremia, hypothyroidism, thoracic radiation
Autoimmune	Lupus, rheumatoid arthritis, arteritis, inflammatory bowel syndrome, post-myocardial infarction
Drug-Induced	Phenytoin, procainamide, hydralazine, cyclosporine
Trauma	Thoracic surgery, thoracic duct injury, chest trauma causing hemopericardium

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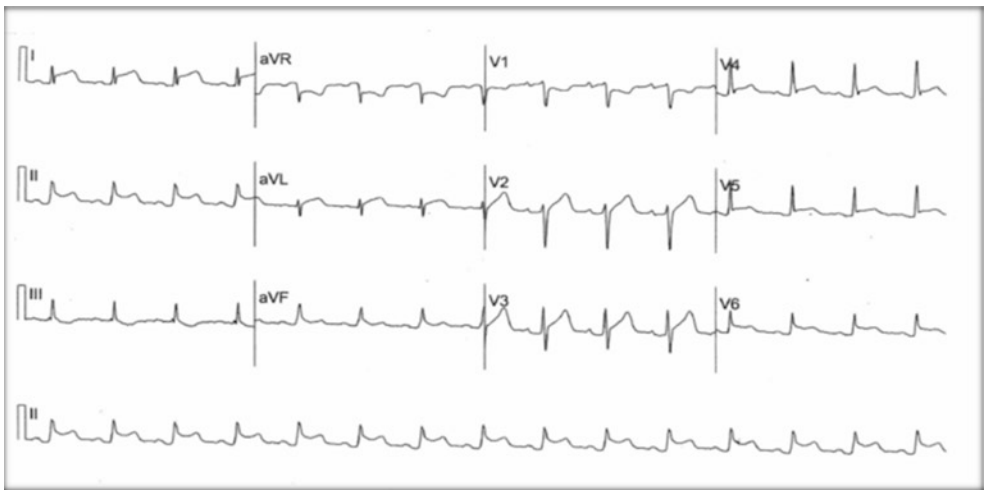

Fig. 16.1 ECG of a patient with positional chest pain and pericardial rub. ECG shows diffuse ST elevation and PR depression in all leads except AVR which shows ST depression with PR segment elevation

Table 16.2 Treatment of acute pericarditis

	Dose	Initial attack
(First line)		
Aspirin	750–1000 mg TID	1–2 weeks
NSAIDs (e.g. Ibuprofen)	600–800 mg TID	1–2 weeks
Colchicine	0.5 mg BID	3 months
	0.5 mg/day (<70 kg or intolerant to high dose)	
(Second line)		
Steroids (prednisone)	0.25–05 mg/kg/day	1–2 weeks

Treatment of acute pericarditis is directed toward symptom relief and decreasing the chance of recurrence. Aspirin, non steroidal anti-inflammatory drugs (NSAIDs), and colchicine are first-line choice for therapy. Colchicine should be added to aspirin/NSAIDS in the initial management of acute pericarditis, as studies have shown significantly reduced recurrence rate with addition of colchicine. Steroids should not be used as first line treatment due to high rates of relapse when stopped. Steroids should only be used when first line treatment choices are contraindicated or in refractory cases [3]. For post myocardial infarction (MI) pericarditis, Aspirin is the drug of choice and colchicine added if high-dose aspirin is ineffective [5]. In post-MI pericarditis steroids and NSAID are not recommended and can be harmful [5]. Table 16.2 summarizes the different medication used in the treatment of acute pericarditis.

Constrictive Pericarditis

Constriction is caused by pericardial scarring, calcification and thickening, although, up-to 18% have normal pericardial thickness [6]. Mediastinal irradiation accounts for 13% cases of constrictive pericarditis [6], other causes are pervious surgery, tuberculosis, and malignant pericardial disease. In constriction, there is dissociation of intra-thoracic and intra-cardiac pressures leading to enhanced inter-ventricular dependence with significant respiratory variation in ventricular diastolic filling. Decrease in left ventricular filling occurs during inspiration with simultaneous increase in right ventricular preload and the opposite changes occur in expiration.

Presenting symptoms are dyspnea and edema in patients with a remote history of radiation. Clinical features include jugular venous distension, Kussmaul's sign, pleural effusions, ascites and a pericardial knock. Diagnosis requires clinical suspicion with imaging evidence of constriction.

Figure 16.2 shows the case of a patient with Hodgkin's lymphoma who received prior radiation and presented with congestion and dyspnea due to constrictive pericarditis. Echocardiographic findings that are highly suggestive of constriction are ventricular septal bounce, medial mitral annulus e′ velocity $\geq$ 9 cm/s, hepatic vein expiratory diastolic reversal ratio $\geq$ 0.79, plethoric inferior vena cava [7, 8]. Reduction in mitral inflow velocity during inspiration and increase during expiration is an important finding [7] (Fig. 16.2). There is decreased longitudinal strain in anterolateral and RV free walls due to restricted motion of the myocardium adjacent to constricted pericardium. Pericardial calcification can be seen on echocardiogram, chest X-ray and CT imaging.

