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Measurement and Physiological Relevance of the Maximal Lipid Oxidation Rate During Exercise (LIPOXmax)

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1. Introduction

The intensity of exercise that elicits a maximal oxidation of lipids has been termed LIPOXmax, FATOXmax or FATmax. The three acronyms refer to three original protocols of exercise calorimetry which have been proposed almost simultaneously and it is thus interesting to maintain the three names in this review in order to avoid confusion. The difference among the three protocols is presented in table 1. Since our team has developed the technique called LIPOXmax (Perez-Martin et al., 2001; Brun et al., 2009b;) this acronym will be more employed in this chapter, keeping in mind that LIPOXmax, FATOXmax or FATmax represent obviously the same physiological concept.

As will be reviewed in this paper, the measurement of LIPOXmax by graded exercise calorimetry is a reproducible measurement, although modifiable by several physiological conditions (training, previous exercise or meal). Its measurement closely predicts what will be oxidized over 45-60 min of low to medium intensity training performed at the corresponding intensity. It might be a marker of metabolic fitness, and is tightly correlated to mitochondrial function. LIPOXmax is related to catecholamine status and the growth-hormone IGF-I axis, and occurs in athletes below the lactate and the ventilatory threshold (on the average around 40% VO_{2max}). Its changes are related to alterations in muscular levels of citrate synthase, and to the mitochondrial ability to oxidize fatty acids. A meta-analysis shows that training at this level is efficient in sedentary subjects for reducing fat mass, sparing fat-free mass, increasing the ability to oxidize lipids during exercise, reducing blood glucose and HbA_{1c} in type 2 diabetes, and decreasing circulating cholesterol. In athletes, various profiles are observed, with a high ability to oxidize lipids in endurance-trained athletes and in some samples of athletes trained for sprint or intermittent exercise a profile showing a predominant use of carbohydrates.

acronym	FATOXmax	FATmax	LIPOXmax	SIN model
initial publication	Dériaz et al., 2001	Achten et al., 2002, 2003, 2004; Jeukendrup, 2003; Venables et al., 2005	Perez-Martin et al., 2001; Brun et al., 2009b;	Chenevière et al., 2009b
Duration of steps	5-6 min (until steady state)	3 min	6 min	5 min
Calculation	Visual determination	Visual determination	Power intensity at which the derivative of the curve of lipid oxidation versus power is equal to zero (eg, top of the bell-shaped curve)	This model includes three independent variables (dilatation, symmetry, and translation). This SIN model has been reported to allow a more accurate calculation of Fatmin/LIPOXzero
Expression of results	% of maximal oxygen uptake (%VO _{2max}) MFO in kJ.min ⁻¹	% of maximal oxygen uptake (%VO _{2max}) MFO in g. min ⁻¹	usually % of theoretical maximal power; also % extrapolated maximal oxygen uptake (%VO _{2max} ACSM)] or % maximal oxygen uptake (%VO _{2max}) determined by a previous test	Fatmax, MFO, dilatation, symmetry and translation

Table 1. Definition of LIPOXmax, FATOXmax or FATmax.

2. The physiological basis for measuring lipid oxidation during exercise

2.1 Balance of substrate oxidation during exercise: The “crossover concept”

Pioneering studies (Zuntz et al., 1901; Krogh et al., 1920; Christensen et al., 1939) have demonstrated that a mixture of carbohydrates and fat is used by the muscle as a fuel at rest and during exercise, and that the ratio between VCO₂ and VO₂ was a reflect of the relative proportion of lipids and CHO used for oxidation. It was clear already at this time that exercise intensity, exercise duration and prior diet modified this balance of substrates.

Recent studies have evidenced that quantitatively, the most important substrate oxidized at the level of the exercising muscle is glucose (Bergman et al., 1999; Friedlander et al., 2007). The maximal rate of CHO oxidation during exercise is about two fold higher than that of lipids (Sahlin et al., 2008). However, when substrate metabolism is assessed on the whole body, lipids remain a major source of fuel at rest and during exercise. At rest, lipids provide >50% of the energy requirements, and they remain an important source of energy during low to middle intensity exercise, while CHO become the main substrate at high intensity (>80% VO_{2max}) (Jeukendrup et al., 1998). As summarized in table 2, exercise may induce a significant amount of lipid oxidation by at least 4 mechanisms (Brun et al., 2011).

During the last quarter of the XXth century the literature became conflictual with several authors emphasizing the importance of carbohydrates and the others the importance of lipids. This controversy was actually clarified by the heuristic proposal of the "crossover concept" by George Brooks (Brooks et al., 1994). The “crossover concept” is an attempt to integrate the seemingly divergent effects of exercise intensity, nutritional status, gender, age and prior endurance training on the balance of carbohydrates and lipids used as a fuel during sustained exercise. It predicts that although an increase in exercise intensity results in a preferential use of CHO, endurance training shifts the balance of substrates during exercise toward a stronger reliance upon lipids (Fig.1).

The idea of developing a simple reliable exercise-test for assessing this balance of substrates thus emerged as a logical consequence of these fundamental studies (Perez-Martin et al.,

2001; Brun et al., 2007, 2011). Accordingly, several teams have developed this measurement and attempted to train patients at a level determined by this exploration, as reviewed below.

« CROSSOVER" CONCEPT

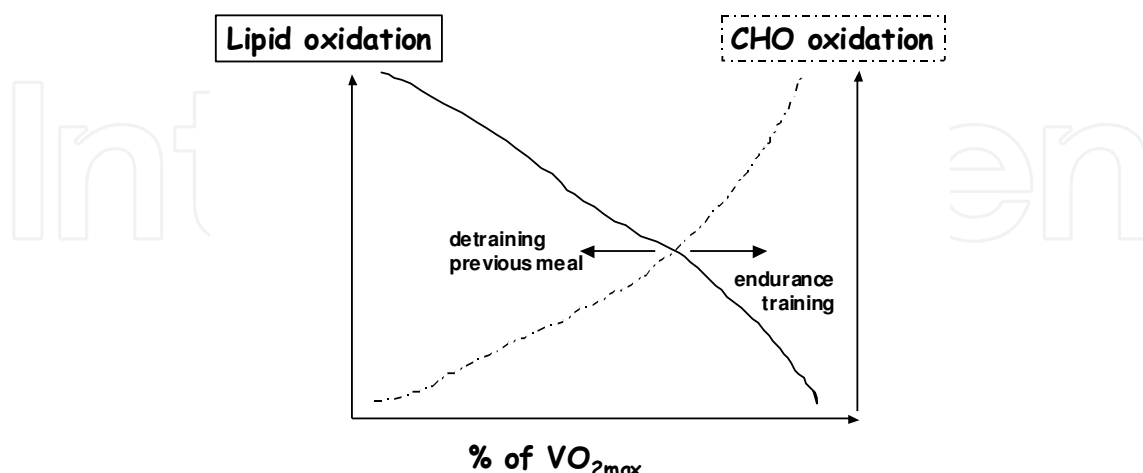


Fig. 1. The crossover concept: the balance of substrates at exercise is a function of exercise intensity, the proportion of lipids used for oxidation continuously decreasing when intensity increases, while CHO become the predominant fuel (>70%) above the “crossover point” (approximately 50% VO_{2max} , see text. This increase in CHO oxidation down-regulates lipid oxidation despite sustained lipolysis. Above the crossover point glycogen utilization scales exponentially. Endurance training, energy supply, overtraining, dietary manipulation and previous exercise modify this pattern. Most trained athletes exhibit a right-shift in this relationship.

a. Muscular contractile activity by its own may use lipids as a source of energy.	During steady state exercise performed at low intensity, fat is oxidized at an almost constant rate (Bensimhon et al., 2006; Meyer et al., 2007), and there is an intensity of exercise that elicits the maximum oxidation of lipids termed <i>maximal fat oxidation rate</i> (MFO).
b. Progressive rise in lipid oxidation with exercise duration	When exercise is heavy and prolonged enough to result in glycogen depletion, there is a shift toward lipids and their oxidation gradually increases (Ahlborg et al., 1974; Bergman et al., 1999; Watt et al.; 2003). This phenomenon is rather slow in mild to medium intensity exercise when the duration of this exercise does not exceed 1 hr.
c. Compensatory rise in lipid oxidation after high intensity exercise	High intensity exercise oxidizes almost exclusively CHO but is frequently followed by a compensatory rise in lipid oxidation which compensates more or less for the lipids not oxidized during exercise (Folch et al., 2001; Melanson et al., 2002), but it is inconsistent and frequently quite low (Malatesta et al., 2009; Lazer et al., 2010), even more if exercise is discontinuous (Warren et al., 2009).
d. Long term regular exercise may increase the ability to oxidize lipids at rest	Long term regular exercise may shift the balance of substrates oxidized over 24 hr toward oxidative use of higher quantities of lipids (Talanian et al., 2007). A training-induced increase in the ability to oxidize lipids over 24-hr is statistically a predictor of exercise-induced weight loss (Barwell et al., 2009).

Table 2. Effects of exercise on lipid oxidation: exercise may increase the oxidative use of lipids by at least 4 mechanisms (after Brun et al., 2011). According to Warren the most important and reliable of these mechanisms is the oxidation during exercise performed around the LIPOXmax or below. (Warren et al., 2009).

2.2 Mechanisms of substrate (fat vs CHO) selection during muscular activity

According to the data presented above, fat is the major energy supply for the muscle below 25% of VO_2max , since in this condition very few glycogen is employed as a source of energy (Romijn et al., 1993). Then, when exercise intensity increases, glycogen will rapidly become the predominant fuel. However, fat oxidation will still increase until the $\text{LIPOXmax}/\text{FATOXmax}$ is reached. Above this level fat oxidation decreases. Interestingly, this decrease in fat oxidation coincides with lactate increase above baseline, as demonstrated in healthy adolescents during incremental cycling (Tolfrey et al., 2010).

The cellular mechanism of this decrease has been reviewed elsewhere (Sahlin et al., 2008) and is still incompletely understood. Theoretically, lipid supply by lipolysis, lipid entrance in muscle cell, lipid entrance in mitochondria, and mitochondrial fat processing may all be limiting steps. Experiments show that extracellular lipid supply is not limiting, since lipid oxidation decreases even if additional fat is provided to the cell. Limiting steps seem to be the entrance in mitochondria, governed by CPT-1, which can be inhibited by Malonyl-CoA and lactate (Starratt et al., 2000), and possibly downstream CPT-I other mitochondrial enzymes such as Acyl-CoA synthase and electron transport chain. All these steps are sensitive to the rate of CHO oxidation and thus a rise in CHO oxidation seems to depress lipid oxidation despite availability of fat and presence of all the enzymes of fat oxidation.

Experiments using intravenous infusion of labeled long-chain fatty acids in endurance-trained men cycling for 40 min at steady state at 50% of VO_2max clearly demonstrate that carbohydrate availability directly regulates fat oxidation during exercise. An increased glycolytic flux results in a direct inhibition of long-chain fatty acid oxidation (Coyle et al., 1997). Conversely, there is a wide body of evidence that glycogen depletion reverses this inhibition and thus increases fat oxidation, as observed during long duration glycogen-depleting exercise.

