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# Detection of exercise adaptations by different specimens analysis

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## Abstract

This literature review is a compilation of the most used methods to monitoring athletes in training and competition. Blood is certainly the best known and proven methodology and a wide range of markers can be analyzed through it, but it can be difficult to obtain, especially among athletes or people who are afraid of needles. The use of saliva is an interesting alternative especially for the easy and less invasive method of collecting. The saliva infact contains a few of compounds diffused in the plasma, like water, electrolytes, proteins, metabolites and hormones. However, new methods yet poorly understood are slowly catching on; sweat for example, may carry far more information, may provide useful biomarkers that can give indications about the physical state of the body (electrolytes, lactate, creatinine, glucose, proteins, amino acids) and may be easier to stimulate, gather, and analyze than previously thought.

**Keywords**:



## Introduction

In the last decade it has emerged the requirement to find other specimens in addition to the blood sample on which evaluated the effects of training. Blood is the most used in sport biochemistry but there are some controversial that affect the using of this biological fluid. First of all, is really stressful and usually it's difficult to take many samples during or at the end of training due to the physical activity and many athletes are afraid of needles. Furthermore, it's necessary to involve specialist that are able to take venous blood samples insofar the procedure is complicate and the sample could become useless if not properly treated. So it is merged more and more the requirement of an alternative to venipuncture that allow overcoming these problems. However there are other biological fluids that may have a story to tell. Many of these fluids are ultra-filtered blood, that have undergone a transformation by the tissues affected, while others are derived from an active transport. These fluids (i.e. saliva or swet) may contain the biomarkers that in the blood are found in different concentrations but nevertheless reflect the trend of the blood values. This,



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however, can be problematic in fluids that do not yet found a great application and for which have not been established reference ranges. New analytical techniques are needed to improve to allow use of these fluids as an alternative to blood sample; since the fluids containing biomarkers in low concentrations, it necessary to benefit of sensitive identification techniques. As research tools in sports medicine, mass spectrometry and proteomics are the best candidates. The objective of this review was to conduct an analysis of the limitations and strengths of the use of these biological fluids alternative to blood as diagnostic specimen in sports medicine.

**Non-invasive detection: saliva**

Using saliva to diagnose diseases and monitor athletes during training and competition is a less invasive and simpler alternative to blood sampling.

Compared to plasma, saliva is a hypotonic fluid that contains several compounds produced by the salivary glands (i.e. immunoglobulin A and α-amylase) as well as water, electrolytes, proteins, metabolites and hormones. The central nervous system controls saliva's production and composition, its volume and ionic/protein profile.

Blood sampling may become a difficult procedure for athletes when it is necessary perform it in different moments of the training: replace it with the venous blood sample from a fingertip can be a less stressful alternative (Nunes et al. 2006). Despite this, if it is possible, analysis of other biological fluids like saliva presents more numerous advantages: indeed, it's a non-invasive method, it does not require any special medical training, the sampling is relatively simple and have no risks (Kaufman et al. 2002).

Saliva comes mainly from three salivary glands: parotid, submandibular and sublingual. In addition, other minor glands and the gingival crevicular fluid can contribute to the formation of what is called "oral fluid" or "all the saliva" (Humphrey et al. 2001). Each salivary gland secretes a characteristic type of saliva, with different ionic concentrations and protein (Kalk et al. 2002; Denny et al. 2008). Normally, adults produce from 0.5 to 1.5 liters of saliva, but this production varies according to the stimulation. Under normal conditions, therefore without stimulation, saliva has a secretion rate of about 0.1 ml/min, with a peak of 7 ml/min when stimulated artificially (Chicharro et al. 1998). During and after the high-intensity exercise, above the anaerobic threshold, the saliva secretion decreases, especially due to the adrenergic action.

The salivary glands include acinar cells, duct cells and myoepithelial cells sprayed by capillary networks. The various grapes are connected by intercalated ducts and saliva secreted is poured into the mouth through ducts striated and excretory.