Cardiac magnetic resonance (CMR) is a validated test to detect pericardial thickening, pericardial-myocardial adherence (myocardial tagging), respiratory variation in septal excursion and real time cine-imaging with greater than 25% respiratory variation in mitral inflow velocities [9].

Definitive diagnosis is possible by simultaneous left and right ventricular pressure tracings [10]. Early rapid

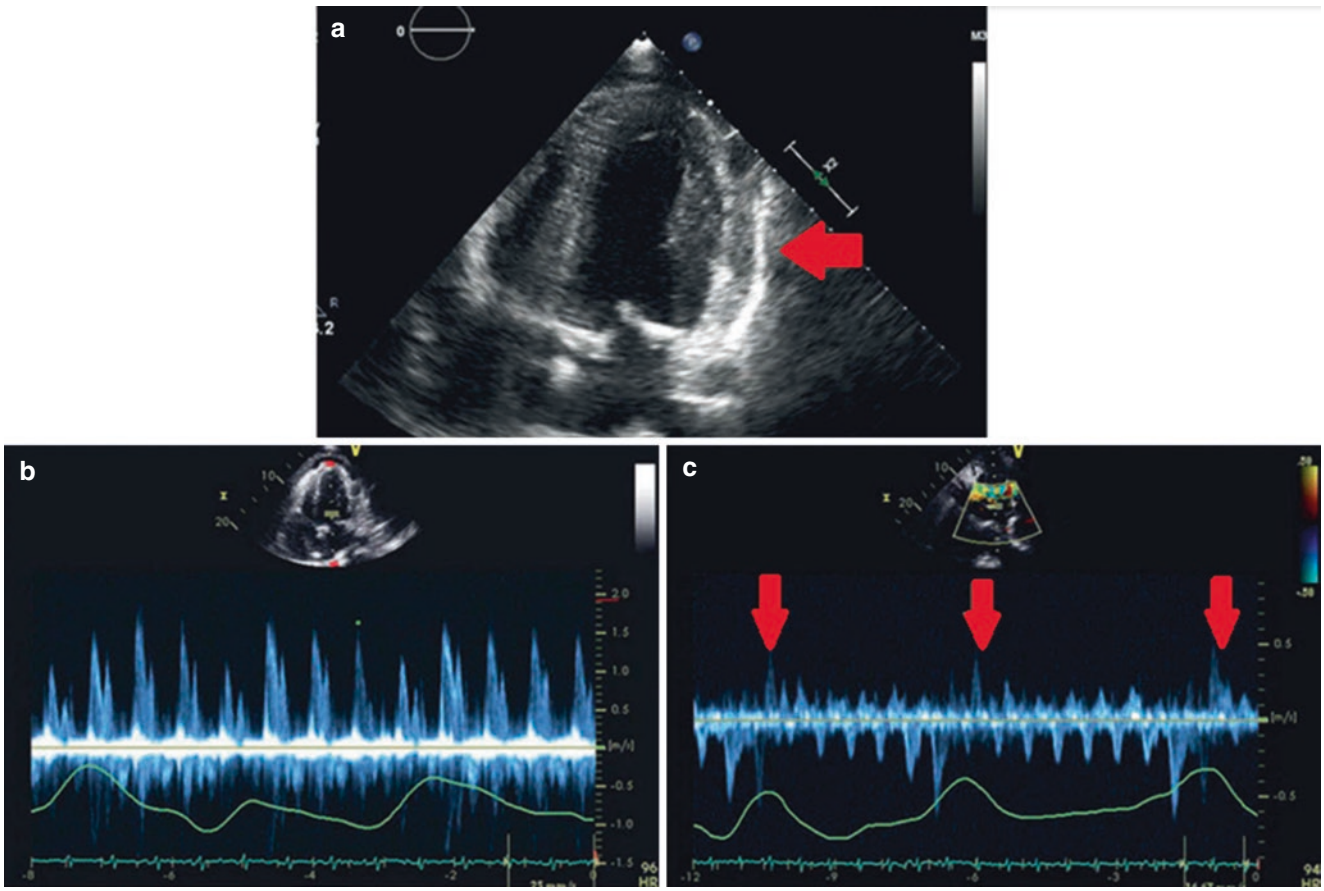

Fig. 16.2 Patient with Hodgkin's lymphoma who underwent radiation therapy in 1984. In 2007, he presented with congestion and dyspnea due to constrictive pericarditis. (**a**) The *red arrow* shows portion of markedly thickened pericardium longitudinally along the lateral wall. (**b**) Mitral inflow variation in constriction, with the typical decreased flow velocities with inspiration, which recover with expiration. (**c**) Hepatic vein diastolic flow reversal at the onset of expiration (see *red arrows*) (With the permission from Yusuf SW et al. 2016 [2])

