Chronic exercise reduces platelet activation in hypertension: upregulation of the L-arginine-nitric oxide pathway

L. R. de Meirelles¹, A. C. Mendes-Ribeiro¹,², M. A. P. Mendes¹, M. N. S. da Silva¹, J. C. John Clive Ellory³, G. E. Mann⁴, T. M. C. Brunini¹

¹Departamento de Farmacologia e Psicobiologia, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, ²Disciplina de Farmacologia, Departamento de Ciências Fisiológicas, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, ³Department of Physiology, Anatomy and Genetics, Sherrington Building, Parks Road, Oxford, UK, ⁴Cardiovascular Division, School of Medicine, King’s College London, London, UK

Corresponding author: Dr. Antonio Cláudio Mendes-Ribeiro, Departamento de Farmacologia e Psicobiologia, Universidade do Estado do Rio de Janeiro, Rio de Janeiro 20551–030, Brazil. Tel/Fax: +00 55 21 2249 5823, E-mail: cribeiro@physiol.ox.ac.uk

Accepted for publication 23 October 2007

Nitric oxide (NO) inhibits platelet function and plays a key role in the regulation of cardiovascular homeostasis. Essential hypertension is characterized by an increased risk of thrombus formation, and by an inhibition of intraplatelet NO bioactivity. We have previously shown that membrane transport of l-arginine is a rate-limiting step for platelet-derived NO synthesis. This study examined the effects of exercise on the platelet l-arginine–NO pathway and aggregation and systemic inflammation markers in 13 sedentary hypertensive patients subjected to 60 min of training activity (exercise group), predominantly aerobic, three times a week for a period of 12 weeks. Six sedentary hypertensive patients participated in the control group. After 12 weeks, l-arginine transport was significantly increased and associated with increased platelet NO synthase activity and cGMP levels and reduced platelet aggregation. Moreover, exercise training reduced plasma concentrations of fibrinogen and C-reactive protein and blood pressure. The control group did not change their previous intraplatelet l-arginine–NO results and systemic inflammatory markers levels. Thus, exercise training reduces inflammatory responses, restores NO synthesis in platelets and thereby contributes to the beneficial effects of exercise in hypertension. The present study adds exercise as a new tool to reduce morbidity and mortality associated with platelet activation in hypertension.

Essential hypertension affects approximately one billion individuals worldwide and 17 million individuals in Brazil (Chobanian et al., 2003; Ministério da Saúde, 2005). As the population ages, the prevalence of hypertension increases further, highlighting the need for more effective and preventive treatments (Chobanian et al., 2003). An alteration in endothelial function, together with increased platelet aggregation, contributes to sustained elevated peripheral resistance and to the premature development of atherosclerosis and thrombosis in hypertensive patients (Brunini et al., 2003; Taddei et al., 2006). In this setting, increased platelet activation in essential hypertension is associated with a disturbance in the bioavailability of nitric oxide (NO), a key modulator of platelet function (Moss et al., 2004; Brunini et al., 2005).

NO is formed from the terminal guanidino nitrogen atom of L-arginine by a family of enzymes, the NO synthases (NOS) (Palmer et al., 1998; Stuehr, 2004; Moncada & Higgs, 2006). Platelets express both inducible and constitutive endothelial isoforms of NOS (Mehta et al., 1995), and we have previously demonstrated that transport of L-arginine via system y¹L is essential for platelet-derived NO production (Mendes-Ribeiro et al., 1999; Brunini et al., 2003). Moreover, decreased rates of L-arginine transport in platelets from hypertensive patients are associated with reduced activity of platelet NOS and increased plasma concentrations of L-arginine (Moss et al., 2004). A deficiency in intracellular L-arginine availability has been implicated as a possible mechanism for the endothelial and platelet dysfunctions in this disease (Brunini et al., 2005).

Inflammatory markers such as C-reactive protein (CRP) are associated with vascular lesions in humans and are risk factors for cardiovascular disease (Manabe et al., 2005; Savoia & Schiffirin, 2006), and elevated CRP levels might be predictive for the development of hypertension (Jae et al., 2006). Despite some controversy, plasma fibrinogen, an acute-phase inflammatory marker that plays an important
role in platelet aggregation, plasma viscosity and fibrin formation, is also a predictor of cardiovascular morbidity and is associated with vascular lesions in hypertensive patients (Minuz et al., 2004).

