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Review Article

EFFECT OF SACUBITRIL VALSARTAN ON CARDIAC FUNCTION IN PATIENT WITH DILATED CARDIOMYOPATHY

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ABSTRACT

Dilated cardiomyopathy is defined as left ventricular enlargement and contractile dysfunction of the heart. The right or may be both ventricle affected. DCM is major causes of heart failure and heart transplantation. There is wide variety of etiologies causes DCM. 20% to 30% of patient have familiar forms of DCM. It is autosomal dominant pattern greater than 20 genes mutation more commonly genes are involved in sarcomere proteins, such as α-cardiac, β and α-myosin, heavy chain α - tropomyosin; troponins T, I and C. The causes of death are progressive heart failure, ventricular arrhythmias and sudden cardiac death. traditional medication include beta-blocker, angiotensin converting enzyme inhibitor(ACEI) or angiotensin receptor blocker(ARB) or mineralocorticoid receptor antagonist. several trail have done on these medications can reduce myocardial injury in patient with DCM and delay the disease with good prognosis on patient with DCM heart failure. But still we don't have satisfaction on these medications because these medication has not good clinical improvement of DCM.PARADIGM-HF trail has been shown sacubitril valsartan further it reduces the risk of cardiovascular death and hospitalization in patient with heart failure compared with enalapril. so, new guidelines for treatment of DCM is sacubitril/valsartan.

Key words: Dilated cardiomyopathy, Heart failure, sacubitril/valsartan.

INTRODUCTION

Cardiomyopathy is heart muscle disease which is characterized by heart muscle weakness and inability to pump blood flow well. Dilated cardiomyopathy is defined as left ventricular(LV) systolic dysfunction and enlargement[1].There is no abnormal pressure or fluid overload or coronary artery disease but left ventricle progressive enlargement and dysfunction[2].

Classification system and Nomenclature: Cardiomyopathies mainly divided into five types:

- Dilated cardiomyopathy(DCM)
- Hypertrophic cardiomyopathy(HCM)
- Restrictive cardiomyopathy(RCM)
- Arrhythmogenic cardiomyopathy(ACM)

Then, the world Health Organization/International society and Federation of Cardiology classification in 1996 added inflammatory and viral cardiomyopathy[3].Based on AHA classification cardiomyopathy divided into two group. Primary cardiomyopathy (I.e. genetics, non-genetics and acquired). It mainly causes systemic disease such as amyloidosis, hemochromatosis, sarcoidosis, autoimmune/collagen vascular disease, toxin, cancer therapy[4]. Recently, The MOGE(S) classification system given five attributes, including morph functional characteristics(M), organ involvement(O), genetics or familial inheritance(G), etiological annotation(E) and heart failure functional status(S)[5].

Epidemiology:

DCM has a prevalence of 1:2500 per 100,000 populations. The prevalence of cardiomyopathy is more in underdeveloped country than developed country. According to report, japan is low incidence of dilated cardiomyopathy (17/10,000). Africa and Latin America is higher than in the united states[6,7].

Table 1 Characteristics of dilated (DCM), hypertrophic (HCM), or restrictive (RCM) cardiomyopathies

Type of cardiomyopathy	Characteristics	Comments
DCM	LV dilatation Systolic dysfunction	Can also be accompanied by RV dilatation or atrial and ventricular (four chamber) dilatation Usually defined as ejection fraction <50 or 45%; the ejection fraction may be 10–20% with advanced disease
HCM	LV hypertrophy No dilatation May be hypercontractile In late stage may occasionally resemble DCM	May show asymmetric septal hypertrophy or concentric LV hypertrophy Hypertrophy occurs commonly with LV wall thickness >15 mm but can be severe (>20 mm) or very severe (>>20 mm), where normal LV wall thickness is ≤12 mm. Normal to smaller LV cavity Ejection fraction at times >80% The "burned out" phase in late-stage disease may show a diminished ejection fraction and at times some dilatation. It is unusual for "true" HCM to present in the "burned out" DCM phase.
RCM	Mild LV hypertrophy Systolic function normal to mildly decreased	RCM is usually defined physiologically, where an elevated left ventricular end diastolic pressure is required to reach a normal left ventricular end diastolic volume. The ejection fraction may be normal and is usually not less than 40%.

