Chapter

Reversible Cardiomyopathies

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Abstract

Cardiomyopathy includes a diverse and heterogeneous group of disorders affecting the myocardium and eventually leading to cardiac dysfunction. Cardiomyopathy is the leading cause of hospitalization in patients older than 65 years of age and it is an important cause for enormous healthcare expenditure. All reversible cardiomyopathies can be associated with cardiomegaly, systolic heart failure, structural changes, and an increase in mortality, but when the offensive agent is identified and stopped, these conditions tend to stop their progression and reverse. The prognosis of reversible nonischemic cardiomyopathies is better than ischemic or other nonreversible cardiomyopathies. Additionally, it is important to diagnose etiology of HF early and precisely to determine prognosis and effective treatment. Most patients with reversible cardiomyopathy present with clinical picture similar to that of systolic heart failure. Here in this book chapter, we discuss about different types of reversible cardiomyopathy including pathogenesis, clinical picture, diagnosis and treatment.

Keywords: arrhythmogenic, cirrhotic, uremic, nutritional, metabolic, inflammatory

1. Introduction

The heart is composed of a special tissue and a unique electrical system. Though there are some hypotheses about the possibility of regeneration, the cardiac tissue is composed of non-regenerative muscle cells called myocytes which have the capacity to revert acute damages before necrosis and subsequent fibrosis are present. It is thought that this reversion could be related to multiple factors. A decrease in inflammatory markers, perfusion recovery, and possible RNA reactions reduce the fiber tension and inflammation that cause the shortening of the dilated fibers, and then the transient condition will improve. All reversible cardiomyopathies can be associated with cardiomegaly, systolic heart failure, structural changes, and an increase in mortality, but when the offensive agent is identified and stopped, these conditions tend to stop their progression and reverse. In a period of 6 weeks, we are usually able to evaluate positive results after the stunning myocardial cells recover. Most patients with reversible cardiomyopathy present with clinical picture similar to that of systolic heart failure (HF) as follows:

- Dyspnea
- Chest discomfort/pain
- Lower extremity edema or peripheral edema

- Weight gain
- Orthopnea or paroxysmal nocturnal dyspnea (PND)
- Decrease in exercise tolerance etc.

In this chapter, we have focused on important types of reversible cardiomyopathy (**Figure 1**).

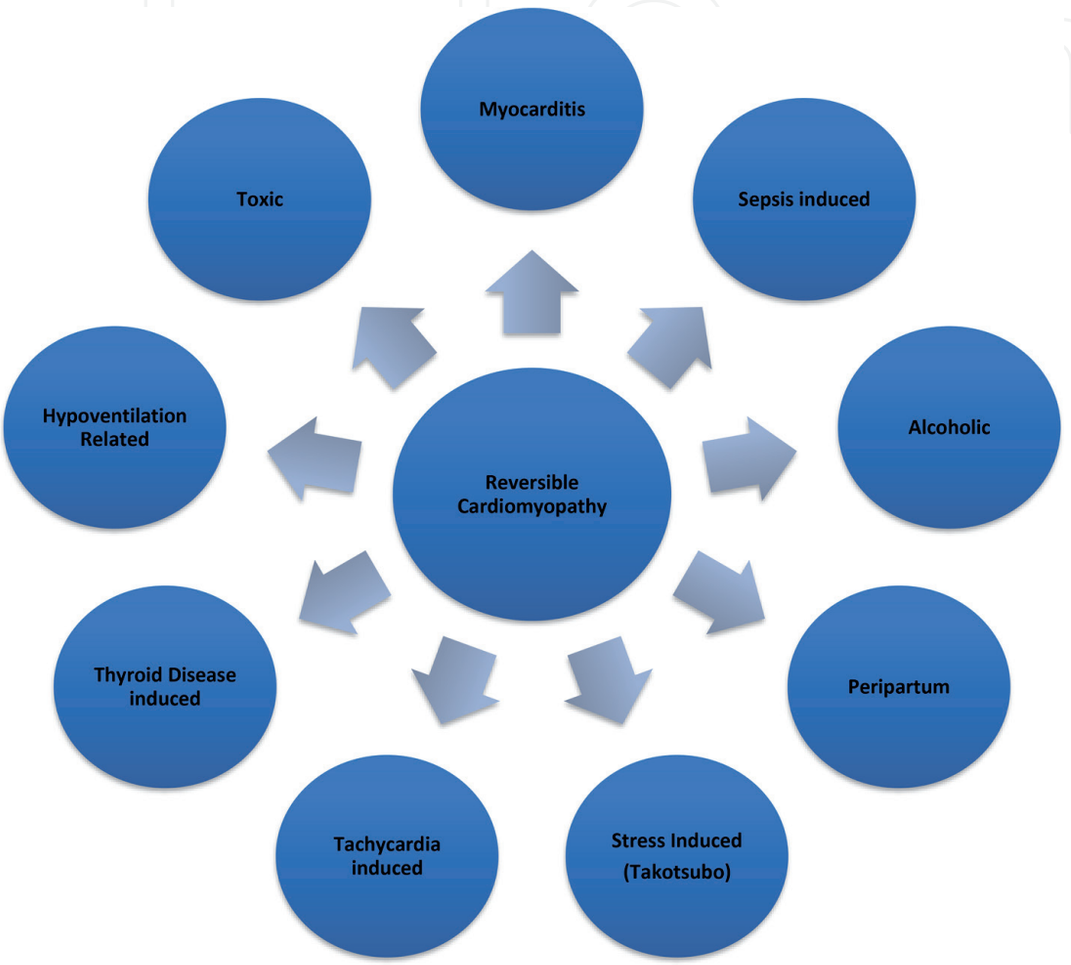

Figure 1.
Different types of reversible cardiomyopathy.

2. Epidemiology

Cardiomyopathy includes a diverse and heterogeneous group of disorders affecting the myocardium and eventually leading to cardiac dysfunction [1]. The HF is a widely prevalent syndrome today and affects 5.1 million adult Americans over the age of 20 [1]. Cardiomyopathy is the leading cause of hospitalization in patients older than 65 years of age and it is an important cause for enormous healthcare expenditure. Interestingly, ischemic cardiomyopathy is responsible for about half of these patients. On the other hand, the prevalence of reversible nonischemic cardiomyopathy is also significant, as per several large clinical trials, and ranges from 20–50% [1]. The prognosis of reversible nonischemic cardiomyopathies is better than ischemic or other nonreversible cardiomyopathies which were suggested by the epidemiological evidence [1]. Additionally, it is important to diagnose etiology of HF early and precisely to determine prognosis and effective treatment.