These processes are governed by cellular factors, that are under the influence of the central nervous system and circulating hormones (Ahlborg et al., 1974; Kiens & Richter, 1998; Kirvan et al., 1988; Thompson et al., 1998). Intracellular pathways have been reviewed elsewhere and this area of knowledge seems to be rapidly expanding. The activation of the AMPK (AMP-dependent kinase) pathway, together with a subsequent increase in the fatty acid oxidation, appear to constitute the main mechanism of action of these hormones in the regulation of lipid metabolism (Koulmann & Bigard, 2006). To summarize the main hormonal regulators of muscular lipid oxidation, epinephrine increases lipolysis (beta effect) and increases glucose oxidation in muscle (de Glisezinski et al., 2009). Norepinephrine increases lipid oxidation in muscle (Poehlman et al., 1994). Cortisol increases adipogenesis and lipolysis, and decreases non-insulin mediated glucose uptake. β -endorphin induces a lipolysis that can be blunted by naloxone (Richter et al., 1983, 1987). Growth hormone (GH) stimulates lipolysis and ketogenesis (Møller et al., 1990b). In the muscle and the liver, GH stimulates triglyceride uptake, by enhancing lipoprotein lipase expression, and its subsequent storage (Vijayakumar et al., 2010). GH also increases whole body lipid oxidation and nonoxidative glucose utilization and decreases glucose oxidation (Møller et al., 1990a). We have shown that GH-deficient individuals have a lower LIPOXmax and MFO that is restored after GH treatment (Brandou et al., 2006a). Downstream GH, IGF-I that mediates many of the anabolic actions of growth hormone stimulates muscle protein synthesis, promotes glycogen storage and enhances lipolysis (Guha et al., 2009).

Interleukin-6 (IL-6) coming from the adipose tissue and the muscle acts as an energy sensor and thus activates AMP-activated kinase, resulting in enhanced glucose disposal, lipolysis and fat oxidation (Hoene et al., 2008). Adiponectin increases muscular lipid oxidation via phosphorylation of AMPK (Dick, 2009). Leptin increases muscle fat oxidation and decreases muscle fat uptake, thereby decreasing intramyocellular lipid stores (Dick, 2009).

Although the information on this issue remains limited, it is clear that the level of maximal oxidation of lipids is related to some of these hormonal regulators : norepinephrine, whose training induced changes are positively correlated to an improvement in LIPOXmax (Bordenave et al., 2008) and growth hormone, whose deficit decreases it, a defect that can be corrected by growth hormone replacement (Brandou et al., 2006a). Downstream GH, IGF-I has also been reported to be correlated to LIPOXmax in soccer players as shown on Fig 5 (Brun et al., 1999), reflecting either a parallel effect of training on muscle fuel partitioning or IGF-I release, or an action of IGF-I (or GH via IGF) on muscular lipid oxidation. Other endocrine axes are surely also involved but this issue is poorly known and remains to be studied.

3. Technical aspects of exercise graded calorimetry

3.1 Methodological aspects

As reminded above, the classic picture of Brooks and Mercier's "crossover concept" (Brooks & Mercier, 1994) has led to the development of an exercise-test suitable for routinely assessing this balance of substrates (Perez-Martin & Mercier, 2001; Brun et al., 2007). Based on our previous studies on calorimetry during long duration steady-state workloads (Manetta et al., 2002a, 2002b; Manetta et al., 2005) we developed a test (Perez-Martin et al., 2001) consisting of five 6-min submaximal steps, in which we assumed that a steady-state for gas exchanges was obtained during the 2 last minutes.

We proposed (Perez-Martin et al., 2001) a diagnostic test including four or five 6-minutes workloads, that may be followed by a series of fast increases in power intensity until the tolerable maximum under these conditions is reached. This final incremental part of the test can be avoided in very sedentary patients and the maximal level can be indirectly evaluated by the linear extrapolation according to the ACSM guidelines (VO_{2max} ACSM) (Aucouturier et al., 2009). The test is performed on an ergometric bicycle connected to an analyzer allowing the analysis of the gaseous exchange cycles by cycle. EKG monitoring and measurements of VO_2 , VCO_2 , and respiratory exchange ratio (RER) are performed during the test. After a period of 3 minutes at rest, and another period of initial warm-up at 20% of the predicted maximal power (PMP) for 3 minutes, the 6-min workloads set at approximately 30, 40, 50 and 60% of PMP are performed. The phase of recovery comprises two periods during which a monitoring of respiratory and cardiac parameters is maintained: active recovery at 20% of the PMP during 1 minute; passive recovery (*ie*, rest) during the 2 following minutes. At the end of each stage, during the fifth and sixth minutes, values of VO_2 and VCO_2 are recorded. These values are used the calculation of the respective rates of oxidation of carbohydrates and lipids by applying the classical stoichiometric equations of indirect calorimetry:

$$\text{Carbohydrates (mg/min)} = 4.585 VCO_2 - 3.2255 VO_2 \quad (1)$$

$$\text{Lipid Oxidation (mg/min)} = -1.7012 VCO_2 + 1.6946 VO_2 \quad (2)$$

These calculations are performed on values of the 5-6th minutes of each step, since at this CO₂ production from bicarbonate buffers compensating for the production of lactic acid becomes negligible. The increment in carbohydrate oxidation above basal values appears to be roughly a linear function of the developed power and the slope of this relation is calculated, providing the *glucidic cost of the watt* (Aloulou, 2002). The increase in lipid oxidation adopts the shape of a bell-shaped curve: after a peak, lipid oxidation decreases at the highest power intensities.

The exact mechanism of this reduction in the use of the lipids at the highest power intensities is actually imperfectly known: a reduction in lipolysis is likely to explain a part of it, together with a shift of metabolic pathways within the muscle fiber. The empirical formula of indirect calorimetry that gives the lipid oxidation rate is, as reminded above:

$$\text{Lipid oxidation (mg/min)} = -1.7 VCO_2 + 1.7 VO_2 \quad (3)$$

It is easy to deduce from this formula that the relation between power (P) and oxidation of lipids (Lox) displays a bell-shaped curve of the form:

$$Lox = A.P (1-RER) \quad (4)$$

The smoothing of this curve enables us to calculate the power intensity at which lipid oxidation becomes maximal, which is the point where the derivative of this curve becomes equal to zero. Therefore the LIPOX_{max} calculation is only an application of the classical empirical equation of lipid oxidation used in calorimetry.

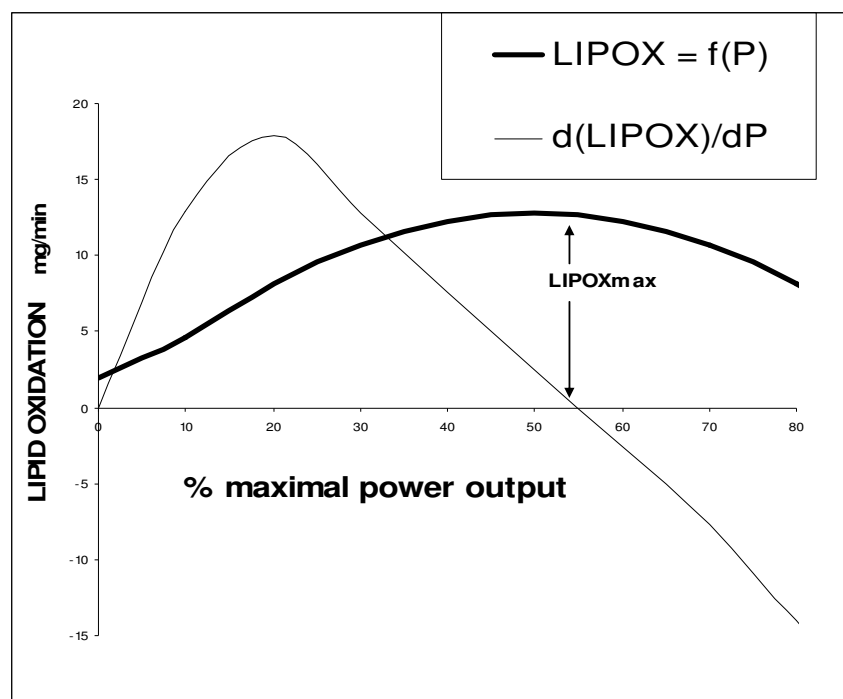


Fig. 2. Calculation of the LIPOX_{max}: The curve of lipid oxidation (mg/min) is given by the empirical formula of calorimetry $Lipox = -1.7 VCO_2 + 1.7 VO_2$. This curve $Lipox = A.P (1-RER)$ (see text) can be derived and the point where its derivative equals zero is the top of the bell-shaped curve and thus represents the LIPOX_{max}. Actually in some subjects this is a broad zone and in others a narrow range of power intensities.

Recently a more sophisticated mathematical model (sine model, SIN) was proposed in order to describe fat oxidation kinetics as a function the relative exercise intensity [% of maximal oxygen uptake ($\%VO_{2max}$)] during graded exercise and to determine the exercise intensity elicits maximal fat oxidation and the intensity at which the fat oxidation becomes negligible. This model which will not be developed here includes three independent variables (dilatation, symmetry, and translation). This SIN model exhibits the same precision as other methods currently used in the determination of LIPOXmax and has been reported to allow a more accurate calculation of Fatmin/LIPOXzero (Chenevière et al., 2009b).

Actually, there is now a large body of literature to support the validity of such protocols of exercise calorimetry (Jeukendrup & Wallis, 2005). The theoretical concern was that, when exercise is performed above the lactate threshold, there is an extra CO_2 production which can be assumed to interfere with the calculations (MacRae et al., 1995). In fact, below 75% of the VO_{2max} , this increase in CO_2 has no measurable effect on calorimetric calculations (Romijn et al., 1992), so that these calculations predict closely oxidation rates measured by stable isotope labeling (Christmass et al., 1999). Clearly, even at high intensity exercise, respiratory gases are mostly the reflect of the balance of substrate oxidation.

A controversial issue appears to be: how to express the results. The crude power and/or heart rate at which lipid oxidation reaches its maximum is the most useful information if one aims at undertaking a targeted training procedure. The difficulty arises when units for reporting data in scientific studies are discussed. A percentage of the actual VO_{2max} is a logic solution, and was used by the team of A. Jeukendrup (Achten et al., 2002, 2003) but this requires to perform another exercise test designed for a precise measurement of VO_{2max} . Alternatively, in the initial protocol proposed by Perez-Martin (Perez-Martin & Mercier, 2001), after the four or five 6-min steps used for calorimetry, a rapid incremental protocol until the maximal level was proposed. However, after 24 or 30 min of exercise, subjects may be tired and unable to reach the actual maximum level which would thus be sometimes underestimated. In fact, in our team, we often express our results as a percentage of the theoretical maximal power calculated with Wasserman's equation. This method allows avoiding a maximal stress, which is sometimes perceived as very harmful by sedentary and obese individuals, and thus improves the acceptability of the test. Two French studies have challenged this approach. Aucouturier and coworkers (Aucouturier et al., 2009) report that a calculation of VO_{2max} according to the American College of Sports Medicine (ACSM) recommendations from submaximal VO_2 values provides a satisfactory evaluation of the actual VO_{2max} while theoretical VO_{2max} values given by Wasserman's equation are sometimes misleading in such subjects. These authors thus propose to express the LIPOXmax as a percentage of VO_{2max} ACSM. This approach was also employed by Lazzer (Lazzer et al., 2010). Michallet et al (Michallet et al., 2008) insisted on the fact that the theoretical design of the test with steps set at 20, 30, 40, 50 and 60% of theoretical maximal aerobic power can be inaccurate, and that a good protocol should include steps at a respiratory exchange ratio below and above 0.9, this value being that of the "crossover point". In a very recent study the team of E Bouhlef proposes an improvement that markedly increases the reproducibility and thus presumably the precision of the measurement : the authors propose a previous determination of the VO_{2max} with a maximal exercise test and then set the power intensity of the steps of the calorimetry according to this test (Gmada et al, 2011). This study has the interest to further demonstrate the precision and reproducibility of the method and to propose a protocol suitable for research purposes, but for the assessment of series of patients

or athletes it is clearly necessary to rely upon a single test, ie, calorimetry if we want to measure the balance of substrates.