filling with characteristic dip and plateau of ventricular diastolic pressures and equalization of end diastolic pressures is seen in all four chambers. This is sensitive but not specific to constriction [10]. There is inspiratory decrease in left ventricular (LV) volume with increase in right ventricle (RV) volume and vice-versa, implying ventricular discordance (Fig. 16.3). Systolic area index i.e. ratio of RV area to LV area in inspiration versus expiration greater than 1.1 is the most specific (100%) and sensitive (97%) diagnostic test [11].

Pericardiectomy is the definitive treatment with mortality rate of 6–12%. Complete normalization of hemodynamics is seen in only 60% of the patients [12].

Restrictive Cardiomyopathy

Restrictive cardiomyopathy in cancer patients can occurs as a consequence of cardiac amyloidosis in multiple myeloma, tumor infiltration of myocardium or transfusion induced hemosiderosis. It can also result from mediastinal radiation induced (>30-Gy dose) myocardial damage and fibrosis [9]. It manifests as heart failure from a stiff myocardium causing diastolic dysfunction.

Figure 16.4 shows an echocardiogram in a patient with a history of multiple myeloma who presented with signs and symptoms of congestive heart failure and had biopsy proven cardiac amyloid. 2D Echocardiographic features in patients with amyloid heart disease, include increased thickness of the LV myocardium, a small LV cavity, and increased atrial size (Fig. 16.4a). As a result, early rapid rise in LV pressure is seen during diastolic filling. Transmitral flow pattern will show short mitral E deceleration time and a low A wave velocity resulting in a high E/A ratio consistent with restrictive filling. E′ velocity by tissue Doppler imaging is usually decreased (Fig. 16.4b). Longitudinal strain in patients with cardiac amyloidosis classically shows a relative apical sparing (Fig. 16.5). A 12 lead ECG in patients with amyloid heart disease may show a pseudo-infarct pattern and low voltage complexes (Fig. 16.6).

Simultaneous LV and RV pressure tracings will show dip-plateau pattern of early diastolic filling. There is no

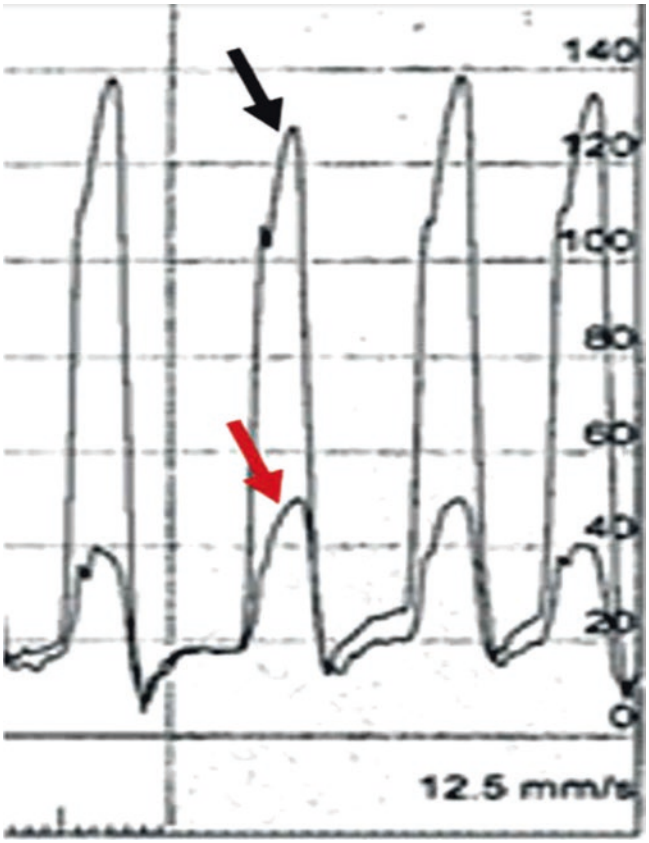

Fig. 16.3 Constrictive Pericarditis: Hemodynamics showing ventricular discordance (Interdependence) with an increase in right ventricular (RV) pressure and a simultaneous decrease in left ventricular (LV) pressure during inspiration in a patient with constrictive pericarditis due to previous thoracic surgery. (The *red arrow* points to the RV and the black arrow points to the LV)

