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Review

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Energetic metabolism in cardiomyocytes: molecular basis of heart ischemia and arrhythmogenesis

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ABSTRACT

Cardiac muscle contraction is a strictly regulated process which conjugates a series of electrophysiological, biochemical and mechanic events, resulting in the pumping of blood to all bodily tissues. These phenomena require a very high energetic demand both for generating the necessary mechanical force, and for maintaining cellular homeostasis during the process. In the myocardium, fatty acids (FA) represent the main energy substrate, although other secondary substrates, such as glucose and ketone bodies, may also be used. Nevertheless, under certain conditions such as heart failure or myocardial ischemia, FA metabolism may become deleterious via mechanisms such as oxidative stress and arrhythmogenesis. In an ischemic milieu, various metabolic changes occur as a consequence of hypoxia, favoring cell necrosis, ventricular arrhythmias, and death. Major events in this context include an increase in extracellular K^+, a decrease in pH, and accumulation of intracellular calcium. This review includes a detailed description of the molecular basis underlying myocardial contraction and energetic metabolism in cardiomyocytes, aiming to promote an integral understanding of the pathophysiology of heart ischemia. This in turn may aid in the development of future, more satisfactory alternative treatments in the management of acute coronary ischemia episodes.

INTRODUCTION

The heart is composed of specialized muscle tissue, the myocardium, which depends on a constant input of energy for adequate functioning, and thus utilizes various sources of carbon for adenosine triphosphate (ATP) production. However, in cardiomyocytes, the majority of the energy produced derives from the mitochondrial oxidation of free fatty acids (FA)[1].

Alterations in myocardial energetic metabolism may lead to conditions such as ischemic heart disease,
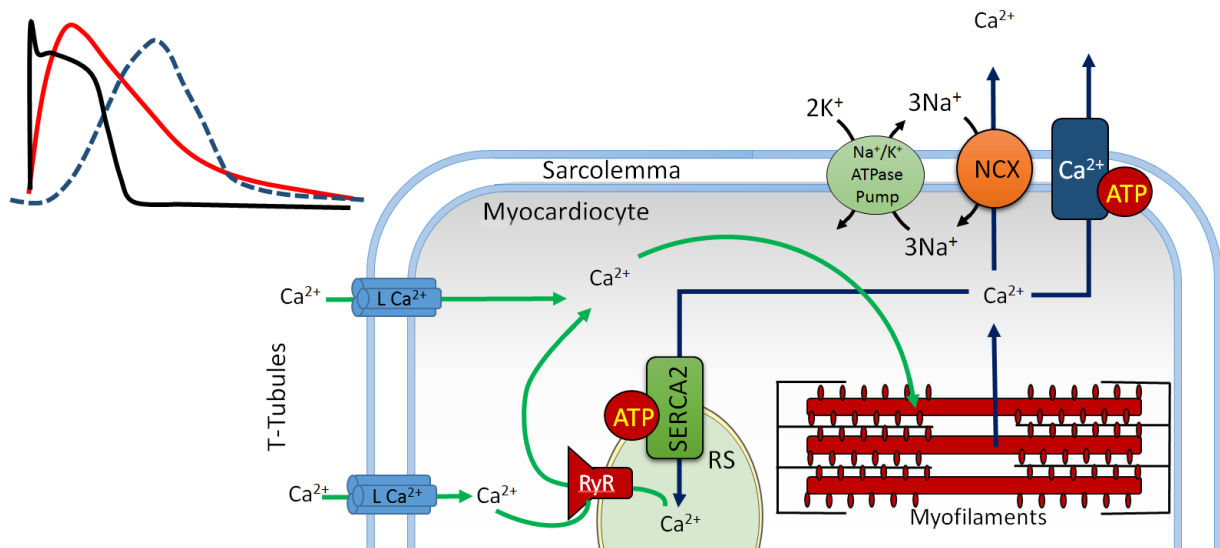
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Figure 1: The role of calcium in excitation-contraction coupling. Green arrows: calcium entry; blue arrows: calcium exit; SR: sarcoplasmic reticulum; RyR: ryanodine receptor; NCX: Na^+/Ca^{2+} exchanger

arrhythmias, heart failure, and others. During ischemia, cardiomyocytes are restricted in both their oxygen and nutrient supplies, rendering these cells unable to oxidize energetic substrates, causing a significant depletion in ATP reserves. This leads to deterioration of cardiac contractility and disruptions in the cardiac conduction system, which may culminate in heart failure and arrhythmias, respectively[2]. Therefore, an understanding of myocardial energetic metabolism is essential, in order to comprehend the physiologic basis of the therapeutic management of acute and chronic heart disease.

