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# Relationships between hemodynamic, hemorheological and metabolic responses during exercise\*

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**Abstract:** Aerobic performance is dependent on both cardio-respiratory and peripheral factors with hemodynamic parameters playing a major role. However, whether blood rheology might affect aerobic performance through an effect on hemodynamic factors is not known. The aim of the present study was to assess the relationships between hemodynamic, hemorheological and metabolic parameters in response to a sub-maximal cycling exercise protocol. Ten young sportsmen participated in the present study. Mean arterial pressure (MAP) was measured manually, with thoracic impedance used to monitor cardiac output ( $Q_c$ ): systemic vascular resistance (SVR) was then calculated. Whole blood viscosity ( $\eta_b$ ) was measured and used to calculate systemic vascular hindrance. Hematocrit (Hct) was determined by micro-centrifugation and red blood cell (RBC) deformability (EI) was determined by ektacytometry. A breath-by-breath gas analyzer was used to measure oxygen uptake ( $VO_2$ ); the Fick equation was used to calculate arterio-venous oxygen difference [(a-v) $O_2$ ] from  $VO_2$  and  $Q_c$ . All measurements were performed at rest, during exercise and during recovery. Compared to baseline,  $Q_c$ , MAP, Hct, EI,  $VO_2$ , and (a-v) $O_2$  increased during exercise.  $\eta_b$  increased above baseline only at 150W and remained elevated during recovery; the increase in  $\eta_b$  during the last level of exercise was associated with a decrease of SVR and systemic vascular hindrance. There was a significant negative correlation between EI and SVR and a significant positive relationship between EI and (a-v) $O_2$  and between EI and  $VO_2$  across all exercise workloads, thus suggesting a potential role for RBC deformability as a factor affecting aerobic performance via oxygen delivery to tissues. These data lend support to the concept that hemorheological parameters may contribute to hemodynamic and cardio-respiratory adaptations in response to exercise in moderately trained sportsmen.

Key words: blood rheology, exercise physiology, hemodynamics, oxygen uptake

Running title: Physical activity and blood rheology

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## 1. Introduction

Aerobic physical fitness is limited by several factors such as pulmonary oxygen diffusion capacity, cardiac output, the capacity of blood to carry oxygen and the capacity of muscles to extract and use oxygen for adenosine tri-phosphate re-synthesis [3]. Since oxygen consumption is the product of cardiac output and arterio-venous oxygen content difference, the rate at which oxygen is delivered to muscles depends on its content in blood and on blood flow rate, with the latter being dependent on pressure gradient and the resistance to blood flow. In turn, flow resistance is determined by systemic vascular hindrance (i.e., the contribution of vascular geometry to flow resistance) and by blood viscosity. Vascular geometry is usually considered to be the main determinant of blood flow resistance with vasomotor tone playing a central role; the impact of blood rheology (e.g., apparent blood viscosity) is very often ignored or underestimated [2,41].

Considering only apparent blood viscosity as the sole hemorheological factor affecting hemodynamic resistance is a reductionist approach [11]. As demonstrated by using intravital microscopy on isolated vessels or whole perfused organs, each determinant of blood viscosity (e.g., RBC deformability, RBC aggregation) may affect blood flow resistance [2]. However, few studies have investigated the relationships between blood rheological parameters and whole body hemodynamic responses to exercise in humans. Toth, et al. [45] compared some blood rheological and hemodynamic parameters between healthy subjects and patients with ischemic heart disease at rest and at peak exercise. Although they found no significant difference in resting hemodynamic parameters between the two groups, patients with ischemic heart disease had higher hematocrit, plasma viscosity and blood viscosity. At peak exercise, these patients had higher hematocrit, plasma viscosity and blood viscosity and a lower cardiac index, possibly explaining their lower relative aerobic capacity [45]; evaluation of RBC rheologic properties was not part of this prior study [45].

While the present literature does not directly address exercise-metabolism-rheology relations, it has been suggested that blood fluidity and RBC deformability may play an important role in aerobic physical fitness by facilitating muscle perfusion [6,15]. The present study was designed to measure the hemodynamic, hemorheological and metabolic responses during exercise in sportsmen, and to evaluate relationships between these variables, thus exploring whether blood rheology may play a role in hemodynamic and metabolic adjustments during exercise. Since training levels may influence many aspects of blood rheological and hemodynamic responses, we focused mainly on a group of moderately trained sportsmen with comparable fitness levels.

