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Increased Cardiac Sympathetic Activity and Insulin-Like Growth Factor-I Formation Are Associated With Physiological Hypertrophy in Athletes

Gian Gastone Neri Sernerri, Maria Boddi, Pietro Amedeo Modesti, Ilaria Cecioni, Mirella Coppo, Luigi Padeletti, Antonio Michelucci, Andrea Colella, Giorgio Galanti

Abstract—Physiological hypertrophy represents the adaptive changes of the heart required for supporting the increased hemodynamic load in regularly trained healthy subjects. Mechanisms responsible for the athlete's hypertrophy still remain unknown. In 15 trained competitive soccer players and in 15 healthy men not engaged in sporting activities (sedentary control subjects) of equivalent age, we investigated the relationship among cardiac growth factor formation, cardiac sympathetic activity, and left ventricular morphology and function. Cardiac formation of insulin-like growth factor (IGF)-I, endothelin (ET)-1, big ET-1, and angiotensin (Ang) II was investigated at rest by measuring artery–coronary sinus concentration gradients. Cardiac sympathetic activity was studied by [³H]norepinephrine (NE) kinetics. Cardiac IGF-I, but not ET-1, big ET-1, and Ang II, formation was higher in athletes than in control subjects ($P<0.01$). NE levels in arterial and peripheral venous blood did not differ between groups. In contrast, coronary sinus NE concentration was higher in athletes than in control subjects ($P<0.01$). Cardiac, but not total systemic, NE spillover was also increased in athletes ($P<0.01$), whereas cardiac [³H]NE reuptake and clearance were not different. Echocardiographic modifications indicated a volume overload–induced hypertrophy associated with increased myocardial contractility. Multivariate stepwise analysis selected left ventricular mass index as the most predictive independent variable for cardiac IGF-I formation and velocity of circumferential fiber shortening for cardiac NE spillover. In conclusion, increased cardiac IGF-I formation and enhanced sympathetic activity selectively confined to the heart appear to be responsible for the physiological hypertrophy in athletes performing predominantly isotonic exercise. (*Circ Res.* 2001;89:977-982.)

Key Words: insulin-like growth factor-I ■ norepinephrine ■ sympathetic nervous system
■ exercise ■ hypertrophy, left ventricular

The heart sustains an increased hemodynamic load by adjusting its mass independently of whether the enhanced workload is due to physiological activity or to pathological alterations in the cardiovascular system. There is much evidence that the development of myocardial hypertrophy results from the interaction of mechanical forces (the increased workload) and cardiac growth factors. The hemodynamic overload leads to myocardial cellular stretch and strain that in turn induce gene expression of cardiac growth factors.^{1,2} In regularly trained healthy subjects, both isotonic and isometric exercise cause cardiac changes resulting in modifications of the ventricular chambers and in a notable enhancement of heart performance. These modifications, called physiological hypertrophy or athlete's hypertrophy, are required for sustaining the tremendous increase in cardiac output during exercise. Cardiac growth factors involved in the development of physiological hypertrophy in humans are still

unknown, and their knowledge might also be relevant for better understanding the mechanisms involved in the cardiac adaptive response to the pathological increase in hemodynamic workload. Cardiac formation of several growth factors, including insulin-like growth factor-I (IGF-I), endothelin (ET)-1, and angiotensin (Ang) II, has been found to be increased in human hypertrophy caused by aortic valve disease and heart failure.^{3,4}

Another major component of cardiac performance during exercise is the enhancement of sympathetic activity, which causes an increase in heart rate and contractility and mediates the cardiovascular and metabolic responses to exercise.⁵ Sympathetic cardiac activation in relation to physical exercise has been studied in habitually sedentary subjects during short-term performance under standardized laboratory procedures,⁶⁻⁹ but information is lacking on sympathetic cardiac activity during long-lasting sport activity under field condi-

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TABLE 1. Characteristics of Subjects Investigated

	Control Subjects (n=15)	Athletes (n=15)
Age, years	27±7	26±4
Heart rate, bpm	72±6	67±4*
Body surface area, m ²	1.87±0.17	1.86±0.09
Septal thickness, mm	9.2±0.9	9.7±0.8
Posterior wall thickness, mm	9.4±0.7	9.7±0.8
RWT, %	37.6±3.5	37.4±4.1
LVEDDI, mm/m ²	26.6±1.9	28.6±1.2*
LVMI, g/m ²	109±13	131±15*
ESS, kdyne/cm ²	69±8	71±12
Vcf	1.17±0.17	1.45±0.13*
LVEF	65±5	65±7
E/A ratio	1.59±0.31	1.77±0.55

RWT indicates relative wall thickness; LVEDDI, left ventricular end-diastolic diameter index; LVMI, left ventricular mass index; ESS, end-systolic stress; Vcf, mean midwall velocity of circumferential fiber shortening; and LVEF, left ventricular ejection fraction.

