ClinicSearch

Clinical Genetic Research

Bon E. I*

Open Access

Review Article

The Development of Hypoxia in Muscle Tissue During Ageing

Fliuryk S [1], Dremza I [1], Maksimovich N [1], Bon E [1*], Kendysh U [1], Pauliuchenkava D [2]

[1] Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

[2] Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

***Correspondence Author:** Bon E, Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

Received Date: May 01, 2023| Accepted Date: May 10, 2023| Published Date: May 22, 2023

Citation: Fliuryk S, Dremza, Maksimovich N, Bon E, Kendysh U, Pauliuchenkava D (2023), The Development of Hypoxia in Muscle Tissue During Ageing, *Clinical Genetic Research*, 2(3); **Doi:**10.31579/2834-8532/023

Abstract

Reduced rate of tissue oxygen consumption, decrease of its redox potential, metabolism of macroergic compounds during oxidative phosphorylation, increased activity of anaerobic glycolysis and lactic acid content, LDH-5 isoenzyme, etc. are indicative of tissue hypoxia. If we are guided by these signs, we can assume that as we get older, hypoxia phenomena begin to develop in muscle tissue. In acute hypoxic hypoxia the onset of secondary tissue hypoxia in old animals occurs at higher values of the average value of tissue and minimum PO2, i.e., 'critical' level of PO2 is increased; the decrease of muscle blood flow rate and the decrease of oxygen extraction from the blood is noted in old animals with less significant deficiency of oxygen in the environment. In older animals the development of tissue hypoxia is accompanied by more pronounced manifestations of lactacidosis and a decrease in the rate of oxygen consumption by the tissue; the compensatory possibilities preventing secondary tissue hypoxia in hypoxic states of various origins are reduced.

Keywords: hypoxia; muscle tissue; ageing

Introduction

Reduced rate of tissue oxygen consumption, decrease of its redox potential, metabolism of macroergic compounds during oxidative phosphorylation, increased activity of anaerobic glycolysis and lactic acid content, LDH-5 isoenzyme, etc. are indicative of tissue hypoxia. If we are guided by these signs, we can assume that as we get older, hypoxia phenomena begin to develop in muscle tissue [7,19,20]. Thus, in particular, a decrease in oxygen consumption rate by skeletal muscles under whole organism conditions in young and old animals has been found. Oxygen consumption by calf muscle of 12-month-old rats determined in vivo by the rate of volumetric blood flow through the muscle and regional arterio-venous oxygen difference ranged from 0.8 to 1.2 ml/min per 100 g of tissue. Oxygen consumption by the calf muscle of old rats (at 28-32 months of age) ranged from 0.65 to 1.0 mL/min per 100 g of tissue, remaining on average lower than that of adult animals. A study of the intensity of tissue (endogenous) respiration in the Warburg apparatus at 37° C, pH 7.4 and PO_2 of gas medium 33.4 mm Hg showed a tendency to a decrease in the intensity of O_2 consumption by myocardium and skeletal muscles of old rats. These data on a decrease in tissue respiration rate of muscles during aging coincide with other studies indicating, in particular, a decrease in oxygen consumption by myocardium [13,25] and diaphragm muscle [16].

Different opinions are expressed in the literature to explain the decrease in the rate of oxygen consumption by muscle (and other) tissues in the later stages of ontogenesis. There is convincing evidence in favor of primary changes in the muscle that occur during aging, leading to impaired oxygen utilization and tissue hypoxia. Such changes include a decrease in the number of active cell elements and mitochondria in muscle tissue [1,4], qualitative changes in mitochondria [6,23], and decrease in respiratory enzymes activity [15].

On the other hand, a characteristic feature of the aging process is the ambiguity of changes in the activity of tissue respiratory enzymes. This feature is expressed in the fact that in a certain tissue along with a decrease in the activity of some respiratory chain enzymes the activity of other enzymes increases, the activity of the same enzyme may change unequally in different tissues and, finally, changes in respiratory enzyme activity may be different in different parts of the same tissue and even cell. [6]

The results of our studies on changes in the activity of respiratory enzymes in muscle tissue during aging have confirmed the existence of such differences. Thus, the activity of Krebs cycle dehydrogenases varies differently in myocardium and skeletal muscle of aged rats compared to 12-month-old rats.