Exercise training is a beneficial, non-pharmacological tool for the management of patients with essential hypertension (Whelton et al., 2002; Stewart, 2004). A meta-analysis of 54 randomized, controlled trials showed that aerobic exercise reduces blood pressure in both overweight and normal-weight hypertensive and normotensive subjects (Whelton et al., 2002). Regular exercise improves the cardiovascular parameters of hypertensive patients, ameliorating endothelial function and left ventricular diastolic volume, as well as alleviating arterial stiffness and systemic inflammation (Stewart, 2004). It is thought that increased shear stress with exercise enhances endothelial cell NO synthesis, which in turn reduces the risk of acute coronary events and inhibits smooth muscle proliferation and leukocyte adhesion (Dag et al., 1994). Few studies are available on the effect of exercise on the platelet function, and the exact effects of exercise training on platelet activation and function is not yet known (El-Sayed et al., 2005).

To our knowledge, there are no reports on the effects of exercise on the L-arginine–NO pathway in platelets from hypertensive patients. In the present study, we have examined the effects of chronic exercise on platelet L-arginine transport, NOS activity and aggregation in hypertensive patients before and after 12 weeks of aerobic exercise training. The effects of exercise on the platelet function were correlated with plasma levels of acute inflammatory markers (CRP and fibrinogen).

**Methods**

**Subjects**

Thirteen sedentary hypertensive patients on stage 1 participated in this study (49 ± 1 years, female/male: 8/5) as the exercise group and six (50 ± 4 years, female/male: 4/2) as the control group. Clinical and laboratory data are summarized in Table 1. The exclusion criteria included chronic heart and renal failure, infection, dyslipidemia and recent blood transfusion. All patients were recruited from the outpatient clinic of the Pedro Ernesto Hospital. The Hospital Ethical Committee approved this work and informed consent was obtained from each of the patients: 61.5% and control group: 50%), β-blockers (exercise group: 46.1% and control group: 33.3%), calcium antagonists (exercise group: 38.4% and control group: 33.3%) and angiotensin-convert ing enzyme inhibitors (exercise group: 30.7% and control group: 50%). The pharmacological treatment was not modified during the study.

**Body mass index (BMI)**

BMI was calculated by dividing body weight in kilograms by height in meters squared (kg/m²). BMI < 25 was defined as eutrophic, between 25.0 and 29.9 kg/m² overweight and ≥ 30.0 kg/m² as obese (Ratliff et al., 2005).

Measurements of waist circumference and skinfold thickness

Waist circumference was measured at the natural waistline in duplicate by the same investigator. The percentage of body fat was estimated by measuring skinfolds at seven sites (chest, midaxillary, triceps, subscapular, abdomen, suprailliac and thigh for both men and women) using Harpenden skinfold calipers. Duplicate measurements were taken in the same order on the right side of the body by the same investigator. The average of the two measurements for each site was used to calculate the sum of the seven skinfolds. The total of the seven skinfolds was then used to calculate body density, and the percentage of body fat was calculated from the density measurements as defined by Jackson and Pollock (Strukova, 2006).

**Exercise testing**

Each subject performed a graded exercise test on the treadmill ergometer before exercise training and at 12-weeks follow-up intervals to evaluate hemodynamic responses to exercise in presence of the antihypertensive treatment. Each test was preceded by an explanation of the protocol and procedures to be used. Subjects underwent a symptom-limited treadmill exercise test with the Bruce protocol. Testing was performed on a motor-driven Quinton treadmill, model Q45. Maximal or maximal VO2 was recorded indirect as the highest VO2 value obtained during exercise testing. A 12-lead electrocardiograph was monitored continuously, and blood pressure and heart rate (HR) were measured for each minute during exercise and throughout the recovery period. All tests were continued until volitional fatigue or dyspnea. The patients performed 60 min of training activities, predominantly aerobic, three times per week for 3 months. A target HR was individually calculated at 75–85% of the maximum HR achieved during the treadmill exercise. Activities included 5–10 min of warm-up exercises and stretching, 40 min of endurance (walking and/or running) and calisthenics, and a 5–10 min cool-down period. Initially, subjects exercised at 75% of their maximum HR (HRmax); the initial weeks were also used to familiarize the subjects with proper pacing and pulse rate determination techniques. After 3 weeks, exercise intensity was gradually increased to 85% of HRmax. Intensity and duration were then maintained until the 12th week. Blood pressure was measured before and after exercising. Exercise HRs were verified periodically during each exercise training session by monitoring HR. The method of aerobic exercise was explained in detail to patients (exercise type, frequency, duration and intensity). The sessions were held at the Pedro Ernesto Hospital gymnasium under the supervision of a physical educator.