FUEL FOR MYOCARDIAL CONTRACTION: THE ROLE OF MACROMOLECULES

The heart is the driving force of the circulatory system, pumping blood to all bodily tissues. This organ consists of various layers, the thickest of which is the myocardium. The main component of this layer is contractile cells termed cardiomyocytes[3], with only 2% corresponding to Purkinje fibers. The Purkinje fibers are organized into an arborized structure which originates in the atrioventricular node and constitutes a specialized conduction system that allows quick and synchronic activation of the ventricles[4,5].

The cytosol of cardiomyocytes contains sarcomeres, complex proteic structures composed of thick myosin filaments and thin actin filaments[6]. Sarcomeres occupy most of these cells' cytosol and mediate calcium-dependent cellular contraction [Figure 1][7]. This phenomenon is regulated by the cardiac conduction system through modulation of ionic transport and

generation of action potentials[8]. These impulses are synchronically propagated throughout the myocardium via gap junctions and ionic channels which facilitate electrical and chemical communication between cardiomyocytes, allowing these to function as a syncytium[9]. Connexins, especially Cx43, Cx40 and Cx45 are key voltage-gated proteic structures found in these gap junctions, each of which can differentially and dynamically intervene in the propagation of the action potential[10-12].

The myocardium is a form of specialized striated muscle, richly innervated by the autonomic nervous system, which is under uninterrupted activity throughout life. Therefore, it requires a constant and substantial energetic input from macromolecules such as carbohydrates, lipids and proteins in order to sustain the process of contraction and relaxation. Indeed, the cardiomyocyte transforms chemical energy from FA, glucose, ketone bodies and other substrates into mechanical energy[13,14]. The energetic metabolism of the cardiomyocyte consists of three key components: (1) capture and utilization of primary substrates, with the incorporation of their metabolites into the tricarboxylic acid (TCA) cycle; (2) oxidative phosphorylation, which occurs in the respiratory chain within the internal mitochondrial membrane; and (3) the phosphocreatine-creatine kinase energy transference system, a network for phosphate transference from ATP to creatine (an "energy-storing" molecule), through mitochondrial creatine kinase and yielding phosphocreatine, an important source of energy under high-demand conditions[15].
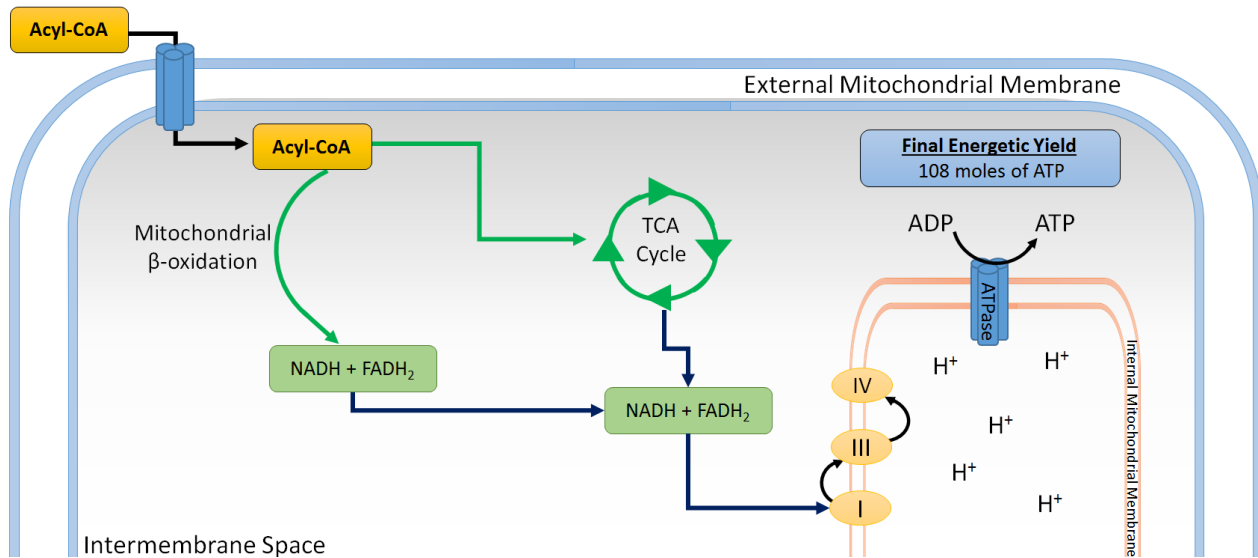
The metabolic machinery of the heart utilizes oxygen

