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Early impairment of the cardiopulmonary exercise capacity of hypertensive patients

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Abstract

A reduction of functional capacity has been reported in severe hypertension. However, the reduced peripheral vasodilation observed in the early stages of hypertension, could also impair the blood supply to exercising muscles in mild hypertensives presenting a normal left ventricular mass. In this paper the cardiopulmonary exercise capacity of early hypertensives has been investigated. Thirty mild hypertensives (9 in stage I and 21 in stage II according to WHO) and 36 normotensives divided into two age and weight-matched groups, were investigated. All subjects underwent a stress test according to the modified Bruce protocol with contemporary assessment of breath-by-breath expiratory gas analysis and measurement of the anaerobic threshold (AT) and of the oxygen consumption at peak exercise (PvO_2). Exercise duration and maximal workload, in stage I hypertensives, were similar to controls but the O_2 consumption was significantly reduced in comparison to controls ($P = 0.043$). On the contrary, in stage II patients exercise duration, maximal workload, PvO_2 and AT were significantly lower than in normotensives. No relationship between myocardial hypertrophy and ergometric or ventilatory (PvO_2, AT, VE) parameters was found. In conclusion an early impairment of the aerobic exercise performance is detectable in uncomplicated (stage I WHO) mild hypertensives.

Key words: Hypertension; Exercise test; Oxygen consumption; Pulmonary ventilation; Left ventricular hypertrophy

1. Introduction

An impaired coronary and peripheral blood flow autoregulation [1–4], coronary and systemic vasomotion [5,6] and a reduced response to vasodilating stimuli [7–9] have been reported in hypertensive patients. These alterations could impair the blood flow supply at exercising muscles and could be responsible for the impaired maximal exercise aerobic capacity observed in severe hypertensives [10].

A reduced response to vasodilating stimuli has also been found in mild uncomplicated hypertensives [7,8]. In those patients the duration of a symptom-limited exercise test [11–13] was not reduced but the ergometric assessment of the exer-

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Table 1
Anthropometric and clinical blood pressure measurements

	Controls	Hypertensives
Stage I		
n	16	9
Age (years)	35.4 ± 5.3	35.4 ± 6.9
Weight (kg)	67.2 ± 5.2	68.4 ± 6.2
Years of hypertension	—	5.6 ± 1.2
Left ventricular mass(g/m^2)	93.2 ± 9.2	95.9 ± 11.3
E/A	1.91 ± 0.26	1.86 ± 0.2
Stage II		
n	20	21
Age (years)	54.8 ± 6.8	53.1 ± 8.7
Weight (kg)	72.1 ± 8.2	71.4 ± 7.1
Years of hypertension	—	12.7 ± 5.2
LVH (*n*)	0	11
Retinopathy (*n*)	0	18
Left ventricular mass (g/m^2)	99.6 ± 15.1	131.5 ± 26.5*
E/A	1.84 ± 0.14	1.15 ± 0.4**

*$P < 0.01$.
**$P < 0.001$.

tified as the value of O_2 consumption (V_{O_2}) at which the linear relation between ventilation (VE) and V_{O_2} was lost, whereas the relation between VE and CO_2 consumption (V_{CO_2}) remained steady. The determination was validated by the analysis of VE/V_{O_2} versus time, V_{CO_2} versus V_{O_2}, end-tidal P_{O_2} versus time. The oxygen consumption at peak exercise was identified as the value of V_{O_2} that remained unchanged during the final 30 s of the last stage of the exercise test [19].

The AT was independently assessed by three operators; two of them were unaware of the result of the test. Interobserver variability and reproducibility of ventilatory AT and V_{O_2} at peak exercise have been previously assessed in our laboratory in nine healthy normotensive control subjects and seven hypertensive patients. Variability was 0.8 ± 0.7 ml/kg per min V_{O_2} (4%) in the controls and 0.9 ± 0.8 ml/kg per min V_{O_2} (7%) in hypertensives; day-to-day reproducibility was high (r = 0.93 in normotensives and r = 0.87 in hypertensives).