**Isolation of platelets**

Blood samples were drawn by venipuncture, anticoagulated with citric acid–dextrose (73.7 mmol/L citric acid, 85.9 mmol/L trisodium citrate and 111 mmol/L dextrose) and centrifuged at 250 g for 15 min at room temperature. Platelets were isolated from platelet-rich plasma (PRP) by centrifugation at 800 g for 15 min at room temperature, and the platelet pellet was washed twice and resuspended in Kreb's buffer (composition in mmol/L: NaCl 119, KCl 4.6, CaCl2 1.5, NaH2PO4 1.2, MgCl2 1.2, NaHCO3 15, d-glucose 11). Any antihypertensive treatment was withdrawn 24 h before blood collection. The present study examined cell preparations for contamination by other cells using a Beckman Coulter Counter and by light microscopy. We did not find a significant contamination of our platelet preparation (0.004 ± 0.002 × 10⁷ total leukocytes/L).
Table 1. Clinical characteristics in the exercise and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group (n = 6)</th>
<th>Exercise group (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>32 ± 2</td>
<td>33 ± 2</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>99 ± 2</td>
<td>100 ± 2</td>
</tr>
<tr>
<td>% Body fat</td>
<td>37 ± 3</td>
<td>37.4 ± 3</td>
</tr>
<tr>
<td>K+</td>
<td>4 ± 0.1</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 ± 0.06</td>
<td>0.92 ± 0.06</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.1 ± 0.6</td>
<td>5.1 ± 0.6</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>91 ± 3</td>
<td>92 ± 3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>222 ± 13</td>
<td>223 ± 13</td>
</tr>
<tr>
<td>Low density lipoproteins (mg/dL)</td>
<td>132 ± 14</td>
<td>133 ± 14</td>
</tr>
<tr>
<td>High density lipoproteins (mg/dL)</td>
<td>37 ± 3</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>152 ± 32</td>
<td>155 ± 32</td>
</tr>
</tbody>
</table>

All results are presented as mean ± SD.

*P<0.05.

**P<0.01 vs baseline.

1P<0.05 vs control group (after 12 weeks).

L-arginine influx in platelets

After isolation, a 0.5 mL aliquot of resuspended platelets was incubated at 37 °C with 1–50 μmol/L L-arginine plus 37 kBq/mL L-[3H]-arginine, and influx was measured over 5 min. Transport was terminated by rapid centrifugation at 2000 g for 15 s at room temperature, followed by washing with Kreb’s buffer and recentrifugation under the same conditions. Platelets were lysed with Triton for β-scintillation counting (Mendes-Ribeiro et al., 1999; Brunini et al., 2003, 2004).

Measurement of platelet NOS activity

Basal NOS activity was determined from the conversion of L-[3H]-arginine to L-[3H]-citrulline (Brunini et al., 2003). Platelet suspensions were incubated at 37 °C in the presence of L-[3H]-arginine (2 μCi/mL) plus unlabelled L-arginine (1 μM) for 45 min. All reactions were stopped by rapid centrifugation (2000 g, 15 s), followed by two washes with Kreb’s buffer. The platelet pellet was lysed with 0.1% Triton and applied to a Dowex cation exchange resin column. L-[3H]-citrulline was eluted with 2 mL water and radioactivity measured by liquid scintillation counting.

Assay of platelet cGMP levels

cGMP content was determined in washed platelets at baseline using a commercial enzyme-linked immunosorbent assay (ELISA) method (Cayman Chemical Company, Ann Arbor, Michigan). Briefly, the aliquots of the platelet suspension were preincubated with 200 μM isobutylmethylxanthine (IBMX, a phosphodiesterase inhibitor), for 30 min. Ice-cold perchloric acid (0.3 mol/L) was added to the platelet suspension, and the platelets were lysed by sonication followed by rapid freezing in liquid nitrogen. Cell debris was then pelleted by centrifugation (2000 g, 20 min). The supernatants containing cGMP were collected and stored at −80 °C until ready for assay by ELISA.

