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The Evolving Face of Heart Failure Associated with Elevated Cardio-Metabolic Risk Factors

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1. Introduction

1.1 Evolving profile of heart failure

There have been many definitions of Heart Failure and yet the most recent definitions rely heavily on clinical manifestations: dyspnoea or undue fatigue on exertion, along with the evidence of fluid retention, supported by objective evidence of structural or functional abnormalities of the heart at rest. A more recent classification also recognizes and emphasizes the need for the above signs and symptoms for both the development and progression of heart failure (Dickstein et al., 2008). The 2009 update of the AHA guideline identifies patients at higher risk of developing or progressing more rapidly to heart failure as traditionally defined. Table 1.

The presence of cardio-metabolic risk factors (hypertension, diabetes, obesity and metabolic syndrome) in addition to atherosclerotic disease puts the patient at twice greater risk of developing and/or progressing to heart failure as currently defined i.e. with structural or functional heart disease at rest. Studies across the world, particularly in India, China and Latin America suggest that overweight, metabolically challenged individuals are at greater risk of heart failure at a younger age and are also twice as likely to have heart failure linked events such as hospitalization or mortality (Clarke et al., 2010).

Echocardiography and Doppler imaging of the heart are the current gold standards for identification of structural and to extent also functional abnormalities. Advances in Echocardiography and Doppler imaging have enabled the identification of an under-diagnosed entity described as diastolic dysfunction, an additional handicap for a failing heart. Prognosis of patients with predominant diastolic dysfunction (Heart Failure with Preserved Ejection Fraction: HFPEF) has been reported to be similar to those who have predominant systolic dysfunction. In some population surveys, up to 50% of patients fall in this category (Paulus, 1998). Many have co-morbidities identified as risk factors in Stage A of the AHA classification. It is therefore pertinent to understand why and how these additional risk factors influence the development and progression of heart failure as different from and often in addition to Atherosclerotic Coronary Artery Disease.

Diabetes, hypertension, dyslipidemia and thyroid dysfunction affecting heart are often considered as factors contributing to coronary artery disease. However, there is evidence to

suggest that diabetes and hypertension may affect myocardial function largely independent of significant epicardial coronary artery disease. The main objective of this chapter is to explain holistic effects of cardio-metabolic risk factors on heart failure. We urge the reader to consider factors beyond the myocardium, such as vascular responsiveness, neuroendocrine maladaptation and renal function and correlate it with clinical manifestations. This chapter elucidates and correlates recent advances in understanding of etiological factors affecting the myocardial function, the mechanisms which could be influencing overall progression and presentation of heart failure, current diagnostic approaches, their limitations and emerging concepts, current medical therapies, their limitations and newer emerging therapeutic approaches.

Subjects at Risk for Heart Failure	
STAGE A High risk for HF Non symptomatic No structural defects	STAGE B Non symptomatic Structural defects present
PATIENTS WITH <ul style="list-style-type: none">– Hypertension– Atherosclerotic disease– Diabetes– Obesity– Metabolic syndromeor– Using cardiotoxins– With FHx CM	PATIENTS WITH <ul style="list-style-type: none">– Previous MI– LV remodeling including LVH & low EF– Asymptomatic valvular disease
THERAPY Goals <ul style="list-style-type: none">• Treat hypertension• Encourage smoking cessation• Treat lipid disorder• Encourage regular exercise• Discourage alcohol intake• Control metabolic syndrome Drugs <ul style="list-style-type: none">• ACEI or ARB in appropriate patients for vascular disease or diabetes	THERAPY Goals <ul style="list-style-type: none">• All measures under stage A Drugs <ul style="list-style-type: none">• ACEI or ARB• β blockers Devices <ul style="list-style-type: none">• In selected patients: Implantable defibrillators

Table 1. Stages in the development of heart failure and recommended therapy by stage. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; EF, ejection fraction; FHx CM, family history of cardiomyopathy; HF, heart failure; LVH, left ventricular hypertrophy; and MI, myocardial infarction. Modified from Jessup M, Abraham WT, Casey DE et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults (Jessup et al., 2009).

2. Cardio-Metabolic Cardiomyopathy (CMCM)

The etiology of cardiomyopathy associated with diabetes is widely debated. While hyperglycemia is regarded as a sole culprit in causation of diabetic cardiomyopathy, there is a cluster of associated risk factors - obesity, hyperlipidemia, prothrombotic state, hypertension, activation of multiple hormone and cytokine systems etc, which are commonly seen in most patients presenting with diabetes of more than five years and these in turn have intricate effects in causation of cardiomyopathy. More and more researchers are now focusing on the overall impact of diabetes and cluster of these observable conditions on altered metabolism and energetics at cellular level of the target end organs, which are known to be most vulnerable to such altered conditions. Increasing evidence are now available which suggest that altered myocyte functioning is more a function of altered cellular metabolism. It is seen that simultaneous over-activation of renin-angiotensin-aldosterone system (RAAS), increased oxidative stress and compromised endothelial function, contributed by each individual component adds to overall dysfunction of myocardium. Effect on peripheral vasculature adds on to the already stressed myocardium and predispose to an early compromise in over all cardiovascular functions.

Many of the changes described occur in predisposed individuals even before the onset of diabetes, often at the stage when they may be diagnosed as having pre-hypertension or impaired glucose tolerance. There is therefore a need for holistic terminology which could represent contribution of not only of diabetes and associated hyperglycemia but equally of other factors - obesity, dyslipidemia, hypertension, in the pathogenesis of cardiomyopathy, for which the term “Cardio-metabolic Cardiomyopathy (CMCM)” seems appropriate (Fig. 1). The terminology CMCM is based on available evidence of altered