Normal ejection fraction usually considered 55–75%. Usual LV wall thickness is 9–11 mm. RCM at times can be difficult to categorize clinically; it can commonly overlap with HCM, and part of this is phenotypic plasticity with genetically mediated HCM/RCM.
LV, left ventricle; RV, right ventricle.

Etiology of DCM on table 2:

Table 2. **Causes of dilated cardiomyopathy**

Generic cause	Examples or causative factors
Genetic	● Cardiac genetic defects: titin, lamin A/C, beta-myosin heavy chain, troponin T, myosin-binding protein C, myopalladin, sodium channel alpha unit, phospholamban ● Neuromuscular genetic defects: Duchenne muscular dystrophy, Becker muscular dystrophy ● Syndromes: mitochondrial diseases, Barth syndrome
Infective	Viral (for example, coxsackievirus), fungal, parasitic, rickettsial and protozoal diseases
Autoimmune	Giant-cell myocarditis, non-infectious myocarditis, polymyositis and dermatomyositis, Churg-Strauss syndrome, granulomatosis with polyangiitis, systemic lupus erythematosus, sarcoidosis
Toxicity	Alcohol, cocaine, amphetamines or iron overload
Nutritional deficiencies	Selenium, thiamine, zinc and/or copper
Drug-induced	Antineoplastic drugs (paclitaxel, anthracyclines, alkylating agents), psychiatric drugs (clozapine, olanzapine, risperidone), others (chloroquine, tretinoin)
Endocrine and/or pregnancy related	Hypo- and hyperthyroidism, Cushing's disease, Addison's disease, phaeochromocytoma, acromegaly, diabetes, peripartum cardiomyopathy
Inborn errors of metabolism	Fatty acid oxidation, carnitine deficiency, glycogen storage diseases, mucopolysaccharidosis, disorders of oxidative phosphorylation, organic acidurias
Electrolyte abnormalities	Hypocalcaemia, hypophosphataemia

Source: Adapted from Weintraub et al (2017)

Genetic of DCM:

Mainly 30 to 150 genes are commonly involved in DCM this report show from USA and Europe genetic laboratories [8]. The gene associated with DCM cause wide variety of proteins playing important role of a structural and functional in the sarcomere, sarcolemma, cytoskeleton, intermediate filaments, SR, nuclear membrane proteins and others. Mutation in sarcomere genes can causes both hypertrophic cardiomyopathy and DCM. Other gene such as MYH7, MYH6, MYBPC3, TNNT2, TPM1, TNNI3, TNNC1 and TTN. Cardiac sarcomeric and cytoskeletal genes (TTN overall) are the most frequently present[9].

Gene	Total coding exons	Encoded protein (AA)	NCBI GenBank accession #	Chromosomal location	Major phenotype
Sarcomere					
MYH7	38	1935	NG_007884	14q11.2	HCM, RCM, DCM, LVNC
MYBPC3	33	1274	NG_007667	11p11.2	HCM, DCM
TNNT2	15	295	NG_007556	1q32.1	HCM, RCM, DCM, LVNC
TPM1	9	284	NG_007557	15q22.2	HCM, DCM
MYL3	6	195	NG_007555	3q21.31	HCM, LVNC
MYL2	7	166	NG_007554	12q24.11	HCM, LVNC
ACTC1	6	377	NG_007553	15q14	HCM, RCM, DCM, LVNC
TNNI3	6	210	NG_007866	19q13.4	RCM
MYH6	37	1939	NC_000014	14q11.2	HCM, DCM
TNNC1	6	161	NG_008963	3p21.1	HCM, DCM, RCM
Desmosome					
JUP	9	563	NG_009090	17q21.2	ARVC
DSP	24	2871	NG_008803	6p24.3	ARVC
PKP2	14	881	NG_009000	12p11.21	ARVC
DSG2	15	1118	NG_007072	18q12.1	ARVC
DSC2	16	901	NG_008208	18q12.1	ARVC
Cytoskeleton, Z-disc, *etc.*					
ACTN2	21	894	NG_009081	1q43	HCM, DCM
DES	9	470	NG_008043	2q35	HCM, RCM, DCM, ARVC
LDB3	13	732	NG_008876	10q23.2	HCM, DCM, LVNC
CSRP3	5	194	NG_011932	11p15.1	HCM, DCM
TCAP	2	167	NG_008892	17q12	DCM
SGCD	8	290	NG_008693	5q33.3	DCM
TTN	311	33423	NG_011618	2q31.2	DCM
DMD	79	3385	NG_012232.1		DCM
MYPN	19	1320	NM_032578.2	10q21.3	HCM, DCM, RCM
PLN	1	52	NG_009082	6q22.31	HCM, DCM, ARVC
VCL	22	1134	NG_008868	10q22.2	HCM, DCM, LVNC
CRYAB	3	175	NG_009824	11q23.1	DCM
CAV3	2	151	NG_008797	3p25.3	HCM
BAG3	4	575	NM_004281.3	10q26.11	DCM
ANKRD1	9	319	NM_014391.2	10q23.31	HCM, DCM
Syndromic					
TAZ	11	292	NG_009634	Xq28	DCM, LVNC
ALMS1	23	4169	NG_011690	2p13.1	
PTPN11	15	593	NG_007459	12q24.13	HCM
RAF1	16	648	NG_007467	3p25.2	HCM, DCM
Others					
LAMP2	9	411	NG_007995	Xq24	HCM, DCM
LMNA	12	664	NG_008692	1q22	DCM, LVNC
EMD	6	254	NG_008677	Xq28	DCM
RYR2	105	4967	NG_008799	1q43	ARVC
ABCC9	38	1549	NG_012819	12p12.1	DCM
SCN5A	27	2015	NG_008934	3p22.2	DCM
TMEM43	12	400	NG_008975	3p25.1	ARVC

