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Protein C System Activity after Physical Exercise: Possible Thrombophilic Implications

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Abstract

The role of influence on protein C anticoagulant system and on PC deficiency-related thrombophilic risk due to strenuous physical exercise is still under discussion. In order to investigate the modification of the protein C anticoagulant pathway after strenuous exercise, we measured ProC® Global assay, a protein C activity dependent clotting time, in 10 healthy subjects before and immediately after maximal treadmill exercise, and at 5, 15, 30 and 60 min in the recovery phase. The most evident change was a shortening of ProC® Global clotting time from a basal values of 123 sec to 84 sec at 30 min in post exercise.

Our study shows that the coagulation unbalance observed after strenuous exercise and with no consequence in healthy individuals with normal PC level, could increase the thrombophilic risk in silent carriers of major defects of the protein C system and occasionally trigger an episode of deep vein thrombosis.

Keywords: ProC® Global; Prot C unbalance after physical exercise; Physical exercise and thrombophilic risk

Cases and Methods

Among the effects of physical exercise on coagulation, the influence on protein C anticoagulant system and on PC deficiency-related thrombophilic risk are still controversial.

Several studies describe the effect of physical activity (PA) on the coagulation system [1]. In particular, it is well known, that PA determines a shortening of the activated partial thromboplastin time (APTT) and an increase of the factor VIII [2]. On the other hand, little is known about the variations of the anticoagulant determinants and specifically of Protein C (PC) system, during PA and in the subsequent recovery phase. Sporadic cases of venous thrombosis in early recovery after exercise were reported in athletes bearing major defects of PC anticoagulant system [3]. Other authors are still debating whether and how PA can trigger deep vein thrombosis (DVT) in subject's carriers a thrombophilic condition [4].

In this study, in order to evaluate whether an unbalance in the PC system, induced by PA, could account for the triggering of thrombosis in subjects with silent major defects of PC system, we analyzed the variations of the PC system in healthy subjects performing a treadmill procedure [5]. In particular, we measured PC concentrations in these subjects before and after a physical exercise and in the subsequent recovery phase (up to one hour). Our purpose is to validate a procedure able to predict possible DVT episode in subjects carrying major defects of the PC system.

To this aim, ten healthy volunteers (six males and four females, age 18-43 y; median: 28 y) endurance trained, were enrolled. All subjects avoided aspirin, anti-inflammatory drugs, and free radical scavengers for two weeks before the test. Normal plasma levels of antithrombin, PC and protein S (PS), activated protein C (APC) resistance and homocysteine (data not shown) were observed. All participants gave informed consent to the study that was performed according to the Helsinki II Declaration and was approved by the Ethics Committee of University of Naples "Federico II".

The study was conducted in the morning after an overnight fast in a quiet room at a constant temperature of $21 \pm 1^\circ\text{C}$. The treadmill procedure is described in detail elsewhere [6]. In essence, subjects performed a graded treadmill exercise starting at 3 Km/h with a 3% uphill inclination and 3% grade increases every two minutes. Electrocardiographic features and arm blood pressure were continuously monitored during exercise. Subjects exercised until they reached their maximal heart rate-targeted endpoint. Blood samples were withdrawn before, immediately after exercise (i.e., peak value), and 5, 15, 30 and 60 minutes after exercise (early recovery phase). Plasma was obtained from blood samples collected in sodium citrate and centrifuged for 20 min at 3500 rpm. Plasma aliquots were stored at -70°C until assayed.

Protein C activity-dependent clotting time (PCAT) was measured on all blood samples by ProC® Global test (Siemens Healthcare, USA).

APTT (Pathromtin SL, Siemens Healthcare, USA) was also assayed with a BCS instrument.

Data analysis was performed with the GraphPad Prism version 3.0 for Windows (GraphPad Software Inc., San Diego, CA). All results are shown as medians with interquartile ranges. For data comparison was used the non-parametric Friedman test with Dunn's post-test. Differences were considered significant at $p < 0.05$.

