
# Preoperative exercise and postoperative lactate clearance

**Pim Knuiman, June 2010**

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## Summary

***Background*** On the metabolic level, major surgery can be compared with exhaustive physical exercise. In both cases lactate metabolism plays a pivotal role in performance and recovery. This literature review examines to what extent the preoperative physical state of a patient influences postoperative recovery. After major surgery, particularly after termination of anesthesia, most patients have increased blood lactate levels. This increased blood lactate levels (hyperlactemia) correlates with mortality after major surgery. The purpose of this literature review is to collect scientific evidence for developing a preoperative exercise intervention aimed at achieving a decreased change of hyperlactemia of people who are undergoing major surgery.

***Methods*** Embase, Pubmed, and Google Scholar were searched using relevant keywords in the field of this literature review. In addition, the snowball method was used by analyzing the list of references of recent articles to find related articles in the same field.

***Results*** It seems that there is a direct relationship between aerobic capacity and the ability to clear lactate in animals and humans. Several studies suggest that aerobic capacity affects lactate metabolism as well and more specifically lactate clearance. Epinephrine (EPI) and Norepinephrine (NEPI) levels are elevated during both endurance exercise (EE) and resistance exercise (RE) and stimulate renal and hepatic gluconeogenesis which is the most important mechanism to clear lactate after surgery. The role of the monocarboxylate transporters (MCTs) 1 and 4 is especially important in improving the lactate shuttle from fiber to the bloodstream and vice versa to increase lactate oxidation via muscle tissues and heart.

***Conclusion*** The final conclusion is that EE and RE result in an improved capacity to clear lactate in muscles and other organs. Particularly, the RE improved clearance in organs including liver and kidneys, seems to be most promising in the prevention of hyperlactemia after surgery. However, more research is necessary to find out whether a decrease of lactate after major surgery truly results in decreased mortality. The results so far justify doing an intervention study aimed at reducing lactate levels after surgery.

***Intervention*** A combination of short endurance related exercise combined with RE (both mainly anaerobic) e.g. time-related circuit training has many favorable consequences for net lactate clearance via the liver and the kidneys.

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# Introduction

## 1. Major surgery and the role of lactate

On the metabolic level major surgery can be compared with exhaustive physical exercise. In both cases lactate metabolism plays a pivotal role in performance and recovery. This literature review examines to what extent the preoperative physical state of a patient influences postoperative recovery. After major surgery, particularly after termination of anesthesia, most patients have increased blood lactate levels (Nichol et al., 2010). This situation can become critical since hyperlactemia is considered an important predictor of mortality on intensive care units (Shapiro et al., 2005 and Demers et al., 2000). Normolactemia (< 2 mM) is associated with a mortality rate of 10 %, but hyperlactemia (>6.0 mM) is associated with a mortality rate of 41% in patients without infection and even of 58% in patients with infection (Del Portal et al., 2010). The lactate clearance plays a very important role in lowering the blood lactate concentration. Different types of exercise influence the lactate clearance in a positive way. The purpose of this literature review is to collect scientific evidence for developing a preoperative exercise intervention aimed at achieving a decreased change of hyperlactemia of people who are undergoing major surgery. The effects of a preoperative exercise intervention on post-operative hyperlactemia and mortality have not been investigated extensively yet. It is plausible that a preoperative exercise intervention program has a positive effect on postoperative recovery and may result in a decrease in mortality after major surgery. It is hypothesized that the beneficial effects of exercise in the preoperative phase are mediated through an improved lactate clearance and transport.

The research question can be formulated as follows: *does preoperative exercise decrease the risk of developing postoperative hyperlactemia in people undergoing surgery?*

## 2. Production of lactate

Glucose can be metabolized via the aerobic and anaerobic glycolysis. When glucose is metabolized in the presence of oxygen (aerobic) it is finally converted to water and carbon dioxide. However, when it is metabolized in the absence of oxygen (anaerobic), lactate is produced. (Phypers and Pierce, 2006)

As far as known lactate can only be formed from pyruvate best known as end product of glycolysis. Glycolysis, converts $NAD^+$ to NADH + $H^+$ (an acidic component) and can only be maintained when $NAD^+$ is regenerated from NADH. A reduction in pH, due to production of $H^+$, inhibits PFK (phosphofructokinase) a rate limiting enzyme of glycolysis. (Schreurs, 2010) In aerobic tissues mitochondria play a role in this regeneration but the process is rather complex. (Newsholme and Leech, 2009)

Cells that lack mitochondrial activity can only regenerate NAD by a reaction in which NADH is used to reduce pyruvate to lactate. This reversible reaction is catalyzed by the enzyme LDH or lactate dehydrogenase (Newsholme and Leech, 2009). Since this reaction is reversible, lactate has to be removed from the cell in order to prevent that glycolysis is inhibited as yet. In this situation lactate can be released to neighboring cells with mitochondrial activity within the same tissue or to the blood (Schreurs, 2010). The latter process may cause an increase in blood lactate level.

## 3. Clearance of lactate

*Clearance in general*

The concentration of blood lactate is a balance between production and clearance. In normal, healthy individuals, this balance is optimally maintained. However, in others, metabolic function, stress from surgery, and other conditions can alter this function. The clearance of lactate can be defined as the rate at which of blood lactate is cleared. Lactate can be cleared by gluconeogenetic tissues (liver, kidneys) and oxidative tissues (muscles and heart).

*Clearance via the liver and kidneys*

Lactate is transported into cells and then converted to glucose via gluconeogenesis in the liver and the kidneys. Even at rest, a low rate of lactic acid is formed from glucose in muscles and released. (Newsholme and Leech, 2009) Most is transported to the liver where it is removed and converted to glucose, known as the Cori cycle. This glucose is released back into the blood, where it is, once again, taken up by muscle and converted to lactic acid (Newsholme and Leech, 2009). Gerich et al., (2001) suggested that the Cori cycle may occur both in the liver and kidneys. Nephrectomy studies in rat, dog and sheep suggest that the native kidney's contribution to the removal of lactate is substantial, with the organ being responsible for the clearance of approximately 20-30% of an exogenous load (Bellomo, 2002).

*Clearance via the heart*

Lactate is transported by monocarboxylate transporter 1 (MCT1) into the cardiomyocytes and is fully oxidized to carbon dioxide. All aerobic tissues are able to oxidize lactate to generate ATP but the heart is especially important, since lactate is readily transported into cardiomyocytes and there is always a demand for ATP. (Newsholme and Leech, 2009)

*Clearance via the muscles*

Oxidative muscle fibers take up lactate at faster maximal rates in comparison to glycolytic muscle fibers. Oxidative muscle fibers predominantly oxidize lactate whereas glycolytic fibers primarily convert lactate to glycogen. Both the rate of muscle lactate uptake and the route of disposal for lactate clearly depend on the fiber type composition of the muscle. (Gladden, 1998) In skeletal muscle, lactate is primarily formed in the white glycolytic muscle fibers where it is exported by MCT4. Subsequently, the lactate is taken up by the red oxidative fibers via MCT1 and MCT4. (Bonen et al., 2000) During sustained heavy exercise, lactate and protons also build up in red muscle fibers. From there, they are removed via MCT1 and MCT4 supported by Ca2+. MCT 1 is nearly found in all tissues studies and has a Km value of 3-5 mM for lactate. MCT4 is a low-affinity, high-capacity carrier with a Km value of 20-35 mM for lactate and is found prominently in glycolytic tissues such as white skeletal muscles and astrocytes. (Becker et al., 2010) This suggests that tissues with a high expression of MCT4 transport lactate to the extracellular space whereas tissues with a high expression of MCT1 transport lactate from the extracellular space to intracellular space for oxidation or gluconeogenesis.