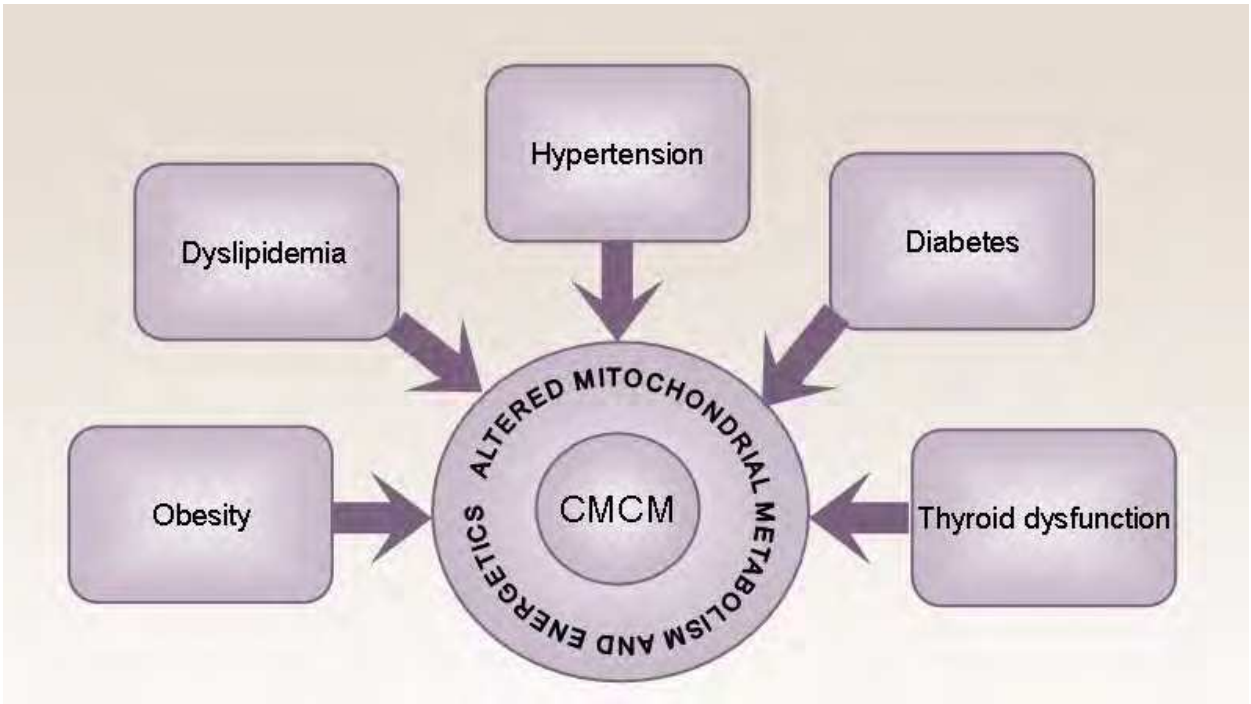


Fig. 1. Various possible risk factors that could contribute to the development of Cardio-metabolic Cardiomyopathy (CMCM).

myocytes metabolism and energetics leading to cardiomyopathy. This would need further support from ongoing and future research to consolidate itself as a new class of cardiomyopathy representing cluster of metabolic derangement and altered energetics of myocytes with a common underlying derangement – diminishing flexibility to use the appropriate fuel to provide adequate energy, resulting in dysfunctional mitochondria.

2.1 Mechanisms of CMCM

2.1.1 Myocardial metabolism in normal heart

A normal healthy heart uses free fatty acid (FFA) as its preferred fuel source and to a lesser extent, circulating glucose (Fig 2). In case of severe starvation it can also utilize lactate,

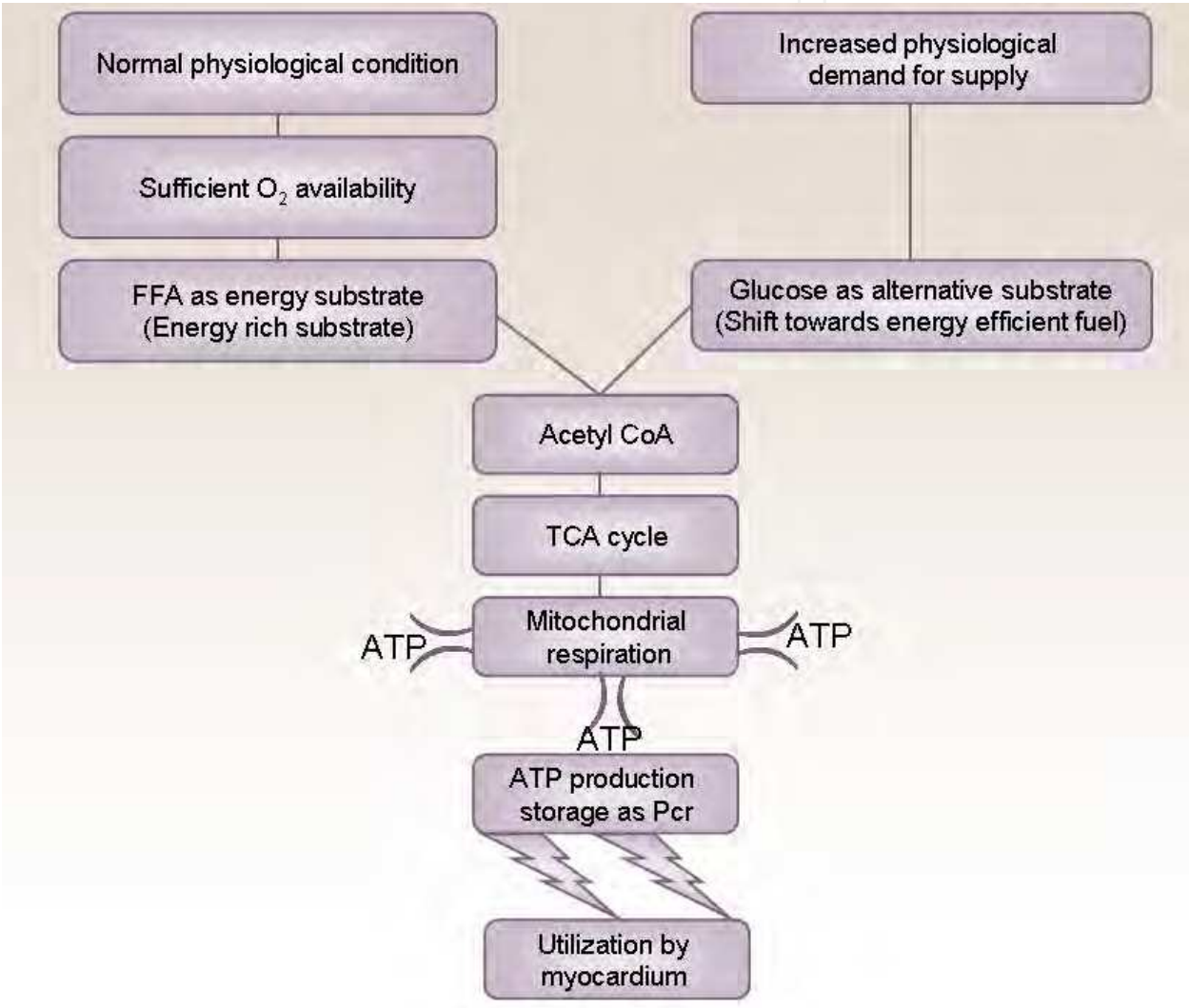


Fig. 2. Myocardial metabolism in normal heart. Normal myocardium at resting state uses FFA as a preferred fuel source, which is energy rich substrate but yield less ATP per mol of O₂. While in the state of increased peripheral physiological demand (e.g. exercise) myocardium uses glucose as energy source which is more efficient energy source and yield more ATP per mol of O₂. ATP, Adenosine triphosphate; FFA, Free fatty acid; O₂, oxygen; Pcr, Phospho creatinine.

ketone bodies and amino acids. The regulation of myocardial metabolism is dependent on the availability and abundance of substrate, hormone levels, coronary blood flow and oxygenation and inotropic state of the tissue. With ageing, relative contribution of glucose as myocardial substrate increases as seen in elderly. The levels of FFA determine its uptake by myocytes. Following uptake and conjugation with acetyl CoA (FA-CoA), FA-CoA enters the mitochondria, via the carnitine acyl transferase shuttle (CPT-1 and CPT-2). CPT-1 is subject to allosteric regulation by malonyl CoA and effective transfer to the mitochondria requires adequate amounts of carnitine (Abel & Doenst, 2011). Upon entering the mitochondrial matrix, FA-CoA undergoes β -oxidation. Post prandial, higher levels of insulin in blood increases muscle glucose uptake by increasing glucose transporters (GLUT-1 and GLUT-4) translocation and by suppressing FFA release from adipose tissues thereby removing FFA mediated inhibition of glycolysis and pyruvate oxidation.

