

# Plasma VEGF Level Changes With Exercise in Patients with Chronic Coronary Artery Disease

## *Variaciones de los niveles plasmáticos de VEGF con el ejercicio en pacientes con enfermedad coronaria crónica*

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### ABSTRACT

**Background:** The aim of this study was to assess the effect of acute and programmed physical exercise on plasma VEGF levels in chronic stable coronary artery disease patients. Following baseline evaluation, 21 patients <75 years underwent an exercise stress myocardial perfusion scan (acute), and were then randomly assigned to perform programmed rehabilitation exercise or continue with their normal therapy. VEGF assessed by SPECT imaging significantly decreased after stress ergometry (from  $49.59 \pm 6.06$  to  $31.83 \pm 5.62$  pg/ml;  $p=0.021$ ). At one month, it increased ( $70.90 \pm 14.44$  pg/ml) though not significantly with respect to baseline values ( $p=0.1$ ) and significantly with respect to immediate post exercise values ( $p<0.01$ ). No significant changes were observed in VEGF at 3 months or when results were compared according to the presence of ischemia or programmed exercise. Acute exercise induced a significant reduction in VEGF values, without differences between programmed exercise and the control group.

**Key words:** Coronary Artery Disease - Exercise - Vascular Endothelial Growth Factor A

### RESUMEN

**Introducción:** Con el objetivo de evaluar el efecto del ejercicio físico agudo y programado sobre los niveles plasmáticos de VEGF en pacientes coronarios crónicos estables, se estudiaron 21 pacientes < 75 años a los que luego de la evaluación basal se les realizó un estudio de perfusión miocárdica con esfuerzo (agudo) y posteriormente se asignaron en forma aleatoria a realizar ejercicios programados de rehabilitación o continuar con el tratamiento habitual.

Los valores de VEGF disminuyeron significativamente en el posesfuerzo de la ergometría de la SPECT (de  $49,59 \pm 6,06$  a  $31,83 \pm 5,62$  pg/ml;  $p = 0,021$ ). Al mes, los valores aumentaron ( $70,90 \pm 14,44$  pg/ml) con tendencia no significativa respecto del valor basal ( $p=0,1$ ) y significativamente respecto de los valores del posesfuerzo inmediato ( $p<0,01$ ). No se observaron cambios significativos en los valores de VEGF a los 3 meses y tampoco al comparar los resultados según la presencia de isquemia o la realización de ejercicios programados.

El ejercicio agudo indujo una reducción significativa en los valores de VEGF, sin diferencias entre el ejercicio programado y el grupo control.

**Palabras clave:** Enfermedad coronaria - Ejercicio - Factor A de crecimiento endotelial vascular

### Abbreviations

DS	Difference or ischemia score	SPECT	Single photon emission computed tomography
ES	Exercise score	VEGF	Vascular endothelial growth factor
RS	Resting score		

### INTRODUCTION

Programmed physical exercise has been effective in improving symptoms, quality of life and sometimes ischemic parameters; therefore, the implementation of cardiovascular rehabilitation programs is a very

important tool to complement medical treatment and myocardial revascularization. (1)

Physical activity promotes angiogenesis by increasing the levels of vascular endothelial growth factor (VEGF) and other factors and/or their half-life.

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Furthermore, ischemia is a major stimulus for VEGF production and local amplification effects. (2, 3)

Although some authors have used intravenous or intracoronary VEGF injection to stimulate angiogenesis (4, 5) scheduled exercise and, perhaps, the production of small repeated ischemic stimuli could be useful mechanisms to increase endogenous VEGF and, therefore, promote the development of collateral circulation.

The aim of this study was to evaluate the effect of acute exercise, as that performed in exercise stress testing during a myocardial perfusion scan, on VEGF plasma levels in chronic stable coronary patients and then to compare the effect of scheduled exercise with a control group.

## METHODS

The study included 21 patients <75 years, with stable coronary disease verified by angiography, previous infarction or positive perfusion studies of more than 6 months evolution, who had not participated in programmed exercise groups within the last 3 months.

After baseline evaluation, all patients underwent an exercise stress myocardial perfusion scan (ergometric test) with SPECT imaging. Subsequently, two randomized groups were formed: one with programmed exercise three times a week for 12 weeks and another that continued with standard medical treatment (control group).

Blood samples were obtained at baseline, during recovery, 30 minutes after exercise and at 1- and 3-month follow-up.

