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# Serum Carboxyl-Terminal Propeptide of Procollagen Type I in Exercise-Induced Left Ventricular Hypertrophy

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**Summary**

*Background:* Left ventricular hypertrophy (LVH) induced by exercise is considered to be a physiologic adaptive mechanism without fibrogenic hyperactivity, as occurs in pathologic hypertrophy.

*Hypothesis:* This study investigated serum markers of collagen synthesis and echo parameters of left ventricular diastolic function (LVdf) in 22 male athletes.

*Methods:* Twenty-two highly competitive male athletes (10 cyclists, 12 soccer players) were studied with full history, clinical examination, Doppler echocardiogram, and serum concentration of the carboxyl-terminal propeptide of collagen type I (PIP). They were divided into two groups: normal left ventricular mass (N) with left ventricular mass index (LVMI) $< 125$ g/m$^2$ (14 athletes) and LVH with LVMI $> 125$ g/m$^2$ (8 athletes).

*Results:* Age, body surface area, blood pressure, heart rate, and systolic function were not different between the groups. Serum concentration of PIP (N: $163 \pm 44.1$ μg/l, LVH: $172.7 \pm 61.2$ μg/l—NS) and LVdf (early to atrial peak mitral flow velocity ratio: [E/A] N:$1.77 \pm 0.47$, LVH: $1.98 \pm 0.70$—NS, and early to atrial peak mitral annulus velocity ratio: [Ea/Aa] N: $2.63 \pm 0.70$, LVMI: $2.55 \pm 0.90$ LV1.61—NS) were similar in both groups.

*Conclusions:* Normal serum concentration of PIP in athletes with LVH in association with normal LVdf indicates the possibility that in this type of physiologic hypertrophy there is mainly an increase of myocyte size without interstitial fibrosis.

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## Introduction

Left ventricular hypertrophy (LVH) induced by exercise is considered to be a physiologic adaptive mechanism without fibrogenic hyperactivity, as occurs in pathologic hypertrophy.[1–4]

The monitoring of collagen synthesis by determination of serological collagen-derived peptides has been used as a marker of fibrillar collagen turnover in several conditions leading to cardiac fibrosis.[5–8]

These findings allowed us to hypothesize that in exercise-induced LVH, serum concentration of carboxyl-terminal propeptide of procollagen type I (PIP) and left ventricular diastolic function (LVdf) should be normal because there is no collagen-type-I-dependent myocardial fibrosis. To test this hypothesis definitively, the present study was designed to compare serum levels of PIP and diastolic function in athletes with exercise-induced LVH and athletes with normal left ventricular (LV) mass.

## Methods

### Subjects

We investigated 22 highly competitive male athletes (10 cyclists and 12 soccer players) aged $27 \pm 9.16$, who were in full sporting activity at the time of the study and trained 3 to 5 h at least five times a week, with long-term athletic conditioning ($> 5$ consecutive years). They were participating in regular national and some international competitions against other professional athletes.

All subjects were nonsmokers, had not taken medications for at least 3 weeks prior to the study, and showed no presence of heart disease. The protocol of this study complies with the principles of the Helsinki Declaration. All subjects gave their informed written consent to participate and to have their blood samples used for the study.

### Assessment of Left Ventricular Structure and Function

Two-dimensional, targeted M-mode, standard Doppler echocardiography and Doppler tissue imaging (DTI) were performed with subjects in partial left decubitus position with an ATL 3500 system (Philips Medical Systems, Cleveland, Ohio, USA).

The thickness of the LV wall and the dimensions of the LV and left atrial cavities were measured on the M-mode echocardiogram according to the recommendations of the American Society of Echocardiography.[9]

Relative wall thickness (h/r) was obtained to characterize the type of LVH, as indicated by Ganau *et al.*[10] Left ventricular mass calculated according to Devereux *et al.*[11] was divided by body surface area to obtain LV mass index (LVMI).

A cutoff point of 125 g/m$^2$ was prospectively chosen to detect LVH in accordance with Devereux *et al.*[12] and Hammond *et al.*,[13] LMVI > 125 g/m$^2$ and h/r > 0.44 were considered concentric LVH.[10]

This cutoff point allowed us to divide all the athletes into two groups: normal (N) with LVMI < 125 g/m$^2$ (14 athletes) and LVH with LVMI > 125 g/m$^2$ (8 athletes).

Left ventricular ejection fraction (LVEF) was obtained to evaluate systolic function according to the recommendations of the American Society of Echocardiography.[14]

Left ventricular diastolic filling was analyzed by Doppler echocardiography, using E and A peak mitral flow velocities (m/s), their ratio E/A,[15, 16] and early (Ea) and atrial (Aa) peak mitral annulus velocities (m/s) with their ratio (Ea/Aa) using DTI.[17]

### Determination of Serum PIP

Serum samples were taken to determinate PIP by radioimmunoassay[8] at the time of clinical studies. The reference interval was 74–93 μg/l for lower limit and 215–260 μg/l for upper limit. The sensitivity (lower detection limit) was 5.1 μg/l and the intra- and interassay variations were 4.3 and 7.8%, respectively.

