Reversible Cardiomyopathies

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ABSTRACT: Cardiomyopathies (CMs) have many etiological factors that can result in severe structural and functional dysregulation. Fortunately, there are several potentially reversible CMs that are known to improve when the root etiological factor is addressed. In this article, we discuss several of these reversible CMs, including tachycardia-induced, peripartum, inflammatory, hyperthyroidism, Takotsubo, and chronic illness–induced CMs. Our discussion also includes a review on their respective pathophysiology, as well as possible management solutions.

KEYWORDS: arrhythmogenic, cardiomyopathy, chronic disease, immunological, inflammatory, metabolic, reversible, sympathoexcitation

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Cardiomyopathy (CM) is a disease of the heart muscle, which can progressively worsen and ultimately lead to chronic congestive heart failure (CHF). There are more than 800,000 new cases of CHF annually in the United States and 1 in 9 deaths are attributed to this chronic illness.[1] CM is classified into either primary CM, which are confined to the heart, or secondary CM, which is systemic in nature and affects the myocardium in a multi-organ approach.[2] There exist many etiological factors that adversely affect the physiological function of the myocardium leading to structural changes, which can lead to CHF and/or arrhythmias. As such, CMs are typically treated with a standard CHF pharmacological regimen in addition to mechanical circulatory support devices or orthotopic heart transplantation in severe refractory cases. Fortunately, there are several reversible CMs that have been proven to show a return to normal cardiac function with the appropriate management.

Arrhythmogenic (Tachycardia-Induced) Cardiomyopathy

Long-standing tachycardia is a known cause of CM, and return of cardiac function can be occur with the correction of the tachyarrhythmia. Tachycardia-induced CM is classified as a primary CM in which persistent tachycardia causes elevated ventricular filling pressures, severe biventricular systolic dysfunction, reduced cardiac output, and elevated systemic vascular resistance. In animal studies, rapid atrial pacing has been shown to decrease the left ventricular ejection fraction (LVEF) by roughly 52%.[3] Similarly, a 36% drop in cardiac index and 34% increase in cardiac size have been shown to occur with rapid right ventricular pacing.[4]

The pathogenesis behind such large rate-induced changes has led to several theories and one proposed explanation includes depletion of myocardial energy resources from persistent tachycardia. Moe et al demonstrated that canine tissue adenosine triphosphate levels were markedly decreased in the right ventricular paced subjects compared to the controls; 2.79 µmol/g versus 4.77 µmol/g, respectively.[5] Similar reduced concentrations of energy reserves are also seen in myocardial ischemia, which is another suspected premise leading to impaired cardiac function. Some studies have also suggested impaired subendocardial flow and vasodilator reserve[6,7] as potential culprits. Abnormalities in intracellular calcium regulation[8] and β-adrenergic receptors[9] have also been proposed; yet, further studies have to be performed to establish a mechanism. Oxidative stress and injury are possible mechanisms for myocardial injury induced by a fast rhythm. Shite et al were able to show that antioxidants contributed to a 20% reduction in the left ventricular (LV) end-diastolic pressure (LVEDP) in subjects receiving three antioxidants compared to the control group.[10] There is growing interest in the genetic basis of tachycardia-induced CM, as individuals with a specific

angiotensin-converting enzyme gene polymorphism may be more susceptible but further study is still required.[11]

Arrhythmias associated with this type of reversible CM include atrial fibrillation (AF), atrial flutter, atrial tachycardia, reentrant supraventricular tachycardia, accessory pathway tachycardia, frequent ectopic beats, and ventricular tachycardia. There is no data on a set rate above which there is an increased risk of tachycardia-induced myopathy, but any sustained rate above 100 beats per minute may be an important prognostic factor.[12] Sinus tachycardia has also been reported as a cause of CM.[13,14]