## 4. Hyperlactemia, causes and types

*Arise of hyperlactemia*

The concentration of blood lactate is the result of the release of lactate from tissues that produce lactate and the uptake by tissues that may clear lactate. The amount of lactate in the blood remains constant as long as release and uptake are in balance (= quantitatively equal). In normal, healthy individuals, the concentration is < 2 mM, known as normolactemia (Levy, 2006). Hyperlactemia can result from increased release (type A hyperlactemia), or decreased uptake (type B hyperlactemia). In case of stress e.g. physical stress or surgery, the balance between release and uptake may be disturbed and may cause a change of the lactate concentration in the blood.

*Hypoxic hyperlactemia*

The classical view explains hyperlactemia as a result of hypoxia due to hypoperfusion. Hypoperfusion can be defined as the reduced blood flow to the organs, for example in the case of a shock (van der Meer and Stehouwer, 2005). Hypoperfusion could lead to permanent cellular dysfunction and eventually death (Bouman and Bernards 2002). Hypoxia is the condition where the body as a whole or a particular part of the body, such as tissues, is not adequately provided with oxygen (Bouman and Bernards 2002). Within this traditional view, hypoxia is mentioned as the cause of increased anaerobic metabolism in patients in a critical condition. Levy (2006) described in his paper that classical hyperlactemia in shock is considered as secondary to tissue hypoxia induced by a decrease in tissue perfusion.

*Non-hypoxic hyperlactemia*

Levy (2005) suggested that increased aerobic glycolysis, results in amounts of pyruvate that exceed the pyruvate dehydrogenase capacity. Such enhanced glycolysis can be triggered by epinephrine-stimulated increased $Na^+$-$K^+$-pump activity. This phenomenon releases more substrate for the glycolysis. Many authors have demonstrated this in animal studies (Luchette et al., 2001, McCarter et al., 2002). Levy et al (2005) found similar results in a study with humans. Levy and his colleagues demonstrated that antagonizing the $Na^+$-$K^+$-pump completely stopped muscle lactate overproduction in patients on the intensive care unit.

## 5. Training and clearance

EE and RE influence the lactate clearance and or production. Many studies are conducted to investigate whether exercise influences the lactate clearance and production, but the precise effects of preoperative exercise on postoperative lactate production and clearance are still unknown these days.

# Methods

**Literature search**
Embase, Pubmed, and Google Scholar were searched using relevant keywords in the field of this literature review. In addition, the snowball method was used by analyzing the list of references of recent articles to find related articles in the same field.

*Criteria for inclusion in this literature review*
In general the search was restricted to publications performed with humans and written in English. Only for demonstrating the relationship between aerobic capacity and lactate clearance also animal studies were included. The quality assessment criteria for selecting the chosen studies are made on the study design, characteristics of the participants/subjects, the specificity, duration, presence of control group, human or animal study and date of publication. Studies published before 1980 were excluded.

Studies included in this literature review were categorized according to the following four topics. Topic 1: animal and human studies that investigated the effects of EE on lactate clearance. The rats and humans included in these studies all underwent a training program aimed at increasing the aerobic capacity and measured in $VO_{2max}$. Only studies that used a control group were included. Topic 2: studies that investigated the clearance via the liver and kidneys. Effects of EE and RE on EPI and NEPI were taken into consideration because both hormones appear to play an important role in stimulating lactate metabolism in these organs. Topic 3: studies that investigated the effects of training on lactate clearance via muscles and heart. Topic 4: studies that investigated the effects of EE and RE on the MCTs. The various databases refer to a number of international scientific journals.

# Results

### 1. Animal and human studies on the effects of EE on lactate clearance

It seems that there is a direct relationship between aerobic capacity and the ability to clear lactate in animals and humans. Several studies suggest that aerobic capacity affects lactate metabolism as well and more specifically lactate clearance. Donovan et al., (1989), Donovan and Pagliassotti, (1990, Figure 1) demonstrated the effects of aerobic capacity on lactate metabolism in endurance trained and non-trained rats. The authors demonstrated that an 8-week-lasting endurance-training protocol, (1 hour per day a around 75% $VO_{2max}$, 38 meters per minute with a slope of 10%) did not alter the resting lactate production, but the rate of lactate clearance was twice as high as in trained animals compared with non-trained. Furthermore, the trained rats showed a 25% increased level of gluconeogenesis. Therefore, for a given production of lactate, trained animals maintained a lower level of lactate through the increased elimination by gluconeogenesis and the oxidation of lactate. The authors only focused on lactate kinetics during steady-state resting conditions.

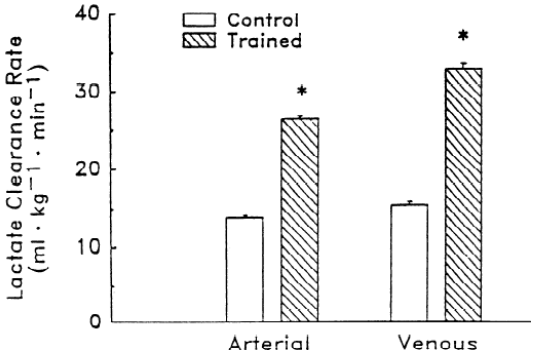


**Figure 1.** Steady-state lactate-clearance rates (means ± SE) in trained and non-trained rats. Values based on arterial and venous lactate concentrations are presented. * Significant difference between control and trained groups ($P < 0.01$) (Donovan and Pagliassotti, 1989).

MacRae et al., (1992), Phillips et al., (1995), and Lampert et al., (1996) confirmed similar findings in studies performed with humans. Lampert (1996, Figure 2) also looked at the lactate kinetics during exercise before and after a training period of six weeks of EE in patients one year after surgery.

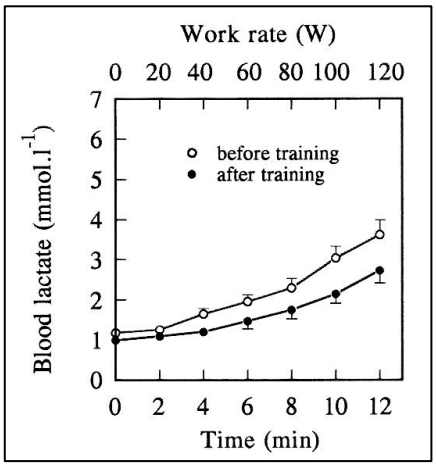


**Figure 2** Venous blood lactate concentrations (mean ± SE) in humans before and after training as a function of exercise time . (n = 8, except for the 60- and 120-W exercise steps, where n = 7). Lactate concentrations are significantly different ($P<0.01$) at the end of each exercise step (Lampert et al., 1996).

The relationship between the aerobic capacity and lactate clearance ability is clear, but it is still unclear what the exact underlying mechanisms are which cause improved lactate clearance. Nevertheless, these studies suggest that lower lactate concentrations in animals and humans result from an increased ability to clear lactate and not from a decreased lactate production. However, further research is needed to verify this. Gladden (1998) described the possible underlying mechanisms responsible for the improved ability to clear lactate as a result of EE. In general, training-induced metabolic adaptations in skeletal muscle might be expected to speed up lactate utilization (Gladden, 2008; Donovan & Pagliassotti, 1989;1990). They suggest that EE can lead to better trained tissues with a higher expression of MCT1 on the sarcolemma and mitochondrial membrane.

### 2. Lactate clearance through the liver and kidneys

The liver is thought to be one of the most important organs in net lactate clearance at rest and under exercise (Gladden, 2004) But there is strong evidence that, under normal physiological conditions, the kidneys also play an important role in lactate clearance (Bellomo, 2002). During exercise e.g. RE at 70%> of the 1RM (Repetition Maximum) the liver and kidneys are stimulated to metabolize lactate. The changes in net lactate uptake and release during exercise are unknown, but Meyer et al., (1999;2003) have shown that increased arterial lactate concentrations are associated with an increase in hepatic and renal net lactate uptake. Consequently, it is clear that the kidneys are an important organ for lactate disposal and that this disposal is only hampered under conditions of extreme (90%) decreases in renal perfusion (Bellomo, 2002).