2.1.2 Metabolic disturbances in cardio-metabolic cardiomyopathy (CMCM)

There are many factors considered as initiators to the functional and structural alterations which contribute to the development and progression of CMCM. Most of these evidence are from animal experimental studies. Though development of CMCM is multi-factorial, metabolic disturbance is the major culprit.

2.1.2.1 Altered fuel supply and altered substrate utilization

Increasing evidence suggests that altered substrate supply and utilization by cardiac myocytes could be the initial trigger in the pathogenesis of CMCM. Under deranged metabolic milieu, inclusive of diabetes, heart use relatively more fat than normal heart (Herrero et al., 2006; Carley & Severson, 2005). The shift towards increased fatty acids and decreased glucose utilization is linked to elevated circulating levels of FFA and triglycerides as a consequence of enhanced adipose tissue lipolysis, increased FFA uptake as well as high tissue FFAs caused by hydrolysis of augmented myocardial triglyceride stores. Animal studies in db/db mice, (a model of type II diabetes with obesity and hyperglycemia), have shown increased cell membrane fatty acid (FA) transporters (FAT/CD36) and FA binding proteins leading to increased FA uptake in db/db mice hearts (Carley & Severson, 2008). To handle this increased FA, there is upregulation of mitochondrial enzymes involved in fat metabolism.

The reduced glucose utilization seen in such condition is partly accounted for by the slow rate of glucose transport across the sarco-lemmal membrane into the myocardium, which is probably due to the cellular depletion/reduced translocation of GLUT-4 caused by insulin resistance (Garvey et al., 1993). High circulating FFA and increased FA oxidation inhibits pyruvate dehydrogenase complex thereby reducing glucose oxidation.

Exercise influences myocardial glucose utilization, perhaps independent of insulin levels. Graded exercise in all cases of heart failure has been documented to be beneficial. It is likely that exercise has a beneficial effect in maintaining the substrate flexibility of the myocardium.

2.1.2.2 Lipotoxicity associated with excessive accumulation of intracellular lipids

When FA uptake exceeds FA oxidation capabilities, lipid accumulation occurs resulting in lipotoxicity. This is evident in diabetics and obese patients but not seen in non-obese. High circulating and cellular FFA necessitates abnormal higher oxygen demand during FFA metabolism in addition to enhancing peripheral insulin resistance. This results in accumulation

of toxic intermediates of FFA metabolism leading to impaired functional performance. Fuel surplus is likely to activate peroxisome proliferators-activated receptor (PPAR- α) with subsequent increase in FA oxidation. Accumulation of palmitate results in increased free radical production and endoplasmic reticular stress which leads to apoptosis (Borradaile et al., 2006). Palmitate accumulation can also promote denovo ceramide production which is also an inducer of apoptosis. Carnitine, an essential substrate for myocardial FFA metabolism is reduced along with abnormal appearing mitochondria (Ashrafian et al., 2007).

Thus, impaired substrate flexibility and inefficient adenosine triphosphate (ATP) generation, resulting in inability in fulfillment of myocardial energy demand, initially on exertion, progressing to inadequacy at rest, is the hallmark of CMCM.

2.1.2.3 Increased generation of advanced glycation and lipoxidation end products along with reactive oxygen species affecting heart in altered metabolic conditions

Advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs) are formed when carbohydrate- or lipid-derived intermediates react with the amino group of proteins to form covalently modified, stable protein adducts. AGEs/ALEs formation results from a combination of hyperglycemia, hyperlipidemia, oxidative/carbonyl stress and/or decreased renal clearance (Miyata et al., 2001). These modifications may be a single change on the peptide chain or multiple modifications that can produce crosslinks within or between proteins. Long-lived proteins like collagen and elastin are highly vulnerable for crosslink formation with AGEs and ALEs. These modifications lead to impaired collagen degradation and thereby increased collagen accumulation and subsequent fibrosis.

AGEs accumulation exert their detrimental effect on cardiac structure and function by different mechanisms. Firstly, structural modification/crosslinkage of myocardial proteins involved in cardiac contraction or relaxation may occur, resulting in impaired systolic or diastolic function and structural alteration. By disrupting intra- and inter-domain tertiary structures of Sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA2a), AGE complexes have shown to compromise structural movements required for translocating calcium ions from the cytosol to the lumen of the sarcoplasmic reticulum. Secondly, AGEs promote trans-differentiation of epithelial cells to myofibroblasts via their specific receptors (e.g., RAGE). Finally, activation of RAGE promotes inflammation and oxidative stress, which can decrease the bioavailability of nitric oxide. This may result in further increased oxidative stress and attenuated contribution of nitric oxide during myocardial relaxation (Goldin et al., 2006). Thus, AGE-RAGE interaction can have a direct functional impact on myocardial relaxation. There is also increased free radical generation and oxidative stress with subsequent activation of many deleterious pathways which lead to apoptosis and cell death. Effects of AGEs leading to increased stiffness of connective tissue, increased permeability and pro-coagulant state due to effects on endothelial functions, increased vascular matrix through mononuclear cell activation and defective vascular relaxation due to decreased nitrous oxide (NO) release, run hand in hand, with direct effects on heart and contribute to overall patho-physiology of CMCM.

Although many studies have not been reported with ALEs, yet, recent evidence suggests that ALEs induce inflammatory pathways and network similar to AGEs leading to vascular complications (Shanmugam et al., 2008). ALEs and AGEs go hand in hand from their generation to effect on different end organs and are not limited to diabetes. Effects of ALEs on myocardium in isolation, could be similar to AGEs, however, need further studies for better understanding.

2.1.3 Dysfunctional calcium homeostasis

Calcium, essential for the process of excitation-contraction, is the primary ionic regulator in the heart. In Type 2 rodent models of diabetes, altered expression, activity and function of many regulatory and contractile proteins/transporters involved in excitation-contraction coupling; SERCA, $\text{Na}^+/\text{Ca}^{2+}$ exchange (NCX), ryanodine receptors (RyR) and plasma membrane Ca^{2+} -ATPase (PMCA), as well as dysfunctional intracellular calcium signaling, have been reported (Pereira et al., 2006; Vetter et al., 2002). These alterations have been attributed to accumulation of toxic molecules such as long-chain acylcarnitines, free radicals and abnormal membrane lipid content as well as to AGEs altering the structure and function of several proteins described above. The consequences of these changes include alterations to the calcium sensitivity of regulatory proteins involved in the regulation of the cardiac actomyosin system, possibly due to phosphorylation of sarcomeric protein troponin I. The diminished calcium sensitivity and altered activity of regulatory and contractile proteins may all contribute to impaired left ventricular (LV) function.