2.3. Statistical analyses

Comparisons between groups of unpaired data were made with analysis of variance, 2-tailed unpaired Student's t-tests or by multivariate analysis of variance. Although the mean age of hypertensives at stage I and II were not statistically different from controls, age was considered as covariate in all statistical comparisons.

To better individuate factors which influence P_{VO_2} in hypertensives, multiple regression analysis was performed with peak V_{O_2} as the dependent variable and weight, age, baseline blood pressure, left ventricular mass index, fractional shortening as independent variables. Results are expressed as mean ± S.D. All tests have been performed by BMDP Statistical Software.

3. Results

At the peak of the exercise test the workload and the exercise duration were significantly lower in the hypertensives (180 ± 64 W and 859 ± 163 s) than in controls (218 ± 47 W, $P < 0.002$ and 959 ± 107 s, $P < 0.001$). The rate-pressure product was 321.5 ± 26.7 in hypertensives and 309.7 ± 47.5 in controls (ns).

Multiple regression analysis, performed with P_{VO_2} as the dependent variable and weight, base-

Table 3
Ventilatory and ergometric parameters achieved by controls and hypertensives during the exercise test (age as covariate)

	Controls ($n = 20$)	Hypertensives (stage II WHO) ($n = 21$)	F-value	2-Tail Prob.
Workload (W)				
AT	109.7 ± 34.5	81.3 ± 48.1	6.21	0.0172
Peak exercise	203.9 ± 43.8	155.1 ± 48.0	14.64	0.0005
Time (s)				
AT	632.2 ± 114.6	511.6 ± 199.6	7.30	0.0102
Total	933.9 ± 102.5	812.0 ± 158.2	13.72	0.0007
Heart rate (bpm)				
Baseline	81.3 ± 13.4	82.3 ± 14.1	0.02	0.8854
AT	117.2 ± 13.4	118.7 ± 15.8	0.02	0.8997
Peak exercise	161.5 ± 15.1	148.0 ± 18.7	11.56	0.0016
Systolic pressure (mmmHg)				
Baseline	125.7 ± 13.3	160.4 ± 15.4	62.91	0.0000
AT	168.7 ± 21.7	185.2 ± 28.9	4.00	0.0527
Peak exercise	190.5 ± 20.0	206.6 ± 29.0	3.85	0.0570
Diastolic pressure (mmmHg)				
Baseline	80.5 ± 3.5	95.2 ± 5.5	97.24	0.0000
AT	87.2 ± 8.9	100.7 ± 10.0	19.95	0.0001
Peak exercise	91.2 ± 8.8	103.8 ± 12.9	12.68	0.0010
Rate-Pressure product				
Baseline	101.8 ± 16.9	131.6 ± 22.1	22.54	0.0000
AT	198.7 ± 39.6	219.2 ± 52.7	1.99	0.2148
Peak exercise	306.6 ± 45.4	310.3 ± 67.1	0.09	0.7675
Vo_2 (ml Vo_2/kg/min)				
Baseline	3.6 ± 1.0	4.7 ± 4.3	1.13	0.2945
AT	19.5 ± 2.0	17.3 ± 4.1	6.78	0.0131
Peak exercise	27.4 ± 4.2	23.1 ± 5.0	12.24	0.0012

groups according to the presence or the absence of myocardial hypertrophy. Ergometric (workload, exercise duration, rate-pressure product) and ventilatory parameters (Pvo_2, AT, VE) did not statistically differ between patients with or without hypertrophy (Table 4). The oxygen consumption at peak exercise and the rate-pressure product were not significantly related to the left ventricular mass ($r = 0.07$, and $r = 0.15$, respectively).