*Role of hormones in stimulating the gluconeogenesis via liver and kidneys*

EPI and NEPI, both sympathetic nervous system hormones and neurotransmitters, are synthesized in the adrenal gland and adrenal medulla respectively (Chu et al., 2000). EPI accelerates the rate at which phosphorylase cleaves glucose from glycogen (McArdle, Katch and Katch, 2007). EPI's action has been termed the glycogenolysis cascade, because the hormone affects progressively greater phosphorylase activation to ensure rapid glycogen mobilization (Febbraio et al., 1999). Acevedo et al., (2007, Figure 3) demonstrated that the intensity of the exercise affects the amount of increase of both hormones.

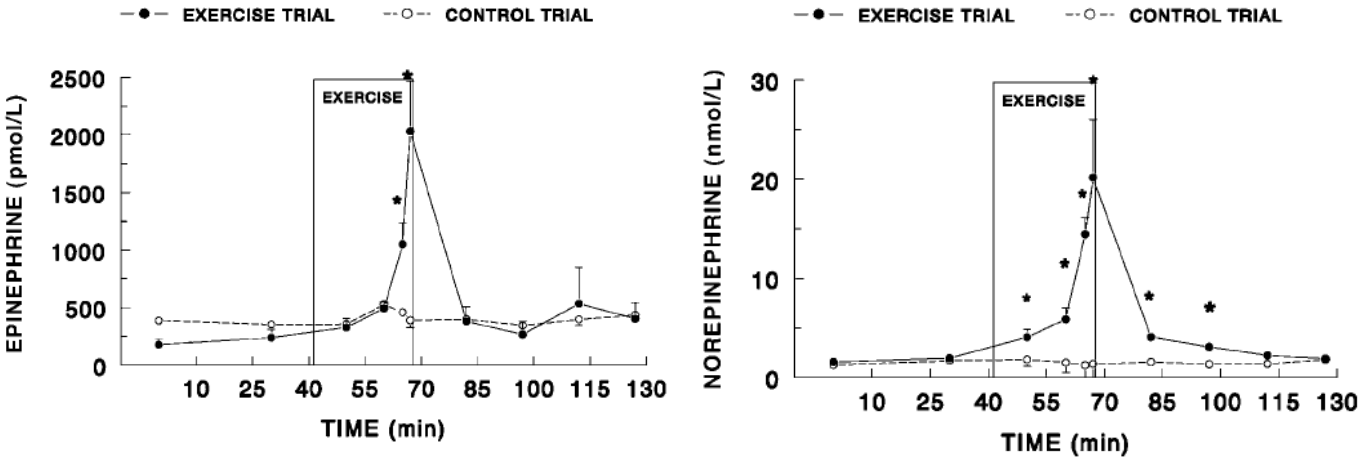


**Figure 3.** EPI and NEPI response to incremental exercise in humans: EPI and NEPI increased significantly as exercise intensity increased, * P<0.05 (Acevedo et al., 2007)

In many cases EPI is modestly increased (50%-70%), whereas NEPI levels increased much higher during RE: levels of 400% above normal are not uncommon during RE at 85% of the 1RM (Koch, 2010). Elevated concentrations of plasma EPI and NEPI stimulate gluconeogenesis and glycogenolysis in the liver and kidneys (Chu et al., 2000 and Gerich et al., 2001). EPI is predominantly elevated through stimulation of β-receptors, whereas NEPI works trough α-receptors (Chu et al., 2000). Goto et al., (2009, Figure 4) investigated the effects of different contractions on EPI, NEPI and lactate. Five-one contractions (5 seconds concentric and 1 second eccentric) caused the highest elevation in EPI, whereas 1-1 contractions (1 second concentric and 1 second eccentric) caused the highest elevations in NEPI.

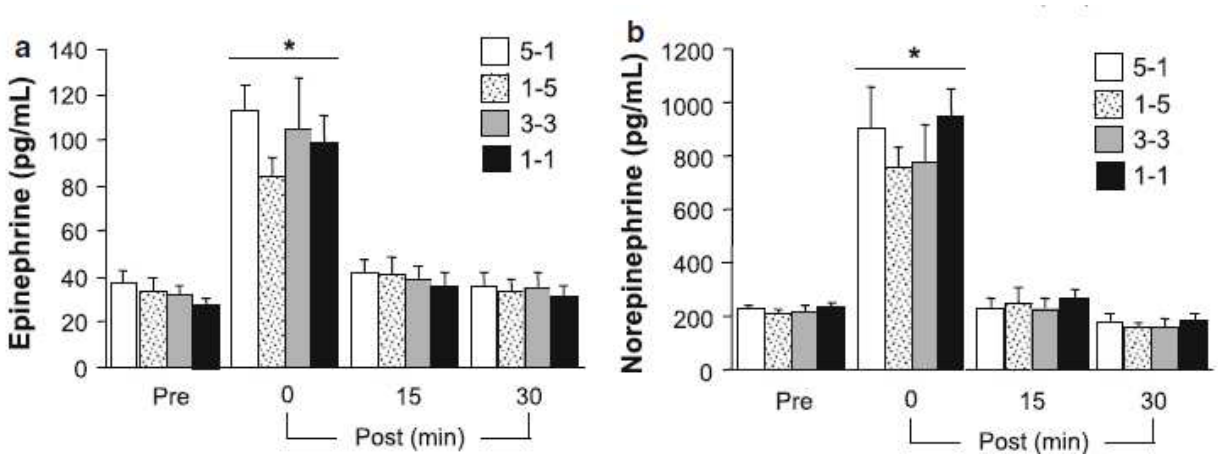


**Figure 4.** Plasma EPI (a) and norepinephrine (b) responses to exercise. Values are means ± SE.. *P <0.05 versus baseline (Pre) values for the respective days (Goto et al., 2009).

### 3. Effect of exercise on lactate clearance in heart and muscles

Although high rates of glycolysis in skeletal muscle make it the main producer of lactic acid in the body, lactic acid can also be taken up by skeletal muscle and heart and used as a respiratory fuel (van Hall, 2010). The balance of the two depends on the type of muscle fiber and the energy demand. The net production of lactic acid by muscle is particularly pronounced in the transition from rest to heavy exercise when there is a rapid increase in energy demand. This is normally not due to insufficient oxygenation but due to other reasons (Gladden, 2004). First, the acceleration of glycolysis at the onset of muscle activity is fast when compared with that of the oxidative pathway. Second, the maximal glycolytic capacity of muscle exceeds the maximal oxidative capacity. The extent to which the ATP-requirements can be met by glycolysis or oxidative phosphorylation is fiber-type dependent with white muscle relying more on the former and red muscle on the latter. In either case, lactate is an important metabolic intermediate, which can exchange rapidly between different cells within a given muscle, between different muscles and between muscle and blood. These processes all require lactic acid transport across the sarcolemma (Juel, 1999; Bonen et al., 1997).

Van Hall (2010) described in his review that lactate is a crucial intermediate metabolite in energy turnover in the skeletal muscle, heart and brain, and potentially in the lungs and gut. He further suggests that the great advantage of lactate metabolism in these tissues is that the valuable glucose and glycogen is not wasted in the process of glycogenolysis/glycolysis with its fast but limited ATP-yield, but that these tissues can take up lactate in large quantities from the circulation and can directly be oxidized without first being transformed to glucose via gluconeogenesis in the kidney and liver.

During resting conditions, the heart exhibits a net lactate uptake similar to skeletal muscle (van Hall, 2010). The lactate uptake by the heart is almost entirely oxidized. Compared with the muscles, the heart does not seem to increase much in its lactate release with enhanced metabolic rate, for example during surgery. Several studies (Baker et al., 1998, Figure 5; Bonen et al., 2000) suggest that the heart is able to oxidize more lactate when MCTs quantities are increased as a result of training.