The activity of alpha-keto-glutarate dehydrogenase decreased to the greatest extent in myocardium by 59.7% ($p<0.001$) and succinate dehydrogenase by 22.8%. Pyruvate dehydrogenase activity decreased less significantly, by 19.4% ($p<0.05$), and malate- and isocitrate dehydrogenase activity changed insignificantly ($p > 0.05$ in both cases). We found more pronounced shifts in the activity of respiratory enzymes in red skeletal muscles during aging than in white ones. Thus, in m. soleus there was a sharp decrease in the activity of malate-, alpha-ketoglutarate- and succinate dehydrogenase - respectively, by 82,1; 66,8 and 62,1% ($p<0,01$) amidst a pronounced increase in the activity of isocitrate dehydrogenase - by 74,6% ($p<0,05$) and a preservation of pyruvate dehydrogenase activity. In m. gastrocnemius in old age the alpha-ketoglutarate and malate dehydrogenase activity decreased by 82.4 % ($p<0.001$) and 26.3 % ($p<0.05$), respectively; succinate and isocitrate dehydrogenase activity did not change essentially, and pyruvate dehydrogenase activity increased by 56.5 % ($p<0.001$). While the activity of

most Krebs cycle dehydrogenases in muscle tissue decreases with aging, the cytochrome c oxidase activity determined by the Strauss method changes little in myocardium and increases in skeletal muscle. This increase was prominent in m. soleus by 47.7% ($p < 0.001$) and m. gastrocnemius by 59.1% ($p < 0.001$). Changes were also detected in in the content of sulfhydryl groups in the muscles of aged animals. Literature data on the content of SH-groups in muscle tissue of animals during aging are contradictory. Thus, according to the data of some authors, in old animals the number of SH-groups in mitochondria, homogenates and insoluble proteins of heart and skeletal muscles decreases, according to the data of other authors it increases or remains unchanged in myocardial homogenates and increases in the myogenic fraction of skeletal muscles. At the same time, recent data [11], obtained by methods of quantitative and inhibitor analysis, have clearly demonstrated that SH-groups play an essential role in the processes of oxidative phosphorylation.

A highly sensitive micromethod was developed to quantify the level of sulfhydryl groups in small portions of biological material. The reaction vessel was a specially designed 2.5 mL plexiglass vessel. Structurally the reference electrode (calomel electrode) was brought in from the side by means of an agar bridge and thus does not occupy additional space in the titration vessel. Microfeeding of the titration reagent (0.005 M sulma solution) was performed using a feeding device consisting of a removable tuberculin syringe, a spring and a micrometer head. An original additional device was developed, which enables to stabilize the performance of the indicator platinum electrode while maintaining the maximum sensitivity of the microgalvanometer. The proposed micromethod gives high repeatability of results when titrating cysteine solutions. Using this method, SH-group titration can be performed in muscle homogenates at high dilution (1: 500, 1 : 300, 1 : 250).

It was found that the number of SH-groups was decreased in the muscle tissue of aged rats: most prominently in red muscle (by 27.8%, $p<0.001$), less prominently in myocardium (by 15%, $p<0.001$) and white muscle (by 11.5%, $p<0.05$). The difference in the content of groups in red and white muscles becomes unreliable with ageing. The observed decrease in the number of SH-groups can be explained either by the general decrease of sulfur-containing amino acids or by their conversion to an oxidized state. This question can be answered with certainty only by determining the number of disulfide bridges in the studied objects. However, it was established that the thiol disulphide metabolism in muscle proteins changes with aging towards a decrease of SH-groups and the amount of the SH/S-S- S ratio, so it is reasonable to suppose that in our experiments the decreased content of sulphhydryl groups is accompanied by a reduced ratio of SH-groups, which may have a negative effect on the energy metabolism of the tissue: energy transformation processes in mitochondria, oxidative phosphorylation in mitochondria, ATP activity of mitochondria and phosphorylating particles, factor conjugate activity in B. In addition, the combined data on SH - groups of succinate dehydrogenase indicate their participation in the initial steps of the catalysis of succinate oxidation (or binding). A decrease in the content of SH-groups in muscle tissue during aging may be accompanied by inhibition of the reactivity of sulfhydryl groups of the active centre of succinate dehydrogenase, which may lead to a decrease in its activity and the activity of the entire succinate-oxidase complex.