Management and restoration of cardiac function is dependent on control of tachyarrhythmias. In cases of AF or atrial flutter causing CM, rate control alone was thought to be effective in normalizing LVEF. Grogan et al demonstrated an improvement in the LVEF of their subjects by a median of 108% with ventricular rate control.[15] Recently, however, new data show that rate control alone may not provide a complete cure and sinus control with ablation may be necessary.[16] Ablation, therefore, remains a viable option for atrial arrhythmias, as well as all other arrhythmias in which sinus control is warranted. There is evidence of premature ventricular contractions (PVCs) leading to CM, in which a patient with a reduced LVEF with over 56,000 PVCs per day was successfully ablated and had normalization of LV systolic function.[17] Though ablation offers effective results, there is concern that it may not offer a permanent solution. In a study by Ling et al, 18 subjects with tachycardia-induced CM underwent successful radiofrequency ablation and subsequently had an increase in LVEF within 3 months. However, at 5 years the same subjects were noted to have an incomplete recovery with diffuse myocardial fibrosis leading to larger LV dimensions, decreased LVEFs, and reduced myocardial strain and twist rates on cardiac imaging studies.[18] As new data emerge, it seems evident that tachycardia-induced CM is reversible, but more permanent management solutions are still required to help maintain normalized cardiac function.

Immunological: Peripartum Cardiomyopathy

This primary CM primarily afflicts pregnant or recently pregnant women and can cause potentially life-altering cardiac dysfunction. Peripartum cardiomyopathy (PPCM) is defined by four criteria: (1) development of heart failure (HF) symptoms either during the last month of pregnancy or within the first 5 months after delivery; (2) no other identifiable causes of HF exist; (3) no evidence of heart disease prior to the last month of pregnancy; and (4) LV systolic dysfunction (either LVEF <45% or reduced fractional shortening).[19] Approximately 30–50% of patients have noted significant improvement in the cardiac function in the first 6 months after presentation.[20] The exact pathogenesis of PPCM is largely unknown, but there are several promising theories. One of the most promising etiological factors is myocarditis, with several studies reporting various incidences of myocarditis in their study population. Midei et al reported a 76% incidence of myocarditis in their subjects with PPCM.[21] One of the reported reasons that they had such a high incidence was because patients were biopsied at the time of presentation. Other confounding factors leading to large variability include inclusion criteria of subjects, geographical variability, and effectiveness of biopsies to establish a diagnosis. Inflammatory cytokines have also been named as possible culprits for PPCM. Plasma levels of cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and Fas/APO-1, a known apoptosis-signaling surface receptor, have been found to be elevated in patients with PPCM.[22] Cytokines are further postulated to lead to PPCM through initiation of an inflammatory cascade when they encounter chimeric fetal cells that have escaped into the maternal circulation. These cells may escape the maternal immune system initially due to either the immunosuppressive state of pregnancy or a weakened immune induction by the paternal haplotype of the chimeric fetal cells. These cells are then able to settle in various organs, including cardiac tissue, leading to an autoimmune trigger when the maternal immune system recovers postpartum.[23] The hemodynamic stress associated with pregnancy, including increase in preload and cardiac output and decrease in afterload, has been show to lead to LV remodeling and hypertrophy.[24] The reduction in LV systolic function brought on by the remodeling process is thought to be more exaggerated in PPCM, though there exists no direct evidence to support this claim. There are, however, animal studies that have supported the role of prolactin in PPCM. Studies in mice have shown that decreased levels of myocardial signal transduction and activator of transcription 3 (STAT3) lead to the catabolism of prolactin to an antiangiogenic and proapoptotic isoform, causing PPCM.[25] These results have been confirmed in patients with PPCM, suggesting a more directed therapy. The final theory of the pathogenesis of PPCM advocates a potential familial link. In a search through the Familial Dilated Cardiomyopathy Research Project database consisting of over 4,000 women from 520 pedigrees, there are 19 cases of PPCM available. Of the 19 cases, 11 have a familial disease and 7 are apparently sporadic (1 subject did not have sufficient family data to be categorized) suggesting a possible genetic link leading to PPCM.[26]

