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ORIGINAL ARTICLE

Metabolic Syndrome-A Detrimental Prognostic Predictor in Middle Aged Individuals with Heart Failure-A Study in South Indians

Bilal Bin Abdullah*, A. Satyasrinivas, Basangouda S. Patil, Syed Mustafa Ashraf and Sharafath Ali

Department of Medicine, Al Ameen Medical College and Hospital, Athani Road, Bijapur-586101 Karnataka, India

Abstract: *Background:* Prognosis of heart failure in metabolic syndrome is not well established because it represents a heterogenous spectrum of myocardial disorders that each may progress at different rates. The present study determines the prognosis of heart failure in metabolic syndrome of middle aged individuals in terms of mortality and morbidity. *Material and Methods:* 100 patients studied (60 with metabolic syndrome, 40 without metabolic syndrome) with moderate – severe symptoms of heart failure associated with an ejection fraction equal or less than 40% and QRS duration of 130 sec or more were randomly selected. These patients were treated with conventional therapy for heart failure and monitored for 24 weeks. Primary end points were NYHA class, distance walked in 6 minutes, and secondary end points were LVEF, LVEDD, SPAP and QRS duration. *Result:* As compared with the patients without metabolic syndrome, metabolic syndrome patients experienced decrease in the distance walked in 6 minutes (336.40 ± 16.0 Vs 285.35 ± 3.30), functional NYHA class improvement (75% Vs 33.3%), LVEF (35.22 ± 1.7 Vs 31.63 ± 2.74), In addition, metabolic syndrome group, required more hospitalizations and intravenous medications (50% Vs 10%). *Conclusion:* Moderate to severe heart failure patients with metabolic syndrome result in less significant improvement in heart failure when compared to heart failure without metabolic syndrome patients.

Key words: Prognosis of heart failure, metabolic syndrome, LVEDD, LVEF

Introduction

According to NCEP ATP III definition of metabolic syndrome ≥ 3 of the following criteria fulfilled.

- Fasting plasma glucose > 6.1 m.mol/l (110 mg/dl)
- Blood pressure ≥ 130 / 85 mm Hg
- Triglycerides ≥ 1.7 m.mol/l (150 mg/dl)
- HDL < 1.04 m.mol/l (40 ml/dl) for men and < 50 mg/dl for women.
- BMI > 29.40 Kg/mm^2 or waist circumference > 102 cm (men), > 85 cm (female).

A modified definition of metabolic syndrome incorporating new cut-off points for waist circumference is studied for Asian Indians in India and migrant Asian Indians in Singapore. The South East Asian definition includes two new parameters; modified waist circumference cut-off point (> 90 cm in males and > 80 cm in females), modified body mass index cut-off point (> 23 kg/m^2).

South Asians classified as 'metabolically obese' or more appropriately dysfunctional. i.e. they have multiple metabolic derangements but are 'non-obese by conventional BMI standards. These 'non-obese' people usually have high body fat, abdominal adiposity. Prevalence of MS varies across the globe. The highest record prevalence world wide is in Native Americans, with nearly 60% of women, ages 45-49 & 45% of men, ages 45-49 meeting NCEP ATP III criteria. Prevalence of MS in Asian population is lower than US and European population. The overall incidence of MS in India – according to Kasiliwal in 2005 is 28.5%, by Guptha 2004 is 25%, by Ram Chandra in 2003 is 41%. In India the overall incidence of metabolic syndrome is 29% highest at age group 40-50 years i.e., 33.7% and at 50-60 years i.e., 20.6.

Heart failure is initiated after an "index event" either damaging the heart muscle, with a resultant loss of functioning cardiac myocytes, or disrupting the ability of myocardium to generate force, thereby preventing the heart from contracting normally. The index event may be an abrupt onset, as in myocardial infarction; it may be a gradual or insidious onset. Regardless of nature following inciting event, the feature that is common to each of these index events is they all, in some manner, decline pumping capacity of the heart. In 1998 DALY (Disability adjusted life years) loss in India by heart failure is 26,932 and a share of total burden is 10% of all cardiovascular morbidities. Patients with HF undergo frequent admissions at rate of 25% over 6 months period after initial hospitalization. Insulin resistance– and its clinical surrogates metabolic syndrome – may have direct myocardial effects in addition to their atherogenic effects, as insulin resistance is associated with systolic & diastolic dysfunction, with LV remodeling. A study conducted by Ingelsson E, Sundstron insulin resistance predicted CHF incidence was independently associated with other established risk factors. Framingham study initially established that clinical history of DM independently associated with risk of developing HF, two fold increased risk in men and five fold increased risk in women. In a study conducted by Ford ES, Giles, the presence of heart failure is consistent with both the NCEP ATP III and WHO definitions of metabolic syndrome.

Metabolic syndrome has numerous plausible direct myocardial effects, related to insulin resistance and hyperinsulinaemia.

- Insulin may function as a growth factor in the myocardium a notification supported by experimental observation of increased myocardial mass and decreased cardiac output [1].
- Hyperinsulinaemia activates sympathetic nervous system, which is a causal factor for heart failure [2].
- Insulin resistance has recently been shown to increase the trophic effect of angiotensin II on cellular hypertrophy and collagen formation in patients with hypertension, which lead to myocardial hypertrophy and fibrosis, both key substrate for heart failure [3].