## **2. Materials and Methods**

### *2.1. Protocol*

All subjects were informed of the procedures and purposes of the study and all gave their written informed consent. The protocol was in accordance with the guidelines set by the Declaration of Helsinki and was approved by the Ethics Committee of the Academics Hospitals of Pointe-à-Pitre.

Ten male subjects (age  $20.8 \pm 1.1$  yrs, mean  $\pm$  SD) who trained regularly in several sports such as sprint running, football, basket-ball, racket sports, water sports and swimming were involved in the study. The duration of sports practice ranged between 8 and 12 hours per week and clinical interviews did not reveal any signs of overtraining. None of the subjects were involved in high level (i.e. national or international) competition and none of them trained specifically in endurance sports. Previous results showed that their maximal oxygen consumption ( $VO_2\text{max}$ ), as determined during a progressive and maximal exercise cycling test (3 min warm-up at 60 W followed by increments of 30 W/min until  $VO_2\text{max}$  was reached), ranged between 45-51 ml/kg/min as determined for 7 of the 10 subjects in the present study.

After a resting-acclimation period of 10 minutes, the subjects underwent a sub-maximal cycling exercise protocol consisting of three nine minute successive levels of 50, 100 and 150 W. Pedalling speed remained constant at 70 RPM during each period with the different levels obtained by varying the cycling resistance. Exercise was then stopped and the subjects had a recovery period of 10 min in the same seated position without pedalling. Hemodynamic parameters and oxygen uptake ( $VO_2$ ) were continuously recorded and a mean value was calculated at the 6<sup>th</sup> min of each level for resting, three levels of exercise and recovery. Also at this six minute point, ear oxyhemoglobin saturation ( $SaO_2$ ) and arterial pressures were measured, and five ml of blood was sampled (EDTA, 1.5 mg/ml) from an antecubital vein for hemorheological measurements.

## *2.2. Hemodynamic parameters*

A validated bioimpedance device using four electrodes was used to non-invasively measure stroke volume (SV) (Physioflow, Manatec type PF05L1, Paris, France). The bioimpedance method of cardiac output ( $Q_c$ ) determination uses changes in transthoracic impedance during cardiac ejection to calculate SV. In addition, two additional electrodes were used for heart rate (HR) determination [8,37,44] based on the R-R interval duration determined using the first derivative of the electrocardiogram (ECG).  $Q_c$  was calculated as the product of HR and SV. Systolic and diastolic blood pressures were manually measured at the brachial artery by the same experienced clinician and mean arterial pressure (MAP) was then calculated as: diastolic pressure + 1/3 pulse pressure; systemic vascular resistance (SVR) was calculated by dividing MAP by  $Q_c$ .

## *2.3. Oxygen uptake, oxyhemoglobin saturation and arterio-venous oxygen content difference*

Oxygen uptake ( $Q_c$ ,  $VO_2$ ) was measured using a breath-by-breath automated exercise metabolic system (Vmax 229, Sensor Medics, USA), with non-invasive pulse oximetry (model 3740, Datex-Ohmeda, Helsinki, Finland) used to assess oxyhemoglobin saturation ( $SaO_2$ ). The arterio-venous oxygen content difference (a-v) $O_2$  was calculated using the Fick equation (i.e.,  $VO_2$  divided by  $Q_c$ ) as previously reported [27,38].

