Chapter 2

The Morphology, Physiology and Pathophysiology of Coronary Microcirculation

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64537

Abstract

The heart is one of the most demanding organs of the human body. The high nutrient and oxygen demands need to be met through an adequate vascularization of the myocardium. In fact, the myocardium vascular supply is achieved through an extensive vascular network that includes larger arteries, also known as coronary arteries, smaller arteries (arterioles) and capillaries. This set of arterioles and capillaries is known as microcirculation. Coronary artery disease is usually associated with larger epicardial coronary arteries. However, several studies have shown an important role of coronary microvascular dysfunction. This review aimed to explore the (a) morphology, with particular interest on the anatomical and histological aspects; (b) physiology, providing an insight on the several endothelium-dependent and endothelium-independent regulatory mechanisms; and (c) pathophysiology of the cardiac microcirculation, with a special focus on the changes in the regulatory mechanisms, on the atherogenesis and on the correlation to the systemic cardiovascular disease.

Keywords: coronary microcirculation, coronary microvascular morphology, coronary microvascular physiology, microcirculation regulatory mechanisms, coronary microvascular dysfunction, coronary microvascular pathology

1. Introduction

The heart is one of the most demanding organs of the human body as it presents high demands for nutrients and oxygen. These demands are physiologically met through an extensive and unique vascular network, which is usually known as *coronary circulation*. The coronary circulation

includes larger arteries, also known as coronary arteries, smaller vessels (with a diameter below 100 μm), such as arterioles, capillaries and venules, that together form the coronary microcirculation and larger epicardial veins [1].

Historically, the large epicardial arteries were considered the coronary circulation. Nowadays, the scientific reports suggest the coronary circulation is characterized by an extreme complexity in terms of morphology but also physiology. Moreover, the theory that the coronary circulation involves the larger epicardial arteries is no longer acceptable given the extensive vascular network present in the myocardium.

Coronary artery disease (CAD) is usually associated with larger epicardial coronary arteries. However, previous studies have shown an important link between microcirculatory dysfunction and cardiovascular disease. In fact, pathological changes in smaller vessels have been detected prior to clinical manifestations of cardiovascular disease [1]. Moreover, microcirculatory dysfunction may even be a risk indicator for metabolic syndrome and associated cardiovascular disease [1, 2].

This review aimed to explore the (a) morphology, with particular interest on the anatomical and histological aspects; (b) physiology, providing an insight on the several endothelium-dependent and endothelium-independent regulatory mechanisms; and (c) pathophysiology of the cardiac microcirculation, with a special focus on the changes in the regulatory mechanisms, on the atherogenesis and on the correlation to the systemic cardiovascular disease.

2. Morphology and basic function

Based on the morphology and function, the coronary circulation involves several types of vessels as follows (from the larger arteries to the largest veins): epicardial arteries or coronary arteries, small arteries or intramural arteries, arterioles, capillaries, venules and epicardial veins. These vessels may be grouped according to their size into (a) *coronary macrocirculation*, referring to vessels with diameter higher than 100 μm (which includes the coronary arteries, the intramural arteries and the epicardial veins) and (b) *coronary microcirculation*, for vessels with a diameter lower than 100 μm, where the arterioles, capillaries and venules may be included.

2.1. Arterioles

The *arterioles* are smaller arteries that originate from the intramural arteries and run parallel to the myocardial fibres [3–5]. These vessels are characterized by a marked decrease in blood pressure, contributing to the blood flow resistance, along their length and by an increasing responsiveness to metabolites, for example hydrogen peroxide, adenosine, among others [3, 4, 6]. Therefore, arterioles represent the main metabolic regulation component of the myocardial blood flow and aim at controlling the blood flow to the capillary network [3, 4, 7].

The anatomy of these vessels varies along their length: the proximal and middle portions tend to present similar characteristics to the larger arteries, although with a thick tunica media

http://dx.doi.org/10.5772/64537

[several layers of vascular smooth muscle cells (VSMCs)], while the distal portions, also termed terminal or precapillary arterioles, may present a thinner tunica media (one to two layers of VSMCs) or not even present any VSMC layer, which is replaced by small unique cells that will be explored in the following subsection, the *pericytes* (**Figure 1**) [8]. Moreover, the internal elastic membrane, in the tunica intima, may not be present [6]. The tunica adventitia is usually thinner in these vessels [6].