Presence of myocardial insulin resistance has been demonstrated in diabetic patients with or without coronary artery disease suggesting that even early stages of altered glycemic control may affect myocardial metabolism.

Framingham heart study highlighted that after age 40, the life time risk of developing heart failure in subjects with blood pressure at 160/100 is twice that in those with blood pressure 140/90 and amplified by CAD, DM, LVH. As systolic pressure and pulse pressure appear to have a greater impact on risk of subsequent heart failure than the diastolic pressure, it has been suggested that stiffening of central aorta, enhanced pulsatile bed, and altered vascular ventricular coupling may also play an important role in heart failure [4]. LVH appears to be an important intermediate in evolving heart failure, while risk of LVH is increasing progressively in relation to LV mass [5]. Among patients with heart failure in the general population, antecedent evidence of LVH is present in approximately 20% by ECG and 60-70% by echo [6]. Concentric LVH is highly coupled to abnormalities of myocardial relaxation and systolic and diastolic ventricular stiffening, progressive hypertrophy is also associated with the development of subtle abnormalities of systolic function, which may also enhance the vulnerability to heart failure development [7].

Other implications in pathogenesis of Hypertension and Heart Failure:

1) By enhancing speed of return to reflected arterial wave, diminished vascular compliance might augment end systolic load, ventricular wall stress and slowing myocardial relaxation [8].
2) Analysis of cardiac structure and function have emphasized that patient with heart failure and preserved ejection fraction are distinguished from those with hypertension by more pronounced abnormalities of active myocardial relaxation and passive diastolic stiffness [9], LV mass and left atrial remodeling [10].
3) Hypertension related vascular changes, particularly at the level of the elastic conduit arteries may play a important supporting role.

Neuroendocrine Activation: Renin-angiotensin system is activated in HF. Site of release of renin is the juxtaglomerular apparatus of kidney and multiple stimuli may contribute to release of renin , reduced renal perfusion pressure, and diuretic therapy. Atrial natriuretic factor and vasopressin may inhibit the release of renin. Renin enzymatically cleaves angiotensinogen, a tetrapeptide produced in the liver, to form the inactive decapeptide angiotensin I. Angiotensin I is converted to angiotensin II by the angiotensin-converting enzyme. Angiotensin II is a potent vasoconstrictor; it promotes sodium reabsorption by increasing aldosterone secretion and by a direct effect on the tubules stimulates water intake by acting on thirst center. Angiotensin II facilitates release of norepinephrine by acting on sympathetic nerve endings.

Neuroendocrine activation appears early in HF, studies suggests- Renin angiotensin aldosterone elevation is associated with poor prognosis in absence of treatment with ACE inhibitors. Plasma norepinephrine has predicted prognosis in several multivariate analyses [11]. Elevated levels of C-terminal and N-terminal atrial and brain natriuretic peptides suggests poor outcome in HF. Elevated natriuretic peptide levels are associated with a poor long term prognosis after myocardial infarction [12]. Plasma endothelin is independent prognostic marker in HF [13]. Endothelin is a potent vasoconstrictor and causes pulmonary hypertension.

Hypertension and Pluricausal Cardiomyopathy: HTN is a risk factor for CAD and LV dysfunction. Myocardial ischemia is induced by atherosclerotic epicardial obstruction of coronary artery which is worsened by hypertensive cardiomyopathy as this increases the resistance to blood flow across myocardial wall, increased wall tension impairs sub endothelial perfusion, and contributes to myocardial stunning. Systolic dysfunction and HF associated with hypertensive cardiomyopathy may develop late as a complication of the hypertensive process. Although resting systolic function remains normal in hypertensive persons for a considerable period, even when LVH is present, systolic dysfunction may become more apparent with exercise [14]. Thus, although diastolic dysfunction maybe the predominant finding in LVH, there is increasing evidence that there are small but important adverse changes in systolic function.

Endothelial Dysfunction in Metabolic Syndrome:

Mechanisms that contribute to alteration in endothelial function

1. Free radical accumulation, known to occur to a greater extent in diabetics is thought to impair endothelium dependent vasodilatation due to the inactivation of nitric oxide.
2. Increased sympathetic nervous system activity play a role in endothelial dysfunction. Tachycardia is able to increase shear stress in blood vessels.
3. Plasma Leptin levels are often increased in over weight patients with type 2 diabetes mellitus and some experimental data suggest that leptin may induce endothelial activation and increase blood pressure probably through sympathetic function.
4. Increased production and angiotensin II subsequent to high sympathetic activity may also reduce available NO leading to endothelial dysfunction.

Endothelial dysfunction may impair glucose uptake and contributes to insulin resistance in cardiac myocyte and causes increase in arterial stiffness and HTN.

Hs-CRP, TNF and IL-6 are increased in patients with HF and correlate with an adverse outcome. High prevalence of abdominal obesity is characteristic of South Asians. In Framingham study, after adjustments for established risk factors, the risk of HF increased by 5% in men and 7% in women with every single increment of BMI [15]. SOLVD registry enrolled 6273 patients, CAD was the underlying cause of CHF in approximately 70% of patients, whereas hypertensive heart disease was considered to be primarily involved in only 7% [16]. In 21 multicentric HF treatment trials involving more than 35,000 patients reported in Nejm since the mid 1980s, CAD was underlying cause of HF in nearly 65% of patients.