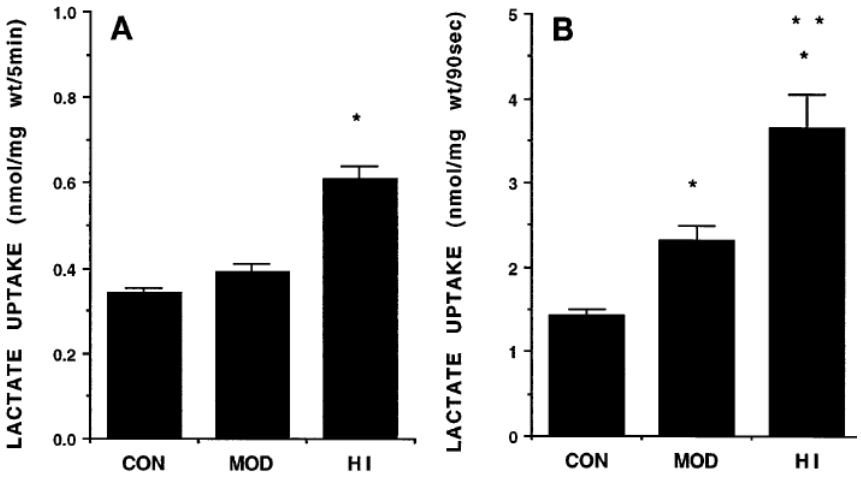


**Figure 5.** Lactate uptake in Soleus muscle (A) and rat hearts (B) from control and 3-wk moderately-trained animals (21 m/min, 8% grade, 1h/day, 5days/wk) and high intensity (31 m/min, 15% grade, 1h/day, 5 days/wk) trained animals. * P<0.05 ** P<0.005 (Baker et al., 1998)

## 4. EE, RE and the role of MCTs

MCT isoforms facilitate the lactate transport activity in the metabolism of all cells (Baker, et al., 1998; Bonen et al., 2000; Juel et al., 2004). Lactate transport seems to be an eminent regulatory mechanism for lactate movement in and out of the skeletal muscle. MCT1 is highly related to the oxidative fiber composition of the skeletal muscle and lactate uptake by muscles is strongly related to the amount of MCT1 in the muscle. (Bonen et al., 2000) MCT4 is mainly found in glytolytic fast twitch fibers (Juel et al., 2004). The length of the EE program (>85% of VO2max) seems to play an important role in the increase in the amount of MCT1 (Baker et al., 1998, Figure 6). A higher amount of this protein is strongly related to the capacity of the muscle to oxidize lactate. MCT1 is highly related to lactate dehydrogenase (LDH) enzymes, which could assist lactate conversion to pyruvate, enabling lactate to be rapidly oxidized (Bonen et al., 2000).

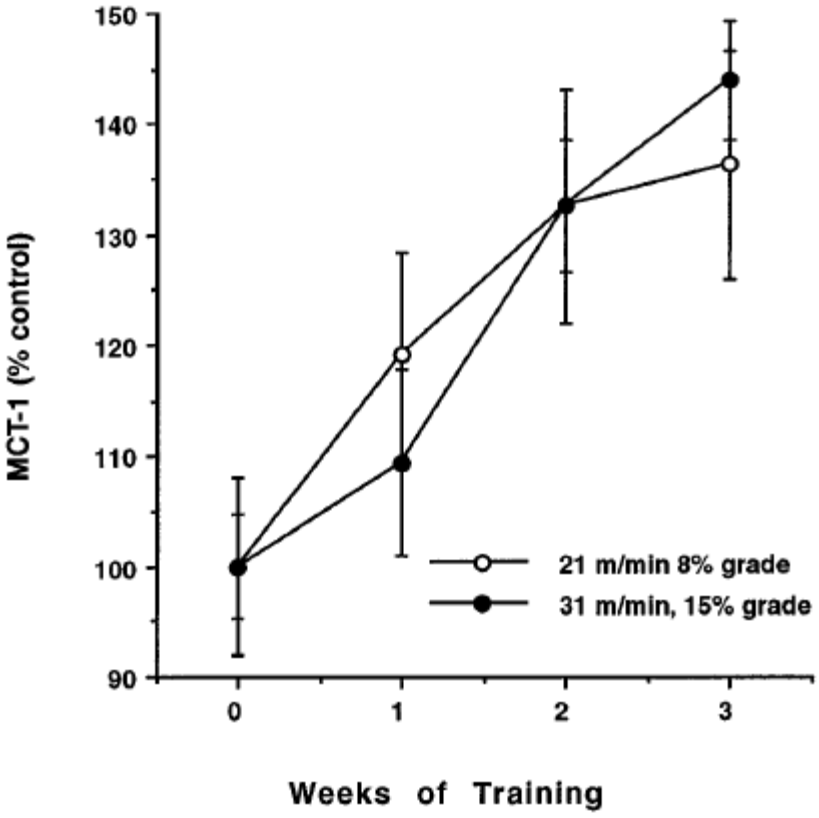


**Figure 6.** MCT-1 in rat hearts at weekly intervals during moderate and high intensity treadmill running (1 h/day). Values are means ± SE; n = 4-5 at each point. For each muscle, MCT-1 content at onset of training (week 0) has been set at 100% (Baker et al., 1998).

In 2004, Juel et al., (Figure 7) demonstrated that RE increases MCT1 by 48% and MCT4 by 32% in previously sedentary elderly healthy individuals. As previously discussed, both MCT1 and MCT4 seems to play an important role in the lactate shuttle.

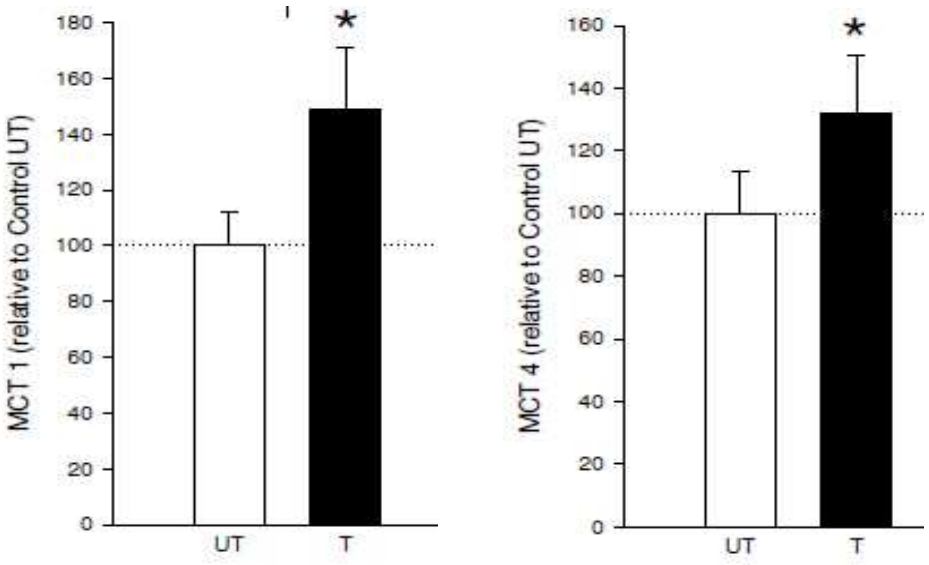


**Figure 7.** MCTs 1 and 4 measured as protein content in skeletal muscle biopsies from ten healthy subjects after completion of 6 weeks of one-legged strength training (Juel et al., 2004).

There is evidence to suggest that the amount of MCT1 correlates with the oxidative capacity of different muscle types. MCT1 is most closely associated with muscle fiber characteristics favoring the uptake of lactate for oxidative disposal (Juel et al., 2004). The over expression of the MCT1 protein alone is sufficient to increase lactate uptake from the circulation (Bonen et al., 2000).

In the end, MCT1 plays an important function and predominantly acts as a lactate influx transporter, promoting the uptake of lactate into skeletal muscle where this substrate can be readily metabolized in the mitochondria (Thomas et al., 2007). Several studies show the effects of EE on MCT1. In summary, it can be stated that EE induces an increase in MCT1. At the same time lactate uptake occurs both in heart and muscle but only increases when the amount of MCT1 is augmented. Mitochondrial MCT1 could participate in increased lactate oxidation after training, but it remains questionable whether MCT1 could also participate in increased lactate oxidation immediately after surgery.