* $P < 0.05$ vs control subjects.

tions. Therefore, we planned this study to answer the following questions: (1) whether cardiac growth factors, specifically Ang II and IGF-I, are involved in the athlete's physiological hypertrophy, and (2) whether and how the cardiac sympathetic system participates in the development and the maintenance of physiological hypertrophy.

Materials and Methods

We investigated 15 professional male soccer players aged 26±4 years who were in full sporting activity at the time of the study. The athletes trained 2 hours at least 5 times a week and participated in regular competitions against other professional athletes. The control group was made up of 15 healthy men, aged 27±7 years, none of whom was engaged in sporting activities (sedentary control subjects) (Table 1).

All subjects were nonsmokers, and none had taken any medications for at least 3 weeks before the study. Both athletes and control subjects were referred to the electrophysiological laboratory of our Institute for arrhythmias (symptomatic sinus bradycardia, n=3; sinus node dysfunction, n=3; narrow QRS complex tachycardia, n=11; ventricular preexcitation, n=9; and type I second-degree atrioventricular block, n=4), documented on resting ECG records or ECG Holter monitoring. The results of physical examination, other routine noninvasive diagnostic procedures, and electrophysiological study did not show the presence of any 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.

Echocardiographic measurements were performed prospectively, as previously described.³ Cardiac formation of IGF-I, ET-1, big ET-1, and Ang II was expressed as the artery–coronary sinus concentration gradient indexed by coronary blood flow (CBF) and cardiac mass.³ IGF-I, ET-1, and big ET-1 plasma concentrations were measured by RIA using specific rabbit polyclonal antibodies after chromatographic extraction, as reported earlier.³ Ang II plasma concentrations were measured by RIA after HPLC separation as previously described.³

The study of [³H]norepinephrine (NE) kinetics was performed according to the method previously reported.¹⁰ Briefly, [³H]NE (1.2 μCi L-[7-³H]NE per minute, specific activity 11 to 16 Ci/mmol, New England Nuclear) was infused for 30 minutes into a peripheral vein to achieve a steady-state plasma concentration. Total systemic and

cardiac NE spillover into the plasma and total systemic and cardiac NE clearance were calculated from the following equations:

$$(1) \quad \text{Total systemic NE spillover} = \frac{[\text{^3H}]\text{NE infusion rate (dpm/min)}}{\text{specific radioactivity of plasma (dpm/pg)}}$$

$$(2) \quad \text{Total systemic NE clearance} = \frac{[\text{^3H}]\text{NE infusion rate (dpm/min)}}{\text{plasma } [\text{^3H}]\text{NE concentration (dpm/mL)}}$$

$$(3) \quad \text{Cardiac NE spillover} = \text{CBF} \times [(\text{NE coronary sinus} - \text{NE artery}) + (\text{NE artery} \times \text{NE extraction})]$$

$$(4) \quad \text{Cardiac NE clearance} = \text{NE extraction} \times \text{CBF}$$

Plasma NE and epinephrine levels were assayed by HPLC with electrochemical detection, and the concentration of [³H]NE was determined in fractions of the eluent by liquid scintillation counting after extraction with alumina.¹⁰

Unless otherwise specified, data are mean±SD. ANOVA was used to compare athletes and control subjects. For multivariate reevaluation of univariate correlations, the following were entered in a stepwise multiple regression analysis as independent variables, considering cardiac IGF-I formation and cardiac NE spillover as dependent variables: septal and posterior wall thicknesses, left ventricular end-diastolic diameter index (LVEDDI), relative wall thickness, left ventricular mass index (LVMI), left ventricular ejection fraction, mean midwall velocity of circumferential fiber shortening (Vcf), end-systolic stress (ESS), and Vcf/ESS ratio.

An expanded Materials and Methods section can be found in the online data supplement available at <http://www.circresaha.org>.