The succinic oxidase system attracts close attention of researchers because, as shown by the works of the last decade [14], succinic acid has an energy advantage over NAD-dependent substrates: a higher rate of oxidation and delivery of hydrogen and electrons into the respiratory chain. In addition, it plays a specific role in a number of biosynthetic processes - synthesis of fatty acids, corticosteroids, porphyrins. There is data on the participation of succinic acid in tissue adaptation to hypoxia [21,22].

Data from various authors on age-related changes in the succinoxidase system in muscle tissue are contradictory. A number of studies have noted an increase in myocardial and skeletal muscle succinoxidase activity during ontogenesis from the prenatal period to old age, with its maximum values recorded in the heart of old animals. Other authors, noting an increase in total cardiac succinoxidase activity with increasing animal weight, indicate that, when recalculating, 1 g of wet weight or 1 g of tissue nitrogen, it increases in a rat's heart when body weight increases from 100 to 300-350 g and decreases with further increase in body weight. Some authors indicate that the rate of oxidation of succinic acid by cardiac tissue is a constant value, changes in which are observed with age are unreliable.

Determination of succinoxidase activity by Schneider and Potter manometric method showed that during animal aging succinoxidase activity significantly decreased in red muscles (by 26.6 %), slightly in multicardium (by 8.9 %) and practically did not change in white muscles.

When comparing changes in the activity of the muscle succinate oxidase system with changes in its key enzymes, succinate dehydrogenase and cytochrome c-oxidase, it was found that in aged rats the succinate oxidase activity changes in parallel only with shifts in succinate dehydrogenase. In literature, there is evidence that succinate dehydrogenase activity is a link limiting the rate of succinic acid oxidation in such a metabolic state of mitochondria, which occurs when dinitrophenol is added. This suggests that the parallelism we found between changes in the succinic oxidase system and succinate dehydrogenase in the absence of one between shifts in the succinic oxidase activity of pytochrome c oxidase may indirectly indicate a decoupling of respiration and phosphorylation processes in the muscle tissue of old animals.

A decrease in the activity of the succinoxidase complex in muscle tissue during aging combined with succinic acid deficiency [18] seems to be one of the factors responsible for the decreased 'stability' of muscle tissue to oxygen deficiency, as will be shown below.

The above facts indicate a general decrease in the level of oxidative processes in muscle tissue during aging, although the activity of individual links may persist and even increase. The question arises: is this decrease the result of primary disturbances in the respiratory apparatus of the cells or does it result from disturbances in oxygen delivery to the muscle? To answer this question, it is necessary to carefully study the conditions and intensity of oxygen delivery to muscle tissue, and the distribution of oxygen tension in the tissue at different stages of individual development.

There are few experimental data on PO_2 in the tissues of the aging organism, but they all indicate its reduction. It has been shown that during aging in humans and animals PO_2 in bone marrow, cerebrospinal fluid and subcutaneous tissue decreases. A decrease of this index was found in the skeletal muscles of old rats, elderly and old people aged 50-83 years. However, at present it is not possible to judge about tissue oxygen regime based only on the results of experimental determination of midline oxygen tension; for this purpose, it is necessary to investigate the mechanisms involved in the formation of this parameter. Tissue mechanisms of oxygen transport and utilization during aging are poorly studied, and muscle tissue is no exception. In literature there are separate reports on the content of myoglobin [24], the capillarization level of different types of muscle [17], and the rate of oxygen consumption by muscle tissue [3,26] in the process of aging. However, in the indicated studies, oxygen tension in muscles was not determined in a parallel manner.

Our comprehensive study not only obtained data on arterial and venous blood oxygen parameters, muscle capillarization indices, muscle blood volumetric rate, muscle oxygen consumption rate, but also used a mathematical model to study the effect of these mechanisms on PO_2 distribution in the calf muscle of rats of different ages.