A commercial "Quantikine" (R&D, cat N° DVE00) kit, consisting of a sandwich enzyme immunoassay technique with an anti-human VEGF monoclonal antibody, was used for VEGF dosage. This technique allows VEGF dosage in concentrations ranging between 15.6 and 1000 pg/ml, with inter- and intra-assay coefficient of variation of about 5% and 8%, respectively.

The images obtained with 99m Tc-MIBI SPECT were analyzed in a 17-segment model, where each segment was assigned a score of 0=normal perfusion; 1=mild hypoperfusion; 2=moderate hypoperfusion; 3=severe hypoperfusion and 4=no perfusion. Resting score (RS), exercise score (ES) and difference or ischemia score (DS) were obtained. A DS≥2 was considered positive for ischemia.

Scheduled exercises were carried out in two weekly sessions in a rehabilitation center and a third session at the patient's home.

## Statistical analysis

Categorical variables were expressed as frequency and percentage. Continuous variables were expressed as mean±standard deviation or standard error of the mean and median (interquartile range) according to their distribution.

The analysis of discrete variables was performed using the chi-square test and Fisher's exact test as appropriate.

Continuous variables were compared using Student's t test for two groups or the Kruskal-Wallis test according to their distribution. Intragroup continuous variables were compared using paired-t test. A p value<0.05 was considered as statistically significant.

## Ethical considerations

The protocol was approved by the institutional Research Ethics Committee and informed consent was obtained from

all participants.

## RESULTS

Twenty-one patients were included in the study. Mean age was 62.5±7 years and 17 patients were men (80.9%). Risk factors were: hypertension in 17 patients (81.0%), diabetes in 2 (9.5%), dyslipidemia in 14 (66.7%) and smoking in 2 (9.5%). Eight patients had history of prior myocardial infarction (38.1%), 7 of angioplasty (33.3%) and 2 of previous surgery (9.5%).

Myocardial perfusion for ES and RS was 5 (0-11) and 0 (0-7.5), respectively. Nine patients had ischemia with a median DS of 4 (2-6), ES of 8 (5.5-19) and RS of 2 (0-16).

There was no difference in the result of exercise stress testing according to the presence of ischemia in the SPECT study. The maximum heart rate during exercise was 120.3±16 bpm in patients with ischemia and 119.3±16 bpm in patients without ischemia (p=0.89).

Ten patients were assigned to programmed rehabilitation exercises and 11 to the control group.

VEGF results in acute exercise are summarized in Table 1. Gamma camera VEGF values after exercise stress decreased significantly (from 49.49±6.06 pg/ml to 31.83±5.62 pg/ml, p=0.021). At 1 month, values markedly increased compared to immediate post exercise stress results (70.90±14.44 pg/ml, p=0.007), with a non-significant trend relative to baseline values (p=0.10). At 3 months, a non-significant increase was observed with respect to baseline (p=0.12), with values similar to those measured at 1 month (Figure 1).

The analysis of myocardial perfusion data according to the presence of ischemia revealed results similar to those of the general population (see Table 1). There was no relationship between VEGF changes and the degree of ischemia observed in SPECT.

**Table 1.** VEGF levels with acute exercise in the total study population (n=21) and in the subgroups according to the presence or absence of ischemia in perfusion studies

