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ORIGINAL PAPER

THE ASSESSMENT OF LACTATE IN EXPERIMENTAL ACUTE MYOCARDIAL INFARCTION

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Abstract

Introduction. Metabolism is the key factor underlying the cardiomyocyte function. The inadequate coronary perfusion results in tissue acidosis due to elevated lactate production, which is considered a sensitive marker of myocardial ischemia. Isoproterenol is a synthetic catecholamine that produces diffuse myocardial necrosis at high doses.
The aim of the study was to assess the changes of serum and tissue lactate content in isoproterenol-induced acute myocardial infarction to evaluate the lactate potential as an early diagnosis marker of cardiac ischemia.
Materials and methods. Forty adult male rats were divided into 5 groups: sham (L1=11), control 0.9% NaCl (L2=11), and with experimental myocardial infarction (L3=6, L4=6; L5=6), induced by the subcutaneous injection of Isoproterenol Hydrochloride solution 100 mg/kg, and sacrificed over 6 hours, 24 hours and 7 days post infarction. The results were presented by median and interquartile range. The groups were compared using Kruskal-Wallis and Mann-Whitney nonparametric tests, and the Spearman correlation coefficient was calculated (SPSS 23.0). A $p \leq 0.05$ was considered statistically significant.

Résumé

L'évaluation du lactate dans l'infarctus du myocarde expérimental aigu

Introduction. Le métabolisme est le facteur clé qui sous-tend la fonction cardio-myocytaire. La perfusion coronarienne inadéquate entraîne une acidose tissulaire due à une production élevée de lactate, qui est considérée comme un marqueur sensible de l'ischémie myocardique. L'isoprotérénol est une catécholamine synthétique qui produit une nécrose myocardique diffuse à fortes doses.
L'objectif de l'étude était d'évaluer les modifications de la teneur en lactate sérique et tissulaire dans l'infarctus du myocarde aigu induit par l'isoprotérénol afin d'évaluer le potentiel du lactate en tant que marqueur de diagnostic précoce de l'ischémie cardiaque.
Matériel et méthodes. Quarante rats mâles adultes ont été divisés en 5 groupes : sham (L1=11), contrôle 0,9% NaCl (L2=11), et avec un infarctus du myocarde expérimental (L3=6, L4=6; L5=6), induit par l'injection de solution de chlorhydrate d'isoprotérénol à 100 mg/kg, et sacrifiés pendant 6 heures, 24 heures et 7 jours après l'infarctus. Les résultats ont été présentés

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Results. Both glucose and lactate serum levels presented a slight decrease in L3, followed by a significant increase in L4, with a repeated fall in L5 group. In homogenate glucose content initially expressed an elevation in L3, with relevant decrease in L4, and inconsistent increase in L5, while lactate values significantly decreased in L3, returned to baseline levels in L4 and slightly declined in L5 compared to sham and control groups.

Conclusion. The collected data suggest the utility of lactate assessment in early diagnosis and risk stratification in acute myocardial infarction.

Keywords: isoproterenol, lactate, anaerobic metabolism, acidosis, acute myocardial infarction

Résultats Les taux sériques de glucose et de lactate présentaient une légère diminution dans le L3, suivie d'une augmentation significative dans le L4, avec une chute répétée dans le groupe L5. Dans l'homogénat, la teneur en glucose exprimait initialement une élévation dans L3, avec une diminution pertinente dans L4 et une augmentation incohérente dans L5, tandis que les valeurs de lactate diminuaient significativement dans L3, retournaient aux niveaux de base dans L4 et diminuaient légèrement dans L5 par rapport aux groupes sham et de contrôle.

Conclusions. Les données recueillies suggèrent l'utilité de l'évaluation du lactate dans le diagnostic précoce et la stratification du risque dans l'infarctus du myocarde aigu.

Mots-clés: isoprotérénol, lactate, métabolisme anaérobique, acidose, infarctus aigu du myocarde

Introduction

Despite intense social and economic efforts, cardiac disorders have a high incidence and an increased mortality worldwide. According to European Cardiovascular Diseases Statistic Report data, in 2017 acute coronary syndrome (ACS) mortality rate accounted for 45% in Europe and 37% in the European Union[1].