2.1.4 Altered thyroid hormone status

Recent evidence indicates that heart failure can lead to down-regulation of the thyroid hormone signaling system in the heart. In the failing heart, there is decrease in thyroid hormone receptor expression; in addition, serum levels of T4 and T3 are decreased with heart failure in the frame of the non-thyroidal illness syndrome (Kinugawa et al., 2001). Thyroid hormone levels have a profound impact on mitochondria, the organelles responsible for the majority of cellular ATP production. The hypermetabolic effects of thyroid hormones are partially due to an increased demand for ATP and partially due to increased uncoupling. In addition, thyroid hormones are potent activators of mitochondriogenesis. Key events in thyroid-hormone-induced mitochondriogenesis include the increased expression of the mitochondrial transcription factors, nuclear respiratory factor-1 (NRF-1) and peroxisome-proliferator-activated receptor gamma co-activator-1a (PGC-1a). In addition, transcriptional and post-transcriptional mechanisms are important for the effects of T3, for example, in the synthesis of cytochrome c oxidase subunits. Thus, thyroid hormones are key regulator of mitochondrial energetics. In animal models, it has been shown that in pressure overload-induced cardiac hypertrophy a decrease of thyroid hormone receptor level occurs. The decrease in T3 serves as an indicator for a bad prognosis in the heart failure patient being linked to increased mortality (Dillmann, 2010).

2.1.5 Up regulated renin-angiotensin-aldosterone and sympathetic system

RAAS and sympathetic system are profoundly dysregulated in metabolic deranged conditions and adipose tissue has a full local renin-angiotensin system that is active at local and systemic level (Sarzani et al., 2008). RAAS is considered to have a prime role in hypertensive cardiomyopathy even though several growth factors influence initiation and maintenance of myocardial hypertrophy. Both angiotensin II and aldosterone are shown to contribute to myocardial fibrosis (Sopel et al., 2011; Struthers & Unger, 2011). Correlation between circulating renin-angiotensin levels and left ventricular mass have long been established and same has been proved by the study showing regression of hypertensive left ventricular hypertrophy upon targeting RAAS (Solomon et al., 2009). Though synergistic effects of angiotensin II and aldosterone are well established with regard to perivascular and

interstitial fibrosis of the ventricle; angiotensin-independent effect of aldosterone on myocardial fibrosis has also been demonstrated. Current evidence shows that aldosterone has some role in the transition of left ventricular hypertrophy to cardiac failure. In addition, aldosterone also has a role in fluid retention. Altered RAAS has implication in chronic kidney disease and impaired kidney function resulting in volume overload which results in exacerbation of symptoms of heart failure and disease progression.

In addition to high RAAS drive, sympathetic hyperactivity present in patients with deranged metabolic profile contributes not only to high blood pressure, but seems to have further adverse metabolic effects also, such as insulin resistance, hyperinsulinaemia and hyperlipidaemia. Experimental evidence has indicated that heightened sympathetic nervous system activity facilitates the development of myocardial hypertrophy in animals and humans. Antihypertensive vasodilators (hydralazine and minoxidil) which are known to have some stimulating effect on sympathetic nervous system fail to reduce left ventricular hypertrophy despite their well-documented antihypertensive effects (Elliott et al., 2008). Thus, if such a relationship between RAAS, sympathetic activation and left ventricular hypertrophy exists, there are all possibilities that cardiomyopathy in hypertensive patients may be resultant of this interaction. This becomes more evident especially since neuroendocrine activation is found in hypertensive cardiomyopathy, with activation of the RAAS and the sympathetic system. All these components are hypothesized to be constituent part of CMCM as both RAAS and sympathetic systems are up-regulated in them.

2.1.6 Diastolic dysfunction, systolic dysfunction and ventricular hypertrophy in CMCM

Ventricular diastolic function is dependent on an active relaxation process in conjunction with passive elastic properties of the myocardium. In diastolic dysfunction, there is impairment in ventricular relaxation and passive filling. About 75% of diabetics show this dysfunction which is more pronounced when other metabolic abnormalities co-exist. In diastolic heart failure, though the ejection fraction may be normal, there is diastolic dysfunction along with elevated end diastolic pressure.

Functional abnormalities occur as a result of structural remodeling. In diastolic dysfunction a moderate increase in left ventricular mass and an elevated ventricular wall thickness to chamber radius is seen (Ozasa et al., 2008). The end diastolic volume is nearly normal. Increase in AGE crosslinks of cardiac SERCA impairs the ability or capacity of SERCA to translocate calcium and thus slows the rate of cardiac relaxation. The reduction in elasticity of the myocardium is due to myocardial collagen deposition and AGE crosslinks with elastin (Van et al., 2008). This early cardiac dysfunction, along with other exacerbating risk factors accelerates the decline in cardiac function.

Under conditions of hyperinsulinemia, a basic component of increased cardio-metabolic risks, insulin stimulates hypertrophy in cardiomyocytes by several pathways, mainly by activation of Akt and ERK. Increased circulating angiotensin II induces cardiomyocyte hypertrophy and interstitial fibrosis (He et al., 2005). Angiotensin II is also reported to increase reactive oxygen species (ROS) production and excess ROS produces cardiomyocyte death and results in replacement fibrosis. Sympathetic activation, in addition to effects on blood pressure, seems to have adverse metabolic effects. Hence, the interstitial fibrosis, protein glycosylation and myocyte hypertrophy are likely factors contributing to reduced diastolic compliance and ventricular hypertrophy in CMCM patients.

In the presence of predominant diastolic dysfunction, supervening reduced systolic reserve is often overlooked by diagnostic imaging at rest. Increased intracellular fatty acids and its metabolites are toxic to the mitochondria and induce apoptosis and damage the contractile apparatus. Many studies have demonstrated that the inhibitory cardiac troponin-I (cTnI) expression is markedly raised in the heart of diabetic rats and in cardiac hypertrophy. GATA binding protein 4 (GATA-4) binding site in the proximal region of cTnI gene is necessary for the transcriptional activation of this gene. GATA-4 found in cardiac myocytes regulates many other cardiac-specific gene expressions, like angiotensin II (AT_{1A}) and endothelin-1 (ET_A) receptors, atrial natriuretic factor (ANF), beta-type natriuretic peptide (BNP), myosin heavy chain (MHC) etc. Studies have shown that activation of MEK/ERK pathway by hyperglycemia-induced ROS or by direct adrenergic stimulation, increase GATA-4 phosphorylation and nuclear translocation, in addition MEK/ERK activation also causes GSK3 β phosphorylation, thereby lowering the export of GATA-4 from nucleus, leading to GATA-4 preservation in the nucleus, which finally leads to an increase in the expression level of cTnI resulting in reduced cardiac contractility (Ku et al., 2011).