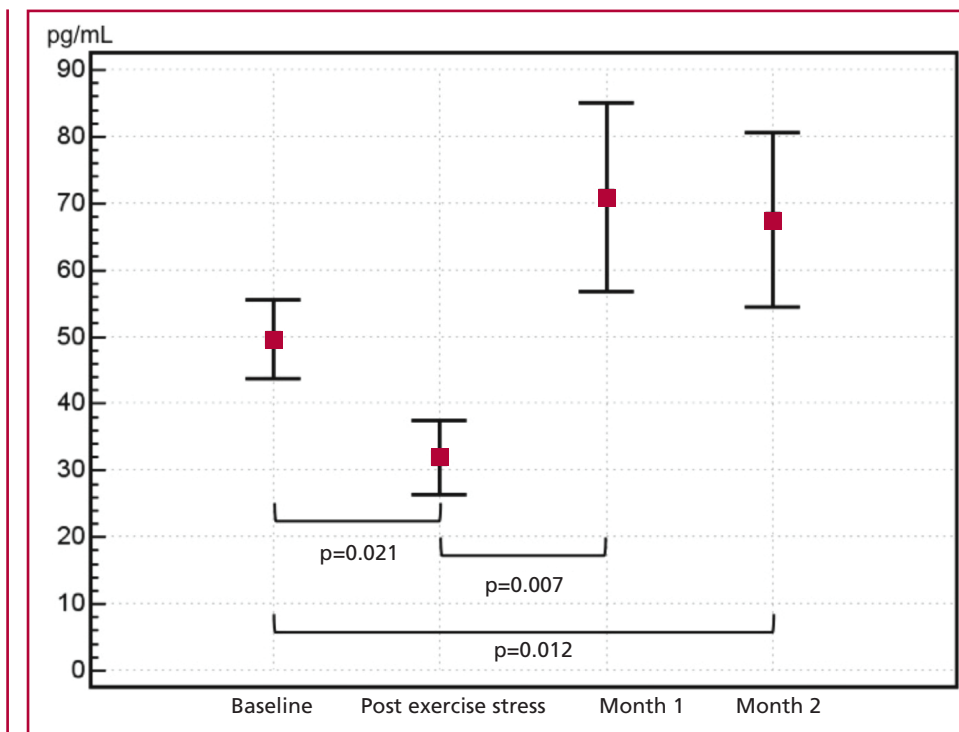
	Baseline	After exercise stress test	Month 1	Month 3
Mean	49.59	31.83*	31.83*	67.48
SE	6.06	5.62	5.62	13.31
<b>Without ischemia (n = 12)</b>				
Mean	46.69	34.29*	34.29*	63.25
SE	6.78	9.60	9.60	17.14
<b>Ischemia (n = 9)</b>				
Mean	53.44	28.56††	28.56††	73.11
SE	11.26	3.65	3.65	22.11

SE: Standard error of the mean.

\* p = 0.021 vs. baseline; † p = 0.007 vs. after exercise stress test; ‡ p = 0.10 vs. baseline.

†† p = 0.05 vs. after exercise stress test; ‡‡ p = 0.057 vs. baseline; § p = 0.07 vs. after exercise stress test

**Fig. 1.** Changes in VEGF levels (pg/ml) with acute exercise and at 1-month and 3-month follow-up.



There were no statistically significant differences at 1- and 3- month follow-up in patients who performed programmed cardiac rehabilitation exercises (Table 2).

There were no differences according to the presence of ischemia in the group of control patients or in that of programmed exercises.

## DISCUSSION

VEGF serum values decreased significantly with “acute” exercise. The trend was similar when the analysis was performed according to the presence of ischemia.

Our results differ from those obtained in a study evaluating VEGF levels before and after exercise in coronary artery disease patients showing a slight non-significant decrease in its value. (6) In most of the studies evaluating a single maximal exercise session no significant changes in VEGF plasma levels were observed. (7-9)

The absence of variation in VEGF levels would be in line with data showing that exercise positively influences angiogenesis which is, however, not directly determined by VEGF elevation but by its effect on VEGF rate. (6)

In acute myocardial infarction elevated VEGF serum levels were observed at 7 and 10 days of the acute event, (10) but other authors showed a significant reduction immediately after reperfusion. (11) Thus, in the presence of an intense stimulus such as the acute ischemia of infarction, there would be an initial decline associated with reperfusion and perhaps a later elevation associated with the inflammatory and repair process, similar to that found with acute exercise test-

**Table 2.** VEGF levels at 1- and 3-month follow-up according to the performance of programmed physical exercises.

	Baseline	Month 1	Month 3
<b>Control group</b>			
(n = 11)			
Mean	45.25	82.41	60.68
SE	9.24	26.68	17.87
<b>Exercise group</b>			
(n = 10)			
Mean	54.35	58.25	74.95
SE	7.89	8.37	20.62

There were no significant differences. SE: Standard error of the mean.

ing, especially in the presence of ischemia during exercise stress.

An increase in VEGF values was detected at 1-month follow-up, without reaching statistical significance relative to baseline values.

This recovery was not very marked in patients who performed programmed exercises, as if routine exercise implied a permanent level of consumption, which was not exhibited in the control group.

The discrepancies observed with published data could result from the different times between exercise and blood withdrawal, and from the intensity and duration of both “acute” and “chronic” exercises.

## Limitations

This is a preliminary study with a small number of

patients; therefore, further studies with a larger number of patients should be undertaken to confirm these results.

### CONCLUSIONS

“Acute” exercise produced a significant decrease of VEGF values, whereas chronic exercise did not determine significant changes with respect to the control group.

### Conflicts of interest

None declared.

(See author’s conflicts of interest forms in the web / Supplementary Material)

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