Chapter

Myocardial Metabolism

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Abstract

Myocardial metabolism alterations are associated with myocardial dystrophy and lead to the heart chambers dilatation, decreased contractility, organs perfusion and depended on symptoms. Nowadays heart failure treatment in veterinary medicine includes neurohormonal, circulatory and contractile aspects of this pathological state. Unfortunately, energy supplying component not presented in modern recommendations. Most of the used medications changing contractile ability, through the control of myocardial filaments sensibility to the different ions, but don't affect the ability of cardiomyocytes to produce enough energy for this work. In order to understand the heart failure syndrome more completely, we should elucidate features, characteristics, and interactions between components of myocardial energy supply.

Keywords: myocardial metabolism, insulin, insulin resistance, adropin, energy metabolism, heart failure

1. Introduction

The myocardium is one of the most energy-dependent structures. It demands about 6 kilograms of ATP per day [115]. In order to sustain an efficient energy supply, it has an advanced system producing enough ATP. In the organism, there are two ways to support this demand: production and accumulation. Accumulation is not suitable for the heart due to specific anatomy—most of the cytoplasms consist of myofibrils. According to this fact, in the adult heart, we observe low concentrations of ATP and many ATP-hydrolases. Total resynthesis of all ATP volume takes only 10 seconds in a normal myocardium [32, 55]. Most of the energy resources (~70%) are used for contraction and the rest—for ion pump function (K, Na, Ca pumps ATPases). This system is well coordinated, which helps to maintain the normal flux of energy substrates and ions.

In average, the heart consumes about 20 g of carbohydrates, 30 g of free fatty acids (FFA), and triglycerides (TG). These substrates are oxidized in 35 L of oxygen to produce ATP from ADP [171].

Oxidative phosphorylation of FFA gives about 60% of all produced ATP, while glucose, lactate, and other carbohydrates oxidation produce about 30% of all macroergic compounds. In addition, for energy supplement ketone bodies and amino acids can be utilized. Glucose utilization can be the main energy source in specific conditions (high-carbohydrate diet). Therefore, in understanding myocardial metabolic features, changes during heart failure could provide vital information for early diagnostics and therapy of myocardial diseases [99, 112].

Heart failure syndrome is a consequence of the main heart disease and associated with compensatory mechanism dysfunction, formation, and activation

of pathological interactions between components of neurohumoral regulation systems [203]. Decompensation is a condition, which is always connected with reduced energy production and suppressed myocardial metabolism. For example, systolic dysfunction leads to sympathoadrenal system hyperactivation, which is associated with increased heart rate. Catecholamines activate beta-adrenergic receptors, which increase myocardial oxygen consumption due to raised FFA utilization to produce enough energy. This situation leads to increased ADP volume and negative inotropic effect, which is badly tolerated during heart failure and geometrically progress during chronic sympathetic tonus [36, 96, 115, 122, 164].

2. Metabolism in the adult healthy heart

The main substrates for ATP production are carbohydrates and free fatty acids [98]. In particular, long-chained FFA, glucose, glycogen, lactate, pyruvate, ketone bodies (acetoacetate, beta-hydroxybutyrate), and amino acids (leucine, valine, and isoleucine). These compounds are metabolized to intermediates, which enter the Krebs cycle as an acetyl-coenzyme A (ACoA) or other metabolic equivalents. During substrate utilization, the proton is generated. This proton produces an energetic gradient between mitochondrial membranes, which stimulates the oxidative chain to produce chemical energy and phosphorylate ADP to ATP [60, 61, 171, 184].

Such diversity of substrates for common energy source production predispose to several concepts: (1) myocardial metabolism is very adaptive to organism condition and substrate environment and can vary between main energy resources; unfortunately, in heart failure this flexibility is mostly lost; (2) myocardial metabolism is a self-regulated mechanism; all the intermediates of the tricarboxylic acid cycle are mediators, controlling the main metabolic path and intensity of energy production (Randle cycle); (3) metabolites can be used as components for cell structure resynthesis, and, at the same time, cellular structures could be used as an energetic substrate; (4) metabolic dysfunction and accumulation of metabolites can damage cellular proteins and change the form and function of contractile filaments; (5) myocardial metabolism is not "intracellular chemistry"; this is a functional system, which is presented with specific structure and mediator mechanisms, assessing adaptation of cardiomyocytes to environmental variations [76, 171].

Myocardial metabolism efficiency is highly dependent on pathway and substratesutilized for ATP production. There is a Kyoto Encyclopedia of Genes and Genomes (KEGG) scheme—a collectively designed map of known molecular interactions and feedback systems of energetic metabolism in the myocardium. This map made helps to understand possible ways of energy production in the myocardium and limit its activity [30, 69]. However, we should observe common features of myocardial metabolism.

In aerobic conditions, mitochondrial oxidative phosphorylation is the main source of ATP (about 90%); the rest of macroergic compounds are produced by anaerobic utilization. Mitochondrial oxidative phosphorylation produces energy due to FADH and NADH dehydration, collected from FFA beta-oxidation and, in lesser amounts, other sources. The schematic structure of metabolic interactions designed by Stanley et al. shows the main features of energy production cycles (**Figure 1**) [140].

Transport of FFA in the cardiomyocyte is presented in two ways: passive diffusion and by specific protein transporters. Long-chained FFA are diffused in the cell, metabolized in acyl-CoA, and transported to the special proteins on the mitochondrial membrane to interact with acetyl-CoA synthase. While active transport, induced by muscle contraction or insulin (Ins) action, is sustained by FATP1, FATP6,