LV Remodeling: The component participating in this process are: (1) The myocytes, (2) Extra cellular matrix, and (3) the microcirculation. Post infarction remodeling has been arbitrarily divided into an early phase (within 72 hours) and a late phase (beyond 72 hours). Left ventricular remodeling results in ventricular thinning and dilatation in the infarct zone, myocyte hypertrophy in the non infarct zones, fibrosis, and activation of neurohormones.

Myocardial-Hibernation/Stunning: Episodes of transient silent myocardial ischemia may cause prolonged LVSD that persists after the ischemic insult itself has resolved. This process is termed s*tunning*, which is similar to more severe and protracted myocardial stunning that results from coronary occlusion and reperfusion [17]. Recurrent episodes of myocardial ischemia that produce repetitive myocardial stunning may contribute to overall LV dysfunction and HF symptoms and contribute to sudden death.

Another important mechanism for LVSD with additive effects on LV performance is myocardial hibernation [18]. Once considered a process in which myocardial contraction is down regulated in response to chronic reduction in myocardial blood supply [19], the current evidence supports the hypothesis that persistent contractile dysfunction in patients with chronic CAD represents a process of programmed disassembly of contractile elements following repeated episodes of reversible ischemia. Thus rather than a "protective" mechanism, hibernation represents a disadvantageous process that, left uncorrected, may lead to apoptosis and myocyte loss, replacement fibrosis, graded and reciprocal changes in α- and β-adrenergic receptor density, progressive LVSD, and the risk of ventricular arrhythmias. This process may affect a substantial number of HF patients. Among patients with HF, CAD, and LVSD, approximately 50% have evidence of viable but dysfunctional myocardium. Hibernation-myocardium should be suspected in all patients with CAD and chronic LVSD of any degree. This may be diagnosed by advanced imaging techniques.

Although hypertension increases the risk of developing heart failure significantly, only minimal evidence exists to suggest that hypertension is an independent outcome risk predictor once heart failure is present [20]. Certainly, hypertension is related to symptomatic deterioration and development of a congestive state. The PRAISE study suggested that history of hypertension was actually associated with a better prognosis [21]. Diabetes was an independent predictor of morbidity and mortality in patients in the SOLVD trial, SOLVD registry, and other studies [22]. Clearly diabetes is a significant risk factor for the development of heart failure in the first place, and is twice as strong risks factor among women than among men [23]. The combination of hypertension and diabetes seems particularly devastating with the risk of developing heart failure increased by a factor of 5.

Pulmonary hypertension: Secondary to LVSD or of any etiology, affects survival by causing right ventricular dysfunction and precipitating malignant arrhythmias.

Systolic pulmonary artery pressure significance in Heart failure: Previous studies have shown SPAP is not just a marker of severe LV dysfunction but could also be one of the mechanisms by which HF progresses. 25% of the HF patients had significantly elevated SPAP, which was measured with right ventricular tricuspid gradient (RVTG). SPAP >45 mm Hg is associated with worsening course of HF. The prognosis of HF with respect to SPAP is strongly dependent to the attributing factors that precipitate pulmonary venous hypertension like LV dysfunction, mitral regurgitation.

In patients who have a PCWP decreased to less than 16 mm Hg on vasodilator therapy 1 year survival is 82% vs. 38% among those who did not [24]. Report noted that in patients with pulmonary vascular resistance greater than 2.5 wood units who were receiving nitroprusside, those that decreased their resistance had a 3 months mortality of about 4% compared with those without change whose 3 months mortality was almost 40%. These observations have lead many clinicians to aggressively tailor medication treatments in patients in an attempt to decrease PCWP & pulmonary artery pressures.

Multivariate analysis has been identified pulmonary capillary wedge pressure at rest and peak exercise stroke work index, as independent predictors of mortality in patients with heart failure [25]. Pulmonary hypertension as a result of LV diastolic failure is common but often unrecognized. It can occur with or without LV systolic failure. The most common risk factors are hypertensive heart disease; coronary artery disease; and impaired LV compliance related to age, diabetes, obesity, and hypoxemia. Symptoms of orthopnea and paroxysmal nocturnal dyspnea are prominent. Many patients improve considerably if LV end diastolic pressure is lowered, but current treatments are unsatisfactory.

Material and Methods

This cross sectional study consists 100 cases of HF with and without metabolic syndrome**.** Patients were randomly selected irrespective of sex and evaluated.

Follow up of the Cases: Patients meeting to the criteria underwent the following evaluations at base line. NYHA class, Six minute walking test, 2-D Echo and QRS interval. Base line variables were reevaluated at one, three, and six months after randomization. The study has 2 primary end points (NYHA and the distance walked in 6 m), and 3 secondary end points (LVEF%, LVEDD (mm),SPAP (mm), QRS duration (ms), and a clinical composite response, which assigns the patients into one of the three response groups.

as
- Improved
- Worsened
- Unchanged

In addition death percentage was considered in account.

