



The Effects of the Aetiologic and Prognostic Values in Heart Failure on Life Expectancy and the Timing of Mechanical Circulatory Support: Are we heading for the bionic heart?

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ABSTRACT

Objective:

The aim of this study was to determine early implantation criteria for diagnosis, prognostic values, life process and mechanical circulatory support in patients with heart failure.

Method:

40 (male, 33; female, 7) patients were enrolled in this retrospective study. Patients were grouped as having dilated, ischemic and hypertrophic cardiomyopathy. New York Heart Association classes were determined, and a short-form 36 quality-of-life assessment questionnaire was administered. INTERMACS[®] has been leveled. VO₂ max and 6-minute walk test, blood sodium and pro-BNP levels, LVEF, RVEF, right atrial filling pressures were examined. Total artificial heart devices were implanted to the patients in our clinic prior to the surgery.

Results:

Rates of the group of dilated CMP, hypertrophic CMP, and ischemic CMP were 75%, 5%, and 20%, respectively. Ratios of the patients according to four classed NYHA classification

(I to IV) were 5%, 25%, 47.5%, and 22.5%, respectively. Diagnostic criteria's used for cardiac device implantation resulted such as; Mean Intermacs levels were 4.90 ± 1.59 and 3.66 ± 1.22 and VO₂ max values were 13.52 ± 6.02 , according to a six-minute walk test, walking distances were 280.55 ± 131.94 meters, LVEF values were 23.10 ± 6.73 .

Conclusion:

High left ventricle end-diastolic diameter and low VO₂ max values were associated with a poor prognosis. Right ventricular ejection fraction as independent variables and the six-minute walk test were associated with death. According to our study survey can be corrected by applying for mechanical circulation support in selected patients with heart failure with high mortality. An increasing number of patients in the future are likely to have these devices implanted as an alternative to transplantation, and of these, all with nonischemic dilated cardiomyopathy are candidates for recovery.

Keywords

Heart failure, life expectancy, cardiomyopathy, mechanical circulatory support, bionic heart

INTRODUCTION

Congestive heart failure (CHF) is a chronic and life-threatening disease, and it is characterized by severe fatigue, dyspnea, functional impairment and fluid retention. The incidence of heart failure and the treatment costs of patients with heart failure are increasing because of the ageing population, improvement in survival after acute myocardial infarction (MI) and decreased mortality due to other diseases. The data suggest that the risk of developing lifetime heart failure is approximately 20%. The incidence of heart failure is 0.3% and its prevalence is approximately 1%–2%, and these values increase with age and with only 35% surviving 5 years after the initial diagnosis (Birks et al., 2006, Bleumink et al., 2004). In the Framingham study, a two-fold increase in heart failure incidence was observed in every decade in people of the age range 45–75 years. The duration of hospitalization of patients with heart failure is longer than that of other patients hospitalized for different reasons. Mortality rate during hospitalization is between 18% and 30%. After being discharged, 14% of the patients died and 30%–40% re-hospitalized. Heart failure (HF) is the primary reason for hospitalization of patients aged over 65 years. Despite all the developments, HF is characterized by increased mortality, progression of symptoms and re-hospitalization after the onset of the symptoms (Jenkinson et al., 1997). In the latest guidelines, early use of biventricular support devices is recommended in patients with severe symptoms or sudden worsening of the condition or in patients with end-stage heart failure when there is left ventricular support devices or ventricular failure in both sides. However, there are few studies examining the correlation between quality of life and clinical variables and new treatment options for patients with heart failure (Ware et al., 1992, Juengen et al., 2002). The most reliable method for determining the functional capacity level in patients with heart failure is to determine the maximal oxygen consumption value using the cardiopulmonary test. In addition, parameters such as blood sodium (Na), pro-brain natriuretic peptide (Pro-BNP), left ventricular ejection

fraction (LVEF), right ventricular ejection fraction (RVEF) and right atrial filling pressures that are predictive values for heart failure affecting the prognosis can also be used. This study aimed to investigate the effect of diagnosis, maximal oxygen consumption values and prognostic factors in patients with heart failure on the clinical status of patients and their correlation with prognosis and to determine the early implantation criteria for mechanical circulatory support (MCS) (Juengen et al., 2002).