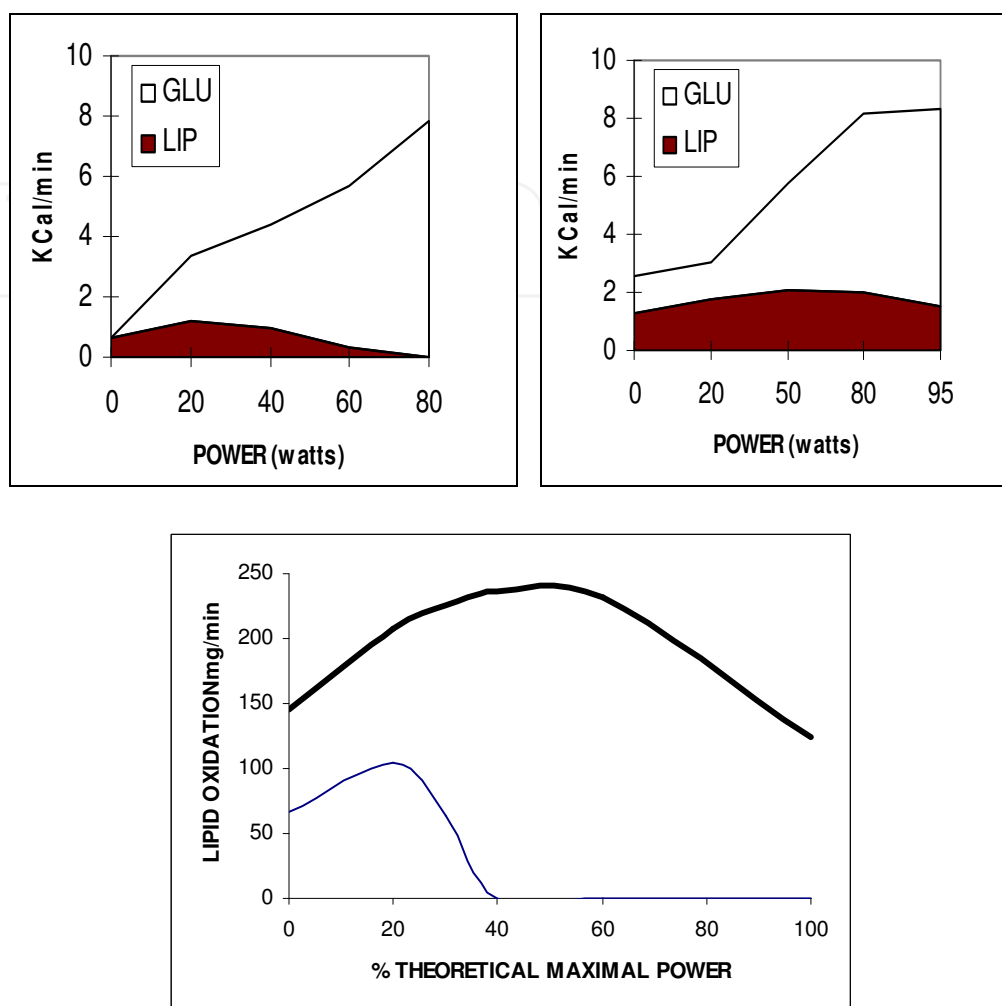


Fig. 3. Examples of individual exercise calorimetries: left; obese woman with "glucodependence" (ie, poor ability to oxidize lipids at exercise) with a peak of lipid oxidation at 135 mg/min located at a power intensity of 34 watts (40% % VO₂max ACSM) ; right, overweight patient who oxidizes 235 mg/min of lipids at a LIPOX_{max} of 68 watts, (55% % VO₂max ACSM.) In the last subject, the LIPOX zone is quite wide, indicating that lipids are oxidized over a wide range of exercise intensities. In the first subject it is restricted to a narrow area. The two curves of lipid oxidation are plotted together on the lower panel, showing their difference in profile according to the theoretical maximal working capacity. Similar discrepancies can be found in athletes.

The maximal fat oxidation rate (MFO) has been expressed in mg/min (Perez-Martin & Mercier, 2001; Dumortier et al., 2002; Brandou et al., 2003, 2005, 2006a, 2006b), g/min (Achten et al., 2003; Achten & Jeukendrup, 2004; Jeukendrup, 2003), mg/min/kg body weight, mg/min/kg fat free mass, and more recently in mg/min/kg muscle mass (Lavault et al., 2011). Muscle can be evaluated from bioimpedance analysis with a validated equation (Janssen et al., 2000), and expression of MFO in mg/min/kg muscle offers at least two advantages: it helps to delineate the effects of training on muscle mass and on the ability of

each kg of muscle to burn lipids; it provides an index which has been shown to be predictive of the effects of exercise on weight loss (Lavault et al., 2011) as indicated below. A MFO lower than $5 \text{ mg}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ muscle mass predicts poor exercise induced weight loss while as a higher MFO value predicts more efficient exercise induced weight loss. MFO ranges on the average between 38 and 1073 mg/min and the boundary of the lowest quartile is 140 mg/min. The LIPOXmax occurs at a very variable level between 3.6 and 101.5% of P_{maxth} so that the boundary of the lowest quartile is 22% (ie, it is at $64.01\% \pm 0.52\%$ of FC_{maxth} the boundary of the lowest quartile is 58%. Expressed in % of the reserve heart rate ie 44.5% of $VO_2\text{max}$. Thus targeting, on theoretical grounds, these values $\pm 5\%$ would be actually set at the LIPOXmax in only 30-40% of subjects, ie 60-70% of patients would not be trained at the expected level. The crossover point occurs on average at 32% of W_{maxth} so that the boundary of the lowest quartile is 23.4%. This corresponds to 45% of $VO_2\text{max}$ (Brun et al., 2009b). Therefore, in an average French population, the LIPOXmax occurs around 30% of W_{maxth} ie 45% of $VO_2\text{max}$. In sedentary obese and diabetic patients, there is now considerable evidence that this level is more or less lowered and is sometimes extremely low. The point where there are no longer lipids oxidized (LIPOXzero or FATmax) is at 80% of P_{max} ie 85-90% of $VO_2\text{max}$ (Brun et al, 2011c).

In addition as shown on Table 4, the LIPOXmax is shifted to lower intensities and the MFO is decreased in many situations referred as "glucodependence" (obesity, diabetes, sleep apnea... etc)

3.2 Physiological relevance of the balance of substrates at exercise as assessed with exercise calorimetry

During steady-state exercise at low intensity (LIPOXmax or below), lipid oxidation remains stable at the level predicted by exercise calorimetry over 45 min or more (Jean et al., 2007; Meyer et al., 2007).

When higher intensities are reached (60% $VO_2\text{max}$ or more) there is a gradual increase in lipid oxidation when the duration of exercise increases. This enhanced fat oxidation results from a decrease in muscle glycogen content which diminishes the availability of CHO in the exercising muscle. For example, a 2hr exercise at 60% $VO_2\text{max}$ induces a 77% reduction in muscle glycogen depletion (Thomson et al., 1979). The shift to lipids has been shown to occur when there is a reduction of 30-40% of glycogen stores (Kirwan et al, 1988).

Exercise calorimetry thus can be used as a basis for targeted training, as discussed below. On the other hand, the ability to oxidize lipids during exercise is likely to reflect a profile of "metabolic fitness" that is impaired in some diseases and improved by training, and which is correlated to muscle physiological status.

3.3 How short can be the steps of an exercise calorimetry?

The basic assumption that underlies exercise calorimetry is that blood lactate generation during exercise has minimal influence on RER after 3-4 minutes of exercise performed at a steady state. In this condition, the extra- CO_2 production from blood HCO_3^- buffers can indeed be regarded as negligible. One can calculate that even the fastest increase (approximately $2 \text{ mmol}\cdot\text{min}^{-1}$) in blood lactate produces an increase of VCO_2 by only 3%. Indeed, if we assume that the volume of distribution of lactate is proportional by a factor of $100 \text{ ml}\cdot\text{kg}^{-1}$ to body mass and thus represents approximately 8 L, this would mobilize 16 mmol HCO_3^- and generate, over 6 min, roughly $1.8 \text{ CO}_2 \text{ l}\cdot\text{min}^{-1}$. Under these conditions,

VCO₂ would increase by less than 0.06 l.min⁻¹, *ie* roughly 3%. Thus, the increase in RER in these exercise conditions is almost completely explained by the balance between oxidized carbohydrates and lipids, independent of blood lactate. The validity of this calorimetric approach is further confirmed by a classical work of Romijn (Romijn et al., 1992) who showed in highly trained sportsmen that up to 80-85% VO₂max calorimetric calculations based on respiratory exchanges during exercise closely fit with much more sophisticated measurements using stable isotopes (MacRae et al., 1995). Concerning proteins, if one compares exercise bouts at 33 and 66% of VO₂max it can be demonstrated that their use for oxidation remains stable at the various levels of exercise, supporting the basal assumption that the balance of substrates may be interpreted in terms of respective percentage of oxidized fat and carbohydrates.

We have presented above our procedure based on 6-minutes workloads. However, other investigators (Achten et al., 2002) have simultaneously developed a procedure based on 3-minutes "ultra-short" workloads. This latter method has been validated by its promoters in athletes and healthy sedentary subjects (Achten et al., 2002, 2003). Actually, there was a paucity of data about its validity in very sedentary patients, in whom it usually takes more time to obtain a steady state of respiratory exchanges. We recently compared calorimetry data obtained with this procedure (2nd-3rd minutes) with the one presented above (5-6th minutes) and found that values measured during the 3 minutes steps are poorly correlated with values measured during the 6 minutes steps, due to an overestimation of steady state RER that can be as high as 0.35. This shift results in an average overestimation of carbohydrate oxidation of 15.8 mg/min (this difference can reach 1200 mg/min). Besides, lipid oxidations are poorly correlated between the two methods. Therefore, among very sedentary patients in whom these tests are used for targeting physical activity, 3-min steps appear too short to allow accurate calorimetric calculations. Our protocol based on 6-minutes workloads seems preferable (Bordenave et al., 2007).

As already developed above, Romijn (Romijn et al., 1992) compared, in highly trained endurance cyclists, calorimetric results and isotopic measurement during exercise tests up to 85% VO₂max and showed that at this level calorimetry is fully reliable. However, a look at the figures of this paper shows that the steady state of RER occurs after 4 min and is not obtained after 2 minutes. In addition, we recently showed that the estimate of lipid oxidation by this method during the 5th and 6th minutes of a 6 min step predicts fairly well the actual lipid oxidation rate that would be observed over 45 minutes performed at the same level (Fig.4). The mean difference between the predicted value and the measured value is only 4.51±8.7 mg/min (Jean et al., 2007). Meyer (Meyer et al., 2007) also reported that VO₂ used for fat oxidation after 6 min closely predicted fat oxidation measured between 30 and 40 min of a constant-load exercise performed at the same intensity. These two observations further support the use of the 6-min steps procedure rather than the 3-min steps procedure proposed by the team of Jeukendrup (Achten et al., 2002) that seems to be accurate mostly for sports medicine and exercise physiology but less reliable in sedentary subjects.