The components in plasma can be in the saliva through several processes such as ultrafiltration through junctions between secretory cells, (ions, water, and certain hormones); the selective transport through the passive diffusion of lipophilic molecules (steroid hormones); active transport through ion channels; active pumping of ions $Na^+$ entry concomitant with $H_2O$.

Saliva also contains substances that have been synthesized mainly in the acinar cells: that is to say that some components of saliva are not related to plasma concentration, but they are related to the local glandular response. Other elements such as bacteria, epithelial cells, erythrocytes, leukocytes, food debris or contamination from gingival crevicular fluid (due to gingival inflammation), may also be present in saliva.

Several factors may alter physiological or pathological saliva production both quantitatively and qualitatively, for example, chewing, psychological factors, medications, age, oral hygiene and physical activity (Chicharro et al., 1998).

Flow and composition of saliva are primarily regulated by the autonomic nervous system: serous glands by the sympathetic nervous system and sero-mucous glands both sympathetic and parasympathetic systems. The α or β-adrenergic stimulation may change amount, viscosity, concentration of protein and ion concentration of the saliva. The α adrenergic stimulation causes a calcium flow into secretory cells, causing a high protein concentration liquid. Due to the low presence of mucins, this type of saliva is low in volume and viscosity, while the results of the β-adrenergic stimulation determines a high-protein liquid, high-viscosity, low-volume and the foamy appearance.

Mucous glands only receive cholinergic stimulation. This kind of stimulation results in watery, high-volume, full of electrolytes saliva, with low viscosity and low protein concentration.

**Salivary components**

Many proteins have been identified and studied through comprehensive analytical techniques, such proline (PRP), albumin, immunoglobulins, lysozyme, lactoferrin, lactoperoxidase, the histatins and α-amylase. Apart from the action of the autonomic nervous system, there are some diseases such as cystic fibrosis, diabetes (Rao et al., 2009), cancer (Jou et al., 2010) and epilepsy that seem to alter the protein salivate. Even exercise can alter salivary protein: α-amylase (AAS) and IgA play a key role in the immune system of the oral mucosa and they increase during exercise (Levine et al. 1993).

Salivary IgA fights against the adherence and penetration of microorganisms in the mucosa and it interrupts pathogens replication. Individuals who have IgA deficiency and low salivary flow commonly have a high incidence of respiratory infections of the upper respiratory tract (Fox et al., 1985). The salivary alpha amylase is synthesized primarily by the parotid gland and it is involved in carbohydrate digestion and immunity of the oral mucosa. Its release depends on the autonomic nervous system through the action of α and β-adrenergic mediators. Recently, salivary alpha amylase has been used as an indicator of physical and psychological stress and it seems involved in changes in serum epinephrine and cortisol levels (Chatterton et al., 1996). Studies have shown that salivary alpha amylase activity increases in response to stress conditions, such as exercise, heat, or cold (Granger et al., 2007).

Another strong activator that may alter the α-amylase concentrations in saliva is physical exercise. Several studies have shown an increase in α-amylase salivary concentration during and after exercise compared to baseline. The enzyme α-amylase, however, is produced by the salivary gland together with other components of the saliva, then other factors that stimulate salivation may influence α-amylase secretion.

In addition to the organic protein compounds in the saliva we can also find non-protein organic compounds in low concentrations; this may happen because of blood contamination by oral mucosal lesions and for this reason it can be found in the saliva of healthy individuals negligible amounts of bilirubin, creatinine, glucose, cholesterol and triglycerides (Rehak et al., 2000).

In patients with renal involvement, salivary urea concentrations can significantly increase (from 6.1 to 29.6 mmol/l), following the increase of its plasma levels (Cardoso et al. 2009).

Even exercise causes acute increases in salivary uric acid levels and therefore the total antioxidant capacity compared to baseline

(Gonzalez et al., 2008).