4. Discussion

This study indicates that an impaired aerobic performance during the exercise test is detectable in uncomplicated (stage I WHO) mild hypertensives. The lower Pvo_2 was found not to be due to an early interruption of exercise, or to an impaired ventilation as the exercise duration and the VE at peak exercise were not different from normotensives. In stage II patients not only the Pvo_2 but also the anaerobic threshold, the duration of test and the maximal workload were impaired in comparison to normotensives. In those patients the early beginning of muscle anaerobic metabolism during exercise seems to be mainly related to the involvement of peripheral vessels rather than to the presence of left ventricular hypertrophy. In fact, the presence of left ventricular hypertrophy did not affect the pattern of Vo_2 consumption.

In mild uncomplicated hypertensives the maximal workload was found to be similar to that of age-matched controls [13]. In severe hypertension a reduction of the maximum oxygen uptake during a bicycle exercise test was reported [12,13] and the O_2 consumption during the exercise seemed to be independent from the presence of myocardial hypertrophy [20]. The contemporary difference in the Pvo_2 and in the diastolic pattern in hyperten-

cise capacity cannot be considered as a sensitive test. On the contrary, the assessment of ventilatory volumes and gas exchanges during a treadmill test represents a useful tool to appreciate an early functional impairment of maximal aerobic exercise capacity. This technique was employed to investigate the early changes during aerobic exercise in mild hypertensives in relation to the severity of hypertension and to the presence of myocardial hypertrophy. The possibility that the diastolic function plays a role in reduced aerobic power has also been evaluated.

2. Methods

2.1. Subjects investigated

Thirty consecutive male patients, aged 19–68 years and affected by essential mild to moderate hypertension, were recruited from the Hypertension Unit of the Clinica Medica I of the University of Florence.

Patients were classified according to WHO classification [14] (stage I, $n = 9$; stage II, $n = 21$). Stage II patients (defined according to the presence of hypertensive retinopathy stage 2–3 or left ventricular hypertrophy) [14] were subdivided into two groups according to the presence ($n = 10$, LVMI > 130 g/m^2) or absence ($n = 11$, LVMI ≥ 130 g/m^2) of myocardial hypertrophy at echocardiographic examination. Briefly mono- and two-dimensional echocardiography were performed by the annular array transducer method (2.5–3.5 MHz) (EsaOte-Biomedica, Florence, Italy). The mono-dimensional measurements were performed under a bi-dimensional guide using short axis projection in order to avoid the interference of chordal apparatus. The measurements were carried out during rest according to the recommendations of the American Society of Echocardiography [15,16]. Each value reported is the mean calculated throughout five cardiac cycles. Left ventricular internal dimensions and volumes, wall thickness and ventricular mass (calculated according to Devereux' formula) [17] were indexed for body surface area. Left ventricular ejection fraction was measured by radionuclide angiocardiography (^{99}Tc) at equilibrium according to standard procedures.

All hypertensive patients had not received antihypertensive medications before the enrolment in the study. Arterial BP was determined with conventional sphygmomanometry at each of four separate clinical visits. At each examination patients were allowed 3 min of rest in a seated position before three measurements were determined using first and fifth phase Korotkoff sounds. Blood pressure results from the four visits were averaged and patients were considered for enrolment if the mean diastolic BP was higher than 90 mmHg (Table 1).

Exclusion criteria included angina pectoris, recent myocardial infarction (within 6 months), heart failure, cerebrovascular accidents, clinically important renal, hepatic or hematologic disorders, secondary hypertension, hyperkaliemia or hypokaliemia, obstructive pulmonary disease or participation in an exercise training program.

Thirty-six age-matched normotensive male subjects, divided into two groups matched by age and weight (Table 1), served as controls. All subjects gave informed consent and were non-smokers. Neither controls nor hypertensives were fitted or had undergone any kind of exercise training programme.

2.2. Cardiopulmonary exercise stress testing

All subjects underwent a symptom-limited treadmill test using the Bruce protocol as modified by the addition of two initial steps at low work load with continuous measurement of ventilatory volumes and gas exchanges by metabolimeter.

