Cardiopulmonary Receptor Reflexes in Normotensive Athletes With Cardiac Hypertrophy

C. Giannattasio, MD, G. Seravalle, MD, G.B. Bolla, MD, B.M. Cattaneo, MD, J. Cléroux, PhD, C. Cuspidi, MD, L. Sampieri, MD, G. Grassi, MD, and G. Mancia, MD

Cardiopulmonary receptor control of the circulation is impaired in a variety of diseases having cardiac hypertrophy as a common feature. Whether this also occurs in the so-called “physiological” cardiac hypertrophy of the athlete, however, is unknown. We studied nine sedentary healthy subjects and 19 age-matched professional runners or hammer throwers who had trained at least 2 hours per day, 5 days per week for 7 years. The left ventricular mass index (echocardiography) was 99±7.4 and 135±5.9 g/m² in the two groups, respectively. Cardiopulmonary receptor stimulation and deactivation were obtained by increasing and reducing left ventricular end-diastolic diameter for 5 minutes by leg raising and lower body negative pressure, keeping both stimuli at a level not affecting blood pressure and heart rate. In the sedentary healthy subjects, forearm vascular resistance (the ratio between mean arterial pressure and forearm blood flow) and plasma norepinephrine fell during leg raising (forearm vascular resistance, −7±1.7 units; norepinephrine, −57.4±1.4 pg/ml) and increased during lower, body negative pressure (forearm vascular resistance, 20±5.3 units; norepinephrine, 97.7±21.5 pg/ml). For similar or greater alterations in left ventricular end-diastolic diameter, the correspondent changes observed in the professional runners or hammer throwers were −5.3±1.3 units (forearm vascular resistance), −35.4±9.6 pg/ml (norepinephrine), 9.1±1.4 units (forearm vascular resistance), and 30.9±6.9 pg/ml (norepinephrine). This represented an attenuation of 25%, 38%, 55%, and 68%, respectively (p<0.01), of the control response. The attenuated response to lower body negative pressure was accompanied by a greater decline in arterial blood pressure during a more pronounced lower body negative pressure stimulus. In contrast, forearm vascular resistance responses to cold pressor test were similar in the professional runners or throwers and in the sedentary healthy subjects. Thus, the pronounced cardiac hypertrophy of professional athletes is accompanied by an impairment of the cardiopulmonary receptor reflex. This may lead to a reduced efficacy of cardiovascular homeostasis. (Circulation 1990;82:1222–1229)

Previous studies have shown that the reflex alterations in sympathetic activity induced by nonhypotensive changes in central blood volume are markedly reduced in patients with heart transplantation, demonstrating their main origin from cardiac receptors.1–3 They have also shown that these alterations are slightly diminished in mild or moderate essential hypertension but that a pronounced reduction occurs when the hypertension is associated with cardiac hypertrophy. Thus, a pathological thickening of the heart impairs the cardiogenic reflex control of the cardiovascular system.4

Professional athletes often show a pronounced cardiac hypertrophy.5,6 Whether this leads to an impairment of the cardiovascular control originating from the cardiopulmonary region, however, is unknown. This is relevant to the debated question of whether the cardiac hypertrophy accompanying physical training leaves cardiac function entirely unaffected and can therefore be regarded as “physiological,” at variance from the hypertrophy induced by cardiovascular disease.

We have addressed this issue by studying the cardiopulmonary reflex in professional runners and in hammer or weight throwers, all of whom had a pronounced cardiac hypertrophy. The results were

From the Centro Auxologico Italiano, Milano, Cattedra di Semeiotica Medica and Istituto di Clinica Medica Generale e Terapia Medica, Universita di Milano, Centro di Fisiologia Clinica di e Ipertensione, Ospedale Maggiore, Milano, Italy.

Address for correspondence: Prof. Giuseppe Mancia, Centro di Fisiologia Clinica e Ipertensione, Via F. Sforza 35, 20122 Milano, Italy.

Received January 23, 1990; revision accepted May 29, 1990.
compared with those of age-matched controls with a normal heart.

Methods

Our study was performed in 28 normotensive subjects of both sexes (18 male and ten female) whose ages were in the range of 17-31 years. None of the subjects was affected by cardiovascular or other major diseases, and none was under pharmacological treatment of any kind.