Figure 2: FA metabolism in myocardiocytes. Once inside cells, FA are esterified with Coenzyme A into acyl-CoA, which in turn can be esterified for storage as triacylglycerides, or transported to the external mitochondrial membrane, where it is carried by a carnitine-dependent system into the intermembrane space. In this process, the acyl group is condensed with carnitine and separated from CoA to form acyl-carnitine, via carnitine palmitoyl transferase I. Then, it binds to acyl-carnitine translocase, which transports it into the mitochondrial matrix, and is converted into acetyl CoA, which goes into the TCA cycle. This process also yields NADH and FADH2 and several reducing equivalents, which can be utilized in the respiratory chain to generate ATP through oxidative phosphorylation. FA: fatty acid; TCA: tricarboxylic acid

up to 80%-90% of the maximum capacity of the electron transport chain; however, at a resting state, the heart operates at only 15%-25% of its maximum oxidative capacity[16]. Cardiomyocytes show an elevated rate of ATP hydrolysis, which is strongly linked to oxidative phosphorylation. Because under non-ischemic conditions, over 95% of these cells' ATP is produced in this process[17], it is indispensable in order to assure the full replenishment of the cardiomyocytes' ATP content every 10 s, and thus maintain constant concentrations of this molecule, even under conditions of increased frequency or force of contractions[18]. Of the total energy produced by ATP hydrolysis, approximately 60%-70% serves as fuel for contraction, while the remaining 30%-40% is used by the Ca^{2+}ATPase pumps in the smooth sarcoplasmic reticulum and other ion pumps[19].

FA metabolism in cardiomyocytes
Cardiomyocytes use FA as their main source of energy, yet their synthesizing capacity for these molecules is relatively low[20] as is shown in Figure 2. As a result, these cells depend fundamentally on the influx of FA from the vascular compartment, and thus, the rate of FA consumption by cardiac muscle is principally determined by the concentration of non-esterified FA in plasma[21,22].

The heart obtains these FA chiefly from exogenous substrates, especially free FA bound to albumin, and FA released from triacylglycerides (TAG) contained

in chylomicrons and very low-density lipoproteins, later undergoing β-oxidation[23-25]. FA may enter cardiomyocytes by passive diffusion or by active transport through the sarcolemma, involving an FA translocase (CD36) or an FA-binding protein in the cell membrane[26]. This translocation is mediated by intracellular vesicles, and may be promoted by electrical stimulation or high-demand conditions[27].

CD36 is one of the main translocases, an 80 kD integral membrane glycoprotein which is stored in intracellular compartments and transported towards the cell membrane in response to increased energy demands[28]. This protein is found in platelets, immune cells, adipocytes, myocytes, enterocytes and various other cells, yet is most abundantly expressed in cardiomyocytes. It is also the most important FA translocase in the heart and plays a key role in the entry of long-chain FA into cardiomyocytes[29]. The extracellular domain of CD36 has three disulfide bridges in its C-terminus end which contain binding sites for FA, oxidized low-density lipoprotein, thrombospondin and *Plasmodium falciparum*-infected erythrocytes. This domain operates actively by generating transduction signals which interact with multiple tyrosine-kinases and generate various structural modifications which modulate the functions of CD36; including phosphorylation, glycosylation, palmitoylation and ubiquitination[30].

As cardiac activity increases, so does the

cardiomyocyte's metabolic demand, which results in an increase in intracellular concentrations of adenosine monophosphate (AMP) and reactive oxygen species[31]. In turn, this upregulates AMP-activated protein kinase (AMPK), a key metabolic regulator. AMPK is a serine/threonine kinase which acts as a metabolic sensor in cardiomyocytes. It is activated during high energy requirement states, enhancing FA availability, uptake and oxidation in these cells by promoting the expression and activation of lipoprotein lipase and CD36, also known as fatty acid translocase[31]. This favors the entry of long-chain FA into the cell, preserving stable levels of ATP in the face of increased metabolic demand[32]. Nevertheless, excessive expression of CD36 has been associated with impaired cardiac insulin sensitivity, reduced uptake of glucose, and excessive uptake of FA, subsequently causing cardiomyocyte lipotoxicity and retention of GLUT4 in their cytoplasm[33]. Recent *in vitro* studies in cardiomyocytes have shown that use of CD36 blockers or deletion of its coding gene ameliorates contractile dysfunction mediated by lipotoxicity, and reduced lipid-induced damage[34,35]. AMPK can also inhibit acetyl-CoA carboxylase, which enhances mitochondrial FA uptake. In addition, in energy depletion states, AMPK increases GLUT4 expression and inhibits its internalization and also enhances glycolysis by phosphorylation of phosphofructokinase 2. It may also facilitate glycogen storage in adequate ATP supply states[36].