Statistical analysis: All end points were analysed for prognostification of heart failure. For categorical, end points differences in distribution of responses to treatment at six months in the two groups were compared with the T value. Data are presented as mean ± SD changes from base line to six months. All p values are two sided.

Inclusion Criteria

1) 60 Patients with moderate to severe symptoms of heart failure in middle age (40-60) years with metabolic syndrome based on NCEP definition with waist circumference in place of BMI associated with an ejection fraction of < 40% and QRS duration > 130 ms.
2) 40 patients of Heart failure in middle age without metabolic syndrome taken with an LVEF < 40% and QRS duration > 130 ms.

Exclusion Criteria

1) Heart failure with valvular disease
2) Patients with pacemaker
3) Patients with Heart Rate > 140 on, SBP less than 80 mm Hg
4) Patients with thyroid dysfunction.

Evaluation of functional parameters

- LVEF
- LVEDD
- SPAP
- NYHA Functional classification
- Walk Test : 6- Minute walk test
- QRS COMPLEX

Results

Table-1: Age wise distribution of cases

Age group	HF with Metabolic Syndrome	%	HF without Metabolic syndrome	%
40-45	5	8.3%	3	7.5%
46-50	8	13.4%	7	17.5%
51-55	27	45.0%	10	25.0%
56-60	20	33.3%	20	50.0%
Total	60	100.0%	40	100.0%

Table-2: Sex wise distribution of cases

	0	%	HF without Metabolic syndrome	%
Male	25	41.6%	22	55.00%
Female	35	58.4%	18	45.00%
Total	60	100.0%	40	100.0%

Table-3: Categorization of patient on each follow up

Time	Improved			Unchanged			Worsened		
	HF with MS	%	HF with out MS	HF with MS	%	HF with out MS	HF with MS	%	HF with out MS	%
1 Month	20	33.3%	28	19	31.6%	8	16	26.6%	1	2.5%
3 Months	25	41.6%	30	15	25.0%	5	12	20.0%	2	5.0%
6 Months	29	48.3%	30	13	21.6%	5	8	13.3%	1	2.5%
		60%			20.0%					
		75%			12.5%					
		75%			12.5%					

Effect on primary end points:

Table-4: Improvement / change in NYHA class - 24 weeks follow up				
	HF with Metabolic Syndrome	**%**	**HF without Metabolic syndrome**	**%**
Improvement by 2 class	20	33.3%	30	75%
Improvement by 1 class	9	15.0%	-	-
No change	13	21.67%	5	12.5%
Worsened	8	13.3%	1	2.5%

Table-5: Change in the distance walked in 6 minutes						
Time	**HF with Metabolic Syndrome**		**HF with out Metabolic Syndrome**		**T**	**P**
	Mean	**SD**	**Mean**	**SD**		
On admission	-	-	-	-	-	-
1 month	262.24	± 34.10	311.78	± 5.7	3.3	<0.002
3 months	211.61	± 33.22	324.39	±11.91	3.6	<0.002
6 Months	285.35	± 3.30	336.40	± 16.0	3.3	<0.002

Effect on secondary end points:

Table-6: Changes in the serial monitoring of ejection fraction						
Time	**HF with Metabolic Syndrome**		**HF with out Metabolic Syndrome**		**T**	**P**
	Mean	**SD**	**Mean**	**SD**		
On admission	29.53	± 1.86	31.08	± 2.60	1.1	<0.240
1 month	30.78	± 2.00	33.47	± 1.59	2.579	<0.010
3 months	31.42	± 2.49	34.64	± 1.59	2.670	<0.008
6 Months	31.63	± 2.74	35.22	± 1.71	2.723	<0.006

Table-7: Changes in the QRS duration						
Time	**HF with Metabolic Syndrome**		**HF with out Metabolic Syndrome**		**T**	**P**
	Mean	**SD**	**Mean**	**SD**		
On admission	146.97	± 4.66	142.03	± 4.11	1.947	<0.052
1 month	145.23	± 5.06	141.11	± 2.26	1.821	<0.070
3 months	144.95	± 5.18	139.11	± 2.36	2.513	<0.012
6 Months	143.92	± 6.07	138.00	± 2.03	2.266	<0.024

Table-8: Changes in LVEDD						
Time	**HF with Metabolic Syndrome**		**HF with out Metabolic Syndrome**		**T**	**P**
	Mean	**SD**	**Mean**	**SD**		
On admission	62.43	± 5.59	51.95	± 3.9	3.4	<0.002
1 month	64.32	± 3.84	53.94	± 2.87	4.915	<0.002
3 months	64.47	± 3.65	54.42	± 2.79	5.305	<0.002
6 Months	65.04	± 3.29	54.61	± 2.76	5.459	<0.002

Table-9: During 24 weeks follow up No. of patients required repeated admissions or use of intravenous medications				
	HF with Metabolic Syndrome	**Percentage**	**HF without Metabolic syndrome**	**Percentage**
No. of Patients	30	50%	10	25%
Total	30	50%	10	25

Table-10: Age wise distribution of deaths				
Age group	**HF with Metabolic Syndrome**	**Percentage**	**HF without Metabolic syndrome**	**Percentage**
40-45	-	-	-	-
46-50	2	3.3%	-	-
51-55	2	3.3%	1	2.5%
56-60	6	9.9%	3	7.5%
Total	10	16.50%	4	10%

Table-11: Sex wise distribution of deaths				
Sex	**HF with Metabolic Syndrome**	**Percentage**	**HF without Metabolic syndrome**	**Percentage**
Male	3	5%	2	5%
Female	7	11.6%	2	5%
Total	10	16.50%	4	10%

Discussion

Diabetic men have more than twice the frequency of HF than non-diabetic cohorts, diabetic women have a 5 fold increased risk of HF. The role of metabolic control of diabetes in the prevention or reversal of myocardial dysfunction is unclear.