Results

Echocardiographic Characteristics

The echocardiographic characteristics of subjects investigated are reported in Table 1. LVMI and LVEDDI, but not septal and posterior wall thicknesses, were on average higher in the athletes than in sedentary control subjects ($P < 0.05$) (Table 1). Relative wall thickness was similar in the 2 groups. Vcf was significantly increased in the athletes compared with sedentary control subjects ($P < 0.001$), whereas left ventricular ejection fraction and the early-to-atrial peak velocity (E/A) ratio did not differ between groups (Table 1).

Cardiac Growth Factor Formation

In sedentary control subjects the artery–coronary sinus concentration gradient of IGF-I was slightly positive (Figure 1), indicating a low IGF-I cardiac formation. Conversely, in the athlete group IGF-I concentration in coronary sinus blood was significantly higher than in arterial blood, resulting in an increased positivity of the transcardiac gradient indicative of enhanced cardiac formation of IGF-I in this group (Figure 1).

The artery–coronary sinus concentration gradients for ET-1, big ET-1, and Ang II were around 0 in both sedentary control and athlete groups (Figure 1).

Total Systemic and Cardiac [³H]NE Kinetics

NE concentration in arterial and peripheral venous blood did not differ between athletes and sedentary control subjects. In contrast, NE levels in coronary sinus blood were significantly

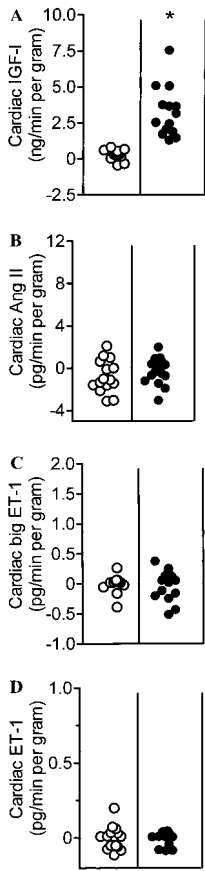


Figure 1. Artery–coronary sinus gradients indexed by coronary blood flow and cardiac mass (cardiac formation) of IGF-I (A), Ang II (B), big ET-1 (C), and ET-1 (D) in control (○) and athlete (●) groups. **P*<0.05 vs control group.

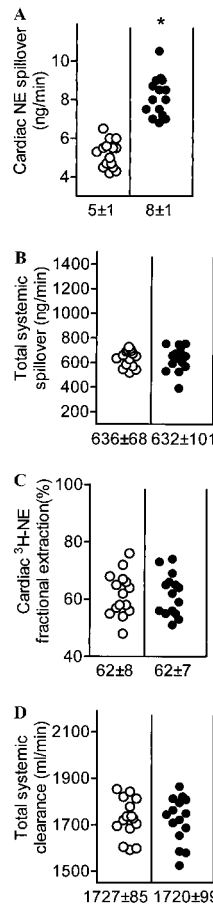


Figure 2. Cardiac NE spillover (A), total systemic NE spillover (B), cardiac [³H]NE fractional extraction (C), and total systemic NE clearance (D) in athletes. Numbers under columns are mean±SD. **P*<0.05 vs control group.

higher in athletes than in control subjects (Table 2), resulting in both a higher artery–coronary sinus NE concentration gradient (Table 2) and cardiac NE spillover (Figure 2 and Table 2). Cardiac [³H]NE fractional extraction and cardiac NE clearance were not significantly different between groups (Table 2).

Finally, the total systemic NE spillover and the total systemic NE clearance did not differ between athletes and sedentary control subjects (Figure 2, Table 2).

Epinephrine concentrations in the peripheral venous, arterial, and coronary sinus blood were not significantly different between groups.

TABLE 2. Cardiac and Total Systemic [³H]NE Kinetics

	Control Subjects (n=15)	Athletes (n=15)
Arterial blood, pg/mL	245±72	223±85
Coronary sinus blood, pg/mL	195±64	321±74
A-CS gradient, pg/mL	-56±26	46±25*
Cardiac NE spillover, ng/min	5±1	8±1*
Cardiac [³ H]NE fractional extraction, %	62±8	62±7
Cardiac NE clearance, mL/min	52±6	53±7
Total systemic NE spillover, ng/min	636±68	632±101
Total systemic NE clearance, mL/min	1727±85	1720±99

A-CS indicates aorta-coronary sinus.
**P*<0.01 vs control subjects.