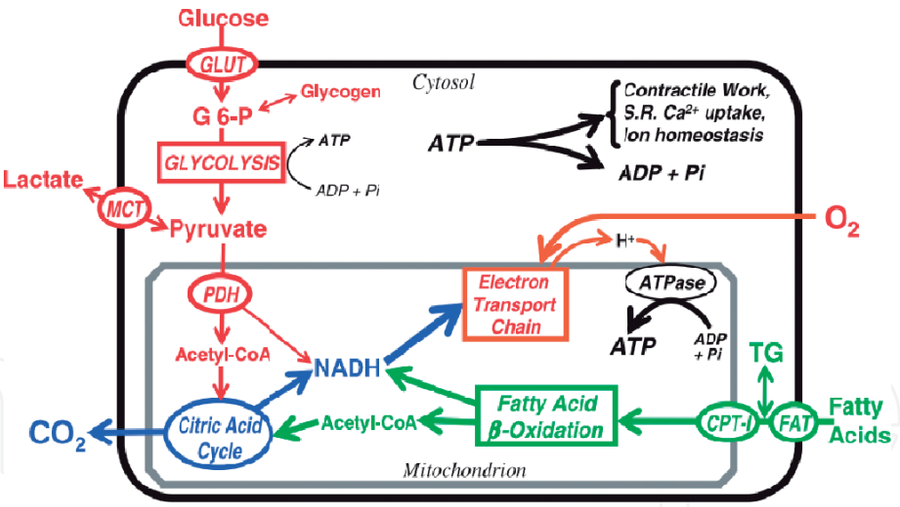

Figure 1.
Coupled metabolic reactions in the cell and mitochondria in cardiomyocyte [161]. GLUT—glucose transporter, G-6-P—glucose 6-phosphate, MCT—monocarboxylate transporter, PDH—pyruvate dehydrogenase, FAT—fatty acid membrane transporter, TG—triglyceride, and CPT-1—carnitine palmitoyltransferase 1.

and CD36 [78]. These proteins translocate FFA through the membrane, and then couple it with CoA, which is transported to lipid beta-oxidation cycle by carnitine-assosiated translocators [102].

Further, cytosolic carnitine palmitoyltransferase-1 (CPT-1) connects acyl-CoA with carnitine, forming long-chained acylcarnitine. This compound is transported with acylcarnitine translocase through the inner mitochondrial membrane and utilized in FFA beta-oxidation cycles with acetyl-CoA production. Then acetyl-CoA is metabolized in the Krebs cycle to ATP, H_2O, and CO_2. For example, in the tricarboxylic acid cycle, palmitate is oxidized with 23 moles of O_2 to produce 105 moles of ATP [63]. Nevertheless, in comparison with glucose, FFA are not effective energy sources due to their high demand for oxygen. The part of transported FFA is esterified and collected in the cytoplasm as lipid droplets (triacylglycerol-TAG) [68, 100, 101, 181]. TAG-produced ATP is about 10% of all gained ATP in physiological conditions [117]. Also, TAG is an important part of FFA oxidation, in cases when TAG-hydrolase blockade lipid beta-oxidation is severely reduced, which leads to massive lipid droplet accumulation in the cardiomyocytes [46].

The next step is activation of the Krebs cycle. This rotor starts with acetyl-CoA, collected from FFA beta-oxidation or pyruvate decarboxylation. Produced NADH and FADH2 transports are equivalent to electron chain, which stimulates ATP resynthesis in oxidative phosphorylation.

Metabolic pathways of energy production are ruled by directing components (enzymes) and feedback connection (substrate-final product). The mitochondria can bear high-energy demand states, increasing oxygen consumption almost on 85% from the basal level. This ability is very important due to the fact that most of the time it consumes only 25% of the oxidative capacity [111]. Therefore, activation/inhibition of enzymatic systems can control ATP synthesis, and, due to feedback, can correct energetic substrates, in cases of increased metabolites collection or regulation disorders. This kind of metabolic flexibility is very useful in myocardial diseases, associated or modulated by energy resources depletion and absence [31, 32].

In addition, in normal conditions myocardium utilizes lactate, which metabolizes to pyruvate by lactate dehydrogenase and gets involved in the Krebs cycle. In cases of metabolic disorders, the myocardium starts to excrete lactate in the bloodstream. This way appears when there is oxygen deficiency and the energy has to be produced by anaerobic glycolysis (ischemia, terminal stages of cardiomyopathies)

[6, 47, 104, 162]. The main transporter controlling excretion and consumption of lactate is the monocarboxylate transporter (MCT). This family consists of four subclasses, in the myocardium only 1 form of MCT-1 is presented. Also, they take a part in ketone body transport [40, 50, 64].

Glycolysis is another coexisting pathway for energy production. The first step of glycolysis starts with glucose transport through the cell membrane by the specific transporter (GLUT). In the cytoplasm glucose is metabolized to pyruvate, which is transported to the mitochondrial matrix by pyruvate dehydrogenase (PDH). Pyruvate is transformed to acetyl-CoA and gets involved to the Krebs cycle [61, 162].

The GLUT family includes 12 classes; the most important for myocardial metabolism are GLUT 1 and GLUT 4, which supplies glucose in the cardiomyocytes. GLUT 4 is insulin dependent and plays a significant role in insulin resistance formation; GLUT 1 is weakly insulin dependent; it is the source of basal glucose transport for myocytes; in addition, it could be additively recruited from cytosol in stress conditions [167]. GLUT 1 is mostly located on the sarcolemma, while GLUT 4 also attenuated to T-tubules, which is useful for "deep" glucose transport during raised energy demand and exercises. In normal conditions GLUT 1 protein expression is higher due to persisting glucose demand as an energy source. GLUT 4 concentration in the myocardium and muscle is almost equal, which means that developing insulin resistance of different etiologies leads to decreased glucose flux both in the skeletal muscle and in the myocardium. GLUT 4 is the main glucose transporter to the muscle cell, but in experiments with GLUT 4 knockout, animals show that glucose can be translocated to the myocyte by different mechanisms [34, 196].

After transport into the cell, glucose was converted to glucose-6-phosphate (G6P) by cytosolic hexokinase 2 (HX2), and then it was utilized in glycolytic reactions or stored as glycogen. Phosphofructokinases—glycolytic enzymes—which irreversibly convert G6P to fructose-6-phosphate, forming fructose-1 and 6-bisphosphate and dephosphorylating ATP to ADP. These kinases are limiting threshold for glycolytic activity and depending on ATP, AMP, citrate concentrations, and pH [131].

After glucose is converted to pyruvate, its metabolism trifurcates to lactate conversion, decarboxylation to acetyl-CoA, and carboxylation to malate or oxaloacetate. Decarboxylation is an irreversible process, catalyzed by pyruvate dehydrogenase (PDH). PDH activation is closely connected with cytosolic Ca^{+2} and Mg^{+2} concentrations, sympathetic tonus, while inhibition depends on FFA concentration in the environment. PDH is a multienzyme complex, consisting of two main parts: pyruvate dehydrogenase itself and pyruvate dehydrogenase kinase assessing pyruvate utilization. Pyruvate consumption increases in cases of decreased FAA utilization or artificial inhibition of lipid beta-oxidation. FFA and glucose turnovers in the mitochondria are controlled by the Randle cycle, and by its ways, we could admit that PDH activity is determined depending on the substrate environment (**Figure 2**) [106, 107, 137, 138].

