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Enzymes in Lymph: A Review

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Summary: Lymph is the minute net volume of contending hydrostatic and osmotic capillary forces. It is built up extravasculary in tissues and reaches the intravasal space by definite lymph collecting vessels, which enter the venous system at the angulus venosus at the root of the neck. Sampling methods for lymph from individual tissues or from lymph collecting vessels of man and various animals are cited and the preparation of lymph for enzymatic analysis is described. The extracellular distribution and transport of enzymes is important for diagnostic enzymology, because enzymes released from cells in continuous physiological processes, or after injury to the tissue, reach the intravasal space mainly via the lymphatics. This is evident from the high lymph-plasma ratios of diagnostically important enzymes. The type of enzyme transport (lymphatic or by direct interstitial-venous entry) depends on the heterogeneity of the capillary barrier characteristic of the different organs. The permeability is extremely high in liver, i.e. enzymes in hepatic lymph originate mainly from blood, which they have reached through the large openings in the sinusoidal endothelial lining; in contrast the permeability is extremely low in skeletal muscle, where lymphatic transport therefore predominates. The phenomenon of increased enzyme activities in plasma after physical exertion is explained by alterations of lymph flow. A table gives a survey of enzyme activities, lymph-plasma quotients, and lymph flow from lymph vessels of various tissues as well as from the lymph collecting vessels of man and animals, with comments on the significance for diagnostic enzymology.

Enzyme in der Lymphe: Eine Übersicht

Zusammenfassung: Lymphe ist das in Geweben extravasal im Widerstreit hydrostatischer und osmotischer kapillärer Kräfte gebildete Flüssigkeitsvolumen und wird über definierte Lymphsammelgefäße dem Intravasalsystem im Venenwinkel am Hals mündend, wieder zugeführt. Techniken der Gewinnung von Lymphe als definierte Organlymphe oder aus Lymphsammelgefäßen bei Mensch und Tier werden zitiert und ihre Aufbereitung für die enzymatische Analyse beschrieben. Die Bedeutung der Transport- und Verteilungsfunktion von Enzymen über die Lymphe für die diagnostische Enzymologie erklärt sich daraus, daß Enzyme, die kontinuierlich als physiologischer Prozeß oder nach Schädigung des Gewebes aus Zellen austreten, den Intravasalraum vorwiegend über die Lymphe erreichen, was sich in hohen Lymph-Plasma Aktivitätsverhältnissen von diagnostisch verwertbaren Enzymen ausdrückt. Die Art des Enzymtransports – direkt interstitiell-venös oder lymphatisch – hängt von dem verschiedenartigen kapillären Barriereverhalten in den unterschiedlichen Organen ab. Die Permeabilität ist extrem hoch in der Leber, d.h. Enzyme in der Leberlymphe stammen überwiegend aus dem Blut, das sie über direkten sinusoidalen Zugang erreicht haben; und die Permeabilität ist extrem niedrig in der Skelettmuskulatur, d.h. hier dominiert der lymphatische Transport. Die nach körperlicher Belastung im Plasma zu beobachtenden Enzymaktivitätsveränderungen werden über Lymphflußänderungen erklärt. Eine tabellarische Übersicht informiert über die in Lymphgefäßen verschiedenster Gewebe und Lymphsammelgefäßen bei Mensch und Tier bestimmten Enzymaktivitäten, die Lymph-Plasmaquotienten und Lymphflüsse aus diagnostisch-enzymologischer Sicht.

Contents

1. Lymph Formation

According to the classical *Starling-Landis* concept, lymph is the minute net volume of the capillary fluid balance, maintained by a dynamic interaction of hydrostatic and osmotic forces acting across the capillary wall.

These forces are considered to be of almost equal magnitude, therefore cancelling each other out (1).

The mechanisms concerned in the formation of lymph have been critically debated (2). However, there has evolved over the years a concept which has been fairly generally accepted. It embraces the view that lymph from any tissue (except kidney medulla and choroid plexus, which lack lymph vessels) contains all the proteins that can be detected in plasma and that lymphatic vessels are, in general, essential for the continual movement of these proteins in one direction throughout the extracellular fluid of the body – from plasma to tissue fluid to lymph and back to the plasma (3).

It has been proposed that materials are transported across capillary walls by different mechanisms: convection, permeation (diffusion), pinocytosis, filtration, escape through small and large pores (leaks) or accompanying the passage of recirculating lymphocytes through the post-capillary venules in the lymph node; the type of transport that predominates depends on the heterogeneity of the barrier characteristics of the different organs (4–12).

The transcapillary escape rates correlate inversely with the molecular weights of the proteins. The extravascular return rate reflects the lymphatic protein transport and is the reciprocal of the extravascular transit time, which covers a wide range: short in liver, kidney and lungs and long (up to 5–6 days) in muscle and skin (13).

It is, however, a controversial whether or not a protein, once it has entered the extravascular space, can gain access to the circulating blood except by way of the lymphatics as stated by *Lassen* et al. (9).

For skeletal muscle and subcutis *Noer & Lassen* (6) propose that escape is negligible, i.e. that maximally 1% of the interstitial albumin can undergo local transendothelial escape by passive forces, such as diffusion and pinocytosis. Experimental findings and theoretical considerations (4), however, are compatible with an uphill albumin transport (14) at least in liver, kidney and skeletal muscle (5).

Nevertheless it can be stated that lymph flow is necessary for the removal of proteins. Otherwise their concentrations would rise progressively in the interstitium and lead to an excessive filtration of fluid. In terms of total volume flow, however, lymph flux may represent only a small corrective process that adjusts the concentration of one type of component in the interstitium in relation to the much more important process of transcapillary filtration and reabsorption (15).

When following the fate of fluid and molecules which have entered the extravascular space, one has to consider the physico-chemical properties of the interstitial space, which is very inhomogeneous, *Guyton* et al. (26, 218) have attempted to synthesize a working system for interstitial fluid regulation and lymph formation: The interstitial fluid spaces are filled with a mat of collagen fibers, and the interstices of this mat contain a mucopolysaccharide gel ground substance, mainly hyaluronic acid. Both the collagen fibers and the gel are elastic structures that can be expanded or compacted.

In normal tissue, almost of the fluid is in the gel state and almost none in the free fluid state. In the com-

pacted state the elastic recoil of the compressed collagen fibers and gel reticular fibrillae seem to cause suction on the fluid within the tissue spaces, thus creating a subatmospheric pressure. Measurements of interstitial fluid pressure indicate that this is normally slightly negative in most soft tissues.

However, even very slight extra filtration of fluid into the tissue spaces increases the interstitial fluid pressure toward more positive values, which in turn increases lymph flow. The increased lymph flow then decreases the interstitial fluid volume and pressure, so that they approach normal values. This occurs by two mechanisms.

Firstly, the direct removal of fluid from the tissue spaces in the lymph and secondly, the removal of protein from the interstitial fluid in the lymph, thus decreasing the interstitial fluid colloid osmotic pressure and allowing more effective osmosis of fluid directly from the interstitial spaces back into the capillaries.

There is more evidence in support of this theory than that of *Zweifach & Silberberg* (15), who propose a continuous positive pressure gradient for fluid flow toward the lymphatic capillaries. The generally accepted subatmospheric interstitial free fluid pressure, however, is not compatible with this concept.

Aside from the possibility of a physical lymphatic pump, *Casley-Smith* (16, 17) has also suggested that an intermittent osmotic effect might also cause movement of fluid through the pores of the lymphatic capillary.

Collection of interstitial fluid is indispensable in studies of transcapillary and interstitial transport of materials and water. Generally, three methods of interstitial fluid sampling may be applied: the capsular technique developed by *Guyton* (18, 19), the liquid-paraffin method described by *Haljamäe* (20) and the wick method by *Auckland & Fadnes* (21). These findings raise the controversial question of whether or not lymph is identical with interstitial fluid (1, 22, 23).

Based on recent biochemical and ultrastructural studies, interstitial fluid exists in two phases, and, depending on the sampling method, different proportions of these two phases may be obtained (15, 24–28).

The general statement, that all the proteins found in plasma are also found in lymph, although in lower concentrations (29) does not hold true for cellular enzymes. On the contrary, most enzymes are found in particulary higher activities in lymph than in plasma, an observation that could be anticipated, in view of the fact that enzymes of cellular origin show a much higher activity in the intracellular than the extracellular space.

This extremely high "gradient" on the other side is cited as evidence for direct venous entry; and often the intravascular activity of a particular enzyme is shown to depend on its molecular weight. The activity ratio between tissue and plasma or lymph – which in fact is extremely high – is erroneously equated with the molar concentration gradient.

Calculation from our data on enzyme concentration in lymph (30) revealed values between 1.0 to 50 nmol/l for alkaline phosphatase and creatine kinase, respectively, as extreme examples. The corresponding values for muscle tissue are 0.016 and 2000 μmol/kg tissue.