It has been shown that in old animals the oxygen tension in arterial blood is significantly reduced and less in venous blood, unlike in year-old rats. The oxygen content in arterial blood of old animals significantly decreases due to reduction in PO_2 (at almost constant oxygen capacity of blood), which coincides with the data of literature [10,12]. The regional arterio-venous oxygen content difference in old rats varies within the range of values typical of adult animals. If, according to data of many authors, the minute volume of the heart decreases with aging, then the rate of oxygen transport by arterial and venous blood should decrease significantly. However, the features of oxygen-binding properties of blood in aging (in particular, the shift of oxyhemoglobin dissociation curve to the right due to a certain decrease in pH), apparently, play a favorable role in oxygen delivery to tissues. This can

be proved by the insignificant change of arterio-venous oxygen difference in older animals in comparison with 12-month-old animals.

Changes in oxygen transport function of the blood in the course of aging, the most constant and typical of which are arterial hypoxemia, shift of oxyhemoglobin dissociation curve to the right, reduction of oxygen transport rate by arterial and venous blood, are accompanied by changes in the regional blood flow. Using hydrogen clearance method, it was found that at rest during normoxia the volumetric blood flow rate through the calf muscle of old rats was slightly decreased in comparison with that of one-year-old animals. This coincides with the information that in old animals the volumetric blood flow velocity in limb muscles, determined by rheographic method, decreases.

It was found that with aging there are significant changes in structural and diffusion indices of capillary channel of myocardium and skeletal muscles. In myocardium and skeletal muscle of aged rats, in contrast to one-year-old rats, capillary density significantly decreased, which, in turn, was accompanied by a corresponding increase in the radii of capillary diffusion cylinder. Lengthening of diffusion pathways during aging is due to an increase in muscle fiber size (decrease in fiber density and increase in mean muscle fiber radius) as well as due to capillary lengthening. Thus, in skeletal muscles of old animals the volume of tissue areas supplied by individual capillaries increases and the shape of capillaries changes - they become more tortuous.

It was found that in the myocardium of old rats the number of capillaries per unit area of the muscle decreased and the ratio of capillary to muscle fibre density slightly decreased.

Changes in capillarization parameters of muscle tissue during aging - decrease in capillary density and surface index, increase in diffusion radius, mean fiber radius, capillary length, volume of tissue sections - result in decreased diffusion surface and partial oxygen pressure gradients between blood and muscle tissue, which worsens oxygen diffusion conditions from blood capillaries to muscle cells.

To assess the role of capillary circulation changes in tissue oxygen supply, we studied the PO_2 dynamics in the subcutaneous tissue during functional tests with oxygen inhalation and reactive hyperemia after limb vessel clamping. It was found out that in elderly and senile patients during the oxygen test the latent period of the increase of PO_2 increases and the time of reaching the half level of the maximum increase of PO_2 decreases in the first and the first two minutes of the oxygen inhalation while during reactive hyperemia the latent period of the increase of PO_2 is prolonged. Such changes in parameters reflecting the state of oxygen diffusion from blood capillaries into tissues indicate age-related disturbances in capillary circulation, which may lead to a deterioration of tissue oxygen supply.

Direct determination of the capillary blood flow rate by cutaneous capillaroscopy revealed a decrease in it in elderly and senile people. In addition to age-related haemodynamic abnormalities, increased tortuosity, dilation of the transitional knee and elongation of the capillary jaws contribute to this.

For oxygen diffusion from capillary blood into muscle cells its structural and ultrastructural features play a certain role.

Using light microscopy, the so-called elastic sheath was detected in myocardial capillary slices in elderly persons and fibrous degeneration of capillary wall was noted. These changes of capillary wall were also noted in electron microscopic study.

Noticeable changes in membrane structures of endothelial cells (focal thickening of plasma membrane and membranes of micropinocytosis vesicles, disturbance of mitochondria membrane integrity, luminescence of cytoplasm matrix of some cells can be referred, apparently, to nonspecific ultrastructural modifications of capillaries, observed under hypoxia of different origin [2,9]. At the same time the ultrastructural features of capillaries revealed during aging such as hypertrophy of part of mitochondria, enlargement of tubules of endoplasmic reticulum and lamellar apparatus, invagination of nuclear membranes testify to the changes of endothelial structures and are of adaptive nature.