Metabolism is the key factor underlying the cardiomyocyte form and function[2]. Substrates' availability, oxidative phosphorylation, ATP transfer and usage mechanisms are major factors determining myocardial metabolism and contractile function under conditions of enhanced adrenergic stimulation such as myocardial ischaemia[3], the functional recovery of the myocardium strongly depending on its metabolic status[4].

Due to high-energy needs, the human heart oxidises multiple substrates[2] and constantly generates adenosine triphosphate (ATP) required for maintenance of ionic homeostasis, acid-base balance and contractile function[3,5]. The mitochondrial oxidative phosphorylation generates 95% of cardiac ATP requirements, the remaining 5% being provided by substrate-level phosphorylation[2,5].

Beadle et al. established that, at rest, the heart primarily metabolizes free fatty acids, and only 20% of energy is produced from lactate[6], while under conditions of increased lactate concentrations up to 60% of heart energy demands will be satisfied by lactate oxidation with direct ATP production via the mitochondrial shuttle[7,8]. The earliest alteration caused by inadequate coronary perfusion is the metabolic switch to anaerobic metabolism and myocardial tissue acidosis due to elevated lactate production[9].

Lactate (2-hydroxypropanoate) is a hydroxycarboxylic acid formed in human cells mainly from glucose (65%) and alanine (16-20%) through their conversion into pyruvate, which is further reduced to lactate by a reversible oxidoreduction reaction catalysed by the cytosolic enzyme L-lactate dehydrogenase (LDH)[5,8,10,11]. The thermodynamically favoured direction of the reaction is pyruvate reduction to produce L-lactate with simultaneous oxidation of reduced nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD^+). The opposite direction is oxidation of L-lactate to form pyruvate while NAD^+ is reduced to NADH[10,12].

Lactate is removed through its conversion into pyruvate (via the system of intermembrane transporters) used for: 1) gluconeogenesis (Cori cycle) – the process exclusive to the liver and the kidney; 2) oxidation at rest state[5,8,10].

A family of proton-linked monocarboxylate transporters (MCTs) facilitates lactate transportation through the cell membrane. There are fourteen MCTs described, but mainly MCT1 – MCT4 are

involved in the lactate-pyruvate transport[8,10]. Based on transport kinetics, *Gerlinger M. at el* have proposed MCT4 as the main transporter responsible for the secretion of lactate out of human cells[13]. Experimental data confirm that an increase in H+ concentration stimulates the transport of lactate, suggesting its role in mediating H+ removal[8].

In the absence of ischemia, the cardiomyocytes simultaneously produce, release, uptake, and oxidize lactate[3,8,10]. The recent data suggest that lactate, a key metabolite in energy homeostasis, is crucial for intercellular cooperation, substrate distribution, and adaptation to injury[8]. The conversion of lactate to pyruvate by lactate dehydrogenase (LDH) and the accumulation of reduced nicotinamide adenine dinucleotide (NADH) activates specific NADH oxidase (NADox), ROS generation and modulates redox homeostasis in cardiac tissue[14]. Hashimoto et al. have suggested that in myocytes, lactate may be involved in mitochondrial biogenesis through: *increased release of ROS; **the upregulation of genes encoding for MCT1 and COX; ***increased expression of the peroxisome proliferator activated-receptor γ coactivator-1α (PGC1α), and ****DNA binding of the nuclear respiratory factor 2 (NFR-2)[15].

Lactate homeostasis is linked to glucose metabolism[10]. Hypoperfusion and tissue hypoxia are promotors of anaerobic glucose metabolism[5], while hyperglycaemia and inflammatory mediators are major determinants of increased lactate production[8,16]. Higher lactate levels indicate a stress response characterized by increased metabolic rate, sympathetic nervous system activation, accelerated glycolysis and a modified bioenergetic supply[12,17]. Acidaemia affects cell function by altering key enzymatic reactions, ATP generation mechanisms, fatty acid biosynthesis, myocardial contractile function, etc[9].