# Discussion

### 1. Effects of EE on lactate clearance

The reviewed articles concerning endurance exercise and lactate clearance show a direct positive relationship between endurance capacity and lactate clearance, both for healthy animals during rest and for healthy humans pre, during and post exercise. The conclusion of this part of the literature review is that EE has a positive effect on lactate clearance during rest.

### 2. Benefits of EE and RE in the pre-operative phase

The question remains what the favorable effects of EE and RE are for the post-operative situation of a patient. The lactate which is produced during EE accumulates and is mainly metabolized in the muscles. During running, cycling or other cardiovascular exercise this mechanism is useful, because of the active red muscle fibers that oxidize lactate. Hence, it seems that this intramuscular lactate clearance mechanism seems not so useful in a post-operative situation, because lactate after surgery arises from another source than the muscles, particularly the lactate that appears in the blood after surgery. It is essential to further investigate the quantitative contribution of EE in stimulating lactate metabolism in the liver and other organs through the gluconeogenetic pathway, and what the effect is on mortality rates in surgical patients.
As mentioned in the results, EE and RE both increase the secretion of EPI and NEPI which stimulate the gluconeogenesis via the liver and kidney and thereby the lactate clearance from the blood. However, RE seems to be more effective in this.

Elevated levels of EPI measured in the early state of the post-operative situation indicated that the most pronounced acute EPI stress response to surgery occurs after termination of anesthesia. This points towards a link between the higher release of EPI immediately after surgery and the effect of EPI on the metabolism of lactate (increased gluconeogenesis).

It is conceivable that major surgery is like an attack on the physiological status of the human body. The improved lactate clearance of the trained subjects was mainly due to an improved gluconeogenesis of the liver and to a lesser extent in the kidneys. The liver is the most important organ responsible for clearance of lactate via gluconeogenesis and this mechanism of lactate clearance is therefore of great importance for a patient in a postoperative situation. MCTs on the membrane of the red muscle fibers may play a role in this, because they increase the efflux of lactate into the extracellular space where the lactate can be oxidized in muscles, heart and liver after transportation to these organs.

### 3. Final conclusion

The final conclusion is that EE and RE result in an improved capacity to clear lactate in muscles and other organs. Particularly, the RE improved clearance in organs, including liver and kidneys, seems to be most promising in the prevention of hyperlactemia after surgery. Nevertheless, more research is necessary to find out whether a decrease of lactate after major surgery truly results in decreased mortality. The results so far justify doing an intervention study aimed at reducing lactate levels after surgery. The set-up of such an intervention study is discussed on the next pages.

# Intervention

### 1. General

For an intervention program, it is important to consider the type of exercise, its intensity and duration. These aspects are discussed in the following sections.

### 2. RE: most effective durations for contractions

Even like the response of EPI and NEPI, lactate response is best on fast short concentric and eccentric contractions e.g. one-second for both concentric and eccentric contractions (Goto et al., 2009). The high release of lactate induces a hyperlactemic situation. In that situation, the liver and the kidneys are forced to clear lactate via gluconeogenesis. Such a situation comes close to a postoperative situation of a patient.

### 3. Optimum intensity and frequency

Effectiveness can be expressed in hypertrophic terms or as the metabolic response during and post the training. In this respect, the lactate response is most relevant for our purposes. Many studies have been conducted with an intensity range from 50-85% of RM1 2-3 times a week. When the total length of the training program was longer than two months, studies found significant increases in muscle mass. Goto et al., (2009) found that 1-1 contraction principle conducted on 80% of the 1RM, all the other contraction forms were conducted at 50% of 1RM. In the end, it is the total combination of contraction forms and intensity that makes RE effective.

### 4. Suggestions for interventions

High-intensity exercise causes high elevations in blood lactate levels. Since, EE and RE both stimulate renal and hepatic gluconeogenesis via the Cori-cycle, a combination of both, as in an interval training, seems to offer the most promising perspective to avoid highly increased lactate levels and to decrease mortality rates after major surgery. Safety plays an important role in the selection of exercise. This is dependent on the physical complications of a patient (Izawa et al., 2004). However, to create a similar hyperlactemia such as after surgery (>6mmol/L), the nature of the exercise must be short and powerful. A combination of short endurance related exercise combined with RE (both mainly anaerobic) e.g. time-related circuit training has many favorable consequences for net lactate clearance via the liver and the kidneys. Examples of body-weighted compound exercises like pushups, squats, supine rows and dips are easy to learn and involve multiple muscles during the movement. Other examples of short and powerful exercises that are less RE-focused, include sprints on the ergometer/treadmill/home-trainer or other short and powerful exercises like skipping or steps. For the RE exercises, the number of repetitions must be between 8 and 12, with a break of 30 seconds between the sets. This intensity (80%) caused the highest response in lactate (Goto, et al., 2009). In total 2 or 3 sets are sufficient for hypertrophy, which is a nice additional benefit after surgery when it comes to revalidation. The time of the sprint exercises must be between 2 and 3 minutes, which causes acidification, and in total this should be as long as the RE sets including the rest periods. The optimum frequency is, like the intensity, dependent on the physical complications of the patient. However, a frequency of 2 or 3 times a week for one hour with a total length of 3-4 weeks is recommended for the expected impact on lactate clearance capacity.

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## References

1) Acevedo, E.O., Kraemer, R.R., Kamimori, G.H., Duran, R.J., Johnson, L.G. and Castracanes, V.D. (2007) Stress hormones, effort sense, and perceptions of stress during incremental exercise: an exploratory investigation. Journal of Strength and Condition Research. Vol. 21. No. 283-288.

2) Baker, S.K., McCullagh, J.A. and Bonen, A. (1998). Training intensity-dependent and tissue-specific increases in lactate uptake and MCT-1 in heart and muscle. Journal of Applied Physiology. Vol. 84. No. 987-994.

3) Becker, H.M., Klier, M., Deitmer, J.W. (2010) Nonenzymatic Augmentation of Lactate Transport via Monocarboxylate Transporter Isoform 4 by Carbonic Anhydrase II. Journal of Membrane Biology. Vol.234. Vol. 125-135.

4) Bellomo, R. (2002) Bench-to-bedside review: Lactate and the kidney. Critical Care. Vol. 6 No. 4.

5) Bonen, A., Baker, S.K. and Hatta, H. (1997) Lactate transport and lactate transporters in skeletal muscle. Canadian Journa; of Applied Physiology. Vol. 22. No. 531-552.

6) Bonen, A.,Tonouchi, M., Miskovic, D., Heddle, C., Heikkila, J.J. and Halestrap, A.P. (2000) Isoform-specific regulation of the lactate transporters MCT1 and MCT4 by contractile activity. American Journal of Physiology Endocrinology and Metabolism. Vol. 279. No. 1131-1138.

7) Bouman, L.N. en Bernards, J.A. (2002). Medische fysiologie. Houten/Mechelen: Bohn Stafleu van Loghum.

8) Chu, C.A., Sindelar, D.K., Igawa, K., Sherck, S., Neal, D.W., Emshwiller, M. and Cherrington, A.D. (2000) The direct effects of catecholamines on hepatic glucose production occur via a1- and b2-receptors in the dog. American Journal of Physiology Endocrinology and Metabolism. Vol. 279. No. 463-473.

9) Demers, P., Elkouri, S. Martineau, R., Couturier, A. and Cartier, R. (2000) Outcome with high blood lactate levels during cardiopulmonary bypass in adult cardiac operation. The Annals of Thoracic Surgery. Vol. 70. No. 2082-2086.

10) Donovan, C.M. and Pagliassotti, M.J. (1989) EE enhances lactate clearance during hyperlactemia. Journal of applied Physiology. Vol. 89. No. 0193-1849.

11) Donovan, C.M. and Pagliassotti, M.J. (1990) Enhanced efficiency of lactate removal after EE. Journal of Applied Physiology. Vol. 90. No. 0161-7567.