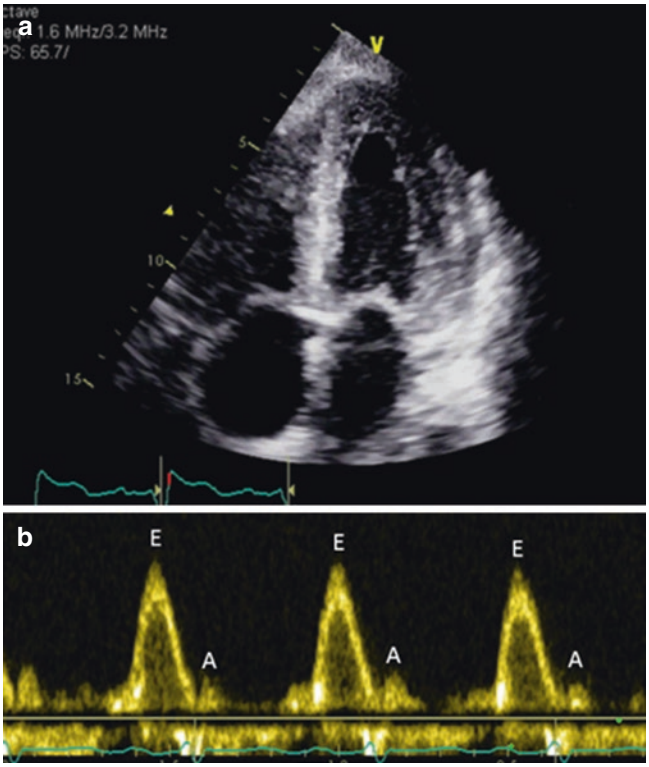

Fig. 16.4 (**a**) Four chamber echocardiographic view in a patient with restrictive cardiomyopathy from cardiac amyloidosis. A thickened left ventricle with small LV cavity and enlarged atria are seen. (**b**) Transmitral flow showing a short mitral E deceleration time and low A velocity resulting in high E/A ratio, consistent with restrictive filling

dissociation of intra-thoracic and intra-cavitary pressures and hence, there is equal lowering of pulmonary wedge and LV diastolic pressures [13]. LV and RV pressures are in concordance during respiration unlike constrictive pericarditis (Fig. 16.7), showing no enhanced inter-ventricular dependence. Other features of restriction pattern that are not specific include LV end-diastolic pressure exceeding RV end diastolic pressure by 5 mmHg or more, pulmonary artery systolic pressure greater than 50 mmHg and RV end-diastolic pressure less than 1/3rd of systolic pressure [13]. Differentiating constriction from restrictive cardiomyopathy can be clinically challenging and the two entities often co-exist. Table 16.3 describes the distinguishing features of both.

Cardiac MRI as a tool to detect myocardial fibrosis is promising but its role remains unclear. T1 mapping can be used to quantify the concentration of gadolinium-based extracellular contrast agents in the myocardium, which is related to collagen content/fibrosis [13]. In patients with cardiac amyloidosis which can lead to restrictive cardiomyopathy, the cardiac MRI shows thickening of the myocardium, atrial enlargement, and global transmural or subendocardial

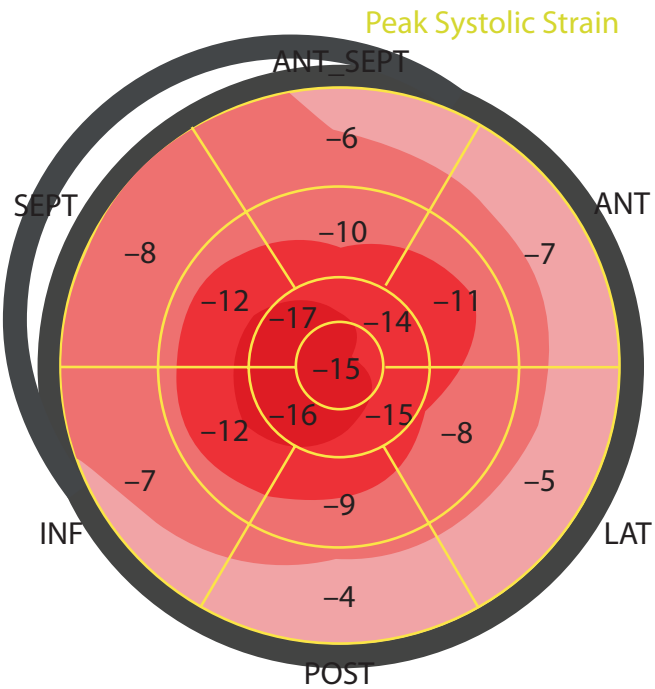

Fig. 16.5 Longitudinal strain in a patient with cardiac amylodosis showing relative apical sparing

