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Endothelial Reprogramming in Sports Traumatology: Role of the Widespread Neuro-Immuno-Endocrine-Endothelial System

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Featured Application: This paper considers the influence of sport on the human organism: "Sport as prophylaxis", "Sport as therapy", "General psycho-physiological connections in sport", "Athlete functional evaluation", and "Sport fitness". In particular, good endothelial function allows greater physique-athletic performances, so the endothelial functional evaluation can be introduced among the parameters tested in "Athlete functional evaluation". Under the theme "Endothelial reprogramming in sport activity", it emerged that a regular physical activity can cause modifications, including stable growth of endothelial vasodilating activity through NO production; a decrease of ET-1 levels; an increase of plasma NO/ET-1 ratio. These modifications can also be verified in elderly people, those with BMI > 25, and in menopausal women. Sport can protect from atherosclerosis, reduce the risk of atherothrombotic events in BMI > 25 people, and represent an alternative therapy of cardiac preservation in menopause. The neuroimmunoendocrine diffused system is the present pattern forming an integrated answer to the stresses. Analyzing, investigating, enriching, and coordinating the current knowledge on E. accumulated, we observe that it also complies with the same standards. Therefore, we propose the concept of the neuro-immuno-endocrine-endothelial diffused system as the new pattern forming an integrated answer to the stresses, offering a completer definition of the system directing omeostasys. So, we propose total plasma antioxidant capacity reckoning as a test that can be added at the routine-tests of sports fitness for those over 30 years of age, since coronary artery silent disease prevalence is higher for this population and endothelial function is a useful coronary artery disease biological marker.

Abstract: This paper deals with the role of the widespread neuro-immuno-endocrine-endothelial system in sport traumatology. The aim of this work is to see if sport or regular physical activity is able to reprogram the endothelium, to advance the new concept of neuro-immuno-endocrine-endothelial diffused system, and to introduce in the practice of sport medicine a new test in the fields of "Athlete functional evaluation" and "Sports fitness". The first object of this paper is to see whether sport or regular physical activity can change the functional structure of the endothelium. The second goal is to frame under a general view the knowledge and individual lines of research on endothelium, to highlight what we believe is, in the organization of homeostasis, the location of this 'organ', namely in the neuro-immune-endocrine system spread.

Keywords: endothelium; neuro-immuno-endocrinology; physical activity

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1. Introduction

The concept of neuro-endocrine system, matured in the 1960s [1,2], is a fundamental anatomo-physiological reality.

Endocrinology began in 1902 [3] with the discovery of a duodenal hormone, secretin. It was thanks to studies carried out in the seventies on gastrointestinal hormones (O.G.I., which demonstrated their presence in central and peripheral neurons), and to the concept of Paraneuroni introduced by Fujita (in which the idea of the common embryological origin was abandoned), that the neuro-endocrine system was renamed as a diffuse neuro-endocrine system. The neuroendocrine system is classically defined as an organized set of cells with neural determination, which produce hormones or neuropeptides, a biochemical-physiological reality [4].

Adrenaline, angiotensin II, vasopressin, and insulin increase (by means of their specific receptors located in E.) the synthesis of ET-1; atrial natriuretic factor (ANF) increase the synthesis of NO, both in E. vascular and E. endocardium (EE). Glucocorticoids block the inducible NOS present in both E. and neutrophils and macrophages, and recalling that the NO released by this enzyme has cytotoxic effects, it can be concluded that glucocorticoids also exert their anti-logistic action through this mechanism.

Endothelin-1 (ET-1) is a potent peptide vasoconstrictor that plays a significant role in regulating vascular homeostasis [5]. The overexpression of ET-1 has been implicated in the etiology of atherosclerotic vascular disease [6]. ET-1 increases the plasma levels of certain hormones [7] such as ANF. To balance its effects, in fact we have seen before that ANF has vasodilatory action. Renin and aldosterone, along with NO, parathormonal, and other substances, control glomerular filtration, while the effects on pressure are discounted. Adrenaline and vasopressin then provide positive feedback.

The blood–brain barrier does not allow the passage of ET-1, yet it has been found in the cerebrospinal liquor and the receptor is present in the brain. Moreover, it is evidently synthesized by neurons. In fact, it has been found in different regions of the brain, and in particular in the hypothalamus, especially since it has been seen that it can act as a neuromodulator. It can therefore be considered a neuropeptide.