HF usually results when HTN coexist with other diseases that affect the myocardium (Ex: CAD, DM_2). Increasing BMI in HF is associated with a lower mortality, but influence is complex and depends on LV systolic function and obesity may indicate an increased risk. Many workers across the globe are studying these interesting combinations.

Variables Relevant to Prognosis of Heart Failure: The clinical variables related to adverse outcome in heart failure have emerged from the observations made in numerous anecdotal reports, case series and clinical trials. Cowborn and Coworkers summarized Peer-reviewed publications containing more than 200 subjects with chronic heart failure in which a multivariate analysis of prognostic factors were reported.

When HF is diagnosed, NYHA classification, LVEDD, LVEF% stroke work index, peak oxygen consumption on metabolic exercise, treadmill testing, pulmonary capillary wedge pressure, hepatic dysfunction, hypertension, hypotension, age and chest x-ray cardiothoracic ratio, pulmonary atrial pressure as independent markers of adverse outcome. Gender is a controversial issue with respect to prognosis.

Age and Sex distribution of cases: HF tends to increase with increasing age. In the present study the number of patients over 56-60 years are 40 (40%). Out of the 40 patients, 20 patients have metabolic syndrome, 20 patients are without metabolic syndrome. In metabolic syndrome group highest number of patients were in 51-55 years age group. This is comparable to Framingham study, which reported that prevalence of HF is 2% by the age of 40 – 49 years, 5% by the age of 50-59 years, 10% by the age over 70 years. In metabolic syndrome highest number of cases in the age group of 51-55 years because the incidence of M.S in India is highest between the age group of 40-50 years (33.7%). In metabolic syndrome group 58.4% are females and 41.6% are males. This can be compared with Framingham study, which reported that the relative risk for diabetic men and women was 3.8 and 5.5 respectively, when compared with non-diabetic patients.In patients without metabolic syndrome group. 45% are females and 55% are males. This can be compared to Framingham study, which recently reported that life time risk of HF is 21% in men and 20% in females. According to Iribareen and colleagues - CHF onset was directly related to HBA_{1C} levels, with a level greater than 10% more than doubled the rate of onset of CHF compared with HBA_{1C} level of less than 7%. This is comparable to the present study. In the present study out of 100 patients with HF 60 patients have metabolic syndrome and 40 patients are without metabolic syndrome.

Effect on Primary End points

1. *Improvement / Change in the NYHA Class:* Gross assessments of the symptomatic severity by the NYHA functional classification.

Previous prognostic studies – used NYHA in prognostification of HF	
Name	**Year**
Keogh	1990 [26]
Bittner	1993 [27]
Compana	1993 [28]
Gianuzzi	1996 [29]
Adams	1996 [30]
Permonkil	1997 [31]
Gomes	1997 [32]
Bart	1997 [33]
Soifer	1997 [34]

In all these prognostic studies patients were considered improved when improvement in NYHA functional class was equal or more than two. In the present study out of 60 patients with metabolic syndrome, after 24 weeks of follow up the no. of patients with improvement in NYHA class by 2 or more are 20 (33.3%), where as out of 40 patients without metabolic syndrome, the no. of patients with improvement in NYHA class by 2 or more was 30 (75%). In the present study Out of 60 patients with metabolic syndrome 13 (21.6%) patients showing no change in the NYHA, while in patients without metabolic syndrome 12.5% are patients showing no change in NYHA.

Based on the previous studies, Gross functional improvement is more in the HF patients without metabolic syndrome, than HF patients with metabolic syndrome.

2. Distance Walked in 6 minutes: According to solved registry – A 6 minutes walk test is safe and simple clinical tool that strongly and independently predicts mortality and morbidity in patients with LV dysfunction.

Previous studies – used 6 min walk test in prognostication of HF	
Name	**Year**
Cohn	1993 [35]
Mahon	2002 [36]
Adams	1997 [37]

In the Solved registry, LVEF and distance walked in 6 min are equally strongly and independent predictors of mortality and morbidity. This is comparable to the present study. The distance walked in 6 min after 24 weeks (in meters) of follow up in patients with metabolic syndrome is 285.35 ± 3.30, where as in patients without metabolic syndrome the distance walked in 6 min after 24 weeks of follow up is 336.40 ± 16.0. The no. of frequent hospitalizations or use of intravenous medication is highest in the metabolic syndrome patients than patients without metabolic syndrome (50% Vs. 25%). Previous studies have shown high death rate in lowest performance group of patients when compared with highest performance group. This is comparable to the present study in which metabolic syndrome group have lowest performance level than patients without metabolic syndrome, the mortality rate is more in the metabolic syndrome group (16.6% Vs. 10%).