MATERIALS AND METHODS

Initial Evaluation

This retrospective study was approved by the ethics committee of the institution with the decision of 08.01.2013/ 04. All patients were informed in detail on the treatments and that written informed consent was obtained in each patient. The study was designed in accordance with Helsinki Protocol. Patients who underwent surgery due to heart failure between 2009 and 2013 were included in the study. Inclusion criteria were as follows: less than 45% of left ventricular ejection fraction, having CHF symptoms for 6 months, aged over 18 years. Patients who failed the exercise test owing to neurological, psychiatric, orthopedic, peripheral vascular or severe pulmonary disease were excluded from the study. Medical treatment was optimized prior to exercise testing according to symptoms and renal functions of the patients. All patients were receiving optimal heart failure treatment for the previous 2 months. A detailed history was obtained and a physical examination was performed for each patient at the beginning of the study. Pulmonary function tests were performed to exclude pulmonary diseases that would prevent exercise testing. According to etiological causes, patients were divided into groups of dilated (idiopathic and valvular), cardiomyopathy and hypertrophic cardiomyopathy. Comorbid conditions were determined. Initial functional status of the patients was evaluated by New York Heart Association (NYHA) functional class, cardiopulmonary exercise test and submaximal exercise tests. For statistical analysis, NYHA classes were

grouped among themselves as class I-II (group 1=living group) and class III-IV (group 2= mortality group).

Pulmonary Function Test

Prior to the cardiopulmonary exercise test, all patients underwent pulmonary function tests to exclude pulmonary diseases. The cardiopulmonary exercise test was administered to all patients by the same person. During the test, none of the patients developed myocardial ischemia.

Submaximal Exercise Test

A 6-minute walk test was used as the submaximal exercise test. Patients walked for 6 min in a quiet, uncarpeted corridor over a fixed distance and were recorded. Patients were asked to walk at their normal walking speed during the test.

Determination of Intermacs level

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS®) Levelling was performed according to the level of physical capacities and inotropic needs and findings of patients. Level 1 describes patients with critical cardiogenic shock; those with life-threatening hypotension; those with critical organ hypoperfusion along with acidosis and lactate levels; and those requiring immediate inotropic support. Increasing levels up to Level 7 indicate a better status of health (Stevenson et al.,2009, Kirklin et al.,2014).

Quality of Life

Quality of life was assessed using the Short Form 36 (SF 36) (Lynson et al.,1994). Parameters that have predictive values for HF such as blood sodium (Na), Pro-BNP, LVEF, RVEF and right atrial filling pressures, were assessed. RVEF was calculated by using right ventricular fractional area change (FAD) and using a relative value estimate to determine whether the inferior vena cava (IVC) diameter is normally 1.2-1.3 cm and shows more than 50% reduction with breathing. The NYHA functional class of all patients was evaluated by an independent cardiologist prior to other

measurements. Patients were followed up by hospital visits or telephone checks. Echocardiography was performed with a 2.5-mHZ probe using a General Electric VIVID 3 device.

Cardiopulmonary Exercise test (CPET)

Oxygen usage was obtained by measuring carbon dioxide production using a CortexMetalyzer 3B device on a Quinton 5000 treadmill exercise device. The anaerobic threshold was evaluated by the V-slope method. Before each test, volume and gas calibration was performed. As an exercise protocol: A 2° inclination increase per minute at a speed of 2.5km/h was used.

Statistical Analysis

SPSS 16.0 (SPSS for Windows, Chicago, USA) package programme was used for statistical analyses. Frequency distribution was used to determine basal characteristics. When comparing NYHA with short form 36 (SF36) and functional parameters, the significance between the two means was tested using the student t-test, and the correlation between variables was evaluated by Pearson correlation analysis. The correlation between the dependent variable KF36 scale and independent variables (maximal oxygen uptake (VO₂ max), 6-min-walk test and ejection fraction) was examined by stepwise linear regression analysis. The effect of diagnosis on mortality was analyzed using logistic regression forward stepwise method. Prognostic indicators and survey findings were evaluated with survival function analysis.