The lactate-lactate dehydrogenase-pyruvate system is made for additive pyruvate production in cases of high demand or its discharge to lactate when the FFA wing is activated in Randle's cycle. In heart failure, FAA consumption is increased due to adrenergic hyperactivation and compensatory mechanisms; this leads to PDH inhibition, and glucose metabolites are converted to lactate, instead of pyruvate, and eliminated to the bloodstream. This causes lactate and pyruvate depletion in the cytosol; the relative lactate/pyruvate ration raises and negatively influences energy supplementation for submembrane structures, which control ion recirculation [20, 98, 121, 136, 153].

The final step of glucose utilization is an oxidation of acetyl-CoA to CO_2 in the Krebs cycle and formation of 31 ATP molecules. Due to produced ATP amounts, oxidative glycolysis is the most effective energy source.

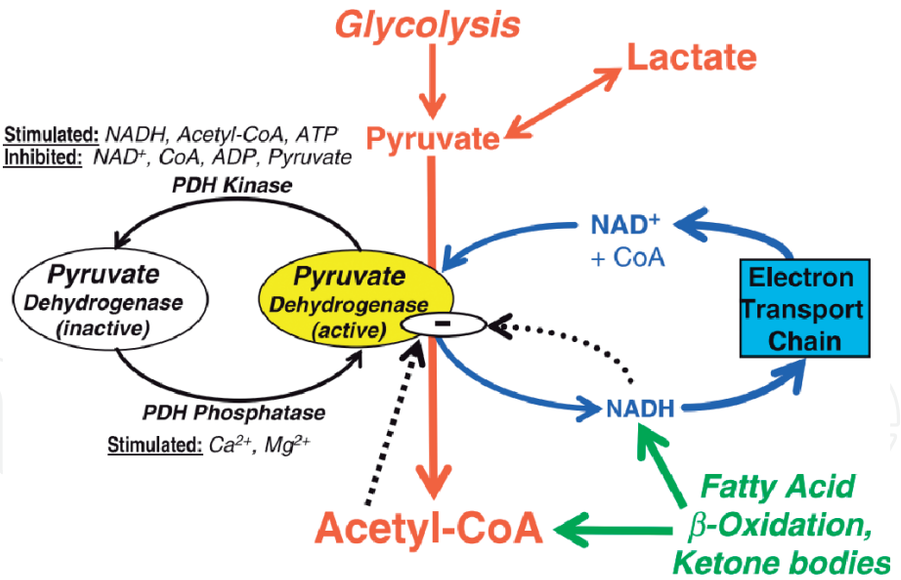

Figure 2.
Pyruvate metabolism in normal myocardium (Stanley et al., 2002).

It should be noted that such intermediates as G6P and lactate can also be metabolized in alternative ways. G6P can be utilized in the pentose phosphate pathway (PPP), producing NADH in association with O_2 or a pentose (substrate for nucleotides) in a hypoxic environment. In addition, G6P can be converted to sorbitol, uridine diphosphate-N-acetylglucosamine, which can provide O-associated glycosylation of contractile filaments and Ca^{+2} ion pumps of the sarcoplasmic reticulum (SR). In cases of massive protein glycosylation, the cell can undergo apoptosis [6, 56, 80, 141].

The intensity of FFA utilization by a healthy myocardium depends on the concentration of non-esterified FFA in the blood, the activity of metabolism modulation mediators (catecholamine, thyroxin, triiodothyronine, insulin, cortisol, adropin) can be increased four times during the day. FFA are transported to cardiomyocytes in non-esterified form, bound with albumin or as chylomicrons, lipoproteins, and then they translocated in the cytoplasm and oxidized. FFA releases are depended on catecholamine-induced activation of hormone-dependent lipase [195]. Therefore, FFA plasma level significantly increased in cases of adrenergic activation, insulin depletion, insulin resistance, hypothyroid condition, hyperadrenocorticism, etc. [98, 128, 201].

In addition, FFA myocardial metabolism is also influenced by secondary messenger, AMP-activated protein kinase (AMPK), which activity is closely connected with the AMP/ATP ratio in the cytosol. This molecule has several actions: (1) AMPK inhibits malonyl-CoA production, switching off acetyl-CoA-synthase, leading to decreased FFA cytosol accumulation; (2) ongoing decrease of malonyl-CoA inhibits bounding of CPT-1 and stimulates transport of acetyl-CoA to the mitochondria for oxidation; and (3) AMPK stimulates expression of FATP and CD36 on cardiomyocyte outer membranes [68, 100, 101, 181].

It should be mentioned that peroxisome proliferator-activated receptor-alpha (PPAR-a) is also a regulator of FFA oxidation. This receptor is a part of ligand-activated family of nuclear receptors. Ligands of the FFA receptor, in active form PPAR-a, activate the synthesis of lipid beta-oxidation enzymes [59]. In experiments, it was observed that this receptor deactivation leads to decreasing FFA oxidation capacity in cardiomyocytes, due to significant depletion of lipid oxidation enzymes. During ischemia and insulin resistance in diabetic mice, induced by streptozotocin, PPAR-a knockout animals were more stable in the ischemia–reperfusion protocol, than the control group mice. This can be explained by the fact that the inhibition

of FFA oxidative utilization promotes glycolysis. Inactivated PPAR-a allows to perform increased oxidative glycolysis (decreased FFA oxidation in the Randle cycle), improve GLUT 4 translocation and PDH activation, and improve the severity of insulin resistance. In cases of hypoxic ischemia, this will give a chance for cardiomyocytes' survival due to glycolysis and energy production. In addition, increased PPAR-a expression promotes GLUT 4 genes suppression, leading to insulin resistance and, indirectly, stimulates FFA oxidation metabolites accumulation, this inhibits glycolysis wing of the Randle cycle, decreases GLUT 4 trafficking activity, and suppresses insulin receptor sensitivity due to PI-3-kinase inhibition [33, 127].