3. Tachycardia-induced cardiomyopathy

Arrhythmia-induced cardiomyopathy (also known as tachycardia-induced cardiomyopathy, tachycardia-mediated cardiomyopathy, or tachymyopathy) is one of the reversible causes of dilated cardiomyopathy. Arrhythmia-induced cardiomyopathy is defined by the presence of a sustained tachycardia (or frequent episodes of tachycardia or very frequent ectopy) which results in left ventricular (LV) systolic dysfunction. It is a relatively rare, but well-recognized entity caused by long-standing tachycardia, which can be treated readily in most instances and have a good prognosis. A common clinical problem is differentiating whether tachycardia is the primary cause of the patient's cardiomyopathy, or if the tachycardia is secondary to another cardiomyopathy of a different etiology. Arrhythmia-induced cardiomyopathy has been reported with nearly all types of tachyarrhythmia and frequent ectopy, both supraventricular and ventricular [2]. Different types of tachyarrhythmias associated with arrhythmia-induced cardiomyopathy include atrial fibrillation (AF), atrial flutter, atrial tachycardia, reentrant supraventricular tachycardias, and ventricular tachycardia. Regardless of the type of arrhythmia, therapy to restore normal sinus rhythm or to slow the ventricular rate (or eliminate ectopy) usually result in an improvement in left ventricular function.

The incidence of arrhythmia-induced cardiomyopathy is unclear, but an association between tachycardia and cardiomyopathy is well known. An insight into the prevalence of arrhythmia-induced cardiomyopathy can be derived from cohort studies. In one study of 1269 patients undergoing ablation for atrial flutter, 184 had reduced ejection fractions (<40 percent) at baseline [3]. In another study with a cohort of 625 patients undergoing catheter ablation for a variety of tachyarrhythmias, tachycardia-induced cardiomyopathy was present in 2.7 percent (17 of 625 patients) [4]. Similarly, in one cohort of 331 patients who had catheter ablation of incessant atrial tachycardia (AT), myocardial dysfunction was present in 9 percent of patients [5]. Additionally, the patients in the cohort with arrhythmia-induced cardiomyopathy were younger, predominantly male, and had continuous or very frequent paroxysmal tachycardia.

In general, chronic tachycardia eventually causes significant structural changes in the heart, including left ventricular dilatation and cellular morphologic changes. However, the exact mechanism by which tachycardia produces such changes is not well explained. Additionally, the morphologic and biochemical changes that result from arrhythmia-induced cardiomyopathy may produce electrophysiological abnormalities. Chronic tachycardia was associated with ventricular arrhythmias (including polymorphic ventricular tachycardia and sudden death) in a canine model which result from a prolongation in repolarization [6]. Many alterations in neurohumoral and cellular activation have been described in arrhythmia-induced cardiomyopathy patients, and several factors may contribute to the development of rate-related myocardial dysfunction. However, data supporting certain potential mechanisms are lacking, and it remains unclear whether such changes play an etiologic role or if they arise because of tachycardia.

The clinical presentation of arrhythmia-induced cardiomyopathy can vary and usually involves signs and/or symptoms related to HF (dyspnea, fatigue, orthopnea, PND, chest pain or discomfort, lower extremities edema), cardiac tachyarrhythmias (palpitations, lightheadedness, dizziness, anxiety, etc) or both. The approach to the patient with suspected arrhythmia-induced cardiomyopathy includes a thorough history and physical examination with appropriately selected tests to establish the diagnosis and assess acuity, severity, and etiology. All patients should have an electrocardiogram (ECG) to determine the cardiac rhythm and ventricular heart rate (**Figure 2**). There are no specific ECG findings that distinguish patients with

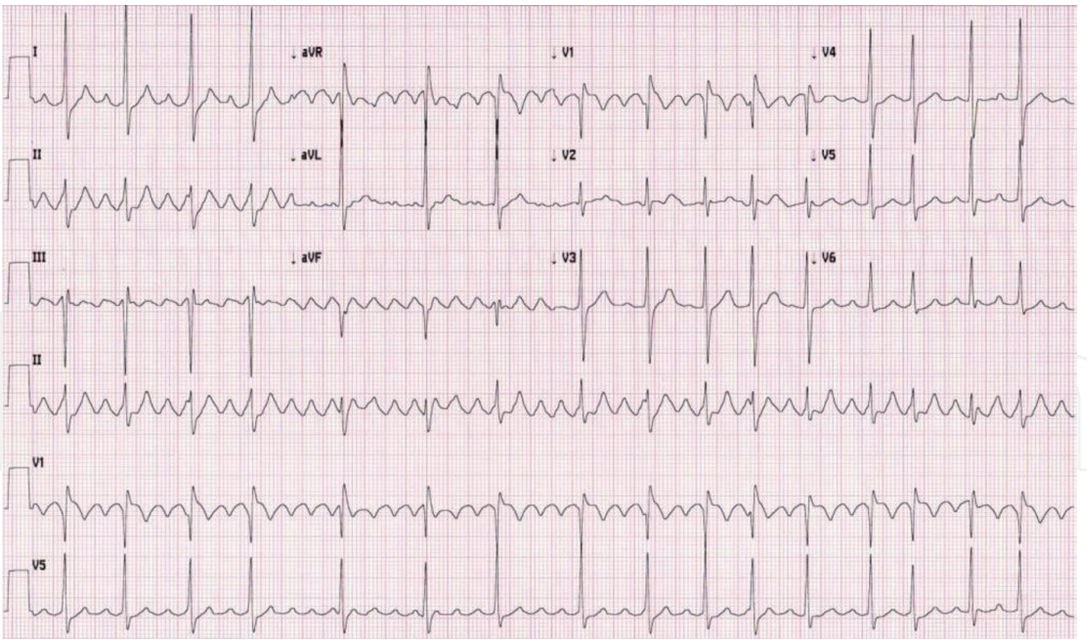

Figure 2.
ECG showing Atrial flutter that can lead to tachycardia-induced cardiomyopathy.