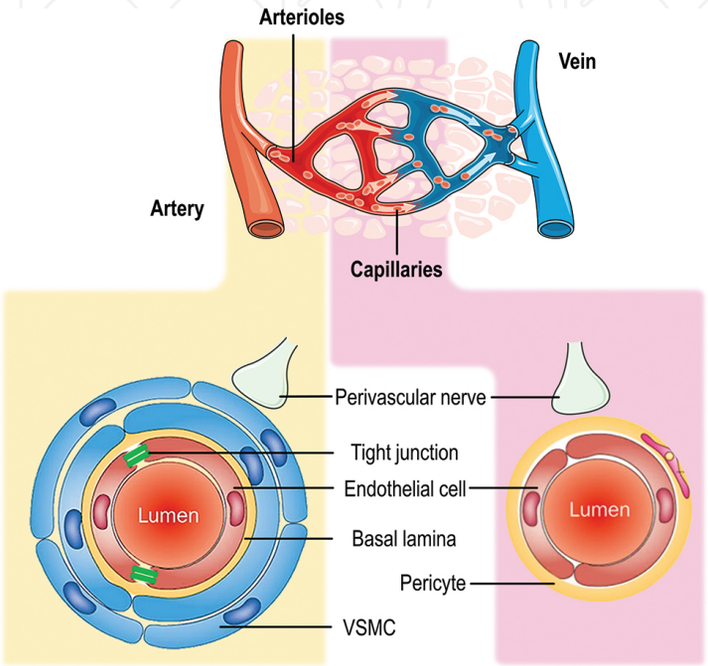

Figure 1. Vascular network and capillary neurovascular unit. As presented in the figure, the larger arteries (with a well-defined smooth muscle layer that may vary in size) present morphological differences to the capillaries, which do not present smooth muscle layer, being substituted by pericytes. The capillary neurovascular unit then includes the endothelium, basal lamina and pericytes, which are surrounded by neuron terminals. Moreover, the vascular network also includes other cell types, such as fibroblasts, collateral blood vessels, among others. Adapted from Zhang et al. [9] and prepared using Servier Medical Art (http://www.servier.com/).

2.2. Capillaries

The connection between the arterial and the venous systems is fundamentally achieved by a capillary network placed amid the arterioles and the venules (**Figure 1**).

The *capillaries*, with a diameter lower than 10 μm (average of 5.7 μm), are microscopic vessels that present numerous anastomotic loops (connections between the arterial and the venous systems), playing a crucial role in the exchange of nutrients and oxygen between the blood and the myocardium [5]. The capillary density may average up to 3500/mm^2 in the healthy myocardium and seems to vary from the subendocardium, which presents a higher oxygen-transport, to the subepicardium [5, 10, 11].

These vessels present structural differences to other vessels as the wall is essentially composed of two layers: an inner layer, the *endothelium*, and its *basal lamina* (**Figure 1**) [6]. In the inner

layer, the endothelial cell junctions may be smaller, forming intercellular clefts, or larger, creating intercellular gaps.

According to their morphology, capillaries may be classified into three main categories: (a) continuous capillaries, (b) fenestrated capillaries and (c) discontinuous capillaries [6]. In the coronary microcirculation, the *continuous capillaries* are the most prevalent type. These vessels are commonly found in muscle, lung and central nervous system and are characterized by the presence of numerous pinocytotic vesicles and the absence of fenestrations [6]. These fenestrations, present in the *fenestrated capillaries*, are microscopic pores (80–100 nm in diameter) that allow the rapid diffusion of smaller molecules or proteins, which is particularly important in some tissues, such as the intestine and endocrine glands [6]. The *discontinuous capillaries*, also known as *sinusoidal capillaries or sinusoids*, present a higher diameter than other capillaries as well as an irregular shape and may be found in the liver, among other tissues [6].

Embedded in the basal membrane of capillaries, between the endothelium and the parenchyma, small contractile cells called *pericytes* may be found (**Figure 1**) [12, 13].

Pericytes may vary morphologically and physiologically depending on the vascular bed and on the position in the vascular bed itself [13]. Nevertheless, they generally extend processes along and around capillaries [12, 13]. In the central nervous system and kidneys, pericytes play an important role in angiogenesis, regulation of the endothelium, among other functions [12, 13]. These cells seem to be particularly relevant in the central nervous system where the regional blood flow regulation is of crucial importance [13]. These pericytes may also present contractile properties [12, 13]. Several proteins have been suggested to confer contractility to pericytes, such as α-smooth muscle actin and tropomyosin [13]. However, previous studies suggest that the contractile mechanisms differ from the VSMCs [13].

Although the role of pericytes in coronary physiology is not yet fully understood, the high number of these cells in cardiac capillaries and the similar characteristics to the central nervous system pericytes indicates these cells may play an important role in the regulation of the vessel diameter as well as permeability [12].

In the capillary network, other structures may be found such as *capillary sinuses*, which consist of reservoir-like spaces that could behave as micropumps [8].

2.3. Venules

After the exchange of nutrients and oxygen at the capillary level, the deoxygenated blood, containing metabolic products, proceeds to the *venules*, which present numerous intercommunications, through confluence of capillaries and postcapillary vessels [5]. Although the coronary circulation has been extensively studied over the years, little is known about the intramural venous system. Nevertheless, previous studies have suggested a larger venous network comparatively to the arterial network in the myocardium [5]. In fact, the existence of two veins per artery has been suggested [5].

The venules usually present a diameter ranging from 10 to 50 μm and similar anatomical characteristics to the arterioles [8]. The proximal venules, that is postcapillary venules, usually

exhibit only two layers: an inner layer, the *endothelium* and an outer layer, the *basal membrane* [6, 8]. The endothelium of the venules seems to be highly responsive to vasoactive agents, namely histamine and 5-hydroxytryptamine, commonly known as serotonin [6]. As well as in terminal arterioles and capillaries, *pericytes* may also be found in the venular wall in a particularly higher extent than in arterioles or capillaries [6, 8].

The distal venules are morphologically different relatively to the postcapillary venules, as they may present a thin tunica media (one to two layers of VSMCs) and a thin tunica adventitia on the outer side of the vessel [6]. The absence of pericytes is a key characteristic of these distal venules [6]. These venules initially course parallel to the muscle fibres, accompanying the arterioles and capillaries, then changing their position and configuration to meet the larger coronary veins [5].