Platelet aggregation protocol

Platelet aggregation was evaluated in PRP by optical densitometry. The platelet concentration in PRP was adjusted with platelet-poor plasma (PPP) to achieve a constant count of 250 × 10⁶/L. PPP was obtained by centrifuging the leftover blood at 800 g for 10 min. Aggregation was induced by collagen (4 mg/L) and responses monitored for 5 min in a four-channel aggregometer (Chrono-Log Corporation, Havertown, PA, USA). Tests were performed at 37 °C with a stirring speed of 900 r.p.m. Maximal aggregation was expressed as a percentage.

Measurement of fibrinogen and CRP

Briefly, plasma samples were isolated and the concentration of fibrinogen was measured by a highly sensitive immunoturbidimetric assay (DiaSys Diagnostic Systems, Holzheim, Germany).

Chemicals

All chemicals were of the highest analytical grade and purchased from Sigma, Poole, Dorset, UK.

Statistics

Data are expressed as means ± SEM of measurements in n control subjects or hypertensive patients. Paired test t and analysis of variance for repeated measures was used to compare before and after exercise values (GraphPad Prism Program). Curves were fitted with Enzfitter (Elsevier), using a non-linear least squares fit to the Michaelis–Menten equation. Correlations between continuous variables were assessed using the Pearson correlation test. Relationships between two variables were determined by linear regression analysis. Statistical significance was determined at P<0.05.

Results

Treadmill test variables

After 12 weeks of supervised physical training, there was an increase in maximal exercise time (MET) and estimated maximal oxygen, as shown in Table 2. The MET maximal was 8% higher after training. Rest
and exercise systolic and diastolic blood pressures and double product were significantly reduced after the training period. A significant reduction in rest HR was also observed after training. The control group did not change their previous physical performance (Table 2).

**Table 2. Treadmill parameters in the exercise and control groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group (n = 6)</th>
<th>Exercise group (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12 weeks</td>
<td>Baseline 12 weeks</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80 ± 5</td>
<td>80.8 ± 5</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>141.7 ± 6</td>
<td>145 ± 6</td>
</tr>
<tr>
<td>DP (bpm mm Hg)</td>
<td>91.6 ± 2</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>163.8 ± 10</td>
<td>174.7 ± 10</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>181.7 ± 6</td>
<td>201.7 ± 10</td>
</tr>
<tr>
<td>Oxygen uptake (mL/kg/min)</td>
<td>33.3 ± 6</td>
<td>33.2 ± 6</td>
</tr>
<tr>
<td>METS (mL/kg/min)</td>
<td>9.5 ± 1.6</td>
<td>9.4 ± 1.6</td>
</tr>
<tr>
<td>DP (beats/min mm Hg)</td>
<td>32 892 ± 2028</td>
<td>33 305 ± 2028</td>
</tr>
<tr>
<td>Exercise time (s)</td>
<td>539.3 ± 91</td>
<td>538 ± 91</td>
</tr>
</tbody>
</table>

All results are presented as mean ± SD.

*P < 0.01.

**P < 0.001 vs baseline.

†P < 0.05 vs control group (after 12 weeks).

SBP, systolic blood pressure; DBP, diastolic blood pressure; DP, double product (HR × BP); HR, heart rate; METS, metabolic equivalents.

L-arginine transport in platelets

L-arginine transport via system y^+L was increased in hypertensive patients post-exercise compared with that at baseline (Fig. 1), whereas the control group demonstrated no change. Neither the $K_m$ for carrier-mediated transport nor non-specific diffusion was altered after 3 months.

Basal NOS activity and cGMP content in platelets

Basal NOS activity and intraplatelet cGMP levels were significantly increased in hypertensive patients after the exercise-training period (Table 3). There was no change in the control group.

Platelet aggregation

Platelet aggregation in response to collagen (4 mg/L) was reduced by 14% in hypertensive patients after exercise training whereas there was no change in the control group (Fig. 2).

Plasma levels of fibrinogen and CRP

The plasma levels of acute inflammatory biomarkers, fibrinogen and CRP, were diminished post-training in hypertensive patients compared with values measured at baseline (Table 4). No changes were found at the control group.