and without arrhythmia-induced cardiomyopathy, and the ECG findings will vary depending upon the underlying tachyarrhythmia. It is important to determine which is the primary pathology, the arrhythmia, or the cardiomyopathy. Usually, the diagnosis of arrhythmia-induced cardiomyopathy can only be made after a successful trial of therapy to slow down the ventricular rate or to restore sinus rhythm after excluding the other potential causes of cardiomyopathy. Patients with suspected arrhythmia-induced cardiomyopathy should have continuous cardiac monitoring for 24 to 48 hours and have non-invasive imaging to assess cardiac structure and function. A transthoracic echocardiogram (TTE) is the preferred modality for assessing cardiac structure and function for most patients due to its widespread availability and ease of performance. However, cardiac magnetic resonance (CMR) imaging is also a reasonable alternative approach in centers with expertise in this modality.

The initial treatments for a patient with HF and suspected arrhythmia-induced cardiomyopathy are similar to those of HF with reduced ejection fraction (HFrEF) and tachyarrhythmias. Treatment of HFrEF generally includes the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, or diuretics. On the other hand, treatment of tachyarrhythmia includes rate-control medications, consideration of antiarrhythmic drugs, and/or cardioversion. Aggressive efforts should be made to achieve good ventricular heart rate control or to restore sinus rhythm due to the potentially reversible nature of arrhythmia-induced cardiomyopathy [2]. Additionally, an adequate trial of medical therapy is required before evaluating the patient for the need for cardiac resynchronization therapy (CRT) or an implantable cardioverter-defibrillator (ICD).

Following the restoration of sinus rhythm or appropriate ventricular rate control, most patients show significant improvement and/or normalization of left ventricular ejection fraction (LVEF) over a period of months. Generally, patients who have not experienced sudden cardiac arrest or sustained ventricular arrhythmia and whose LVEF has improved to 40% or greater, do not require implantation of an ICD. If arrhythmia-induced cardiomyopathy recurs, then these patients are at substantial risk for sudden death and ICD implantation should be considered.

In some patients, the LV chamber may remain somewhat enlarged even after LVEF has normalized. Patients will also have ultrastructural abnormalities of the myocardium, despite improvement in cardiac function when a tachycardia has been terminated or rate controlled [7].

4. Alcoholic cardiomyopathy

Long-term excess alcohol consumption is a leading cause of secondary dilated cardiomyopathy and is associated with up to 40% of dilated cardiomyopathy. Alcohol use can cause atrial enlargement, global chamber dilation, cardiomegaly, and heart failure. Once the structural changes are present, patients with alcoholic cardiomyopathy are at high risk for arrhythmias, especially atrial fibrillation (AF). The prevalence of alcoholic cardiomyopathy is similar in men and women; however, there is a higher disease burden in men. It is more common in the age group of 45–59 years old. Most patients who develop alcoholic cardiomyopathy have been drinking more than 80 to 90 g of ethanol per day for more than five years. This corresponds to approximately eight bottles of beer, one liter of wine, or one-half pint of hard liquor every day. The pathogenesis of alcoholic cardiomyopathy is not well understood, but experimental data have suggested that alcohol consumption may directly or indirectly cause oxidative stress, apoptosis, impaired mitochondrial bioenergetics, altered fatty acid metabolism, and increased myocardial protein catabolism via its metabolites. The pathophysiology of alcoholic cardiomyopathy can also be explained by myocardial toxicity due to adenosine accumulation caused by the impairment of ATP production secondary to thiamine deficiency (Thiamine serves as a co-factor for ATP production).

Common clinical features include classic symptoms of HF (dyspnea, fatigue, orthopnea, PND, chest pain or discomfort, lower extremities edema) and cardiac arrhythmias (palpitations, lightheadedness, dizziness, anxiety, etc). Patients may have a normal physical exam but can also have findings of heart failure such as the decreased intensity of the heart sounds, new S3 or S4 gallop, new murmurs due to valvular insufficiency, increased jugular venous pressure, hepatojugular reflux, and peripheral edema. An EKG usually does not show any specific findings, but may show atrial fibrillation, atrial enlargement, or left ventricular hypertrophy as the most common findings. The mainstay of treatment is abstinence from alcohol which can help in reversing the disease and management of HF. Thus, prognosis in such patients is usually good if they continue to avoid alcohol. If the patient does not stop drinking alcohol, the alcoholic cardiomyopathy may cause severe HF and could advance to severe valvular insufficiency, fatal arrhythmias, and sudden cardiac death.

5. Cardiomyopathy due to acute myocarditis

Myocarditis is a global cardiomyopathy that leads to acute chamber dilation. It is a major cause of death in young adults, reaching up to 20% of deaths. The incidence of myocarditis, according to the International Classification of Diseases' diagnosis codes, was 22 patients per 100,000 patients in the 2013 world population. Myocarditis is an inflammatory disease of the heart that may occur because of infections, immune system activation, or exposure to drugs. The common causes include coxsackievirus (most common), Lyme disease, Chagas disease [8], rheumatic fever, toxic (monoxide, diphtheria, doxorubicin, daunorubicin, cocaine) [9, 10], autoimmune or systemic diseases (SLE, sclerosis, sarcoidosis) [11]. Most

patients diagnosed with acute myocarditis recover without clinically relevant residual damage. Patients usually present with viral illness (Fever, malaise, fatigue, etc.) [12]. Patients can also present with symptoms of acute heart failure and conduction abnormalities (Premature atrial complex, supraventricular tachycardia, ventricular ectopies, bradyarrhythmia) including fatal arrhythmia (Ventricular tachycardia, fibrillation) leading to sudden cardiac death [13].

Common physical examination findings may include chest pain, new gallop, friction rub, or new valvular insufficiency on auscultation; hepatomegaly, cardiogenic shock, tachypnea with or without respiratory distress [14]. The ECG in some patients with myocarditis is similar to the ECG pattern of acute isolated pericarditis (which is suggestive of myopericarditis) or acute MI, myocarditis may be associated with regional ST elevations and Q waves like acute MI [15]. Laboratory tests can reveal elevated levels of troponin, pro-BNP, and CK-MB [16]. Echocardiography can be useful by showing wall motion abnormalities and acute valvular insufficiency [17].