Management of PPCM includes the standard CHF regimen, but careful consideration must be made to avoid all teratogenic drugs, including angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-receptor blockers (ARBs). Hydralazine and nitrates may be safely used as alternative therapies. β-adrenoceptor blockers may also be used during pregnancy, but β_1–selective agents are generally preferred as they do not interfere with uterine relaxation. Patients who have biopsy-proven myocarditis and have not improved with 2 weeks of the standard CHF regimen could be given immunosuppressive therapy, as it may lead to improved LV systolic function and prognosis.[27] Further

study is still required, however, to determine the efficacy of immunosuppressive agents in PPCM. Immunoglobulins have shown merit in treatment of PPCM as proven in a study by Bozkurt et al, in which subjects with PPCM given immune globulin therapy improved their mean LVEF by 26 LVEF units, compared to the controls who improved by 13 LVEF units.[28] Bromocriptine may also be a potential treatment option in the future, as it is a known dopamine receptor agonist and can suppress prolactin secretion. In a small study conducted in South Africa, it was shown to improve the LVEF by more than 100%.[29] Larger trials and further studies are required to establish its efficacy, but initial data have shown promising results.

Inflammatory/Infectious Cardiomyopathy

Inflammatory cardiomyopathy (IC), classified as primary CM, is defined as inflammatory disease of the myocardium (myocarditis) in association with cardiac dysfunction. There are both non-infectious and infectious causes of IC. Non-infectious origins include toxins, alcohol, cytotoxic chemotherapy, and metabolic abnormalities. Infectious causes of IC are predominately viruses, of which the most common culprits are Coxsackie viruses. Other viruses include various respiratory tract viruses, cytomegalovirus, parvovirus, mumps virus, and hepatitis C virus. Other less commonly implicated pathogens include bacteria, mycobacteria, fungi, protozoa, rickettsiae, chlamydiae, and parasites.[30]

The pathogenesis of IC has been postulated to be attributed to an autoimmune response that was dependent on the role of T-cells. As early as 1974, it was shown that mice treated with antithymocyte serum had a reduction in myocardial inflammation and injury when inoculated with Coxsackie virus B_3.[31] It was not until about a decade later that a more defined theory emerged explaining the pathogenesis of IC to include the concept of molecular mimicry. In a study by Weller et al, it was shown that monoclonal antibodies directed against receptors on the Coxsackie virus also recognized receptors on cardiomyocytes.[32] Further study by Rose and Hill showed that this cascade was dependent on the function of TNF-α and interleukin-1 (IL-1).[33] Another theory attributed IC to viral infection directly causing cardiac injury through destruction of dystrophin[34] and/or activation of the mitogen-activated protein kinase pathways leading to increased intracellular calcium and thus cell death.[35]

An important entity to discuss here is HIV-associated CM. It is estimated that in the AIDS population the prevalence of CM could be as high as 1.6% per year. The etiology appears to be direct infection of myocytes with HIV-1 virus leading to a patchy form of myocarditis. Unlike other HIV-associated systemic manifestations, no evidence exists from prospective trials to support a role for highly active antiretroviral therapy (HAART) in reversing this CM. However, there have been reports on improvement in LVEF and wall stress with the use of intravenous immunoglobulin (IVIG).[36]

An endomyocardial biopsy based on the Dallas classification system[37] is one of the prime methods of diagnosing IC. However, there remains some controversy on the reliability of a biopsy due to difference in expert opinion possibly secondary to varying results obtained from different biopsy locations.[38] Once a diagnosis of IC is established, supportive care is usually the first line of treatment as many cases of IC have been shown to spontaneously resolve. Fulminant cases of IC typically require a CHF regimen, but may progress to include inotropic therapy and/or mechanical support. Due to the inflammatory nature of IC, there has been more discussion into the use of anti-inflammatory therapy as a possible treatment strategy. In as early as 1989, Parrillo et al were able to show that patients with biopsy-proven IC had an average 5.5% improvement in their LVEF with the use of steroids.[39] These results were further collaborated in 2001 by Wojnicz et al, who conducted a 2-year study on the benefits of prednisone plus azathioprine in patients with biopsy-proven IC and increased human leukocyte antigen (HLA) expression on tissue biopsy. Their study revealed no difference in the morbidity and mortality of their patient population at the 2-year mark, but showed significant improvement in the LVEF of the test group compared to the control group at 3 months and 2 years.[40] Although there was a significant improvement in LVEF, further studies are still required to further determine the optimal pharmaceutical therapy, including monotherapy versus combination therapy, duration of treatment, and patient selection.