2.4. Special circulatory considerations

2.4.1. Arteriovenous shunts

In healthy conditions, the myocardial blood supply is fundamentally provided through the normal coronary circulation. However, in the presence of cardiac disease, such as chronic cardiac disease or regional ischemic injuries, the myocardial perfusion may be compromised [4, 5]. Compensatory circulatory communications named *arteriovenous anastomoses or shunts* seem to play a key role in the preservation of the myocardial perfusion in these situations [4, 5, 14]. This collateral circulation links directly the arteries or arterioles to the veins or venules, bypassing the capillary bed [14]. The arteriole of these shunts frequently presents morphological particularities: a *thicker tunica media* with a higher content in VSMCs, a more *developed tunica adventitia*, forming a capsule of connective tissue, *abundant innervation* and are frequently *coiled* [6].

2.4.2. Heart chamber-coronary circulation direct communication

The direct communication between the heart chamber and the coronary circulation is generally referred to *Thebesian vessels* [5]. These vessels were first described by Thebesius in 1708 [15] and involve the communication between the heart chamber and the capillaries and venules, referring to a venular connection [5, 16, 17]. These veins usually present a diameter of 200–400 μm and are more frequent in the right ventricle [5]. This type of chamber-vessel communication was later studied by Wearn et al. [18] who further described and defined this and other types of vessels, namely the arteriosinusoidal vessels and the arterioluminal vessels [5, 16, 18]. The *arteriosinusoidal vessels* provide a communication between a heart chamber and a myocardial sinusoid and are irregularly shaped short branches (diameter from 50 to 350 μm) composed of just an endothelial layer [5, 18]. The *arterioluminal vessels* are smaller vessels (diameter from 40 to 200 μm) that provide a direct communication to a heart chamber (more frequently the left ventricle), presenting a morphology similar to arterioles [5, 18]. Although previous studies have demonstrated the presence of these special vessels, their clinical significance is still debatable [5].

3. Microcirculatory physiology

3.1. General considerations

The physiologic behaviour of the coronary circulation is inherently linked to a balance between the blood supply and the metabolic demand of the heart [19]. Furthermore, the physiological responses in the microcirculation seem to depend on the vessel size and type and appear to vary within the microcirculation itself and from those in the macrocirculation [19–21]. Physiologically, the coronary microcirculation is able to respond to a wide range of stimuli, such as growth and physical exercise, through adaptive processes, essential to the maintenance of its physiology [19]. In fact, vessels present a high adaptation ability and may undergo both acute and chronic adjustments. The acute adjustments involve changes in the vascular smooth muscle tone, while the chronic adjustments involve wall structure changes [19].

The *vascular tone* is defined as the ratio between baseline and maximal vessel diameter and is determined by the vascular smooth muscle function [19]. In turn, this is regulated by several mechanisms, such as (a) the myogenic tone, which is an intrinsic property of the VSMC, (b) the metabolic control exerted by adjacent cells, (c) the endothelial function responding to changes in the shear stress and (d) autonomic innervation and circulating factors, such as hormones [19].

3.2. Myogenic tone

The *myogenic tone* is produced by the response of the VSMCs to changes in transmural pressure that leads to stretching of the vessel wall [19, 22, 23]. This relation seems to be linear, that is increasing transmural pressure leads to higher vasoconstriction (reduction in the lumen diameter) [19]. The mechanism underlying this response appears to involve the opening of ion channels, namely nonspecific cation channels, with an increase in intracellular sodium and calcium and consequently the depolarization of the VSMCs [19]. Several receptors have been implicated in the myogenic response, such as (a) integrins [24], (b) transient-receptor potential channels (TRPs) [25, 26] and (c) G protein-coupled receptors [27].

3.3. Metabolic regulation

The coronary blood flow is intrinsically linked with metabolic demands of the myocardium, namely of oxygen. At rest, the myocardial oxygen extraction averages 60–70%, which leads to the coronary venous pO_2 of about 20 mmHg [28]. During physical exercise, several mechanisms of adaptation are triggered in the myocardium, pO_2 seems to be kept constant, which highlights the role of several pathways, namely the myocardial aerobic metabolism [28]. This energy production is generally dependent on mitochondrial oxidative phosphorylation pathways [19]. Among several metabolites produced in these intracellular pathways, carbon dioxide (CO_2) and reactive oxygen species (ROS) seem to play an important role in physiological conditions [19, 28].

As previously mentioned, CO_2 production is linked to metabolic demands and therefore dependent on the myocardium oxygen consumption [19, 28]. This metabolite results from two

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main metabolic pathways: (a) the pyruvate dehydrogenase reaction and (b) the citric acid cycle [28]. The pyruvate dehydrogenase reaction converts pyruvate into acetyl-CoA, which is a substrate for the production of citrate, according to the following reaction:

$$\text{Pyruvate} + \text{CoA} + \text{NAD}^+ \xrightarrow{\text{Pyruvate dehydrogenase}} \text{Acetyl} - \text{CoA} + \text{CO}_2 + \text{NADH} + \text{H}^+ \quad (1)$$

After the conversion of oxaloacetate into citrate, the citric acid cycle involves several reactions in chain. Some of them also involve the production of CO_2, such as the production of α-ketoglutarate (reaction 2) and succinyl-CoA (reaction 3).

$$\text{D - Isocotrate} + \text{NAD}^+ \xrightarrow{\text{Isocitrate dehydrogenase}} \alpha - \text{Ketoglutarate} + \text{CO}_2 + \text{NADH} + \text{H}^+ \quad (2)$$

$$\alpha - \text{Ketoglutarate} + \text{CoA} + \text{NAD}^+ \xrightarrow{\alpha-\text{Ketoglutarate dehydrogenase}} \text{Succinyl} - \text{CoA} + \text{CO}_2 + \text{NADH} + \text{H}^+ \quad (3)$$

The increased production of CO_2 may also induce a decrease in pH due to the increase in proton concentration, as presented in the following reaction:

$$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}^+ + \text{HCO}_3^- \quad (4)$$

This change in pH seems to promote the coronary vasodilation [28–30].