Coronary angiography should be considered in patients when acute coronary syndrome (ACS) cannot be distinguished from the myocarditis clinically [18]. CMR is indicated in patients with suspected myocarditis with elevated troponin level and/or ventricular dysfunction, without a clear cause such as ischemic heart disease [19]. The definitive diagnosis of myocarditis can be made by endomyocardial biopsy (EMB). The need for an EMB should be based upon the likelihood that the results will change management. Histologic examination of EMB in myocarditis reveals cellular infiltrates, which are usually histiocytic and mononuclear with or without associated myocyte damage; specific histological forms of myocarditis include eosinophilic, granulomatous, and giant cell myocarditis. Possible late complications include severe valvulopathies, biventricular failure, and conduction abnormalities [20]. The mainstay treatment is to treat the underlying cause. Most patients with acute myocarditis have partial or full clinical recovery. In some cases, the process may continue subclinically which eventually causes DCM [21]. The likelihood of these late complications is increased in patients who present with greatly diminished left ventricular function.

6. Sepsis-induced cardiomyopathy

Sepsis-induced cardiomyopathy is a reversible condition causing left ventricular dilation that could lead to low filling pressures and low ejection fraction. It usually starts to normalize within 10 days of treatment of underlying sepsis [22]. Sepsis-induced myocardial dysfunction is one of the major predictors of morbidity and mortality in sepsis [23]. It is usually present in more than 40% of cases of sepsis and its presence can increase the mortality rate up to 70% [24, 25]. The exact physiopathology is not completely understood but the role of cytokines and endotoxins is thought to have an important role in the myocardial depression found in this condition. Other factors that are also related are metabolic disturbances, hypoxia, coagulopathies, and oxygen deprivation leading to myocardial injury [26]. Another theory is the high consumption of oxygen by the mitochondria creating an energy imbalance. Pro-inflammatory factors from infectious agents cause a release of cytokines and endotoxins that accelerate the oxygen consumption in a low oxygen environment eventually leading to the production of e metabolites such as free radicals and nitrogen species [27]. These metabolites then create a toxic environment and a transient myocardial injury [28, 29]. Sepsis can also cause Takotsubo cardiomyopathy which is described separately.

The clinical features include fever, elevated WBCs, weakness, and malaise along with clinical features of HF. Physical exam findings may include rash, conjunctivitis, wounds, or evident infection. Patients may also present with hypotension, chest pain, or altered mental status. EKG usually does not show any specific findings, but may show findings suggestive of ACS due to underlying myocardial inflammation [30]. Laboratory tests may show elevated inflammatory markers, such as elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin due to systemic inflammation [31]. Additionally, cardiac markers may be also elevated due to underlying myocardial injury [32, 33]. Furthermore, cultures should be obtained to identify the causative agent before starting a patient on antibiotics. The treatment mainly includes treatment of underlying sepsis and stabilization of the patient when they are hemodynamically unstable to avoid myocardial injury secondary to profound hypotension or arrhythmia. The prognosis of the patient usually varies depending on the severity of sepsis, but generally, the prognosis is reserved.

7. Stress cardiomyopathy or Takotsubo cardiomyopathy

Stress cardiomyopathy is also known as Takotsubo cardiomyopathy or broken heart syndrome, and the clinical presentation mimics acute myocardial infarction [34]. This condition is most common in post-menopausal women. The possible reason for involvement in such a patient group could be explained by hypotheses demonstrating a potential protective effect of estrogen in stress CM [35–37]. The patient with such type of cardiomyopathy should be treated as ACS until the obstructive coronary disease is ruled out by coronary angiography. The pathophysiology behind stress cardiomyopathy is not well understood [38], but the possible mechanism can be explained by the sudden release of catecholamine (Norepinephrine, epinephrine, and dopamine) [39, 40] that causes cardiac stunning by myocyte perfusion impairment and lead to myocardial tissue edema, necrosis, and fibrosis [41].

The clinical features include anxiety, tachycardia, and chest pain which can mimic chest pain of acute MI. EKG may vary from ST segment elevation (most common finding), ST segment depression (less common), QT interval prolongation, T wave inversion, abnormal Q waves, and non-specific abnormalities. Serum cardiac troponin levels are elevated in most patients with stress CM, while creatine kinase (CK) levels are generally normal or mildly elevated. Furthermore, brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels are elevated in most patients with stress CM. Radionuclide myocardial perfusion imaging is generally not indicated in patients presenting with suspected stress cardiomyopathy since most have high-risk features for ACS and will require coronary angiography. Patients with suspected non-ST elevation ACS with low to intermediate-risk features may undergo radionuclide myocardial perfusion imaging. An echocardiogram can show a decrease in LVEF and LV wall motion abnormalities (**Figure 3**). Patterns of LV wall motion abnormality in patients with stress-induced cardiomyopathy include the apical type (most common), and atypical variants including mid-ventricular, basal, focal (limited to an isolated segment), and global types. CMR may be helpful in the diagnosis and evaluation of stress cardiomyopathy when the echocardiogram is technically suboptimal and/or there is coexistent coronary artery disease. Late gadolinium enhancement (LGE) on CMR is usually absent in stress cardiomyopathy in contrast to MI in which intense subendocardial or transmural LGE is seen.

Stress-induced cardiomyopathy is generally a reversible disorder that is managed with supportive therapy [42]. Rapid resolution of symptoms can be usually seen with conservative treatment and resolution of the physical or emotional

stress. However, some patients may develop acute complications such as shock and acute HF that require intensive therapy. Appropriate management of shock varies and depends on whether significant left ventricular outflow tract (LVOT) obstruction is present [43]. HF management during an acute presentation and following stabilization is generally performed according to standard guidelines. However, caution should be performed to avoid volume depletion and with use of vasodilator therapy in patients with LVOT obstruction. Recommendations for anticoagulation to prevent thromboembolism in patients with stress cardiomyopathy with LV thrombus or severe LV systolic dysfunction are similar to those for post-MI patients [44, 45].