Finally, remember that E. is part of the so-called 'renin-angiotensin-aldosterone system', as it synthesizes angiotensin II, and therefore it not only has endocrine-paracrine activity, but is an inseparable part of the SE.

On the subject of "Endothelial reprogramming in sport", regular physical activity can cause changes in the endothelium: a stable increase in the endothelial vasodilatory activity of NO production; decrease in ET-1 levels; increase in the NO/ET-1 ratio. These changes can also be made in older people, those with BMI > 25, and in menopausal women. Sport protects against atherosclerosis, reduces the risk of atheroscombotic events of subjects with BMI > 25, and represents an alternative of cardioprotection in menopause. The diffuse neuro-immuno-endocrine system is the current integrated stress response model.

The beneficial effects of training on endothelial function can be mediated in several ways. The mechanisms responsible for the benefits of exercise training in terms of endothelial function may be related to either direct hemodynamic effects or secondary effects, mediated through risk factor modification [8]. Different degrees of physical exercise would correspond to as many behaviors of the immune profile in the dual component, i.e., cellular and humoral [9].

Exercise can also trigger systemic molecular pathways associated with angiogenesis and chronic anti-inflammatory action, resulting in a change in endothelial function. Its benefit depends on the type and intensity of training performed [10]. An important scientific study [11] showed that Exercise training enhances endothelium-dependent dilation in young men of average fitness. This may contribute to the benefit of regular exercise in preventing cardiovascular disease.

In light of this, we propose the determination of the total plasma antioxidant capacity, as a test to be integrated into the routine of examinations to establish sports fitness in subjects over 30 years of age. Since this population has a higher prevalence of silent coronary artery disease, endothelial function is a useful biological marker of coronary artery disease [12,13].

The accumulation of evidence has shown that there is an important correlation between endothelium and the osteo-muscular system. This relationship is important in sports traumatology. Endothelial functions are essential to ensure the proper maintenance of vascular homeostasis. Endothelial dysfunction is the hallmark of a wide range of cardiovascular diseases associated with pathological conditions towards vasoconstriction, thrombosis and inflammatory state [14]. But the proper functioning of the endothelium is also important in traumatic situations, in which it is necessary to restore the physiological conditions, thanks to the intervention of endothelial cells.

In general, the adaptation of arterial stiffness in response to exercise is mainly attributed to the increased rate of nitric oxide utilization and improved endothelial function. During exercise, an increase in shear stress leads to elevated NO production in endothelial cells which promotes vascular smooth muscle relaxation [15]. Chronic exercise alters many variables that could influence endothelial function (e.g., blood pressure, blood lipid levels), and the repeated exposure to increases in shear stress during exercise appears to be critical to exercise-induced adaptations in endothelial function. This includes stimulating alterations in endothelial gene expression which result in a more vasoprotective or "atherosclerosis-inhibiting" cell phenotype [16].

Anaerobic exercise causes excessive repetition of muscle contraction, which causes muscle damage because inflammation increases. The intensity of the exercise and the resulting DOMS induce neutrophil infiltration into the damaged tissue and muscle injury [17]. This mechanism is very important in sports traumatology. Endothelial cells constitute the inner lining of blood vessels and secrete the growth factors, controlling the recruitment of osteoclasts, osteoblasts, and bone-forming cells. The endothelial cells incorporated into these condensations form a vascular network serving as a "template" for bone mineral deposition [18]. Moreover, not only does a functional co-dependency between the osteogenesis and vessel formation occur during skeletal development, but also continuous bone remodeling and healing. This underlines the important correlation that exists between endothelium and the osteo-muscular system.

The endothelial function is positively correlated with the VO2 (work of Allen et al.), so much so that the authors conclude that the subjects that can achieve higher performances produce more NO.

During the assessment of sports activity, strenuous exercise can cause cardiac arrest, arrhythmias, and sudden death, especially in the age classes from 30 to 50 years, among which the prevalence of silent coronary heart disease is higher [19].

In this regard, we recall that Japanese authors [20] recently found a sensitivity and a specificity of the NO/ET-1 ratio in indicating a coronary heart disease, 90% and 80% respectively, compared to 80% and 78% found using the evaluation of ST segment substandard, suggesting that the NO/ET-1 ratio is a useful biological marker of coronary heart disease.

Work carried out by researchers of the Department of Internal Medicine of the University of Pisa [21], published in April, leads to the conclusion that the total plasma antioxidant capacity is usable for an assessment of endothelial function.