A recent study further addressed this issue in prepubertal children. Comparison of 10 min and 3 min steps showed that the 3 min procedure yielded a satisfactory assessment of the power intensity where the maximum was reached (55% VO₂peak) with 95% satisfactory limits of agreement ± 7% VO₂peak, but that the value of the lipid oxidation rate was less precisely assessed in this population with the 3 min procedure. The authors concluded that, in children, the 3 min procedure provides a valid estimation of the power intensity but was less precise for assessing the flow rate (Zakrzewski & Tolfrey, 2011).

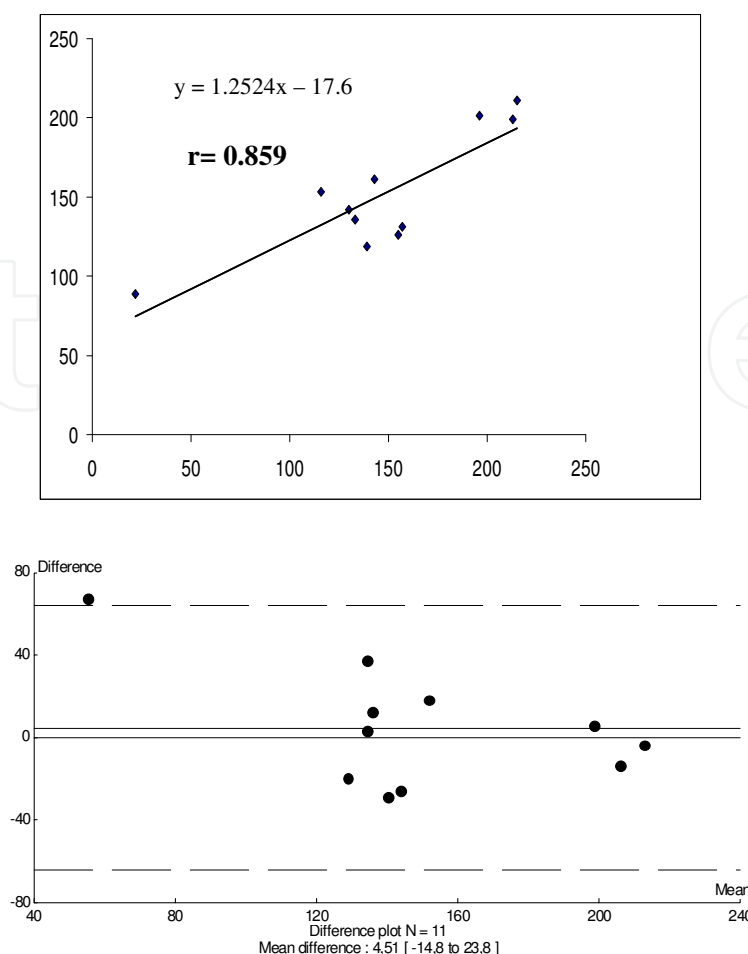


Fig. 4. Correlation and Bland-Altman plot showing the agreement between the measurement of MFO with LIPOXmax protocol and the average lipid oxidation rate maintained over 45 min during a steady state exercise set at this intensity level.

3.4 Factors of variation and reliability of LIPOXmax/FATmax

Initial studies on exercise calorimetry unanimously reported a fair reliability, which seems to be confirmed by daily clinical practice. The coefficient of variation (CV) for the LIPOXmax (at that time it was manually determined) was found to be 11.4% (Perez-Martin et al., 2001) and with Achten and Jeukendrup's procedure in 10 males tested three times it was 9.6% ie ± 0.23 l/min (Achten et al., 2003). Similarly Michallet in 14 subjects aged 19-50 years found with the current LIPOXmax procedure a CV equal to 8.7%. The crossover point PCX appeared somewhat less reproducible with a CV of 17% (Michallet et al., 2006). However, Meyer investigating this methodology, reported variability as high as ± 0.91 l/min that was supposed to be too wide (Meyer et al., 2009). Meyer's paper actually investigated the reproducibility in non-standardized conditions concerning recent exercise and food intake, two major modifiers of the balance of substrates, and therefore his conclusions are restricted to subjects tested in similarly non standardized conditions. More recently a careful methodological study proposing a more standardized approach based on prior determination of VO_{2max} by a maximal exercise test evidenced an even better reproducibility as low as 5.02% (Gmada et al, 2011). Therefore, on the whole, it is clear that the LIPOXmax is a fairly reproducible measurement, unless conditions of measure are not standardized for

the major factors of variation such as exercise or prior meal (see Table 3). This last remark is important because, like all physiological parameters, the LIPOXmax can be acutely modified by several factors (see Table 4).

Author (reference)	Parameters of reproducibility	remarks
(Perez-Martin et al., 2001)	CV= 11.4%	Early LIPOXmax protocol, visual determination
(Achten et al., 2003)	CV= 9.6% ie ± 0.23 l/min	FATmax protocol
(Michallet et al., 2006)	CV = 8.7%	Current LIPOXmax protocol
(Meyer et al., 2009)	Variability ± 0.91 l/min	Not standardized for prior exercise and feeding
(Gmada et al, 2011)	CV= 5.02%	Standardized determination after prior maximal test to determine VO_{2max} markedly increases reproducibility of the LIPOXmax protocol

Table 3. reproducibility studies of the LIPOXmax/FATmax: reproducibility is fair unless patients are not fasting and not standardized for recent previous exercise, and reproducibility is even greater if the protocol is more standardized

4. LIPOXmax/FATmax in sports medicine

As reviewed below, most literature on the LIPOXmax/Fatmax deals with alterations of this parameter in patients and its potential interest for exercise targeting. However, there are some reports suggesting that this parameter has some interest in athletes.

Modifying factor	Effect	references
previous meal taken less than 3 hr before	decreased MFO and shifted LIPOXmax to a slightly lower intensity	Bergman & Brooks, 1999; Jeukendrup, 2003; Friedlander et al., 2007
high-fat diets in which more than 60% of the energy is derived from fat	decreases fat oxidation during exercise, even if the diet is consumed for only 2 to 3 days, due to reduced muscle glycogen stores	(Coyle et al., 2001).
previous exercise performed just before the exercise calorimetry	MFO slightly increased	(Chenevière et al., 2009a)
puberty	LIPOXmax and MFO are higher in prepubertal children and gradually decrease throughout puberty to reach adult values at the end of puberty	(Brandou et al, 2006b; Riddell et al., 2008 ; (Zakrzewski & Tolfrey, 2011b).
type of exercise	Higher during running than cycling in adults and in pre- to early pubertal children	(Achten et al., 2003; Zakrzewski & Tolfrey, 2011a).

Modifying factor	Effect	references
gender	Women oxidize slightly more lipids and on average their LIPOXmax occurs at higher power intensity. This difference is confirmed in all studies but is actually quite moderate and has probably little relevance. On the opposite, fat oxidation is higher in pre- to early pubertal boys compared with girls at similar relative (but not absolute) intensities.	(Friedlander et al., 1998a, 1998b; Chenevière et al., 2011; Brun et al., 2009a; Zakrzewski & Tolfrey, 2011b).
temperature	Shift to preferential CHO oxidation during exercise in hot environments. Reversal after acclimation and training.	Febbraio et al., 1994; del Coso et al., 2010
highly trained athletes	Most of them exhibit a markedly high ability to oxidize lipids during exercise but in some sports like soccer, a preferential use of CHO is observed.	(Bergman & Brooks, 1999; Achten et al., 2003; Venables et al., 2005; González-Haro et al., 2007; Varlet-Marie et al., 2006).
Obesity and diabetes	LIPOXmax values markedly shifted to lower power intensities and MFO lowered.	(Perez-Martin et al., 2001; Sardinoux et al., 2009)
Metformin	increases fat oxidation during exercise and decrease its postexercise rise.	(Malin et al., 2010).
type 2 diabetes	Lower ability to oxidize lipids when compared to subjects matched for body mass index (difference not found by others).	(Ghanassia et al., 2006; Mogensen et al., 2009)
type 1 diabetes	Lower ability to oxidize lipids.	(Brun et al., 2008).
sleep apnea syndrome	Lower ability to oxidize lipids at exercise. Training improves both apnea-index and lipid oxidation at exercise.	(Desplan et al., 2010).

Table 4. Factors of variation of LIPOXmax/FATmax

4.1 Endurance training improves the ability to oxidize fat during exercise

Over the 60-70 the literature is full of papers showing that endurance training allows fat to become the predominant substrate for endurance exercise, while other leading authors in that time emphasized the importance of CHO-derived energy stores for exercise performance (see review in Brooks & Mercier, 1994). According to the initial formulation of the crossover concept, it could be expected that endurance athletes would exhibit a profile of "lipid oxidizers" proportional to their fitness and the efficacy of their training. Most of the exercise calorimetry studies in athletes confirm this early statement. They show that on the average endurance-trained athletes oxidize more lipids. Data from cross-sectional and longitudinal studies have supported the notion that training reduces the reliance on CHO as an energy source, thereby increasing fat oxidation during submaximal exercise (Achten et al., 2004). In pre- to early pubertal children, brisk walking or slow running promotes higher fat oxidation (Zakrzewski & Tolfrey, 2011). A specific study on the effects of endurance training in women shows that endurance-trained women had a higher fat oxidation rate, but their peak values occur at a very similar intensity ($56 \pm 3\%$ VO_2max) compared with the untrained women ($53 \pm 2\%$ VO_2max) (Stisen et al., 2006). González-Haro and coworkers have fairly evidenced in high competitive level triathletes and cyclists various profiles of high

lipid oxidation which differ among sports (González-Haro et al., 2007). However, the reason for the inter-individual variability of these parameters remains poorly understood (Achten & Jeukendrup, 2003, 2004; Brun et al., 2000; Jeukendrup & Wallis, 2005). Clearly, energetic pathways favored by specific training programs may be markedly different among sports.

4.2 Endocrine correlates of this profile of high lipid oxidation

In soccer players relationships between the GH-IGF-I axis and the LIPOXmax were reported (Brun et al., 1999). These correlations are likely to reflect either a parallel effect of training on muscle fuel partitioning or IGF-I release, or an action of IGF-I (or GH via IGF) on muscular lipid oxidation (Fig. 5).

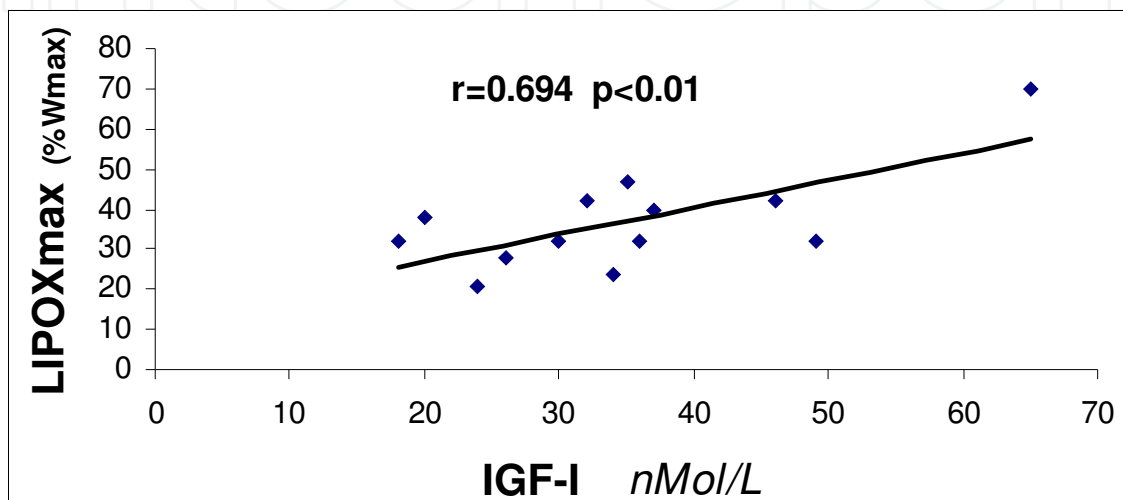


Fig. 5. Correlation between Insulin-like growth factor 1 (IGF-I) levels and the LIPOXmax in soccer players (Brun et al., 1999).