#### *2.4. Hemorheological-hematological measurements and systemic vascular hindrance*

Blood was stored at 4°C until tested and all hemorheological measurements were carried out within 4 hours following venipuncture to avoid rheological alterations [48]. Apparent viscosity of blood at 25°C for the as-drawn samples ( $\eta_b$ ) was measured at a shear rate of 225 s<sup>-1</sup> using a cone/plate viscometer (Brookfield DVII+ with CPE40 spindle, Brookfield Engineering Labs, Natick, MA). Hematocrit (Hct) was measured by the micro-method (16,000 g, 10 min, 25°C). RBC deformability, as an Elongation Index EI, was determined at a shear stress of 3 Pa by laser diffraction analysis of dilute cell suspensions using the Laser assisted Optical Rotational Cell Analyzer (LORCA, RR Mechtronics, Hoorn, The Netherlands) operating at 37°C. At constant shear stress, EI increases with increasing cell deformation [24]. Note that blood flow in arteries, arterioles and capillaries causes shear stresses up to about 5 Pa [26], and hence we elected to use a shear stress of 3 Pa for RBC deformability measurements. RBC aggregation at stasis, as an Aggregation Index AI, was determined at 37 °C using the LORCA for blood samples whose Hct was adjusted to 40% by appropriate combination of RBC and autologous plasma; AI increases with the extent of aggregation. Systemic vascular hindrance, a parameter reflecting the contribution of geometric factors to SVR, was calculated by dividing SVR by  $8\eta_b$  and multiplying it by  $\pi$  [9].

#### *2.5. Statistical analysis*

Results are presented as mean  $\pm$  SD. The effects of exercise on hemodynamic, hemorheologic and metabolic parameters were investigated using a one-way analysis of variance with repeated measures, with the Spearman correlation used to investigate relationships between these parameters. Tukey post hoc tests were used when necessary to locate the differences. The significance level was defined as  $p < 0.05$ . Analyses were conducted using Statistica (v. 5.5, Statsoft, USA).

### **3. Results**

#### *3.1. Hemodynamic parameters*

As shown in the Table 1, exercise increased HR and  $Q_c$  above resting values which remained higher than resting during recovery. SV also increased at 50, 100 and 150 W compared to resting value and return to baseline during recovery. MAP measured at 50 W was not significantly different from resting level, but increased above baseline at 100 and 150 W and remained elevated during recovery. SVR decreased below baseline from 50 W to 150 W, and tended to be lower than resting during recovery ( $p = 0.09$ ).

#### *3.2. Oxygen uptake, oxyhemoglobin saturation and arterio-venous oxygen content difference*

These parameters are presented in Table 2:  $VO_2$  and (a-v) $O_2$  increased with exercise intensity and returned to resting levels during recovery, with no significant change in Sa $O_2$  observed during exercise or recovery.

#### *3.3. Hemorheological-hematological measurements and systemic vascular hindrance*

As shown in Figs. 1A and 1D, Hct and EI increased during exercise and remained above resting levels during the recovery. Blood viscosity (Fig. 1B) measured at 50 and 100 W was not significantly different from the resting value but increased above the resting value at 150

W and remained elevated during recovery. RBC aggregation (AI, Fig. 1C) decreased below the resting value at 50 W and then returned to the resting level during the following exercise steps. Systemic vascular hindrance decreased progressively during the three exercise steps and remained below the resting level in the recovery period (Fig. 2).

### 3.4. Correlations

A significant negative correlation was found between EI and SVR ( $r = -0.35$ ,  $p < 0.01$ ), with positive correlations between EI and  $VO_2$  ( $r = 0.37$ ,  $p < 0.01$ ) and EI and (a-v) $O_2$  ( $r = 0.35$ ,  $p < 0.01$ ). No significant relationship was found between blood viscosity and SVR ( $r = -0.05$ ,  $p > 0.05$ ). We also calculated the change in blood rheological properties, vascular resistance and (a-v) $O_2$  difference between rest and each workload (i.e. 50, 100 and 150 W), and then tested several correlations between the change of (a-v) $O_2$  and the changes of the other variables. We found no significant relationships between the changes between rest and 50 W or between rest and 100 W. In contrast, there was a positive correlation at 150 W between the changes of (a-v) $O_2$  and blood viscosity ( $r = 0.66$ ;  $p < 0.05$ ). Finally, to test the effects of Hct on blood viscosity, we tested the correlations between the two parameters at each exercise level: a significant relationship was found at 150 W ( $r = 0.87$ ;  $p < 0.05$ ) but not at the two lower levels of exercise.