12) Febbraio, M.A., Lambert, D.L., Starkie, R.L., Proietto, J. and Hargreaves, M. (1998) Effect of epinephrine on muscle glycogenolysis during exercise in trained men. Journal of applied physiology. Vol. 98. No. 0161-7567.

13) Gerich, J.E., Woerle, H.J., Meyer, C.H. and Stumvoll, M. (2001) Renal Gluconeogenesis. Its importance in human glucose homeostasis. Diabetes Care. Vol. 24. No. 2.

14) Gladden, B. (1998) Muscle as a consumer of lactate. Medicine & Science in Sports & Exercise. Vol. 195. No.3204-3210.

15) Gladden, B. (2004) Lactate metabolism a new paradigm for the third millennium. Journal of Physiology. Vol. 558. No. 5-30.

16) Gladden, B. (2008) A lactatic perspective on metabolism. Medicine & Science in Sports & Exercise. Vol. 08. No. 4003-0477.

17) Goto, K., Ishii, N., Kizuka, T., Kraemer, R.R., Honda, Y. and Takamatsu, K. (2009) Hormonal and metabolic responses to slow movement resistance exercise with different durations of concentric and eccentric actions. European Journal of Applied Physiology. Vol. 106. No. 731-739.

18) van Hall, G. (2010) Lactate kinetics in Human tissues at rest and during exercise. Acta Physiologica. Vol. 10. No. 1748-1716.

19) Izawa K., Hirano Y., Yamada S., Oka K., Omiya K. and Iijima S. (2004) Improvements in physiological outcomes and health-related quality of life following cardiac rehabilitation in patients with acute myocardial infarction. American Heart Association Circulation. 2004; 68: 315–320.

20) Juel, C. and Halestrap, A.P. (1999) Lactate transport in skeletal muscle – role and regulation of the monocarboxylate transporter. Journal of Physiology. Vol. 517. No. 633-642.

21) Juel, C., Holten, M.K. and Dela, F. (2004) Effects of strength training on muscle lactate release and MCT1 and MCT4 content in healthy and type 2 diabetic humans. Journal of Physiology. Vol. 556. No. 297-304.

22) Koch, A.J. (2010) Immune Response to Resistance Exercise. American Journal of Lifestyle Medicine. Vol. 4. No. 244.

23) Lampert, E., Oyono-Enguelle, S., Mettauer, B., Freund, H. and Lonsdorfer, J. (1996) Short EE improves lactate removal ability in patients with heart transplants. Medicine & Science in Sport & Exercise. Vol. 28. No. 801-807.

24) Levy, B., Gibot, S., Franck, P., Cravoisy, A., Bollaert, P.E. (2005) Relation between muscle Na+K+ATPase activity and raised lactate concentrations in septic shock: a prospective study. The Lancet. Vol. 365. No. 871-75.

25) Levy, B. (2006) Lactate and shock state: the metabolic view. Current opinion in critical care. Vol. 12. No. 315-321.

26) Luchette, F.A., Jenkins, W.A., Friend, L.A., Su, C., Fischer, J.E. and James, J.H. (2001) Hypoxia Is Not the Sole Cause of Lactate Production during Shock. The Journal of trauma, injury, infection and critical care. Vol. 53. No. 3.

27) MacRea, H.S.H., Deniis, S.C., Bosch, A.N. and Noakes, T.D. (1992) Effects of training on lactate production and removal during progressive exercise in human. Journal of Applied Physiology. Vol. 0161. No. 67-75.

28) McCarter, F.D., Nierman, S.R., James, J.H., Wang, L., King, J.K., Friend, L.A. and Fischer, J.E. (2002) Role of skeletal muscle Na+ -K+ ATPase activity in increased lactate production in sub-acute sepsis. Life Sciences. Vol. 70. No. 1875-1888.

29) Meer van der, J. en Stehouwer, C.D.A. (2005). Interne geneeskunde. Houten: Bohn Stafleu van Loghum.

30) Meyer, C., Dostou, J.M. and Gerich, J.E. (1999) Role of the human kidney in glucose counterregulation. Diabetes. Vol. 48. No. 943-948.

31) Meyer, C., Stumvoll, M., Welle, S., Woerle, H.J., Haymond, M. and Gerich, J. (2003) Relative importance of liver, kidney, and substrates in epinephrine-induced increased gluconeogenesis in humans. American Journal of Physiology Endocrinology and Metabolism. Vol. 285. No. 819-826.

32) Nichol,. A.D., Moritoki, E., Pettila, V., Bellomo, R., French, C., Hart, G., Davies, A., Stachowski, E., Reade, C.M., Baily, M. and Cooper, D.J. (2010) Relative hyperlactemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Critical Care. Vol. 14. No. R25.

33) Newsholme, E.A. and Leech, T.R. (2009) Functional Biochemistry in Health and Disease. Oxford: Wiley-Blackwell.

34) Phillips, S.M., Green, H.J., Tarnopolsky, M.A. and Grant, S.M. (1995) Increased clearance of lactate after short-term training in men. Journal of Applied Physiology. Vol. 95. No. 0161-7567.

35) Phypers, B., Pierce, T.M.T. (2006) Lactate physiology in health and disease. Continuing Education in Anaesthesia, Critical Care & Pain. Vol. 6. No. 3.

36) del Portal, D.A., Schofer, F., Mikkelsen, M.E., Dorsey, P.J., Gaieski, D.F., Goyal, M., Synnestvedt, M., Weiner, M.G. and Pines, J.M. (2010) Emergency Department Lactate is Associated with Mortality in Older Adults Admitted With and Without Infections. Society for Academic Emergency Medicine. Vol. 17. No. 260-268.

37) Shapiro, N.I., Howell, M.D., Talmor, D., Nathanson, L.A., Lisbon, A., Wolfe, R.E. and Weiss, J.W. (2005) Serum lactate as a predictor of mortality in emergency department patients with infection. Annals of Emergency Medicine. Vol. 45. No. 5.

38) Schreurs, V.V.A.M. and Schaafsma, G. (2010) Lactic acid and lactates: In health and wellness. Nutra foods, Vol. 9. No. 7-16.

39) Thomas, C., Bishop, D., Moore-Morris, T. and Mercier, J. (2007). Effects of high-intensity training on MCT1, MCT4, and NBC expressions in rat skeletal muscles: influence of chronic metabolic alkalosis. American Journal of Physiology Endocrinology and Metabolism . Vol. 293. No. 916-922.

# Appendix

## 1. The preoperative physiological parameters

The physiological parameters non-invasive are measurable levels which can be influenced by physical and nutritional changes in the preoperative phase of the patient. The table below shows an overview of the different usable non-invasive parameters. During the preoperative phase, these parameters can be important predictors of survival after surgery.

Table 1. Overview non-invasive parameters for physical assessment. Left = outcome measures, middle = method for obtaining the outcome measure, right = relevance of the outcome measure.

| Outcome measures | Method | Relevance |
|---|---|---|
| **Body weight** | Scale | Bodyweight loss |
| **Body mass index** | Weight / height squared | General health |
| **Muscle circumference** | Centimeters | Strength, muscle/protein loss |
| **Body fat, mineral and lean mineral mass** | DXA | Body composition |
| **Body fat** | BODPOD | Body composition |
| **Hand grip power** | Hand grip dynamometry | Muscle/protein loss |
| **VO2max** | ASTRAND test<br>HARVARD STEP TEST<br>6 MINUTEN WANDELTEST | Aerobic capacity |
| **Oxygen saturation** | Pulse oximetry | General health |
| **Muscle volume** | Muscle echography | Muscle loss |

## 2. Description physiological parameters

*BMI and muscle size*

Physical anthropometry refers to the measurement of body parameters (Jochem and Joosten, 2006). Height and weight are likely to be interesting during the PREOP and the postoperative phase (POSTP). The Body Mass Index (BMI) is an appropriate health parameter which measures the weight in kg in relation to the squared length in meters. A normal BMI is between 20 and 25; a subject who has a BMI of 30 or higher; is considered to be seriously overweight or obese (Mackenbach and van der Maas, 2004). By measuring the muscle size PRE and POST, a probable muscle reduction can be detected. In general, there is no direct relationship between BMI and lactate metabolism. It can be stated that people who are more fit have in many cases a lower BMI than people with overweight or obesity. Suggested is that fitter people can better utilize lactate because of the benefits of exercise on the body.