Sepsis-induced cardiomyopathy (SICM) is a very common phenomenon that has been receiving increasing attention. Cardiac dysfunction during sepsis and septic shock occurs in up to 60% of patients[41] and has been associated with increased mortality.[42] It is mainly manifested as biventricular dilatation and depressed LVEF.[43] Nonetheless, LV stroke work index appears to be a very sensitive indicator of myocardial depression in these patients as it is present in 94%.[44] Increased LVEDP is indicative of diastolic dysfunction in sepsis patients.[45] Contradictory to the old belief that depressed LVEF is considered a poor prognostic factor, Charpentier et al found that higher brain natriuretic peptide (BNP) levels might confer a worse outcome.[46]

The pathophysiology of SICM is very complex and not entirely understood; nevertheless, it is agreed upon that inflammatory cytokines (eg, TNF-α and IL-1)[47] as well as nitric oxide (NO)[48] play a pivotal role in the process.

There are ongoing efforts to establish therapeutics that directly target the cardiovascular process. However, targeting the underlying infectious process with the appropriate antibiotics and providing hemodynamic support is still the therapeutic approach of choice.

Metabolic: Thyroid Disease–Induced Cardiomyopathy

Metabolic CM is a secondary CM that results from disturbed energy production leading to impaired cardiac function. It may be caused by a myriad of endocrine disorders, familial storage

diseases, and/or nutritional deficiencies. We have chosen to specifically focus on how the imbalance in thyroid hormones might lead to reversible cardiac dysfunction.

Thyroid hormones have been shown to affect myocytes by acting on various thyroid hormone receptors in the mycocardium, including α-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).[49] These interactions help upregulate α-chains, but downregulate β-chains in myocytes, which ultimately leads to faster myocardial fibril shortening.[50] 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.[51] In addition to affecting the myocardium, thyroid hormones have been known to have a vasodilatory effect on peripheral arteries.[52] The combined effort of these mechanisms can lead to systemic changes in cardiac function due to reduced peripheral vascular resistance, activation of the renin–angiotensin mechanism, increased LV end-diastolic volume (LVEDV) and increased preload.[53] The increased preload and decreased peripheral vascular resistance leads to a high cardiac output, even at rest, resulting in CM. In contrast to hyperthyroidism, hypothyroidism causes a low cardiac output CM 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 CM.[54]

Management of CM induced by dysthyroidism (hyper- or hypothyroidism) follows a similar algorithm to the CM mentioned above, which includes the typical CHF regimen. Management also includes addressing the root etiology, whether it be excess or deficiency of thyroid hormones. There is, however, promising data showing that the use of β-adrenergic blockade may be beneficial in these patients. In a small study by Biondi et al, hyperthyroid patients treated with the selective β_1-adrenoceptor antagonist bisoprolol experienced normalization of the LV mass index and LV systolic function after 6 months of treatment.[55] 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 CM caused by hyperthyroidism.[56]

It is also worth mentioning the association between hyperthyroidism and AF. One study estimated the prevalence of AF in thyrotoxicosis to be 13%. This is very important as uncontrolled AF is associated with a tachycardia-induced CM as discussed above.[15,16]

Sympathoexcitation-Induced Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM) is also known as stress CM, apical ballooning syndrome, or broken-heart syndrome. This primary CM occurs, in its typical form, when the contractile function of the mid and apical segments of the LV are depressed and there is hyperkinesis of the basal walls, producing a balloon-like appearance of the distal ventricle with systole. Reverse Takotsubo,[57] right ventricular Takotsubo,[58,59] and global hypokinesis[60] have also been described as atypical forms.