## 4. Discussion

The present study investigated the hemorheological, hemodynamic and metabolic responses in sportsmen performing a submaximal exercise protocol. We observed that hemorheological parameters, notably blood viscosity and RBC deformability, were influenced by exercise; our results suggest that these changes could play a role in the hemodynamic and metabolic adjustments.



As anticipated [43],  $Q_c$ , HR, SV and MAP increased with exercise intensity and reached their highest values at the maximum exercise level of 150 W (Table 1). The increase of  $Q_c$ , together with the widening of (a-v) $O_2$ , is consistent with the increase of  $VO_2$  with exercise intensity [4].

Blood pressure tends to increase during graded exercise, yet MAP remained unchanged at 50 W in spite of the increased  $Q_c$  (Table 1). Since MAP is proportional to the product of  $Q_c$  times SVR, this suggests the presence of a compensatory decrease of SVR. As indicated in Fig. 1B, blood viscosity was not elevated at 50 W and thus the decrease of SVR at 50 W was solely related to the decrease of systemic vascular hindrance, thereby indicating marked changes of vascular geometry (i.e., vasodilation) at this exercise level. However, at the two higher levels of exercise, MAP increased above the resting value, indicating a greater rise of  $Q_c$  than the decrease of SVR [4], with the decrease of SVR associated with a further decrease of systemic vascular hindrance (Table 1, Figure 2).

As suggested by many authors, the progressively increased vasodilatation with exercise is probably related to metabolic mechanisms in response to tissue hypoxia and to the release of vasodilator substances such as ATP, potassium or hydrogen ions [10,31,40]. Although blood viscosity was increased by about 10% above the resting value at 150 W (Fig. 1B) due mainly to the increased Hct at this exercise level (Fig. 1A), SVR was below the resting value, indicating that the small hematocrit-mediated increase of blood viscosity did not, by itself, counteract the decrease of systemic vascular hindrance. The lack of significant correlation between SVR and  $\eta_b$  supports this conclusion.

Nitric oxide (NO) elicits vasodilation, with fluid shear stress at the vessel wall being one of the main stimuli of NO production by endothelial cells [52]; wall shear stress is effective for both acute activation of nitric oxide production and for the chronic expression of endothelial

nitric oxide synthase [20,46]. Increased wall shear stress therefore stimulates NO release, leading to vascular relaxation and decreased systemic vascular hindrance. Since wall shear stress can be estimated as the product of blood viscosity times shear rate, the increase of  $Q_c$  and flow rate during exercise would be expected to increase shear stress, thereby contributing to the decrease of systemic vascular hindrance (Fig. 2). The elevated blood viscosity at 150 W (Fig. 2B), combined with the increased  $Q_c$ , could have generated a greater shear stress than during the previous exercise steps, with a greater contribution to the decrement of SVR at that exercise intensity. Therefore, it could be argued that increased blood viscosity may be viewed as beneficial during exercise by eliciting vasodilation and greater tissue perfusion; the correlation found between the change from rest to 150 W of blood viscosity and of  $(a-v)O_2$  supports this view. It is interesting to note that previous studies employing blood substitutes have demonstrated that an elevated viscosity elicits a vasodilatory response due to increased shear stress [39,47]. In addition, Tsai et al. [47] reported that increased plasma viscosity stimulates nitric oxide generation by the endothelium and decreases vascular resistance.

Although Hct increased above the resting value at 50 and 100 W (Fig. 1A), blood viscosity did not significantly change at these times (Fig. 2B). This unchanged viscosity was most likely due to the relatively small increase in hematocrit (i.e., 1 or 1.5 hematocrit units) and the slight improvement of RBC deformability (Fig. 1D). At 150 W, the much more pronounced increase in hematocrit (i.e., 2.5 or 3 hematocrit units) was not compensated for by the slight improvement of RBC deformability, and hence there was a significant increase of blood viscosity at that level. The mechanisms responsible for the transient decrease of RBC aggregation during graded exercise (Fig. 1C) are not yet understood and require further studies.