The longitudinal fibres responsible for long-axis contraction lie in the sub-endocardium and are particularly susceptible to the effects of fibrosis, ischemia or hypertrophy. Initially the long-axis systolic dysfunction is associated with a compensatory increase in radial thickening and mass, thus preserving left ventricular ejection fraction (LVEF). The preservation of ejection fraction is directly related to the presence of LV hypertrophy and the effect of increased muscle mass. However, reserve systolic functions are reduced and these patients show enhanced systolic functional abnormalities only during stress or exercise. Clinical studies have demonstrated that diabetic patients have an increased end-systolic diameter and volume, a diminished ejection fraction and a decreased minor axis shortening and velocity of circumferential fiber shortening in the absence of coronary artery disease. This is exaggerated when exposed to stress like exercise. These dysfunctions coupled with dysfunction in peripheral vasculature in CMCM translate into profound compromise in overall exercise reserve.

2.2 A central role for mitochondrial dysfunction in CMCM

2.2.1 Normal role of mitochondria

Myocardial contractile function is energy (ATP) dependent. Mitochondria are the major site of substrate oxidation and ATP production in cardiomyocytes. In addition, mitochondria also contribute to intracellular ROS generation. It is by oxidative phosphorylation in the mitochondrial system through which the oxidation of energy substrates in a cell is coupled to the activity of ATP synthase in the mitochondrial inner membrane. The activity of ATP synthase is powered by the electrochemical gradient existing across the mitochondrial inner membrane. The ATP produced drives energy demanding reactions not only in the mitochondrion but also in the cytoplasm.

2.2.2 Abnormal mitochondrial morphology and function

Lines of evidence have shown that mitochondrial dysfunction contributes to the development of insulin resistance and metabolic syndrome. The causes of mitochondrial dysfunction are complex, but over-nutrition and sedentary life style are among the best known causes of mitochondrial dysfunction (Kim et al., 2008). The cardio-metabolic conditions such as insulin resistance, diabetes, hypertension, dyslipidemia and sub-clinical

hypothyroidism are characterized by altered mitochondrial function. Visceral obesity and related cardio-metabolic disorders are linked to defective mitochondrial biogenesis and oxidative metabolism with decreased ATP production. The hypertrophy-related changes in myocardium are likely related to mitochondrial structural and functional alterations that leads to altered mitochondrial efficiency for substrate oxidation and ATP production. Studies have revealed distinct patterns in mitochondrial structural and functional alterations in pathological and physiological cardiac hypertrophy. Among many signaling pathways that conspire to impair mitochondrial function include, decreased expression or activity of transcriptional regulators that govern mitochondrial biogenesis and oxidative capacity (i.e. PGC-1 α , ERR α , and PPAR- α) and decreased transcription of mitochondrial DNA. Increased G-protein-coupled receptor signaling activates Class1B PI3K γ that leads to constitutive activation of Akt, which may repress mitochondrial function. Activation of HIF-1 α leads to a PPAR- α mediated increase in FA uptake and lipogenesis that may promote lipotoxicity, which could further impair mitochondrial function. Reduced cardiolipin content and remodeling of the mitochondrial proteome also contribute to mitochondrial dysfunction. Mitochondrial dysfunction promotes oxidative stress that leads to a vicious cycle of progressive mitochondrial damage.

At functional level, activities of mitochondrial complex I and III reduce at the stage of compensated cardiac hypertrophy, but this is accompanied by reduced mitochondrial ROS and oxidative damage that only becomes evident after the transition to heart failure. Hypertrophied hearts do not lose mitochondrial membrane potential in the context of ischemia and re-perfusion injury. However, the increase in mitochondrial membrane potential correlates with an increased risk of arrhythmias. By the time compensated hypertrophy progresses to pathological LV hypertrophy, altered mitochondrial morphology and function are evident. Pathological hypertrophic cardiomyopathy displays swollen cardiac mitochondria with disrupted cristae and substantial mitochondrial DNA depletion. Mitochondrial membrane permeabilization is a rate limiting step of apoptosis and is mediated by the mitochondrial permeability transition pore (mtPTP). mtPTP is a nonspecific pore, permeable to all molecules of less than 1.5 kDa and is formed by the voltage-dependent anion channel (VDAC), members of the pro- and anti-apoptotic Bax/Bcl2 protein family, cyclophilin D and adenine nucleotide translocase (ANT). The ANT mediates nucleotide transfer from mitochondria to cytosol. The ATP synthesized in the mitochondria is exchanged for cytosolic adenosine diphosphate (ADP) by ANT to provide a continuous supply of ADP to mitochondria. ATP/ADP exchange by ANT is essential for the maintenance of ATP synthase activity.

On the other hand, in states of impaired function of ATP/ADP exchange, ANT plays a major role in generating ROS and inducing cell apoptosis (Kim et al., 2010). Thus, impaired ANT activity could contribute to deficient energy availability in pathological cardiac hypertrophy. Reduced level of cardiac ANT has been reported in some, but not all models of pressure overload cardiac hypertrophy. Additional proteins that were proposed to be part of the mtPTP complex are hexokinase, creatine kinase, and peripheral benzodiazepine receptor. mtPTP opening causes swelling of the mitochondrial matrix and rupture of outer membrane.

Cardiolipin, an important component and one of the most abundant phospholipid of the inner mitochondrial membrane, is essential for the optimal function of numerous enzymes that are involved in mitochondrial energy metabolism, where it regulates the activity of the

mitochondrial electron transport chain, ATP synthesis and mitochondrial bioenergetics (Abel & Doenst, 2011). Abundance of linoleic acid and close proximity to the site of ROS production, i.e. the inner mitochondrial membrane make cardiolipin particularly more susceptible to damage by oxidative stress. Cardiolipin is identified as the only phospholipid in mitochondria that undergoes early oxidation during apoptosis (Kagan et al., 2005). Cardiolipin peroxidation by ROS thus affects its binding with cytochrome c and affects the activity of complex I, III, and IV of the mitochondrial respiratory chain (Paradies et al., 2004). Mitochondrial cardiolipin content is reduced in heart failure and ischemia/reperfusion and correlates with reduced electron transport chain activities. Patients with obesity and insulin resistance have poorer outcomes after myocardial infarction compared with lean subjects. These changes are associated with reduced myocardial cardiolipin content (Sparagna et al., 2007). Thus, reduced myocardial cardiolipin content contributes to the reduced mitochondrial efficiency in diabetes and metabolic syndrome and may exacerbate the progression of CMCM.

3. Diagnosis

Cardiac dysfunction caused by a constellation of metabolic abnormality may have variety of presentations. On one hand it includes myocardial dysfunction and coronary artery disease and on the other hand it may be arrhythmias and sudden death. When a patient presents with features of heart failure like, exercise intolerance, fatigue, and dyspnea with exertion as prominent symptoms in background of metabolic abnormalities like impaired glucose metabolism, dyslipidemia and hypertension with or without subclinical hypothyroidism then CMCM should be considered.

Clinical assessment of patients of heart failure with metabolic disorder should start with a thorough history followed by evaluation of pulmonary function to rule out non cardiac causes of dyspnoea. This should be followed by evaluation of functional limitations and status of the structural defect in the heart. Thereafter, causes of heart failure and extent of compromise in hemodynamic (perfusion and volume) status should be assessed. Because progression of heart failure is relatively rapid in metabolically challenged patients, it is very important to identify defects early in asymptomatic patients in order to prevent progression to symptomatic disease.