In the process of aging there are a number of ultrastructural rearrangements of myocardial capillaries, prominent in edema of endothelial cell cytoplasm, a decrease in the number of micropivopitose vesicles, expansion and compaction of noncellular component of basal layer. These changes indicate a deterioration of the conditions of transendothelial transport and transcapillary exchange, which, apparently, can limit kinetic oxygen transport into pericapillary and pericellular spaces.

In the passage of oxygen molecule through capillary endothelium and cell membranes the catalyzing effects of biologically active components of the tissue are superimposed on the physical laws of oxygen mass transfer. For example, a special case of oxygen diffusion catalysis in the muscle cell itself with the help of myoglobin. It can be speculated that changes of myoglobin content or distribution in muscle fiber in the course of aging will have some influence on oxygen transport to mitochondria.

Studies have shown that myoglobin levels decrease in both heart and skeletal muscles of old rats. Compared to yearlings, the amount of myoglobin in the myocardium in old rats (28–32-month-old rats) decreased by 11.1 %, in the soleus muscle by 20.9 % in the calf muscle by 12.8 %.

The distribution of myoglobin in muscle fibres also changes in older animals. It is especially prominent in the soleus muscle, in which the content of red, muscle fibres are significantly reduced in comparison with that of 12-month-old animals. In the thin muscle fibres of old rats, in contrast to those of one-year-old rats, the content of myoglobin is not higher than in thick muscle fibres. Myoglobin is distributed irregularly in the fibre sometimes only under the sarcolemma. Reaction to myoglobin is completely absent in homogenised sections of the fibre. Myoglobin content increases at the border of such areas, but in these areas' myoglobin granules are distributed haphazardly, without a clear orientation to the discs, forming clumps. In old rats in the same fibre the granules differ in colour intensity and size.

According to other data, a decrease in myoglobin concentration was found in the heart and skeletal muscles of old rats. Histochemical determination of myoglobin revealed a change in its distribution in myometrium in elderly women compared to that in young ones.

Apparently, changes in the content and distribution of myoglobin in old animals may lead to a decrease in the oxygen depot as well as worsen oxygen diffusion conditions in muscle due to a decrease in the PO_2 gradient between the cytoplasm and mitochondria and a reduced contribution of facilitated diffusion to oxygen transport through the myoplasm.

Studies have shown that even in normoxia there are impaired biophysical conditions of tissue respiration in the skeletal muscles of old rats compared to those of adults, which is reflected in a reduction of the average value of PO_2 (38 mmHg) and "dead angle" tension (26 mmHg) and in an increased number of muscle cells functioning at reduced PO_2 values.

Summarizing the data obtained, we can conclude that the deterioration of oxygen delivery conditions to muscle cells during aging is caused by the development of arterial hypoxemia, a decrease in the diffusion area and O_2 gradients between blood and muscle tissue due to a decrease in capillarization index, a decrease in the contribution of facilitated oxygen diffusion due to a decrease in myoglobin content and, apparently, by several other factors. As indicated, when analyzing the distribution of oxygen tension in skeletal muscle, the model did not take into account the natural variation (distribution frequency) of individual parameters (diffusion radius, capillary diameter and length, etc.); such consideration would probably allow to reveal the existence of hypoxic areas with very low values of PO_2. In addition, in old age, the critical level of PO_2 for skeletal muscle may be higher. This is indirectly evidenced by the results of experimental determination of oxygen consumption rate by tissue preparations (muscle pieces): with the same decrease of PO_2 in the breathing medium, the decrease of oxygen consumption in these experiments was more pronounced in old animals. Since the activity of "classical" cytochrome c-oxidase is increased in the muscle tissue of old animals, it is possible that such increase of the

critical level is related to the appearance of the so-called aberrant terminal oxidases, reduced affinity to oxygen in the tissue [8]. Further studies should give clearer answers to the raised questions, but so far on the basis of the literature and our own data on disorders of oxygen delivery and oxidative processes in muscle tissue during aging we can assume that they create sufficient preconditions for tissue hypoxia development (especially with additional influences on the oxygen transport system), pathogenesis of which is likely to be of mixed nature.