Nineteen subjects (age, 21.7±1.5 years [mean±SEM] were professional long-distance runners (n=10) and hammer or weight throwers (n=9), who trained 2–3 hours per day for 5–7 days per week for 7 years. The remaining nine subjects (age, 23.3±1.2 years) were sedentary controls. All subjects gave informed consent to the study after being informed of its nature and purpose. The protocol of the study was reviewed and approved by the ethical committee of our institution.

Hemodynamic, Plasma Norepinephrine, and Echocardiographic Measurements

Hemodynamic measurements consisted of arterial blood pressure, heart rate, forearm blood flow, and forearm vascular resistance. Arterial blood pressure was measured by a digital photoplethysmographic device capable of providing accurate beat-to-beat systolic and diastolic values.7 Heart rate was measured by a cardiotachometer triggered by the R wave of an electrocardiographic lead. Forearm blood flow was measured by venous occlusion plethysmography (model EC4, Hokanson, Issaquah, Wash.)8 by using a mercury-in-Silastic strain-gauge plethysmograph applied around the forearm contralateral to the arm used for blood pressure measurement. The strain-gauge was placed 4–5 cm below the antecubital crease, and the measurement was made at constant room temperature (23–24°C), whereas circulation to the hand was arrested by application of a suprasystolic pressure in a cuff encircling the wrist. Forearm vascular resistance was calculated from the ratio between mean arterial pressure (diastolic blood pressure plus one third of pulse pressure) and forearm blood flow.

Plasma norepinephrine concentration was measured by high-pressure liquid chromatography9 by using blood samples (5 ml) withdrawn from an antecubital vein of the arm from which blood pressure was monitored. The samples were collected in EDTA glutathione-treated tubes and kept at −70°C until assayed.

In all subjects, left ventricular diameters were measured by monodimensional echocardiography by using bidimensional Doppler echocardiography to perform the measurements from the septal leading edge to the posterior wall leading edge. The measurements were made at the peak of the R wave of the electrocardiogram and were accompanied by measurements of septal wall thickness and left posterior wall thickness. Left ventricular mass index was calculated according to the Penn convention formula.10 Echocardiographic data were also used to calculate left ventricular ejection fraction and other indexes of left ventricular systolic function. Diastolic function was assessed by measuring, through Doppler echocardiography, early and late (or atrial) diastolic transmital peak flow velocity. As documented by comparison with angiographic and radionuclide techniques,11,12 this describes the pattern of left ventricular diastolic filling and allows the calculation of diastolic compliance.13,14 In our laboratory, the reproducibility of left ventricular mass measurement was 4%, and the reproducibility of transmital flow velocity was 6%.

Deactivation and Stimulation of Cardiopulmonary Receptors

Deactivation of cardiopulmonary receptors was obtained by reducing venous return through application of negative pressure to the lower body.15 To this objective, the subjects were reclined in the supine position and enclosed in a Plexiglas box sealed at the level of the anterosuperior iliac crests. The pressure within the box was reduced below the atmospheric pressure by a commercial vacuum cleaner, and the stimulus was maintained for 5 minutes. The applied negative pressure was kept at approximately 15 mm Hg to only moderately affect venous return and to avoid a reduction in blood pressure and an increase in heart rate that could engage the arterial baroreceptor reflexes.15–17

Cardiopulmonary receptor stimulation was obtained by increasing venous return through passive elevation of the legs and the lower part of the pelvis.15 The elevation was limited to 60° to prevent an excessive increase in venous return that could raise blood pressure and involve the arterial baroreflexes.15–17 This stimulus also was applied in the supine position and maintained for 5 minutes.

In all subjects, lower body negative pressure also was applied for 5 minutes at −40 mm Hg to cause a reduction in blood pressure and thus deactivate not only cardiopulmonary but arterial baroreceptors as well. This allowed assessment of the reflex responses to a stimulus involving both reflexogenic areas.15–17 Because cardiopulmonary receptors are sensitive to changes in central blood volume during both leg raising and lower body negative pressure, the alterations in cardiopulmonary receptor stimuli were assessed from the changes in left ventricular end-diastolic diameter.18 The reflex responses were assessed from the changes in forearm circulation and plasma norepinephrine because of the major impact of cardiopulmonary receptor activity on both these variables.15,16,19

Cold Pressor Test

In all subjects, the blood pressure, heart rate, and forearm vascular responses to a cold pressor test were evaluated before and during the last 10 seconds of 1-minute immersion of a hand in ice water (4°C). This was done to determine the hemodynamic
responsiveness to a neurogenic stimulus unrelated to that originating from cardiopulmonary receptors.20