Laboratory evaluation of patients should start with complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, fasting blood glucose (glycohemoglobin), lipid profile and liver function tests. Thyroid dysfunctions may be subclinical with normal serum free T4 (fT4), free T3 (fT3) levels but deranged serum thyroid stimulating hormone (TSH) levels. Use of biomarkers for diagnosis of heart failure includes a number of neuroendocrine hormones, including norepinephrine, angiotensin II, renin, aldosterone, vasopressin and most recently BNP. Association of abnormal levels of these biomarkers with abnormal myocardial function and the unfavorable prognostic significance are increasingly being recognized and used. Patients with history of diabetes and elderly patients who are at high risk of developing myocardial dysfunction have a high prevalence of elevated plasma BNP levels. Thus, these high risk populations with elevated plasma levels of BNP or NT-proBNP can be identified for detailed evaluation of cardiac functions by echocardiography and/or cardiopulmonary exercise testing (CPET).

Insulin resistance can be an important etiologic factor in the development of heart failure with metabolic disorder as adaptive responses of myocardium to different stress are compromised in presence of insulin resistance. Insulin resistance has strong correlation with development of hypertension, left ventricular hypertrophy and left ventricular dysfunction and subsequent development of heart failure. There is also increased prevalence of myocardial ischemia in patients with insulin resistance and heart failure itself causes insulin resistance (Wilson, 2001; Nikolaidis et al., 2004). Evidence of insulin resistance should be evaluated by measuring fasting insulin levels.

Assessment of myocardial wall thickness, LV size and pericardium by comprehensive two-dimensional Echocardiography along with Doppler imaging are useful diagnostic tests in the evaluation of patients of heart failure. The most common abnormality associated with insulin resistance and diabetes mellitus is abnormality in diastolic function which is independent of ischemic heart disease (Fang et al., 2004; Schannwell et al., 2002). Evaluation of ventricular filling pattern by color Doppler imaging evaluating diastolic dysfunction becomes important for diagnosing such symptomatic patients who have preserved ejection fraction. A comprehensive echocardiographic examination helps in these distinctions when more than one abnormality affects the cardiac functions.

Most of the above mentioned methods of evaluation examine patients at rest, thus have limitations. Physical limitations during exercise, like shortness of breath and fatigue are caused by dynamic dysfunctions in myocardium occurring under stress and may not manifest at rest. Thus, markers of diminished cardiac reserve often go undetected by echocardiography. Stress echocardiography can detect ventricular dysfunction including wall motion abnormalities (hypokinesia, akinesia, dyskinesia or diastolic dysfunction) when exposed to stress either by dobutamin or exercise. This can pick up early cases with compromised ventricular functions, however, peripheral components of heart failure may still not be factored in it.

CPET is a well-established method of evaluating cardiopulmonary functions in heart failure. This is highly reproducible measurement and helps in differentiation of cause of symptoms associated with heart failure. Using CPET for evaluation of limitation in cardiac functions in the patients with heart failure associated with metabolic disorder will not only evaluate dynamic response of heart to physiological stress but also peripheral component of hemodynamics which often coexists. Symptoms such as fatigue and disproportionate dyspnoea may be explained by inadequate and inappropriate vascular responsiveness (capillary recruitment) to demand generated by exercising skeletal muscles (Joshi et al., 2010). Maximal aerobic capacity (peak VO_2), Ve/VCO_2 and oxygen uptake efficiency slope (OUES) parameters obtained from CPET aids in early diagnosis of subtle pathology and helps in following the progression of the disease. These have important prognostic value also.

Impedance cardiography can be used non-invasively to measure hemodynamic parameters to diagnose covert cases of CMCM. Experimental studies in diabetic patients measuring stroke volume and cardiac output by impedance cardiography at the time of rest and exercise suggest, compromise in cardiac reserve even in the absence of any clinical symptoms of heart failure (Joshi et al., 2010). Compromise in cardiac reserve was contributed to, by an inappropriate increase in stroke volume due to diastolic compromise exaggerated by increase in heart rate. There was decrease in stroke volume and it had to be compensated for, by further increase in heart rate to maintain cardiac output. This “inflection point”, the heart rate at which the stroke volume starts decreasing, occurred at a relatively

low heart rate. Recent evidence that limiting heart rate increase has favorable outcome in heart failure independent of beta blockade suggests ways of managing this dysfunction (Swedberg et al., 2010). There is speculation as to what should be the target heart rate to be achieved with such therapy. Perhaps studies such as done by Joshi et al., may provide the answer.

4. Treatment

Routine management of heart failure depending upon the status of decompensation, should be integral part of any case of CMCM. Along with this, therapy directed to pathophysiology like insulin resistance, hypothyroid state, lipid abnormality and therapies modulating the metabolic properties of myocytes should be considered.

4.1 Improving insulin resistance

Therapies which reduce insulin resistance improves outcome. There are evidence to support that therapies directed to treat heart failure also reduce insulin resistance even in non-heart failure population. Similarly, exercise improves both heart failure outcome and insulin sensitivity in non-ischemic heart failure (Kemppainen et al., 2003). Angiotensin converting enzyme inhibitor and angiotensin receptor blockers also improve insulin sensitivity in addition to their effect on heart failure (Yusuf et al., 2000; Pfeffer et al., 2003).

Drug therapy improving insulin resistance in CMCM can be at multiple levels. Different approaches consisting of lowering circulating FFA levels, facilitating glucose uptake and metabolism have been identified. These can be both anti-diabetic medication and metabolic modulator.

Drugs improving insulin sensitivity like metformin and thiazolidinediones are expected to improve outcome in cardiomyopathy associated with insulin resistance. Metformin can also improve calcium handling in myocytes (Ren et al., 1999), however, potential of causing lactic acidosis limits its utility in heart failure, especially in the context of renal dysfunction. Insulin or insulin-secretagogues could be another option as they directly promote glucose metabolism and decrease circulating FFAs but they have also failed in different animal models (Ren et al., 1996). Insulin therapy is expected to reduce catecholamine-induced myocardial damage in the heart however like with thiazolidinediones, there is danger of fluid retention and hypoglycemia that may be detrimental. Several studies attempting to demonstrate the beneficial effects of tight glycemic control with insulin and secretagogues have failed to show any superiority and in fact have resulted in higher cardiovascular events.

Under the circumstances of insulin resistance, the body's compensatory mechanisms (hyperinsulinemia, up-regulation of the RAAS, catecholamines, vasopressin) are maladaptive and can further worsen the cardiomyopathy. Many counter-regulatory hormones like epinephrine, norepinephrine, glucagon, cortisol, growth hormone are upregulated and increases insulin resistance and alter glucose disposition (Nikolaidis et al., 2004). They also contribute to the pathogenesis of cardiomyopathy. Adrenergic blockade with carvedilol, long acting metoprolol and nebivolol improves myocardial efficiency by reducing consumption of FFA by myocardium and increasing preference to glucose as fuel (Nikolaidis et al., 2006) because chronic stimulation of beta-receptor seen in cardiac decompensation is known to inhibit insulin-mediated glucose uptake and insulin receptor

activation (Morisco et al., 2005). These patients are expected to achieve dramatic responses to angiotensin converting enzyme inhibition and beta-adrenergic blocking therapy, often with recovery of LVEF to normal or near-normal levels.