It often presents with signs and symptoms of an acute coronary syndrome (ACS), without any angiographic evidence of spasm or stenoses and is most prevalent in older women.[61] TCM was first described in Japan in 1990 and has seen a surge in incience, as evidenced by over 300 publications in the past 20 years.[62]

Symptoms are typically preceded by exposure to emotional or physical stressors, leading to symptoms typical of acute myocardial infarction (AMI), including chest pain and dyspnea. There have been several proposed mechanisms hypothesizing the pathophysiology leading to this reversible CM, one of which suggests that the structural findings of TCM may be secondary to coronary microvascular impairment. In a small study by Yoshida et al, test subjects were shown to have severe metabolic abnormalities with slightly reduced myocardial perfusion based on findings from ^{18}F-fluorodeoxyglucose myocardial positron emission tomography and thallium-201 myocardial single-photon emission computed tomography, respectively.[63] These findings may help confirm another postulated theory suggesting catecholamine cardiotoxicity as a potential etiology. Increased levels of circulating catecholamines, especially epinephrine, have been shown to increase the levels of intracellular concentration of calcium leading to myocardial dysfunction.[64] Elevated levels of circulating catecholamines were confirmed by Wittstein et al, who showed that subjects with TCM had 2–3 times and 7–34 times the levels of catecholamines when compared to patients with AMI and normal published values, respectively.[65] However, the catecholamine excess theory was recently challenged by the recent published findings of normal plasma epinephrine and metanephrine levels in the majority of 33 TCM patients. In that study, some patients had mild to moderate elevations in plasma levels of studied catecholamines, which was attributed mainly to HF.[66] Nevertheless, it is well documented that increased catecholamines lead to increased SVR, systemic blood pressure, and cardiac afterload. They also lead to hypercontraction and possible left ventricular outflow tract (LVOT) obstruction, leading to increased stress in the LV apex. The LV apex is more prone to the effects of catecholamines, in large part due to a greater concentration of β-adrenoreceptors.[67] The catecholamine theory was further supported by a recent publication by Shao et al in the pathogenesis of inverted TCM. They have suggested that a catecholamine-induced increase in LV afterload produces changes in the LV similar to those described in acute pulmonary embolism; that is, akinesis of the RV mid-free wall with the apex retaining its systolic function (also known as McConnell's sign).[68]

Additionally, there have been numerous reports linking this entity to certain medications and toxins such as albuterol,[69] high-dose intravenous cytarabin,[70] 5-fluorouracil,[71] entacapone,[72]

and allopurinol[73] as well as the inhalation of hypochlorite gel exhalations.[74] Furthermore, a case has been reported on a possible link to cocaine abuse.[75]

Despite Guillian-Barre syndrome (GBS) being an infectious disease, we elected to mention it briefly here as a cause of a reversible TCM-like CM as some case reports attributed this phenomena to excess catecholamines secondary to autonomic dysfunction in these patients.[76,77]

In TCM, the LV function usually returns to normal within a few weeks. On the cellular level, changes such as cytoskeletal protein derangements, increased extracellular matrix proteins, and intracellular glycogen accumulation were shown to also be nearly completely reversible in correlation with the normalization of the LVEF.[78] In the interim, symptoms can usually be managed with β-adrenoceptor blockers, as well as ACE-Is or ARBs. The use of β-adrenergic blockers in the acute management is still debated, given that it can lead to unopposed stimulation at the α-adrenoceptor level. As such, it is generally recommended to use agents with both α- and β-adrenoceptor blocking ability.[79] The prognosis is typically encouraging, yet there remains an 11.4% rate of recurrence in 4 years.[80]

Cardiomyopathy of Chronic Diseases: Cirrhosis, Obesity, and Uremia

In the intricate balance of the human body, chronic disease in other organ systems can have direct deleterious effects on the heart leading to a secondary CM. Three such chronic diseases that can result in reversible CM are cirrhosis, obesity, and kidney failure leading to uremia. Cirrhotic CM is defined as an increase in the baseline cardiac output with systolic and/or diastolic dysfunction, but without evidence of HF at rest, and a possible increased QT_C interval.[81] Obesity-associated CM, also known as lipotoxic CM, results from hemodynamic changes associated from excess adipose accumulation.[82] Uremic CM is manifested by LV hypertrophy due to chronic kidney disease or end-stage renal disease secondary to a persistent uremic state.[83]