That means that the extracellular concentrations are negligible and the gradient therefore depends only on the intracellular enzyme concentration and the thickness of the cell membrane; even for creatine kinase with its extremely high activity in muscle, the gradient in fact is very low. For other enzymes and tissues, respectively, this gradient is at least a hundred times smaller.

Enzymes in plasma and lymph therefore do not participate in the colloid osmotic forces acting at the capillary.

There is, however, a controversial discussion as to whether enzymes from the extracellular space can reach the intravasal space directly by traversing the capillary.

The statement by *Lassen* et al. (9) must be mentioned again: the back flux of proteins at the microvascular level is negligible; once a protein molecule has crossed the capillary wall, it will return to the plasma via the lymph.

From this general formulation, whose limitations have been discussed above, it is questionable whether enzymes in heart and muscle reach the intravascular space directly, as proposed by several authors (31–40).

2. Lymph Collecting Vessels

The thoracic duct drains lymph from the abdominal viscera and lower extremities, the left upper limb, left side of the head and neck and parts of the heart, while the right lymphatic duct drains most of the lungs, heart, serous cavities, right upper extremities and right side of the head and neck (29, 41–43).

Compared with these two main lymph systems, the lymph flow from the cervical and subclavian lymph ducts, which also finally enter the intravasal compartments at the root of the neck, is small. Thoracic duct lymph flow in mammals is 1–2 ml/kg · h and 3–5 ml/kg · h in ruminants (29), whereas right duct lymph flow amounts to only about 5–20% of this value (29, 41, 44, 45). Hepatic and intestinal lymph probably make equal contributions to the total lymph in the thoracic duct (46, 47, 48).

In conscious or excercising animals, however, lymph flow exceeds the values reported above for anaesthetized animals by 50 and nearly 300% respectively.

This increase is probably due in part to enhanced lymph flow from excercising muscles by the action of the tissue pump and in part the increased liver lymph flow due to the increased pressure and massaging effect to the abdominal lymphatics by muscular movement.

During anaesthesia and at rest, an extravascular fluid pool would seem to be accumulated, which is then emptied during excercise (30, 46, 49, 50, 51).

The driving force for the propulsion of thoracic duct lymph in the anaesthetized state is the "respiratory pump", whereas in the conscious state the importance of the "tissue pump" and "vis a tergo" come to the fore (52).

3. Sampling Methods for Lymph from Regional Lymphatics

Detailed descriptions of lymph sampling methods in man and various animals are given by *Yoffey & Courtice* (29) (1970) and by *Rusznyak* et al. (53) (1969). Since the appearance of these publications, the number of definite lymphatics of various animals and man from which lymph can be collected has been increased; classical sampling techniques have been modified or revised, mainly due to newly available catheter material. In addition, chronic methods and shunt-techniques have been developed, which allow sampling of lymph from conscious probands under more physiological conditions, thus avoiding the multifarious disadvantages of fistula-techniques, such as the permanent fluid-, protein- and cell loss (54) and the general reduction of lymph flow under anaesthesia (49, 52, 55).

The following brief and comprehensive review of sampling techniques from various lymphatics in man and the most commonly used animals therefore focusses mainly on techniques described since 1970.

3.1 Man

The classical technique of thoracicus duct fistula of *Bierman* et al. (56) interrupts the thoracic duct at the site of cannulation and creates a permanent external end fistula. Detailed descriptions of this kind of cannulation are also given by *Tilney & Murray* (57) and *Werner* (58).

The "thoracic duct to duct shunt" and "thoracic duct side fistula", which leave the thoracic duct circulation unimpaired, are outlined by *Liljeqvist* et al. (59) and *Girardet & Benninghoff* (54, 60). Reviews on indications and techniques of thoracic duct cannulation in man are given by *Lob* et al. (61) and *Evans & Holyoke* (62).

The right duct lymph has been sampled by *Hallen & Hansson* (63).

Based on the normal anatomy of the lymphatic system in the human leg (64) a chronic cannulation of peripheral leg lymph has been worked out by *Engeset* et al. (65) and was improved by *Olszewski* (24).

3.2 Sheep

The collection of lymph in conscious animals requires them to be adequately restrained to prevent them from chewing or pulling out the cannula. Sheep are ideal subjects as they are extremely cooperative and placid and show no inclination to interfere with cannulae or collection vessels (66).

The cited authors all used the fistula technique in conscious animals.

Lascelles & Morris (67) describe ductus thoracicus, intestinal and mammary gland cannulation. The preparation of chronic lung lymph fistulas in sheep by *Staub* et al. (68) has become widespread in investigations on shock. Renal lymph appeared originate nearly entirely from the renal cortex (69, 70).

Hepatic lymph was sampled according to *Lascelles & Morris* (67) and *Smith* et al. (70).

Testicular lymphatics and lymph from the lactating and non lactating mammary gland were described by *Cowie* et al. (71), *Morris & McIntosh* (72) and *Lascelles & Morris* (67), respectively. Peripheral leg lymph was sampled from popliteal (73, 70), praescapular (70, 74) and praefemoral lymphatics (70, 75).

Surgical techniques for establishing chronic fistulae in the thoracic duct, intestinal, lumbar and popliteal lymph duct of foetal lambs in utero are described by *Smeaton* et al. (76) and for the thoracic duct alone by *Pearson* et al. (77).

3.3 Dog

The dog is the most commonly used animal in experimental lymphatic research. Investigations on thoracic duct and heart lymph are especially numerous.

In the last decade successful attempts were undertaken to change from classical fistula techniques and anaesthetized animals to improved methods with shunt techniques and conscious animals, respectively.

Glauser et al. (44) and *Vreim & Okhuda* (78) delineate an improved method for the cannulation of the right lymph duct. From the many descriptions of thoracic duct cannulation with an end-fistula, the simplified and revisited methods of *Witte* et al. (79) and *Briscoe* (80) should be noted. Whereas *Nelson* et al. (81) used the fistula technique for long term catherization, this is now superceded by advanced techniques that leave the lymph circulation unimpaired; thus *Doemling & Steggerda* (82) and *Brown & Hardenbergh* (83) used thoracic duct-venous shunt preparations, and *Girardet & Benninghoff* (84) used thoracic duct to duct shunt and thoracic duct side fistula. The great variations in the canine thoracic duct system are demonstrated by *Kagan & Breznock* (85).

Helpfull aids for collection of heart lymph are given by *Kluge & Ullal* (86) *Ullal* (87), *Ali* et al. (88), *Feola & Glick* (89) and *Leeds & Uhley* (90). *Michael* et al. (91), however, describe a technique for obtaining cardiac lymph from conscious dogs.

Lung lymph cannulation is outlined by *Parker* et al. (92). Both hepatic and intestinal lymph was investigated by *Nix* et al. (46), *Cain* et al. (47) and *Grindlay* et al. (93).

Methods for differentiation between capsular and hilar renal lymph are given by *Keyl* et al. (94) and *Le Brie* (95), respectively. Both sampling sites are compared by *Bell* (96) and *O'Morchoe* et al. (97).

Collection of peripheral leg lymph has been done by *White* et al (98), *Garlick & Renkin* (11) and *Joyner* et al. (99). The anatomy of the lymphatic trunks in the dog hind leg is described by *Pflug & Calnan* (100).

3.4 Rabbit

Gibson & Segal (101) sampled right duct lymph. Cannulation of the thoracic duct is not as difficult as described by *Sanders* et al. (102), but it is easier with the technique of *Zilversmit* et al. (103). In contrast to the cervical approach of these authors, *Redgrave* (104) chose an abdominal access at the cysterna chyli.

For the collection of lymph from liver or kidney, reference should be made to, e.g. *Vogel & Ströcker* (105) and *Courtice* (106) or *Gärtner* et al. (107) and *Vogel & Ströcker* (105), respectively; the latter authors also collected lymph from the lumbar trunk. Peripheral leg lymph from different regions was collected by *Roberts & Courtice* (108) and *Courtice* (109). Examples of cannula implantation in the femoral lymphatic for acute (110) and chronic purposes (111) are given.

The same author also describes a method for collecting muscle lymph separately from that draining the skin (112).

3.5 Rat

Besides the classical *Bollmann* technique of thoracic duct end fistula (113, 114) a thoracic duct to duct shunt and a T-tube side thoracic duct fistula is presented (54), which obviates the constant loss of lymph attending the standard *Bollmann* fistula. In contrast to the above cited authors, who used an abdominal approach *Reinhardt* (115), *Saldeen & Linder* (116) and *Azargoschasb* (117) used a cervical approach at the site of entrance of the lymph into the junction of internal jugular and subclavian veins with the left vena cava cranialis.

Descriptions of hepatic and/or intestinal lymph sampling are given by *Bollman* et al. (113), *Friedman* et al. (118) *Warshaw* (119) and *Lee* (219).