Relationship of Cardiac Growth Factors and of Cardiac NE Spillover to Echocardiographic Parameters

Cardiac formation of IGF-I was positively related to LVMI (*r*=0.77, *P*<0.001) and LVEDDI (*r*=0.72, *P*<0.001). In the multivariate stepwise analysis, the most predictive independent variable for cardiac IGF-I formation was LVMI (*r*=0.77, *P*<0.001) (Figure 3 and Table 3). Univariate regression analysis showed that cardiac NE spillover was positively correlated with the indexes of ventricular contractility (Vcf, *r*=0.81, *P*<0.001; Vcf/ESS, *r*=0.66, *P*<0.001). The multivariate stepwise analysis revealed that Vcf was the most predictive independent variable for cardiac NE spillover (*r*=0.81, *P*<0.001) (Figure 3, Table 3).

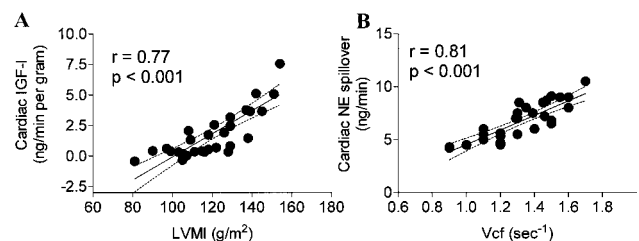


Figure 3. Correlation between IGF-I cardiac formation and LVMI (A) and between cardiac NE spillover and velocity of Vcf (B) in athletes.

TABLE 3. Univariate and Stepwise Multiple Regression Between IGF-I Cardiac Formation or Cardiac NE Spillover and Echocardiographic Parameters

	IGF-I		NE Spillover	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
LVMI, g/m ²	0.77*	<0.001	0.54*	<0.01
LVEDDI, mm/m ²	0.72	<0.001	0.63	<0.01
Posterior wall, mm	0.46	<0.01	0.23	NS
Vcf, s ⁻¹	0.43*	<0.05	0.81*	<0.001
Septum, mm	0.36	NS	0.16	NS
Vcf/ESS	0.29	NS	0.66	<0.001
Ejection fraction, %	0.16	NS	0.23	NS
ESS, kdyne/cm ²	0.02	NS	-0.21	NS
Relative wall thickness, %	0.18	NS	0.00	NS
Multiple regression	0.79	<0.001	0.87	<0.001

LVMI indicates left ventricular mass index; LVEDDI, left ventricular end-diastolic diameter index; Vcf, mean midwall velocity of circumferential fiber shortening; and ESS, end-systolic stress.

*Independent variable at stepwise regression analysis.

Discussion

The results of this study show for the first time that increased cardiac IGF-I formation and enhanced sympathetic activity selectively confined to the heart are associated with, and likely responsible for, the physiological hypertrophy of professional athletes performing mainly isotonic exercise, such as soccer players.

Echocardiographic Characteristics

The development of athlete's hypertrophy is associated with important and specific adaptations of the cardiovascular system. Cardiac adaptations, in particular, are characterized by an increase in left ventricular mass and ventricular wall thickness, with or without cavity dimension increase.^{11,12} Different types of exercise and athlete training influence the characteristics of cardiac hypertrophy. Generally, but not necessarily,¹³ eccentric hypertrophy occurs predominantly in endurance athletes doing isotonic exercise, as a result of a volume-loading effect,¹⁴ whereas concentric hypertrophy is seen in strength athletes performing isometric exercise resulting in a pressure-loading effect.^{11,13,15} The echocardiographic changes found in our athlete group were characterized by increases in LVMI, LVEDDI, and, to a lesser extent, left ventricular wall thickness. These echocardiographic modifications are characteristic of cardiac hypertrophy mainly as a result of volume overload, as occurs in soccer players.^{16,17} Although the LVEDDI of athletes was higher than that of sedentary subjects, it remained within generally accepted normal limits.^{11,12,18,19} Moreover, the increase in LVEDDI was associated with enhanced myocardial contractility indicating that cavity dilatation in these subjects is an expression of cardiac physiological adaptation to a well-accepted volume overload with consequent improvement of myocardial response to the Frank-Starling relationship and consequent increase in stroke volume.