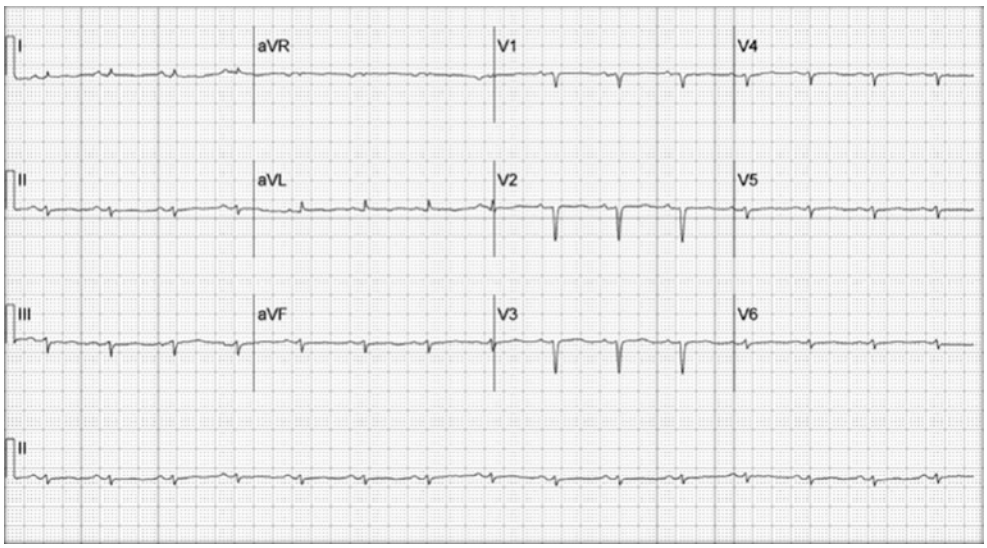

Fig. 16.6 A 12 lead ECG from a patient with cardiac amyloidosis, showing pseudo-infarct pattern and low voltage complexes

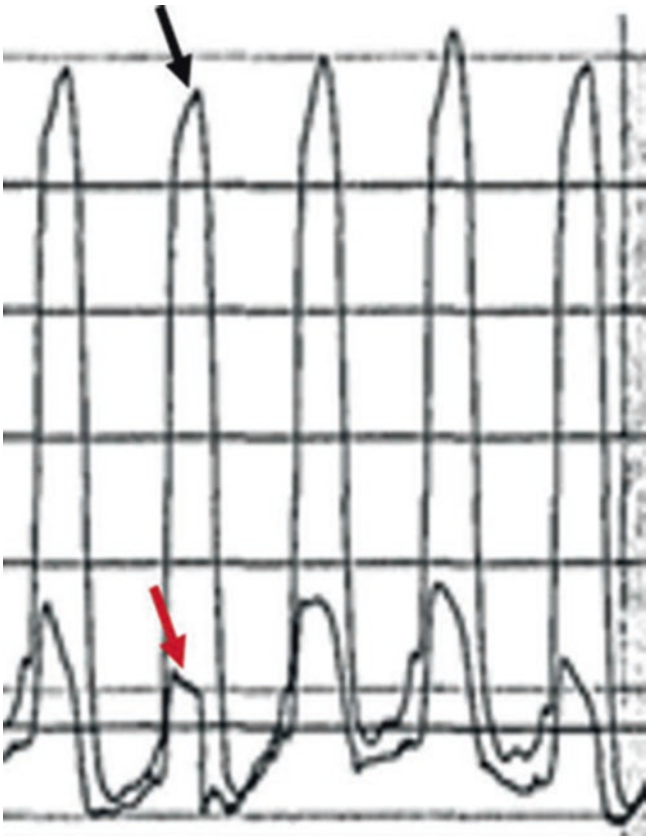

Fig. 16.7 Restrictive cardiomyopathy: Hemodynamics showing ventricular concordance with a concomitant decrease in LV pressure and a RV pressure during inspiration in a patient with restrictive cardiomyopathy due to cardiac amyloidosis. (The *red arrow* points to the RV and the black arrow points to the LV)

late enhancement of the myocardium as in Fig. 16.8 [14]. Treatment of restrictive cardiomyopathy is challenging and includes management of heart failure and in appropriate cases, cardiac transplantation.