4.3 Are there 'glucodependent' sports

While low intensity training, as shown above, increases lipid oxidation, high intensity training has been reported to improve the ability to oxidize carbohydrates (Manetta et al., 2002a, 2002b).

Varlet-Marie et al (Varlet-Marie et al., 2006) described the profile of lipid oxidation in 90 trained athletes: 28 cyclists, 32 male soccer players, 19 male rugby players, 11 rugbywomen (national level in soccer and male rugby and regional level in cyclism and female rugby) and 41 healthy sedentary volunteers. All athletes had been involved in regular training for several years (>3 years), and trained 10.69 ± 0.9 hr/wk. The soccer team performed over the year a combination of endurance training under the form of interval training, strength training, speed training, skill and tactical training, in various proportions according to the period. Rugbymen and rugbywomen underwent an heavy training mostly based on strength training. The cyclists performed 14 hours of cycling (*ie*, about 450 km) per week during a nine-month training period. During the first month, training sessions were performed at low intensity with a specific target (below their ventilatory threshold: VT). During the other months, they added interval-training sessions to their endurance training, wherein they performed at high intensity with a specific target heart (above their VT).

When expressed as raw power values, the LIPOXmax and the crossover point ranked as follows: rugbymen > cyclists > male controls > rugbywomen > female controls > male soccer players (Figure 6).

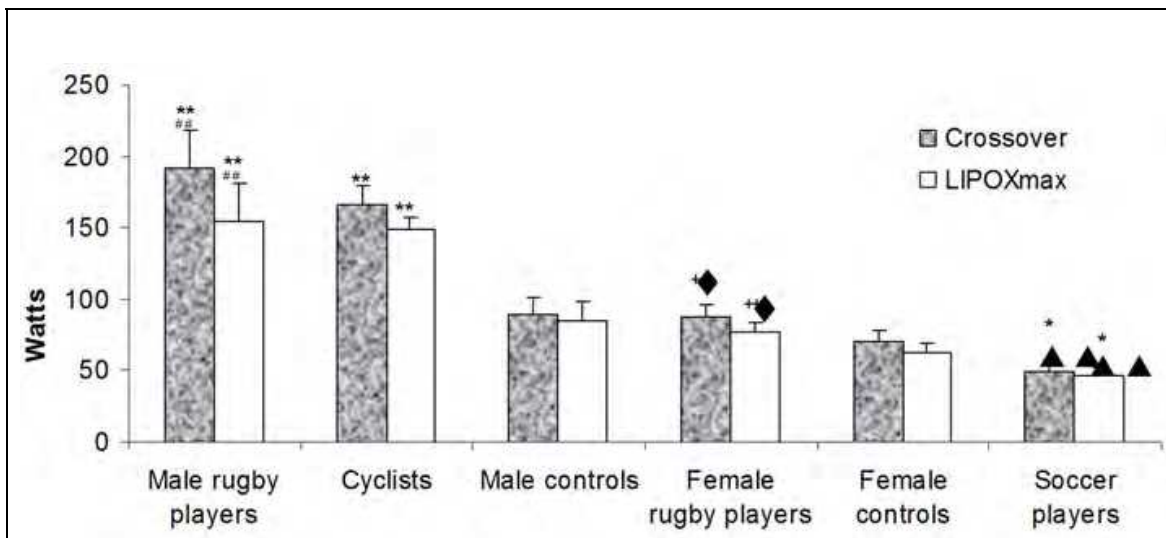


Fig. 6. Comparison of the power at which occur the crossover point and the LIPOXmax in control subjects and in various groups of athletes. * $p < 0.05$; ** $p < 0.0001$ (male athletes vs. male control subjects); ## $p < 0.0001$ (male rugby players vs. soccer players); ▲▲ $p < 0.0001$ (cyclists vs. soccer players); ♦ $p < 0.05$ (female rugby players vs. female control subjects); ++ $p < 0.0001$ (female rugby players vs. male rugby players)

When they were expressed as percentages of theoretical maximal power this ranking became: cyclists > rugbywomen > rugbymen > female controls > male controls > soccer players (Figure 7). Raw lipid oxidation rates at the level of the LIPOXmax ranked as follows (Figure 8): rugbymen > cyclists > rugbywomen > sedentary male controls > soccer. If lipid oxidation is expressed per kg of body weight this ranking became: cyclists > rugbymen > rugbywomen > sedentary female controls > sedentary male controls > soccer players (Figure 9).

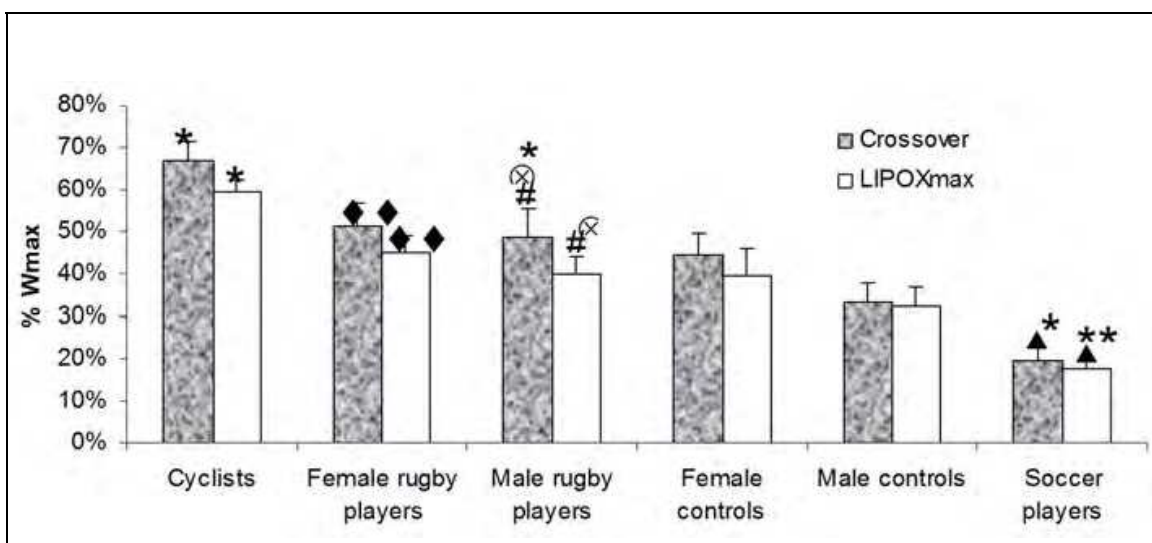


Fig. 7. Comparison of the crossover point and the LIPOXmax, expressed in % of Wmax, in control subjects and in various groups of athletes. * $p < 0.05$; ** $p < 0.0001$ (male athletes vs. male control subjects); ## $p < 0.0001$ (male rugby players vs. soccer players); ▲▲ $p < 0.0001$ (cyclists vs. soccer players); ♦♦ $p < 0.0001$ (female rugby players vs. female control subjects); ⊗ $p < 0.05$; ⊗⊗ $p < 0.0001$ (cyclists vs. male rugby players)

This study evidences markedly different patterns of balance of substrates among groups of athletes. Clearly, cycling and rugby are rather characterized by high rates of lipid oxidation which peaks at high exercise intensities, while in soccer there is an early predominance of CHO.

The finding of a high ability to oxidize lipids in athletes submitted to regular endurance training, like cyclists, is consistent with previous literature (Achten & Jeukendrup, 2003). By contrast, it is interesting to notice in soccer players, a pattern of “glucose dependence” that implies a reduced reliance on lipids at exercise. Although in our study we can only present data on soccer, this pattern is likely to occur in several sports. Since exercise training at high intensity (Manetta et al., 2002a, 2002b) and intermittent exercise (Perez-Martin et al., 2000) both increase the ratio between CHO and fat used for oxidation during muscular activity, this pattern may reflect an adaptation of muscle metabolism to short repeated bouts of high intensity. Interestingly, such a “glucose dependence” is also found in obesity (Perez-Martin et al., 2001) and type 2 diabetes (Blanc et al., 2000). In this case it can be rapidly reversed by a few weeks of targeted exercise training at the level of the LIPOXmax (Dumortier et al., 2002, 2003). Since physical inactivity rapidly shifts the balance of substrates at rest towards a lower ratio of lipid/CHO used for oxidation (Blanc et al., 2000) it can be assumed that sedentarity explains at least in part the glucose dependence of these patients.

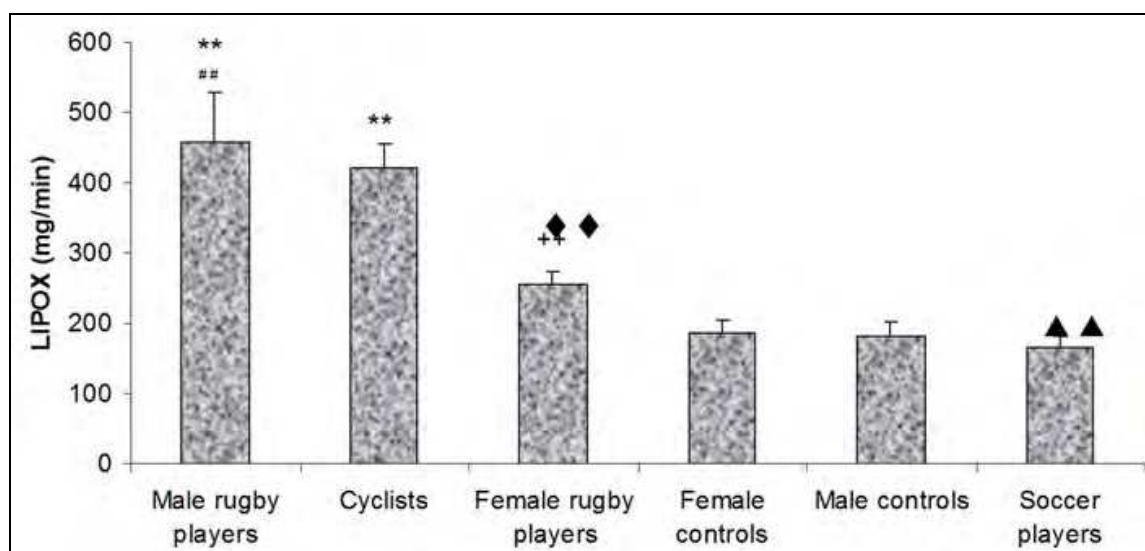


Fig. 8. Lipid oxidation rates in control subjects and in various groups of athletes, expressed in mg/min. ** $p < 0.0001$ (male athletes vs. male control subjects); ## $p < 0.0001$ (male rugby players vs. soccer players); ▲ $p < 0.0001$ (cyclists vs. soccer players); ♦ $p < 0.0001$ (female rugby players vs. female control subjects); ++ $p < 0.0001$ (female rugby players vs. male rugby players)

4.4 Shifts in the balance of substrates during exercise with overtraining

According to the energy pathway mostly involved in a type of activity, training increases thus the ability to oxidize either lipids or CHO. This was clearly evidenced in a study conducted on competitive road cyclists in whom high intensity endurance training increased the ability to oxidize CHO above the ventilatory threshold, while at the end of the season most patients exhibited symptoms of overreaching associated with a reversal of this increase in CHO oxidation (Manetta et al., 2002a). By contrast overreaching in endurance athletes submitted to exercise calorimetry showed lowered ability to oxidize fat at low

intensities, leading to the concept that training effects on the balance of substrates at exercise are reversed by overtraining (Aloulou et al, 2003). This issue remains poorly documented and requires more investigation.