2. Materials and Methods

An extensive scientific literature review was conducted using Scopus, Pubmed, and GoogleScholar databases. We selected 40 publications. After approximately 25 years of research, the endothelium is still of great interest to hundreds of researchers, proving its complexity and importance.

The endothelium releases various vasoactive factors. see Figure 1. These can be vasodilatory factors see Figure 2 such as nitric oxide (NO), prostacyclin (PGI2), and endothelium derived hyperpolarizing factor (EDHF), or vasoconstrictive factors, such as thromboxane (TXA2) and endothelin-1 (ET-1) [22].

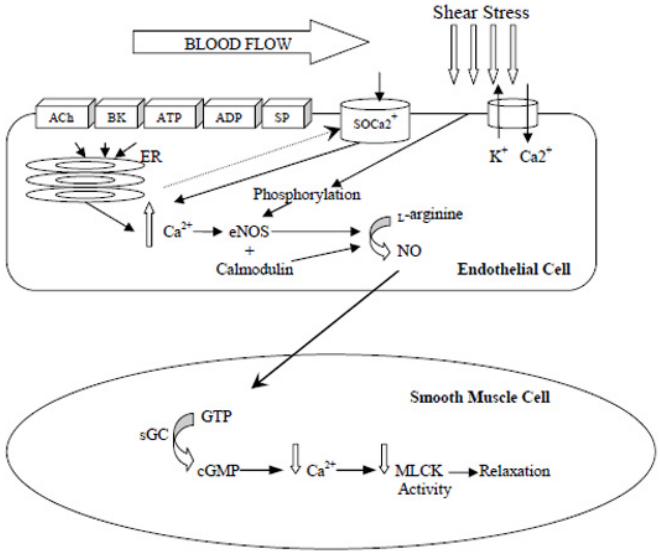


Figure 1. Endothelial nitric oxide production and it actions in the vascular smooth muscle cell.

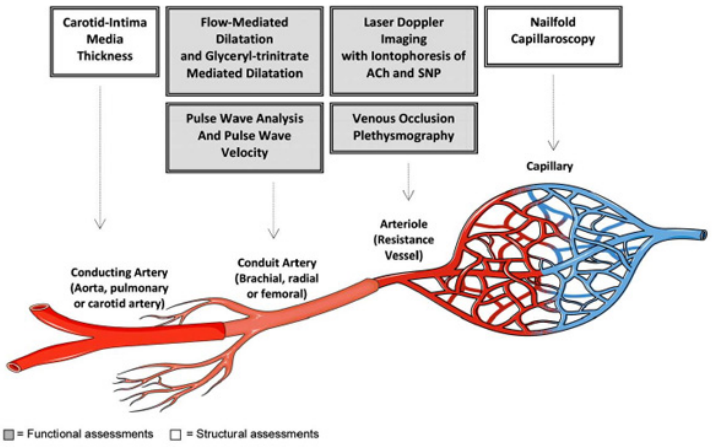


Figure 2. Endothelial function and vascular structure performed in different vascular beds.

The NO has anti-thrombotic action, while the ET-1 has pro-thrombotic action [23].

Based on these and other properties and after years of research, E. has been called into question as an "organ" involved in regulating blood flow in general [24] and coronary and renal [25] in particular, in regulating blood pressure and in the pathogenesis of certain cardiovascular diseases, such as essential arterial hypertension, heart failure, atherosclerosis, and ischemic heart disease. Can sport intervene in all this by changing the synthesis of its mediators and reprogramming it?

There is some research on rats and people. In the first study, carried out by researchers of the Cardiological Division of the University Magna Grecia of Catanzaro [26], in two groups of rats (one group subjected to exercise, the other sedentary), the consequences of the use of a stent or vascular damage induced by a balloon catheter angioplasty were evaluated.

The authors saw that the arteries isolated from the group of trained rats showed higher levels of Enos [27], and in addition had less neointimal hyperplasia and earlier orientation in the case of stent use, while they showed a lower probability of risténosi, a lower platelet aggregation, and a more favorable vascular remodeling in the case of insult induced by angioplasty.

In a third group, the administration of monomethyl-L-arginine, inhibitor of the synthesis of NO [20], prevented the expression of the benefits observed in trained rats. It should

be noted that these results agree with the physiology data recalled at the beginning of this paragraph. Moreover, before illustrating the next study, it is necessary to remember that the role of E. is mandatory [28] for the vasodilation induced by Ach (acetylcholine) [29], see Figure 3.