Cirrhotic CM is caused by an interplay of several different pathophysiological mechanisms brought on by the hyperdynamic circulation in cirrhosis. One such mechanism is an impairment of stimulatory β-adrenergic receptor signaling pathways. Ma et al were able to show that rats with induced cirrhosis had multiple adrenergic signaling defects due to increased cholesterol composition in their cardiomyocyte plasma membranes. The increased cholesterol to protein ratio leads to decreased membrane fluidity and thereby protein receptor dysfunction.[84] Cardiomyocyte contractile impairment is also hindered by the overproduction of negative inotropic agents, including NO and carbon monoxide. Both agents are known to stimulate an increase in cGMP, which works to inhibit calcium release from the sarcoplasmic reticulum and therefore reduce contractility.[85,86] Endocannabinoid production, a known negative inotropic agent in humans, is also shown to be increased in cirrhotic CM, possibly due to increased hemodynamic requirements.[87]

Hyperdynamic circulation is also present in obesity CM and is brought about by a metabolic surge due to increased adipose tissue metabolism. Increased blood volume and cardiac output lead to structural changes, including LV hypertrophy and dilatation.[88] Obesity is also directly linked to a state of insulin resistance and thus hyperglycemia. Hyperglycemia has been shown to cause glucotoxicity by inducing cardiomyocyte apoptosis via creation of advanced glycation end-products and post-translational extracellular protein, which can alter the function and expression of intramyocellular calcium channels.[89] The state of chronic inflammation induced by obesity is also a culprit for the pathophysiological changes seen in this CM. The Multi-Ethnic Study of Atherosclerosis showed the association between obesity and HF through an inflammatory pathway, with IL-6 showing a higher correlation with HF.[90] The specific role of adipokines in obesity CM still remains unclear, but new research has brought forth some new insight. Adiponectin has been shown to modulate anti-inflammatory and prosurvival reactions by inhibiting cardiac remodeling, while leptin stimulates cardiac hypertrophy and has negative inotropic effects via stimulation of NO.[91] It is speculated that an imbalance in the adiponectin-leptin ratio may play a role in CM, but further research is warranted before conclusive statements can be made. Cardiac lipotoxicity or cardiac steatosis also plays a role in obesity CM by increasing the oxidative stress of cardiomyocytes. Fatty acids, especially saturated long-chain fatty acids, are common culprits and are increased due to the excess adipose tissue, as well as due to increased insulin levels secondary to insulin resistance. Excess fatty acids are shunted to the non-oxidative pathways, which can ultimately cause defective intracellular signaling, promote inflammation, induce intracellular dysfunction, and cause apoptosis.[92]

Uremic CM occurs due to a state of increased pressure and volume, in addition to uremic overload. Increased pressure and volume initially lead to LV hypertrophy, but with continued stress cause dilatation and ultimately lead to LV systolic dysfunction. Myocardial fibrosis may also occur, which contributes to diastolic dysfunction. A uremic state can causes cardiac dysfunction, as proven by McMahon et al who noticed LV hypertrophy in rats who underwent nephrectomy.[93] Hypertrophy in the uremic state is theorized to be the result of accumulation of hypertrophic substances, such as cardiotonic steroids. These endogenous cardiotonic steroids are inducted into a signal cascade that is capable of producing reactive oxygen species (ROS) molecules, as well as the other mentioned pathophysiological changes. Further research is still warranted as the mechanism is still not well differentiated.[94]

CMs of chronic disease, not unlike the other CMs mentioned above, can be addressed with a standard CHF regimen of diuretics, β-adrenoceptor blockers, and ACE-Is/ARBs. This specific group of CMs, however, can be reversed with a surgical approach correcting the organ inducing the CM. Torregrosa et al were able to show reversal of cardiac alterations after orthotopic liver transplantation for patients with cirrhotic CM.

Table 1. Summary of common reversible cardiomyopathies and proposed mechanisms.