Table 16.3 Differentiating features of constrictive and restrictive cardiomyopathy

Features	Constriction	Restriction
Pericardial thickening	Present	Absent
Pericardial knock	Present	Absent
Rapid 'y' descent in JVP	Present	Absent
Inter-ventricular septal bounce	Present	Absent
Respiratory variation >25% in mitral Inflow	Present	Absent
Mitral annulus medial e' velocity	Normal/increased	Decreased
Hepatic vein flow diastolic reversal in expiration	Present	Absent
Simultaneous LV/RV tracings	Discordant pattern	Concordant pattern
Systolic area index	>1.1	<1.1
Pulmonary artery systolic pressure >50 mmHg	Uncommon	Often present
RVEDP/RVSP	>1/3	<1/3
LVEDP—RVEDP	<5 mmHg	>5 mmHg

Pericardial Tamponade

Pericardial tamponade is the accumulation of fluid into the pericardial space that can lead to reduction in ventricular filling and hemodynamic compromise. Patients may present with symptoms of shortness of breath, tachycardia, hypotension, pulsus paradoxus, and eventually cardiogenic shock due to a drop in cardiac output.

12 Lead ECG

The ECG in cardiac tamponade classically shows electrical alternans, but while it has a high positive predictive value in detecting cardiac tamponade, its negative predictive value is

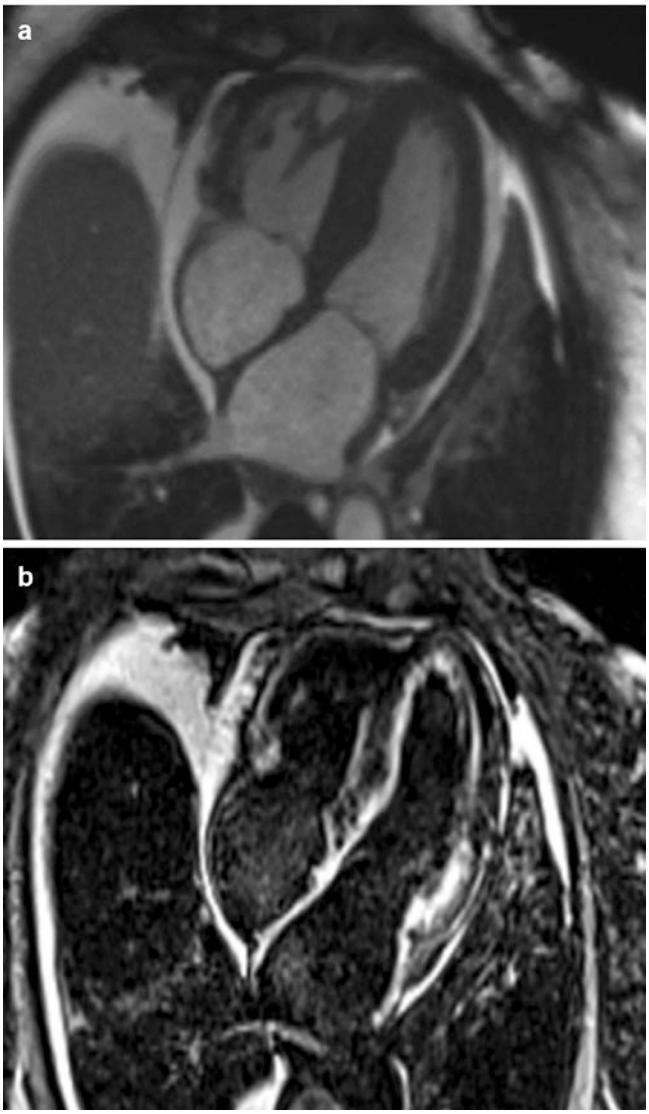

Fig. 16.8 Cardiac MRI of a patient with cardiac amyloidosis. Image (**a**) shows thickening of the myocardium along with dilated atria. The T1 image (**b**) shows global subendocardial hyperenhancement which is characteristic of cardiac amyloid

low. Hence due to a low negative predictive value, a 12-lead ECG cannot be used as a screening tool to exclude cardiac tamponade [15] (Fig. 16.9).

2D Echocardiographic and Doppler Evaluation

Echocardiography is the diagnostic test of choice for diagnosis of pericardial tamponade. Echocardiography can help determine the size and location of the pericardial fluid. Furthermore, it allows the determination of whether cardiac tamponade physiology is present.

With increased in pericardial pressure due to the accumulation of fluid in the pericardial space, there is a reduction in RV chamber size, collapse of the RV during early diastole, and RA inversion during atrial diastole [16, 17]. In particular, with RV collapse there is an associated 21% decrease in cardiac output [18]. RA inversion or collapse can also be seen with cardiac tamponade. In particular, a RA inversion time index ≥0.34 has the highest sensitivity and specificity in detecting cardiac tamponade in patient with a large pericardial effusion [19].

Table 16.4 list the sensitivity and specificity of echocardiographic signs for cardiac tamponade.