Protocol and Data Analysis

One to five days before the study, each subject was brought to the laboratory to be familiarized with the various maneuvers that had to be performed. The study itself was conducted in the afternoon. In one half of the subjects, the sequence was as follows: 1) the subjects were reclined in the supine position and fitted with the lower body negative pressure device, 2) the venous cannula was inserted, and the echocardiographic, blood pressure, and blood flow–measuring devices were readied, 3) after an interval of 20 minutes, the lower body negative pressure of −15 mm Hg was applied and after a 15-minute interval, followed by the lower body negative pressure of −40 mm Hg, 4) the lower body negative pressure device was removed, and 20 minutes later, the leg raising maneuver was performed, 5) after 20 minutes more, the cold pressor test was performed.

In the other half of the subjects, the protocol was the same except that the leg raising preceded the lower body negative pressure stimuli.

Blood pressure, heart rate, left ventricular end-diastolic diameter, forearm blood flow, and forearm vascular resistance were measured 1 minute before and during the fifth minute of the lower body negative pressure and leg raising stimuli. Each blood pressure and heart rate measurement was the average of the values occurring within a 30-second period, whereas each left ventricular end-diastolic diameter was the average of two consecutive values. Each forearm blood flow measurement was derived from the average of three consecutive values. All measurements were made by an investigator unaware of the experimental design. Blood samples for plasma norepinephrine measurements were withdrawn 1 minute before and during the fifth minute of the lower body negative pressure and leg raising stimuli, simultaneously with the hemodynamic measurements. The withdrawal time was approximately 30 seconds.

Results are expressed as mean±SEM. Statistical significance of the difference in the mean was assessed by one-way analysis of variance. The t test for unpaired observations was used to locate the differences between the groups of subjects. A p value of less than 0.05 was the level of statistical significance.

Results

Baseline Values

Table 1 shows that septal wall thickness, posterior wall thickness, and left ventricular mass index were significantly and markedly greater in athletes than in sedentary subjects. The left ventricular diameters and the echocardiographic indexes of left ventricular systolic and diastolic functions were not significantly different in the two groups of subjects. Heart rate and forearm blood flow were significantly lower in the athletes, whereas mean arterial pressure, vascular resistance, and plasma norepinephrine were similar in the two groups of subjects (Figure 1).

Leg Raising and Lower Body Negative Pressure

As shown in Figure 2, left ventricular end-diastolic diameter increased during leg raising and decreased during lower body negative pressure at −15 mm Hg. In both instances, the changes were similar in the athletes and the sedentary subjects. In both groups of subjects, the increase and the reduc-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Athletes (n=19)</th>
<th>Sedentary subjects (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal wall thickness (mm)</td>
<td>11.1±0.3*</td>
<td>9.0±0.4</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>10.1±0.3*</td>
<td>8.5±0.3</td>
</tr>
<tr>
<td>Left ventricular end-diastolic</td>
<td>52.9±0.9</td>
<td>50.2±0.9</td>
</tr>
<tr>
<td>diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>135±5.9*</td>
<td>99±7.4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>71.9±1.4</td>
<td>72.1±2.4</td>
</tr>
<tr>
<td>Fraction shortening (%)</td>
<td>34.9±1.2</td>
<td>35.5±1.6</td>
</tr>
<tr>
<td>Early transmitral flow velocity</td>
<td>81.5±2.7</td>
<td>75.4±3.4</td>
</tr>
<tr>
<td>(E) (mm/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial transmitral flow velocity</td>
<td>36.6±1.8</td>
<td>39.7±1.6</td>
</tr>
<tr>
<td>(A) (mm/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A</td>
<td>2.2±0.1</td>
<td>1.9±0.1</td>
</tr>
</tbody>
</table>

Data shown are mean±SEM. *p<0.01 vs. sedentary subjects.

Figure 1. Bar graphs showing baseline hemodynamic and humoral values in athletes (n=19) and sedentary subjects (n=9). Data are shown as mean±SEM. MAP, mean arterial pressure; HR, heart rate; FBF, forearm blood flow; FVR, forearm vascular resistance; NE, plasma norepinephrine.
tion in left ventricular end-diastolic diameter induced by leg raising and lower body negative pressure at $-15$ mm Hg caused small and nonsignificant changes in arterial blood pressure and heart rate (Figures 3 and 4, upper panels). In contrast, during the increase in left ventricular end-diastolic diameter, there was a reduction in forearm vascular resistance and plasma norepinephrine, which were both increased during the lower body negative pressure at $-15$ mm Hg. All responses were significantly less pronounced in the athletes compared with the sedentary subjects. The reduction was particularly pronounced for the responses to lower body negative pressure with the responses of the athletes being less than 40% of those of sedentary subjects (Figures 3 and 4, lower panels).