### Statistical Analysis

Data were expressed as mean ± standard deviation. Differences between means were assessed by the unpaired Student's *t*-test. Linear regression analyses were performed to assess univariate relations. A two-tailed p value of < 0.05 was considered to indicate statistical significance.

## Results

### Clinical Characteristics of Study Group

The two groups were comparable in age (N: 26.3 ± 6.74 years, LVH: 28.5 ± 12.8 years, NS), body surface area (N: 1.91 ± 0.06 m$^2$, LVH: 1.90 ± 0.11 m$^2$, NS), blood pressure (N:103.5 ± 29.2/68 ± 12.5 mmHg, LVH: 120 ± 11.02/77 ± 9.26 mmHg) and heart rate (N: 61.6 ± 10.3, LVH: 58 ± 9.89 beats/min, NS).

TABLE I Cardiac dimensions and function as assessed by echocardiography in athletes with normal left ventricular mass and with left ventricular hypertrophy

| Measure | LVH | N | p Value |
|---|---|---|---|
| LVEDD (mm) | 56 ± 5.01 | 53.36 ± 3.41 | NS |
| LVESD (mm) | 31.88 ± 7.3 | 28.82 ± 5.4 | NS |
| ISdt (mm) | 12.6 ± 2.19 | 9.21 ± 1.24 | < 0.01 |
| PWdt (mm) | 10.88 ± 1.13 | 9.25 ± 1.70 | < 0.02 |
| LVM (g) | 285 ± 37.5 | 172.1 ± 63.8 | < 0.01 |
| LVEF (%) | 78.38 ± 11.9 | 73.29 ± 63.8 | NS |
| E (m/s) | 0.80 ± 0.13 | 0.82 ± 0.14 | NS |
| A (m/s) | 0.43 ± 0.15 | 0.47 ± 0.06 | NS |
| Ea (m/s) | 0.16 ± 0.01 | 0.165 ± 0.1 | NS |
| Aa (m/s) | 0.062 ± 0.005 | 0.062 ± 0.05 | NS |

LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end-systolic dimension, ISdt = interventricular septum end-diastolic thickness, PWdt = posterior wall end-diastolic thickness, LVM = left ventricular mass, LVEF = left ventricular ejection fraction, E = early peak flow mitral velocity, A = atrial peak mitral flow velocity, Ea = early peak mitral annulus velocity, Aa = atrial peak mitral annulus velocity, LVH = left ventricular hypertrophy.

### Left Ventricular Structure and Function

*Structure:* Left ventricular end-diastolic dimension ranged from 48 to 62 mm (mean 54.3 mm) and exceeded the normal value for a nonathletic population (< 54 mm)[18, 19] in 11 athletes (50%) including 2 in whom the dimension was > 60 mm. This diameter was similar in athletes with or without LVH (Table I).

Interventricular and posterior LV thickness ranged from 7 to 17 mm (mean 10.5 mm) and from 7 to 13 mm (mean 9.8 mm), respectively; 4 of 22 (18%) were found to have LV wall thickness > 13 mm. The athletes with LVH had greater wall thickness (Table I).

The h/r was found elevated in athletes with LVH (LVH: 0.43 ± 0.08, N: 0.35 ± 0.07, p < 0.02) (Fig. 1); r/h > 0.44 was found in 4 of 22 (18%) athletes.

*Function:* Left ventricular ejection fraction was normal in the 22 athletes (0.53–0.86), and no difference was found between the groups (Table I).

Indices of LV diastolic filling obtained with standard Doppler and DTI were within normal limits in the 22 athletes. The

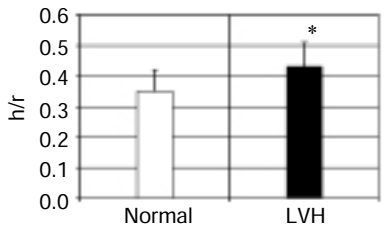


FIG. 1 Left ventricular structure. Relative wall thickness (h/r) in normal and left ventricular hypertrophy as defined in text. *p < 0.01.