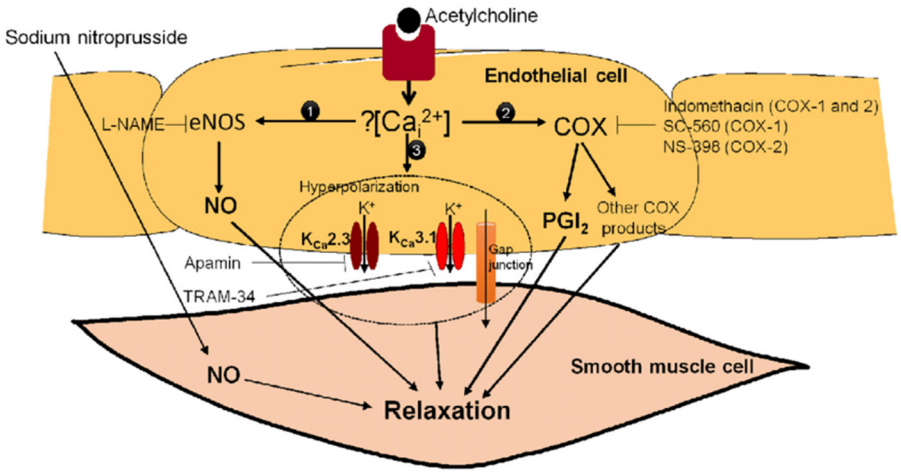
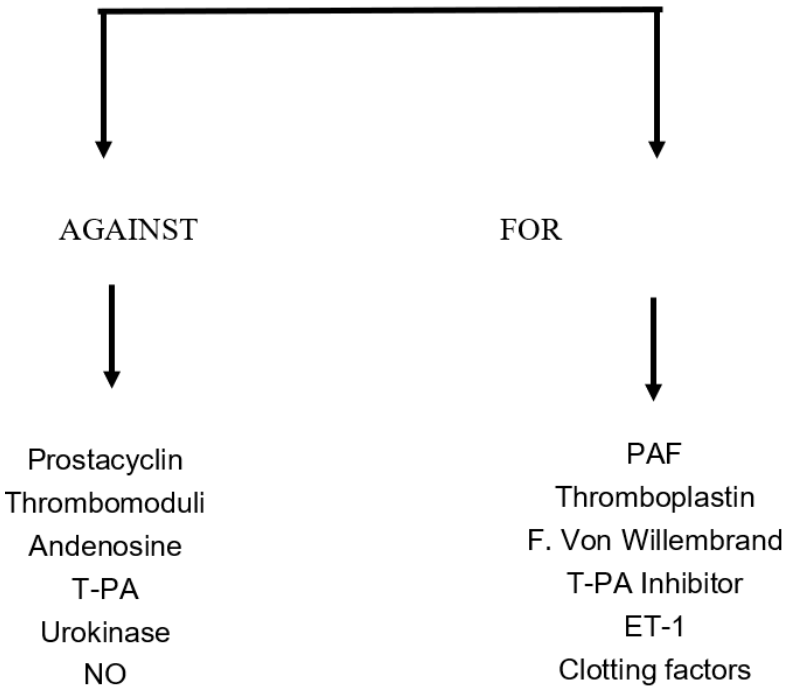


Figure 3. Endothelium-dependent vasodilation.

In 2003, other researchers [30] proposed to verify if the activity of E. is greater in athletes than in less trained subjects.

Based on the assumption that endothelial activity (see Scheme 1) can be tested by comparing the level of vasodilation induced by an E.-dependent vasodilator (Ach) to that induced by an E.-independent vasodilator (sodium nitroprusside, SNP), using the LDF (laser doppler fluxometry) technique, the authors measured the cutaneous perfusion induced by Ach in a group of athletes and a group of less trained people.



Scheme 1. Modified by (1).

Response to Ach was found to be 1.6 times greater in athletes than with $p < 0.05$ (therefore a statistically significant difference), while response to SNP was not different,

the study concluded that E. is more active in athletes. Another study carried out [31] in 28 healthy subjects calculated ET-1 concentrations before and after a cycloergometer test using the ELISA method: the mean concentrations were lower after the test ($p < 0.01$, highly significant difference).