Few studies have investigated RBC aggregation in response to exercise and the results are not in agreement: some studies describe no change [13], an increase [19] or a delayed

decrease of RBC aggregation [51]. The reasons for these various results are unclear, but may be related to: 1) the population tested (i.e., sportsmen in the present study, very well endurance trained subjects in [13], sedentary and endurance trained subjects in [19] and sedentary subjects in [51]); 2) the exercise performed (sub-maximal cycling exercise in the present study of less than 30 min duration, ramp exercise test conducted to VO<sub>2</sub>max in [13], sub-maximal cycling test of 3 hrs duration in [19] and a supra-maximal Wingate exercise test in [51]); 3) the technique used to measure aggregation (backscattered technique in our protocol with light transmission used in [13,19,51]). Note that aggregation at 100 W, 150 W and during recovery did not differ from the resting level, suggesting that RBC aggregation probably played only a minor role in the regulation of SVR during this exercise.

It is well known that RBC deformability is an important determinant of flow resistance in blood vessels with dimensions similar to the size of RBC [2]. Entrance of RBC into true capillaries is characterized by a dramatic increase in flow resistance [28,29], with the magnitude of the increase dependent on RBC deformability; RBC transit times through the microcirculation are prolonged when suspensions of RBC rigidified by glutaraldehyde treatment are perfused [30]. Although the presence of rigid RBC may disturb the microcirculation [30,42], they may also cause hemodynamic abnormalities in larger vessels [29]. RBC deformability increased by seven to eight percent in the current study (Fig. 1D), suggesting the possibility that this improvement may have contributed to the decrease of SVR. This suggestion is partly supported by the significant negative correlation found between RBC deformability and SVR ( $r = -0.35$ ,  $p < 0.01$ ). In addition, Parthasarathi and Lipowsky [34] reported that impairment in RBC deformability may adversely affect capillary recruitment and physiological mechanisms that ensure adequate delivery of oxygen to tissue. A decrease of RBC deformability may result in reduced capillary perfusion and O<sub>2</sub> delivery to

tissues [17]. Our results lend support to this concept since we found a significant positive correlation between RBC deformability and both  $(a-v)O_2$  and  $VO_2$ .

The effects of exercise on RBC deformability have been examined in several studies, with most reporting a decrease [5,19,21,22,32,36,50,51]. Correlations between the increment in blood lactate level during exercise and the decrement in RBC deformability have been shown [5], suggesting that lactate could be responsible for the decrease of RBC deformability. Recently, we have reported a significant positive correlation between RBC monocarboxylate transporter (MCT-1) activity and RBC rigidity: MCT-1 is a co-transporter lactate/ $H^+$  [14] and is responsible of about 90% of the total lactate uptake by RBC [16]. RBC MCT-1 could therefore play a role in the regulation of RBC rheology.

It is notable that rather than finding a decrease in deformability with exercise, the present study and others [12,23,49] indicate an increase of RBC deformability during exercise by trained subjects in spite of elevated blood lactate concentrations. The increase of RBC deformability found by Connes et al. [12] was around 6 percent, which is quite close to the seven to eight percent found in the present study. Although this percent increase is not large, it is in marked contrast to other reports of RBC deformability decreases ranging from 4% to 100% [7,18,21,36]. We have investigated the effects of lactate anion on blood rheology in trained and untrained subjects and found a strong effect of training: RBC deformability decreased with increased lactate concentration in untrained subjects but increased in trained athletes [12].

Another possible explanation for the differing effects of exercise on RBC deformability relates to the blood oxygen saturation level during exercise. Closer evaluation of the results obtained in the study of Connes et al. [12] indicated two different responses: 1) unchanged deformability in subjects who exhibited a phenomenon called exercise induced hypoxemia (i.e., EIH, an impairment of blood gas homeostasis with more than a 4% decrease of  $SaO_2$

during exercise); 2) increased deformability in subjects who did not exhibit EIH. In the current study *none* of the subjects had EIH, and thus the increase of deformability was in the absence of hypoxia (Table 2, Fig. 1D). Therefore, it seems that changes in RBC rheological properties during exercise are dependant on the fitness level of subjects and also on their “hypoxemic status”.