The reactions of external respiration, gas exchange, and hemodynamics of an aging organism to hypoxic effects differ in a number of ways. As a result of these differences, the aging organism acquires increased sensitivity and decreased resistance, in particular to acute and chronic hypoxic hypoxia [5]. However, the issue of the peculiarities of the emergence and development of secondary tissue hypoxia under different hypoxic influences in old age remains poorly studied.

In the literature, there are indications that the development of myocardial hypoxia in old animals when administrating vasopressin is accompanied by earlier and more pronounced disturbances of energy generation in the heart muscle. In acute hypoxic hypoxia (animals staying in a pressure chamber at heights > 6000 and 8000 m) in old rats the processes of pinocytosis, micropinocytosis and hydration of myocardial capillary endothelial cells, phenomena of discomplexation and destruction of cristae in large myocyte mitochondria, i.e., the signs characteristic of hypoxia at ultrastructural level, were more expressed than those of 8-month-old animals.

At the same degree of hypoxic influence (12.5% O2 in inhaled mixture) the decrease of PO_2 (by 52-45%) appears to be greater in subcutaneous tissue of elderly and old people (in young people PO_2 decreases by 34%). In the same work, age-related differences in the dynamics of cutaneous microcirculation under hypoxic hypoxia (17 and 12.5% O_2 in the gas mixture) were also found. In elderly and old age inadequate capillary circulation reactions to (narrowing of arterial and venous branches of capillaries, reduction of the number of functioning capillaries) were revealed, at the same time the latent period of cutaneous capillary reaction increased in elderly and old aged people.

Studies have shown that in acute hypoxic hypoxia the decrease (in absolute values and as a percentage of baseline) in arterial blood tension, saturation and oxygen content is greater in old age than in middle age. This is (to a lesser extent) also characteristic of venous blood.

The factors responsible for sharper increase of hypoxemia in old age under hypoxic hypoxia and the factors of natural hypoxemia in old age under relative rest conditions seem to be the same. They include the impairment of size and uniformity of alveolar ventilation, pulmonary diffusion capacity, pulmonary ventilation and perfusion blood flow, the structure of aerohematic barrier, the increase of venous blood discharge through anatomical shunts in lungs, and some others.

When a mixture of 16% O_2 is inhaled, the rate of oxygen consumption by the muscles of old animals is not reduced due to the compensatory mechanisms acting on the systemic and tissue levels. At the same time, under influence of a 14% O_2 mixture, the rate of oxygen consumption in the muscles of old rats decreases against the background of a significant increase in lactic acid in the blood (36.3 ± 2.21 against 15.9 ± 0.38 mg %), i.e., at this degree of hypoxic action of the muscle tissue in old animals, in contrast to 12 - month-old animals, hypoxia begins to develop. At the same time volumetric blood flow rate in the muscle of old rats decreases (to 16.2 per 100 g of tissue), in contrast to the growth of this index in adults.

An investigation of the effect of gas mixture with 10% O_2 showed that old animals showed a more pronounced reduction of muscle oxygen uptake and increased lactic acid in the blood than yearlings. Decrease of PO_2 in the muscle correlates in aged animals with both decreased rate of blood flow through the muscle and (in contrast to the yearlings) with a significant decrease of regional arterio-venous oxygen difference. Of other differences in response to acute hypoxic hypoxia, it should be noted that in the aging organism we did not observe a shift towards alkalosis in arterial blood, which is typical for individuals, while the shift towards acidosis in venous blood, when inhaled mixture with 14 and 10% O_2 was more significant in older animals. Therefore, it can be stated that in aging, the effect of hypoxia on quantitative indices of blood oxygen transport in muscular tissue is greater than in middle-aged animals; lactacidemia increases more rapidly; arterial blood alkalosis does not develop with a higher degree of acidity; a decrease in the rate of volumetric muscle blood flow and a decrease in oxygen extraction from the blood occur with a lower degree of hypoxia, and thus secondary tissue hypoxia develops with a higher PO_2 in the inhaled mixture.