As can be seen in **Figure 2**, the metabolic production of *ROS* also plays an important role in the metabolic regulation of the coronary blood flow involving a feedforward mechanism [19, 28]. Among the several ROS, hydrogen peroxide (H_2O_2) seems to be one of the most important metabolites being considered a feedforward vasodilator [31]. H_2O_2 results from the conversion of superoxide anions ($O_2^{\cdot -}$) by the superoxide dismutase (SOD) [28]. In turn, the superoxide anions result from the reduction in O_2 by electrons released from mitochondrial complexes (I and III) [28]. This pathway may be stimulated by shear stress in human coronary resistance arteries [32].

The vasodilator properties of H_2O_2 have long been studied, but the precise underlying mechanisms are not yet fully established [28]. Previous studies suggested H_2O_2 behaves as an endothelium-derived hyperpolarizing factor (EDHF) [34, 35], as described in the following subsection. However, other previous studies suggested the mechanism may involve the stimulation of the nitric oxide (NO) production or be mediated by the guanylyl cyclase in human coronary arterioles [36]. These pathways will be further discussed in the following subsections.

Other studies have suggested additional mechanisms involved in the metabolic regulation exerted by H_2O_2 on the coronary blood flow. The involvement of oxidation of thiol groups as a pathway of coronary metabolic dilation in isolated coronary arterioles has been previously

proposed [37]. The thiol groups are involved in many pathophysiological mechanisms and play a key role in the biological protection against oxidative injuries [38, 39]. This oxidation process promotes modifications in the protein conformation and includes the conversion of protein-bound thiols (-SH) into sulfenic (SO^-, reaction 5), sulphinic (SOO^-) and sulphonic ($SOOO^-$) acids as well as disulphide bridges (S-S, reaction 6) [37, 39].

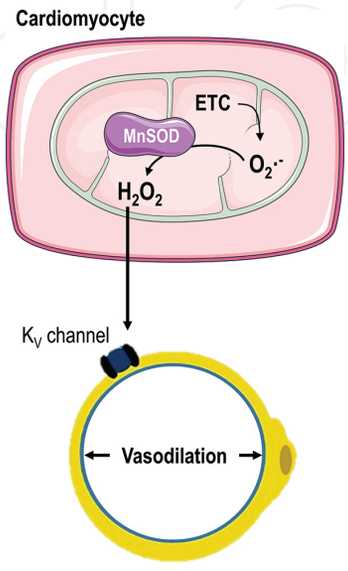

Figure 2. Feedforward reactive oxygen species-dependent metabolic regulation of coronary blood flow. The increased metabolic demands of the myocardium trigger an increase in mitochondrial metabolism and flux, through the electron transport chain (ETC), increasing the production of $O_2\cdot-$ and subsequently of H_2O_2 by manganese SOD (MnSOD). H_2O_2 then diffuses to the VSMC and activates voltage-dependent K^+ (K_V) channels promoting the hyperpolarization of the VSMCs and thus the vasodilation in the coronary microcirculation. Adapted from Muller-Delp [33] and prepared using Servier Medical Art (http://www.servier.com/).

$$R-SH+H_2O_2 \rightarrow R-SOH+H_2O \tag{5}$$

$$R-SOH+RSH \rightarrow R-SS-R+H_2O \tag{6}$$

Furthermore, these modifications in the redox state of the cell may also affect the hyperpolarization mediated by thiol-dependent voltage-dependent K^+ (K_V) channels, which will be further explored in the following subsection [40].

Other metabolic vasodilators may also be involved, such as adenosine (which concentration is dependent on the metabolism) and potassium ions, which will be explored further below.

3.4. Endothelial function

The *endothelial function* plays a crucial role in the vascular physiology, especially in the regulation of the vascular tone. The endothelium is responsible for the production of a number of different vasoactive substances, such as: (a) *endothelium-derived contracting factors* (EDCFs),

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such as endothelin, prostanoids and 20-hydroxyeicosatetraenoic acid (20-HETE) and (b) *endothelium-derived relaxing factors* (EDRFs), such as NO, prostaglandins (e.g. prostacyclin) and EDHFs, for example H_2O_2 and epoxyeicosatrienoic acids (EETs) [35, 41–47].

