

# The correlation between left ventricular ejection fraction and clinical severity of manifestations in subjects with Coronary Artery Disease

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## Abstract

We have studied the correlation between Left Ventricular Ejection Fraction (LVEF) and severity of clinical symptoms classified according to New York Health Association (cNYHA) in subjects admitted for Coronary Artery Disease (CAD). Two hundred subjects were considered. Informed Consent was obtained by the patients and the study was approved by the Ethical Committee. The following variables were examined: ACP1 genotype, p53 codon 72 genotype, age, sex, diabetes, obesity, hypertension, total cholesterol, history of previous infarction. Statistically significant differences in the correlation between LVEF and cNYHA were observed for ACP1 genotypes, sex and age. Carriers of \*C allele of ACP1, females and subjects aging more than 65 years show a higher correlation between LVEF and cNYHA as compared respectively to other ACP1 genotypes, males and subjects aging 65 years or less. The correlation between LVEF and cNYHA increases with the number of variables for which an increase of such correlation has been observed.

The data suggest that subjects with CAD aging more than 65 years who carry \*C allele of ACP1 if show a LVEF lower than 50% have a high probability to manifest severe clinical symptoms.

## Introduction

A very useful index of ventricular function based on echocardiography is the Ejection Fraction (E.F.) which is the systolic volume divided by the end-diastolic volume. A normal E.F. is 0.55 or greater.

The clinical classification of patients with heart disease proposed by the New York Health Association (NYHA) is based on the severity of symptoms. Class 1, patients with no limitation of activities: they suffer no symptoms from ordinary activities. Class 2, patients with slight, mild limitation of activity: they are comfortable with rest or with mild exertion. Class 3, patients with marked limitation of activity: they are comfortable only at rest. Class 4, patients who should be at complete rest, confined to bed or chair: any physical activity brings on discomfort and symptoms occur at rest.

The correlation between echocardiographic and clinical parameters has been scarcely considered in the literature. In the present note we have analyzed in subjects with coronary artery disease (CAD) the correlation between the two parameters in relation to variables that have a significant role in the susceptibility and in the clinical course of the disease.

## Material and methods

We have studied 200 subjects admitted to the Hospital for CAD. Clinical data on these subjects have been reported in a previous paper [1]. ACP<sub>1</sub> and p53 codon 72 genotypes were determined by DNA analysis as previously reported [1,2]. Informed Consent was obtained by the subjects and the study was approved by the Council of Department.

Statistical significance of difference between correlation coefficients was calculated according to Snedecor and Cochran [3]; other analyses were performed by commercial software (SPSS) [4].

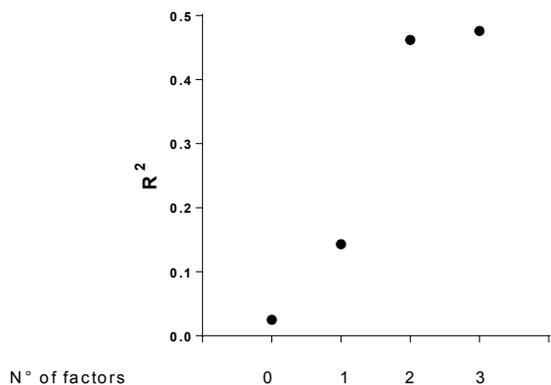
## Results

Table 1 shows the correlation between LVEF and cNYHA class in relation to nine variables including ACP1 and p53 codon 72 genotypes in patients admitted for CAD. Differences between correlation coefficients are statistically significant for ACP<sub>1</sub>, sex and age. The correlation is stronger in females than in males, in subjects aging more than 65 than in those aging 65 yrs or less and in carriers of \*C allele as compared to other ACP<sub>1</sub> genotypes. The table also shows the difference between squared  $r_s$ , a parameter that measures the proportion of variance of cNYHA class explained by LVEF *i.e.*, the strength of correlation between the two variables.

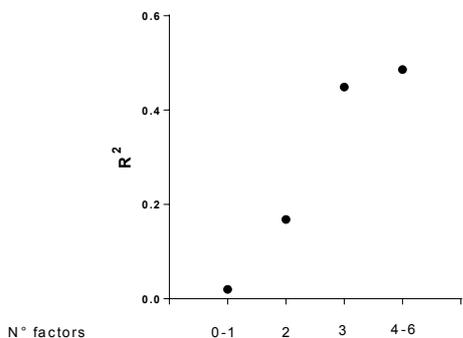
We have considered the three variables for which the difference between correlation coefficient is statistically significant and depicted in Figure 1 the relationship between the number of factors for which an increase of  $r_s$  between LVEF and cNYHA has been observed and the strength of negative correlation ( $r_s^2$ ) between the two parameters: the minimum value is observed when no factor is present and a maximum

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**Figure 1.** The relationship between the number factors for which an increase of correlation between LVEF and cNYHA has been observed and the strength ( $R^2$ ) of correlation between the two variables. In this figure only ACP<sub>1</sub>, age and sex have been considered.