*DUAL-ENERGY X-RAY*

Dual-energy x-ray absorptiometry (DXA) is a reliable and accurate method for quantifying non-fat and bone mass. DXA measures also the minerals in the deep bone structures (Heyward, 2001). DXA method divides the body into three parts, according a three-compartment model: total-body mineral, mineral-free mass and fat mass (Hansen, et al., 1993, Mazess et al., 1996 and Lohman et al., 1990). DXA is a reliable method for measuring body composition. In a validation study, where DXA was compared with hydrodensitometry (underwater weighing), considered as the ‘golden standard’, for measuring body fat percentage and / or the body composition. The difference in fat was less than 0.4% compared with the golden standard (Going et al., 1993, Prior et al., 1992 and Friedl et al., 1997). DXA is a good alternative to hydrodensitometry because the method is fast and safe and can be conducted by one or two investigators.

*BODPOD*

BODPOD measures body volume by comparing the volume of the empty cabin with that of the cabin with the person in order to measure the body volume (Katch and Katch, 1980). To increase measurement reliability and accuracy, the person who is going to be measured, wears a tight swimsuit (Katch and Katch, 1980). The body volume is determined by the initial volume minus the volume of the cabin with the person in it. The person breathes several times in a pulmonary air circulation system that measures gas volume. Recent studies show different results. For children and elderly BODPOD seems to be a reliable and valid instrument for measuring body composition (McCrory et al., 1995). A recent study with African people shows an average overestimation of about 2% body fat (Wagner et al., 2000). Another study in American Football players, showed an average underestimation of 2% compared to the golden standard (Collins et al., 1999).

*6 MINUTES-walk test*

A simple way to estimate the maximum oxygen consumption (VO2max) is performing a 6-minute walk test. It is an aerobic sub maximal exercise test. The 6-minute walk test is especially suitable for patients with poor functional status because they are in a difficult position to perform a maximum exercise test. Patients with severe heart and lung disease have a lower load capacity when it comes to aerobic exercise. The 6-minute walk test is primarily validated and reliability tested in chronic obstructive pulmonary disease (COPD) patients and in patients with heart failure (Sadaria et al., 2001 and Solway et al., 2001). The 6-minute walk test is an intensive effort that can be used to test the functional ability of a patient effort to map. The test can be applied to various disorders, but must be corrected depending on the type of disorder. The reliability of the 6-minute walk test is good. Over a wide range of diseases the test retains its reliability and makes it a broad tool for monitoring the functional exercise capacity of a patient. In some diseases, the test-retest reliability is questionable (ICC <0.8) (Portney and Watkins, 2000 and McKenzie, 2005).

*HARVARD STEP TEST*

The Harvard test consists of two seconds stepping on a bench each two seconds (height = 45 cm) for five minutes long. That is 30 steps per minute and 150 steps in total for the full five minutes. The heartbeat is recorded three times, the first, second and third minute after the test. Then the ratio 3000 / sum of the heart beats per minute measured at the end is calculated. The results are interpreted with the reference table of McArdle et al, (2000). The Harvard step test correlates well with the measured VO2max levels test and is therefore considered as a valid method (McKenzie, 2005). The reliability depends on the degree of strictness of the investigator who is conducting the test.

*ASTRAND TEST (treadmill)*

The starting speed of the treadmill is 8.05 km/hr (5 mph) and a gradient of 0%. After three minutes the gradient increases to 2.5%, then the gradient increases every two minutes with 2.5%. The test ends when the participant cannot keep up longer. The estimated VO2max is calculated as follows: (time in seconds x 1444) + 14.99. Unlike the Astrand test on the bike (exercise bike), the Astrand treadmill test has been validated. It correlates well with the actual measured VO2max (McKenzie, 2005). Like the HARVARD STEP TEST, the reliability depends on the degree of strictness of the investigator who is conducting the test.

*Hand grip dynamometry*

A common method for measuring the grip strength is hand grip dynamometry. The maximum grip strength of the hand provides a good estimate of the peripheral muscle function and is related to the total amount of muscle (protein) in the body (Humphreys et al., 2002). A grip strength of less than 85% of the standard can be interpreted as an indicator of muscle protein loss. A loss of 10% of the muscle proteins indicates a decrease in muscle strength (Humphreys et al., 2002). There are several external factors that may influence the grip strength of an individual. Age, sex, weight and height seem to play an important role. It also seems that dominance of the hand (the most commonly used hand) makes a difference in grip strength. What has been examined with great certainty is that men have greater grip strength than women, regardless of what instrument is tested (Agnew and Maas, 1982, Crosby et al., 1994, Harth and Vetter, 1994 and Robertson et al., 1996). There is a curvilinear relationship between age and grip strength (Humphreys et al., 2002). The peak in grip strength is between 30-45 years and decreases with age (Hinson and Gench, 1989, Bechtol, 1954 and Balogun et al., 1991). There is also a positive correlation between the grip strength, body weight and height in healthy people (Fraser and Benten, 1983 and Smith et al., 1989). This positive correlation goes up to 98 kg (215 lb) in weight and 190 cm (75 in) in length (Amosun et al., 1995). The positive relationship between grip strength, weight and height does not apply to people with one hand deviation (Robertson et al., 1996).

*Oxygen saturation*

Pulse oximetry is a simple and inexpensive way to estimate the bound hemoglobin oxygen saturation (SpO2) in the blood. Pulse oximetry also seems an accurate method for estimating oxygen saturation in humans (Jensen et al., 1998). The value is expressed as a percentage and is considered as healthy at levels >95% (Jensen et al., 1998). In some cases, pulse oximetry gives an overestimation or underestimation compared with direct measurement of SpO2.

Jones et al., (2010) addressed the potential utility of lactate clearance as a substitute for ScvO2 in a randomized trial among patients presenting to the emergency department with severe sepsis and septic shock, with the primary hypothesis that early resuscitation targeting lactate clearance as the marker of adequacy of oxygen delivery was noninferior to the currently recommended ScvO2 monitoring for the outcome of in-hospital mortality. Jones et al., (2010) did not found any difference in mortality for patients with severe sepsis and septic shock resuscitated with a protocol that used lactate clearance compared with a protocol that used ScvO2 as the method of measuring total body oxygen metabolism.

*Muscle Ultrasound*

Muscle Ultrasound is an accurate method for measuring muscle wasting. This method is relatively simple and at the same time a cost-effective manner for measuring the muscle volume. The muscle-ultrasound method is validated with MRI, a traditional method for measuring muscle volume. Both methods show similar results (Arbeille et al., 2008). Because of the accurately, non-invasive and cost efficient features of this method, muscle ultrasound seems to be a suitable method for people who have long-term bed rest (Arbeille et al., 2008).

### 3. Physiological parameters invasive

The physiological parameters invasive are measurable physiological values which can be influenced by physical and nutritional changes in the preoperative phase of the patient.

Table 2. Overview invasive parameters for physical assessment. Left = outcome measures, middle = method for obtaining the outcome measure, right = relevance of the outcome measure.

| Outcome measure | Method | Relevance |
|---|---|---|
| **Muscle biopsy** | Biopsy | Many aspects |
| **Plasma lactate** | Serum blood | Clearance |

*Muscle Biopsy*

Muscle biopsy is a diagnostic method that uses a piece of removed muscle for examination. Usually a piece of muscle is taken with a hollow needle , for example from the quadriceps (Gibney, 2005). Muscle biopsy is an invasive method that should be performed by a clinician (doctor, pathologist). It is an expensive method that requires the necessary precision. A major advantage of muscle biopsy is that many aspects (fiber type, metabolic, endocrine, inflammation) may be considered within the muscle biopsy.