RESULTS

A total of 40 patients were enrolled to the study. Medical treatments of the patients were optimized a minimum 6 months in advance. The Characteristics of the patients are summarized in Table 1- 2.

Table 1. Characteristics of patients with congestive heart failure

Demographic Characteristics	
Age	45,17 ±11,69
BMI (kg/m ²)	26,34±4,42
Gender	Male %82,5 (n:33) Female %17,5 (n: 7)
Etiological Cause	
Dilated Cardiomyopathy (%) n: 30	%75
Hypertrophic Cardiomyopathy (%)n: 2	%5
Ischemic Cardiomyopathy (%)n: 8	%20
NYHA Class	
Class I n: 2	%5
Class II n: 10	%25
Class III n: 19	%47,5
Class IV n: 9	%22,5
Functional Measurements	
VO ₂ Max.(ml/kg/dk)	13,52±6,02
6 minute walk test, m	280,55 ± 131,94
LVEF, %	23,10±6,73
Medications	
Angiotensin Receptor Blocker	%2,5
ACE inhibitor	%77,5
Beta Receptor Blocker	%87,5
Aspirin	%92,5
Digital	%52,5
Diuretic	%100,0
Antihyperlipidemic	%12,5
Antiarrhythmic	%30,0
Pulmonary Function Tests	
VC	3,43±0, 90
FEV1	2,67±0, 86
FVC	3,37±0, 89
FEV1/FVC	73,90±9,06
Comorbidities	
Coronary Disease	%27,5
MI	%12,5
Valvular Disease	%77,5
iCD Presence	%35,0

Table 2. Correlation between NYHA and other parameters

Parameters	NYHA (Mean + SD)	
	Class I Class II	Class III Class IV
Age (years)	49,00 ±11,06	43,53± 11,75
VO ₂ Max (ml/kg/dk)	16,16 ±4,66	12,39 ±6,24
6 Minute Walk test, (m)	359,41±50,53	246,75±141,97*
LVEF (%)	25,16 ±9,21	22,21±5,31
RVEF (%)	37,08 ±11,37	33,57±11,22
VC	3,48 ±0,83	3,41±0,94
FEV1	2,54 ±0,71	2,73±0,92
FVC	3,39 ±0,82	3,36±0,94
FEV1/FVC (%)	73,41 ±7,35	74,10±9,82

* P < 0.01

Statistical correlation between NYHA and Quality of Life Parameters were shown in Table 3.

Table 3. Comparison of SF36 scale and NYHA classes in CHF patients

SF 36 scale	NYHA (mean±SD)		
	Class I-II	Class III-IV	p
General health	37,08 ±18,02	38,75 ±19,37	0.439
Physical function	49,16 ±25,92	47,67 ±21,19	0.427
Physical role	31,25± 32,20	16,07 ±29,03	0.297
Vitality	45,00 ±11,48	42,85 ±16,46	0.154
Social function	54,58± 11,00	52,69± 10,71	0.987
Pain	64,79± 22,79	56,78 ±27,35	0.365
Mental health	61,33± 18,07	60,42 ±18,77	0.787

Results of statistical evaluation between quality of life and functional variables were given in Table 4.

Table 4. Correlation between LVEF, VO₂, 6-minute walk test and Quality of life parameters

Parameters	General health	Physical Function	Physical Role	Vitality	Social function	Pain	Mental health
LVEF	0,124	-0,074	0,055	- 0,096	-0,074	0,084	-0,005
VO ₂ max	0,106	-0,065	0,102	- 0,198	-0,065	-0,128	-0,015
6-min walking	0,041	0,136	0,020	- 0,114	0,136	-0,251*	-0,172

* p<0.05 LVEF: Left ventricular ejection, VO₂ max: Maximal oxygen consumption

Statistical correlation between NYHA and Functional variables were shared in Table 5.