After exercise stopped,  $(a-v)O_2$  and  $VO_2$  rapidly returned to resting values despite the persistent elevation of  $Q_c$ ; the elevated  $Q_c$  during recovery was attributable to an increased HR reflecting high circulating catecholamine levels. Since SVR tended to be lower than resting during recovery, the increased MAP was due to the elevated  $Q_c$ ; the low SVR reflects the continuing low systemic vascular hindrance indicating vasodilatation. The “mismatch” between the return of  $VO_2$  to baseline, the elevated  $Q_c$ , and the continued decrease of systemic vascular hindrance suggests that blood flow during recovery is not directly regulated by the need of oxygen in the exercised muscles [1]. This hyperemic response during recovery is likely linked to locally released factors, such as ions and metabolites, but may also be influenced by the elevated blood viscosity due to higher hematocrit. As mentioned above, both elevated  $Q_c$  and blood viscosity favor high wall shear stress and the release of nitric oxide, and thus rheological factors may contribute to the recovery process following cessation of exercise.

A potential limitation of the present study resides in the approach to data analysis that did not explicitly consider the complexity of hemodynamic changes in response to exercise. The changes we observed for the SVR are not only the results of decreased systemic vascular hindrance and/or changes in RBC deformability/blood viscosity. Rather, additional factors are likely involved: 1) the redistribution of  $Q_c$  occurring during exercise [25,33]; 2) the intensity-dependent constriction in non-active vascular beds; 3) the vascular reactivity differences

between upper and lower extremities [35]. Nevertheless, the experimental approach used in the present study has been used by some investigators during exercise stress or in patients [41,45], and does provide interesting information about hemodynamic changes and their relationships with blood rheology. Our results are in agreement with the previous classical descriptions of hemodynamical responses during exercise, and our results also support the idea that blood rheology, and particularly RBC deformability, might play a role in cardiorespiratory and hemodynamic adaptations during exercise in sportsmen. Additional studies focusing on higher exercise intensity will be necessary to confirm this suggestion, and to determine the extent to which our results are applicable to the general population.

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**Table 1:** Hemodynamic parameters; values are means  $\pm$  S.D.

|  | Rest            | 50 W             | 100 W            | 150 W            | Recovery        |
|--|-----------------|------------------|------------------|------------------|-----------------|
| HR (beats/min)                               | 78 $\pm$ 12     | 104 $\pm$ 10*    | 124 $\pm$ 11*    | 153 $\pm$ 19*    | 97 $\pm$ 16*    |
| SV (l)                                       | 0.10 $\pm$ 0.02 | 0.11 $\pm$ 0.02* | 0.11 $\pm$ 0.02* | 0.12 $\pm$ 0.02* | 0.10 $\pm$ 0.02 |
| <i>Qc</i> (l/min)                            | 7.5 $\pm$ 1.5*  | 11.5 $\pm$ 1.5*  | 14.1 $\pm$ 2.3*  | 18.7 $\pm$ 2.9*  | 9.6 $\pm$ 2.0*  |
| MAP (mmHg)                                   | 94 $\pm$ 6      | 97 $\pm$ 8       | 106 $\pm$ 9*     | 114 $\pm$ 6*     | 104 $\pm$ 7*    |
| SVR (dynes/cm <sup>5</sup> /m <sup>2</sup> ) | 2043 $\pm$ 451  | 1359 $\pm$ 299*  | 1219 $\pm$ 270*  | 978 $\pm$ 200*   | 1772 $\pm$ 439  |

\*different from resting value ( $p < 0.05$ ).

**Table 2:** Oxygen uptake, oxyhemoglobin saturation and arterio-venous oxygen content difference; Values are means  $\pm$  SD.

|                                 | Rest            | 50 W             | 100 W            | 150 W            | Recovery        |
|---------------------------------|-----------------|------------------|------------------|------------------|-----------------|
| VO <sub>2</sub> (l/min)         | 0.21 $\pm$ 0.05 | 0.71 $\pm$ 0.07* | 1.12 $\pm$ 0.08* | 1.63 $\pm$ 0.10* | 0.23 $\pm$ 0.09 |
| (a-v)O <sub>2</sub> diff (vol%) | 3.0 $\pm$ 1.0   | 6.3 $\pm$ 1.2*   | 8.2 $\pm$ 1.2*   | 8.9 $\pm$ 1.5*   | 2.5 $\pm$ 1.1   |
| SaO <sub>2</sub> (%)            | 98 $\pm$ 1      | 98 $\pm$ 1       | 99 $\pm$ 1       | 97 $\pm$ 2       | 99 $\pm$ 1      |

\*different from resting value ( $p < 0.05$ ).