Lactate is another important compound in sports. Some studies have analyzed salivary lactate response during exercise in an attempt to determine the intensity of training or assess the relationship between blood and salivate lactate.

The saliva contains mainly water and strong and weak ion such as $Na^+$, $K^+$, $Mg^+$, $Ca_2^+$, $Cl^-$, bicarbonate and phosphate, which can work as buffer agents. Electrolyte concentrations in saliva can be quantified by flame photometry and ion-selective electrode. $K^+$ concentration in the saliva is well above plasma values; in contrast, $Na^+$ and $Cl^-$ concentration in this fluid is lower than in plasma. Exercise of varying intensity and duration may change the ionic concentration of the saliva, especially $Na^+$ and $K^+$. The salivary concentrations of $Na^+$, $K^+$ and $Cl^-$ are connected with the anaerobic threshold during incremental test; these changes may be related to sympathetic stimulation, which induces changes in salivary flow, reabsorption and secretion of electrolytes in the secretory cells.

Most of the hormones in the blood can be measured in saliva and this is possible thanks to a connection between salivary glands and plasma. Steroid hormones and other small molecules diffuse into saliva by passive diffusion. The salivary glands are sprayed from the capillary networks and many of the fat-soluble components of the blood pass easily through the walls of the capillaries in the salivary glands[57]. Whey protein and globulins that the hormones are large molecules that do not pass through the cell membranes of the salivary glands, which is why, not only hormones linked in the plasma can spread in saliva. Then, unbound steroid hormones, such as cortisol, estriol, progesterone and testosterone, spread primarily at an intracellular level, for this reason do not affect the salivary flow (Gröschl et al., 2008).

Steroids electrically charged or those conjugates with proteins are able to pass, even if in small quantities, through the junctions between the cells of the salivary glands. This process is very slow, which is why these hormones have salivary concentrations much lower than plasma (Vining et al., 1980). It should be kept in mind that these concentrations may vary due to contamination with blood: small amounts of blood caused by oral lesions and gum can result in a false increase in the concentrations of specific salivary analytes (Schwartz et al., 2004).

Some studies reveal that the free fraction of plasma cortisol is related with the salivary concentrations, allowing the use of this marker in the evaluation of responses to physical and psychological stress (Sapolsky et al., 2000).

Physical activity is able to greatly increase the concentration of salivary cortisol in athletes subjected to various forms of exercise (Aubets et al., 1995); in addition to assessing the adaptive responses to training, cortisol may be a useful biomarker interesting to investigate the levels of tolerance or intolerance to training, when run in conjunction with the measurement of testosterone (Urhausen et al., 2002). Despite the convenience of the use of salivary cortisol in the evaluation of athletes and patients with diseases that alter the secretion of corticosteroids, caution is needed in interpreting the results obtained with saliva samples.

Other hormones synthetic androgens or natural that are administered illegally, with the aim of improving the performance, can spread passively in the saliva. Although it is possible to quantify the testosterone, epitestosterone, tetrahydrogestrinone and other hormones used by athletes for illicit purposes, the World Anti-Doping Agency (WADA) does not provide information on the use of saliva in the detection and control of doping.

**Saliva sampling: beneficial and detrimental**

Saliva can be easily collected through passive drool directly into the plastic tubes: this method provides a sampling of saliva without stimulation. The passive collection is the most recommended method, since the majority of