In addition to their plasma concentration, an important long-term regulator of FA β-oxidation is the modulation by peroxisome proliferator-activated receptor (PPAR)[37]. Numerous coactivator proteins, such as PPAR-γ co-activator 1-α can powerfully induce the transcription of PPAR target genes, including those involved in FA storage (such as diacylglycerol acyltransferase, promoted by PPARα), FA oxidation (such as medium-chain acyl-CoA dehydrogenase, promoted by PPARα/β/δ/γ), and glucose metabolism (such as pyruvate dehydrogenase kinase 4, promoted by PPARα)[38,39].

PPAR also plays an important role in the regulation of oxidative stress in the cardiovascular system, with several isoforms implicated in various transcriptional mechanisms for antioxidant genes[40,41]. For example, PPARα and PPARγ promote the transcription and activation of Cu/Zn-superoxide dismutase (SOD1), Mn-superoxide dismutase (SOD2) and catalase in cardiac tissue. Furthermore, PPARα augments IGF-1 transcription, subsequently activating the IGF-1/PI3K pathway, inhibiting apoptosis and protecting cardiomyocytes under ischemic stress[42].

Carbohydrate metabolism in cardiomyocytes

Carbohydrates are also a valuable source of energy in the myocardium, with glucose providing roughly a quarter of the total energy produced in a well-irrigated heart. Of this total ATP, approximately 10%-40% derives from the oxidation of glucose-lactate within the TCA, and only 2% derives from glycolysis[43].

Glucose enters the cardiomyocyte through glucose transporter proteins (GLUT). Fourteen different GLUTs have been described in humans, all of which appear to be able to transport hexoses or polyols, although it is suspected that many other GLUT substrates remain undiscovered[44]. GLUT 1-5 are the most studied to date, and they are well-known to be glucose and/or fructose transporters in various tissues and cell types[45]. In cardiomyocytes, GLUT4 is the main transporter, translocating to the membrane in response to signaling by insulin, increased work demand, or ischemia, with GLUT1 playing an accessory role[14].

The products of glycolysis are utilized in both the TCA cycle and the respiratory chain in order to generate ATP through oxidative phosphorylation[46]. Although only 2% the heart's ATP is produced in glycolysis, it becomes very important under anaerobic or ischemic conditions. Indeed, in heart failure and hypertrophy, there is a metabolic switch towards favoring carbohydrate over FA metabolism in the heart, with a notable change being the acceleration of glycolysis[47]. This increase in the glycolytic flux appears to be due to a functional upregulation in the pathway's enzyme, rather than a clear increase in the expression of glycolytic enzymes[48].

This shift towards utilization of glucose in the hypertrophic myocardium had traditionally been considered a maladaptive change. Nevertheless, recent studies in bioengineering-modified mice have demonstrated glucose-dependence not to be harmful in adult hearts, and a decrease in the utilization of glucose appears to be deleterious in failure and hypertrophy[49]. For example, mice with GLUT1 overexpression - and thus, increased glycolysis - appear to be protected against heart failure and left ventricular dilatation, even when subjected to pressure overload[50,51]. On the other hand, those with deletion of GLUT4 and insulin receptors in the heart failure, and showed worse responses to cardiac hypertrophy-promoting stimuli[52].

The phosphocreatine-creatine kinase system incardiomyocytes

Because both the systole and diastole are active,

highly ATP-dependent processes, the demand for these metabolites in cardiomyocytes is very high, with the heart requiring approximately 20 times its weight in ATP per day in order to sustain its energetic demands[53]. After synthesis, ATP must be transported from the mitochondria to the myofilaments and membrane proton pumps, a process in which the phosphocreatine-creatine kinase system intervenes substantially[54].

Creatine kinase (CK) is a key enzyme for phosphate transference in cells with high energetic demand, and works in harmony with other enzymatic machinery in order to facilitate intracellular energetic communication[55]. CK synthesizes phosphocreatine (PC) from creatine and a phosphate group from ATP in a reversible reaction, acting as a functional ATP reserve. CK associated with myofilaments catalyzes the transference of the phosphate from PC towards adenosine diphosphate (ADP), replenishing ATP in ATPase active sites, such as myosin heads. In cardiomyocytes, CK isoenzymes and the highly diffusible PC are responsible for sustaining the transference of energy from producing centers (mitochondria and glycolysis) towards ATP-consuming sites (myofilaments and ATPase pumps)[15].