Dennhardt & Gartemann (120) developed an exteriorized intestinal lymphatic-vena cava shunt. The anatomical arrangement of renal and systemic lymphatics are shown in figures by *Sakai* et al. (121) and *Hargens* et al. (122).

After resuscitation from anaesthesia, the rats can be restrained in a cage, which limits the activity (123), for long term sampling of lymph from different sites in conscious animals.

3.6 Mouse

Techniques for collecting thoracic duct lymph by a abdominal approach in conscious mice are described by *Shrewsbury* (124), *Boak & Woodruff* (125), *Gesner & Gowans* (126) and *Deaton* (127), *Morse & Riester* (220) and *Mandel* (221). A cervical approach to thoracic duct lymph in mice has recently been outlined by our group (222).

4. Preparation of Lymph for Enzyme Activity Determination

It is advisible to add an anticoagulant, because lymph contains all coagulation factors and components of the fibrinolytic system. Although the lymph does not contain any thrombocytes, thromboplastin formation is sufficient for clot formation (128, 129, 130).

Lymph contains a high level of leukocytes, and small contaminations of erythrocytes (29, 131). In view of the high intracellular enzyme activity of these cells (132, 133), lymph must be centrifuged.

Storage of lymph plasma at −70 °C causes no loss in activity, at least for those enzymes measured by our groups (30, 51, 134, 135), but systematic studies on changes of activity in lymph kept at different temperatures, are lacking.

Lipaemic intestinal or thoracic duct lymph can easy be clarified by using an Airfuge Ultracentrifuge with the rotor ACR-90 (Beckman Instruments), by flotation of the chylomicrons after 10 min of centrifugation at 107000 *g*. Frigen (Hoechst), which is also used to clarify lipaemic serum and which does not interfere with enzyme activity in plasma (136) can also be used.

5. Significance of Extracellular Distribution and Transport of Enzymes for Diagnostic Enzymology

Enzymes released from cells, as the result of physiological processes of cell-turnover or due to a pathological event, can reach the circulating blood on three different ways. If the cells of origin are in direct contact with the blood, such as blood cells or the endothelial cells of the blood vessels, the released enzymes are rapidly distributed all over the intravasal space, so that the extent of the initial dilution depends on the plasma volume. If the cells of origin have direct contact with the interstitial as well as to the intravascular space and/or if the capillary permeability of that region is high (e.g. liver and spleen) the released enzymes are again rapidly distributed all over the intravascular compartment, but in addition they also become distributed in parts of the interstitial compartment and the lymphatic systems. If the cells of origin are in direct contact with the interstitial space only and/or the permeability of the capillary membranes is low (e.g. skeletal muscle), the released enzymes reach the intravasal compartment preferably by lymphatic transport and hardly at all by direct interstitial-venous entry. Because of the time-consuming lymphatic transport, the time course of appearence of enzymes in plasma lags behind the interstitial-lymphatic increase.

It is almost impossible to experimentally accomplish an isolated and controlled elevation of enzyme activities in the interstitial compartment, which would be necessary for the quantitative investigation of extracellular enzyme transport. All one can do is to injure a limited region of tissue, whose cells have no direct contact with the intravascular space.

According to reported data (5, 137, 138, 139), peripheral skeletal muscle is a tissue with a particular low capillary permeability. Furthermore, skeletal muscle offers the great advantage that, in contrast to other organs, the rate of outflowing lymph can easily be influenced by changes in its physical activity (39, 46, 49, 140, 141).

If enzymes, released from muscle cells, reach the intravascular compartment exclusively by lymphatic transport, damage to muscle cells should be detectable by measurement of enzyme activities in blood plasma only if the lymph flow from the respective region can be maintained.

Lymph flow from muscle is mainly a function of muscular activity: it stagnates completely with immobility and is stimulated by active as well as passive motion (50, 98, 142).

Consequently an injury to cells of skeletal muscle, kept immobile, should not result in an increase of enzyme activities in blood plasma. These considerations are strongly supported by experimental findings of our group.

In anaesthetized dogs one limb was made hypoxic by clamping the femoral artery for one hour and enzyme activities were followed thereafter for several hours in thoracic duct lymph (51), truncus lumbalis lymph (30) and peripheral leg lymph (135).

It was proven beyond any doubt, that enzymes from skeletal muscle are transported from the interstitial into the intravascular compartment mainly by lymphatic transport.

Indications were found that the interruption of blood flow to skeletal muscle for one hour did not result in an enzyme release from muscle cells. The lymphatic pathway, however, is called in question by *Bolter & Critz* (39, 40) and *Szabo* et al. (36, 37, 38).

The experimental design of these groups, however, who provoked active motion of muscle by electrical stimulation, seems to be far beyond any physiological condition, in particular because of the high frequency (8−10 s^{-1}) and amplitude (50−70 V) of the stimula they used.

Friedel (143) pointed out the practical importance of lymph flow and its impairment by comparison of creatine kinase activities in plasma after myocardial infarction and lesions to skeletal muscle.

Although the latter contains nearly 10 times more creatine kinase than the myocardial muscle, even severe lesions do not result in the distinct elevations of enzyme activity that are observed after a myocardial infarction. The explanation for this obvious discrepancy seems very simple: The injured muscle will be reflectively kept immobile which results in a stagnation of lymph flow.

The enzymes released from injured cells remain in the interstitial space because there is no way of transportation. After myocardial infarction, however, lymph flow does not cease, because most parts of the muscle are still working, and enzymes are transported by this route. The lymphatic transport accounts for 15–50% of the totally released enzymes (31–35), whereas the greater part can reach the blood directly due to the much higher capillary permeability within the myocardium than in skeletal muscle (138).

The significance of diagnostic enzymology in hepatic diseases is probably due to the extremely high capillary permeability. Hepatic alkaline phosphatase molecules for example probably pass freely through the large openings in the sinusoidal endothelial lining and are transported out of the liver chiefly in sinusoidal blood, which flows more rapidly than liver lymph (144).

Generally it seems that hepatic lymph derives the bulk of its proteins from the plasma (145, 146, 147).

Even under physiological conditions several enzyme activities in the thoracic duct lymph are several fold higher than in plasma (51, 134). From these data and from lymph flow the extent to which enzymes are continuously added to the blood just by means of lymphatic inflow can be calculated, e.g. creatine kinase with a recirculation index of 2.07 per day and γ-glutamyltransferase and lactate dehydrogenase with 0.88 and 0.66, respectively.

Actually these calculated exchange rates may be even somewhat higher because the dogs were anaesthetized and therefore lacked the physiological stimulation of lymph flow by physical activity.

Data from conscious humans, as reported by *Werner* (148), however, are of restricted value, because they might be influenced by the pathologic conditions which gave rise to the cannulation of the thoracic duct.

If the concept of the significance of lymphatic transport of enzymes holds true, one would expect that the mere lymph flow change can alter enzyme activities in plasma. The most impressive example for a physiological increase in lymph flow is physical exercise.

Animal experiments have demonstrated that even during moderate excercise thoracic duct lymph flow increases two and threefold (46, 50). This phenomenon exemplifies how an absolutely physiological process affects enzyme activities in plasma just because the system of flux equilibria gets disturbed. The most commonly used explanation for changes of enzyme activities in plasma during and after physical exertion is an enzyme release from cells, due to a relative transient hypoxia, which is believed to lead to an increased permeability of the cellular membrane for macromolecules caused by a depletion of cellular energy (149, 150).

Thereby enzyme release from muscle cells should contribute to the main part of elevated enzyme activities in plasma (150), whereas other authors attribute more importance to the liver (151, 152).

Further factors, which can contribute to changes of enzyme activities in plasma are haemoconcentration (153), intravascular haemolysis (154, 155) and the type, intensity (154), duration (150), and extent of the work executed (156).

All these studies performed in humans, however, are phenomenological interpretations from enzyme activities in plasma. Taking into consideration the simpliest fundamentals of circulation physiology and the proportions of the intravasal and interstitial distribution space, however, in that the latter is fourfold greater than the former, it becomes questionable whether during and after physical exercise a release of enzymes from cells occurs at all. The following concept of enzyme activity changes in plasma during and after physical exertion is based mainly at experimental findings and considerations by *Friedel* et al. (134, 143, 153, 157) and our group (30, 51, 158) and taking into consideration the major part of clinical as well as experimental observations by other authors.

During physical exertion the system of flux equilibria between the interstitial and the intravascular compartment becomes disturbed. The first acute effect is a decrease in plasma volume, because of an increased systemic blood pressure and consequently an intravascular concentration of macromolecules in an order of magnitude of 10–15%. In skeletal muscle, this increased hydrostatic pressure leads to an increased filtration of solution into the interstitium,

thus causing an enhanced lymph flow from muscle which is propulsed by the action of the tissue pumps of the active working muscle. The lymph entering the intravascular compartment contains enzymes, which become concentrated because the capillary membranes within skeletal muscle are almost impermeable to proteins, whereas fluid is filtered back at nearly the same enhanced rate as it flows into the plasma.