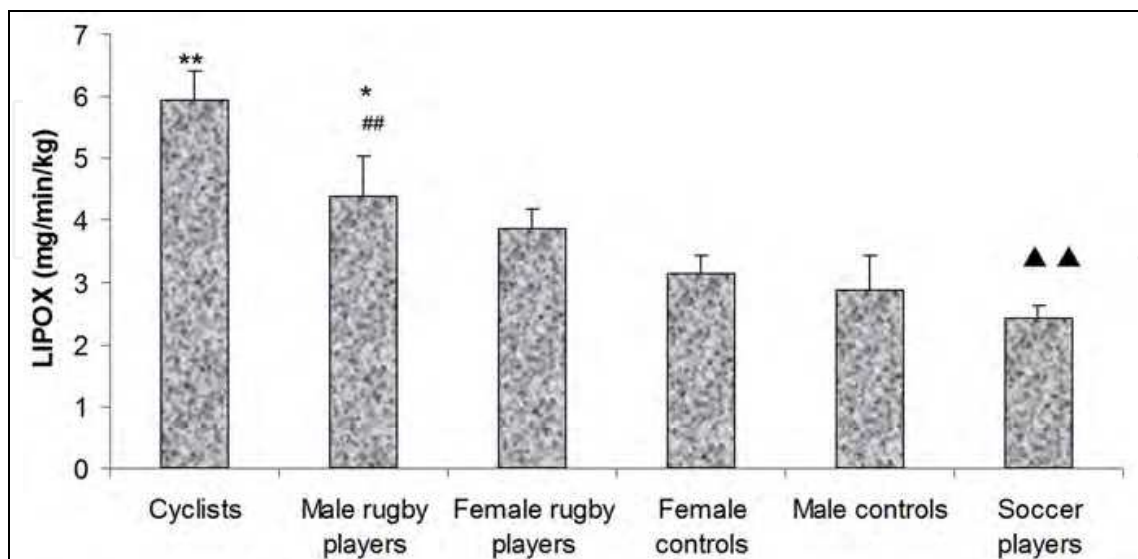


Fig. 9. Lipid oxidation rates in control subjects and in various groups of athletes, expressed in mg/min/kg of body weight. * $p < 0.05$; ** $p < 0.0001$ (male athletes vs. male control subjects); ▲▲ $p < 0.0001$ (cyclists vs. soccer players); ## $p < 0.0001$ (male rugby players vs. soccer players)

5. Interest of the LIPOXmax as a target for structured training in obesity and diabetes

5.1 Scientific background

It is now unanimously recognized that exercise is an efficient tool for : 1) preventing the onset of type 2 diabetes (Lindström et al., 2006; Kim et al., 2006); 2) improving blood glucose control (Marwick et al., 2009) and 3) preventing further weight regain in weight-reduced obese individuals (Bensimhon et al., 2006). Exercise is also beneficial for cardiovascular health, due to its positive effects on blood pressure (Pescatello et al., 2004; Pescatello, 2005), blood lipids (Kelley et al., 2006), inflammation (Fabre et al., 2002), blood viscosity (Brun et al., 2010b), mood (Krogh et al., 2010) and cognitive function (Fabre et al., 2002; Angevaren et al., 2008).

However the effects of exercise as a weight reducing procedure have been considered during many years as rather limited and almost negligible. It is beyond any doubt that regular exercise attenuates the metabolic drive to regain weight after long-term weight loss (MacLean et al, 2009). The interest of physical activity was thus mostly to prevent weight gain, to improve stabilization after slimming, and to reduce obesity-related co-morbidities but not to reduce weight by its own (Jakicic & Otto, 2005, 2006; Duclos et al., 2010).

This traditional view has been challenged by studies demonstrating that even without any change in diet, exercise alone may reduce body weight (Ross et al., 2000; Slentz et al., 2004). This has been further evidenced by a recent meta-analysis that concludes that exercise on its own improves the effects of a diet by on average 1.4 kg (Wu et al., 2009). It seems now well demonstrated that exercise considered alone can reduce body weight. The last American consensus (Donnelly et al., 2009) indicates that more than 250 min of weekly moderate-intensity physical activity is associated with clinically significant weight loss. Accordingly,

lower weekly amounts of moderate-intensity exercise (between 150 and 250 min per week) is effective to prevent weight gain, but can provide only modest weight loss by their own. They can result in significant weight loss if associated to moderate diet restriction but, interestingly, not severe diet restriction.

The picture is thus slightly modified. Exercise appears nowadays as an effective means to reverse overweight, but its effects are shown to be very variable, sometimes impressive, but often poor. A major explanation for this heterogeneity is that exercise may induce marked compensatory changes in energy intake (King et al, 2008). Therefore exercise should be combined with a dietary approach based on correction of compensatory behaviors and errors (Bouchard et al, 1990; Caudwell, 2009). This approach is surely more logic than the traditional restriction which has some short-term efficiency but almost always result in a subsequent weight gain due to homeostatic mechanisms of fat mass preservation (MacLean, 2011).

What is the most important: duration or frequency? Chambliss (Chambliss, 2005) examined the effect of duration and frequency of exercise on weight loss and cardiorespiratory fitness in 201 previously sedentary, overweight women (Chambliss, 2005) over 12 months. He found a mean weight loss after 1 year was 8.9, 8.2, 6.3 and 7.0 kg, for the vigorous intensity/high duration, moderate intensity/high duration, moderate intensity/moderate duration, and vigorous intensity/moderate duration groups, respectively, but there was no effect of exercise duration or exercise intensity on changes in body weight or in BMI. Duration of exercise (at least 150 min/week in walking) was more important than vigorous versus moderate intensity in achieving these goals.

Most of the studies make little or no reference to the substrate (lipid or CHO) that is oxidized during exercise. However, there is a rationale to do so, as largely described above. Multiple studies have show that fatty acid handling and oxidation is impaired in skeletal muscle of obese, impaired glucose-tolerant, and T2D individuals (Blaak, 2004; Corpeleijn et al., 2008, 2009; Kelley et al., 1999; Mensink et al., 2001). This defect leads to propose exercise protocols aiming at restoring muscular ability to oxidize lipids. For this reason, LI protocols designed for oxidizing more lipids during exercise sessions were described by several authors (Blaak & Saris, 2002; Blaak, 2004) and were shown to improve both the ability to oxidize lipids and body composition (Schrauwen et al., 2002).

As shown on the meta-analysis of 12 LIPOXmax training studies, 3 or 4 weekly sessions of 45 min cycling at the LIPOXmax result in a weight loss of -2.25 % [confidence range -3.53 to -0.97] which is at least as efficient as the various protocols studied in the literature (Romain et al., 2010). Therefore, LIPOXmax training is one of the strategies that can be proposed to reduce body weight in obese subjects. A comparison with other more classical protocols remains to be done.

The issue of the exercise protocol that should be recommended for weight maintenance remains incompletely studied. Cross sectional studies show that weight maintenance is improved with physical activity > 250 min per week. However, no evidence from well-designed randomized controlled trials exists to judge the effectiveness of physical activity for the prevention of weight regain after weight loss (Donnelly et al., 2009). According to this consensus document, resistance training does not enhance weight loss but may increase fat-free mass and increase loss of fat mass and is associated with reductions in health risk. Existing evidence indicates that endurance PA or resistance training without weight loss improves health risk. There is no evidence that PA prevents or attenuates obesity-related detrimental changes (Donnelly et al., 2009).

5.2 Standardized vs personalized targeting?

There is an important discussion that underlies all the controversies about exercise prescription in chronic diseases. This is: should we use standard or personalized exercise prescriptions. Some current rules of prescription emphasize the need for taking into account the personal characteristics of each patient, but they are by essence “standardized”, ie, they do not take into account the specific physiologic profile of each subject. All is based on the assumption that the most important mechanism underlying the metabolic effect of exercise is to generate an energy deficit, regardless of the actual quantity of lipids or CHO that have been oxidized (Strasser et al, 2007).

Such a standardized approach was used in pneumology and cardiology, before it was challenged by a new paradigm: the “individualization concept”. Personalized targeting of exercise has been promoted in respiratory and cardiac chronic diseases and was shown to provide better results (Vallet et al., 1997). The “Hippocratic” concept of superiority of the individualized approach is taken into account by a number of practitioners and appears in national guidelines (Guidelines, 2005). However, some guidelines do not mention it, considering that evidence for counseling is not sufficient (Rochester, 2003).

In metabolic diseases, such a discussion about the “individualization concept” has not yet been initiated. Usual French recommendations for exercise in diabetes (Gautier et al, 1998; Gautier, 2004) do not take into account the individual metabolic background. Authors only indicate a broad zone of % VO_2max or heart rates assumed to be the most accurate.

Extending the individualization concept to obesity and diabetes raises the question of a specific individual target, and obviously the LIPOXmax/FATOXmax appears as a logic candidate for this purpose. Accordingly, several teams have undertaken the study of the metabolic effects of exercise training targeted at this level.

5.3 Targeting endurance exercise close to the LIPOXmax vs higher intensity levels

A topic which has generated a lot of discussion over the last decade is the selection of the optimal exercise protocol that could be used for the management of obesity and diabetes. Initially, low intensity endurance training (LI), as it was known to be the variety of exercise that oxidized the highest quantity of lipids, was logically proposed (Thompson et al., 1998). However, later focus was given on other kinds of exercise such high intensity endurance training (HI), resistance training (RT) and interval training (IT). All of them were evidenced to exert beneficial effects when applied to obese (Jakicic & Otto, 2005, 2006) and diabetic (Praet & van Loon, 2007, 2009) patients. On the whole, LI remains the easiest and the most widely evaluated procedure. It is also the best demonstrated as shown by a recent meta-analysis on exercise and diabetes that selected 34 from 645 papers. This paper confirmed that endurance exercise alone improves HbA1c (-0.6%), blood pressure, (-6.08 mmHg), and triglycerides (-0.3 mmol/L), while RT has no effects demonstrable by meta-analysis on these parameters (Chudyk & Petrella, 2011).

An overlook at the rapidly expanding body of knowledge in the field of molecular biology of muscle shows that either LI, HI, RT or IT are able to improve muscular function and to be helpful for the correction of metabolic disturbances (Burgomaster et al. 2008). It is however important to emphasize that RT and ET act on separate and antagonistic intracellular pathways (Koulmann & Bigard, 2006), hence they are independent tools that cannot be expected to provide equivalent effects on muscle cells.