Table 5. Comparison of prognostic values and NYHA classes in patients with CHF

Parameters	NYHA (mean±SD)	
	Class I-II	Class III-IV
Age	49,00 ± 11,06	43,53 ± 11,75
VO ₂ max	16,16± 4,66	12,39±6,24
6-min-walktest	359,41±50,53	246,75±141,97
VC	3,48±0,83	3,41±,94
FEV1	2,54±0,71	2,73±0,92
LVEF	25,16± 9,21	22,21± 5,31
RVEF	37,08± 11,37	33,57±11,22

Statistical correlation between patient characteristics in mortality and clinical variables were given in Table 6.

Table 6. Patient characteristics in mortality

Parameters	Living Patients	Ex Patients	P
Age	44,83±10,28	46,33±16,36	0,008
Male	78,8%	21,2%	0,179
Female	71,4%	28,6%	
Coronary Disease	%12	%11	0,779
MI	%22	%44	0,076
Valvular Disease	%70	%100	0,000*
ICD Presence	%38	%22	0,029*
CNS Involvement	%03	%22	0,000*
Diabetes	%16	%33	0,061
HT	%12	%22	0,211
CABG History	%09	%22	0,071
LVEF	23,25± 7,25	22,55± 4,82	0,318
LVDEV	6,15±0,98	6,94±1,85	0,023*
LVDED	6,46±1,21	6,98±1,46	0,237
RA pressure	11,75± 2,74	12,33± 2,64	0,621
LVEF	36,67± 11,01	27,55± 9,42	0,425
Peak VO ₂ (ml/kg/min)	14,45± 6,45	10,31± 2,36	0,012*
6 Min Walking (m)	321,51±102,71	139,44±128,09	0,173
INTERMACS	4,90±1,59	3,66±1,22	0,273
Sodium	132,32±5,17	130,00±6,28	0,571
Pro-BNP	3025,18±5794,10	2674,91±891,63	0,497
Functional Capacity NYHA			
Class I-II	83,3%	16,7%	0,335
Class III-IV	75,0%	25,0%	-
Heart Rate Resting beats/min	89,03± 18,89	97,22± 24,09	0,642
Heart Rate Max. beats/min	121,29±31,81	131,55±24,26	0,337

Age, MI history, valvular disease and central nervous system (CNS) involvement and implantable cardioverter defibrillator (ICD) presence were significantly different between the two groups. Age, MI history, presence of valvular disease and CNS involvement were associated with poor prognosis in the mortality group in fact diabetes mellitus (DM) ratio was significantly higher in the mortality group. Although dilated and hypertrophic CMP were not significant in terms of mortality according to etiological diagnosis, ischemic CMP was statistically significant ($p < 0.05$). Patient characteristics in mortality are shown in (Table 7). Left ventricular end diastolic diameter (LVEDD) and VO₂ max values ($p < 0.05$) were statistically significant and high left ventricular end diastolic volume (LVEDV) and low VO₂ max values were associated with poor prognosis. Although not statistically significant, LVEF and Intermacs values were found to be low in the mortality group.

According to the NYHA class, right atrial pressure and Pro-BNP values increased from Class I to Class IV, whereas VO₂ max values exhibited a decreasing trend.

In the multivariate analysis, RVEF was associated with mortality as an independent variable. Mortality rate was higher in patients with low RVEF ($p < 0.05$). Similarly, the 6-min walk test was also found to be an independent predictor of mortality.