The accumulated proteins and enzymes also slowly get back into the interstitial space, but preferably in such regions where the capillary permeability is high, as in the liver. They thereby also induce an increase of lymph flow from the liver, because the organism tries to keep the colloidosmotic equilibrium in balance.

For other organs the intravascular concentration of macromolecules with an increasing colloidosmotic pressure leads to a reduction of fluid filtration into the interstitium and thus to a reduction in lymph flow from these organs.

To which extent all these physiological mechanism affect the plasma activity of a particular enzyme depends on its lymph-plasma activity ratio, especially for lymph from skeletal muscle. Since creatine kinase in plasma originates mainly from skeletal muscle and therefore has a considerably higher lymph-plasma activity ratio in muscle lymph, than plasma proteins and other enzymes, it is not astonishing, that the most distinct increase in plasma activities during and after exercise is usually found for this particular enzyme.

It must be mentioned again, however, that due to the proportions of the interstitial and intravasal space of 4:1, the concentration of macromolecules with a lymph-plasma ratio less than one can rise considerably in plasma during physical activity.

It is highly probable that the effect which physical exertion has on enzyme activities in plasma is caused mostly, if not totally by an alteration in the extracellular distribution of cellular enzymes, so that the total extracellular activities do not change at all.

This statement definitely does not imply that, during exertion, there is absolutely no enzyme release from the active working muscle, a phenomenon which depends, as outlined at the beginning, on the duration and type of the work executed. It calls in question, however, the often made assumption that even the short term general hypoxia, which occurs during strenuous exercise, can be the cause for an enzyme release from cells of muscle and/or other organs. An enzyme release on the basis of "blebbing" (159) is unlikely, considering the energy status of muscle after tourniquet application of up to 2 h duration (160–163).

6. Enzymes in Different Lymphatics of Man and Various Animals (Tab. 1).

Tab. 1. Enzyme catalytic activity concentrations, protein and albumin concentration, lymph-plasma activity ratio and lymph flow from different lymphatics in man, sheep, dog, cat, rabbit, guinea pig and rat.
The data were taken from the authors cited under Reference. ~ denotes, that values were estimated from figures.
Values are given as mean with standard deviation (SD) or standard error of the mean (SEM).
Units: Catalytic concentrations are given in U/l (lymph) or U/g (protein); the numbers in this column refer to following notes:

1. Sigma units/ml
2. Phenolphthalein released, µg/100 ml × h (at 37 °C)
3. Phenolphthalein released, µg/100 ml × h
4. Octopamine formed, nmol/ml × 20 min
5. *p*-Nitrophenol released, µg/ml × h
6. Phenolphthalein released, µg/ml × h
7. β-Phenylethanolamine formed, µmol/ml × 20 min
8. Tyrosine, 10^{-5} mEq/h × g protein
9. *p*-Nitrophenol released, µmol/min × g protein
10. Phenolphthalein released, µg/2 h × g protein
11. 4-Nitrocatechol released, mg/h × g protein
12. *Berger-Broida* – U/ml
13. Nucleotides released, mg/ml × h
14. ΔA280 nm/ml × unit time
15. Counts/min per hour

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
6.1 Ductus thoracicus lymph								
Alkaline phosphatase	3.1.3.1	4.9	U/l	0.44	–	Data from patients with biliary obstruction	man	164
Aspartate aminotransferase	2.6.1.1	44	U/l	0.44				
Alanine aminotransferase	2.6.1.2	34	U/l	0.45				
Protein		41	g/l	0.60				
Diverse		no quantitative data		–	–	Data from patients with liver cirrhosis and from 2 normal persons	man	165
α-Amylase	3.2.1.1	775 ± 15.3 SD	U/l	–	–	Enzymes in lymph after administration of a combination of coumarin and rutin sulphate	man	166
Lipase	3.1.1.3	27 ± 9 SD	U/l	–				
Alkaline phosphatase	3.1.3.1	150	U/l	–	148.7 ml/h	Evidence that intestinal alkaline phosphatase enters the circulation via lymph	man	167
Alkaline phosphatase	3.1.3.1	Is given in a	U/l	0.63	4.2–	The biochemical composition of	man	148
Acid phosphatase	3.1.3.2	table for each	U/l	0.58	152.4	the human thoracic duct lymph		
Aspartate aminotransferase	2.6.1.1	patient	U/l	0.72	ml/h	is presented		
Alanine aminotransferase	2.6.1.2		U/l	0.71				
Lactate dehydrogenase	1.1.1.27		U/l	0.77				
Aldolase	4.1.2.13		U/l	1.87				
Protein			g/l	0.66				
Albumin			g/l	0.79				
α-Amylase	3.2.1.1	~1.9	µkat/l	~0.83	–	Protective effect of the lymphatic system due to alcohol	man	168
Lipase	3.1.1.3	~0.65	µkat/l	~0.86				
Creatine kinase	2.7.3.2	Data in percent	U/l	5.9	14.5 ± 3.8	Enzymes from muscle are	dog	51
Lactate dehydrogenase	1.1.1.27	change	U/l	7.0	µl/min	transported from the interstitial		
Aspartate aminotransferase	2.6.1.1	compared to a	U/l	3.1	× kg	into the intravasal compartment		
Alanine aminotransferase	2.6.1.2	100% control	U/l	0.91		mainly by lymphatic transport		
Protein		value	g/l	0.55				
Acid phosphatase	3.1.3.2	0.09 ± 0.05 SD	①	1.13	0,5	In both haemorrhagic and endo-	dog	169
β-Glucuronidase	3.2.1.31	803 ± 334 SD	①	0.88	ml/min	toxin shock, lysosomal enzymes gain access to the circulation via the lymphatics		
α-Amylase	3.2.1.1	1585 ± 317 SD	U/l	0.79	–	Protective effect of a combination of coumarin and rutin sulphate on canine experimental pancreatitis	dog	170
Trypsin	3.4.21.4	145 ± 1.9 SD	U/l	1.37				

Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
Lactate dehydrogenase	1.1.1.27	Shown in a figure	U/l	–	–	Significance of the lymphatic system in resorption of enzymes from the damaged kidney	dog	171
Acid phosphatase β-Glucuronidase	3.1.3.2 3.2.1.31	1.18 0.75	U/l U/l	0.56 0.63	–	Lymph is probably not the main route of entry for lysosomal enzymes into the circulating blood in haemorrhagic shock	dog	172
Lysozyme	3.2.1.17	Shown in a figure as output by D. th.	U/l	–	–	More direct indication in lymph than in blood for the degree of hepatosplanchnic cellular impairment in canine haemorrhagic and endotoxin shock	dog	173
α-Amylase Lipase	3.2.1.1 3.1.1.3	495 170	U/l U/l	0.57 1.35	– –	In drained dogs the values of the enzymes in blood, urine and peritoneal exsudate were lowered after an acute pancreatitis	dog	174
Acid phosphatase	3.1.3.2	11–15	U/l	4.4–5.7	0.59–0.62 ml/kg × 15 min	During haemorrhagic shock the majority of lysosomal enzymes released from the intestine gain access to the blood via lymph	dog	175
Acid phosphatase	3.1.3.2	Expressed as lymphatic output	U/l	–	0.57–0.65 ml/min	Protective effect of methylprednisolone on total accumulation of serum and lymph acid phosphatase in haemorrhagic, endotoxic and cardiogenic shock	dog	176
Lactate dehydrogenase Malate dehydrogenase Glutamate dehydrogenase Aspartate aminotransferase Alanine aminotransferase Leucine aminopeptidase Alkaline phosphatase Acid phosphatase Protein	1.1.1.27 1.1.1.32 1.4.1.3 2.6.1.1 2.6.1.2 3.4.11.1 3.1.3.1 3.1.3.2	44.2 ± 9.7 SEM 90.0 ± 19 3.0 ± 1.1 8.3 ± 1.2 4.6 ± 1.3 8.4 ± 1.3 24.4 ± 3.5 3.4 ± 0.9 39.4 ± 1.4	U/l U/l U/l U/l U/l U/l U/l U/l g/l	0.40 1.01 1.00 1.24 1.00 0.86 0.93 0.72 0.69	–	Increased activities of lactate dehydrogenase and malate dehydrogenase after 30 min of renal ischaemia and of lactate dehydrogenase, malate dehydrogenase and alkaline phosphatase after 2 hours of renal ischaemia	dog	177
Phosphodiesterase I Nucleotide pyrophosphatase Alkaline phosphatase	3.1.4.1 3.6.1.9 3.1.3.1	36 5.6 64	⑨ ⑨ U/l	1.33 – –	–	Organ distribution and activities in body fluids of these enzymes	dog	178
Lactate dehydrogenase Aspartate aminotransferase Creatine kinase Protein	1.1.1.27 2.6.1.1 2.7.3.2	6.5 ± 4.4 SEM 16.1 ± 3.4 25.5 ± 5.8 50 ± 2	U/l U/l U/l g/l	0.81 1.45 1.00 0.72	–	Lactate dehydrogenase and aspartate aminotransferase reach the circulating blood directly from the intracellular compartment in contrast to creatine kinase	dog	40
Creatine kinase Aspartate aminotransferase Lactate dehydrogenase Protein	2.7.3.2 2.6.1.1 1.1.1.27	~30 ~16 ~6.5 ~50	U/l U/l U/l g/l	~1.2 ~1.45 ~0.81 ~0.70	10–12 ml/min	The increase of creatine kinase, aspartate aminotransferase and lactate dehydrogenase in plasma during 30 min electrical muscle stimulation were not altered by draining lymph	dog	39
Lactate dehydrogenase	1.1.1.27	36.4 ± 5.7 SD	U/l	0.46	–	Lactate dehydrogenase is transported from the tissues by lymphatics as well as by blood capillaries	dog	38
Sorbitol dehydrogenase Lactate dehydrogenase Malate dehydrogenase Glutamate dehydrogenase Aspartate aminotransferase	1.1.1.14 1.1.1.27 1.1.1.32 1.4.1.3 2.6.1.1	3.4 ± 0.7 SEM 33.2 ± 5.9 96.3 ± 15.6 2.3 ± 0.9 18.6 ± 2.8	U/l U/l U/l U/l U/l	3.70 0.45 1.22 0.98 1.56	35 µl/kg × min	A significantly higher lymph-plasma ratio for sorbitol dehydrogenase, malate dehydrogenase, aspartate aminotransferase and creatine kinase than for protein	dog	134

Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
Alanine aminotransferase	2.6.1.2	10.3 ± 1.3	U/l	0.81		suggests a predominantly lymphatic pathway, whereas for the other enzymes a partly lymphatic entry into the blood is proposed. There is a close relationship between the molecular weight of enzymes and their lymph-plasma ratio		
γ-Glutamyltransferase	2.3.2.2	1.5 ± 0.5	U/l	0.71				
Creatine kinase	2.7.3.2	10.2 ± 3.2	U/l	1.62				
Leucine aminopeptidase	3.4.11.1	9.3 ± 0.7	U/l	0.78				
Aldolase	4.1.2.13	5.2 ± 1.3	U/l	0.79				
Protein		43.6 ± 2.5	g/l	0.73				
β-Glucuronidase	3.2.1.31	~23	③	~1.05	2.2 ml/kg × h	Protective effect of lymph diversion in haemorrhagic shock because of lymphatic transport of lysosomal enzymes into the blood	cat	179
Dopamine β-hydroxylase	1.14.17.1	3.6 ± 0.6 SD	④	0.64	2.2 ± 0.6 ml/h	Lymphatic transport of dopamine β-hydroxylase, although a direct entry cannot be excluded	cat	180
N-Acetyl glucosaminidase	3.2.1.30	~20	⑤	always	~2.5	Lymphatic pathway is not essential for the increased levels of acid hydrolases in the plasma following haemorrhage	rabbit	181
β-Glucuronidase	3.2.1.31	~15	⑥	<1	ml/h			
Acid phosphatase	3.1.3.2	~60	⑤					
Protein		~42	g/l					
Lipase	3.1.1.3	551 ± 306 SD	U/l	2.38	0.61 ± 0.11 ml/45 min	No activity in lymph after stimulation of the damaged pancreas by secretin and pancreomyzin	rat	182
Alkaline phosphatase	3.1.3.1	~180	U/l	~1.0	0.6 ml/h	Direct entry of liver alkaline phosphatase by way of the hepatic sinusoids	rat	144
Alkaline phosphatase	3.1.3.1	–	U/l	–	0.6 ml/h	Hepatic alkaline phosphatase enters the serum directly by traversing the hepatic sinusoidal gaps	rat	183
Aspartate aminotransferase	2.6.1.1	62 ± 3.2	U/l	0.50	0.31 ±	Determination of various components in lymph and plasma	rat	184
Alanine aminotransferase	2.6.1.2	15.0 ± 2.0	U/l	0.41	0.02 ml/			
Aldolase	4.1.2.13	36.4 ± 5.8	U/l	0.49	100 g × h			
Acid phosphatase	3.1.3.2	0.70 ± 0.1	U/l	0.38				
Alkaline phosphatase	3.1.3.1	3.62 ± 0.3	U/l	1.16				
Protein		41 ± 2.1	g/l	0.72				
6.2 Right duct lymph								
Aspartate aminotransferase	2.6.1.1	15–60	kU/l	0.60–0.61	–	Right duct lymph contained significant amount of heart lymph in only 60% of patients operated upon with open heart surgery	man	185
Alanine aminotransferase	2.6.1.2	11–21	kU/l	0.48–0.70				
Creatine kinase	2.7.3.2	56–58	U/l	0.88–1.23				
Lactate dehydrogenase	1.1.1.27	217–433	kU/l	0.58–0.75				
Aspartate aminotransferase	2.6.1.1	Presented in figures and tables	kU/l	–	–	Efflux of enzymes in lymph and serum after coronary perfusion and ischaemic arrest	man	186
Alanine aminotransferase	2.6.1.2		kU/l					
Creatine kinase	2.7.3.2		kU/l					
Lactate dehydrogenase	1.1.1.27		kU/l					
Dopamine β-hydroxylase	1.14.17.1	95 ± 25 SEM	⑦	0.37	–	Significant correlation between activity in lymph and serum	man	187
Albumin		–	g/l	0.66	–			
Creatine kinase	2.7.3.2	~80	U/l	~2.86	–	No change of enzyme activity in lymph during peripheral muscle stimulation	dog	39
Aspartate aminotransferase	2.6.1.1	~18	U/l	~1.80	–			
Lactate dehydrogenase	1.1.1.27	~ 7	U/l	~1.75				
Protein		~42	g/l	~0.68				

Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
6.3 Cardiac lymph								
Creatine kinase Lactate dehydrogenase	2.7.3.2 1.1.1.27	1357 ± 306 SD 785 ± 250	U/l U/l	4.98 13.1	–	Determination of various constituents in cardiac lymph	dog	188
Cathepsin D	3.4.4.23	1.05 ± 0.04 SD	⑧	4.04	2.4 ml/h	Increase in lymph and pericardial fluid but not in plasma after ligation	dog	189
Creatine kinase Lactate dehydrogenase Malate dehydrogenase	2.7.3.2 1.1.1.27 1.1.1.32	0 93 105	U/l U/l U/l	–	–	Increase to 40 (creatine kinase), 1720 (lactate dehydrogenase) and 4930 (malate dehydrogenase) 60 min after 90 min ischaemia	dog	190
Creatine kinase Lactate dehydrogenase Malate dehydrogenase Aspartate aminotransferase Alanine aminotransferase	2.7.3.2 1.1.1.27 1.1.1.32 2.6.1.1 2.6.1.2	~500 ~500 – – –	U/l U/l U/l U/l U/l	–	–	Increase to 10000 (creatine kinase), 5000 (lactate dehydrogenase), 10000 (malate dehydrogenase), 1000 (aspartate aminotransferase) and 600 (alanine aminotransferase) after 120 min ischaemia	dog	34
Aspartate aminotransferase Alanine aminotransferase Lactate dehydrogenase Malate dehydrogenase Isocitrate dehydrogenase Acid phosphatase	2.6.1.1 2.6.1.2 1.1.1.27 1.1.1.32 1.1.1.42 3.1.3.2	31.0 ± 12.7 SD 5.3 ± 3.6 130 ± 79 180 ± 120 3.8 3.0	U/l U/l U/l U/l U/l U/l	4.31 0.77 3.10 2.25 0.55 1.0	–	After experimental myocardial infarction the enzyme escape via heart lymph increased, except for acid phosphatase	dog	32
Acid phosphatase	3.1.3.2	0.08 ± 0.01 SD	U/l	–	–	Protective effect of steroids on increase of acid phosphatase	dog	191
Aspartate aminotransferase Lactate dehydrogenase	2.6.1.1 1.1.1.27	1840 ± 220 SD 1177 ± 329	U/l U/l	–	1.2 ml/h	After ligation of the coronary sinus lymph flow increased 3.9 fold and aspartate aminotransferase and lactate dehydrogenase fell to roughly half the control value	dog	192
Acid phosphatase Protein	3.1.3.2	0.90–1.94 SD 44.6–48.0	U/l g/l	1.7 0.8	3.09–3.59 ml/2 h	No protective effect of methylprednisolone on increase of acid phosphatase	dog	88
Phosphodiesterase I Nucleotide pyrophosphatase Alkaline phosphatase	3.1.4.1 2.6.1.9 3.1.3.1	1.8 3.4 21	⑨ ⑨ U/l	0.67 0.40 0.40	–	Organ distribution and activities in body fluids of these enzymes	dog	178
Aspartate aminotransferase	2.6.1.1	54.9 ± 29 SD	U/l	–	2.8–95 µl/min	Decrease of aspartate aminotransferase after thrombin infusion	dog	193
Creatine kinase	2.7.3.2	–	U/l	–	2.5–3.2 ml/h	2.5-fold increase in lymph and 3 to 4-fold in plasma above control values after ischaemia	dog	194
Lactate dehydrogenase Malate dehydrogenase Creatine kinase Aspartate aminotransferase Alkaline phosphatase Acid phosphatase	1.1.1.27 1.1.1.32 2.7.3.2 2.6.1.1 3.1.3.1 3.1.3.2	245 ± 34 SEM 235 ± 19 0.9 ± 0.2 58 ± 24 – –	U/l U/l U/l U/l U/l U/l	6.7 3.1 1.4 7.2 1 1	–	Lymphatic activity of lactate dehydrogenase, malate dehydrogenase, aspartate aminotransferase and creatine kinase increased after occlusion of the coronary artery. Plasma levels rise later. Alkaline phosphatase and acid phosphatase did not differ from controls	dog	195
Lactate dehydrogenase Protein	1.1.1.27	140 ± 45.3 SEM 37.0	U/l g/l	1.86 –	–		dog	38
Aspartate aminotransferase Alanine aminotransferase Creatine kinase Lactate hydrogenase	2.6.1.1 2.6.1.2 2.7.3.2 1.1.1.27	~30–100 10– 40 5– 15 ~50–110	U/l U/l U/l U/l	– – – –	–	The time course of activity increase was identical for all enzymes after myocardial infarction	dog	31