Twelve standard electrocardiographic leads were monitored with a computerized analysis of the ST segment (CASE 12, Marquette, Milwaukee, WI). Expired air was collected by a facemask for quantification of ventilatory volumes and gas exchanges by a metabolimeter (Sensormedics 4400 unit, Anaheim, CA, USA) which allowed a breath-by-breath expiratory gas analysis.

Blood pressure was measured using a manometer cuff against mercury during the final 30 s of each 3 min stage. Exercise duration was defined as the time, to the nearest tenth of a minute, from the onset of stage 0 to the point of test termination. In all subjects but two the tests were terminated because of fatigue and dyspnea.

The anaerobic threshold (AT) [18] was iden-

metaboreflex system which further activates the sympathetic nervous system and increases peripheral vascular resistence during exercise.

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Table 4
Ventilatory and ergometric parameters achieved by stage II hypertensives with and without left ventricular hypertrophy

	LVH ($n = 10$)	No LVH ($n = 11$)	F-value	2-Tail Prob.
LVM (g/m^2)	155.5 ± 15.1	109.8 ± 11.9	39.30	0.0000
Workload (W)				
AT	81.7 ± 44.2	81.0 ± 49.2	1.44	0.2450
Peak	142.6 ± 43.4	166.6 ± 46.9	0.02	0.8927
Time (s)				
AT	546 ± 161	480 ± 216	2.80	0.1116
Peak	821 ± 179	803 ± 127	4.37	0.0511
Heart rate				
Baseline	81.3 ± 16.5	83.2 ± 10.7	0.00	0.9634
AT	113.3 ± 15.2	123.7 ± 13.8	1.17	0.2937
Peak	141.8 ± 21.7	153.7 ± 12.0	0.46	0.5083
Systolic pressure				
Baseline	156.0 ± 12.0	164.5 ± 16.4	2.91	0.1053
AT	182.0 ± 20.5	188.1 ± 33.5	0.22	0.6467
Peak	199.5 ± 23.8	213.1 ± 30.5	0.65	0.4298
Diastolic pressure				
Baseline	94.5 ± 4.7	95.9 ± 5.9	0.30	0.5903
AT	101.0 ± 8.3	100.4 ± 10.9	0.02	0.8832
Peak	104.5 ± 11.2	103.1 ± 13.7	0.11	0.7406
Rate-pressure				
Baseline	126.0 ± 22.7	136.7 ± 20.1	1.04	0.4324
AT	203.7 ± 42.4	233.3 ± 54.7	1.02	0.3270
Peak	289.3 ± 65.7	329.5 ± 59.0	0.79	0.3856
Vo_2 (ml Vo_2/kg/min)				
Baseline	5.8 ± 5.8	3.7 ± 1.0	1.88	0.1868
AT	17.0 ± 2.7	17.5 ± 4.9	0.27	0.6124
Peak	24.0 ± 4.7	22.4 ± 5.0	3.66	0.0692

The aerobic performance of early hypertensives was assessed by breath-by-breath expiratory gas analysis during exercise stress test in 9 stage I and 21 stage II (according to WHO) hypertensive patients and in 36 age-matched controls. The measured variables (exercise duration, maximal workload, rate pressure product, Vo_2 peak) were reduced in patients at stage II. In stage I hypertensives the peak oxygen consumption was reduced ($P = 0.043$) even in the absence of maximal workload changes.

sive patients seems to suggest an impaired peripheral response to exercise, probably related to complex modifications involving peripheral blood flow and muscular metabolism [21]. In fact chronic hypertension produces morphological and functional changes in vascular muscle [22,23]. In particular, when compared to controls, hypertensives experience a reduced blood perfusion of exercising muscle in spite of an increased systemic blood pressure response. This pattern is due to abnormalities of the vasomotor tone, with reduced response to vasodilatory stimuli and a relatively higher increase in peripheral vascular resistance in comparison to controls. A reduced flow dependent vasodilation has been recently reported in hypertensives [24,25]. This impaired peripheral vascular relaxation rather than central mechanisms might influence cardiovascular response to exercise in hypertensives causing a reduction in O_2 consumption.