The accumulation of lactate has serious pathophysiological and clinical consequences such as altered acid-base balance and acidosis. According to pathogenic mechanisms, two types of lactic acidosis are described: *type A (fast) caused by oxygen deficits, and **type B (slow) due to compromised lactate metabolism without hypoxia (major metabolic dysregulation, certain drugs or toxins effects, congenital abnormalities in carbohydrate metabolism)[11,18]. The experimental studies have demonstrated that acidosis decreases the cardiac response to catecholamines and is a risk factor for arrhythmia development[9,19].

Acute coronary syndrome, caused by impaired tissue oxygenation, stimulates anaerobic metabolism, increases production of lactic acid and delays its clearance, and leads to acidosis[18]. According to the published data, lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients, being a predictor of decreased long-term survival[20]. Therefore, lactate can be considered a marker of tissue hypoperfusion and/or oxygen debt[8], myocardial ischemia, and acidosis[21].

Knowledge of the metabolic changes associated with acute myocardial ischaemia allows an early diagnosis to prevent the irreversible tissue damage.

Isoproterenol [1–(3,4–dihydroxyphenyl)–2–isopropyl-aminoethanol hydrochloride (ISO)] is a synthetic catecholamine and powerful non-selective β-adrenergic agonist that at high doses (within 85–300 mg/kg range) provokes severe stress, resulting in diffuse myocardial necrosis and fibrosis[22]. Isoproterenol induced myocardial injury is caused by generation through the autoxidation of highly cytotoxic free radicals and altered energy metabolism due to excessive oxidative stress, hyperglycaemia and acidosis[22].

There is less data available in literature regarding the impact of isoproterenol on the lactate metabolism in vivo. Concomitantly there is a lack of conclusive evidence about the correlation between serum and tissue values of lactate in experimental cardiac ischemia.

The objective of the study was to assess serum and homogenate modifications of lactate in isoproterenol-induced acute myocardial infarction in rats, to evaluate the lactate potential as an early diagnosis marker of cardiac ischemia.

Material and methods

The study was approved by the Research Ethics Committee of the "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova (23.03.2015). Manipulations were carried out in the Laboratory of Biochemistry of the "Nicolae Testemitanu" State University of Medicine and Pharmacy in accordance with the institutional and national guide for the care and use of laboratory animals.

Study design

An experimental study was performed on 40 healthy white male rats (Ratta albicans) weighing 180-230 grams. The animals were kept at "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova, in standard vivarium conditions: temperature 24±2°C, 12-hours day/night cycle, free access to adequate food and water. The animals were fasted and received no water 12 hours prior to the sacrifice.

Myocardial infarction was induced by subcutaneous injection of a single dose of 100 mg/kg Isoproterenol Hydrochloride (Sigma Aldrich Chemie

Table 1. Serum levels of glucose and lactate.

Group		Glucose (mM/L) p=0.0002***	Lactate (mM/L) p=0.169
L1	Sham	6.25 (IQR 0.45)	4.91 (IQR 1.57)
L2	Control	6.53 (IQR 0.94)	4.69 (IQR 1.06)
L3	AMI.6h	4.56 (IQR 0.55)	4.09 (IQR 1.30)
L4	AMI.24h	7.00 (IQR 1.56)	5.85 (IQR 2.76)
L5	AMI.7d	6.02 (IQR 0.75)	4.48 (IQR 1.67)

Note: statistically significant difference in relation to the values of the sham group: * p <0.05; ** p <0.01; *** p <0.001

Table 2. Glucose and lactate values in cardiac homogenate.

Group		Glucose (mM/g/prot) p=0.113	Lactate (mM/g/prot) p=0.007**
L1	Sham	4.94 (IQR 1.09)	4.32 (IQR 0.41)
L2	Control	4.43 (IQR 1.02)	4.28 (IQR 0.64)
L3	AMI.6h	4.97 (IQR 0.84)	3.47* (IQR 0.80)
L4	AMI.24h	4.37 (IQR 0.56)	4.33 (IQR 0.44)
L5	AMI.7d	4.72 (IQR 0.35)	3.91** (IQR 0.23)

Note: statistically significant difference in relation to the values of the sham group: * p <0.05; ** p <0.01; *** p <0.001

GmbH) dissolved in NaCl 0.9% solution. According to the study design, the animals were randomly divided into 5 groups: sham (L1=11) – no intervention; control (L2=11) – animals that were administered NaCl 0.9% solution; experimental (L3 = 6; L4 = 6; L5 = 6) – animals receiving 100 mg/kg isoproterenol hydrochloride subcutaneously. The rats were sacrificed under sterile conditions and sulphuric ether anaesthesia over 6 hours (L3 AMI6h), 24 hours (L4 AMI24h) and 7days (L5 AMI7days) post infarction.