At the cellular level (Koulmann & Bigard, 2006) endurance training induces a set of regulatory adaptations that improve mitochondrial function and protein synthesis and overall, the enzymes for both CHO and fat oxidation are increased. As a result of these cellular adaptations, exercise training improves whole body lipid metabolism and carbohydrate tolerance, thus consisting in a fully recognized tool for reducing both blood lipids and glucose (see below).

As reminded above, most exercise physiology papers describe exercise protocols applied at a given percentage of maximal aerobic capacity without reference to exercise calorimetry. When exercise is performed at 40% VO_{2max} or below, it is likely to be performed in the LIPOXmax zone, but, since LIPOXmax is frequently much lower in obese subjects, a significant percentage of subjects are likely to exercise above this zone, in the range where lipid oxidation is close to zero and CHO almost becomes the exclusive energy source.

Therefore, LIPOX training represents a better defined exercise protocol, whose effects on lipid oxidation are predictable. Exercise performed above this zone results in more CHO oxidation. This CHO oxidation may be followed by some degree of fat oxidation after exercise but may frequently fail to induce this lipid oxidation rise. Although the energetic balance is assumed to result in both cases in a negative fat balance, these two types of exercise do not involve the same energetic pathways.

At the date of redaction of this article, there are several studies (or abstracts) published in peer-reviewed journals reporting the results of LIPOX training (table 4). Therefore, these effects of LIPOX training can now be well described on the basis of a recent meta-analysis (Romain et al., 2010) that included 16 studies shown in table 1, *ie*, 247 participants belonging to 5 different populations: obese teenagers, metabolic syndrome, HIV patients with lipodistrophy, type-2 diabetics, and psychiatric patients treated by neuroleptics. Study length ranged between 2 to 12 months. Weekly frequency of sessions ranged between 2 and 4. Preliminary results showed that LIPOXmax was shifted to a higher power intensity by 4.93 watts (95% confidence interval (CI) 4.74-5.13; $p < 0.0001$). Weight decreased by -2.9 kg (95%CI: -4.1; -1.7; $p < 0.0001$). Fat mass decreased by 1.7% (95% CI 1.82 - 1.64; $p < 0.0001$), and waist circumference decreased by -4.9 cm [95%CI: -6.6; -3.2] ($p < 0.0001$).

We have not included in this meta-analysis an interesting study by the team of A. Sartorio (Lazzer et al, 2011) that compared over three weeks energy-matched programs of low intensity (40% VO_{2max}) and high intensity (60% VO_{2max}) endurance, and showed that the exercise in the LIPOX zone was twice more efficient for fat loss. This protocol was not exactly targeted on the LIPOXmax but designed to train the subjects in this zone, and its results are in agreement with those pooled in the meta-analysis.

The results of these studies demonstrate the efficiency of training targeted at the LIPOXmax on weight loss, even over a short time period. In diabetics, HIV-infected patients, and psychiatric patients under neuroleptics, the efficiency of this procedure seems to be lower than in obesity or metabolic syndrome. As expected, the association with a diet improves the efficiency of this training. However, two thirds of the studies were without added diet and thus most of the weight-lowering effects of LIPOX training are likely to be due to the effects of exercise alone on energy balance and eating behavior. Therefore, it is clear that LIPOX training alone decreases body fat, even if no specific diet is applied. This effect is clearly and constantly evidenced in training protocols containing as few as 2 or 3 sessions per week. In fact, the number of sessions per week seems to improve the results and a dose-relationship can be postulated. However, this issue remains to be specifically investigated.

A crucial issue is that the extent of fat loss in response to exercise training varies quite widely among individuals (Snyder et al., 1997; King et al., 2008; Byrne et al., 2006), even when differences in compliance to the exercise program and energy intake are accounted for. In other terms, exercise is very efficient to lose weight in some individuals while in others it fails to induce weight loss and even more may induce weight gain. Focus on the specific profile of responders and nonresponders helps to understand this variability. It appears to be explained by two variables: eating behavior and fat oxidation.

A role for fat oxidation is suggested by recent studies. In sedentary premenopausal women, a 7-week endurance-type exercise training program reaching progressively to 5 x 60 minutes per week at 65% -80% of predicted maximum heart rate resulted in a mean change in fat mass for the group was -0.97 kg (range +2.1 to -5.3 kg). The strongest correlate of change in fat mass was exercise energy expenditure, as expected. However, the change in fasting RER correlated significantly with the residual for change in fat mass after adjusting for the effects of both exercise energy expenditure and change in energy intake. This means that training-induced increase in fat oxidation explains 7% of the variance of exercise-induced weight loss. In multiple regression analysis, exercise energy expenditure and change in fasting RER were the only statistically significant predictors of change in fat mass, together explaining 40.2% of the variance. Thus, fat loss in response to exercise training depends not only on exercise energy expenditure but also on exercise training-induced changes in RER at rest. Whether it is also the case for RER during exercise is suggested by recent studies (Lavault et al., 2011). This suggests that development of strategies to maximize exercise-induced fat loss may be useful for optimizing exercise-induced slimming (Barwell et al., 2009).

Another important issue in these exercise-based strategies would be to control changes in eating behavior (Bouchard et al., 1990). Muscular activity may induce a temporary postexercise anorexia, which is dose-dependent on the intensity and duration of the exercise (King et al., 1994; Westerterp-Plantenga et al., 1997). On the long term, the effect of exercise on eating behavior are complex and variable and largely explain the variability of weight loss responses. In fact, recent studies show that the effects of regular exercise on appetite regulation involves at least 2 processes: an increase in the overall (orexigenic) drive to eat and a concomitant increase in the satiating efficiency of a fixed meal (King et al., 2009). The former may be related to glycogen deficiency, which increases appetite (Melanson et al., 1999), so that exercise protocols that spare glycogen may avoid this increase in orexigenic drive (Hopkins et al., 2011). Exercise targeted at the LIPOXmax, due to its greater reliance on fat, is likely to spare more glycogen and thus to be less orexigenic than acute exercise that oxidizes mostly carbohydrates.

Clearly, exercise may be an efficient and safe technique to lose fat as shown by the results obtained in responders. The study of non responders suggests that focus on the two parameters explaining the lower efficacy of exercise (fat oxidation and eating behavior) may help to improve the results. Targeting on lipid oxidation during exercise may be a way to better control these two parameters. More studies are needed to verify this concept (Hopkins et al., 2011).

5.4 LIPOX training improves mitochondrial respiration and enzymes of lipid oxidation

Bordenave (Bordenave et al., 2008) described the effects of ten weeks of mild exercise training targeted at the LIPOXmax (45 min of cycling, twice a week). This training was not sufficient to significantly decrease weight, but it exhibited marked effects on whole body

lipid oxidation and muscle oxidative capacities. Indeed, after training, the LIPOXmax was shifted to higher power intensity and the MFO was significantly increased compared with pre-training values (+51 mg.min⁻¹). This study included biopsies and evidenced LIPOX training-induced improvements in mitochondrial respiration and citrate synthase activity. Changes in whole body lipid oxidation were associated with changes in parameters of muscle oxidation. In another study the 3-Hydroxyacyl-CoA dehydrogenase (HAD), an important enzyme that functions in mitochondrial fatty acid beta-oxidation by catalyzing the oxidation of straight chain 3-hydroxyacyl-CoAs, was studied in trained and untrained women. It was shown that HAD activity and fat oxidation rates were highly correlated indicating that training-induced adaptation in muscle fat oxidative capacity is an important factor for enhanced fat oxidation (Stisen et al., 2006).

5.5 Does LIPOX training increase REE and resting fat oxidation?

There is no study on the effects of LIPOX training on resting fat oxidation. Endurance training at higher levels yields conflicting results and it is likely that this effect is not constant with endurance protocols. A study by Van Aggel-Leijssen (Van Aggel-Leijssen et al., 2001) using a low-intensity exercise training program (40% VO₂max, ie the LIPOXmax zone) three times per week for 12 weeks showed that this variety of training increased the contribution of fat oxidation to total energy expenditure during exercise but failed to do so at rest in obese women (Van Aggel-Leijssen et al., 2001). However, another study may suggest an effect of endurance training in the LIPOXmax zone or below on resting fat oxidation. A very mild exercise consisting in an increase of regular physical activity equivalent to 45 min of walking 3 days/week induces some improvements in lipid metabolism such as an increase in skeletal muscle protein expression of PPARdelta and UCP3 in type 2 diabetic patients (Fritz et al., 2006), and improves lipid oxidation without changes in mitochondrial function in type 2 diabetes (Trenell et al., 2008). This protocol of walking an extra 45 min per day over an 8-week period is an insufficient stimulus to induce detectable mitochondrial biogenesis but demonstrates physical activity-induced enhancement of resting lipid oxidation, independently of intramuscular lipid levels. A specific study on LIPOXmax training and lipid oxidation at rest in obese and nonobese people remains to be done.

5.6 Low intensity training targeted at the LIPOXmax training improves inflammatory status

Low-grade systemic inflammation is suggested to play a role in the development of a variety of chronic diseases including obesity, diabetes and cancer. A number of studies suggest that in these diseases regular exercise has anti-inflammatory effects therefore it may contribute to suppress systemic low-grade inflammation (Mattusch et al., 2000; Stewart et al., 2007; Goldhammer, et al., 2005). Overall, both endurance and resistance training decrease C-Reactive Protein (CRP) (Martins et al., 2010). In two studies, LIPOXmax training has been shown to decrease CRP (Ben Ounis et al., 2010; Brun et al, 2011b). In these studies, inflammatory parameters were also measured and changes in CRP were negatively related to those of lipid oxidation during exercise, suggesting that the improvement in the ability to oxidize lipids during exercise is associated with an anti-inflammatory effect. Further studies are needed.

5.7 LIPOXmax training maintains fat-free mass

All the aforementioned studies show that LIPOXmax training maintains fat-free mass, and in some of them an increase is found. This is a constant finding, while protocols using higher intensities in patients give less consistent result on fat-free mass (Brandou et al., 2005; Brun et al., 2010a). Obviously, it is well demonstrated that correctly performed resistance training is an efficient way to improve fat free mass (Schoenfeld et al., 2010), but low intensity exercise has also been demonstrated to protect lean mass and to prevent protein breakdown. A 45-min walk on a treadmill at 40% VO_2 peak induced short-term increases in muscle and plasma protein synthesis in both younger and older men (Sheffield-Moore et al., 2004).

In a study on dieting postmenopausal women with a total energy expenditure of 700 kcal/wk, *ie*, 8 kcal.kg body weight⁻¹wk⁻¹ with LI being at 45-50% of heart rate reserve (HRR) and HI at 70-75% (vigorous-intensity) of HRR (Nicklas et al., 2009) found that with a similar amount of total weight loss, lean mass is preserved with either moderate- or vigorous-intensity aerobic exercise performed during caloric restriction and concluded that FFM is equally preserved with LI and HI. Both resistance (RE) and endurance (EE) exercise are able to stimulate mixed skeletal muscle protein synthesis, but the phenotypes induced by RE (myofibrillar protein accretion) and EE (mitochondrial expression) training are different and this is probably due to differential stimulation of myofibrillar and mitochondrial protein synthesis (Koulmann et al., 2006; Wilkinson et al., 2008; Harber et al., 2009). A mechanism that may play a role in this protective effect of LI is glycogen sparing. It has been shown that CHO availability influences the rates of skeletal muscle and whole body protein synthesis, degradation and net balance during prolonged exercise in humans (Howarth et al., 2010). On the whole, although more investigation is required, LIPOXmax training is an efficient way to maintain or even to improve fat-free mass by increasing the mass of metabolically active muscle. At the beginning of training protocols in very sedentary patients, it may be used for this purpose. For example, studies in undernutrition situations such as anorexia nervosa are in progress.