However, in cases of active oxidation in tricarboxylic acid cycle with high production of malonyl-CoA, normal transport of FFA to the mitochondrial inner membrane is stopped. Also, membrane translocation of lipids is inhibited by insulin [28, 72].

Utilization of amino acids (predominately leucine, valine, and isoleucine) in energy metabolism is less effective than glycolysis and FFA beta-oxidation. Active amino acid utilization leads to metabolite accumulation; this state is associated with cardiomyopathies and respiratory chain damage in the mitochondria. Metabolism of this substrate is associated with ketoacid formation; part of them could be converted to acetyl-CoA and used in the Krebs cycle [145].

Another substrate are ketone bodies (beta-hydroxybutyrate and acetoacetate). These compounds are produced by the liver during FFA oxidation, and under normal conditions, their level in the plasma is very low, and so they do not actively utilize in myocardial energy metabolism. However, lipomobilization and insulin depletion (diabetes mellitus) could be exceptions for this situation; this condition leads to decreased glycolysis and lactate consumption by cardiomyocytes. In addition, ketone body utilization inhibits FFA oxidation, altering the process of dissociation of acetyl- CoA to free CoA. This complex promotes secondary to heart failure often noted in patients with diabetes mellitus [49, 95, 160].

In experimental models, it was noted that ketone utilization inhibits lactate oxidation for 30–60% and palmitate for 22%. Later, in vivo experiments admitted that parallel administration of FFA and hydroxybutyrate markedly inhibits FFA oxidation in pigs. It has to be noted that the levels of malonyl-CoA and acetyl-CoA were unchanged. In a similar experiment, it was shown that high concentration of ketone bodies promotes the Krebs cycle blockade and downregulates contractility of cardiomyocytes. So, ketones could be energy substrate to the myocardium, but it blocks other more useful ways of energy production, due to significant demand for oxygen [160, 173].

Some intercellular conditions can influence on metabolism intensity and oxidative potential. The significant parameter of the functional condition of the cell is redox potential. Pyridine compounds (NAD, NADH, NADP, NADPH) play the most important role in this state. One of the simplest estimations of redox potential in a cell is cytoplasmic and mitochondrial NAD/NADH ratio. It is considered that NAD depletion and NADH raise characterize inhibition of oxidation in the mitochondria and slowing of Krebs cycle. This was also noted during hypoxia, enzyme defects, and lack of energy substrates [93].

There are complexes of cytoplasmic oxidoreductase enzymes dependent on NAD concentration. The most active one is lactate dehydrogenase (LDH). LDH, depending on the intracellular environment, can produce NAD and lactate from pyruvate, or reverse this reaction to produce pyruvate and NADH. There are many malate dehydrogenases (MDH) in the mitochondria, which is the part of the malate–aspartate shuttle. In particular, MDH catalyzes the metabolism of oxaloacetate and NADH to malate and NAD, and then malate is transported to the mitochondria, while the NAD/NADH ratio increased in the cytoplasm. In addition,

MDH takes part in nitrogen metabolism, rarely can be activated to produce energy from aspartate [12, 67, 85, 146].

High NAD/NADH ratio promotes normal substrate oxidation and saves redox potential to sustain electron transport in oxidative metabolism. As already been said, LDH and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) both use NAD/NADH as a cofactor. GAPDH produces NADH, which is oxidized to NAD by LDH. In anaerobic conditions, both of these enzymes produce NAD, which is utilized in glycolysis. In the aerobic state, NADH reoxidation is connected with its utilization in the mitochondrial respiratory chain. Due to impermeability of mitochondrial membranes to NAD and NADH, there are several shuttles for NADH transport and NAD resynthesis. Discussed above, the malate–aspartate shuttle is predominant in the myocardium [55, 118].

Increased ATP consumption promotes oxidative phosphorylation and increases NAD/NADH ratio. This condition activates several NAD-dependent enzymes: isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and MDH which increase the Krebs cycle intensity [163, 189].

3. Regulation of carbohydrates and FFA oxidation

The main regulator of carbohydrates oxidation is FFA utilization. Increased FFA consumption leads to its intermediate accumulation, which blocks PDH. At the same time, decreased FFA consumption promotes glycolysis and lactate oxidation, due to citrate, NADH, and acetyl-CoA deficiency in the mitochondrial matrix. The last part is often noted in cardiomyopathies and during ischemia [54, 161].

Modern researches showed an impressive role of small molecule proteins—energy homeostasis regulators. Of course, there are many molecules and factors that control energy metabolism, one stimulates appetite (ghrelin, galanin, neuropeptide Y) and another is an anorexigenic (leptin, nesfatin-1) [71, 155]. The first found molecule, which regulates energetic homeostasis, was insulin (Ins); its action was first noted as neurogenic appetite suppression. Later leptin was found—hormone, produced by adipose tissue—and elucidates general adipose tissue state [199]. Then ghrelin and nesfatin-1 were found, with antagonist action to leptin effects on adipose tissue [77, 120]. On the next decades, there was intensive research in the field of lipid homeostasis and appetite-controlling peptides. Many molecules were found; the most important are preptin, irisin, and adropin.

Insulin (Ins) is a hormone with a huge specter of physiological influence, but in this papers, we discuss only three effects: on heart pump function, on Ca^{+2} ion circulation, and as a mediator between cell communication. Ins-induced transport of glucose is the main mechanism of energy production of membrane-associated ATPases and ion pumps. Controlling pump function, Ins indirectly influences cytoplasmic concentration and equilibration of Ca^{+2}; it mediates cascades of reactions to stimulate Ca consumption or excretion. Ins is involved in endothelial function, regulating NO production and tissue perfusion (including coronary vessels). And, of course, it influences on the contractile ability of cardiomyocytes due to energy metabolism modulation.

As an indirect effect, abilities of Ins to control the availability of energy substrates (effects on liver and adipose tissue) and tissue perfusion should be noted. Ins inhibits TG hydrolysis in adipose tissue (depressing lipomobilizating hormones), decreasing the level of circulating FFA. In addition, reactive Ins secretion increases tissue perfusion due to blood vessels smooth muscle relaxation. This effect plays a significant role during exercise, hypertension, and acute and chronic heart failure [70, 136, 165].