The PC-CK system represents the first line of energetic reserves in cardiomyocytes, providing a quick source of ATP and favoring its transportation to its utilization sites, especially myofilaments[56]. In animal models, disruptions in the PC-CK system have been linked to impaired myocardial contractility and increased risk for arrhythmias[57,58]. Moreover, alterations in the functionality of CK have been identified as an independent risk factor for heart failure[59].

CK is composed of dimers, which consist of subunits M and B, and originate three isoenzymes: CK-MM, -MB and -BB. A fourth isoenzyme is found in mitochondria (mi-CK) and accounts for 20%-40% of all CK activity in the heart[60]. CK is not evenly distributed within the cell, and is rather a part of a compartmentalized metabolic pathway, bound to myofilaments and the sarcoplasmic reticulum to form functional complexes which accelerate ATP synthesis[61].

The mi-CK isoform is coupled to the external surface of the internal mitochondrial membrane, near the ATP-ADP translocases, also termed adenine nucleotide translocases (ANT). During oxidative phosphorylation, the ATP generated in the mitochondrial matrix is exported by ANT to the intermembrane space

and transphophorylated by mi-CK to PC and ADP, with the latter being immediately available for oxidative phosphorylation, stimulating cellular respiration[55]. Another isoform of CK is associated with myofilaments, acting as a structural protein within M-bands, which is functionally coupled to the myosin ATPase and can transfer phosphate from PC to ATP, providing sufficient energy for maintaining maximum contractility[61].

In a healthy heart, approximately two thirds of all creatine is phosphorylated by CK to yield PC. In heart failure, the level of PC is lower in relation to the concentrations of ATP, with a lower PC/ATP index[62]. Lower values of this index have been related to increased mortality[63]. Human and animal models have demonstrated a progressive reduction in the creatine pool of up to 60% in patients with heart failure, with a directly proportional relationship between the decrease of the index and the severity of the condition[64].

Fatty acids *vs.* glucose as energetic substrates

The selection of energetic substrates in cardiomyocytes is a fundamental step for the constant generation of ATP which depends on the dynamic metabolic milieu in each body at a given time[65]. This flexibility is present during fetal development; however, after birth, FA becomes the preferential substrates, due to the increased availability of oxygen and dietary fats[66-68]. Infants with mutations in genes involved in FA metabolism have been documented to develop cardiomyopathy when under stress, highlighting the essential role of FA in this tissue[66]. Likewise, in heart failure and left ventricular hypertrophy (when the oxidative capacity of mitochondria in cardiomyocytes is diminished), there is a shift towards a predominance for glucose metabolism[69,70].

FA are known to be the main source of energy in cardiomyocytes when the heart is at rest and during fasting periods: most of the acetyl CoA that enters the TCA cycle (60%-90%) originates in the β-oxidation of free FA[13], while the remaining 10%-40% is produced by oxidation of pyruvate, which derives from the oxidation of glucose or lactic acid[71]. Several reports have shown that cardiac efficiency, in terms of oxygen consumption, is greater when oxidizing glucose and lactate rather than FA[72]. Studies using ranolazine - an inhibitor of β-oxidation which induces oxidation of carbohydrates - have found enhanced left ventricular function and improved metabolic efficiency when utilizing glucose as the main energetic substrate[73]. Similarly, potentiating FA use in the heart with

heparin or TAG infusions has been reported to result in a 26% increase in oxygen consumption without changes in mechanical capacity of the left ventricle[74], which suggests a greater functional capacity for this chamber when utilizing glucose[75]. This may be due to the higher level of oxidative stress caused by the oxidation of FA in comparison with carbohydrates, due to the increased oxygen consumption rate in the former[76].

The ATP synthesis/oxygen consumption rates for glucose and lactic acid are 3.17 and 3.00, respectively; whereas they are 2.80 and 2.86 for palmitate and oleate, respectively. Although these are theoretical values which may be lower *in vivo* as a consequence of the constant proton efflux through the mitochondrial membrane, the differences between substrates remain substantial[77]. For example, when comparing palmitate with glucose, the complete oxidation of 1 molecule of palmitate yields 105 ATP molecules and requires 46 oxygen atoms, while 1 molecule of glucose generates 31 ATP molecules and uses 12 oxygen atoms. Thus, despite FA clearly yielding greater amount of ATP, this occurs at the expense of larger oxygen requirements[39]. Furthermore, β-oxidation of FA generates more lipid peroxidation due to increased delivery of NADH and FADH2 to the electron transport chain and production of superoxide anion[78].