However, whatever the responsible mechanism is, the impaired aerobic metabolism could represent an important factor in conditioning the response to exercise of hypertensives. The reduced aerobic metabolism of exercising muscle could cause an increased activation of muscle

line blood pressure, left ventricular mass index and Doppler diastolic function as independent variables, showed a significant correlation between PVO_2 and body weight ($P = 0.02$), blood pressure ($P = 0.001$ for both systolic and diastolic basal pressures), and for Doppler diastolic function ($P = 0.05$) but not with left ventricular mass index ($P = 0.81$).

3.1. Stage I hypertensives

The exercise duration, maximal workload and rate-pressure product achieved in stage I hypertensives without myocardial hypertrophy were not significantly lower from age-matched normotensives (Table 2). On the contrary, the PVO_2 was significantly lower than in controls (27.9 ± 5.1 vs. 33.2 ± 6.6 ml VO_2/kg per min, $P = 0.042$). The AT did not differ from that of normotensives (Table 2).

No significant reduction of the systolic function was found (ejection fraction echocardiographically assessed was 65 ± 6%). No impairment of diastolic function was detectable at Doppler echocardiography with a rate of peak E/A of 1.91 ± 0.2 vs. 1.86 ± 0.2 (ns).

3.2. Stage II hypertensives

In stage II patients the exercise duration and the maximal workload were significantly lower than that of normotensives (Table 3). The rate-pressure product was not significantly different (Table 3). In these patients both the PVO_2 and the AT were significantly lower than those of age-matched normotensives. In stage II patients no significant reduction of the ejection fraction echocardiographically assessed was found (63 ± 7%). Patients belonging to stage II showed an impaired left ventricular diastolic function with a rate of peak E/A of 1.15 ± 0.4 vs. 1.84 ± 0.14 ($P < 0.001$).

Stage II patients were then subdivided into two

Table 2
Ventilatory and ergometric parameters achieved by controls and hypertensives during the exercise test (age as covariate)

	Controls ($n = 16$)	Hypertensives (stage I WHO) ($n = 9$)	F-value	2-Tail Prob.
Workload (Watt)				
AT	106.5 ± 38.5	127.4 ± 52.6	1.94	0.1746
Peak exercise	232.3 ± 48.5	217.8 ± 65.3	0.26	0.6173
Time (s)				
AT	621.6 ± 93.3	666.9 ± 135.9	1.44	0.2399
Total	984.8 ± 110.5	951.7 ± 134.4	0.24	0.6259
Heart rate (bpm)				
Baseline	90.0 ± 22.4	88.6 ± 18.3	0.03	0.8643
AT	127.8 ± 20.1	132.3 ± 17.2	0.45	0.5086
Peak exercise	181.8 ± 9.3	172.1 ± 11.9	5.64	0.0244
Systolic pressure (mmHg)				
Baseline	123.4 ± 13.9	161.1 ± 11.5	60.08	0.0000
AT	156.8 ± 16.1	186.5 ± 16.7	23.41	0.0000
Peak exercise	175.5 ± 24.1	200.3 ± 17.9	9.33	0.0048
Diastolic pressure (mmHg)				
Baseline	77.3 ± 6.5	98.0 ± 8.5	55.89	0.0000
AT	80.0 ± 9.4	96.5 ± 13.2	15.57	0.0005
Peak exercise	81.3 ± 11.6	98.4 ± 14.7	12.68	0.0013
Rate-Pressure product				
Baseline	110.9 ± 30.2	139.4 ± 36.3	5.37	0.0277
AT	201.3 ± 39.9	250.6 ± 47.5	9.79	0.0040
Peak exercise	319.2 ± 46.7	344.0 ± 37.2	3.44	0.0737
VO_2 (ml VO_2/kg per min)				
Baseline	4.0 ± 1.1	4.8 ± 2.6	2.85	0.1022
AT	21.2 ± 2.2	20.9 ± 3.6	0.04	0.8392
Peak exercise	33.2 ± 6.6	27.9 ± 5.1	4.50	0.0425