Direct Ins action regulates key enzymes (6-phosphofructokinase 1 and 2, glycogen phosphorylase and synthase, PDH, hormone-dependent lipase, acetyl-CoA carboxylase) and transporters (GLUT family, CPT-1, CD36/FAPT). Interactions between main metabolic substrates (glucose and FFA) are elucidated by Randle's cycle [136]. Transmembrane glucose transport by GLUT 1 and GLUT 4 is modulated by Ins (both transporters are Ins-determined, but GLUT 1 is less dependent). GLUT 4 is significantly presented in myocardium tissue; this helps to sustain myocardial energy flexibility in exercises and heart failure. Ins influence on glycogen accumulation in several ways: decreasing glucose utilization (FFA oxidation predominance, leads to PDH blockade, glucose intermediates converted to glycogen); HX2 converting capacity in overloaded glucose transport (Ins-dependent GLUT 4 exocytosis); glycogen utilization in glucose depletion. It should be mentioned that glycogen is oxidized more actively, than glucose, due to its already intracellular location and production of more ATP. In addition, Ins stimulates glycogen synthase directly and through G6P raise [52, 86]. Ins and PDH interactions are not clear. We should consider the effects of FFA oxidation suppression (decreased acetyl-CoA concentration in mitochondria), influence on PDH phosphatase, NAD/NADH ratio, and Ca^{+2} concentration. Generally, Ins is controlling glycolysis indirectly by metabolite and substrate availability and directly through enzymatic systems (mentioned above). Ins' influence on FFA oxidation is closely connected with its effects on glycolysis and partly described above. By the way, Ins suppresses CPT-1 function, due to malonyl-CoA concentration. It can be explained by the fact that malonyl-CoA is produced by acetyl-CoA carboxylase, which is in direct control of Ins [57, 58].

Mediator effect of Ins between cells is described by its effects on PDH, HX2, phosphofructokinase, glycogen synthase, acetyl-CoA carboxylase, hormone-dependent lipase, PDH kinase, MAP kinase, and lactate intercellular shuttle and based on metabolic influence.

As for leptin, its effects were observed in recent research of dogs with chronic degenerative valve disease. In the experiment the raise of circulating leptin and leptin microRNA in this disease was noted. Observed dogs were not suffering from obesity, so found leptin changes are connected with heart failure syndrome. In addition, the correlation between leptin level and heart failure severity was found [45].

Preptin is a hormone modulating carbohydrate metabolism; it is a part of the insulin family (as insulin, insulin-like growth factor-1, proinsulin-like factor-2, relaxin-2). In experiments, it was found that it is secreted together with insulin and promotes glucose utilization in insulin-like ways. There was a strong connection between preptin expression and insulin resistance. Generally, this hormone plays a role in hepatic glycogenesis and bone density (osteoclasts proliferation) and modulates sensitivity to insulin and adaptation to energetic substrates [1, 10, 126, 186].

Adropin is a recently found hormone controlling lipid metabolism. Adropin regulates energy metabolism, depending on the diet type (significantly raised on a high-fat diet). Systemic administration of adropin decreases hepatosteatosis and hyperinsulinemia severity (moderating carbohydrate-FFA metabolism in peripheral tissues). In researches, a connection between heart failure severity and circulating adropin concentration (high severity of heart failure-high adropin level) was noted. Also in insulin resistance, the level of circulating adropin is decreased and correlated with atherosclerosis risks in diabetes mellitus. Low levels of adropin were associated with endothelial dysfunction and high risk of heart X syndrome. Adropin suppresses the activity of PDH kinase 4, which promotes normal pyruvate utilization in Krebs cycle and decreases CPT-1 activity and traffic of CD36 transporters, decreasing FFA transport in cardiomyocytes. The main functions of adropin consist of regulating NO availability, decreasing lipogenic gene expression,

decreasing dyslipidemia and hepatic steatosis, modifying insulin resistance and glucose tolerance, and controlling metabolic homeostasis [37–39, 82, 91, 168].

Irisin is a hormone controlling the conversion of white to brown adipose tissue. The white adipose tissue has a lack of mitochondria and lots of TG and FFA and produces leptin, ghrelin, nesfatin-1 [15, 27, 135, 178]. While the brown adipose tissue contains lots of mitochondria and lipid droplets. In this cell, high amounts of uncoupling protein-1 are presented. This protein promotes uncoupling of ATP production from FFA oxidation, instead of ADP phosphorylation, and produces heat [62]. In experiments, it was noted that high amounts of circulating irisin are presented in cases of obesity, which can be characterized as irisin resistance (insulin resistance-like) [166]. Irisin is predominantly synthesized in skeletal muscles during exercises. The main actions of this hormone are toward decreasing of white adipose tissue, controlling temperature homeostasis, increasing of glucose tolerance, decreasing obesity, and modulating insulin resistance [144, 198].

Besides, there are also biologically active molecules, which have paracrine effects. This molecule does not affect myocardial metabolism by itself, but promoting reactions could affect the contractile ability of cardiomyocytes. Among them are cytokines, thrombocyte-activating factor (TAF), reactive oxygen species (ROS), arachidonic acid, and nitrogen oxide (NO). The sources of these peptides are the cardiomyocyte itself, endotheliocytes, and migrating immune cells (mononuclear phagocytes, lymphocytes, etc.) [159].

Cytokines include TNF-a, IL-1, and IL-6. TNF-a is produced in cardiomyocytes during injury; the most effects of this peptide are described in ischemia–reperfusion syndrome, due to its significant negative inotropic effect. The main promoters of TNF-a production are hypoxia and ROS. Negative inotropic effect development is staged. First, immediately after the injury, sphingosine is produced from sphingomyelin, which inhibits RyR2 receptors of SR and decreases Ca^{+2}-dependent Ca^{+2} release, suppressing contractility. In parallel, direct cytotoxic effect developed, due to mitochondrial oxidation uncoupling. And then, NO-dependent Ca^{+2} transport suppression is developed. Produced NO-superoxide promotes contractile filament damage and cardiomyocyte apoptosis [2, 43, 105, 123, 148].

Interleukins are the main inflammatory mediators; their action closely interacted with TNF-a, developing NO release, suppression of Ca^{+2} turn over regulation genes and decreasing cAMP in cardiomyocytes [41, 42, 74, 179].