analytes can be quantified, without obstacles. However, in this case the volume of saliva collected is very low (Chiappin et al., 2007). The stimulated saliva can be collected by stimulation with chewing or using citric acid (Kaufman et al., 2002). There are some commercial devices that facilitate the collection of saliva. Most of them contain a solid base, usually consisting of a small piece of cotton or polyester for the absorption of saliva and a conical tube that by centrifugation allow to recovery the sample. Furthermore, with these methods, the analysis of the sample can vary considerably, mainly due to the fact that some analytes may adhere to the cotton, causing a false lower values (Michishige et al., 2006). Among the most common commercial systems that use solid support are: Oral Salimetrics Swab (Salimetrics® LLC) Salivette® and Cortisol® Salivette (Sarstedt, Newton, NC) and Orapette (Trinity Biotech, Dublin, Ireland). Another collection system, currently available, is the Saliva Collection System (SCS) ® (Greiner Bio-One, GmgH, Kremsmuenster, Austria), that uses a buffer of citric acid for saliva collection (Gröschl et al., 2008). The saliva collected, is subsequently transferred into graduated tubes that allow to quantify the total volume (Nunes et al., 2011). These systems are usually utilized for measurement of calcium, magnesium, α-amylase, uric acid, IgA, cortisol and therapeutic drugs (Raggam et al., 2008). However, some analytes are influenced by the pH variation and the additives in the extraction solution. Compared with the other commercially available systems, SCS method's requires further attention during collection and washing well as extraction solutions are not enough, and also is very expensive.

One of the most important pre-analytical interference is the requirement to record the time and the volume of saliva collected in order to estimate the rate of its secretion. The flow of saliva through the salivary ducts determines, for example, the concentration of electrolytes. The increase in salivary flow via artificial stimulation can change the ionic composition, resulting in $Na^+$, $Cl^-$ and bicarbonate increase and $K^+$ concentration decrease. Some salivary components such as IgA and dehydroepiandrosterone sulfate (DHEAS) depend on salivary flow (Vining et al., 1983). For instance the use of citric acid and gum as stimulator of salivary secretion or materials as cotton or polyester may incorrectly increase level of salivary testosterone; collection devices with cotton is not recommended for the hormones analysis due to the possibility of interference in the immunoassays test performance (Gröschl et al., 2008). The cotton can indeed bind to cortisol and dehydroepiandrosterone (DHEA) and cause a misleading variation (Hansen et al., 2003). Besides the choice of a suitable collection system, the collection time must always be standardized and observed. Hormones and other saliva components can change significantly because of circadian cycles, which may require a collection schedule setup. Alcohol, caffeine intake as well as protein diets can alter cortisol levels. Saliva samples should be refrigerated (4°C) if treated within 3-6 hours from collection. When the sample is stored for long periods, the temperature should be maintained at -80°C or -20°C to prevent bacterial growth. The salivary cortisol is stable at 5°C for three months and up to one year when stored at temperatures between -20 and -80°C. Repeated freezing and thawing cycles do not affect the cortisol concentrations (Hansen et al., 2008).

**Obstacles in the development of saliva tests for diagnosis and future perspectives**

One of the technological hurdles in the development of diagnostic salivary tests is the low concentration of the analytes in saliva compare with blood in which it is 1000 times

higher (Floriano et al., 2009). Based on saliva test, law enforcement agencies had the instruments to evaluate the use of drugs and alcohol to combat the abuse of these substances (Kidwell et al., 1998; Schramm et al., 1992). New technologies open the door to the development of methods to detect diseases and monitor the health of a subject by saliva test. There is a great requirement for affordable and accurate diagnostic tools that can be used in non-invasive manner. Currently, there are devices based on the use of the saliva that allows diagnosis and/or rapid screening of diseases. However, there has been progress in the development of handheld devices that allow an easier sampling of saliva (Christodoulides et al., 2005). Following the work done in the late 1960s, in which they indicated salivary calcium concentration increase in patients with cystic fibrosis, the saliva was seen as an important diagnostic fluid (Mandel et al., 1967). However, the opportunity to use saliva for diagnosis was put aside due mostly to limitations in detection technology and because of the lack of correlation between molecules in blood and in saliva. Many companies deal saliva tests that have been approved by the Food and Drug Administration. Several studies have shown that the saliva test to evaluate antibodies to HIV, which is the best approaches known of diagnostic tools based on saliva, with high sensitivity and specificity then a blood test. This test is mainly used from insurance company as a screening tool to assess the suitability of a person to apply for life insurance. Tests that use saliva could soon be marketed to detect antibodies to hepatitis A and B and measles, mumps and rubella (Kefalides et al.,1999). When saliva is used as a diagnostic fluid is important to reduce the number of variables that could affect the results, because these will have deleterious effects on the diagnosis and treatment of the patient. The early diagnosis of cardiovascular disorders by detection of biomarkers in the saliva can lead to early intervention, reducing the morbidity and mortality associated with the disease. In future, both specific biomarkers panels and high diagnostic sensitivity and specificity, may be required to allow the saliva to become a clinically useful diagnostic tool. The development of specific and standardized kit of analysis, defining interval reference, will do of saliva a real tool of diagnostic in the future particularly for the early diagnosis of cardiovascular disease and cancer.