CARDIOMYOPATHY TYPE	SUBTYPES EXAMPLES	KEY SPECULATED MECHANISM(S)
Tachyarrythmia-induced	*Sinus tachycardia* *Rapid AF/Aflutter* *Ventricular tachycardia* *Reentrant tachycardia*	1) Tissue adenosine triphosphate depletion due to sustained tachycardia 2) Impaired subendocardial flow and vasodilatory reserve
Autoimmune mediated	*Peripartum*	Cytokine/autoimmune mediated myocarditis
Inflammatory/Infectious	*HIV cardiomyopathy* *Viral Myocarditis* *Sepsis/Septic shock induced*	1) T-cell autoimmune-dependent response 2) Direct destruction of dystrophin 3) Activation of the mitogen-activated protein kinases (MAPKs) pathway →↑Ca^{+2} influx → cellular death
Sympathoexcitation	*Takotsubo* *Autonomic dysfunction* *Medication-induced*	1) Myocardium microvascular impairment 2) Catecholamines Excess →↑intracellular Ca^{+2} → myocardial dysfunction 3) Chronic stimulation of myocardial β-adrenoreceptors from an exogenous source
Metabolic	*Hyperthyroidism* (high cardiac output CM) *Hypothyroidism* (Low cardiac output CM)	*Interaction with the following: (↑interaction with *Hyperthyroidism*/ ↓interaction with *Hypothyroidism*) 1) α-myosin heavy chain fusion (α–MHC), 2) Sarcoplasmic Reticulum Calcium-activated ATPase (SERCA), 3) Cellular membrane Na^+/K^+ pump (Na^+/K^+ ATPase), 4) β-adrenergic receptor
Chronic Diseases	*Cirrhosis*	1) ↑Cholesterol:protein ratio→ ↓membrane fluidity→protein receptor dysfunction (adrenergic receptors) 2) ↑ negative-inotropic agents (Endocannabinoid, CO, NO)→ ↑cGMP→↓sarcoplasmic Ca^{+2} release →↓ contractility
	Obesity	1) Insulin resistance→Glucotoxicity→Cardiomyocyte apoptosis 2) Chronic inflammatory state(IL-6) → Apoptosis via (Ca^{+2} influx) 3) Cardiac steatosis
	Uremia	1) Cardiac hypertrophy caused by→Accumulation of cardiotonic steroids → Sustained ↑ volume and pressure 2) Cardiac fibrosis

Two-dimensional echocardiography images taken 6–12 months post-transplant showed an improvement in the LVEF from 73 ± 5% to 67 ± 5%, LV end-diastolic diameter (LVEDD) from 49 ± 6 to 47 ± 5 mm, and LV posterior wall thickness from 10.2 ± 1.3 to 9.5 ± 1.2 mm; all with $P < 0.05$. Stress test findings also showed similar improvements during physical exertion.[95] In patients with obesity CM, weight loss has been shown to be the most effective approach to manage these patients. A common and effective method has been through bariatric surgery, which has shown favorable results. McCloskey et al were able to show a 50.4% reduction in weight for patients with obesity CM after 6 months post-procedure with an improvement in the LVEF from 23 ± 2% to 32 ± 4% ($P < 0.05$).[96] Bariatric surgery is also effective in reducing LV mass, LV cavity size, oxygen consumption rate, and LV diastolic function.[97] Similarly, kidney transplantation appears to be the most effective solution for uremic CM, as seen by an improvement in the LVEF from 31.6 ± 6.7% pre-transplant to 52.2 ± 12.0% 12 months post-transplant.[98]

Conclusion

We have discussed various reversible CMs here (summarized in Table 1), as well as mentioned the most appropriate therapeutic approaches. Reversible CMs have been shown to have a transient impact on the heart if correctly diagnosed and treated, with improvement in both the functional and structural cardiac regulation. Further research is still warranted, however, as there is much to be learned about these CMs, as well as others, to ensure the most efficient management strategies for patients afflicted with these morbid conditions.

Author Contributions

Conceived and designed the experiments: TJV. Analyzed the data: TJV. Wrote the first draft of the manuscript: HP and TJV. Contributed to the writing of the manuscript: RM, SKV, CEK. Agree with manuscript results and conclusions: HP, RM, SKV, CEK, TJV. Jointly developed the structure and arguments for the paper: TJV. Made critical revisions and approved final version: TJV. All authors reviewed and approved of the final manuscript.

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