Thrombocyte-activating factor (TAF) is a phosphoglyceride with a potent pro-inflammatory effect. This cytokine is produced by cardiomyocytes, endotheliocytes, and histiocytes. TAF pathological effects are associated with significant vasoconstriction, contractility decrease, ROS, and superoxide release and autolysis activation [35, 48].

Arachidonic acid and its metabolites is part of membrane phospholipids in cardiomyocytes, but in case of injury, these compounds are degraded by phospholipase A2, which is high Ca^{+2} concentration-dependent. Arachidonic metabolites damage ionic channels components, receptors, intercalated disks and provoke cytoplasmic acidosis, Ca^{+2} hyperaccumulation [192].

Adenosine is a metabolite of adenine nucleotide; it has a wide specter of action: coronary artery dilatation, negative chronotropic, dromotropic, and inotropic effects by means of A1 and A2 receptors. Adenosine is also a catecholamine antagonist (decreases cAMP activity), stimulates protein kinase C (PKC), promotes macroergic compounds restoration, and inhibits some ROS and neutrophils activity [88, 157].

PKC is a part of intracellular myocardial metabolism regulation. This kinase is sensitive to Ca^{+2} cytoplasm accumulation, angiotensin II, phenylephrine, and endothelin stimulation. As a response to this stimulation, PKC downregulates troponin; sensitivity of troponin to Ca^{+2} promotes myofibrillar disruption and decreases

contractile ability, fibrosis, and hypertrophy of cardiomyocytes. In experiments, it was noted that increased PKC expression provokes myocardial hypertrophy and fetal metabolic genotype activation and significantly alters Ca^{+2} ion transmembrane circulation [7, 185, 187]. This can be explained by decreased SERCA2 and phospholamban protein expression, suppression of Na/CA and Na/H ionic pumps, PKC-dependent phosphorylation of the myofilament and troponin proteins, and downregulation of Ca^{+2}-dependent membrane transporters, which indirectly negatively influence on energy metabolism [174].

CaMKK II—calmodulin-dependent kinase— is activated by Ca^{+2} accumulation in the cytoplasm. CaMKK II independently or by AMPK stimulation promotes GLUT 4 trafficking and exocytosis. In experiments a compound stimulation of GLUT 4 exocytosis and its retention on the outer part of the cell membrane by AMP, PKC, and CaMKK II was elucidated. By these means, muscle contraction promotes GLUT 4 exocytosis and glucose transport, but in cases of pathologic Ca^{+2} cytoplasm accumulation, GLUT 4 could not move into the cell, which alters glucose consumption and promotes increasing of FFA utilization (Randle cycle). Catecholamine-induced tachycardia provokes altered GLUT 4 endocytosis, insulin resistance, and glycolysis inhibition [90].

As already been said, there are many regulating mediators. However, Ca^{+2} ions can influence myocardial metabolism by themselves. The raise of Ca cytoplasmic concentration (SR release) is determined by the following mechanisms: Ca^{+2}-dependent Ca^{+2} release (calcium sparks), SR depolarization, pH changes, voltage-dependent changes of T-tubules and triad membranes, and inositol-dependent release. Calcium provokes GLUT 4 exocytosis and increases glucose consumption. First, this effect was described in experiments with caffeine influence on cardiomyocytes. Myocytes began to utilize glucose, while being incubated with low caffeine concentration.

Nitric oxide decreases cardiomyocyte utilization of glucose due to cGMP effects. In experiments, it was noted that NO-synthase blockade promotes stabilization of ischemic myocardium metabolic state. Some researchers pointed at fact that cGMP and glucose metabolism are not connected, so the real influence of No on metabolism is not clear, but its effects should be noted. In addition, NO has a negative inotropic effect in inhibiting Ca-channel and producing superoxide (peroxynitrite) [17–19, 83, 170, 197].

4. Energy substrates and contractility

Muscle contraction is a multifactor process, including energy status changes (ATP/AMP ratio variation), increased intercellular Ca^{+2} accumulation, stretch, GLUT 4 exocytosis, glucose and FFA consumption, etc.

Many types of research showed the high effectiveness of myocardial contractility in conditions of intensive glucose utilization, and, at the same time, increased FFA consumption on 26% did not promote equal raise in contractility, but only oxygen demand raised [109, 154]. Target disabling FFA oxidation reactions and FFA bounding to not available compounds decreases oxygen demand and increases the mechanic power of rat's heart contraction. Combination of insulin and glucose promotes to decrease the heart's oxygen demand to 39% [79]. These effects are not clearly understood because theoretically palmitate or oleate utilization need fewer molecules of O_2 to produce one molecule of ATP in comparison with glucose or lactate. A possible explanation is connected with interactions between long-chained FFA and Ca^{+2} channels (increases ATP demand for a pump ATP-ase) [75, 109, 154].

Recent studies showed that increased concentration of FFA and TG in the cytoplasm can provoke lipotoxicity in the myocardium, presented in neutral lipids and

ceramides accumulation, leading to cell's apoptosis and decreased contractility. In experiments, Zhou showed that in the diabetic rat, high rates of TG and ceramides were accumulated, promoting DCM-phenotype changes, decreased contractility, and high indexes of cardiomyocytes apoptosis. Nevertheless, in the case of troglitazone, the manifestation of the FFA block mentioned significantly decreased. By this time lipid-induced myocardium remodeling is still mostly unknown, but this process could be associated with cell apoptosis, decreased contractility due to intensive FFA utilization and significantly depressed glycolysis [53, 108, 125, 150, 151, 156, 158, 180, 194, 195].

Heart failure syndrome, despite etiology, development is always associated with an energy deficit. During this state individual cardiomyocytes are under the increased workload associated with the high demand for macroergic substrates, but their production is severely depleted. This state is so-called an engine out of fuel due to decreased amounts of creatine phosphate and ATP [115]. Compensatory and pathological cardiomyocyte hypertrophy is associated with decreased creatine phosphate/ATP ratio, and later ATP decreases too. The creatine phosphate/ATP ratio is a reliable prognostic marker in heart failure worsening [114].