In **Table 1**, APTT values decreased slightly, i.e., from a basal value of 37.5s (34-44.5) to 34.5s (32.5-41) and to 35.5s (32-38.5) at 15 and at 30 min post-exercise respectively. On the other hand, the Pro C values progressively dropped from a median basal level of 123s (115-152) to 84s (78-90) at 30 min post-exercise and turned versus baseline levels at 60 min post-exercise.

Table 1 Time course of APTT and PRO C test in subjects undergoing a maximal treadmill test. Sampling and assays were done before exercise, at peak (immediately after ending exercise) and at 5, 15, 30, 60 min after (recovery phase).

| | Basal | Peak | 5' | 15' | 30' | 60' |
|------------|-------------|-------------|------------|------------|------------|-------------|
| APTT (Sec) | 37.5 | 36 | 36 | 34.5 | 35.5 | 36.5 |
| | 34.0-44.5 | 33.0-43.0 | 32.5-41.5 | 31.5-41.0 | 32.0-38.5 | 32.0-41.0 |
| | 34.0-56.0 | 30.0-47.0 | 30.0-45.0 | 30.0-48.0 | 30.0-47.0 | 31.0-47.0 |
| ProC (Sec) | 123 | 109 | 101.0* | 87.0** | 84.0** | 115 |
| | 115.0-152.0 | 103.0-126.0 | 88.0-112.0 | 74.0-96.0 | 78.0-98.0 | 109.0-135.0 |
| | 104.0-178.0 | 89.0-164.0 | 79.0-131.0 | 70.0-115.0 | 75.0-110.0 | 65.0-167.0 |

Values are maintained as median, interquartile range and range

Comparison with basal levels: * $p < 0.05$ ** $p < 0.001$

Discussion

According to some studies, post-exercise hypercoagulability is counterbalanced by hyperfibrinolysis whereas other investigators report that the increased level of fibrinolytic activity falls sharply during the recovery phase, and that activation of coagulation persists [7].

Our results show that the maximal hypercoagulability develops not during exercise but progressively during the first 30 min of subsequent recovery phase, peaking at 30 minutes.

The exercise-related hypercoagulability develops during recovery phase to an extent greater than at exercise peak, likely as consequence of hemorheological variations occurring from exercise to resting phase.

It still controversial whether post-exercise hypercoagulability, after a maximal treadmill, may induce or enhance a thrombophilic risk [8,9]. In this study we showed that a temporary imbalance of PC system occurs before 30 minutes, probably this phenomenon may be compensated in healthy subjects by a normal anticoagulant level.

The alteration of protein C levels and activity may be easily related to an endothelial dysfunction due to physical exercise.

From a pathophysiological point of view the reported alteration may have several implication in a prothrombotic way: the protein C activity in fact is not only associated to inactivation of factor V and factor VIII but also to hypofibrinolysis because the role of thrombomodulin.

So the prothrombotic state may be associated to clinical thrombosis by two different way an acquired thrombophilia because the reduced action of protein C and an induced hypofibrinolysis.

More over our results suggest that the subjects with silent major defects of the PC system, as those described in previous report [3], could be particularly vulnerable to hypercoagulability during the early recovery phase. A possible explanation is that, in this phase the coagulation wave, amplified by the slowing of blood flow, could overwhelm the significantly reduced anticoagulant potential and trigger occasionally an episode of DVT, depending on the association to other circumstantial/environmental factors [10].

Conclusion

The knowledge about the changes in coagulation status should be further examined and also further studies involved

in physical training will definitely be essential in future to better understand the complex mechanism of coagulation balance. Therefore, the possibility to evaluate the PC system activity together with the treadmill test in subjects that perform activity might represent a screening strategy to predict possible DVT episode in individuals carrying major defects in the coagulation cascade.

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