Vasoconstrictors. The stimulation of receptors in the endothelial cell membrane may trigger the production of several EDCFs, namely prostanoids and endothelin, particularly endothelin-1, among others (**Figure 3**) [35, 41]. The *prostanoids* are vasoactive substances that result from the arachidonic acid pathway. Following the stimulation of specific membrane receptors, such as muscarinic receptors for acetylcholine and purinergic (P_2Y) receptors for adenosine triphosphate (ATP), the increase in intracellular Ca^{2+} promotes the production of arachidonic acid from membrane phospholipids by phospholipase A_2 [41]. The arachidonic acid is then converted by the endothelial cyclooxygenase-1 (COX-1) to endoperoxides and ultimately to prostanoids, namely thromboxane A_2 (TXA_2) and prostaglandins, such as prostacyclin (PGI_2) [41]. Additionally, the COX-1 activity might also promote the production of ROS [41]. Those vasoactive substances (i.e. TXA_2 and prostaglandins) may then diffuse to the smooth muscle layer where they activate thromboxane-prostanoid (TP) receptors, promoting the contraction of the VSMCs [41].

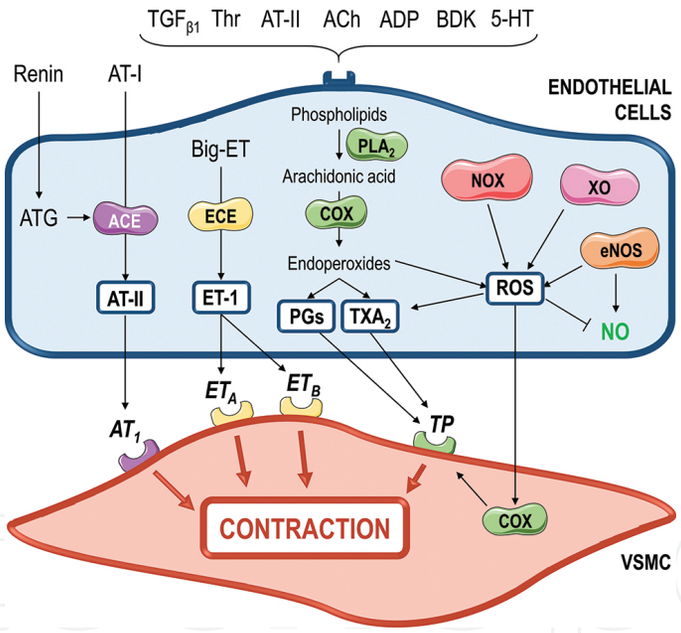

Figure 3. Multitude of pathways involved in the endothelium-dependent contraction. Abbreviations: 5-HT, 5-hydrotryptamine; ACE, angiotensin-converting enzyme; ACh, acetylcholine; ADP, adenosine diphosphate; AT-I, angiotensin-I; AT_1, angiotensin receptor; AT-II, angiotensin-II; ATG, angiotensinogen; BDK, bradykinin; COX, cyclooxygenases; ECE, endothelin-converting enzyme; ET-1, endothelin-1; ET_A, endothelin receptor A; ET_B, endothelin receptor B; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; NOX, NADPH oxidase; PGs, prostaglandins; PLA_2, phospholipase A_2; ROS, reactive oxygen species; $TGF_{\beta1}$, transforming growth factor; Thr, thrombin; TP, thromboxane-prostanoid receptor; TXA_2, thromboxane A_2; VSMC, vascular smooth muscle cell; XO, xanthine oxidase. Adapted from Virdis et al. [49] and prepared using Servier Medical Art (http://www.servier.com/).

Endothelin (ET) is considered a major vasoactive substance in the EDCF family and a major vascular function regulator. In fact, this term refers to a group of peptides synthesized by the

endothelin-converting enzyme (ECE) that may mediate vasoconstriction through the stimulation of receptors, namely ET_A and ET_B receptors, in the VSMC membrane [48, 49]. Among the several peptides, ET-1 is the most known, and its vasoactive properties have been extensively researched. This peptide promotes a long-lasting vasoconstriction essential to the vessel tone control in coronary arterioles, as reduction ET-1 induces an elevation of coronary blood flow in increased demand situations, that is increased metabolism [50, 51].

20-HETE is a metabolite that results from the conversion of arachidonic acid by the 4A and 4F families of cytochrome P450 mono-oxygenases (CYP), particularly in the VSMCs but also in the endothelial cells [35]. This metabolite seems to play an important role in the regulation of the vascular tone, behaving as a potent endogenous vasoconstrictor in several vascular tissues, namely in the brain and in the heart [35, 52].

Vasodilators. NO is the most researched EDRF worldwide and is produced in the endothelial cells by the endothelial nitric oxide synthase (eNOS). This constitutive enzyme converts L-arginine to L-citrulline and requires several cofactors, such as calcium, calmodulin, 3,4-tetrahydrobiopterin (BH_4) and nicotinamide adenine dinucleotide phosphate (NADPH) [53]. The NO-mediated vasodilation primarily involves the conversion of guanosine triphosphate (GTP) to cGMP by soluble guanylyl cyclase (solGC) [34]. However, other mechanisms may also be involved in the NO-mediated vasodilation, namely the hyperpolarization of the VSMCs [34, 54], which will be further explored below. The production of NO may be regulated by several mechanisms, which have been previously explored and published [55]. In addition to the stimulation of receptors on the endothelial cell membrane, the eNOS-mediated production of NO may also be stimulated by shear forces exerted by the blood flow on the vessel wall, as explored further below.