Definitely the use of saliva as diagnostic fluid has a great potential, although it is still necessary to evaluate pre-analytical variables such as the collection system, biomarkers to quantified, times of harvest, quantification of the volume of sample and the prevention of contamination of blood from lesions in the oral mucosa. Noteworthy is that the assessment of the composition of saliva is feasible and reliable tool that can provide information on the monitoring of several steroid hormones and stress biomarkers in sport and physical exercise.

**Sweat generation**

Perspiration is not a new diagnostic tool. For decades, and still today, doctors have screened for cystic fibrosis in newborns by measuring levels of sodium and chloride in their sweat (Grimaldi et al. 2015; Domingos et al. 2015; Doorn et al. 2015) and tested for the metabolites of illicit drugs (De Giovanni et al. 2013). Sweat is produced by eccrine and apocrine glands originating in the skin dermis and terminating in secretory canals that flow into the skin surface and hair follicles. Notwithstanding it contains a vast amount of medical information and can provide it in almost real time, it has been a biofluid with scant use as clinical sample, because in the past, the process of collecting, transporting, and measuring was vastly more complicated than an ordinary blood test.

Nowadays, there are a lot of studies that focus their attention on the development of patches or wearable sensors that can collect sweat and monitor what it contains (Baker et al. 2015; Porucznik et al. 2015).

Recently, using 3D-printing technology Roda and collegues developed a disposable

minicartridge that can be easily prototyped to turn any kind of smartphone or tablet into a portable luminometer to detect chemiluminescence derived from enzyme-coupled reactions (Roda et al. 2014).

Rose and collegues built a sodium sensor, a communications antenna and a controller chip onto a patch that's externally powered (like an RFID chip) by a smartphone. They printed it onto a flexible substrate and coated it with a sweat-porous adhesive so that it could stick to the skin, a distinct advantage for chronological monitoring of biomarkers in sweat (Rose et al. 2014).

Sweat is rich in electrolytes, like sodium, chlorine, and potassium (Sonner et al. 2015), with concentrations from ones to tens of millimoles per liter, but not only. Sweat contains useful biomarkers that can give indications about the physical state of the body: ammonia, urea, lactate (the transport of lactate from plasma to sweat remains not fully understood and inherently complex, but its concentration is in the micromolar to millimolar range, a relatively high biological concentration) cortisol (in saliva, free cortisol is carried by the bloodstream to acinar cells at the ends of the salivary glands where its lipid-soluble nature allows for passive transport into the salivary glands, causing salivary cortisol levels to be independent of salivary rates) (Umeda et al. 1981; Alvear-Ordenes et al. 2005; Russel et al. 2014), peptides and small proteins like neuropeptides and cytokines, including IL-6, whose levels have similar concentrations in sweat then in plasma (Marques-Deak et al. 2006).

Another advantage of the sweat-technology is that sweat-sensing patches will measure multiple electrolytes, metabolites, and other biomarkers at the same time and they offer minute-by-minute monitoring: this might allow physicians to conduct several tests and analysis without drawing blood.

The researchers knew the wealth of information carried in sweat, but they have not been able to take advantage of it due to the difficulty of collecting, transporting, and analyzing samples: with the recent progress in the collection, processing, and wearable technology we are on the brink of a revolution in diagnostics.

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