In different recent works authors questioned whether the NO/ET-1 ratio was useful for diagnosing coronary artery disease, given that it was recently considered crucial in the early stages of atheogenesis, as well as the maintenance and progression of plaque [32].

Hence, 63 people were randomized, 38 with normal coronary and average age of 60 years, 25 suffering from stable angina and average age of 69 years.

For the determination of plasma levels of ET-1, they used the radioimmunological assay. Since they could not directly measure NO because of its short half-life, they measured plasma nitrates (NOx) whose main source during exercise turns out to be the NO. They then performed a limited physical symptom test and then calculated the NO/ET-1 ratio.

A lower ratio was obtained in the group of people with coronary disease (1.2 +/− 1.1 vs. 2.7 +/− 2.2, $p < 0.01$), and a sensitivity and specificity of the NO/ET-1 ratio was found in indicating coronary heart disease of 90% and 80% respectively, compared to 80% and 78% found using the evaluation of the substandard segment ST.

Therefore, the NO/ET-1 ratio is a useful biological marker of coronary heart disease.

It should be noted that, according to the above, exercise is able to change this ratio. Among other things, we have already seen how it is able to decrease the ET-1 and increase the expression and activity of Enos. Therefore, sport, through the modifications induced on 'E., protects from atherosclerosis.

There is an anti-pro-thrombotic balance in which E is involved.

In fact, the release, by the E., of t-PA (tissue activator of plasminogen, considered the primary defense mechanism against thrombogenesis [33] and obesity) is associated with an increased risk of atheroscopic events [34]. The authors who have approached this research have demonstrated the influence of obesity on t-PA release capacity as well as the effects of regular aerobic exercise [35].

Subject were randomized. Hence, 66 sedentary adults: 28 with BMI < 25, 22 with 25 < BMI < 30, 16 with BMI > 30. The release capacity of t-PA was evaluated in response to bradykinin-related infusion and SNP (sodium nitroprusside). A second mixed group, between obese and overweight, of 17 adults who had completed a three-month aerobic training program.

In the 66 sedentary subjects, t-PA release was 45% lower ($p < 0.01$), in both the obese and overweight groups, compared to the normal weight group. The mixed group of 17, on the other hand, after three months of training, showed an almost double release capacity (from 37.1 +/− 4.9 ng/100 mL tissue/min before training, to 65.4 +/− 6.3 ng/100 mL tissue/min after training $p < 0.01$), which was effective with that of sedentary.

These results indicate that regular physical activity can correct endothelial dysfunction present in subjects with BMI > 25 and thereby reduce their atheroscopic risk. According to our studies, in agreement with other research groups in this field, the adoption of a lifestyle has been shown to be able not only to significantly reduce the risk of developing diabetes, but also to prevent important complications that can be fatal for the patient's life or in any case strongly disabling [36]. Another published paper [21] allowed us to assess the relationship between long-term physical activity, plasma antioxidant capacity, and endothelial function in young and non-young subjects. Four groups were then compared: one consisting of 16 young athletes, one of 16 older athletes, a group of young sedentary, and finally the group of older sedentary subjects, all in good health.

Hence, as a reference, in the brachial artery, they measured, by means of high-resolution ultrasound, the E.-dependent vasodilation (VED) and the E.-independent (VEI, caused by trinitroglycerin) and plasma capacity, to eliminate peroxylic and hydroxyl radicals. These are the results: the older sedentary group reported the lowest values, on both sides (VED, antioxidant capacity), with significant differences compared to the other three groups, which were substantially homogeneous.

The authors conclude that sedentary ageing increases oxidative stress and, for this and other reasons, worsens endothelial function. However, regular physical activity can reverse this course. It also confirms that sport can reprogram the endothelium that can be considered as an "organ" capable of regulating blood flow in general, coronary and renal, and, in particular, blood pressure; as an adjuvant in cardiovascular diseases by acting on blood pressure, heart failure, atherosclerosis, and ischemic heart disease [37], see Tables 1–6.

Table 1. Endocrine/paracrine activity factors.

Weight	240 GR ABOUT
DEVELOPED AREA	27.156 mq ABOUT
Endocrine or paracrine activity factors produced	ABOUT 30
Recognized Functions	Vasomotor Immunological Heart regulator Pro-Anti-Thrombotic VFG control Angiogenetics Morphogenetics Placentation

Table 2. Cardiovascular Effects.