8. Peripartum cardiomyopathy

Peripartum cardiomyopathy is an important cause of dilated cardiomyopathy and HF. It is also known as pregnancy-associated cardiomyopathy [46]. The diagnosis can be missed due to the lack of regular screening and overlap between clinical signs or symptoms of HF signs or symptoms of the pregnancy [47]. Peripartum cardiomyopathy usually occurs during the last trimester or within the 6 months of the postpartum period. Several risk factors have been identified which include greater age, multiple gestations, African descent, and a history of preeclampsia, eclampsia, or postpartum hypertension. The pathophysiology is not clearly understood but Honigberg and Givertz suggested the possible role of oxidative stress on myocardium caused by elevated prolactin levels [48].

The clinical features of peripartum cardiomyopathy are usually masked by signs and symptoms of pregnancy and are difficult to diagnose solely based on clinical findings. Patients usually present with similar clinical presentation as HF patients (shortness of breath, fatigue, orthopnea, lower extremities pitting edema). An echocardiogram is the modality of choice for definitive diagnosis of peripartum cardiomyopathy and usually shows dilated cardiomyopathy with an impairment of the ejection fraction [49]. Echocardiogram generally reveals a global reduction in LV systolic function with LVEF nearly always <45 percent. Management is similar to the treatment of HF with reduced EF, such as ACE inhibitors or ARBs or ARNI, beta-blockers, and diuretics. In addition to this treatment, use of bromocriptine should also be considered [50]. However, prophylactic anticoagulation should always be considered along with bromocriptine treatment as thromboembolic events have been noticed during the use of bromocriptine [50]. Patients should get a repeat echocardiogram six weeks after diagnosis has been made for prognostication [51].

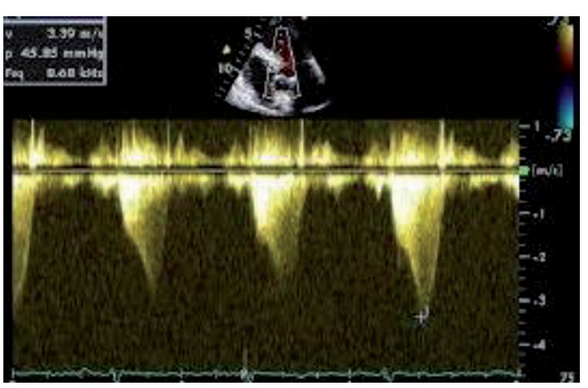

Figure 3.
Doppler image showing LVOT obstruction in a patient with Takotsubo Cardiomyopathy.

9. Thyroid disease induced cardiomyopathy

Metabolic cardiomyopathy is a secondary cardiomyopathy that results from disturbed energy production leading to impaired cardiac function. It may be caused by a myriad of endocrine disorders, nutritional deficiencies, and familial storage diseases [52]. Thyroid hormones have been shown to affect myocytes by acting on various thyroid hormone receptors in the myocardium, including a-myosin heavy chain fusion, sarcoplasmic reticulum calcium-activated ATPase (SERCA), the cellular membrane Na+/K+ pump (Na+/K+ ATPase), β-adrenergic receptors, cardiac troponin I, and atrial natriuretic peptide (ANP) [53]. These interactions help upregulate α-chains but downregulate β-chains in myocytes, which ultimately leads to faster myocardial fibril shortening [54]. Thyroid hormones have also been shown to affect the ion channels, including Na+/K+ ATPase, Na+/Ca + 2 exchanger, and various K+ channels by inducing positive inotropic effects, thereby prolonging activation of Na + channels and shortening action potential durations [55]. Additionally, thyroid hormones have been known to have a vasodilatory effect on peripheral arteries [56]. The combined effort of these mechanisms can cause systemic changes in cardiac function by reducing peripheral vascular resistance, activating the renin-angiotensin mechanism, increasing LV end-diastolic volume (LVEDV), and increasing preload [57]. The increased preload and decreased peripheral vascular resistance lead to a high cardiac output, even at rest, resulting in cardiomyopathy. In contrast to hyperthyroidism, hypothyroidism causes a low cardiac output cardiomyopathy via the same pathways mentioned above, however, by downregulating the previously mentioned receptors/channels causing decreased myocardial excitation and contractility leading to a low-output cardiomyopathy [58]. The clinical features are similar to those seen in patients with HF.

Management of thyroid disease-induced cardiomyopathy follows a similar algorithm to the cardiomyopathies mentioned above, which includes the typical HF treatment regimen. Management also includes addressing the root etiology, whether it be excess or deficiency of thyroid hormones. However, there is promising data showing that the use of β-adrenergic blockade may be beneficial in these patients. Biondi et al. conducted a small study which demonstrated that hyperthyroid patients treated with the selective β1-adrenoceptor antagonist bisoprolol experienced normalization of the LV mass index and LV systolic function after 6 months of treatment [59]. Similar results were established in a case study published a year later in which the use of β-adrenoceptor blockers showed clinical improvement in a patient with dilated cardiomyopathy caused by hyperthyroidism [60]. It is also worth mentioning the association between hyperthyroidism and AF. The prevalence of AF in thyrotoxicosis is estimated to be 13% according to one study. This is especially important as uncontrolled AF is associated with tachycardia-induced cardiomyopathy as discussed above [61, 62].

10. Cardiomyopathy related to obstructive sleep apnea or hypoventilation

Obstructive sleep apnea (OSA) is a potentially life-threatening condition that is characterized by repeated cessation of breathing while sleeping mostly due to complete or partial pharyngeal obstruction [63]. There has been evidence supporting the associations between obstructive sleep apnea and cardiovascular morbidity and mortality. The National Commission on sleep disorders research estimated that sleep apnea is probably responsible for 38,000 cardiovascular deaths per year [64]. Also, obstructive sleep apnea increases the risk of coronary artery disease by 30%,

heart failure by 140%, and stroke by 60% [65]. OSA can be identified by a combination of symptoms and laboratory results, such as repetitive apneas and hypopneas accompanied by hypoxia, sleep arousals, and hemodynamic changes [66–69]. Furthermore, activation of the sympathetic nervous system during respiratory events potentiates vasoconstriction and often triggers increases in blood pressure and heart rate [67, 70]. OSA is also associated with several cardiorespiratory problems such as loud snoring, loud gasps, and daytime breathlessness [71, 72].