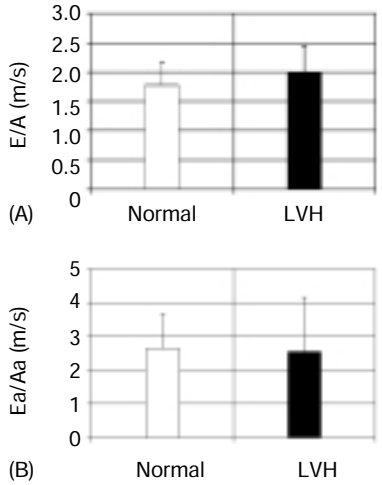


FIG. 2 Assessment of left ventricular diastolic function. (A) Early-to-atrial mitral peak flow velocity (E/A). (B) Early-to-atrial mitral annulus velocity (Ea/Aa) in normal and left ventricular hypertrophy.

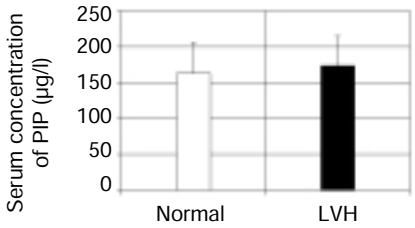


FIG. 3 Propeptide of procollagen type I (PIP) serum level concentration. Serum concentration of PIP in normal and left ventricular hypertrophy.

early-to-atrial mitral peak flow velocity (E/A) ratio was not different between groups (LVH:1.98 ± 0.46, N: 1.77 ± 0.39, NS) (Fig. 2). The same results were obtained when using DTI to analyze mitral annulus velocity (LVH: 2.63 ±1.05, N: 2.55 ± 1.61, NS) (Fig. 2).

### Serum PIP

As shown in Figure 3, serum concentration of PIP was similar in both groups (N: 165 ± 43.4 µg/l, LVH: 172.7 ± 42.1 µg/l, NS). No direct correlation was found between serum PIP level and LVM in all the athletes studied (r = 0.16, NS).

## Discussion

The main findings of this study are as follows: (1) increased LVM in professional athletes, performing a combined dynamic and static exercise, is not associated with high serum level of PIP; and (2) diastolic LV function is normal in these endurance athletes with LVH.

### Pathophysiologic Significance

*Left ventricular hypertrophy:* The development of the athletes' hypertrophy is characterized by an increase in LV mass, ventricular wall thickness, or cavity dimension.[18–20] However, different types of exercise and athlete training influence the characteristics of cardiac adaptation.[21–23] According to Pluim *et al.*,[21] our endurance athletes belong to a combination of dynamic and static type of exercise group. Although the greater LVM observed in some athletes is mainly due to the presence of a large ventricular cavity,[18] the echocardiographic changes found in our athlete group with LVH were characterized by an increase in LVM, LV wall, and relative wall thickness without significant changes in LV dimension.

None of our study subjects had LV wall thickness exceeding 16 mm. This is consistent with data from Pelliccia *et al.*[19] in a study of 947 highly trained athletes.

*Collagen synthesis:* Taking into account that hepatobiliary function was normal in the athletes studied and that it seems that serum concentration of PIP represents a level of production of the peptide,[6] then an increased level of PIP could be a marker of stimulated fibrogenesis. Accordingly, the elevated serum concentration of PIP in hypertensive subjects with myocardial fibrosis[6, 8, 24] reinforces the idea that this type of hypertrophy represents a condition characterized by fibrogenic hyperactivity.

The similar level of serum concentration of PIP in athletes with and without hypertrophy in our observations suggests that exercise-induced LVH consists of myocyte hypertrophy without pathologic fibrosis.

*Diastolic filling:* We observed, as have other authors,[17, 22] a normal or enhanced diastolic function in athletes with or without LVH.

Generally, a normal or slightly enhanced diastolic function in athletes, and mainly in those with exercise-induced LVH, may be considered as a positive finding because in hypertensive patients the increase in LV mass and wall thickness is associated with diastolic filling abnormalities.[25, 26]

### Limitations of the Study

Some limitations of the study should be acknowledged. We did not have a matched control sedentary group to compare the serum PIP level; yet the level of serum PIP found in this study was within the normal reference values given for the normal population (for men: 87–234 mg/l). Thus, the similar levels of serum PIP in athletes with and without LVH found by our observations could be useful to support the conclusions from this research in spite of the absence of a matched control sedentary group.

Second, it is obvious that PIP detectable in serum is not exclusively heart specific. Nevertheless, other extracardiac sources able to alter serum PIP can be excluded in our athletes, reinforcing the significance of this peptide in the LVH study.[24]

## Conclusions

The present results have broadened our knowledge of exercise-induced LVH. The normal serum levels of PIP in athletes with LVH in association with normal diastolic function allow us to consider that in this type of physiologic hypertrophy there is mainly an increase of myocyte size without interstitial fibrosis. Thus, the conventional echo study and the measurement of serum PIP could be practical and useful to look for pathologic hypertrophy in athletes. Nevertheless, because of limitations of this investigation, we are aware that further extensive studies are necessary to validate this approach definitively.