Limiting increase in heart rate independent of beta blockade has been shown to be of benefit in heart failure; ivabradine therapy in patients with systolic dysfunction and resting sinus rhythm of more than 70 bpm despite beta blockers or in beta blocker intolerant patients (Swedberg et al., 2010).

4.2 Metabolic modulators

Metabolic modulators target molecular metabolism within the myocardium and decrease consumption of FFA while increasing metabolism of glucose. Currently these drugs are used as antianginals as they increase energy efficiency in myocardium. Inhibitor of final enzyme in β -oxidation of FFA trimetazidine improves myocardial energy stores by increasing myocardial ATP/phosphocreatine levels (Aussedat et al., 1993). Trimetazidine improved LVEF and NYHA class in a study in 65 heart failure patients (Fragasso et al., 2006). Notably, benefits were more in nonischemic cardiomyopathy than the ischemic cardiomyopathy subgroup. Similarly perhexiline inhibit FFA metabolism and has demonstrated substantial improvements in LVEF, VO_2 max and quality of life in a clinical trial with 56 heart failure patients (Lee et al., 2005). However, hepatotoxicity and peripheral neuropathy associated with perhexiline limits its clinical utility. Ranolazine is a third metabolic modulator which can potentially be used in CMCM to switch from FFA to glucose.

Although role of thyroid hormone therapy in treatment of heart failure is still not clear, its role in improvement of LV function, remodeling and microcirculation are being investigated. Use of l-thyroxin both in frank cases of hypothyroid and subclinical hypothyroid has shown reversal of structural abnormalities detected by echocardiography and is accompanied by clinical improvement. Gene therapies to modify thyroid hormone receptor or deiodinase expression and activity along with thyroid hormone replacement with T3 and/or T4, use of thyroid hormone analogs (e.g. diiodothyropropionic acid) will need further studies for proving its efficacy and safety in management of such cases (Gerdes & Iervasi, 2010).

4.3 Emerging therapies

4.3.1 AGE inhibitors and breakers

It is well established that AGEs, a heterogeneous group of molecules formed by the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids and nucleic acids contribute significantly to diabetic complications, both macro- and micro-vascular.

4.3.1.1 Pharmacological intervention against AGE formation in vivo

Classically, efforts to target AGE-related complications had been approached either with intentions to inhibit the ongoing process of AGE formation or to cleave already formed AGE protein-protein crosslinks.

4.3.1.2 Pharmacological approach to inhibition of AGE crosslink formation

Accumulation of substantial evidence indicating AGEs as one of the culprits for diabetic complications, triggered active search for intervention in the process “by pharmacological

approaches. Careful study of structural aspects lead researchers to target ketone group of the 1-amino-1-deoxyfructose residue in the amadori product, which was the key to subsequent AGE-forming reactions and that chemical deactivation of this ketone group would prevent AGE formation (Ulrich & Cerami, 2001).

Aminoguanidine was one such compound identified having desirable features to be studied for its ability to inhibit AGE crosslink formation. Prior to be explored for its AGE inhibition capabilities, some published reports existed for its experimental use in humans for unrelated purposes, without significant side-effects. During subsequent years, several researchers demonstrated effectiveness of aminoguanidine in inhibiting AGE formation in vivo in a wide variety of systems and tissues.

Usefulness of aminoguanidine has also been demonstrated in improving left ventricular end-diastolic (LVED) compliance in streptozotocin induced diabetic rats. Simultaneous administration of aminoguanidine with AGE-modified albumin prevented consequent glomerular hypertrophy (Bucala & Vlassara, 1995). Clinical utility with aminoguanidine was limited by its side effect potential, which was due to its inhibitory effect on diamine oxidase. This inhibition of diamineoxidase, results in an increase in histamine levels with attendant risk of vascular and respiratory complications. Aminoguanidine being a hydrazine derivative, its association with antihistone and antinuclear cytoplasmic antibody results in a clinical situation similar to lupus.

Few other less talked inhibitors of AGE formation have been reported, however none of them have reached advanced trials in humans. Pyridoxamine, a derivative of vitamin B6 has been suggested to prevent the degradation of protein-amadori intermediates to protein-AGE products. It is shown to reduce hyperlipidemia and prevents AGE formation in rats (Wu et al., 2011; Degenhardt et al., 2002; Stitt et al., 2002). Some preliminary clinical trials evaluating effect in diabetic nephropathy with this agent have been performed (Williams et al., 2007).

OPB-9195, a thiazolidine derivative has shown to be inhibitor of advanced glycation and to produce some benefits in attenuating progression of nephropathy in spontaneous diabetic rats (Nakamura et al., 1997). There is no current clinical experience with this compound nor is there any evidence for planned clinical trials.

LR-90, yet another compound capable of inhibiting AGE formation is being studied for its usefulness pre-clinically. Evidence are available for evaluating this compound in diabetic nephropathy and retinopathy (Figarola et al., 2008; Bhatwadekar et al., 2008). The compound has also shown to possess some anti-inflammatory properties (Figarola et al., 2007) with the potential for additional protective effects against diabetic vascular complications. However, future developmental strategy for this compound is not yet fully disclosed.

4.3.1.3 Pharmacological approach to cleave preformed AGE cross-linkages

Although attractive, approach to prevent AGE formation suffers from limitation of being unable to break preformed AGE crosslinkages. Thus, AGE breaker compounds are more desirable, as they open possibility for restoration of AGE damaged tissue to their original functionality, without relying on the body's much-slower, removal and repair mechanisms. Two such molecules, a thiazolium compound alagebrium (ALT-711) and pyridinium derivative TRC4186 are being evaluated for the treatment of heart failure in patients who are metabolically challenged.

Alagebrium: Upon administration to various animal models of diabetes, it has resulted in an improvement in large-vessel elasticity, decrease in stiffness and peripheral resistance

(Wolffenbuttel et al., 1998; Candido et al., 2003), an attenuation in several functional and structural manifestations of diabetes related nephropathy (Peppia et al., 2006). Clinical studies with alagebrium in patients having uncontrolled systolic hypertension, of whom only an insignificant number were diabetic, found that the data did not indicate a treatment-related benefit (Zieman et al., 2007). Pulse wave velocity and arterial pressures, indicators of conduit vessel stiffness, were unchanged; however, brachial flow mediated dilatation, an indicator of endothelial function, was improved. In the DIAMOND study in elderly and PEDESTAL in adults with diastolic heart failure, alagebrium significantly decreased left ventricular mass, improved left ventricular diastolic filling and improved effort tolerance assessed by the 6-minute walk test. However, the trials did not meet the primary endpoint of improvement in ejection fraction. Here again, diabetes or impaired control of glycemia was not a precondition for inclusion of patients. Subsequently, further development of this compound is terminated.