The underlying mechanisms showing the associations between OSA and cardiovascular disease are not completely understood, but several intermediate mechanisms have been proposed. They include sustained sympathetic activation, changes in intrathoracic pressure and oxidative stress, and later vascular inflammation caused by nocturnal hypoxia and reoxygenation cycles [73, 74]. These mechanisms then results in increases in systolic blood pressure that might eventually lead to hypertension or worsening of this condition. A similar mechanism might explain the link between OSA and tachyarrhythmia [75]; whereas bradyarrhythmia, which is more common than tachyarrhythmia, might be the effect of an increase in vagal tone due to stimulation of receptor sites in the upper airway [76]. Other abnormalities observed among patients with OSA such as disorders in coagulation factors, endothelial damage, platelet activation, and an increase in inflammatory mediators might also be involved in the pathogenesis of cardiovascular disease [74, 76–79]. Patients with OSA have characteristically higher levels of endothelin and lower levels of nitric oxide than healthy sleepers [74, 77]. This increased endothelin level is known to impair blood pressure regulation as well. Thus, patients with OSA often experience greater blood vessel constriction. Interestingly, with continuous positive airway pressure (CPAP) treatment, levels of endothelin and circulating nitric oxide invariably return to normal [77].

Recently, research interests have centered on the relative contribution of oxidative stress in explaining the associations between sleep apnea and cardiovascular morbidity [74, 79, 80]. Investigators have proposed that hypoxia, which is commonly observed in sleep apnea, promotes the formation of reactive oxygen species (ROS), which could activate the transcriptional activator hypoxia-inducible factor 1 (HIF-1), particularly during the reoxygenation period [81, 82]. ROS regulates the activation of critical transcription factors that are redox-sensitive, resulting in increased expression of genes, which encode proteins promoting adaptation to hypoxia [81]. It has been suggested that redox-sensitive transcription factors, which elicit inflammatory pathways are also activated, thereby affecting inflammatory and immune responses by promoting activation of endothelial cells, leukocytes, and platelets [74]. These cells once activated can express adhesion molecules and proinflammatory cytokines that may lead to endothelial injury and dysfunction, which inevitably lead to the development of cardiovascular morbidity [74]. Observing this chain of events, investigators surmise that atherogenesis apparently starts soon after the onset of sleep apnea [74]. Substantial atherosclerotic insults are likely incurred by the time a diagnosis is rendered since symptoms often become apparent around the age of 45 years [74, 80]. It is unclear whether such atherogenic damages can be reversed, but treatment can retard their progress [83].

Using CPAP therapy, investigators have shown significant reductions in levels of C-reactive protein and interleukin-6 [83], and atherogenic plaque regression has been observed among patients with dyslipidemia [84]. Therefore, sleep apnea diagnosis and treatment should be made as early as possible in order to prevent cardiovascular morbidity. The use of CPAP or bilevel PAP therapy have showed positive benefits in clinical trials. This therapeutic modality is highly effective in improving left ventricular ejection fraction and quality of life by decreasing blood pressure and sympathetic activity and reducing mortality among patients with congestive heart failure [85, 86]. Additionally, CPAP treatment significantly reduces risks of ACS,

cardiovascular death, and hospitalization for heart failure among patients with coronary artery disease [87]. Furthermore, CPAP therapy has significant effects on lipid levels. CPAP studies show significant improvement in insulin sensitivity and left ventricular function with a corresponding decrease in blood pressure [88].

11. Toxic cardiomyopathy

Dilated cardiomyopathy can result from direct exposure to toxins, such as cocaine, alcohol, medications, particularly chemotherapeutic drugs, and radiation in the absence of abnormal underlying cardiovascular conditions such as hypertension, valvular disease, or coronary artery disease. The true prevalence of toxic cardiomyopathy in the general population is not known. The mechanism of toxic cardiomyopathy caused by some common toxic substances has been mentioned here. Alcoholic cardiomyopathy has been discussed separately. Patients with toxic cardiomyopathy usually present with clinical features similar to patients with systolic HF and the treatment involves the avoidance of toxic substances along with treatment for systolic HF.

11.1 Cocaine

Cocaine use is associated with the development of cardiomyopathy. However, the relationship is not well understood as compared to the relationship between cocaine use and coronary ischemia. Multiple mechanisms have been explained including the excessive sympathetic stimulation with increased myocardial oxygen consumption, direct toxic effect, and infectious cardiomyopathy in a parenteral cocaine user. In young persons, cardiomegaly with otherwise unexplained HF should raise the suspicion of cocaine abuse. Abstinence from cocaine usually leads to complete reversal of the myocardial dysfunction.

11.2 Medications

A number of medications such as anticancer drugs, anti-diabetic drugs, or antiretroviral drugs are associated with cardiomyopathy, and discontinuation of such drugs may result in significant improvement in cardiac function.

Anticancer drugs, such as anthracycline, trastuzumab, and cyclophosphamide are known to cause CM. Anthracycline-induced cardiomyopathy has been the most extensively studied. The mechanisms of anthracycline-induced cardiotoxicity are primarily due to its mechanisms of action as anticancer drugs which is inhibition of topoisomerase II β and DNA cleavage. Additionally, metabolic or oxidative stress factors may play a part, together with interference with iron metabolism. On the other hand, trastuzumab is a monoclonal antibody directed against the c-erbB-2 (HER2/neu) receptor that is used in the treatment of breast cancer. Since the HER2 signaling pathway plays an important role in cardiac development and protection, there is biological plausibility for cardiac toxicity with the use of trastuzumab [89, 90]. cardiomyopathy is also known to develop when a loss of function mutation occurs in HER2 in ventricular myocytes [91].

Antidiabetic medications such as thiazolidinedione class drugs are known to cause cardiotoxicity. The possible mechanisms of cardiotoxicity caused by these drugs include oxidative stress and interference with mitochondrial respiration. On the other hand, antiretroviral medications like azidothymidine are also cardiotoxic as a result of mitochondrial toxicity. Azidothymidine also increases the production of mitochondrial reactive oxygen species (ROS) in addition to energy depletion.