5.8 Comparison between high intensity (HI) and low intensity (LI) training

It is clear that during LI even more if it is targeted at the LIPOXmax quite important quantities of lipids are oxidized. By contrast, HI oxidizes mostly or exclusively CHO. HI is sometimes followed by a slight rise in oxidation of lipids, but this quantity of lipids oxidized postexercise remains low (Chenevière et al., 2009a; Warren et al., 2009) even more when HI is not continuous (interval training [INT]). Therefore, LI and HI or INT are not equivalent tools and have distinct properties.

This is clearly evidenced in a recent study comparing INT and LIPOX training in T2D (Brun et al., 2010a). 63 type-2 diabetics were compared over a period of 3 months without nutritional intervention: 39 were trained at the LIPOXmax determined with exercise calorimetry, 12 were submitted to a square wave endurance exercise-test (SWEET) protocol of training, and 12 untrained patients served as controls. After 3 months, both training procedures increased $\text{VO}_{2\text{max}}$ (SWEET training +42% vs LIPOXmax training +14%) and this effect was stronger with SWEET than with LIPOXmax. SWEET training reduced resting systolic blood pressure (-12mmHg) and total cholesterol (-0.29 mmol/l), while LIPOXmax training did not. Both procedures decreased weight and BMI. As expected, the LIPOXmax training improved the ability to oxidize lipids (maximum lipid oxidation rate +53 mg/min) shifted to a higher power intensity (+21 watts), decreased fat mass (-1 kg), increased fat-free

Author	Journal	number	population	protocol	Duration (month)	Weight (Kg)	Waist circumference (cm)	Change in Fat Mass (Kg)	Change in total cholesterol (mmol/l)
Ben Ounis et al., 2008	Diabetes & metabolismism	8	Obese adolescent	Training	2	-1,9	-1,8	-1,7	-0,21
Ben Ounis et al., 2008	Diabetes & metabolismism	8	Obese adolescent	Training +diet	2	-11,5	-12,3	-11,2	-0,51
Brandou et al., 2003	Diabetes & metabolismism	14	Obese adolescent	Training	2	-3,72	-3,73		0,04
Brandou et al., 2005	Diabetes & metabolismism	7	Obese adolescent	Training +diet	3	-5,2		-5,07	
Dumortier et al. 2003	Diabetes & metabolismism	28	Metabolic syndrome	Training	2	-2,6	-3,53	-1,4	
Fedou et al., 2008	Science et Sport	10	AIDS	Training	12	-0,92		-0,01	-0,28
Ben Ounis et al., 2009a	Science et Sport	18	Obese adolescent	Training	2	-2	-2,9	-2	
Ben Ounis et al., 2009a	Science et Sport	18	Obese adolescent	Training +diet	2	-6	-6,9	-7	
Dumortier et al., 2002	Clinical Hemorheology	21		Training	2				0
Bordenave et al., 2008	Diabetes & metabolismism	11	T2D	Training	2			-3,13	
Ben Ounis et al., 2009b	Annales d'endocrinologie	9	Obese adolescent	Training	2	-1,2		-1,4	
Ben Ounis et al., 2009b	Annales d'endocrinologie	9	Obese adolescent	Training +diet	2	-9,5		-5,9	
Jean et al., 2006	Annales d'endocrinologie	28	T2D	Training	3	-1,3	-3,94	-0,66	-0,01
Romain et al., 2009	Science et Sport	17	Neuroleptic treated	Training	3	-2,9			
Jeukendrup, 2008	Med Sci Sports Exerc	8	Obese	training	2*4 wk	-0,2		-0,1	
Mogensen et al., 2009	diabetes, obesity and metabolismism	12	T2D	training	2,5	0	-2,8	-1,5	
Elloumi et al., 2009	Acta Paediatrica	7	Obese adolescent	training	2	-1,7			
Brun et al., 2010a	Diabetologia	39	Obese adolescent	Training +diet	2	-12,3	-10,5	-12,1	
			T2D	Training	3	-2,23			

Table 5. Studies of training at the LIPOXmax/FATmax

mass (+1 kg), decreased waist circumference (-3.8 cm) and hip circumference (-2.2 cm) while SWEET training did not significantly modify any of those parameters. Over this short period, the effects of training on HbA1c were significant in the LIPOXmax group (-0.15%) but not in the SWEET group.

Roffey (Roffey, 2008) compared, in a randomized experiment, supervised cycling training at a constant-load FATmax intensity with high intensity interval training (HIIT) with intervals at 85% VO₂max, both protocols being matched for total mechanical work volume (11250 kCal). Although both procedures reduced fat mass, the effect was twice more important in FATmax trained subjects than HIIT. A decrease in waist circumference and total cholesterol was evidenced with FATmax but not HIIT. Both procedures decreased systolic blood pressure and increased VO₂max.

Put together, these studies show that interval training improves aerobic working capacity, blood pressure and lipid profile, while low intensity endurance training (LIPOXmax training) improves the ability to oxidize lipids during exercise, increases fat free mass, decreases fat mass and decreases HbA1c. The benefits of these two procedures are thus quite different and both are probably interesting to associate in the management of 2 type 2 diabetes.

The psychological tolerability of LIPOXmax training, and more generally low intensity endurance training, compared to high intensity training is poorly known. There is no specific study about the psychological tolerance of LIPOXmax training but some information exists about the effects of prescribing moderate vs higher levels of intensity and frequency on adherence to exercise prescriptions (Perri et al., 2002). In 376 sedentary adults randomly assigned to walk 30 min per day at a frequency of either 3-4 or 5-7 days per week, at an intensity of either 45-55% or 65-75% of maximum heart rate reserve, analyses of percentage of prescribed exercise completed showed greater adherence in the moderate intensity condition. The authors concluded that prescribing a lower frequency increased the accumulation of exercise without a decline in adherence, whereas prescribing a higher intensity decreased adherence and resulted in the completion of less exercise.

Interestingly, Roffey (Roffey, 2008) in his randomized work comparing FATmax training and HIIT, observed a number of clinically significant improvements in health-related quality of life in the FATmax but not the HIIT group.

5.9 Which exercise for diabetes?

Both endurance as well as resistance-type training have been shown to improve whole body insulin sensitivity and/or glucose tolerance and are of therapeutic use in diabetic and insulin-resistant subjects (Praet et al., 2007). Prolonged endurance-type exercise training has been shown to improve insulin sensitivity in both young, elderly and/or insulin-resistant subjects, due to the concomitant induction of weight loss, the upregulation of skeletal muscle glucose transporters GLUT4 expression, improved nitric oxide-mediated skeletal muscle blood flow, reduced hormonal stimulation of hepatic glucose production, and the normalization of blood lipid profiles.

Long-term resistance-type exercise interventions have also been reported to improve glucose tolerance and/or whole body insulin sensitivity. Other than the consecutive effects of each successive bout of exercise, resistance-type exercise training has been associated with a substantial gain in skeletal muscle mass, assumed improve whole body glucose-disposal capacity on the basis on the undemonstrated belief that the higher fat free mass, the higher insulin sensitivity.

While a recent meta-analysis concluded that the effects of both procedures on glucose homeostasis were similar, achieving a reduction in HbA1c by 0.6 to 0.8 (Snowling & Hopkins, 2006; Praet & Van Loon, 2009), a more recent one, after rigorous selection of papers for their methodology, concluded that endurance exercise alone improves HbA1c, blood pressure, and triglycerides, while RT has no demonstrable effects (Chudyk & Petrella, 2011). This issue remains thus controversial, and clearly the best demonstrated method remains endurance training.

When applying endurance-type exercise, energy expenditure should be equivalent to 1.7-2.1 MJ (400-500 kcal) per exercise bout on 3 but preferably 4-5 days/wk, since many of the benefits of exercise are temporary. More vigorous exercise in uncomplicated insulin-resistant states will further improve glycemic control and enhance cardiorespiratory fitness and microvascular function.

Endurance-type exercise combined with resistance (ie, intermittent intensity-type exercise) forms a lower cardiovascular challenge and improves functional performance capacity to a similar extent. Therefore, the combination of endurance- and resistance-type exercise is generally recommended, since it increases the diversity and, as such, the adherence to the exercise intervention program. This is in agreement with the above-reported study in which we compared INT and LIPOX training in T2D (Brun et al., 2010a) and which evidenced that SWEET training improves aerobic working capacity, blood pressure and lipid profile, while low intensity endurance training (LIPOXmax training) improves the ability to oxidize lipids at exercise, increases fat free mass, decreases fat mass and decreases HbA1c. This study shows that benefits of two procedures are rather different and both are probably interesting to associate in the management of type 2 diabetes. A study comparing LIPOX training to more traditional protocols is currently in progress.

Another important advance in this issue comes from a meta-analysis in diabetes (Umpierre et al, 2011) which shows that structured exercise is much more efficient for improving HbA1c than exercise advice alone, and that more than 150 minutes of endurance per week is twice more efficient than exercise performed less than 150 minutes per week.

6. Conclusions

LIPOXmax/Fatmax is a parameter that can be measured with validated protocols. It appears to be a reproducible measurement, although modifiable by several physiological conditions (training, previous exercise or meal). Its measurement closely predicts the amount of lipids that will be oxidized over a 45-60 min of low to medium intensity training performed at the corresponding intensity. It might be a marker of metabolic fitness, and reflects mitochondrial respiration. LIPOXmax is related to catecholamine status and the growth-hormone IGF-1 axis. Its changes are related to alterations in muscular levels of citrate synthase, and to the mitochondrial ability to oxidize lipids during exercise, reducing blood pressure and HbA1c in type 2 diabetes and decreasing circulating cholesterol. Whether the specific targeting on lipid oxidation during exercise has beneficial effects superior to those obtained by a similar energy deficit obtained by other protocols of exercise is suggested by recent studies but remains a current matter of research.

Little is known about the usefulness of these parameters in sports, but classification of athletes according to their metabolic profile during exercise may help to understand their ability to perform endurance sports or short term all out exercise, and to detect overtraining-related alterations in metabolic adaptation to exercise.

7. References

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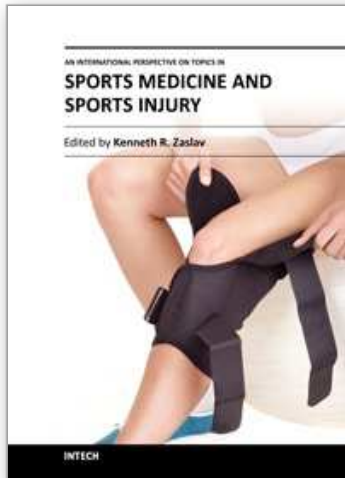
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For the past two decades, Sports Medicine has been a burgeoning science in the USA and Western Europe. Great strides have been made in understanding the basic physiology of exercise, energy consumption and the mechanisms of sports injury. Additionally, through advances in minimally invasive surgical treatment and physical rehabilitation, athletes have been returning to sports quicker and at higher levels after injury. This book contains new information from basic scientists on the physiology of exercise and sports performance, updates on medical diseases treated in athletes and excellent summaries of treatment options for common sports-related injuries to the skeletal system.

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