TRC4186: TRC4186/TRC4149 is shown to act via multiple mechanisms, which include breaking of pre-formed AGE cross-links, reducing accumulation of carbohydrate as well as lipid derived AGEs and a potent free radical scavenging activity. Treatment of diabetic spontaneously hypertensive (SHR) rats, with TRC4149 resulted in a reduced AGE burden as evident by reduced immunochemical staining for AGE and significant reduction in VCAM expression in aorta. Ultimately, the combined actions translate into better preservation of endothelial function as well as an improved cardiac function (Pathak et al., 2008). Evaluation of TRC4186 in a more complex animal model of metabolic syndrome, ob-ZSF1 rats, demonstrated its capability to attenuate overall disease progression. The compound successfully prevented rise in blood pressure following salt loading and preserved ventricular functions. Although the exact mechanism of AGE breaking is not very clear, reduction in AGE load and all ensuing downstream events, including attenuation of the associated inflammatory response, likely contributed to the improvement observed on treatment with TRC4186. These outcomes are substantially supported by suitable histopathological and immunohistochemical findings (Joshi et al., 2009).

AGE breakers are likely to be beneficial in diabetic heart failure patients in whom there is usually a significant component of diastolic dysfunction and vascular unresponsiveness, when assessed for meaningful clinical endpoints such as physical attributes of Minnesota Living with Heart Failure Questionnaire and OUES, that are able to assess not only myocardial reserve but also vascular (nutritive perfusion) reserve. Other measures such as NT pro-BNP would be useful to assess diastolic dysfunction and fluid retention that could be exaggerated in patients with compromised renal function, a common co-morbidity in these patients. TRC4186, currently under investigation for use in diabetic patients has successfully completed phase 1 clinical trial and results of its phase 2 clinical trial Prospective Evaluation of AGE Breaker in Heart Failure (PEACH-F) are awaited.

Researchers have also focus on the possibility of preventing AGE-RAGE interaction thereby preventing subsequent deleterious downstream events contributing to AGEs related pathophysiology. Conceptually this has been attained by infusing soluble RAGE (sRAGE), and by RAGE antibodies. Though it is clear that blocking AGE receptors using antibodies would prevent AGE-RAGE interaction; it remains yet to be elucidated as to whether sRAGE acts as an antagonist inhibiting RAGE dependent signaling pathways, or scavenge AGEs and AGE precursor from circulation (Zieman & Kass, 2004). There are presently no small molecule inhibitors of RAGE, and this approach has yet to be tested in clinical studies.

Finally, intracellular signalling pathways upregulated by AGEs can be inhibited by AGE signal transduction inhibitors (e.g. PK-C inhibitors incadronate disodium, cerivastatin, and curcumin) (Peyroux & Sternberg, 2006).

4.3.2 Emerging therapy targeting mitochondrial energetics

Visceral obesity and related cardiometabolic disorders are linked to defective mitochondrial biogenesis and oxidative metabolism with a decreased ATP production. The defective mitochondrial function, a common pathophysiologic feature of these cardiometabolic disorders is a key etiopathological factor exacerbating the CMCM.

The effectiveness of beta-adrenergic blockers and angiotensin-converting enzyme inhibitors to improve ventricular function in patients with heart failure, may be, due in part to the action of these agents in decreasing energy demand. Other compounds that may also have beneficial effects in hypertrophied hearts include vanadyl sulfate, which improves tolerance of ischemia by stimulating membrane glucose transport, and propionyl-L-carnitine, which prevents myocardial mechanical alterations associated with pressure overload. There is evidence that administration of propionyl-L-carnitine increases both glucose and palmitate oxidation in hypertrophied hearts and improves the efficiency of translating ATP production into cardiac work.

On this basis, a restoration of metabolic demand by restoring mitochondrial energy efficiency may have potential as a new therapeutic treatment of the hypertensive heart and heart failure (Fujii et al., 2004). Although as yet no agent exists that promote mitochondrial biogenesis, PGC-1 alpha has generated interest. Sirt1 activators have also shown potential to increase mitochondrial biogenesis. The nitric oxide-cGMP-dependent pathway may also control mitochondrial biogenesis and may ameliorate energy deficiency in heart failure. Indeed, phosphodiesterase 5 inhibitors such as sildenafil that increase cGMP have, in preliminary studies, improved LV function and exercise capacity in heart failure.

The implications for thyroid hormones on the efficiency of energy expenditure and the handling of ROS are important. One of the thyroid hormone analog, DIPTA has been tested for heart failure in early clinical trials; however agents with greater therapeutic margin are yet desirable. Thus, there is still much scope for research into the energetic effects of thyroid hormones. The preclinical evidence of TRC150094 has shown potential to improve mitochondrial substrate oxidation capacity and mitochondrial efficiency as well as improve various cardiometabolic risks with acceptable safety (Cioffi et al., 2010; Zambad et al., 2011). However this molecule is yet to be proven in a clinical setting. The discovery of such newer agents improving mitochondrial energetics will help to explore the role of these agents in the treatment of CMCM. It would be interesting to follow the progress of some investigational drugs such as TRC150094 which are in early clinical development.

5. Conclusion and key learning

- Diabetes, hypertension, dyslipidemia and thyroid dysfunction often occur concomitantly in metabolically challenged individuals who are overweight. When present together, their effect on myocardium as well as on the vasculature contribute significantly to the clinical manifestations of patients diagnosed with heart failure not predominantly due to epicardial Coronary Artery Disease (cardio-metabolic cardiomyopathy).

- Impairment in mitochondrial energetics resulting in inflexibility in fuel utilization has a significant role in development and progression of CMCM.
- Currently recommended diagnostic methods such as Echocardiography and tissue Doppler imaging are carried out at rest and may result in underestimation of heart failure in the absence of a suitable provocative diagnostic method capable of assessing the ability of the heart to augment cardiac output (cardiac reserve) on exertional demand.
- Dynamic assessment of cardiac response during exercise with assessment of peripheral flow, distribution and nutritive perfusion such as CPET may provide an objective and sensitive measure of cardiac and microvascular correlates of the composite with better correlation to clinical manifestation and possibly also help in more accurately assessing the onset and progress of cardiovascular malfunction.
- Some of the newer emerging non-conventional diagnostic methods and therapies may offer a solution for the management of CMCM.

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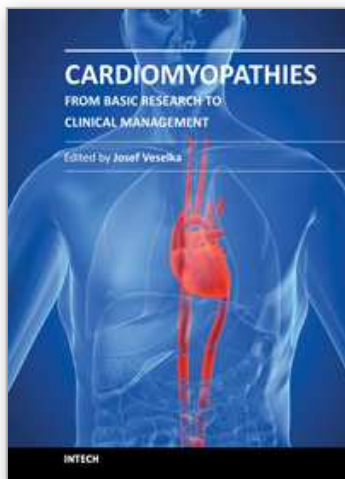
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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