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## References

1. Colan SD: Mechanics of left ventricular systolic and diastolic function in physiologic hypertrophy of the athlete's heart. *Cardiol Clin* 1977;15:355–372
2. Pluim BM, Lamb HJ, Kayser HW: Functional and metabolic evaluation of the athlete's heart by magnetic resonance imaging and dobutamine stress magnetic resonance spectroscopy. *Circulation* 1998;97:666–672
3. Katz AM: Cardiomyopathy of overload: A major determinant of prognosis in congestive heart failure. *N Engl J Med* 1990;332:100–110
4. Eisenhofer G, Rundqvist B, Friberg P: Determinants of cardiac tyrosine hydroxylase activity during exercise-induced sympathetic activation in humans. *Am J Physiol* 1998; 274:R626–R634
5. Weber KT: Monitoring tissue repair and fibrosis from a distance. *Circulation* 1997;96:2488–2492
6. Diez J, Panizo A, Gil MJ, Monreal I, Hernández M, Pardo Mindán J: Serum markers of collagen type I metabolism in spontaneously hypertensive rats: Relation to myocardial fibrosis. *Circulation* 1996;93:1026–1032
7. Diez J, Laviades C, Mayor G, Gil MJ, Monreal I: Increased serum concentrations of procollagen peptides in essential hypertension: Relation to cardiac alterations. *Circulation* 1995;91:1450–1456
8. Varo N, Etayo JC, Zalba G, Beaumont J, Iraburu MJ, Montiel C, Gil MJ, Monreal I, Diez J: Losartan inhibits the post-transcriptional synthesis of collagen type I and reverses left ventricular fibrosis in spontaneously hypertensive rats. *J Hypertens* 1999;17:107–114
9. Sahn DJ, De Maria A, Kisslo J, Weymann A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographs measurements. *Circulation* 1978;58:1072–1083
10. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargu P, Simongini I, Laragh JH: Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992;19:1550–1558
11. Devereux RB: Detection of left ventricular hypertrophy: Anatomic validation, standardization, and comparison to other methods. *Hypertension* 1987; 9(suppl II):II-19–II-26
12. Devereux RB, Lutas EM, Casale PN: Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 1984;4:1222–1230
13. Hammond IW, Devereux RB, Aldermann MH: The prevalence of and correlates of echocardiography left ventricular hypertrophy among employed patients with uncomplicated hypertension. *J Am Coll Cardiol* 1986;7: 639–650
14. Schiller NB, Shah P, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnitiger L, Silverman NH, Tajik AJ: Recommendations for quantitation of the left ventricule by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;2:538–367
15. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J: Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophy cardiomyopathy. *J Am Coll Cardiol* 1987;10:733–742
16. Spirito P, Maron BJ: Doppler echocardiography for assessing left ventricular diastolic function. *Ann Intern Med* 1988;109:122–126
17. Caso P, D'Andrea A, Galderisi M, Liccardo B, Severino S, De Simone L, Izzo A, D'Andrea L, Mininni N: Pulsed Doppler tissue imaging in endurance athletes: Relation between left ventricular preload and myocardial regional diastolic function. *Am J Cardiol* 2000;85:1131–1136
18. Maron BJ: Structural features of the athlete's heart as defined by echocardiography. *J Am Coll Cardiol* 1986;7:190–203
19. Pelliccia A, Maron BJ Spataro A, Proschan MA, Spirito P: The upper limit of physiological cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;324:295–301
20. Spirito P, Pelliccia A, Proschan MA, Granata M, Spataro A, Bellone P, Caselli G, Biffi A, Vecchio C, Maron BJ: Morphology of the "athlete's heart" assessed by echocardiography in 947 elite athletes representing 27 sports. *Am J Cardiol* 1994;74:802–806
21. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE: The athlete's heart: A meta-analysis of cardiac structure and function. *Circulation* 2000;101:336–344
22. Urhausen A, Montz T, Kindermann W: Echocardiographic criteria of physiological left ventricular hypertrophy in combined strength- and endurance-trained athletes. *Int J Card Imaging* 1997;13:43–52
23. Fagard H: Impact of different sports and training on cardiac structure and function. *Cardiol Clin* 1997;15:397–412
24. Querejeta R, Varo N, López B, Larman M, Artiñano E, Etayo JC, Martínez Ubago JL, Gutíerrez-Stampa M, Emparanza JI, Gil MJ, Monreal I, Pardo Mindán J, Díez J: Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation* 2000;101:1729–1735
25. Smith VE, White WB, Karimeddini MK: Echocardiographic assessment of left ventricular diastolic performance in hypertensive subjects. *Hypertension* 1987;9:81–84
26. Fouad FM, Slominski JM, Tarazi RC: Left ventricular diastolic function in hypertension: Relation to left ventricular mass and systolic function. *J Am Coll Cardiol* 1984;3:1500–1506