Figure 16.10 shows a subcostal view of an echocardiogram of a patient with evidence of RV chamber collapse who presented with shortness of breath, tachycardia and hypotension. Figure 16.11 shows RA collapse of a different patient who presented with similar symptoms.

Doppler echocardiographic measurements are also altered in cardiac tamponade. E-velocity changes with respiration have been demonstrated across the mitral and tricuspid valves in patients with cardiac tamponade. The percentage change in E-velocity was determined as (INSP-EXP)/EXP where INSP was defined as the first beat of inspiration and EXP was defined as the first beat of expiration. In one early study, with cardiac tamponade the

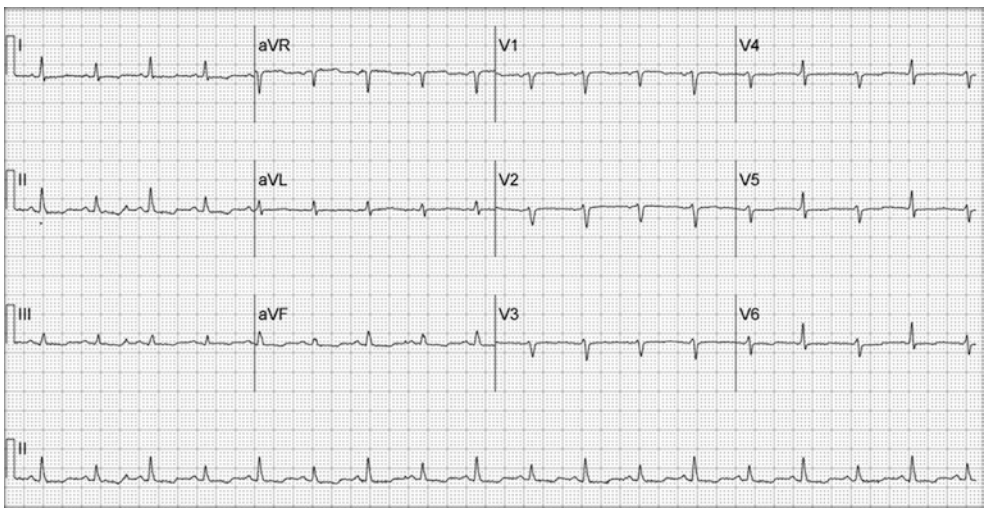

Fig. 16.9 A 12 lead ECG showing low voltage complexes and electrical alternans, in a patient with large pericardial effusion and tamponade

Table 16.4 Sensitivity and specificity of signs of pericardial tamponade in patient with large pericardial effusions (modified from *Shrairer et al. Cardiology in Review. 2011; 19; 233-238*)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
RA collapse	55	88	10	99
RA collapse-1/3 cardiac cycle	94	100	–	–
RV collapse	48	95	38	99
IVC plethora	97	66	7	99
Large PEF	73	97	45	99

RA right atrium, *RV* right ventricle, *IVC* inferior vena cava, *PEF* pericardial effusion, *PPV* positive predictive value, *NPV* negative predictive value

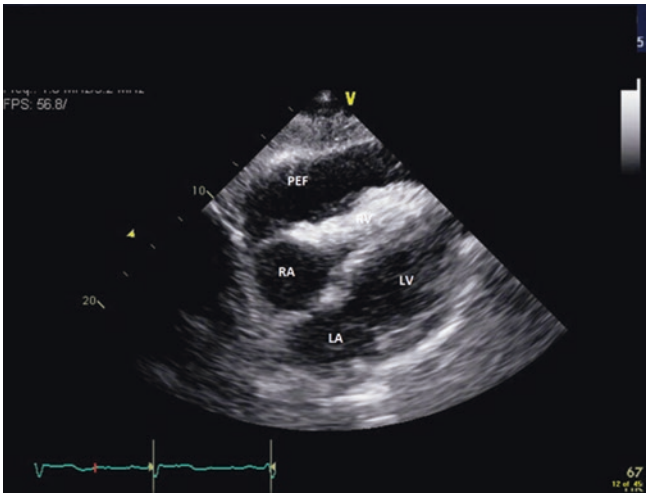

Fig. 16.10 Echocardiogram showing RV chamber collapse. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *PEF* pericardial effusion