Anthropometric parameters and biochemical data

Baseline clinical characteristics in the 13 hypertensive patients before exercise and the six hypertensive control are summarized in Table 1. The baseline values for all parameters were similar in the two groups. As 12-week period of exercise significantly diminished the BMI, waist and body fat percentage. Moreover, after the 12 weeks of aerobic exercise serum concentrations of glucose, triglyceride, total cholesterol and low-density lipoprotein (LDL) cholesterol were reduced significantly while low-density lipoprotein (HDL) cholesterol was increased.
Table 3. Effects of chronic exercise on basal nitric oxide synthase (NOS) activity and cGMP levels in platelets in the exercise and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group (n = 6)</th>
<th></th>
<th>Exercise group (n = 13)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12 weeks</td>
<td></td>
<td>Baseline 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>
| NOS (pmol/10^8 cells) | 0.10 ± 0.02           | 0.10 ± 0.03 | 0.11 ± 0.001            | 0.25 ± 0.07*,
| cGMP (pmol/10^8 cells) | 0.04 ± 0.008          | 0.04 ± 0.009 | 0.03 ± 0.002            | 0.05 ± 0.008* |

All results are presented as mean ± SD.
* P<0.05 vs baseline.
† P<0.05 vs control group (after 12 weeks).

Fig. 2. Effects of chronic exercise on platelet aggregation (%) in hypertensive patients. Scatter graph of individual variables for platelet aggregation in hypertensive patients before and after 12 weeks. Medians are indicated by horizontal bars.

Correlation coefficients for experimental parameters before and after exercise training

Pearson-product moment correlations uncovered a number of relationships between measures of adiposity and other indicators of cardiovascular disease and biochemical values (Table 5). Maximal oxygen uptake was positively correlated with the $V_{\text{max}}$ for system y^+L transport and inversely correlated with total body fat and CRP plasma concentration both pre- and post-exercise. The waist circumference was positively correlated with BMI (Table 5). Additionally, body fat was positively correlated with diastolic blood pressure and negatively correlated with the $V_{\text{max}}$ for L-arginine transport via system y^+L in platelets.

Discussion

The present study provides the first evidence that after a 3-month aerobic training period there is an increase in L-arginine transport in platelets from hypertensive patients, leading to enhanced NOS activity and cGMP production, which are associated with a reduction in platelet aggregation.

Accumulating evidence suggests that NO is involved in the abnormalities of platelet function in hypertension, which can predispose patients to thrombotic events (Moss et al., 2004; Brunini et al., 2005; Taddei et al., 2006). We and others have previously reported that platelets taken from hypertensive patients generate half the amount of NO compared with healthy controls (Camilletti et al., 2001; Brunini et al., 2005). The present findings suggested that aerobic exercise improves NO bioavailability, as a result of enhanced L-arginine transport and NO synthesis. Moreover, it seems that exercise can also reduce oxidative stress mediated inactivation of NO (Rush & Denniss, 2005).

Membrane transport of L-arginine is a rate-limiting step for NO synthesis in platelets (Brunini et al., 2003), and an activation of L-arginine transport in these cells, induced by chronic exercise, may provide a mechanism for sustained substrate supply, thus increasing NO synthesis and reducing platelet activation in hypertension. We have identified a positive correlation between L-arginine transport and maximum oxygen consumption before and after exercise training.

Although molecular studies have shown that an association of y^+LAT with the heavy chain antigen 4F2hc induces system y^+L transport activity
(Torrents et al., 1998), the mechanisms involved in the modulation of this transport system (either at the level of expression or function) have not been fully investigated. Several mechanisms could be responsible for the diminished activity of system y^+L hyper-tension and its enhancement after exercise. These include a reduction in increased levels of angiotensin II and adrenergic and inflammatory responses present in hypertension, which are known to modulate L-arginine transport via other amino acid transport systems in different cells (Mann et al., 2003). An alternative explanation for the activation of system y^+L in hypertensive platelets after exercise could be changes in plasma levels of endogenous L-arginine analogues (ADMA and L-NMMA), because they are systemically elevated and are potent inhibitors of L-arginine transport in platelets from hypertensive patients (Boger, 2004; Brunini et al., 2004). Further studies on the modulation of L-arginine transport in platelets are needed to clarify the benefits of exercise training on platelet function in hypertensive patients.