11.3 Methamphetamine

Methamphetamine and related compounds are the second most widely used illicit drug in the United States after cannabis [92]. Methamphetamine-associated cardiomyopathy (MACM) may be seen in chronic methamphetamine users. The primary mechanism of action of methamphetamine is the increased release and decreased uptake of catecholamines at the neuronal synapse producing a marked effect on the cardiovascular system [92]. The increased levels of catecholamines can stimulate alpha and beta-adrenergic receptors leading to hypertension and tachycardia. Methamphetamine can lead to irreversible structural and functional changes in the heart which eventually lead to decompensated heart failure and ultimately requiring heart transplantation.

11.4 Carbon monoxide

Carbon monoxide (CO) exposure is known to cause cardiomyopathy by causing hypoxic injury. CO causes direct toxic damage to the mitochondria leading to an impairment of the mitochondrial respiratory chain at the cytochrome c oxidase level and a decrease of glutathione concentrations and ATP production. In survivors of an acute exposure, there is no evidence for a delayed dilated cardiomyopathy. In one retrospective study of 626 patients with CO exposure, only 3.04% (n = 19) patients had CO induced CM [93].

11.5 Trace elements

Trace elements are known to play an important role in myocardial metabolism and their accumulation (cobalt, arsenic) or deficiency (selenium) can be responsible for a form of dilated cardiomyopathy that is indistinguishable from an idiopathic CM. The role of trace elements was assessed in one study in which myocardial and skeletal muscle biopsies were obtained from 13 patients with an idiopathic DCM, 35 patients with valvular or ischemic heart disease, and 4 normal subjects [94]. Patients with a dilated cardiomyopathy had a significant increase in the myocardial concentration of mercury (22,000 times normal), antimony (12,000-fold higher), gold (11-fold higher), chromium (13-fold higher), and cobalt (4 times higher). On the other hand, patients with valvular or ischemic heart disease had myocardial concentrations of trace elements that were ≤ 5 times greater than normal. Concentrations of trace elements in skeletal muscle were normal in all groups of patients.

Cobalt-associated cardiomyopathy probably results from interference with energy production and contractile mechanisms. Cobalt associated cardiomyopathy has been reported in drinkers of beer containing cobalt sulfate for foam stabilization (known as Quebec beer-drinkers' cardiomyopathy) [95], individuals with work-related cobalt exposure, and in some individuals exposed to cobalt from metal hip prostheses [96]. There have been some reported cases where degeneration of metallic hip implants can lead to cobalt cardiomyopathy [97, 98]. Antimony may cause lethal oxidative stress and cell death mediated by elevation in intracellular calcium. Proposed mechanisms for mercury toxicity include depletion of glutathione, ROS production and interruption in selenium-dependent endogenous enzymatic reactions. The existence of lithium-induced cardiomyopathy is still debated.

12. Uremic cardiomyopathy

Cardiovascular diseases are the leading cause of morbidity and mortality in chronic kidney disease (CKD) patients [99]. These adverse cardiovascular

consequences are due to CKD related cardiomyopathy, which is termed uremic cardiomyopathy [100]. Uremic cardiomyopathy in patients with CKD or end-stage renal disease (ESRD) is the result of pressure overload, volume overload, and the uremic state itself. Epidemiological studies and studies using cardiac MRI have suggested that the primary manifestation of uremic cardiomyopathy is LV hypertrophy (LVH). It is present even in patients with very early stages of CKD. The prevalence of LVH in pre-dialysis patients is up to 65%. The pathogenesis of uremic cardiomyopathy is poorly understood and is generally multifactorial. Patients with CKD usually continue to have abnormal myocardial remodeling despite improvements made to dialysis and advancements in the treatment of CKD, hypertension, hypervolemia, anemia. Two factors play an important role in the pathophysiology of patients with CKD and mineral and bone disease (CKD-MBD) which include the hormone FGF23, and its cofactor, αKlotho. FGF23 is deleterious to the myocardium, while αKlotho is protective. Although αKlotho is an obligatory cofactor for FGF23 action as the primary phosphaturic hormone in phosphorus homeostasis, both factors are seen to have independent and antagonistic effects on the myocardium. Briefly, the main pathophysiology of uremic cardiomyopathy includes a triad of hyperphosphatemia, αKlotho deficiency, and elevated FGF23 levels [100].

The cause for very high cardiovascular risk in CKD patients can be explained by effects of traditional and non-traditional cardiovascular risk factors which are augmented by sequelae of CKD, such as uremia, anemia, hypervolemia, oxidative stress, inflammation, and insulin resistance eventually leading to faster progression of cardiovascular disease and increasing the number of cardiovascular events and mortality [101]. About 40% of deaths in dialysis patients are due to sudden cardiac death (SCD) which outweighs deaths due to HF, acute myocardial infarction (MI), and stroke in such population [102]. The major reason for sudden cardiac death in patients with uremic cardiomyopathy is fatal arrhythmia which is in contrast to the general population where the most common reason for SCD is acute MI. The risk factors for adverse cardiovascular events in dialysis patients include anemia, high parathyroid hormone levels, hypo or hypercalcemia, hyperphosphatemia, fast electrolyte shift, chronic volume overload, inflammation, coronary artery disease, autonomic dysfunction, atrial fibrillation, heart failure with systolic dysfunction, and left ventricular hypertrophy (LVH) [103].

The clinical features in uremic cardiomyopathy patients are similar to that of HF patients such as dyspnea, orthopnea, fatigue, weakness, elevated jugular venous pressure, an S3 gallop, rales, and peripheral edema. ECG can show findings suggestive of LVH and may show nonspecific ischemic changes. Echocardiography may reveal LV systolic dysfunction, LV diastolic dysfunction, or valve dysfunction. Laboratory tests may show elevated natriuretic peptides and cardiac enzymes like other cardiomyopathies, but the interpretation of those tests is difficult in a patient with CKD or ESRD as these patients usually have elevated levels of cardiac biomarkers at baseline due to poor renal clearance. Thus, an entire clinical picture with lab tests, ECG findings, and echocardiogram findings should be taken to make a diagnosis of uremic cardiomyopathy.