In addition, elevated free FA are harmful in the ischemic myocardium, augmenting cell damage. In the first hours of an acute myocardial infarction (AMI), free FA can act as detergents on the cell membrane of cardiomyocytes[79-81]. Moreover, there is increased generation of free radicals, which can inactivate IRS-1 via phosphorylation of serine residues. This directly promotes insulin resistance and simultaneously stimulates the release of proinflammatory cytokines, such as TNF-α and IL-6[82]. Therefore, all conditions of metabolic inefficiency in the heart favor insulin-mediated left ventricular remodeling and diastolic myocardial dysfunction[83].

Considering this, various systemic conditions such as obesity cause elevated serum free FA which can potentiate β-oxidation, and thus increase lipid traffic in cardiomyocytes, prompting a phenomenon termed lipotoxicity[13,84]. This process can lead the cell towards contractile dysfunction, insulin resistance and ultimately apoptosis in association with accumulation of ceramides[85].

On the other hand, pre-clinical and clinical evidence suggests partial inhibition of free FA oxidation in the myocardium can prevent or diminish tissue damage and dysfunction under conditions of ischemia or reperfusion, diabetic cardiomyopathy, and AMI. This occurs because the heart shifts towards glucose as the main source for ATP synthesis, which reduces the oxygen demand by 11%-13% and therefore improves cardiac efficiency and protects mitochondrial function[43,86]. Nonetheless, the real benefits of this partial inhibition remain uncertain when contemplating the potential consequences of excessive lipid accumulation within cardiomyocytes[86].

ARRHYTHMOGENIC METABOLIC CHANGES DURING MYOCARDIAL ISCHEMIA

Cardiac sudden death is responsible for approximately half of all cardiovascular mortality[87]. The majority of these are attributed to ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation), which are frequently caused by myocardial ischemia[88]. The mechanisms through which myocardial ischemia leads to local electrophysiological disorders and arrhythmogenesis have been extensively explored [Figure 3][2,89].

Severe metabolic changes begin a few seconds after coronary occlusion: high-energy phosphates are hydrolyzed, intracellular pH lowers as a consequence of the activation of anaerobic glycolysis, and extracellular potassium levels increase[90,91]. The latter lasts for roughly 10 min, during which the resting membrane potential decreases, approaching the firing threshold potential, thus accelerating electrical conduction[92]. The intracellular acidosis also drives an increase in cytosolic calcium, facilitating early and late depolarization, as well as spatial and temporal fluctuations in the duration of action potentials[93]. Additionally, ischemia leads to dephosphorylation of connexin-43 in gap junctions, which impairs intercellular electrical coupling and anisotropy[94]. Lastly, sympathetic stimulation not only promotes calcium release from the sarcoplasmic reticulum, but it also prompts lipolysis, elevating circulating free FA levels and therefore predisposing to ischemia-induced arrhythmogenesis[95].

Other possible mediators of cardiac arrhythmia include thrombin and endothelin-1. Patients with ST-elevation myocardial infarction (STEMI) complicated with ventricular fibrillation have been found to have higher levels of thrombin activity markers[96]. The production of thrombin at sites of coronary occlusion has been suggested to favor accumulation
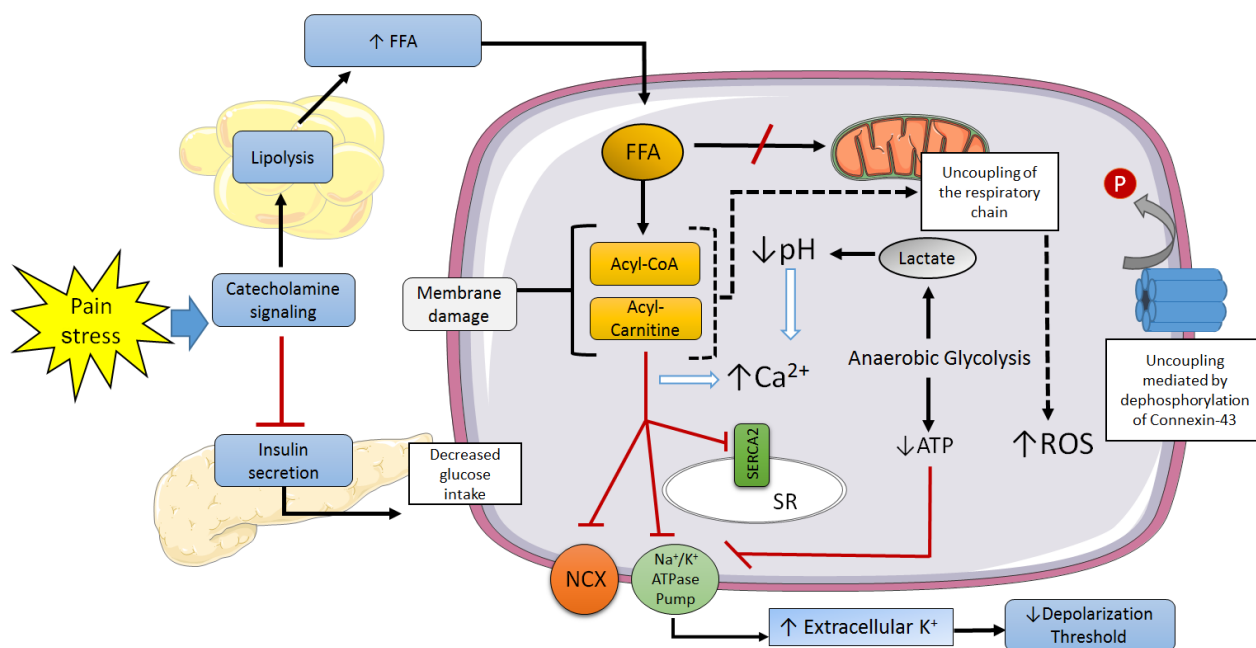
Figure 3: Mechanisms involved in the genesis of ventricular arrhythmias in the ischemic myocardiocyte. SR: sarcoplasmic reticulum; NCX: Na^+/Ca^{2+} exchanger; ROS: reactive oxygen species; FFA: free fatty acids; P: phosphate