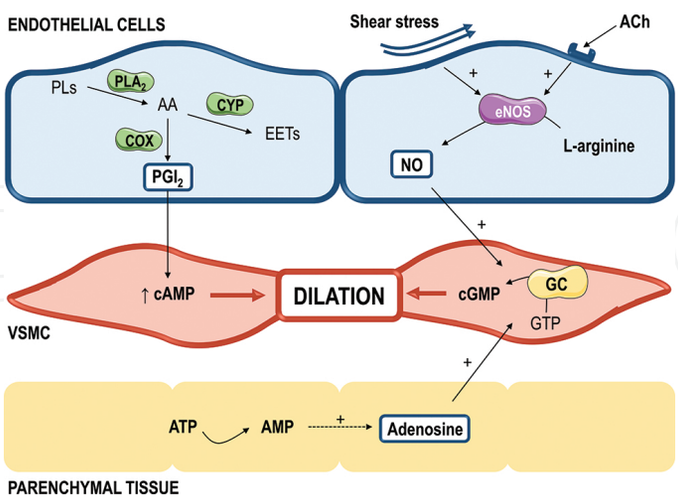

Figure 4. Pathways involved in the endothelium-dependent and endothelium-independent relaxation of the VSMC. Stimulation of the endothelial cells by acetylcholine (ACh) or other agents (e.g. bradykinin and shear stress) results in the formation and release of an EDRF identified as nitric oxide (NO). Substances such as adenosine, nitroprusside (NP), H^+, CO_2 and K^+ can be produced in the parenchymal tissue and elicit vasodilation by direct action on vascular smooth muscle. Adapted from Koeppen et al. [58] and prepared using Servier Medical Art (http://www.servier.com/).

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Although NO is considered the major pathway of endothelium-mediated vasodilation in the systemic circulation, multiple pathways may be involved in this physiological response, such as the prostaglandins-induced vasodilation (**Figure 4**). The *prostaglandins* are constitutively produced by cyclooxygenases (COX) [34]. The main substrate of these enzymes is arachidonic acid, which is converted from diacylglycerol or phospholipids, respectively, by phospholipase A_2 and phospholipase C [34]. Several prostaglandins are produced by COX, although the main vasoactive prostaglandin produced in the endothelium is PGI_2 [35, 56, 57]. Similarly to NO, PGI_2 may diffuse from the endothelial cells to the VSMCs where they activate their (IP) receptors and trigger the conversion of ATP into cyclic adenosine monophosphate (cAMP) by adenylyl cyclase (AC) [34, 57]. This activation promotes the hyperpolarization of the VSMCs and hence the vasodilation [34, 57]. However, these prostaglandins, namely PGI_2, may also elicit vasoconstriction in disease, as previously discussed [35, 41].

Several vasoactive substances have been included in the *EDHFs* family, such as H_2O_2, carbon dioxide (CO_2), hydrogen sulphide (H_2S), C-natriuretic peptide (CNP), EETs, potassium ion (K^+), among others [34, 35, 54, 59]. Previous studies suggested these factors play a key role in the VSMC hyperpolarization in smaller vessels rather than in larger ones [19, 34].

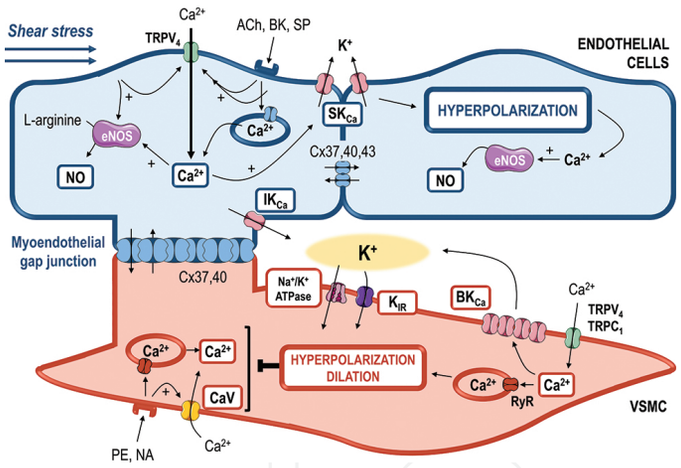

Figure 5. Hyperpolarization of the VSMC. Abbreviations: ACh, acetylcholine; BK, bradykinin; BK_{Ca}, large conductance Ca^{2+}-activated K^+ channels; Ca_V, voltage-activated Ca^{2+} channels; Cx, connexin; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; IK_{Ca}, intermediate conductance Ca^{2+}-activated K^+ channels; K_{IR}, inwardly rectifying K^+ channels; NO, nitric oxide; PE, phenylephrine; RyR, ryanodine receptor; SK_{Ca}, small conductance Ca^{2+}-activated K^+ channels; SP, substance P, TRPC1, transient receptor potential canonical channel 1; TRPV4, transient receptor potential vanilloid channel 4; VSMC, vascular smooth muscle cell. Adapted from Félétou et al. [35] and prepared using Servier Medical Art (http://www.servier.com/).

The hyperpolarization of the VSMC may involve several ionic channels, such as the voltage-activated Ca^{2+} (Ca_V) channels, which regulate the intracellular Ca^{2+} concentration, the K_V channels and the Ca^{2+}-activated K^+ (K_{Ca}) channels [35, 40]. The K_{Ca} channels may be subdivided into small (SK_{Ca} or K_{Ca} 2.3 isoform), intermediate (IK_{Ca} or K_{Ca} 3.1 isoform) and large (BK_{Ca}) conductance Ca^{2+}-activated K^+ channels, which are located in specific cellular and subcellular sites [35]. The hyperpolarization of the VSMCs may be triggered directly, through receptors

on the VSMC membrane, or indirectly, through the hyperpolarization of the endothelial cells [35].