Sample collection

Apical cardiac tissue (300 mg) was homogenized in ice with 3 mL of 0.25 M sucrose buffer (pH=7.4). The obtained homogenate was treated with 30 µL of Triton X-100, placed in the refrigerator for 30 minutes, and centrifuged at 4°C at 3000 rpm for 10 minutes. The supernatant was stored at –40°C until analysis.

The collected blood samples were placed for 30 minutes into test-tubes allowing clotting, and then centrifuged for 10 minutes at 1500 rpm. Serum was collected in Eppendorf tubes and kept at –40°C until analysis.

Biochemical analysis

Glucose and lactate levels were assessed in serum and tissue samples. Both glucose and lactate were measured using the ELITech assay kit (France) and manufacturer's instructions and the results were expressed in mM/L (serum) and mM/ g*protein (tissue). The markers were measured in five groups, including sham, control and experimental animals.

Statistical analysis

The obtained data were processed using SPSS 23.0 software. The descriptive statistics methods were used for median and interquartile range (IQR) calculation. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were applied to analyse data distribution. The homogeneity of variance was evaluated by Levene's test. The groups were compared using Kruskal-Wallis and Mann-Whitney nonparametric tests. The correlation coefficient was calculated by the Spearman correlation test. The p<0.05 value was considered statistically significant.

Results

The groups showed a statistically significant difference in serum glucose (p=0.0002***) and statistically insignificant difference for serum levels of lactate (p=0.17). Both glucose and lactate serum levels presented a slight decrease in L3, followed by a significant increase in L4, with a repeated fall in L5 group (Table 1).

There were no differences in glucose (p=0.113) content in the homogenate, while tissue lactate values registered statistically significant variations (p=0.007**). Glucose content initially expressed an

elevation in L3, with relevant decrease in L4, and inconsistent increase in L5, while tissue lactate values significantly decrease in L3, return to baseline levels in L4 and slightly decline in L5 compared to sham and control groups (Table 2).

We identified the tendency of a strong negative correlation between lactate variables in serum and homogenate in L3 ($\rho = -0.714$, p (one tailed) = 0.055). No correlations were found between serum glucose and lactate levels (p = 0.84), neither between glucose and lactate values in the homogenate (p = 0.371).

Discussion

Lactate, a compound widely produced in tissues, is pivotal for energy homeostasis. Enhanced adrenergic stimulation results in increased production of lactate and stress hyperlactatemia[7,17] that has a deleterious effect on the myocardium.

In 2018, Di Marino et al. noticed that prolonged myocardial ischaemia is biochemically well profiled by the release of cell injury markers, while early short periods of ischaemia are usually undiagnosed[23]. The previously published data suggested that the development of tissue acidosis and lactate production can be considered sensitive markers of the onset of myocardial ischemia, due to inadequate oxygenation of myocardium[24].

Jovanovic et al. suggested that low tissue oxygenation and anaerobic glucose metabolism lead to amplified lactate production in acute myocardial infarction[18]. Wang et al reported that under conditions of ischemia, lactate values reliably reflect the metabolic modifications caused by tissue hypoxia, oxidative stress, and cardiac injury[21]. Therefore, myocardial production of lactate is considered a marker of anaerobic metabolism that correlates to the degree of ischemia[25], while myocardial extraction of lactate is an accepted standard for the quantification of myocardial ischaemia[23].

Our study identified a decrease in serum lactate level by 20% AMI.6h group, then an increase in lactate concentration by 36% in AMI24h group, and the repeated decrease by 28 % in AMI.7d group. Tissue values of lactate showed the same tendency to change, but at a lower level in the state of infarction, they have initially decreased by 20% in AMI6h group compared to sham animals, then dynamically returned to the baseline in AMI24h group, and inconclusively declined by 10% in AMI7d group.