Effect on the Secondary End Points

1. Serial Monitoring–Absolute change in the LVEF: According to V-HeFT data. In HF patients a single measurement of LVEF provides important prognostic information and serial measurements of LVEF provide additional important prognostic information. According to SOLVD registry, EF is a strong and independent predictor of mortality and HF hospitalization during follow up.

Previous prognostic studies - used EF as prognostic predictor in HF	
Name	**Year**
Gradman	1989 [38]
Sterenson	1992 [39]
Bittner	1993 [27]
Giannuzzi	1996 [29]
Adams	1996 [30]
Gomes	1997 [32]
Bart	1997 [33]
Venkateswar	1999 [40]
Juliano	2002 [41]
Sarnak	2002 [42]

The present study comparable to SOLVD registry, in metabolic syndrome group after 24 weeks of follow up the EF was 31.63 ± 2.74, where as in patients without metabolic syndrome after 24 weeks of follow up the EF was 35.22 ± 1.71. This results in increased mortality and frequent hospitalizations in metabolic syndrome group (16.6% Vs 10% and 50% Vs. 25%). The present study is comparable to V-HeFT data, on serial monitoring of EF the improvement in EF is more in patients without metabolic syndrome and improvement after 24 weeks of follow up is more in patients without metabolic syndrome than patients with metabolic syndrome (75% Vs. 33.3%).

2. *Change in the LVEDD:* LVEDD vary widely, well coordinated male athlete have an average LVEDD of 56 ± 3 mm. In normal women the average LVEDD is 47 ± 3 mm. According to Unverferth (1984), patients with HF with a very dilated heart are known to have poor prognosis. This is comparable to present study. In the present study both groups have increase in LVEDD. LVEDD is significantly more in the MS group (65.04 ± 3.29 Vs. 54 ± 2.76) and with this the overall prognosis is poor (Mortality 16.6% Vs. 10% and Morbidity 50% Vs 25%).

Previous prognostic studies-used LVEDD as prognostic predictor in HF	
Name	**Year**
Demaria	1992 [43]
Saxon	1993 [44]

According to Lee TH (1993), Echocardiographic measurements - LVEDD > 75 mm or > 40 mm / m^2 is associated with sudden death. In the present study no patient have LVEDD > 75 mm.

Change in the QRS duration: A study conducted by Heather J. Shenkman showed that there was a linear relationship between increased QRS duration and increased EF. This is comparable to present study. In the M.S. group after 24 weeks follow up the QRS duration is 143.92 ± 6.07 and EF is 31.63 ± 2.74 where as patients without MS after 24 weeks follow up the QRS duration was 138.0 ± 2.83 and EF was 35.22 ± 1.71. According to Cleland (1987), Xiao HB (1996), Olshausen (1988), Brembilla parrot B (1997), intraventricular conduction delay with LBBB and prolongation of QRS interval has been associated with poor outcome in patients with HF and dilated cardiomyopathy.

Previous prognostic studies used QRS duration as prognostic predictor in HF	
Name	**Year**
Venkateswar	1999 [40]
Juliano	2002 [41]

The present study is comparable to above observations, the QRS interval after 24 weeks of follow up is 143 ± 6.07 in metabolic syndrome group and 138 ± 2.03 in the patients without metabolic syndrome.

The prognosis i.e. mortality and morbidity is highest in the QRS prolonged group i.e. metabolic syndrome group (16.6 Vs. 10%, 50% Vs. 25%)

Age and Sex wise distribution of Death: The SOLVD data identified diabetes as a strong predictor of mortality in patients with CHF. The present study is comparable to the above data as more deaths are noticed in the metabolic syndrome group. In the Rancho Bernardo Study, diabetic women had ischemic heart disease mortality rates higher to both nondiabetic and diabetic men, while nondiabetic women had a clear longevity advantage. In addition, case fatality rates following a myocardial infarction are as great or greater for diabetic women relative to nondiabetic women as for diabetic men. In the present study, out of 60 patients with metabolic syndrome 7 females and 3 males died, where as in 40 patients without metabolic syndrome 2 females and 2 males died. Age is one of the stronger and consistent predictor of adverse outcome in chronic heart failure.

In V-Heft trial, in the older cohorts, the risk of death or repeated hospital admission for congestive heart failure over a 12 months period of time approached 50%. This is comparable to metabolic syndrome group, as highest deaths are noted in the age group 56-60 years.

Observations during 24 weeks follow up

Electrocardiography: In the present study atrial fibrillation worsened heart failure in 4 patients with metabolic syndrome and 1 patient without metabolic syndrome. When high frequency premature contractions, couplets, are non sustained ventricular tachycardia is present during ambulatory monitoring, heart failure patients seem to be worse. In the present study in patients with metabolic syndrome 4 patients had sudden death.

First and Second degree atrial ventricular block and intraventricular conduction delay with left bundle branch block has been associated with poor outcome with heart failure and dilated cardiomyopathy. Interestingly, intraventricular conduction delay or left bundle branch block is not as powerful a predictor of high mortality when compared ischemic heart disease is the etiology.

Conclusion

In 100 cases of moderate to severe heart failure (60 with metabolic syndrome, 40 without metabolic syndrome) were monitored for a period of 24 weeks. The primary end points were improvement in NYHA distance walked in 6 minutes. Secondary end points were LVEF, LVEDD, QRS duration.