**Figure 2.** The relationship between the number factors for which an increase of correlation between LVEF and cNYHA has been observed and the strength ( $R^2$ ) of correlation between the two variables. In this figure the following variables have been considered: ACP<sub>1</sub>, sex, age, positive history of previous infraction, obesity and diabetes.

when at least two factors responsible for the increase of correlation are present. The figure suggests that the predictive value of LVEF on the severity of clinical symptoms (*i.e.*, cNYHA) is increasing with the number of factors present in the patient.

Figure 2 shows a similar analysis considering ACP<sub>1</sub>, sex, age, diabetes, obesity and positive history of previous infarction. The pattern of relationship between the number of variable and  $r_s^2$  is similar to that observed in Figure 1.

In Table 2 we have considered a combined variable LVEF/cNYHA in order to analyze the concordance of severity of both LVEF and cNYHA with ACP<sub>1</sub>, age and sex. The concordance between the severity of the two parameters is much higher in subjects carrying the \*C allele of ACP<sub>1</sub> that in other ACP<sub>1</sub> genotypes. The concordance is much higher in subjects aging 65 years or more than in subjects aging less than 65 years. The concordance is higher in females than in males but such difference doesn't reach the level of statistical significance.

### Discussion

Our analysis shows that the correlation between LVEF and cNYHA class in CAD is dependent on many variables. Considering cumulatively the effect of the variables examined the correlation doesn't exceed 0.7 suggesting that about 50% of cNYHA variance can be explained by LVEF.

The most important variables are ACP<sub>1</sub> and age: subjects aging more than 65 years carrying the \*C allele of ACP<sub>1</sub> and showing a LVEF lower than 50% have a high probability to manifest severe symptoms.

ACP<sub>1</sub> controls the synthesis of cytosolic Low Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP), a polymorphic enzyme showing quantitative variation of enzymatic activity among genotypes. There are three codominant alleles with enzymatic activity increasing

**Table 1.** Correlation between LVEF and cNYHA class.

	$r_s$	$r_s^2$	Significance of difference
Carriers of *C allele	-0.632	0.399	
ACP <sub>1</sub> genotype	-0.332	0.110	p=0.035
Other genotypes			
Sex			
females	-0.554	0.307	
males	-0.334	0.112	p=0.045
Age			
≥65yrs	-0.622	0.387	
<65yrs	-0.368	0.135	p=0.050
Positive history of previous infarction	-0.605	0.366	
yes			
no	-0.423	0.179	p=0.140
Obesity	-0.537	0.288	
yes			
no	-0.348	0.221	p=0.170
Diabetes	-0.486	0.236	
yes			
no	-0.323	0.104	p=0.180
Total cholesterol <sup>o</sup>	-0.508	0.258	
high			
low	-0.430	0.185	p=0.790
p53 codon 72 genotype	-0.531	0.282	
*Pro carriers			
*Arg/*Arg	-0.481	0.231	p=0.800
Hypertension <sup>oo</sup>	-0.546	0.289	
yes			
no	-0.491	0.241	p=0.900

<sup>o</sup>Total cholesterol: high > 200 mg/dl

<sup>oo</sup>Hypertension: arterial tension ≥ 130/85 mmHg

**Table 2.** The effect of ACP<sub>1</sub> age and sex on the concordance between severity of LVEF and cNYHA parameters.

ACP <sub>1</sub>	ACP <sub>1</sub> genotypes carrying the *C allele	Other ACP <sub>1</sub> genotypes	Chi square test of independence
LVEF <50 and cNYHA class ≥3  total n°	30.7%  39	8.1%  161	$\chi^2$ df p 12.782 1 0.00035 OR=5.00 95% C.I. 1.91-13.41
<b>AGE</b>	≥65 yrs	<65 yrs	
LVEF <50 and cNYHA class ≥3  total n°	24.8%  133	1.5%  67	$\chi^2$ df p 15.558 1 0.00008 OR=21.78 95% C.I. 3.07-100.68
<b>SEX</b>	females	males	
LVEF <50 and cNYHA class ≥3  total n°	15.5%  91	9.2%  109	$\chi^2$ df p 1,800 1 0.180 OR=1.95 95% C.I. 0.77-4.99

in the order \*A<\*B<\*C and correspondingly six genotypes. The enzyme acts as phosphotyrosine phosphatase and as flavin-mononucleotide phosphatase [5]. The cLMWPTP dephosphorylates a negative phosphorylation site in ZAP 70 tyrosine kinase in T cell [6] with important effect on the activity of these cells. The enzyme is involved in the negative modulation of insulin signal transduction, in flavoenzyme activity and in dephosphorylation of Platelet Derived Growth Factor (PDGF) receptor [5,7,8]. Recent studies suggest that PDGF exert a protective role on contractile function of cardiomyocyte and protects these cells from apoptosis [9].

The present study could have clinical relevance in CAD for the prognostic value of LVEF on the clinical severity of the disease. The main limitation is represented by the relatively low number of the subjects examined.

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