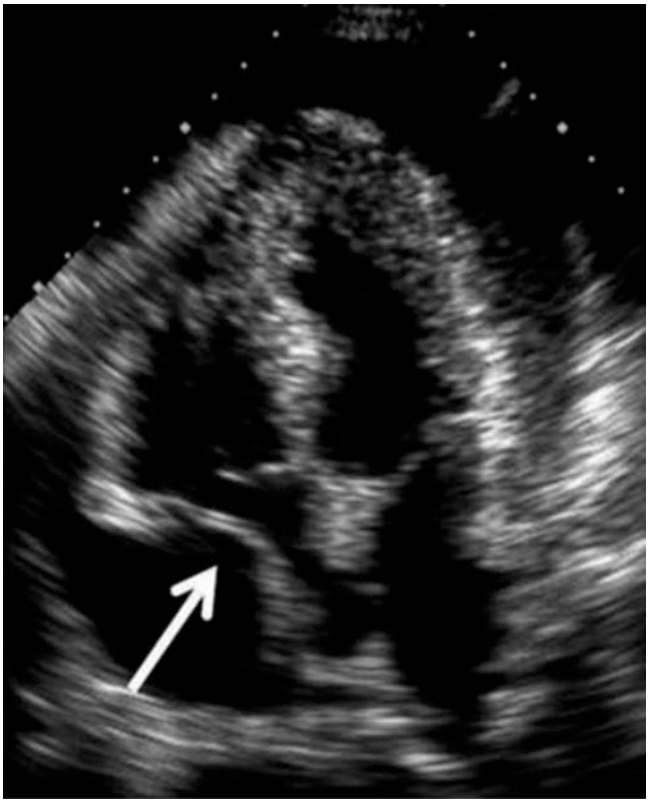

Fig. 16.11 Echocardiogram showing RA chamber inversion/collapse (*arrow*)

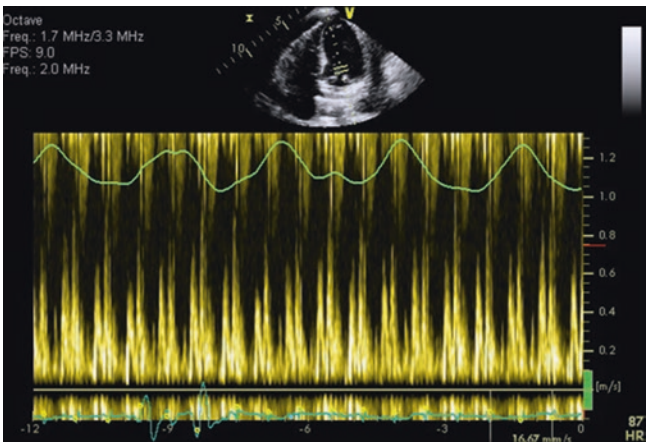

Fig. 16.12 E-wave velocity across the MV valve showing >25% respiratory variation

mitral E-velocity decreased by 43% during inspiration. The tricuspid E-velocity increased by 85% with inspiration [20].

Figures 16.12 and 16.13 show the mitral and tricuspid valve velocity in a patient with cardiac tamponade who presented with dyspnea and tachycardia. In general, variations in E-wave velocities during respiration across the mitral valve and tricuspid valve greater than 25% and 50%, respectively, may indicate cardiac tamponade. However, when evaluating for changes across the valves, other disease states such as COPD, pericardial constriction, and severe tricuspid regurgitation should be accounted for. One way to distinguish between cardiac tamponade and COPD, is that the maximal change in e-velocity during inspiration will occur in the very first beat after inspiration as opposed to the more gradual drop seen in e-wave velocity with pulmonary conditions such as asthma [21].

With hemodynamically significant pericardial effusions and cardiac tamponade, RA pressure will invariably be increased which leads to dilation of the inferior vena cava that can be easily studied by echocardiography. An estimated RA pressure can be calculated form these findings [22].

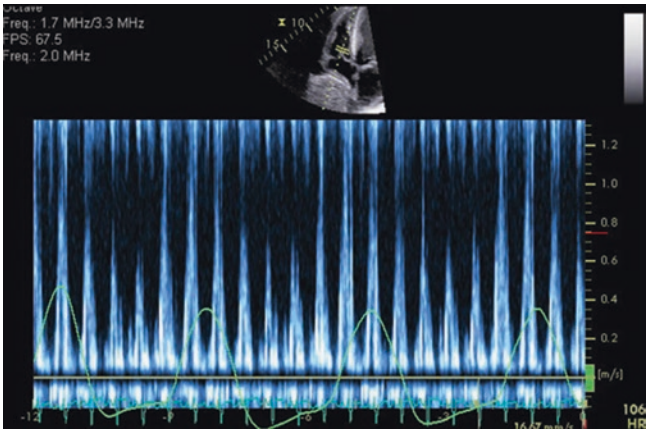

Fig. 16.13 E-wave velocity across the TV valve showing >50% respiratory variation

Large pericardial effusion or effusion with tamponade can be drained via percutaneous approach. For recurrent pericardial effusion a pericardial window is indicated.

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