Effect on End points:

End Points	HF with Metabolic Syndrome		HF with out Metabolic Syndrome	%	T	P
Change in NYHA Class		**%**		**%**		
Improved by 2 or more class	20	33%	30	75%		
Improved by 1 class	9	15%	-	-		
No change	13	21%	5	12.5%		
Worsened	8	13%	1	2.5%		
Distance walked in 6 minutes		**SD**		**SD**		
Mean	285.35	± 3.30	336	± 1.60	3.3	<0.002
Absolute change in LV EF%						
Mean	31.63	± 2.74	35.22	± 1.71	2.7	<0.006
Change in LVEDD (mm)						
Mean	65.04	± 3.29	54.61	± 2.7	5.4	<0.002
Change in QRS interval (ms)						
Mean	143.92	± 6.07	138.00	± 2.03	2.26	<0.002

Effect on primary End points: As compared with metabolic syndrome group, patients without metabolic syndrome had improvement in the distance walked in 6 minutes, and the NYHA functional class ($p < 0.002$ and 75% improved.

Effect on Secondary End Points: As compared with metabolic syndrome, patients without metabolic syndrome had an improvement in two measures LVEF and QRS intervals. At the end of 24 weeks follow up, the condition of more patients in group without metabolic syndrome was considered to be improved (75% Vs 48.3%) and fewer were considered worsened (2.5% Vs 13.3 %)

Effects on death and on worsening heart failure: In the intention to treat analysis, there were 10 deaths in metabolic syndrome group and 4 deaths in patients without metabolic syndrome (16.6% Vs. 10%) – "mortality". Differences between the groups in the frequency of hospitalizations (or) the use of an intravenous medication were significant (50% Vs. 25%) – "morbidity".

Summary

"Metabolic Syndrome is a detrimental prognostic predictor of middle aged individuals with heart failure and retrieves the outcome in reference to age, sex, NYHA improvement, distance walked in 6 min, LVEF, LVEDD, SPAP and QRS duration. As such innumerable prognostic predictors are pointed till date. Metabolic syndrome perse could be an independent prognostic predictor and there yet remains paucity of its literature. Patients of metabolic syndrome with HF once being symptomatic prognosis is relatively poor with mortality rate of 16.6% and morbidity of 50%.

Heart failure with metabolic syndrome is associated with considerable morbidity that impairs quality of life by interfering with their ability to perform activities of daily living.

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References

1. Holmang A, Yashida N, Jennische E, et al. The effects of hyperinsulinaemia on myocardial mass, blood pressure regulation and central haemodynamics in rats. *Eur J Clin Invest* 1996; 26: 973-8.
2. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care* 2003; 26: 2433-41.
3. Sartori M, Ceolotto G, Papparella I, et al. Effects of angiotensin II and insulin on ERK1 /2 activation in fibroblasts from hypertensive patients. *Am J Hypertens* 2004; 17: 604-10.
4. Haider AW, Larson MG, Franklin SS, et al. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk of congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2003: 138(1): 10-6.
5. Verdecchia P, Carini G, Circo A, et al. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. *J Am Coll Cardiol* 2001; 38 (7): 1829-35.
6. Devereux RB. Is the electrocardiogram still useful for detection of left ventricular hypertrophy? *Circulation* 1990; 81 (3): 1144-6.
7. Aurigemma GP, Silver KH, Priest MA, et al. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. *J Am Coll Cardiol* 1995; 26 (1)): 195-202.
8. Mitchell GF, Tardif JC, Arnold JM, et al. Pulsatile hemodynamics in congestive heart failure. *Hypertension* 2001; 38 (6): 1433-9.
9. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular vascular function in persons with heart failure and preserved ejection fraction from Olmsted Country, Minnesota, *Circulation* 2007; 115 (15): 1982-90.
10. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling / dysfunction. *J Am Coll Cardiol* 2007; 49 (2): 198-207.
11. Gottlieb SS, Kukin ML, Ahern D, Packer M: Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. *J Am Coll Cardiol* 1989; 13: 1534-1539.
12. Omland T, Aakvaag A, Bonarjee B, et al : Plasma brain natriuretic peptide as an indicator of left ventricular systolic function in long term survival after acute myocardial infarction. *Circulation* 1996; 93: 1963-1969.
13. Pousset F, Isnard R, Lechat P, et al: Plasma endothelin-1 is a strong prognostic marker in chronic heart failure. *Eur heart J* 1997; 18: 254-258.
14. Devereux RB, Roman MJ: Hypertensive cardiac hypertrophy: Pathophysiologic and clinical characteristics. IN Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. *New York Raven Press,* 1995; 409-32.

15. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002; 347 (5): 305-13.
16. Bourassa MG, Gurne O, Bangdiwala SI, et al: Natural history and patterns of current practice in heart failure. The Studies of Left Ventricular Dysfunction (SOLVD) investigators. *J Am Coll Cardiol* 1993; 22: 14A-19A.
17. Bolli R: Mycoardial "Stunning" in man *Circulation* 1992; 86: 1671-1691.
18. Wijns W, Vatner SF, Camici PG: Hibernating myocardium. *N Engl J Med* 1998; 339: 173-181.
19. Shan K, Bick RJ, Roindexter BJ, et al: Altered adrenergic receptor density in myocardial hibernation in humans: A possible mechanism of depressed myocardial function. *Circulation* 2000; 102: 2599-2606.
20. O'Connor Cm, Anderson SA, Meese RB, et al: Clinical determinants of outcome in advanced heart failure: Insights from the PRAISE trail. *J Am Coll Cardiol* 1997; 129: 246A.
21. Bart BA, Shaw LK, McCants CV, et al: Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *J Am Coll Cardiol* 1997; 30: 1002-1008.
22. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death and prevention in patients with advanced ventricular dysfunction. *Circulation* 1993; 88: 2953-2957.
23. Malone S, Liu PP, Holloway R, et al : Obstructive sleep apnea in patients with cardiomyopathy. Effects of continuous positive ventilatory pressure. *Lancet* 1991; 338: 1480-1485.
24. Griffin BP, Shah PK, Ferguson J, Rubin SA: Incremental prognostic value of exercise hemodynamic variables in chronic congestive heart failure secondary to coronary artery disease or to dilated cardiomyopathy. *Am J Cardiol* 1991; 67: 848-853.
25. Lipkin DP, Sciven AJ, Crake T, et al: S ix minute walking test assessing exercise capacity in chronic heart failure. *Br Med J* 1986; 292: 653-660.
26. Keogh AM, Baron DW, Hickie JB: Prognostic guides in patients with idiopathic or chronic dilated cardiomyopathy assessed for cardiac transplantation. *Am J Cardiol* 1990; 65: 903-908.
27. Bittner V, Weiner DH, Yusuf S, et al: Prediction of mortality and morbidity with a six minute walk test in the patient with left ventricular dysfunction. *JAMA* 1993; 270: 1702-1707.
28. Campana C, Gavazzi A, Berzuini C, et al: Predictors of prognosis in patients awaiting heart transplantation. *J Heart Lung Transplant* 1993; 12: 756-765.
29. Gianuzzi P, Temporelli PL, Bosimini E, et al: Independent and incremental prognostic value of Doppler – derived mitral acceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. *J Am Coll Cardiol* 1996; 28:383-390.
30. Adams KF, Dunlap SH, Sueta CA, et al: Relation between gender, etiology, and survival in patients with symptomatic heart failure. *J Am Coll Cardiol* 1996; 28: 1781-1788.
31. Pernenkil R, Binson JM, Shah AS, et al : Course and prognosis in patients greater than 70 years of age with congestive heart failure in normal versus abnormal left ventricular ejection fraction. *Am J Cardiol* 1997; 79: 216-219.
32. Gomes JA, Mehta D, Ip J, et al: Predictors of long term survival in patients with malignant ventricular arrhythmias. *Am J Cardiol* 1997; 79: 1054-1060.

33. Bart BA, Shaw LK, McCants CV, et al: Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *J Am Coll Cardiol* 1997; 30: 1002-1008.
34. Soifer S, Nul DR, Grancelli HO, et al: Different predictors in sudden or progressive heart failure death in severe heart failure. *J Am Coll Cardiol* 1997; 129: 246A.
35. Chin MH, Goldman L: Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996; 156: 1814-1820.
36. Mahon NG, Blackstone EH, Francis GS, et al: The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol* 2002; 40: 1106-1113.
37. Adams KF, Califf RA, Harrell FEJ, et al: Simple clinical characteristics not hemodynamics predict survival in advanced heart failure (FIRST database). *Proc Heart Fail, Cologne,* 1997; 57.
38. Gradman A, Deedwani A, Cody R, et al: Predictors of total mortality and sudden cardiac death in mild to moderate heart failure. *J Am Coll Cardiol* 1989; 14: 546-570.
39. Stevenson WG, Middlekauf HR, Stevenson LW, et al: Significance of aborted cardiac arrest and sustained ventricular tachycardia in patients referred for treatment of advanced heart failure. *Am Heart J* 1992; 124: 123-130.
40. Gottipaty VK, Krelis SP, et al: The resting electrocardiogram provides a sensitive and inexpensive marker of prognosis in patients with chronic congestive heart failure. *J Am Coll Cardiol* 1999; 33 (2): 145A.
41. Juliano S, Fisher SG, Karasik PE, et al: QRS duration and mortality in patients with congestive heart failure. *Am Heart J* 2002; 143: 1085-1091.
42. Sarnak MJ, Tighiouart H, Manjunath G, et al: Anemia as a risk factor for cardiovascular disease in the atherosclerosis risk in communities (ARIC) study. *J Am Coll Cardiol* 2002; 40: 27-33.
43. DeMaria R, Gavazzi A, Caroli A, et al: Ventricular arrhythmias in dilated cardiomyopathy as an independent prognostic hallmark. *Am J Cardiol* 1992; 69: 1451-1457.
44. Saxon LA, Stevenson WG, Middlekauf HR, et al: Predicting death from progressive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; 72: 62-65

*All correspondences to: Dr Bilal Bin Abdullah, Professor and Head, Department of Medicine, Al Ameen Medical College, Athani Road, Bijapur-586108 Karnataka, India. Email:drbilal28@yahoo.com