DISCUSSION

Chronic heart failure is becoming more common owing to the aging population and the number of patients with chronic heart failure is increasing daily. Despite recent advances in treatment, HF still has high mortality and morbidity rates. Previous studies have shown that the quality of life is impaired in patients with heart failure (Seferovic et al.,2021, Moradi et al.,2020). In our study, as the NYHA functional class worsened, the SF36 parameters also worsened; however, a significant correlation was found only between the pain parameter of SF36 and the 6-min-walk test. SF36 parameters were correlated with each other. Other studies have demonstrated a significant correlation between NYHA functional class and all parameters of SF 36 (Karapolat et al.,2006). In our study, a nonsignificant correlation was found between the two groups of NYHA class I-II (group 1) and class III-IV (group 2) in terms of quality of life parameters. However, physical role parameter values, which indicate the accomplishment of daily activities and effortful tasks, were 50% lower in group 2 than in group 1. Rose et al. have also published similar results. However, the determinants of quality of life deterioration remain unclear (Rose et al.,2001). Although other studies have reported a significant correlation between NYHA functional class and all parameters of SF36, no such correlation was found in our study. This can be attributed to new treatment approaches and psychological support given to the patient by increasing awareness, there by increasing patient comfort. Lee et al. also demonstrated that an improvement in psychological support and functional health parameters increased the

quality of life (Lee et al.,2005). Clark et al. also reported higher values of quality of life in patients with positive life beliefs who receive social support and are in communication with their physicians (Clark et al.,2003). In their study, Hobbs et al. showed that beta-blockers and angiotensin-converting enzyme (ACE) inhibitors increased the quality of life (Hobbs et al.,2002). The results of our study are consistent with those of these studies. The mean survival time for advanced-stage heart failure is 2–3 years (Poggin et al.,2010). High-risk patients are identified by evaluating the patient's clinical status, functional capacity and left ventricular functions at rest (Laincbury et al.,2002). However, all these measurements are insufficient to determine the prognosis of patients. In our study age, MI history, presence of valvular disease and CNS involvement were associated with poor prognosis. DM rate was significantly higher in the mortality group. DM also poses a risk for cerebrovascular accident, carotid artery disease, and coronary artery disease (Isik et al., 2021). Although not homogeneously distributed, the presence of ICD was found to be higher in living patients, which can be argued to contribute to the survey by preventing ventricular arrhythmias. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study, the effects of amiodarone on surveying patients with sustained ventricular tachycardia and ventricular fibrillation were compared at 45.5 months of follow-up. In that study, ICD implantation was shown to reduce death risk by 23%, although amiodarone showed a similar effect to that of placebo (McMurray et al., 2012, Bardy et al.,2005). In our study, although dilated and hypertrophic CMP were not significant in terms of mortality based on etiological diagnosis, ischaemic CMP was statistically significant. Furthermore, right atrial pressure and proBNP values increased from Class I to Class IV, whereas VO_2 max values exhibited a decreasing trend. In their study included 45 year follow-up Ladenvall et al. showed that VO_2 max is an important independent indicator of mortality, and low VO_2 max values were associated with poor prognosis and Altes et al. reported that increased right atrial pressure was an independent indicator of mortality. (Ladenvall et al.,2016, Altes et al. 2019). Mayer et al.

investigated the prognostic value of N-terminal fragment of the BNP precursor (NT-proBNP) in patients with chronic coronary heart disease without clinical HF and found that mortality rate due to all causes was higher in the group with a NT-proBNP level of 862pmol/L compared with lower NT-proBNP levels (3.46%/year vs. 1.08%/year) (Mayer et al.,2009). As explained above, our patient group also showed poor prognosis and the results were consistent with those of other studies. In multiple regression analysis, RVEF was associated with mortality as an independent variable. Mortality rate was higher in patients with low RVEF. Mortality was observed in 5 of 6 patients (83%) with RVEF of $\leq 25\%$. Meyer et al. investigated the RVEF effects in patients with chronic heart failure and reported that $<20\%$ RVEF was an independent predictor of mortality and hospitalization. In this series of 2008 patients, the mortality rate was 8% when RVEF was $<40\%$, and it increased to 18% when RVEF was $<20\%$ (Meyer et al.,2010). In our study, RVEF was also found as an independent predictor of mortality; however, a larger patient population is required for a more clear evaluation of mortality and statistical significance. Similarly, the 6-min-walk test was also found as an independent predictor of mortality. Mortality rate was significantly higher in the mortality group at low walking distance. When compared with all patients, the mortality rate was 53% at a walking distance of ≤ 200 m. Mortality was observed in 7 of 13 patients. Arenaza et al. evaluated patients with severe aortic stenosis having NYHA class III and IV symptoms, and found that mortality or stroke rate was 13% in the group with <300 m 6-min-walk test and 3.9% in the group with <600 m, and concluded that less walking distance was an independent predictor of mortality or stroke (Arenaza et al.,2006). Cardiopulmonary exercise test (CPET) is recommended for the measurement of functional capacity, prognosis and follow-up of medical treatment success and evaluation of new treatment alternatives for patients with heart failure (Poggin et al.,2010, Laincbury et al.,2002). With CPET, the exercise capacity of patients can be objectively determined. Maximal oxygen consumption value provides information about the patients with higher risk of