As can be seen in **Figure 5**, the *direct hyperpolarization* may be promoted through the stimulation of BK_{Ca} channels on discrete locations of the VSMC layer, that is smooth muscle plasmerosome, associated with the TRP canonical channel 1 (TRPC1) and the TRP vanilloid channel 4 (TRPV4). These signal complexes promote (a) the influx of Ca^{2+}, which is then stored through ryanodine receptor (RyR) on the endoplasmic reticulum and (b) the efflux of K^+, contributing to the formation of a potassium cloud in the intercellular space, which functions as a negative-feedback mechanism. This ionic cloud may activate inwardly rectifying K^+ (K_{IR}) channels and Na^+/K^+-ATPase promoting the influx of K^+ to the VSMC, thus leading to the hyperpolarization and vasodilation. This hyperpolarization also inhibits the Ca^{2+} influx through Ca_V channels that may be stimulated by the binding of noradrenaline or phenylephrine to the adrenergic receptors on the membrane of VSMCs. The stimulation of these receptors leads to the increase in the intracellular Ca^{2+} concentration triggering the depolarization of the VSMC. Furthermore, this increase in intracellular Ca^{2+} may subsequently activate K_V and BK_{Ca} channels, which then promote the efflux of K^+ ions to the intercellular space, thus controlling the ionic balance and contributing to the formation of the potassium cloud [35, 57].

Moreover, the VSMCs may be *indirectly hyperpolarized* through the hyperpolarization of the endothelial cells [35]. Following activation of endothelial receptors and action of shear stress, the increased intracellular calcium in the endothelial cell triggers the opening of SK_{Ca} (located at the homocellular endothelial gap junctions and caveolin-rich domains) and IK_{Ca} channels (preferentially located at the myoendothelial gap junctions or MEJ) leading to K^+ efflux and consequently to the hyperpolarization of the endothelial cell [35]. In turn, this may ultimately lead to the hyperpolarization of the VSMCs by direct electric coupling through MEJs, which consist of a cell-cell contact resulting from the projection of an endothelial cell or a VSMC through the internal elastic membrane (**Figure 5**) [35, 60]. These contacts are essentially established through connexins (Cx), namely Cx40 and Cx37 [35, 61]. Particularly, at the level of the MEJs, the IK_{Ca} channels may be activated directly or through the generation of Ca^{2+} pulsars, contributing further to the potassium cloud in the intercellular space, eventually promoting the activation of K_{IR} channels and Na^+/K^+-ATPase involved in the hyperpolarization of the VSMCs. The influx of Ca^{2+} from the intercellular space to the VSMC, through Ca_V channels may be detected by Ca^{2+}-sensing receptors (CaSR), which may activate IK1 gene, involved in the hyperpolarization of the VSMC [35, 57].

Besides the hyperpolarization of the VSMCs, the EDHFs, particularly H_2O_2, may also promote vasodilation through other mechanisms, namely by stimulating the production of prostaglandin E_2 in the endothelial cell, thus promoting the endothelium-dependent vasodilation [62].

The relative importance of each pathway is still unestablished, but it has been proposed to depend for example on the activation state of the VSMCs, the density of MEJs and the expression of K_{IR} and Na^+/K^+-ATPase [57].

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3.4.1. Shear stress

As previously mentioned, in addition to the stimulation of receptors on the endothelial cell membrane, other factors may modulate the endothelial function, namely the forces exerted by the blood flow on the vessel wall. There are two major forces: (a) one perpendicular to the wall and (b) another parallel to the wall, known as *wall shear stress* that results from the friction of blood flow on the endothelial cells [63]. These shear forces trigger several pathways, such as (a) production, release and binding of bradykinin to endothelial cell membrane receptors and (b) bradykinin-independent pathways, namely the activation of the Akt phosphorylation pathway and the ROS-mediated hyperpolarization of the VSMC. The production and release of *bradykinin*, which may bind to its G_q-coupled endothelial receptors, increases the activity of eNOS thus promoting the synthesis of NO [64]. The activation of the *Akt phosphorylation* pathway also promotes the production of NO by eNOS [64, 65]. In human coronary arterioles, the shear forces exerted on the vessel wall may also promote the *ROS-mediated hyperpolarization of the VSMC* through two main mechanisms: one involving the EETs and other involving the direct stimulation of ROS production (**Figure 6**). First, the shear stress may induce the production of EETs by triggering the cleavage of arachidonic acid from the cellular membrane by phospholipases. The arachidonic acid then works as a substrate to CYP for the production of EETs, which may activate the $TRPV_4$ channels promoting an increase in intracellular Ca^{2+}, thus stimulating the mitochondrial production of $O_2\cdot^-$. The production of ROS may also result