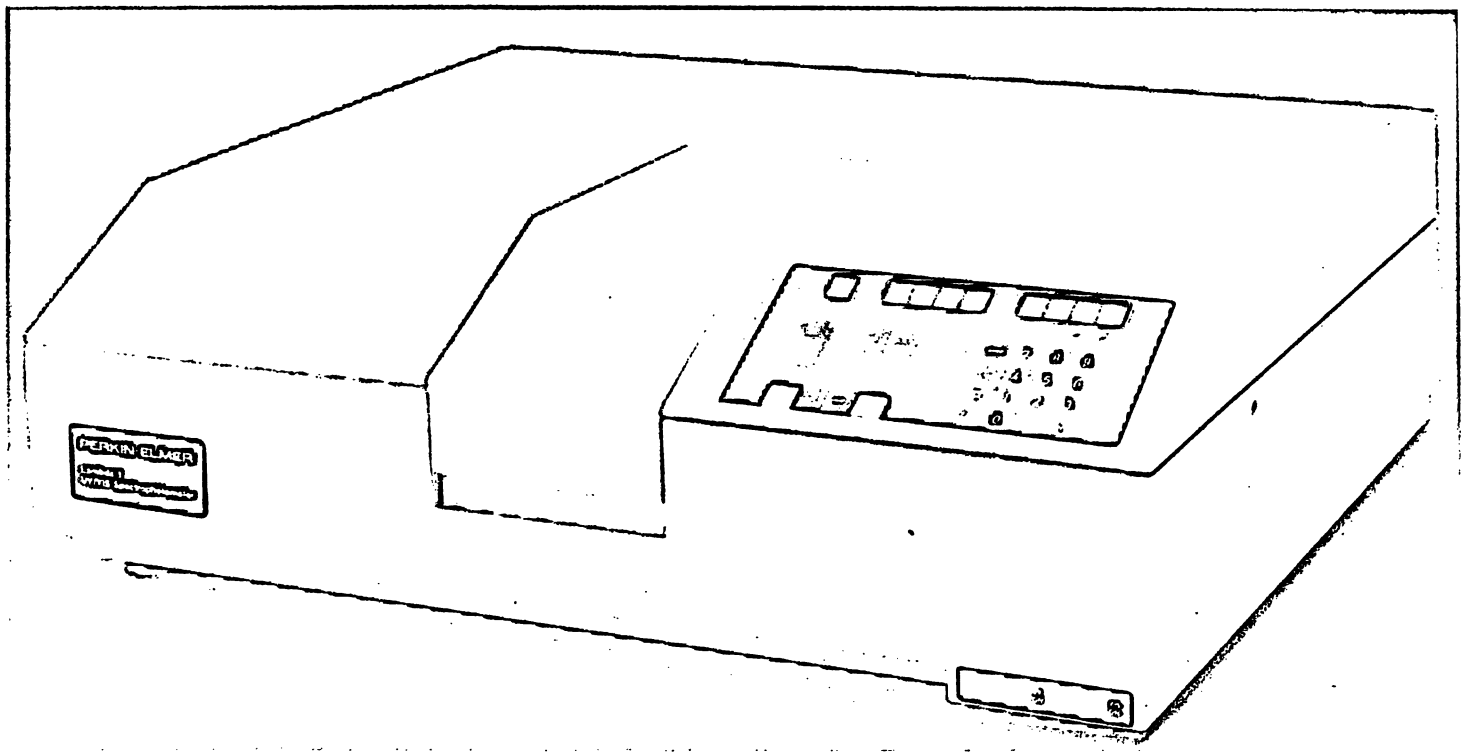
Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
Aspartate aminotransferase	2.6.1.1	18– 82	U/l	–	0.8–6.1 ml/h	Significant amount of aspartate aminotransferase reached the blood via lymph	dog	196
Creatine kinase	2.7.3.2	280 ± 48 SEM	U/l	1.8	–	20–30% of liberated enzymes after infarction reach the blood via the lymphatic system	dog	35
Lactate dehydrogenase	1.1.1.27	188 ± 33	U/l	2.5				
Malate dehydrogenase	1.1.1.32	628 ± 157	U/l	4.0				
Alanine aminotransferase	2.6.1.2	12 ± 2	U/l	1.3				
Aspartate aminotransferase	2.6.1.1	60 ± 12	U/l	3.2				
Phosphorylase a	2.4.1.1	0– 0.13	U/l	–	–	Increase after short term ischaemia (20 min) in lymph from conscious animals	dog	197
Creatine kinase	2.7.3.2	241 ± 14.4 SD	U/l	6.6	4.2–4.34 ml/2 h	Acid phosphatase increased 30% and creatine kinase rose 62% after 2 h occlusion of the left coronary artery	dog	89
Acid phosphatase	3.1.3.2	2.2 ± 0.22	U/l	2.4				
Aspartate aminotransferase	2.6.1.1	1283 ± 521 SD	U/l	28.5	2.3 ± 0.43 ml/h	Only slightly increased activities in the group with congestive heart failure	dog	198
Lactate dehydrogenase	1.1.1.27	775 ± 200	U/l	11.1				
Creatine kinase	2.7.3.2	680	U/l	7.6	–	Under physiological conditions activities of all enzymes in lymph are higher than in serum. Including flow rates of myocardial lymph and coronary blood enzyme transport, rate of lymph after infarction is about 15%	dog	33
Malate dehydrogenase	1.1.1.32	1200	U/l	6.7				
Lactate dehydrogenase	1.1.1.27	540	U/l	6.8				
α-Hydroxybutyrate dehydrogenase		400	U/l	13.0				
Aspartate aminotransferase	2.6.1.1	150	U/l	7.5				
Alanine aminotransferase	2.6.1.2	60	U/l	4.0				
Creatine kinase	2.7.3.2	0	U/l	–	–	Marked increase after 90 min ischaemia	rabbit	199
Lactate dehydrogenase	1.1.1.27	93	U/l					
Malate dehydrogenase	1.1.1.32	105	U/l					
6.4 Lung lymph								
β-Glucuronidase	3.2.1.31	3.2 ± 1.5 SD	(10)	0.24	4.7 ± 1.1 ml/30 min	Haemorraghic shock: increase of β-glucuronidase in plasma, not in lymph, no lung injury. Endotoxin shock: increase of both enzymes in lymph and plasma; severe lung injury	sheep	200
Aryl sulphatase	3.1.6.1	1.3 ± 0.2	(11)	0.18				
Protein		37 ± 3	g/l	0.60				
Albumin		17 ± 4	g/l	0.65				
β-Glucuronidase	3.2.1.31	2.8 ± 0.7 SD	(10)	0.14	16.0 ± 0.3 ml/h	After 50% full-thickness burn increase of both enzymes in plasma and lymph; time course in lymph lagged behind by 1 to 3 hours	sheep	201
Aryl sulphatase	3.1.6.1	1.8 ± 0.4	(11)	0.12				
Angiotensin converting enzyme	3.4.15.1	5.3	kU/l	0.93	4.7 ml/h	Bacteraemia increased release of angiotensin converting enzyme by the lung into lymph. No rise in plasma	sheep	202
Albumin		–	g/l	0.79				
Lactate dehydrogenase	1.1.1.27	401–566 SD	(12)	0.5	7.0 ± 4.2 ml/30 min	Haemorrhagic shock produced a systemic cellular injury reflected in an increased plasma lactate dehydrogenase activity, but not in lung lymph	sheep	203
Protein		35 ± 9	g/l	0.5				
Albumin		20 ± 5	g/l	0.7				
β-Glucuronidase	3.2.1.31	2.1 ± 0.6 SD	(10)	0.21	5.5 ± 0.9 ml/30 min	The degree of systemic and pulmonary injury after endotoxin shock corresponds to the increase in plasma and lymph enzyme activity, respectively. The mechanism of injury and activity increase appears to be different for the two systems	sheep	204
Aryl sulphatase	3.1.6.1	1.5 ± 0.3	(11)	0.28				
Protein		39 ± 2	g/l	0.64				
Albumin		20 ± 2	g/l	0.71				

Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
6.5 Gastric lymph								
Creatine kinase	2.7.3.2	31.7 ± 6.2 SD	U/l	0.7	15–20	Various constituents in gastric	dog	205
Protein		68.1 ± 4.9	g/l	0.8	µl/h	lymph		
6.6 Liver lymph								
β-Glucuronidase	3.2.1.31	~15	⑥	~0.77	~0.9 ml/h	Liver is likely source of the	rabbit	181
N-Acetyl glucosaminidase	3.2.1.30	~10	⑤	~0.58		increased plasma levels of acid		
Acid ribonuclease	2.7.7.16	–	⑬	–		hydrolases in haemorrhagic		
Cathepsin D	3.4.4.23	–	⑭	–		shock. Lymphatic pathway not		
Acid phosphatase	3.1.3.2	~35	⑤	0.36		essential for increased levels		
α-Amylase	3.2.1.1	72.2 ± 8.2 SD	kU/l	2.3	8.8 ml/	After obstruction of small	dog	206
Lipase	3.1.1.3	2.4 ± 0.3	kU/l	2.0	30 min	intestine or bile duct no marked increase in lymph or serum enzyme levels were noted		
α-Amylase	3.2.1.1	72.2 ± 8.2 SD	kU/l	2.3	8.8 ml/	Following pancreatectomy there	dog	207
Lipase	3.1.1.3	2.4 ± 0.3	kU/l	2.0	30 min	is a progressive decline in the activities in serum and hepatic lymph		
Lactate dehydrogenase	1.1.1.27	78.5 ± 6.6 SD	U/l	1.05	–	Comparison of lactate dehydrogenase content in various lymph vessels	dog	38
6.7 Intestinal lymph								
α-Amylase	3.2.1.1	60.3 ± 8.7 SD	kU/l	1.89	6.8 ml/	After obstruction of small	dog	206
Lipase	3.1.1.3	1.9 ± 0.2	kU/l	1.58	30 min	intestine or bile no marked increase in lymph or serum were noted		
α-Amylase	3.2.1.1	60.3 ± 8.7 SD	kU/l	1.89	6.8 ml/	Following pancreatectomy there	dog	207
Lipase	3.1.1.3	1.9 ± 0.2	kU/l	1.58	30 min	is a progressive decline of both enzymes in the serum and lymph		
Lipase	3.1.1.3	671 ± 103 SD	U/l	2.41	–	Lipase was absorbed by the duodenum into lymphatics	dog	208
Lactate dehydrogenase	1.1.1.27	68.2 ± 11.9 SD	U/l	0.91	–	Comparison of lactate dehydrogenase contents of various lymph vessels	dog	38
Acid phosphatase	3.1.3.2	36.6 ± 2.2 SD	⑤	1.53	–	Acid phosphatase was added to	sheep	209
β-Glucuronidase	3.2.1.31	0.67 ± 0.1	⑥	0.14		the capillary filtrate at a regional		
N-Acetyl glucosaminidase	3.2.1.30	12.0 ± 1.0	⑤	0.35		tissue level, whereas both other		
Protein		30.2 ± 2.7	g/l	0.53		enzymes in lymph derived by filtration from the blood plasma on a molecular weight basis		
Sialyltransferase	2.4.99.1	~100	⑮	~0.79	0.55 ±	Elevation of sialyltransferase,	rat	210
Maltase	3.2.1.20	5.0 ± 0.46 SD	kU/g	–	0.05 ml/	alkaline phosphatase and lactate		
Sucrase	3.2.1.26	1.5 ± 0.06	kU/g	–	10 min	dehydrogenase after colchicine		
Lactate dehydrogenase	1.1.1.27	0.8 ± 0.09	U/g	–		treatment, whereas maltase and		
Alkaline phosphatase	3.1.3.1	2.5 ± 0.29	U/g	–		sucrase remain unchanged		
Diamine oxidase	1.4.3.6	1.3	U/l	–	–	Lymph-plasma ratio in rat and	rat	211
		0.12	U/l	–		rabbit higher than in guinea pig.	guinea	
						This difference was even more	pig	
		1.9	U/l	–		pronounced after heparin injection	rabbit	
Alkaline phosphatase	3.1.3.1	As enzyme transport (U/h)	U/l	–	–	Role of intestinal alkaline phosphatase in fat transport	rat	212

Sicherheit für Ihre kinetische Analyse



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```
        PERKIN-ELMER
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  MODE = KIN
  CUR WL = 340.0 NM
  LAG =   60 SEC
  CALS =   06
  DEL =   30 SEC
  EN FAC = 2570
  REC OUT = ABS
  ORD MAX = 1.000
  ORD MIN = 0.000
  CONC FAC = 127.7