Cardiac Growth Factor Formation and Its Relationship to Echocardiographic Changes

In the present study, cardiac formation of growth factors was estimated only by measuring the artery–coronary sinus concentration gradient of the individual growth factors because, for ethical reasons, we did not perform myocardial biopsies to quantify mRNA levels of the relative peptides. There is no evidence that IGF-I and ET-1 undergo important metabolic changes during the transcatheter passage, and in previous studies significant increases or decreases in the aorta–coronary sinus concentration gradients of IGF-I or ET-1 were associated with concomitant changes of their mRNA levels,^{3,4} thus indicating that the measurement of the transcatheter gradients of these growth factors may serve as a reliable index of their cardiac production at rest. In contrast to IGF-I and ET-1, both angiotensins undergo important metabolic changes during transcatheter passage. In normal subjects, ≈30% of the Ang I passing through the heart is extracted, partially converted to Ang II, and partially degraded by angiotensinases into smaller inactive peptides.²⁰ Ang II is also partially extracted (≈20%) during the transcatheter passage.²⁰ The final result of these metabolic changes of both angiotensins is that in normal subjects the aorta–coronary sinus gradient is ≈0, notwithstanding the cardiac generation of Ang I and Ang II.²⁰ When cardiac Ang formation is increased, the aorta–coronary sinus concentration gradient of both angiotensins is significantly increased^{3,4} and parallels elevated myocardial levels of angiotensin-converting enzyme and angiotensinogen mRNAs.^{3,4,20} Thus, the lack of difference between concentration gradients of ET-1, big ET-1, and both angiotensins in the athlete group and those of the sedentary control group suggests that cardiac formation of these growth factors is not increased in well-trained soccer players.

Conversely, IGF-I appears to be the only cardiac growth factor associated with the hypertrophy of trained soccer players, because the IGF-I artery–coronary sinus concentration gradient was significantly higher in the athlete group than in the sedentary control subjects, thus indicating increased cardiac IGF-I formation. The isolated increase in IGF-I formation and the absence of enhanced cardiac generation of ET-1 in this group are consistent with the volume overload–induced eccentric hypertrophy, resulting from an essentially dynamic exercise, such as that performed by soccer players. Thus, it is not surprising that the pattern of cardiac growth factor formation in physiological hypertrophy is similar to that found in volume-overload hypertrophy caused by the experimental creation of an aorta-cava fistula, where IGF-I appears to be the only cardiac growth factor produced,²¹ whereas hypertrophy due to aortic stenosis is associated with increased cardiac formation of both IGF-I and ET-1.³ The increase in cardiac IGF-I formation in both physiological hypertrophy of athletes and pathological hypertrophy due to aortic valve disease suggests that enhanced cardiac IGF-I formation is the primary nonselective cardiac response to increased workload, whereas a more selective stimulus, such as pressure overload, is required to induce the formation of other cardiac growth factors, such as ET-1 or Ang II. Consequently, it is conceivable that cardiac hypertrophy in athletes performing isometric exercise might be supported by increased formation of other growth factors in addition to IGF-I.

IGF-I is provided with both hypertrophying and direct inotropic effects^{22–25} and enhances shortening velocity and cellular compliance.²⁶ The cellular basis for IGF-I-induced positive inotropism is not yet completely understood, because in experimental studies IGF-I has been found either to sensitize the myofilaments to Ca^{2+} ^{27,28} or to increase Ca^{2+} availability for myofilaments.²⁵ These cellular activities of IGF-I are consistent with the modifications of the echocardiographic parameters found in the athlete group. As suggested by the univariate and multivariate stepwise analyses of physiological hypertrophy, the enhanced IGF-I formation seems to be mainly addressed to increasing left ventricular mass and myocardial contractility. Although not specifically investigated in this study, previous investigations have shown that serum IGF-I levels were significantly increased after both endurance and strength types of exercise and frequently remained elevated after the end of training.^{29–31} Therefore, we cannot exclude that circulating IGF-I, too, may have a role in the development of hypertrophy in the soccer players.