The magnitude of the overall change in forearm vascular resistance induced by leg raising and lower body negative pressure at $-15$ mm Hg was slightly less ($35.0\pm4.9$ vs. $59.4\pm7.5$, $p<0.05$) in throwers than...
in runners, but the concomitant changes in plasma norepinephrine were similar in the two groups of subjects. In the group as a whole, both responses did not bear any relation with the indexes of systolic and diastolic left ventricular function ($r$ always less than 0.35, NS). No relation was found between the responses and left ventricular diameter, left posterior wall thickness, and left ventricular mass index. There was, on the other hand, a marginally significant relation between the reflex change in forearm vascular resistance and the septal wall thickness ($r=0.44$, $p<0.05$).

The results obtained by lower body negative pressure at $-40$ mm Hg are shown in Figure 5. In both the athletes and the sedentary subjects, this maneuver caused a greater decline in left ventricular end-diastolic diameter than with the lower body negative pressure at $-15$ mm Hg. This was associated with a decrease in arterial blood pressure, an increase in heart rate, and an increase in forearm vascular resistance and plasma norepinephrine greater than with the milder lower body negative pressure stimulus. The decreases in left ventricular end-diastolic diameter and blood pressure were significantly more pronounced in the athletes than in the sedentary subjects, whereas the increase in heart rate and forearm vascular resistance were significantly smaller in the athletes compared with the sedentary subjects. Athletes also showed a tendency to a smaller increase in plasma norepinephrine, but the difference with sedentary individuals was not statistically significant.

**Cold Pressor Test**

As shown in Table 2, immersion of one hand in ice water caused an increase in blood pressure, heart rate, and forearm vascular resistance. The tachycardic response was significantly less in athletes than in sedentary subjects. In contrast, both the pressor and the vasoconstrictor responses were not significantly different in the two groups of subjects.

**Table 2. Hemodynamic Changes Induced by Cold Pressor Test**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Forearm vascular resistance (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Change</td>
<td>%</td>
</tr>
<tr>
<td>Athletes ($n=19$)</td>
<td>92.8±2.0</td>
<td>15.2±2.1</td>
<td>16.4±1.9</td>
</tr>
<tr>
<td>Sedentary ($n=9$)</td>
<td>99.1±1.9</td>
<td>17.2±3.3</td>
<td>17.3±3.3</td>
</tr>
</tbody>
</table>

* $p<0.05$, † $p<0.01$, statistical difference between athletes and sedentary subjects.
Discussion

In our study, the increase in forearm vascular resistance and plasma norepinephrine accompanying a reduction in venous return and left ventricular end-diastolic diameter devoid of blood pressure and heart rate effects was less pronounced in athletes with cardiac hypertrophy than in age-matched sedentary subjects with a normal heart. Furthermore, the reduction in forearm vascular resistance and plasma norepinephrine accompanying an increase in venous return and left ventricular end-diastolic diameter devoid of blood pressure and heart rate effects was also less evident in the athletes compared with the sedentary subjects with a normal heart. This indicates that reflex influences originating from deactivation and stimulation of cardiopulmonary receptors are impaired by physical training so pronounced and long lasting that the result is a structural alteration of the heart.