  ID#   TIME      AV ABS    DELTA A

  01      60 S    1.2123
          90 S    1.2034    -.0089
         120 S    1.1932    -.0101
         150 S    1.1846    -.0086
         180 S    1.1744    -.0101
         210 S    1.1651    -.0092
         240 S    1.1551    -.0010
       EA        DA         LF        SD
       48.980   -.0190   -1.258     0.00
```

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kartoniert DM 79,–
Klinische Chemie in Einzeldarstellungen, Band 1

„In den neuen Jahren seit Erscheinen der ersten Auflage, mit der das seinerzeit weit verstreute Wissen auf dem Gebiet der Säure-Basen-Physiologie und der Blutgasanalytik zusammengefaßt wurde, hat dieser Sektor eine enorme Weiterentwicklung erfahren.

Die 2. Auflage vermittelt einen Überblick über den gegenwärtigen pathobiochemischen und klinischen Wissensstand auf diesen Gebieten.

Auch die methodisch-technologische Entwicklung der Blutgasanalytik wird berücksichtigt, die heute aus wenigen Mikrolitern Blut in kürzester Frist einen kompletten Blutgas- und Säure-Basen-Status zu erstellen gestattet.

Die Funktionsprinzipien der Geräte, Ursachen, Prophylaxe und Beseitigung von Störungen sowie Möglichkeiten der Qualitätssicherung werden eingehend dargestellt."

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Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
Sorbitol dehydrogenase	1.1.1.14	4.4 ± 0.91 SEM	U/l	0.31	12.8 ±	Distribution and transport of cell	rat	134
Lactate dehydrogenase	1.1.1.27	163 ± 17.7	U/l	1.32	1.3 µl/min	enzymes within the extracellular		
Malate dehydrogenase	1.1.1.32	168 ± 18.5	U/l	1.96		space. Cell enzymes are trans-		
Glutamate dehydrogenase	1.4.1.3	5.6 ± 0.53	U/l	0.54		ported preferably by the		
Aspartate aminotransferase	2.6.1.1	61.3 ± 7.5	U/l	1.09		lymphatics. There is a close		
Alanine aminotransferase	2.6.1.2	34.4 ± 2.6	U/l	0.80		relationship between the		
Pyruvate kinase	2.7.1.40	127 ± 24.9	U/l	0.56		molecular weight of enzymes		
Creatine kinase	2.7.3.2	312 ± 44.9	U/l	2.78		and their lymph-plasma ratios		
Aldenylate kinase	2.7.4.3	125 ± 13.5	U/l	1.82				
Alkaline phosphatase	3.1.3.1	147 ± 15.0	U/l	1.32				
Leucine aminopeptidase	3.4.11.1	2.4 ± 0.31	U/l	0.26				
Aldolase	4.1.2.13	7.4 ± 0.50	U/l	0.94				
Protein		38.1 ± 3.6	g/l	0.56				
6.8 Renal lymph								
Lactate dehydrogenase	1.1.1.27	69.6 ± 16 SEM	U/l	0.93	–	Lactate dehydrogenase content in various lymph vessels	dog	38
Lactate dehydrogenase	1.1.1.27	29.0 ± 8.0 SEM hilar	U/l	0.74	–	Similar pattern in capsular and hilar lymph indicate a pre-	dog	213
		35.0 ± 9.0 capsular		0.90		dominantly cortical origin of both lymph samples		
Lactate dehydrogenase	1.1.1.27	70.6 ± ± 19.6 SEM	U/l	0.64		Hilar lymph was sampled. After 30 min of renal ischaemia there	dog	177
Malate dehydrogenase	1.1.1.32	132 ± 29.2	U/l	1.48		was a marked increase of cyto-		
Glutamate dehydrogenase	1.4.1.3	2.7 ± 0.5	U/l	0.90		plasmic enzymes in lymph and		
Aspartate aminotransferase	2.6.1.1	4.6 ± 1.0	U/l	0.69		urine which after 2 hours of		
Alanine aminotransferase	2.6.1.2	4.2 ± 1.1	U/l	1.02		ischaemia was followed by a rise		
Leucine aminopeptidase	3.4.11.1	3.6 ± 1.1	U/l	0.37		in activities of mitochondrial		
Alkaline phosphatase	3.1.3.1	10.1 ± 2.6	U/l	0.39		and lysosomal enzymes		
Acid phosphatase	3.1.3.2	0.6 ± 0.4	U/l	0.13				
Protein		32.7 ± 1.0	g/l	0.58				
Creatine kinase	2.7.3.2	94 ± 21 SD	U/l	0.35		Determination of various	dog	188
Lactate dehydrogenase	1.1.1.27	30 ± 6.3	U/l	0.55		components in lymph		
6.9 Truncus lumbalis lymph								
Creatine kinase	2.7.3.2	110 ± 13.8 SEM	U/l	6.5	9–10.5 ml/15 min	Hypoxia for one hour on the hind leg muscle does not	dog	30
Malate dehydrogenase	1.1.1.32	197 ± 14.8	U/l	5.3		provoke release of enzymes.		
Lactate dehydrogenase	1.1.1.27	98.1 ± 7.7	U/l	4.0		Enzymes from muscle have to be		
Adenylate kinase	2.7.4.13	85.5 ± 9.9	U/l	3.8		transported into the blood by		
Aspartate aminotransferase	2.6.1.1	19.4 ± 1.7	U/l	2.4		lymph flow and not via a direct		
Aldolase	4.1.2.13	15.3 ± 1.2	U/l	2.3		interstitial-venous entry		
Alkaline phosphatase	3.1.3.1	28.8 ± 3.6	U/l	0.6				
Alanine aminotransferase	2.6.1.2	15.1 ± 1.3	U/l	0.54				
Leucine aminopeptidase	3.4.11.1	6.3 ± 0.5	U/l	0.53				
Choline esterase	3.1.1.8	408 ± 32.0	U/l	0.21				
Lactate dehydrogenase	1.1.1.27	88 ± 14 SEM	U/l	3.0	–	A two-compartement model of	rabbit	23
Aspartate aminotransferase	2.6.1.1	105 ± 19	U/l	2.4		tissue fluid is presented		
Protein		29 ± 4.2	g/l	0.5				
6.10 Peripheral leg lymph								
Aspartate aminotransferase	2.6.1.1	2.6 ± 0.27 SD	??	0.43	–	Superficial leg lymph vessel;	man	214
Alanine aminotransferase	2.6.1.2	2.0 ± 0.10	??	0.64		in lymph draining skin and		
Acid phosphatase	3.1.3.2	3.7 ± 0.84	??	0.57		subcutaneous tissue only a small		
Alkaline phosphatase	3.1.3.1	2.8 ± 0.50	??	0.43		admixture of locally released		
Lactate dehydrogenase	1.1.1.27	11.2 ± 2.0	??	0.26		enzymes could be detected		
Protein		23.9 ± 0.40	g/l	0.39				

Tab. 1. Continued.

Analyte	EC	Value	Unit	Lymph/ plasma ratio	Lymph flow	Experimental conditions; conclusions	Species	Ref.
Acid phosphatase β-Glucuronidase N-Acetyl glucosaminidase Protein	3.1.3.2 3.2.1.31 3.2.1.30	22.5 ± 2.1 SD 0.73 ± 0.05 13.6 ± 1.0 25.3 ± 1.0	⑤ ⑥ ⑤ g/l	1.09 0.13 0.61 0.38	–	Efferent popliteal lymph vessel; indication that acid phosphatase was added to the capillary filtrate at a regional tissue level, whereas β-glucuronidase and N-acetyl glucosaminidase in lymph derived from filtration from the blood plasma compartment on a molecular weight basis	sheep	209
Creatine kinase Lactate dehydrogenase Aspartate aminotransferase Alanine aminotransferase Aldolase Adenylate kinase Malate dehydrogenase Leucine aminopeptidase Alkaline phosphatase Choline esterase Protein	2.7.3.2 1.1.1.27 2.6.1.1 2.6.1.2 4.1.2.13 2.7.4.3 1.1.1.32 3.4.11.1 3.1.3.1 3.1.1.8	~ 50 ~300 ~ 30 ~ 22 ~ 20 ~ 60 ~300 ~ 5 ~ 38 ~300 ~ 20	U/l U/l U/l U/l U/l U/l U/l U/l U/l U/l g/l	3.6 9.0 2.7 0.6 3.3 3.8 6.9 0.5 1.0 0.2 0.3	3.0 ml/ 15 min	Femoral deep lymphatic; from lymph-plasma ratios of enzymes (all were significantly greater than that of choline esterase – an enzyme which is exclusively synthesized in liver and which may get into the lymph only by a limited escape in the capillary area) it is concluded that cellular enzymes have to be transported into the intravascular space by lymph flow, and scarcely via a direct entry across capillaries	dog	135
Lactate dehydrogenase	1.1.1.27	137 ± 6.6 SEM	U/l	1.8	–	Saphenous lymph vessel	dog	38
Lactate dehydrogenase Aspartate aminotransferase Alanine aminotransferase β-Glucuronidase Acid phosphatase Protein	1.1.1.27 2.6.1.1 2.6.1.2 3.2.1.31 3.1.3.2	Depends on various experimental protocols	U/l U/l U/l U/l U/l g/l	–	16 ± 3 µl/min	Superficial and deep femoral lymph vessel; the activities of aspartate aminotransferase were about the same; alanine aminotransferase and lactate dehydrogenase somewhat lower, that of acid phosphatase and β-glucuronidase was somewhat higher than those usually present in plasma	cat	110
Acid phosphatase β-Glucuronidase Lactate dehydrogenase Protein	3.1.3.2 3.2.1.31 1.1.1.27	20.8 ± 1.5 SEM 1.5 ± 0.2 336 ± 26 21.8 ± 0.9	⑤ ⑥ U/l g/l	0.28 0.08 1.63 0.38	–	Hind paw; no appreciable release of lysosomal enzyme after 4 hours tourniquet, whereas lactate dehydrogenase increased in lymph	rabbit	215
Lactate dehydrogenase Alanine aminotransferase β-Glucuronidase Protein	1.1.1.27 2.6.1.2 3.2.1.31	445 ± 75 SD 6 ± 1 2950 ± 850 22 ± 2	U/l U/l U/l g/l	–	11.4 ± 2.4 µl/min	Femoral lymph vessel; the effect of anti-inflammatory agents on the changes in local lymph after thermal injury was investigated	rabbit	216
Lactate dehydrogenase Aspartate aminotransferase Alanine aminotransferase β-Glucuronidase Acid phosphatase Protein	1.1.1.27 2.6.1.1 2.6.1.2 3.2.1.31 3.1.3.2	249 38 4 7150 80 29	U/l U/l U/l U/l U/l g/l	0.97 1.36 0.33 0.18 0.47 0.53		Femoral lymph vessel; limbs were injured by burning at 80 °C and 60 °C and by freezing	rabbit	217
Lactate dehydrogenase Aspartate aminotransferase Alanine aminotransferase	1.1.1.27 2.6.1.1 2.6.1.2	– – –	U/l U/l U/l	–	5.3 ± 1 µl/min	Muscle lymph; total femoral flow was 21.5 ± 5 µl/min, while muscle lymph flow was 5.3 ± 1. Increase of enzymes in muscle lymph after thermal injury	rabbit	112
Lactate dehydrogenase Aspartate aminotransferase Alanine aminotransferase Isocitrate dehydrogenase Acid phosphatase β-Glucuronidase Cathepsin D Protein	1.1.1.27 2.6.1.1 2.6.1.2 1.1.1.42 3.1.3.2 3.2.1.31 3.4.4.23	Depends on various experimental protocols	U/l U/l U/l U/l U/l U/l kU/l g/l	–	–	Femoral lymph vessel; various thermal injuries were investigated for changes in lymph and plasma	rabbit	111

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