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DIABETES MELLITUS, ISCHEMIC HEART DISEASE AND ARTERIAL HYPERTENSION

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Annotation: *Diabetes mellitus is one the strongest risk factors for cardiovascular disease and, in particular, for ischemic heart disease (IHD). The pathophysiology of myocardial ischemia in diabetic patients is complex and not fully understood: some diabetic patients have mainly coronary stenosis obstructing blood flow to the myocardium; others present with coronary microvascular disease with an absence of plaques in the epicardial vessels. Ion channels acting in the cross-talk between the myocardial energy state and coronary blood flow may play a role in the pathophysiology of IHD in diabetic patients. In particular, some genetic variants for ATP-dependent potassium channels seem to be involved in the determinism of IHD.*

Keywords: *risk factors, pathophysiology, myocardial energy, coronary blood.*

Over time, high blood sugar can damage blood vessels and the nerves that control your heart. People with diabetes are also more likely to have other conditions that raise the risk for heart disease: High blood pressure increases the force of blood through your arteries and can damage artery walls. From the physiological point of view, the coronary blood flow adapts itself to the metabolic and oxygen demands of the myocardium, which continuously change. The main site of coronary total resistance regulation is in the microcirculation, which is composed of small arteries and arterioles, which have diameters between 200 and 50 μm . Vascular processes whereby diabetes and hypertension predispose to cardiovascular disease. Common risk factors promote diabetes and hypertension, which are associated with atherosclerosis, vascular inflammation, endothelial dysfunction, and structural remodelling, which lead to macrovascular and microvascular disease.

Several mechanisms regulate coronary blood flow and their contribution is different depending on the considered district. Neuro-humoral regulation and shear-stress-related vasodilatation are the main regulatory mechanisms of the epicardial arteries district, while the distal district represents the main metabolic and myogenic

regulation site of coronary blood flow . Modifying vasal tone, these mechanisms allow the coronary blood flow to adapt to cardiomyocyte metabolic demand.

The myocardial oxygen consumption (MVO2) is defined by the following formula: MVO2 = coronary blood flow × arterial − venous oxygen difference . At rest, the myocardium has an oxygen consumption of 10 mL of oxygen, per minute, per gram of myocardial tissue and it extracts about 80% of oxygen carried by coronary blood flow. Growing oxygen demand by the myocardium is satisfied with an increase of coronary blood flow through a constant modulation of coronary vascular tone. There are many important regulatory mechanisms of coronary blood flow. The autoregulation contributes to maintaining the basal vascular tone in resistance arteries, ensuring a constant blood flow to the myocardium and minimizing vascular wall stress. The main action mechanism of autoregulation is therefore the myogenic regulation. From the molecular point of view, the changing of smooth muscle contraction induced by autoregulation is determined by variation in intracellular calcium values. As regards the neuro-humoral regulation, the coronary arteries have both sympathetic and parasympathetic innervation. Both the innervation systems have a tonic activity, which contributes to determining the vascular basal tone. Endothelial-dependent regulation is a mechanism through which vascular resistances and vasal tone are modulated by several paracrine factors, such as nitric oxide, arachidonic acid metabolic products, endothelial-derived hyperpolarizing factors, and endothelin's. Moreover, there are several hormones which contribute to coronary blood flow regulation. Among them, 17β-estradiol, progesterone, testosterone, antidiuretic hormone, and histamine determine vasodilatation, while growth hormone and angiotensin II are vasoconstrictors. Insulin seems to have a double effect. It determines vasoconstriction, activating the sympathetic system, and also vasodilatation, inducing endothelial nitric oxide production. Another important mechanism is metabolic regulation, which ensures that adequate blood flow and oxygen are provided to the myocardium in relationship with its metabolic demand. This regulation mechanism has an important role in coronary vascular resistance control and it acts through several molecules produced by cardiomyocytes, such as oxygen, carbon dioxide (CO2), adenosine, adenine nucleotides, and reactive oxygen species, and some ion channels: the triphosphate adenosine-sensitive potassium channels , calcium-dependent potassium channels, and voltage-dependent potassium channels (Kv).

Regulation of coronary blood flow is heterogeneous and complex. Several ion channels play a pivotal role in this regulation and in its homeostasis. Alteration in these mechanisms can lead to , which represents one the most frequent cause of mortality in the world. By convention, is the expression of; however, clinical, angiographic, and autoptic findings show that coronary microvascular dysfunction, impairing vasomotor tone, is able to provoke independently from the presence of an atherosclerotic stenosis. In the determinism of, diabetes mellitus is one of the strongest risk factors. However, the

pathophysiology of myocardial ischemia in diabetic patients is not fully understood. In the last decades, an increasing number of studies have shown the importance of ion channels as end effectors of several regulation mechanisms, such as coronary blood flow and glucose homeostasis. Impaired ion channel activity might be associated with the alteration of these regulatory mechanisms, causing predisposition to several pathologies. In this work, we mainly focused on the pathophysiological role of coronary artery and pancreas islet cell ion channels in the determinism of both diabetes mellitus and. Through the systematic review of the most recent international literature, we highlighted that there are some ion channels whose impaired function is strongly associated with diabetes mellitus and susceptibility. We also highlighted the most important that modify these channels' activity, with particular reference polymorphisms of which we also studied in our previous work. We previously identified t in the gene, encoding for subunit of channels, as a protective independent factor for in Caucasians. Performing a post hoc analysis on subgroups of diabetic and nondiabetic patients, diabetes mellitus was not significantly associated with either acute coronary syndromes observed clinical associations are in contrast with those classically described as associated with diabetes mellitus, which is one of the strongest risk factors for ACS, CAD, and microvascular dysfunction.+

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