The mechanisms of the impaired cardiopulmonary reflex observed in athletes are only partly clarified by our data. Because the responses to cardiopulmonary receptor stimulation and activation were both affected, and the prestimulus plasma norepinephrine and forearm vascular resistance were similar in athletes and control subjects, the impairment could not be explained by differences in baseline values. Furthermore, because the pressor and vasoconstrictor effects of cold pressor test were similar in athletes and control subjects, this impairment did not originate from a vascular hyporeactivity to neural stimuli but rather reflected a malfunction of the neural portion of the reflex arch. This is supported by the norepinephrine responses to cardiopulmonary receptor manipulation being blunted in the athletes to a degree not less pronounced than the vascular responses. Further understanding of the cardiopulmonary reflex malfunction, however, is only a matter of speculation. One possibility to be considered is that in athletes, the secretion of norepinephrine in response to reflex modulation of sympathetic activity is impaired. Another possibility is that the central integration of the cardiopulmonary reflex is altered in athletes due to a modification of reflexes known to interact with cardiopulmonary receptor influences at a central level. It is also possible that the alteration involves the signal originating from the most important source of reflex influences within the cardiopulmonary region, that is, cardiac stretch receptors. We favor the last possibility because an impaired cardiopulmonary reflex has been shown in a variety of conditions (renovascular hypertension, essential hypertension, aortic stenosis, and aging) having as a common feature an increased cardiac mass. Furthermore, in our subjects, there was a significant although modest relation between the reduction in the reflex effects of cardiopulmonary receptor manipulation and the increase in septal wall thickness. Finally, studies on experimental hypertension demonstrated that the responsiveness of stretch receptors are altered by the thickening of the structure in which the receptors are located. This can be explained by a reduction in compliance. Cardiac compliance, however, is reduced when cardiac hypertrophy is induced by hypertension but not when it is induced by physical training. This was also the case in our athletes who showed no reduction in left ventricular volume changes in response to changing venous return and no impairment of ventricular compliance as assessed by echo-Doppler transmitial flow velocity. Furthermore, another determinant of cardiac receptor firing, that is, left ventricular contractility, was apparently similar in athletes and sedentary control subjects. Considering that all those techniques provide only an approximate evaluation of cardiac function, it can be speculated that in athletes with cardiac hypertrophy, a cardiac receptor abnormality may depend on an alteration of the mechanical properties of the heart but that other factors (receptor-myocardial uncoupling and receptor dysfunction) may play a role.

The impairment of the cardiopulmonary reflex observed in athletes with cardiac hypertrophy means that this condition is associated with a reduced effectiveness of an important mechanism involved in cardiovascular homeostasis. This may explain why the pronounced reduction in venous return obtained by lower body negative pressure at −40 mm Hg resulted in a greater hypotension in athletes than in sedentary subjects. It may also explain why athletes are more prone to orthostatic hypotension. Thus, the cardiac hypertrophy of the athlete may not be entirely benign. This, however, may apply only to the pronounced hypotension of the heart, which develops in response to a pronounced and long-lasting physical training and may not necessarily extend to trainings and hypertrophies of a lesser degree. This possibility is supported by the observation that in trainees with a left ventricular mass only slightly above the normal range, no abnormality of the cardiopulmonary reflex was found.

Finally, physical training has been shown to be followed by a greater bradycardic response to arterial baroreceptor stimulation, suggesting a potentiation of the baroreflex. In our study, however, the increase in heart rate induced by lowering systolic arterial pressure through lower body negative pressure at −40 mm Hg (i.e., a reflex response dependent on arterial baroreceptor deactivation) was 5.5 ± 1.8 beats·min⁻¹·mm Hg⁻¹ in control individuals and only 2.1 ± 0.5 beats·min⁻¹·mm Hg⁻¹ in athletes (p < 0.05). Thus, pronounced and long-lasting physical training does not potentiate but rather modifies the baroreflex in a way that favors reflex bradycardia but opposes reflex tachycardia. This phenomenon (which may be part of a more general tendency of training to oppose tachycardia [see the reduced heart rate response to cold pressor test in our athletes]) may favor cardiovascular function during the increase in blood pressure associated with exercise because, under this circumstance, a reduced tachycardic response reduces car-
diac oxygen consumption and improves myocardial perfusion. It may be disadvantageous, however, during the decrease in blood pressure induced by hemorrhage or orthostasis because, in these instances, a pronounced tachycardic response is an important component of cardiovascular homeostasis.

Acknowledgment

We thank Mr. F. Sar, the staff, and the athletes of “Gruppo Sportivo SNIA” of Milan for their kind cooperation.

References

23. Mancia G, Donald DE, Shepherd JT: Inhibition of adrenergic outflow to peripheral blood vessels by vagal afferents from the cardiopulmonary region in the dog. Circ Res 1973;33:713–721
39. Ferguson DW, Thames MD, Mark AL: Effects of propranolol on reflex vascular responses to orthostatic stress in humans:

**KEY WORDS** • cardiac receptors • exercise • cardiac hypertrophy • hypertension • nervous system, autonomic • diastolic function
Cardiopulmonary receptor reflexes in normotensive athletes with cardiac hypertrophy.
C Giannattasio, G Seravalle, G B Bolla, B M Cattaneo, J Cléroux, C Cuspidi, L Sampieri, G Grassi and G Mancia

_Circulation_. 1990;82:1222-1229
doi: 10.1161/01.CIR.82.4.1222

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/4/1222

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/