of lysophosphatidylcholine, which activates Na^+ channels and Na^+/H^+ exchangers, enhancing the entry of Na^+ into the cell[97]. On the other hand, endothelin-1 activity increases exponentially during acute ischemia, mediating direct and indirect electrophysiological effects through type-A endothelin receptors, and possibly playing a protecting role through type B endothelin receptors during the early stages of ischemia[98].

Acute pro-inflammatory cytokines - including TNF-α, IL-1β, IL-6 - and metalloproteinases are also found in greater proportions in the myocardium following an AMI, and may account for the electrophysiological changes observed in the cardiomyocytes within the border zone of the infarction[99]. This suggests an inflammatory process is involved in the remodeling and arrhythmogenic changes seen after an infarction. Patients with post-AMI arrhythmias tend to display higher levels of pro-inflammatory cytokines than those without arrhythmias[100,101]; and subjects without AMI or structural myocardial damage with systemic inflammation have shown an increased risk of ventricular tachyarrhythmias[102].

This catalogue of arrhythmogenic changes occur heterogeneously along the penumbra of the infarction zone, impairing its functionality as a syncytium and the electrical coupling among cardiomyocytes[103,104]. These phenomena are complex and appear to occur erratically due to the dynamic nature of reperfusion,

low pH, oxygen depletion, increased intracellular calcium and potentiated sympathetic signaling[105]. These events, along with the high proportion of electrical decoupling and the auto-oscillatory activity of individual cells lay the foundation for a very variable syncytial behavior[106]. This leads to the continuous generation of mini-reentry circuits from individual ectopic rhythmic foci within the decoupled cell areas, which then spread to the better coupled zones within the penumbra, constituting the genesis of arrhythmias[107]. In concert, these changes are thought to be the triggers and substrates for ventricular arrhythmias, although further research is required to elucidate them in more detail.

LIPOTOXIC PHENOMENA IN ISCHEMIA AND ARRHYTHMIA

In 1968, Oliver *et al.*[108] determined patients with AMI and especially those with elevated free FA levels had a greater incidence of ventricular arrhythmias in comparison with normolipemic patients. This finding has been also been found by various authors ever since[109]. More recently, in the Paris Prospective Study - a research realized in 5,250 male subjects followed during 22 years - high plasma free FA levels have been associated with sudden cardiac death, yet appeared to be unrelated to other causes of AMI[110].

The exact mechanism through which the shifts in FA/ glucose metabolism in the cardiomyocyte lead to

arrhythmia remain unclear, yet various alternatives have been proposed[111]. During an infarction, numerous events develop in parallel, with some of the earliest being precordial pain and increased sympathetic activity[112]. Although a moderate increase in catecholamines may aid in maintaining cardiac contractility in the face of oxygen depletion, excessive signaling can augment the energetic demands of the myocardium, impairing functionality[113].