This is confirmed by studies using a mathematical model. The analysis of PO22 distribution in the calf muscle of old animals under hypoxia revealed a number of features of this distribution. The effect of hypoxia on average and minimum PO2 values was more pronounced in old rats than in 12-month-old animals. A decrease in muscle oxygen consumption and an increase in blood lactic acid levels in the old rats when the mixture with 14% O_2 was inhaled occurred in parallel with the decrease of P and Pmin values to 33 and 22 mmHg, respectively. We regard this decrease in muscle tissue oxygen consumption accompanied by lactacidemia as a manifestation of secondary tissue hypoxia due to a decrease in PO_2 in the worst tissue oxygen supply zone to a critical level or lower.

A similar decrease in PO_2 combined with lactacidemia occurs in one year old rats at more severe hypoxia (10% O_2 gas mixture) and correlates with lower values of the average tissue and minimum PO_2 value, 22 and 18 mmHg, respectively.

Thus, in acute hypoxic hypoxia, the development of secondary tissue hypoxia in the skeletal muscles of old animals occurs at higher values of midline and minimal PO_2 (increase of the critical level). Under hypoxic conditions (as well as under normoxia), skeletal muscles in old age are less supplied with oxygen than in adulthood: the number of muscle cells functioning at reduced PO_2 values increases.

Calculations showed that the increase of blood volume rate in a single capillary (12-month-old rats inhaling 14% O_2 mixture, old ones - 16% O_2) evidently plays a compensatory role in maintaining relatively higher PO_2. The development of secondary tissue hypoxia in both adult and aged animals is accompanied by a decrease in capillary blood flow rate. When exposed to 10% O_2 mixture, such a reduction is about 10%, which corresponds to the data. In old rats the volumetric blood flow rate in muscle tissue decreases, but the volumetric blood flow rate in a single capillary remains 1.2-1.4 times higher than in yearlings both in normoxia and in hypoxia.

Experimental and theoretical (using a mathematical model) studies allow us to conclude that conditions for the occurrence of secondary tissue hypoxia, mechanisms of its development and compensation in the skeletal muscle of old animals during acute hypoxic effects differ from those in middle-aged animals as follows.

In acute hypoxic hypoxia the onset of secondary tissue hypoxia in old animals occurs at higher values of the average value of tissue and minimum PO_2, i.e. 'critical' level of PO_2 is increased; the decrease of muscle blood flow rate and the decrease of oxygen extraction from the blood is noted in old animals with less significant deficiency of oxygen in the environment. In older animals the development of tissue hypoxia is accompanied by more pronounced manifestations of lactacidosis and a decrease in the rate of oxygen consumption by the tissue; the compensatory possibilities preventing secondary tissue hypoxia in hypoxic states of various origins are reduced.

References:

1. Andrew C Betik , Russell T Hepple (2008). Determinants of PO_2 max decline with aging: an integrated perspective.
2. Benson Ham 3rd, Raghavan Raju (2016). Mitochondrial function in hypoxic ischemic injury and influence of aging.
3. Birte Plitzko , Sandra Loesgen. (2018). Measurement of Oxygen Consumption Rate (OCR) and Extracellular Acidification Rate (ECAR) in Culture Cells for Assessment of the Energy Metabolism.