## Figure captions

Fig. 1. A: Time course of venous hematocrit; B: Time course of blood viscosity; C: Time course of red blood cell aggregation; D: Time course of red blood cell deformability, \*different from resting value ( $p < 0.05$ ). Measurements were made at rest, at the 6<sup>th</sup> minute point of each exercise step and at 10 min recovery.

Fig. 2. Time course of systemic vascular hindrance, \*different from resting value ( $p < 0.05$ ). Measurements were made at rest, at the 6<sup>th</sup> minute point of each exercise step and at 10 min recovery.

Figures 1A, 1B, 1C and 1D

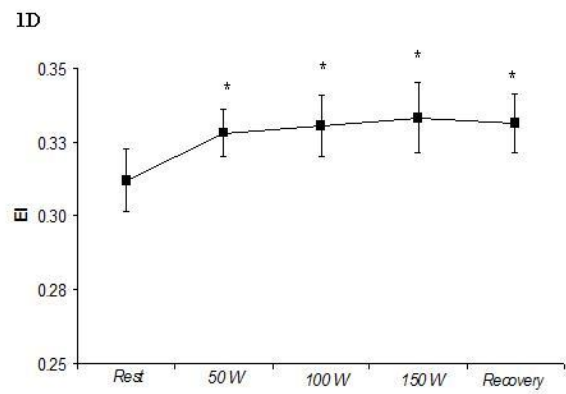
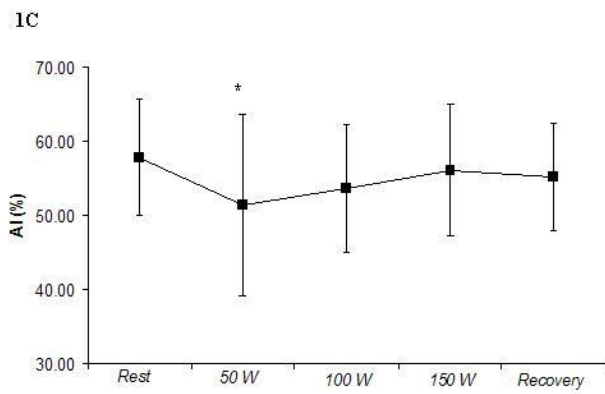
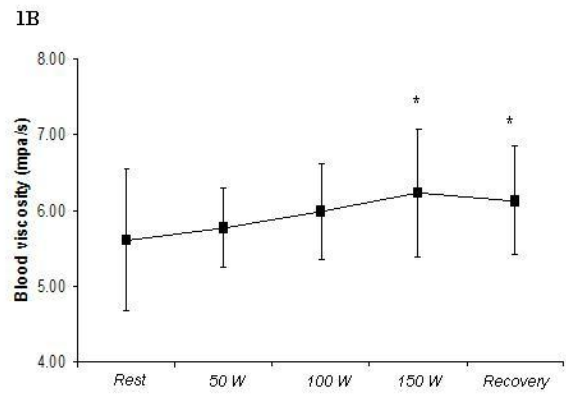
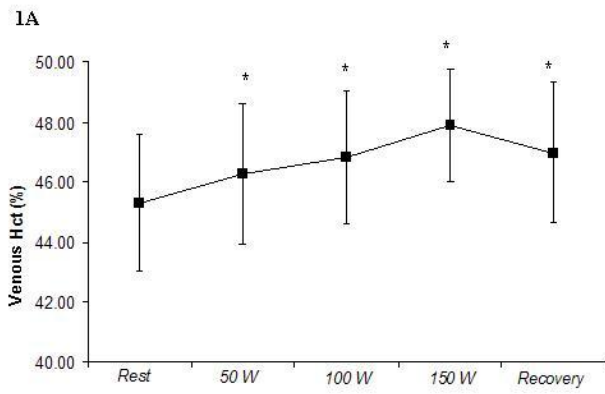


Figure 2