Cardiovascular Effects	
Heart	**Blood Vessels**
• Ionotropic and positive chronotropic effect • Coronary vasoconstriction	• Intense pressure effect

Table 3. Effects on Smooth Muscles.

Effects on Smooth Muscles
• Contraction of vascular and non-vascular smooth muscles

Table 4. Renal Effects.

Renal Effects
• Increased renal vascular resistance • Decrease in glomerular filtration, renal blood flow and glomerular ultrafiltration coefficient

Table 5. Neuroendocrine Effects.

Neuroendocrine Effects
• Increased plasma levels of ANF, renin, aldosterone, and catecholamines • Modulation of the synaptic transmission

Table 6. Promitogenic Effect.

Promitogenic Effect
• Stimulation of mitogenesis in smooth muscle cells, fibroblasts and mesangial glomerular cells

All this reinforces the hypothesis already proposed by researchers at the Institute of Human Anatomy of the University of Palermo [38], according to which it seems safe to say that the flow regulates the endothelium. "Exercise can be used as an alternative

to oral estrogen therapy for the improvement of endothelial dysfunction in menopausal women" [39]. Moreover, this study has the presumption to interpret that both exercise and estrogen therapy in menopause increase endothelial function. Our purpose is to verify if exercise can make estrogen treatment superfluous.

This study followed by 13 menopausal women aged 54 and 14 women aged 28. In the two groups, the VED in brachial artery is measured, first in rest conditions, then for the group in menopause, after an exercise carried out with VO_2 at 60% of Vmax, which lasted 45 min.

Results: VED was markedly worse at rest in the menopausal group than in the fertile age group (5.3% +/− 0.5% vs. 12.1% +/− 1.5%, $p < 0.01$), but was significantly improved after exercise (from 5.3% +/− 0.5% to 9.9% +/− 0.6%, $p < 0.01$). After administration of estrogen, at rest, the VED was equally improved ($p < 0.01$), but not further improved by performing exercise. There was no significant difference between estrogen effect and exercise effect (11.5% +/− 0.6% vs. 9.9% +/− 0.5%, $p = 0.3$).

Research data confirm that both physical activity and estrogen therapy improve endothelial function, but their action is not additive and "one is the same", especially in the context of adverse cardiovascular conditions in which there is a contraindication relating to replacement therapy.

3. Conclusions

We know that sport modifies the neuro-immuno-endocrine diffuse system. In this study, we demonstrate that endothelium can be reprogrammed through sport and exercise. It is therefore demonstrated that there is "an endothelial reprogramming in sport". Sport has a prophylactic action against coronary heart disease and the "general psychophysiological adaptations in sport", "cardiovascular adaptations to training" and "neuroimmunoendocrine behavior in sport", but such roles must be revisited in the light of the endothelium.

Therefore, the data obtained on "Neuroimmunoendocrine behavior in sport", and those on endothelial reprogramming in sport, increase the data and considerations in favor of better efficiency of the immune system in those who regularly practice physical activity. It is also true that the type of action exercised by sport on this system is an important issue that is still open. Functional evaluation of the athlete and evaluation of endothelial function are the most easily detectable parameters during functional tests. These must be provided for both amateur and professional level, so that there is more attention on the subject.

Analyzing, deepening, enriching, and coordinating the scientific literature on E., we have seen that it also meets these criteria, so we propose the concept of neuro-system-immuno-endocrine-endothelial diffuse as new model of integrated response to stress, a more complete vision of the system that governs homeostasis.

During sports, it is not uncommon to observe the appearance of a series of traumatic lesions of soft tissues, caused by the action of exogenous or endogenous forces These are caused by continuous and frequent hypersolicitations of soft tissues or by neglected microtraumas.

Often, these are diseases in which the inflammatory and painful components are very evident due to the intense reactivity of the tissues, subjected to the noxa pathogen and participation in the process of the micro-arteriovenous and lymphatic micro-circle.

For this reason, we believe that it is important to treat endothelial activity, in sport traumatology, as a process of repair to tissue damage, both as a tool of prevention and post traumatic treatment.

A new perspective exists on the influence of sport on the human body: "Sport as prophylaxis", "Sport as therapy", "General psychophysiological adaptations in sport", "Functional evaluation of the athlete", and "Sports fitness". In particular, good endothelial function allows higher physical-athletic performance, so the evaluation of endothelial function can be inserted between the parameters to be followed and to work on in the "Functional evaluation of the athlete".

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