Conventional hemodialysis is the main treatment for uremic cardiomyopathy, and it may cause regression of LVH. Hemodialysis is also known to reverse the systolic dysfunction and thus improve LVEF in some patients with ESRD. However, patients tend to continue to have cardiac dysfunction or uremic cardiomyopathy even while on hemodialysis treatment, thus conventional hemodialysis may not be adequate treatment despite being the treatment of choice. Renal transplantation has been shown to reverse uremic cardiomyopathy and to confer a significant survival advantage over hemodialysis [104]. Future therapies targeting the underlying cellular mechanisms of uremic cardiomyopathy may help to reduce the burden of

uremic cardiomyopathy in the CKD and ESRD population. In a study on uremic mice, Rapamycin has been shown to reduce cardiac hypertrophy and fibrosis [105]. Thus, rapamycin has the potential to be an effective therapy for uremic cardiomyopathy. LVH is the early and pertinent manifestation of uremic cardiomyopathy as well as a powerful independent predictor of survival in CKD. The regression of LVH can reduce cardiovascular risk and improve survival.

13. Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy (CCM) is defined as a cardiac dysfunction in patients with cirrhosis, which is characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation, with electrophysiological abnormalities, in the absence of other known cardiac disorder [106–108]. For years CCM was confused with alcoholic cardiomyopathy, but in 1953, Kowalski and Abelmann demonstrated the existence of a circulatory dysfunction specific to liver cirrhosis [109]. Since then many experimental and clinical studies have established the existence of CCM different than alcoholic cardiomyopathy. Cirrhosis of the liver leads to a hyperdynamic circulatory state, which induces cardiac dysfunctions that characterize the CCM syndrome which includes a combination of systolic and diastolic dysfunctions, prolonged ventricular repolarization, and the inability of the sinus node to increase heart rate during exercise [108].

CCM is a condition in which patients usually remain asymptomatic for months to years as they have a near-normal cardiac function at rest and develop symptoms only under conditions of physical or pharmacological stress [110]. Thus, the diagnosis of CCM is challenging and the actual prevalence of this condition remains unknown. Pathogenesis of CCM includes mechanisms such as the increased activity of the vasodilator pathway through the actions of NO, cytokines, cannabinoids, carbon monoxide, and cytokines, decreased beta-adrenergic function, and sodium and calcium transport kinetics downregulation in the cardiac muscle which can lead to an impaired contractile function of the cardiomyocyte. CCM is generally a silent condition as patients at rest do not develop any signs or symptoms of heart failure as peripheral vasodilatation protects the heart by reducing afterload [108]. However, CCM should be suspected in patients with cirrhosis presenting with a decrease in exercise tolerance and HF symptoms in the absence of any other underlying heart disease.

Echocardiogram and ECG are the most important tests to diagnose CCM. ECG can reveal prolongation of QT interval in such patients. The most common echocardiography finding in such patients is first-degree diastolic dysfunction which is characterized by reduced early diastolic ventricular filling and increased atrial filling (E/A < 1.0), deceleration time > 200 ms, and prolonged isovolumetric relaxation time (ITVR >80 ms) representing increased resistance to ventricular inflow [111]. Stress echocardiography is also a useful method that should be used in patients with advanced liver disease as it can detect subtle systolic and diastolic dysfunctions before the ventricular ejection fraction is decreased [112]. Laboratory tests usually show elevated levels of troponin, atrial natriuretic peptide (ANP), and NT-proBNP. Additionally, CMR can also serve as a useful tool in the diagnosis of CCM. In patients with CCM, late gadolinium enhancement has a diffuse myocardial distribution in MR images with the appearance of myocarditis [113].

The treatment of CCM is similar to the treatment of HF in non-cirrhotic patients. However, reduction in afterload is not recommended in patients with advanced cirrhosis as these patients are already significantly dilated. However, in

patients with final-stage liver disease and associated with CCM, liver transplantation is the only effective established treatment. Liver transplantation has been shown to reverse the systolic and diastolic dysfunction and prolonged QT interval [114, 115]. However, the unavailability of organ donors and cost concerns should be considered. The candidates must be well evaluated, as patients are at risk of death by HF, coronary artery disease, tachyarrhythmias, and other cardiac deaths in the post-operative term of liver transplantation. There is no accurate data on the prognosis for liver transplantation in patients with CCM. Patients with CCM should avoid physical effort and other forms of stress and should be provided with oxygen in some situations.

14. Conclusion

Reversible cardiomyopathies have been considered as one of the under diagnosed etiologies of non-ischemic cardiomyopathy that require careful clinical insight. Although reversible in nature but if remain undiagnosed, it can lead to catastrophic effects. It is hypothesized to have better prognosis compared to ischemic cardiomyopathy. Early diagnosis is warranted to guide efficient treatment. Further research regarding diagnostic and therapeutic algorithm for this subset of cardiomyopathy is needed to improve long term outcomes (**Table 1**).

Etiology of cardiomyopathy	**Pathophysiology**	**Management**
Myocarditis	Inflammation due to infectious agent, most commonly viral.	Natural course with recovery, no definitive treatment. Steroid may be used in Giant cell myocarditis
Sepsis-induced	Not well understood. Probably reaction due to cytokines release.	Treatment of underlying infection.
Alcoholic	High incidence of cardiomegaly. Toxicity mediated due to adenosine accumulation.	Alcohol cessation
Peripartum	Most commonly in the last trimester. Could be misdiagnosed. Not clear mechanism.	Standard CHF treatment. Bromocriptine may be helpful
Stress Induced	Known as Takotsubo Cardiomyopathy. Caused by sudden release of catecholamine due to stress.	Spontaneous recovery
Tachycardia induced	Arrythmia such as atrial tachycardia and PVC induced	Arrythmia ablation
Thyroid disease-induced	It is a part of Metabolic Cardiomyopathy. Caused by hyper or hypothyroidism. Could lead to arrhythmias especially atrial fibrillation.	Treatment of underlying condition
Hypoventilation Related	Most commonly due to OSA. Could cause structure and hemodynamic changes.	Better prognosis if early intervention of the OSA before severe changes in the intracardiac pressures.
Toxic	Could be cause by licit or ilicit agents that results cardiotoxic	Most of the times reversible once the agent is stopped.

Table 1.
Summary of Reversible Cardiomyopathies.

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