5. Myocardial metabolism in heart failure

Developing heart failure leads to decreased flexibility of myocardial metabolism. On the certain stages, HF has a tendency to switch FFA utilization as the main energy substrate to glucose oxidation. Decreased FFA consumption, depleted FFA oxidation enzymes, and mitochondrial oxidation biomarkers characterize this stage. This switch is usually early noted. In experiments, it was admitted that metabolic changes in rat myocardium are found in the second week after artificial aortic constriction, while decreased contractility presented only on the 20th week after bandage [24]. Some researchers say that glycolysis predomination is a marker of terminal myocardial metabolism dysfunction. These changes are associated with adaptation because glycolysis demands 12% less oxygen to produce same the amounts of ATP, then FFA oxidation [3, 79].

Transition to glycolysis promotes increased glucose consumption and raised GLUT 1 expression. In parallel, glucose oxidation is also altered, which leads to uncoupling of glycolysis and glucose oxidation. The combination of depressed FFA utilization and glucose oxidation shows decreased mitochondrial oxidative potential ГЛЮТ1 [87, 110].

During glycolysis and glucose oxidation uncoupling, due to PDH inhibition by PDK, pyruvate is not transported to the mitochondria but metabolized to lactate by LDH. This leads to cellular acidosis, and, by the way, this anaerobic glucose utilization gives only two molecules of ATP (while aerobic—32) [103]. Described changes promote cardiomyocyte hypertrophy, energy metabolism depression, ionic pump dysfunction, Ca^{+2} accumulation, decreased contractility, apoptosis, and fibrosis. It should be noted that this pattern of myocardial dysfunction development is the same for all cardiomyocytes; even in cases of pulmonary hypertension and compensatory hypertrophy of the right heart, metabolic alterations will be identical to the changes observed in the left heart failure [129].

In available data is also admitted that heart failure promotes myocardial tissue insulin resistance, partially due to neurohormonal remodeling, and is an independent predictive factor of sudden heart death in humans [23, 116]. Insulin resistance leads to decreased glucose utilization and ATP production [116, 169]. In some data, it was elucidated that the TG accumulation in muscles (found by 1H NMR method) promotes insulin resistance [81]. The dependence between TG accumulation and

insulin resistance is explained by Randle' cycle: high FFA intracellular accumulation promotes raised acetyl-CoA/CoA and NADH/NAD ratios, which inhibits PDH and leads to citrate accumulation and phosphofructokinase inhibition. Associated G6P accumulation inhibits HX2, promoting intracellular glucose accumulation and decreasing intracellular glucose transport.

Insulin resistance also can be associated with high circulating insulin concentrations. Adrenergic hyperactivity, concomitant to heart failure, leads to increased glucose mobilization, hormone circulation, and insulin synthesis, lipomobilization due to catecholamines (noradrenaline). Insulin stimulates GLUT 4 and CD36 exocytosis, on the first stages it helps to produce enough ATP from glycolysis and oxidative phosphorylation. But insulin receptors have variable action mechanism. Insulin receptors have two places of connection for insulin. One of them has high affinity to hormone and promotes fast response to insulin stimulation; another is a "slow" one and is activated in cases of high insulin concentration and due to geometrical conformation partially blocks the "fast" part of the receptor. In general, insulin resistance is based on the blockade of all "fast" receptors, increased insulin concentration, and fixation of the hormone on "slow" locus of the insulin receptor [9, 11, 13, 14, 94, 116, 152, 175, 190]. Also, a high concentration of circulating FFA decreases insulin-stimulated GLUT 4 translocation. This can be explained by inhibition of Pi 3 kinase of IR-1, which phosphorylation is decreased by TG and phospholipid (FFA-acetyl-CoA, diacylglycerol, ceramides) accumulation in the cytoplasm [26]. GLUT 1 increased expression also takes a part in this process. Increased glucose flux from GLUT 1 promotes decreased GLUT 4 exocytosis and increased GLUT 4 tissue concentration. Developing GLUT 4 function reduction pathological cardiomyocyte hypertrophy and systolic dysfunction occurs [92, 177, 188]. Another factor is pyruvate utilization in anaplerotic reactions, which leads to decreased acetyl-CoA production for Kreb's cycle, glycolysis and oxidative phosphorylation uncoupling, and PDK 4 activation (promotes inhibition of insulin-stimulated glycolysis) [133].

Also it should be noted that in diabetes and insulin resistance, HX2 activity is decreased. In cell culture experiments, it was found that insulin is HX2 gene expression and protein resynthesis regulator. So, the severity of insulin resistance is a suppressor of HX2 function, leading to G6P accumulation and cytoplasm protein glycosylation. It should be admitted that decreased HX2 microRNA is associated with GLUT 4 genes and protein depletion. These interactions between insulin, HX2, and GLUT can be controlled by insulin sensibilization—by thiazolidinediones (pioglitazone, troglitazone) [124, 132].

Often heart failure is accompanied by all energy-producing enzyme dysfunction. Significant reduction of activity is noted in creatine kinase (CK) function. This enzyme regulates transfer between ATP and creatine. CK is a dimer and consists of two parts M and B, and there are three isoforms: MM, BB, MB, and mitochondrial-CK [193]. MM-CK is closely connected with SR and coupled with Ca^{+2}-ATPase, producing energy for Ca^{+2} circulation [182]. Mitochondrial-CK is located on the inner membrane of the mitochondria and works with the ADP-ATP translocator. Produced ATP is transported by translocator to mitochondrial-CK and further to creatine phosphate or ADP. This compartment distribution provides effective control of local ATP/ADP ratio and promotes mitochondrial ATP production (decreased ratio) or increases enzymes activity. But in conditions of cardiomyopathy, the normal compartment system is altered. Decompartmentalization leads to uncoupling of the mitochondria—mitochondrial-CK-ATP and phosphocreatine interactions [29, 176].

One experimental research elucidated CK activity in rats with induced heart failure. General CK activity was decreased to 45% from normal value; in particular,

the most damaged was mitochondrial isoenzyme (activity was suppressed to 17% of normal). This depletion is connected with mitochondrial dysfunction. Effectiveness of mitochondrial oxygen utilization was experimentally evaluated by ADP concentration changes in presence of creatine. During this experiment, the point of ADP concentration where oxygen utilization does not raise independently to increasing APD was noted. And this level was significantly lower in the heart failure group, but at the same time, the oxidative activity of mitochondria was raised up to 30% higher than in the control group. This data shows inhibition of mitochondrial-CK function, also, indirectly, can show that mitochondrial population is decreased, but its oxidative function is upregulated [184].