Our findings demonstrated that a 3-month physical training period significantly improved maximum oxygen consumption and systolic blood pressure at rest and at maximal exercise in hypertensive patients. The magnitude of blood pressure reduction is comparable to what has been reported in other studies using a variety of non-pharmacological approaches (Fletcher et al., 1996; Kavanagh, 2001). We have also confirmed that chronic exercise raises HDL cholesterol and reduces LDL cholesterol. These findings are consistent with previous studies on long-term exercise (Neunteufel et al., 1998; Kavanagh, 2001; Ioka et al., 2002; Vinagre, 2002). Other cardiovascular risk factors, such as BMI, waist and body fat percentage of hypertensive patients were also improved in the present study following exercise training (Rao et al., 2001; Moncada & Higgs, 2006).

Some inflammatory cytokines promote an increase in inflammatory acute-phase proteins such as fibrinogen (Esmon, 2000). Our group has previously shown higher plasma levels of TNF-α in hypertensive patients compared with controls (data not shown). The present study confirms previous findings of a reduction in systemic levels of acute inflammatory biomarkers (fibrinogen and CRP) in hypertensive patients undertaking chronic exercise (Plaisance & Grandjean, 2006). We have also confirmed an inverse association between cardio-respiratory fitness and levels of CRP (Church et al., 2002; Aronson et al., 2004) (Table 5). Several observations have indicated that inflammatory markers such as CRP can down-regulate NOS, leading to impaired NO production and increased atherogenic and thrombotic effects (Mann et al., 2003; Brunini et al., 2005). It is possible that chronic physical training, by diminishing inflammation, improves NO bioavailability, thereby reducing platelet aggregation.

Excessive vascular production or diminished metabolism of reactive oxygen species (ROS) by dysregulation of antioxidant enzymes is likely to be involved in the reduced vascular reactivity and NO production in hypertension (Brunini et al., 2005). Increasing evidence has shown that exercise can reduce oxidative stress (Di et al., 2004; Cleenhiss et al., 2005). An increase in plasma total antioxidant capacity and superoxide dismutase activity was observed in sedentary individuals after physical training together with enhanced nitrate/nitrite (NOx) content in both plasma and platelet cytosol (Di et al., 2004).

In conclusion, our results suggest that exercise training activates the L-arginine–NO pathway in platelets in hypertension. Consequently, aerobic training may attenuate platelet hyperaggregability in this disease. Exercise, which improves platelet function and reduces cardiovascular risk factors, seems to be an important non-pharmacological tool.
in the treatment and prevention of cardiovascular disease. Further clinical trials will need to confirm the therapeutic potential of exercise on L-arginine–NO pathway in patients with hypertension.

**Perspectives**

Platelets from hypertensive subjects present with an inhibition of L-arginine uptake which is rate-limiting for the decreased rates of NO production leading to platelet hyperaggregability and thrombosis (Camilletti et al., 2001; Moss et al., 2004; de Meirelles et al., 2007). Most studies investigating the effects of exercise in patients with essential hypertension have reported a reduction of blood pressure and an improvement of several conventional cardiovascular risk factors (Pinto et al., 2006; Edwards et al., 2007; Fagard & Cornelissen, 2007), however, these studies have not explored the possible involvement of the L-arginine–NO pathway in platelet abnormalities. In present study, novel findings obtained in hypertensive subjects undergoing chronic exercise establish that a non-pharmacological treatment (exercise) normalizes reduced rates of L-arginine transport and intraplatelet NO and cGMP levels, leading to decreased platelet activation. Moreover, in agreement with previous studies, there are potential anti-inflammatory benefits of improving physical fitness in hypertension (Edwards et al., 2007). Exercise seems to be a useful strategy to treat hypertensive patients with measures that could reverse the abnormalities in NO synthesis in platelets and reduce inflammation.

**Key words:** L-arginine transport, platelets, nitric oxide, hypertension, aggregation, exercise.

**Acknowledgements**

We gratefully acknowledge the financial support of a Wellcome Trust Collaborative Research Initiative Grant (ACMR, JCE and GEM, Ref: 067933-Z-02-Z), FAPERJ and CNPq-PQ (Brazil).

**References**


Jae SY, Fernhall B, Lee M, Heflernan KS, Lee MK, Choi YH, Hong KP, Park WH. Exaggerated blood pressure...