Cardiac Sympathetic Activation

The second goal of our study was to investigate functional activity of the cardiac sympathetic drive in trained athletes rather than demonstrate the effect of acute physical exercise on either plasma NE or the respective rate of spillover to plasma from heart or total circulation, as previous studies did.^{7,8}

Measurement of transmitter release by the study of [³H]NE kinetics is a well-established technique for the assay of organ-specific NE spillover to plasma both in physiological and pathological conditions.³² In our investigation, the athletes showed a significantly higher cardiac NE spillover without significant changes in reuptake and clearance. This finding is consistent with the marked positivity of the artery–coronary sinus gradient of endogenous NE. Because cardiac neuronal reuptake of NE was unaffected, the increased cardiac spillover to plasma is proportional to the rate of cardiac sympathetic nerve firing³² and points to an increase in cardiac sympathetic drive at rest. Although a variety of factors may influence the rate of NE released in the interstitial space and its passage into the plasma, and the method of Esler³² underestimates the actual NE released by sympathetic nerve endings,³³ the clear difference in both NE spillover and artery–coronary sinus concentration gradient between competitive athletes and sedentary control subjects indicates that repetitive dynamic exercise may induce a persistent cardiac sympathetic activation that is maintained even after exercise has ended. A prevailing cardiac sympathetic activation evaluated by spectral analysis was found in athletes (swimmers) examined during the rest period of the year, ie, during a nontraining period.³⁴

The [³H]NE kinetics indicated that sympathetic activation in the athlete group was selectively confined to the heart, because plasma catecholamine concentrations and, in particular, the total systemic NE spillover and clearance in athletes were not significantly different from control subjects. This last finding contrasts with the results of a previous study⁸ that showed a reduction in total systemic NE spillover in 8 normal healthy male subjects after a month of bicycle ergometer exercise, 1 hour 3 times per week. The reduction in total NE spillover to plasma was attributed to lowering resting renal, but not cardiac, NE

spillover, which tended to increase.⁸ We did not investigate renal NE spillover, but the discrepancies between the results of the Meredith et al⁸ study and those of our study are probably due to differences in the subjects investigated, duration of training, and type of exercise.

It is worth noting the different pattern of cardiac sympathetic activation as evaluated by [³H]NE kinetics between physiological hypertrophy and heart failure. In both conditions there is an increase in cardiac NE spillover, but in the latter reuptake and clearance are notably reduced.³⁵

Although several studies on isolated cardiomyocytes seem to suggest a role of NE in inducing hypertrophic changes,^{36–38} there is no clear evidence that NE is able to directly induce myocardial hypertrophy in humans. In physiological hypertrophy cardiac NE synergically acts with IGF-I in increasing inotropism because NE enhances influx of Ca^{2+} through slow calcium channels.³⁹ Thus, physiological hypertrophy related to prevalently isotonic exercise appears to be supported by the concerted action of growth factors, ie, IGF-I and sympathetic drive.

Heart rate at rest was significantly lower in the athlete group than in sedentary control subjects. A training-dependent decrease in heart rate at rest and during exercise is an adaptation process known for a long time in isotonic athletes.⁴⁰ The low heart rate guarantees optimum ventricular filling and keeps the loss of energy not converted to contractile force at high heart rates from increasing disproportionately.⁴¹ Sinus bradycardia has been attributed to an increase in vagal tone or to an alteration in total neural input to the heart, including a decreased resting sympathetic tone.^{42,43} The hypothesis that sinus bradycardia is dependent on a reduced resting sympathetic cardiac drive contrasts with our results of the [³H]NE kinetics studies that demonstrate an increased cardiac NE release and, hence, enhanced cardiac sympathetic nerve firing or nerve density.³² However, a sympathetic component seems to participate in the athletes' bradycardia at rest, because recent studies have shown a dissociation between increased catecholamine response and unchanged heart rate after endurance exercise training,⁴⁴ suggesting a decrease in sensitivity to chronotropic stimulation. This uncoupling of inotropic and chronotropic responses might be attributed to a selective exercise-induced downregulation in β -adrenergic receptors located in the right atrium,⁴⁵ but further investigations are required. Therefore, in the athletes a training-dependent resetting of sympathovagal equilibrium occurs at a higher level than in sedentary people, resulting in the apparent paradoxical combination of simultaneous increase in vagal and sympathetic cardiac activity.

In conclusion, the present results extend our knowledge of the general mechanisms regulating the development of cardiac hypertrophy and for the first time contribute to clarifying the mechanisms responsible for the physiological hypertrophy of endurance athletes performing isotonic exercise. Selective increase in cardiac IGF-I formation and sympathetic drive are associated with, and most likely cause, the eccentric cardiac hypertrophy mainly due to volume-overload characteristics of soccer players.

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