*Plasma lactate*

Many studies demonstrate the usefulness of lactate as a prognostic indicator in various stages of shock (Shapiro et al., 2005, Husain et al., 2003 and Pittard, 1999). Increased blood lactate concentrations are strongly correlated with mortality in a variety of life-threatening situations of patients (Weintraub et al., 1989, Howell et al., 2007, Shapiro et al., 2005, Watts et al., 2003, Husain et al., 2003, Weil et al., 1970, Abramson et al., 1993 and Vincent et al., 1983).

## References appendix


1) Abramson, D., Scalea, T.M., Hitchcock, R., et al. (1993) Lactate clearance and survival following injury. Journal of Trauma. Vol. 35. No. 584–8.

2) Agnew, P., & Maas, F. (1982). Hand function related to age and sex. Archives of Physical Medicine and Rehabilitation. Vol. 63. No. 269–271.

3) Amosun, S. L., Moyo, A., & Matara, C. (1995). Trends in hand grip strength in some adult male Zimbabweans. British Journal of Occupational Therapy. Vol. 58. No. 345–348.

4) Arbeille, P., Kerbeci, P., Capri, A., Dannaud, C., Trappe, S.W. & Trappe, T.A. (2008). Quantification of muscle volume by echography: comparison with MRI data on subjects in long-term bed rest. Ultrasound in Medcine & Biology. Vol. 35. No. 7.

5) Balogun, J. A., Akinloye, A. A., & Adenlola, S. A.(1991). Grip strength as a function of age, height, body weight and Quetelet index. Physiotherapy Theory and Practice. Vol. 7. No. 111–119.

6) Bechtol, C. O. (1954). The use of a dynamometer with adjustable handle spacings. Journal of Bone and Joint Surgery. Vol. 36A. No. 820–824.

7) Collins, M.A., Millard-Stafford, M.L., Sparling, P.B., Snow, T.K., Rosskopf, L.B. and Webb, S.A. (1999) Evaluation of the BodPod for assessing body fat in collegiate football players. Medicine & science in sports & exercise. Vol. 31. No. 1350-56

8) Crosby, C. A., Wehbé, M. A., & Mawr, B. (1994). Hand strength: Normative values. Journal of Hand Surgery, Vol. 19A. No. 665–670.

9) Fraser, C., & Benten, J. (1983). A study of adult hand strength. British Journal of Occupational Therapy. Vol. 46. No. 296–299.

10) Friedl, K.E., DeLuca, J.P., Marchitelli, L.J., Vogel, J.A.. (1992) Reliability of body-fat estimations from a four compartment model by using density, body water, and bone mineral measurements. American Journal of Clinical Nutrition. Vol. 55. No.764-70.

11) Going, S.B., Massett, M.P., Hall, M.C., Bare, L.A., Root, P.A., Williams, D.P., et al. (1993) Detection of small changes in body composition by dual-energy x-ray absorptiometry. American Journal of Clinical Nutrition. Vol. 57. No. 845-50.

12) Hansen, N.J., Lohman, T.G., Going, S.B., Hall, M.C., Pamenter, R.W., Bare, L.A., et al., (1993) Prediction of body composition premenopausal females dual-energy x-ray absorptiometry. Journal of applied physiology. Vol. 75. No. 1637-41.

13) Harth, A., & Vetter, W. R. (1994). Grip and pinch strength among selected adult occupational groups. Occupational Therapy International. Vol. 1. No. 13–28.

14) Heyward, V. (2001) ASEP Methods Recommendation: Body Composition Assessment. Official Journal of The American Society of Exercise Physiologists (ASEP). Vol. 4 No. 4

15) Hinson, M., & Gench, B. E. (1989). The curvilinear relationship of grip strength to age. Occupational Therapy Journal of Research. Vol. 9. No. 53–60.

16) Howell, M.D., Donnino, M., Clardy, P., et al (2007) Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Medicine. Vol. 33. No.1892–1899.

17) Humphreys J, et al. (2002) Muscle Strength as a Predictor of Loss of Functional Status in Hospitalized Patients. Nutrition. Vol. 18: No. 616-620.

18) Husain, F.A., Martin, M.J, Mullenix, P.S., Steele, S.R. and Elliot, D.C. (2003). Serum lactate and base deficit as predictors of mortality and morbidity. The American Journal of Surgery. Vol. 185. No. 485-491.

19) Jensen, L.A., Onyskiw, J.E. & Prasad, N.G.N. (1998) Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. Journal of Heart and Lung. Vol. 27. No. 6.

20) Jochems, A.A.F. en Joosten, F.W.M.G. (2006). Zakwoordenboek der Geneeskunde. Doetinchem: Elsevier gezondheidszorg.

21) Katch, F.I. and Katch, V.L. (1980) Measurement and prediction errors in body composition assessment and the search for the perfect equation. Research quarterly for exercise & sport. Vol. 51. No. 249-60.

22) Lohman, T.G., et al., (1996) Dual energy x-ray absorptiometry. Human body composition. Human kinetics. Vol. 2. No. 63-75.

23) Mackenbach, J.P. en van der Maas, P.J. (2004). Volksgezondheid en gezondheidszorg. Maarssen: Elsevier gezondheidszorg.

24) Mazess, R.B., Barden, H.S., Bisek, J.P. and Hanso, J. (1990) Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. American journal of clinical nutrition. Vol. 57. No. 845-50.

25) McCrory, M.A., Gomez, T.D. Bernauer, E.M. and Mole, P.A. (1995) Evaluation of a new air displacement plethysmograph for measuring human body composition. Medicine & science in sports & exercise. Vol. 27. No. 1686-91.

26) McKenzie, B. (2005) 101 performance evaluation tests. Electric world PLC. No. 1-905096-18-6.

27) Portney LG, Watkins MP (2000). Foundations of clinical research: applications to practice. 2nd ed. Upper Saddle River, New Jersey: Prentice Hall. Edition 2000a.

28) Robertson, L. D., Mullinax, C. M., Brodowicz, G. R., & Swafford, A. R. (1996). Muscular fatigue patterning in power grip assessment. Journal of Occupational Rehabilitation. Vol. 6. No.71–85.

29) Wagner, D.R., Heyward, V.H. and Gibson, A.L. (2000) Validation of air displacement plethysmography for assessing body composition. Medicine & science in sports & exercise. Vol. 32. No. 1339-1344.

30) Sadaria K.S. and Bohannon, R.W. (2001) The 6-minute walk test: a brief review of literature. Clinical Exercise Physiology. Vol. 3. No.127-32.

31) Shapiro N.I., Howell, M.D., Talmor, D. et al (2005) Serum lactate as a predictor of mortality in emergency department patients with infection. *Annuals Emergency Medicine*. Vol. 45. No.524–528.

32) Smith, G. A., Nelson, R. C., Sadoff, S. J., & Sadoff, A. M. (1989). Assessing sincerity of effort in maximal grip strength tests. American Journal of Physical Medicine and Rehabilitation. Vol. 68. No.73–80.

33) Solway, S., Brooks, D., Lacasse, Y., Thomas, S. A. (2001) Qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest. Vol. 119. No. 256-70.

34) Vincent J.L., Dufaye P., Berre J., et al. (1983) Serial lactate determinations during circulatory shock. Critical Care Medicine. Vol. 11. No.449–51.

35) Watts J.A. and Kline J.A. (2003) Bench to bedside: The role of mitochondrial medicine in the pathogenesis and treatment of cellular injury. Academic Emergency Medicine. Vol.10. No.985–997.

36) Weil MH, Afifi AA, et al. (1970) Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation. Vol. 41. No.989–1001.

37) Weintraub, EL Jones, J Craver, R Guyton and C Cohen (1989) Determinants of prolonged length of hospital stay after coronary bypass surgery. American heart association. Vol. 80. No. 276-284.