It has been proposed that for the ischemic cardiomyocyte, glucose metabolism is more beneficial, and FA metabolism is deleterious[114]. However, FA availability is much greater: catecholamines induce lipolysis in adipose tissue, abruptly rising circulating FA levels[115], and inhibit insulin signaling, reducing glucose entry into the myocardium[116]. Likewise, FA can inhibit glucose oxidation and potentiate oxygen consumption in ischemic myocardial areas, leading to a preferential utilization of FA over glucose during ischemia[117].

The mechanisms underlying FA-related toxicity appear to be fundamentally linked with adrenergic stimulation[118]. However, FA also exhibit direct arrhythmogenic activity. Even without ischemia, a sufficiently high free FA/albumin molar rate can inhibit β-oxidation, leading to accumulation of acyl-carnitine and acyl-CoA in the cytosol. In turn, acyl-carnitine inhibits Ca^{++} pumps in the sarcoplasmic reticulum, as well as the Na^+/Ca^{++} exchanger and the Na^+/K^+ ATPase pump, finalizing in an overload of Ca^{++} in the cytosol[119].

Furthermore, other metabolic processes activated upon elevation of free FA levels, such as membrane lipid peroxidation, inhibition of β-oxidation, uncoupling of proteins in the mitochondrial respiratory chain, accumulation of CoA derivates and extracellular K^+ with shortening of action potentials, are all harmful for the ischemic cardiomyocyte[120]. On this basis, strong arguments propose the reduction of circulating free FA as a therapeutic measure in AMI, although further evidence is required to encourage this practice. Regarding instrumentation, the glucose-insulin-potassium (GIK) infusion is a well-known and viable alternative, as it promotes glucose entry into the myocardium and inhibits lipolysis, with the metabolic benefits this implies in cardiomyocytes[121]. Despite early clinical trials failing to demonstrate the utility of GIK at decreasing sudden death during the first 3 days following an AMI[122], more recent reports, such as the IMMEDIATE study have shown better outcomes at a 1-year follow-up: in patients with STEMI, 1-year mortality and hospitalizations for heart failure decreased significantly[123]. Theoretically,

drugs for rapid inhibition of lipolysis would yield better results, yet research efforts in this line remain scarce and poor.

Quick myocardial FA availability has been closely related with epicardial adipose tissue (EAT) or the epicardial fat pad which is found between the myocardium and the visceral pericardium. This isin close proximity with the coronary arteries and so facilitates the activity of anti-inflammatory and pro-inflammatory adipokines and FA in the myocardium and arterial walls[124,125]. The Framingham Heart Study[126] has identified the EAT volume as a predictor of atrial fibrillation - the most frequent arrhythmia in clinical practice - independent of other methods for the measurement of adiposity such as the body mass index. Other studies have reported the EAT volume to be associated with the prevalence and severity of atrial fibrillation[127].

The EAT has also been found to release pro-inflammatory messengers such as activin A, which induces the expression of the transforming growth factor β1 (TGF-β1) and several metalloproteinases. These are key regulators in the homeostasis of the extracellular matrix - in particular by modifying collagen fibers - and mediate the profibrotic effect of EAT in the atrial myocardium[128]. Many other inflammatory mediators secreted by EAT also intervene in the pathogenesis of atrial fibrillation, including TNF-α, IL-8, and the monocyte chemotactic protein 1 (MCP-1)[129].

Finally, increased EAT has been associated with fatty infiltration in the myocardium, which contributes to tissue disorganization and promotes an arrhythmia-prone environment[130]. At the same time, these deposits favor the proliferation of myofibroblasts and increase the amount of dystrophic cardiomyocytes[130]. In this context, the EAT has been proposed as a novel therapeutic target in the management of cardiovascular disease[125].

CONCLUSION

The cardiomyocyte is the protagonist cell in the heart which allows it to function as a pump. This capacity requires strict electrophysiological and mechanical control and large amounts of ATP. These energetic demands are covered by a dynamic selection of substrates, shifting between carbohydrates and FA depending on various intracellular and systemic circumstances. Myocardial metabolism has been historically described as the "lost child of cardiology"[131], as clinicians have rather focused on

thrombolysis and angioplasty, and very little practical value has been obtained from its study. Nonetheless, the evidence suggesting metabolic causes for arrhythmias grants a "resuscitation" of this cause[120]. Indeed, further research is required in order to explore and exploit the therapeutic implications of myocardial metabolism.

DECLARATIONS

Authors' contributions
Article conception and design: M.S. Martínez, A. García
Acquisition and analysis of bibliographic information: M.S. Martínez, A. García, E. Luzardo, L.C. Olivar
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Critical revision and final approval: V. Bermúdez, M. Velasco, J.J. Rojas Quintero

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