Our results coincide with those reported by Di Marino et al. (2018), who have observed that in balloon-induced ischemia systemic arterial lactate concentration decreased constantly, being after 10 minutes by 30% lower than the initial level[23].

The prognostic role of lactatemia in patients with acute coronary syndromes is still controversial[18]. Khuri et al. have reported a direct correlation between the severity of acidosis during myocardial ischemia, and the patients' outcome[20]. Jovanovic et al. established that lactate levels indicate increased risk for poor outcome in diabetic patients with acute myocardial infarction[18]. Onorati et al. have shown that higher lactate levels during reperfusion correlated with severe hemodynamic complications[24].

The research performed by Rao et al. established that during reperfusion the continuous release of lactate is suggestive for delayed return to normal (aerobic) myocardial metabolism and postoperative low output syndrome[26]. According to results published in 2012 by Attana, the dynamic changes in serum lactate (absolute values) reflect the haemodynamic status, allow an early risk stratification, as well as the monitoring and evaluation of the therapeutic strategy[17].

The available data indicate that serum lactate concentration influences on prognosis of cardiovascular diseases[5]. Multiple studies showed off the utility of serum levels of lactate as independent predictors, which reflects the severity of complications and the outcomes. Lazzeri et al. (2012) and Hayiroglu et al. (2017) demonstrated the relationship between blood lactate and in hospital short-term mortality in STEMI patients[16,27]. Attana et al. established that serum lactate levels, assessed on arrival in emergency department, are predictive for future severe complications (congestive heart failure, arrhythmias, cardiogenic shock, etc.), and poor short-term outcome after AMI[17]. Kawase et al. (2015) have reported the relation between elevated blood lactate at presentation and increased mortality in acute decompensated heart failure[28]. Frydland et al. identified an independent association of admission lactate concentration with 30-day mortality and development of late cardiogenic shock[29].

The study conducted in 2018 by Gjesdal et al. noticed that, in patients with acute coronary syndrome and signs of heart failure, lactate analysed as a continuous variable significantly correlated to short- and long-term mortality[30]. According to the published data, the serial lactate measurements are more reliable and advisable for risk stratification in acute cardiac patients[7], as well as for prognosis assessment[8].

The recently published data suggest the use of lactate as a cost-effective diagnostic tool to evaluate the risk of serious complications[7], and as prognostic marker in patients with acute coronary syndrome and cardiogenic shock[16,17,31].

Both the lack of correlation between glucose and lactate levels in serum and homogenate, and the tendency of a strong negative correlation between lactate variables in above-mentioned samples suggest the

need for a careful interpretation of lactate levels in blood considering the clinical context.

The dynamic changes of lactate in ISO-induced cardiac ischemia reflects the anaerobic glucose metabolism due to perturbation of tissue oxygenation that leads to the oxidative stress[18]. Multiple clinical trials have shown that elevated lactate values are associated with severe complications[17], increased mortality[7,27-29], being used as markers of acute ischemic heart lesions, and/or as prognostic factors. It is incontestable that the regularly found metabolic changes facilitates the identification of acute cardiac ischemia and can be used as reliable predictors of disease prognosis.

Conclusions

The study findings confirm the changes in serum and tissue values of lactate in experimental myocardial infarction induced by isoproterenol and highlights biochemical mechanisms underlying its detrimental effects. The accumulation of lactate reflects the degree of tissue hypoxia and oxidative stress, predicting the severity of myocardial lesions and the risk for developing major complications. The assessment of serum and tissue levels of lactate is useful for the diagnosis and risk stratification in acute myocardial infarction.

Author Contributions:

Conceptualization, V.T. and T.T.; methodology, T.T.; software, V.T; validation, V.T. and T.T.; formal analysis, V.T.; investigation, V.T. and T.T; data curation, V.T. and T.T.; writing–original draft preparation, V.T.; writing–review and editing, T.T.; supervision, T.T. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the institutional and national guide for the care and use of laboratory animals, as well as the national law."

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