4. David A Hood, Jonathan M Memme, Ashley N Oliveira, Matthew Triolo. (2018). Maintenance of Skeletal Muscle Mitochondria in Health, Exercise, and Aging.
5. Eui-Ju Yeo. (2019). Hypoxia and aging.
6. Friederike Cuello, Anika E Knaust, Umber Saleem, Malte Loos, Janice Raabe, Diogo Mosqueira, Sandra Laufer, Michaela Schweizer, Petra van der Kraak, Frederik Flenner, Bärbel M Ulmer, Ingke Braren, Xiaoke Yin, Konstantinos Theofilatos, Jorge Ruiz-Orera, Giannino Patone, Birgit Klampe, Thomas Schulze, Angelika Piasecki, Yigal Pinto, Aryan Vink, Norbert Hübner, Sian Harding, Manuel Mayr, Chris Denning, Thomas Eschenhagen, Arne Hansen. (2021). Impairment of the ER/mitochondria compartment in human cardiomyocytes with PLN p.Arg14del mutation.
7. Gulshan Sharma, James Goodwin. (2006). Effect of aging on respiratory system physiology and immunology.
8. Jacob Schäfer, Hannah Dawitz, Martin Ott, Pia Ädelroth, Peter Brzezinski. (2015). Regulation of cytochrome c oxidase activity by modulation of the catalytic site.
9. John Sieh Dumbuya, Lu Chen, Jang-Yen Wu, Bin Wang. (2021). The role of G-CSF neuroprotective effects in neonatal hypoxic-ischemic encephalopathy (HIE): current status.
10. Julie-Ann Collins, Aram Rudenski, John Gibson, Luke Howard, Ronan O'Driscoll. (2015). Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve.
11. Kelly K Andringa, Shannon M Bailey. (2010). Detection of protein thiols in mitochondrial oxidative phosphorylation complexes and associated proteins.
12. Kim Prisk, John B West. (2019). Deriving the arterial Po_2 and oxygen deficit from expired gas and pulse oximetry.
13. Lorenzo Nesti, Nicola Riccardo Pugliese, Paolo Sciuto, Nicolò De Biase, Matteo Mazzola, Iacopo Fabiani, Domenico Trico, Stefano Masi, Andrea Natali. (2021). Mechanisms of reduced peak oxygen consumption in subjects with uncomplicated type 2 diabetes.
14. Lukyanova Kirova, Germanova. (2018). The Role of Succinate in Regulation of Immediate HIF-1α Expression in Hypoxia.
15. Mari Kannan, Darlin Quine. (2012). Mechanistic clues in the protective effect of ellagic acid against apoptosis and decreased mitochondrial respiratory enzyme activities in myocardial infarcted rats.
16. Matthew J Fogarty, Natalia Marin Mathieu, Carlos B Mantilla, Gary C Sieck. (2020). Aging reduces succinate dehydrogenase activity in rat type IIx/IIb diaphragm muscle fibers.
17. Mélina Bailly, Léonard Féasson, Bruno Pereira, Amandine Boileau, Christophe Hourdé, Natacha Germain, Bogdan Galusca, Daniel Courteix, David Thivel, Julien Verney. (2020). Two new reliable immunohistochemical methods for simultaneous identification of capillaries, the three types of fibers and basal lamina in human skeletal muscle.
18. Mengdi Zhang, Yao Cheng, Yujie Zhai, Yaru Cui, Wenshen Zhang, Hongwei Sun, Wenyu Xin, Ling Zhou, Xue Gao, Shucui Li, Hongliu Sun. (2022). Attenuated succinate accumulation relieves neuronal injury induced by hypoxia in neonatal mice.
19. Padula, Costa, Karadayian, Lores-Arnaiz, Czerniczyniec. (2023). Differences in mitochondrial function between brain and heart of senile rats exposed to acute hypobaric hypoxia. Role of nitric oxide.
20. Proshchaev, Zabinyakov, Azarov, Dovgii. (2014). Studies of the structure and functions of blood cells in senile patients with pneumonia on the biological model of hypoxia by scanning probe microscopy.
21. Prikhodko, Selizarova, Okovityi. (2021). Molecular mechanisms for hypoxia development and adaptation to it. Part I.
22. Prikhodko, Selizarova, Okovityi. (2021). Molecular mechanisms for hypoxia development and adaptation to it. Part II.
23. Shu Hashimoto, Naoharu Morimoto, Masaya Yamanaka, Hiroshi Matsumoto, Takayuki Yamochi, Hiroya Goto, Masayasu Inoue, Yoshiharu Nakaoka, Hiroaki Shibahara, Yoshiharu Morimoto. (2017). Quantitative and qualitative changes of mitochondria in human preimplantation embryos.
24. Shun Takagi, Ryotaro Kima, Norio Murase, Masatsugu Niwayama, Shizuo Sakamoto, Toshihito Katsumura. (2021). Skeletal Muscle Deoxygenation and Its Relationship to Aerobic Capacity During Early and Late Stages of Aging.
25. Yael Yaniv, Magdalena Juhaszova, Steven J Sollott. (2013). Age-related changes of myocardial ATP supply and demand mechanisms.
26. Xiaotong Hong, Pura Muñoz-Cánoves. (2023). Measuring Oxygen Consumption Rate (OCR) and Extracellular Acidification Rate (ECAR) in Muscle Stem Cells Using a Seahorse Analyzer: Applicability for Aging Studies.