cardiac death and long-term prognosis. Peak VO_2 value is the most widely accepted parameter for prognosis. Cardiovascular mortality rapidly increases when peak VO_2 falls below 14 ml/kg/min. Similar to previous studies, 36-month follow-up mortality was found to be 22.5% in patients with a peak VO_2 level below 14 ml/kg/min in our study. The mortality rate in patients increased, particularly when the maximal oxygen consumption decreased below 10 ml/kg/min. In this patient group, 47% of patients survived at the end of 36 months. However, all patients with peak VO_2 values of <14 were alive at the end of follow-up. These findings are consistent with the 5-year follow-up survey rates of 25% in males and 38% in females reported by Poggin et al (Poggin et al., 2010). In addition to peak VO_2 , New York Heart Association functional class, pro-BNP values, LVEDD, RVEF and 6-min-walk test were found to be associated with prognosis in our study. When all patients were compared, the mortality rate in NYHA class I-II was 16.7%, and it increased to 25% in NYHA class III-IV. The mortality rate was 77% in NYHA class III-IV patients in the mortality group (7 of 9 patients) and this group had lower Intermacs values than the living group (3.66 versus 4.90). Mortality rate was 16.6% in patients treated with left ventricular assist device (LVAD). It should be noted that patients were selected to be treated with LVAD were patients in the NYHA class III and IV group, and their probability of benefiting from medical treatments was so limited or they were patients in the mortal limit who were unable to tolerate maximal treatments owing to side effects. Accordingly, as mentioned above, the mortality rate we found in this group decreased from 77% to 16%. This result is consistent with the findings of Rose et al. investigating long-term use of left ventricular assist devices in end-stage heart failure, where in a 48% reduction in mortality risk was obtained compared with the medical treatment group (Rose et al., 2001). Similar results are found in auxiliary devices that provide continuous current (Slaughter et al., 2009). A total artificial heart device is an implantable machine that replaces the heart and provides temporary life-saving situations for the bridge to heart transplantation (Vis et al., 2022). It maintains perfusion

support mechanically until the patients recover or prior to heart transplantation (Cavga, 2022). Total artificial heart (TAH) implantation provides emergency hemodynamic repair and clinical stabilization by correcting end organ failure in patients close to death and allows for transplantation. Jack and colleagues found that the survey bridge to transplantation was 79% in patients who underwent this procedure. Previous studies reported surveys up to transplantation as 51%–71% for LVADs and 58%–61% for biventricular assist devices (BIVAD)s. The mortality and morbidity benefits of TAH devices for bridging patients with biventricular insufficiency to transplantation are superior to those of BIVADs (Copeland et al., 2004).

Previous studies have shown that quality of life is impaired in patients with heart failure. Positive life beliefs, social support, psychological support, patient communication with physicians and improvement of functional health parameters increase quality of life. However, the parameters predicting deterioration of quality of life remain unclear and multicenter studies with large series are required. Because comorbid conditions are associated with poor prognosis, it would be appropriate to evaluate these conditions in large series. According to the etiologic diagnosis, patients with dilated and ischemic CMP (due to their high mortality) should be carefully followed. We believe that early and correct decisions regarding support devices for this group will directly have an impact on survival and quality of life.

Conflict of Interest:

The authors declared no conflicts of interest

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