CK and mitochondria interactions are very complicated and not only functional but also structural. In the cell, the mitochondria forms a crystal-like structure, predisposed to effectively produce energy sources and preserve contractility. Due to the partial isolation of the mitochondria, the contractile function is controlled by small compartments, surrounding each sarcomere and named "Intracellular Energetic Unit" (IEU). One of the most important roles in this system is played by CK isoenzymes (see above). But destructuration of this compartment will lead to substrate supplementation uncoupling and energy starvation [25, 44, 66, 183].

Heart failure is associated with morphological changes in the mitochondria: size reduction, number increase, edema, cristae deformation, homogenization, and IEU damage. The severity of mitochondrial matrix loss is correlated with heart failure stage, and, in addition, mitochondria size variability characterizes respiratory chain damage [4, 65].

Also, the mitochondria serves as controller of Ca^{+2} homeostasis in the cytoplasm. The mitochondria regulates Ca-dependent signaling by the means of ion accumulation and energy supplementation for ion pumps, producing an ionic gradient between membranes. The mitochondria directly (SERCA) or indirectly (Na/K pumps) control Ca^{+2} circulation [16, 119]. Decreased ATP synthesis promotes free Mg^{+2} accumulation, and its competing effect blocks Ca-dependent Ca release from SR [84]. Then Ca and Na accumulates due to increased activity of Na/H and Na/Ca^{+2} pumps, provoking acidosis in cardiomyocytes and decreased buffering ability of the mitochondria [200]. Usually, free Mg^{+2} concentration is low in the cytoplasm, because it is mostly bounded to ATP, but during ATP loss Mg-ion amounts raise. In this way, we can assume that increased intracellular concentration of free Mg^{+2} is a marker of decreased energy production.

In cases of ATP depletion or oxidative phosphorylation alterations, acidosis is developing. This condition promotes NA accumulation due to activation of Na/H cotransporter. Then inhibition of Na/K pump occurs. While Na accumulates in the cytoplasm, Na/Ca^{+2} exchange pump activates provoking pathological Ca^{+2} storage in the cytoplasm, mitochondrial membrane depolarization, and its inability for ionic excess buffering. This condition is predisposing to the accelerated Ca turnover and associated arrhythmias [200].

In general, switching from FFA oxidation to glycolysis during HF characterizes changing of adult heart metabolic pattern to fetal type [97]. This condition leads to disturbances in energy metabolism component gene expression. In experimental models of HF, isogenies, which switched from adult to fetal type, were sequenced [8, 149]. This fetal genotype activation promotes myocardial hypertrophy. One study analyzed 13 metabolism regulating components and expression of the atrial natriuretic peptide (ANP) and heavy beta-myosin chains (beta-MHC) in a normal adult, fetal heart, and in heart failure [139]. The ANP was upregulated in fetal and failing heart, but in HF ANP was not bound to fetal gene overexpression. Stretch, adrenergic hyperactivation, and tachycardia were the reasons for increased ANP in failing heart [147]. Beta-MHC expression was predominant in all three groups in

comparison with alpha-MHC. Beta-MHC isogenies were downregulated in fetal and failing hearts, but this is connected with myofilament reduction [51, 73]. Alpha-MHC was reduced by more than 30% in both groups in comparison with the adult heart. These changes are explained by less beta-MHC oxygen and energy demand, but its contractility is also low. In addition, in fetal and failing hearts, FFA oxidation enzymes genes were also suppressed [51, 113, 143].

Fetal genotype is conditioned by hypoxic conditions during embryogenesis, and glycolysis is predominating, while after birth energy metabolism is switched to FFA oxidation. In conditions of pathologic hypertrophy, cardiomyocytes again switched to fetal metabolism in order to survive in the hypoxic environment and energy starvation. In cases of hypertension, this switch appears earlier than in cardiomyopathy [172].

In the adult heart GLUT 4 microRNA expression is rising, while GLUT 1 is decreasing in comparison with fetal heart. In the heart, failure version is observed. The same changes were endured by PDK2, PDK 4, and glycogen synthase. During maturation the amount of mitochondria rises, and, in parallel, citrate synthase gene expression increases. But in failing heart, the mitochondria and citrate synthase are depleted [139].

Adrenergic hyperactivation is associated with high amounts of catecholamines circulating, which promotes reactive oxygen spices (ROS) production. In addition, high amounts of ROS are produced not only by direct stimulation (anthracyclines, tachycardia-induced cardiomyopathy, dilated cardiomyopathy, and etc.) but also by cardiomyocytes overstretch (heart failure with volume overload: valvular diseases, inherited defects) [5, 130, 191].

The main ROS are superoxide ($-O_2$), hydrogen peroxide, and hydroxyl radicals (−OH). Increased formation of this compounds promotes lipid membranes perforation of organelles, DNA, and mitochondria injury [202]. Then this leads to a decrease in SR ATPase, Ca^{+2} pump, and Na/K pump and Ca^{+2} accumulation in the cytoplasm [21, 22]. Prolonged exposition to H_2O_2 provokes CA ion oscillations, leading to Ca-dependent protease activation, mitochondrial membranes perforation, and increasing Ca ion flux through mitochondrial membranes. Combinations of these factors provoke myofilament contracture, damage, and petrification of the mitochondria, and proapoptotic factors release [89].

In veterinary literature, there are studies which elucidate some aspects of the antioxidant system and oxidative stress in dogs with the valvular disease. In these studies, an effect of ROS on valvular structures and on pathogenesis was elucidated, but the certain mechanism is still unknown [134, 142].

As described above there are principal differences between healthy and failing hearts; failing hearts have many similarities with fetal heart metabolic profile. The first stages of metabolic adaptation could differ, while the terminal stage of heart failure has a mostly identical phenotype. Unfortunately, myocardial metabolism in veterinary patients with heart failure is not clearly described. We have lack of proper information and can use some information from human medicine studies (mostly on mice and rats and rarely on dogs, cats, ovine, and embryos). Despite new drugs presented on the veterinary pharmacology market, we can treat heart diseases only on clinical stages and do not have pharmacological tools for prophylaxis. Also, we need to provide specific treatment for some inherited forms of myocardial diseases, such as PDK-dependent dilated cardiomyopathy, and identify the role of taurine and carnitine in arrhythmogenic right ventricle dysplasia/cardiomyopathy.

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