View about heart failure:

Heart failure is a clinical syndrome caused by impaired of systolic ejection, diastolic dysfunction of myocardium or combination of both. It can result from structural or functional damage of the myocardium[10]. The main clinical sign and symptoms are dyspnea, fatigue, acute pulmonary edema, tachycardia, raised JVP, rales, wheezing, ascites, hepatomegaly or anasarca etc. New York Heart Association (NYHA) functional classification[11].

	ACC/AHA stages of HF	NYHA classification of HF
A	At high risk for HF but without structural heart disease or symptoms	None
B	Structural heart disease but without signs and symptoms of HF	Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
C	Structural heart disease with current or prior symptoms of HF	Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF Class II: Slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in symptoms of HF Class III: Marked limitation of activity. Comfortable at rest but less than ordinary activity causes symptoms of HF
D	Refractory HF requiring specialized interventions	Class IV: Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest

Adapted from Yancy *et al.*[27] HF: Heart failure; ACC/AHA: American College of Cardiology/American Heart Association; NYHA: New York Heart Association

Diagnostic and laboratory evaluation of DCM:

Complete history and physical examination, Genetic family history, complete blood count, comprehensive metabolic panel, thyroid function tests, iron studies, cardiac bio-markers, B-type natriuretic peptide assay, chest radiography, Echocardiography, cardiac magnetic resonance imaging(MRI) with gadolinium, Electrocardiography, Endocardial biopsy, cardiac catherization[12].

Medical management:

The treatment of DCM with evidenced - based therapies are beneficial in term of survival and reduced of hospitalization. Angiotensin- converting enzyme inhibitors(ACE), Angiotensice ii receptor blockers(ARB), Beta - blockers, aldosterone antagonist, cardiac glycosides, Diuretics, Nitrates, vasodilator and sacubitril valsartan.

Sacubitril valsartan is the new drug which further reduce of mortality and hospitalization. Valsartan is an angiotensin receptor blocker, and it works on blocking the RASS system. Because neprilysin will result in an accumulation of angiotensin II. for this reason, a neprilysin inhibitor cannot be used alone; it must always be combined with an ARB to block the effect of the excess angiotensin II[13].

PARADIGM -HF - trial has shown sacubitril/valsartan compared with eanapril can further reduce the risk of cardiovascular death or hospitalization patient with heart failure. Heart failure hospitalization reduced by 20 % and all causes death by 16 %. PARADIGM -HF trail of sacubitril valsartan approved by American and European regulatory authorities[14].

CONCLUSION

DCM is broad spectrum of disease which is part of heart failure. Evidence medicine which is major goal of treatment of DCM and heart failure. Like sacubitril/valsartan is new drug regimen in the hospitalized patient. This medicine has further reduced death, hospitalization and improve heart function and exercise tolerance.

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