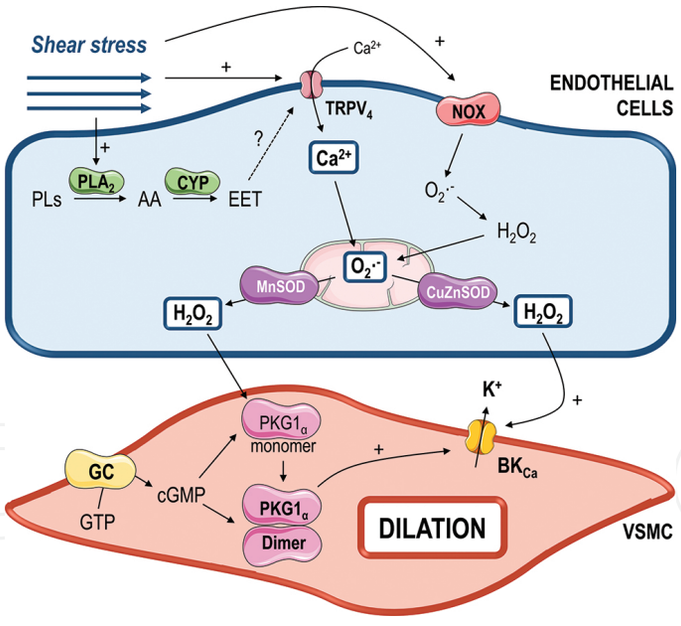

Figure 6. Flow-mediated dilation in the human coronary arterioles. Abbreviations: AA, arachidonic acid; BK_{Ca}, large conductance Ca^{2+}-activated K^+ channels; cGMP, cyclic guanosine monophosphate; CuZnSOD, copper-zinc superoxide dismutase; CYP, cytochrome P450; CYS 42, cysteine residue; EETs, epoxyeicosatrienoic acids; GC, guanylyl cyclase; GTP; guanosine triphosphate; H_2O_2, hydrogen peroxide; K_{Ca}, Ca^{2+}-activated K^+ channels; MnSOD, manganese superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; $O_2\cdot-$, superoxide anion; $PKG1_\alpha$, protein kinase G 1_α; PLA_2, phospholipase A_2; PLs, phospholipids; $TRPV_4$, transient receptor potential vanilloid channel 4. Adapted from Durand et al. [34] and prepared using Servier Medical Art (http://www.servier.com/).

from the direct stimulation of $TRPV_4$ channels and NADPH oxidases. The $O_2{\cdot}^-$ produced through both these mechanisms is then dismutated to H_2O_2, which diffuses to the VSMCs to oxidize cysteine residues of protein kinase G 1_α ($PKG1_\alpha$), activating this enzyme. The activation of this enzyme promotes the opening of BK_{Ca} channels and the hyperpolarization of the VSMCs resulting in vasodilation of coronary arterioles [32, 34, 66, 67].

Previous studies showed the sensitivity to these pathways of vasodilation increases with decreasing vessel diameter thus assuming a particularly important role in the coronary microcirculation [19]. Previous studies have also suggested the relative weight of these pathways changes from childhood to adulthood and between healthy and pathological conditions. In a preliminary study with human-isolated arterioles, Zinkevich et al. [68] proposed the flow-mediated dilation (FMD) in infants was exclusively COX-dependent, that is mediated by prostaglandins, while in adulthood the main pathway involved the NO. However, in the presence of coronary artery disease (CAD), both these mechanisms seem to remain as secondary pathways as the EDHF-mediated vasodilation (especially by H_2O_2) gains importance, serving as backup mechanisms in disease [66]. In fact, low response to shear forces and high mechanical stress seem to predispose to vascular dysfunction and disease [63].

3.4.2. Endothelium-cardiomyocyte interaction

The heart is a highly organized organ where several cells may be found, namely endothelial cells and cardiomyocytes. Therefore, the physiological mechanisms depend on the communication between the several types of cells. Until today, many endothelial-derived cardio-active factors have been identified and characterized (**Figure 7**). The cardiac modulator effects of some of these factors, such as NO, PGI_2, ET-1 and neuregulin-1 (NRG-1), have been previously acknowledged. Other factors, namely Dickkopf-3 (DKK3), periostin, thrombospondin-1 (TSP-1), follistatin (FST), apelin and connective tissue growth factor (CTGF), also appear to

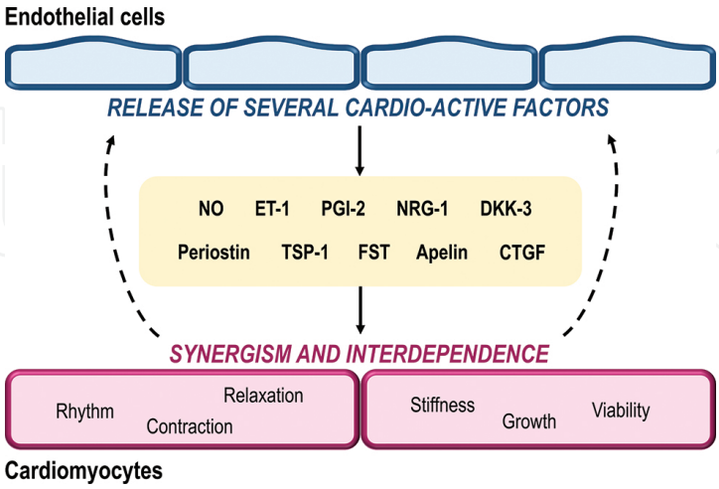

Figure 7. Communication between endothelial cells and cardiomyocytes. Abbreviations: CTGF, connective tissue growth factor; DKK3, Dickkopf-3; ET-1, endothelin; FST, follistatin; NO, nitric oxide; NRG-1, neuregulin-1; PGI-2, prostacyclin; TSP-1, thrombospondin. Adapted from Lim et al. [69].

modulate the cardiomyocyte function, though with little evidence so far. These cardio-active factors seem to be interdependent (additive, synergistic or inhibitory) as their modulator effects may be exerted on the same target cell [69].

3.5. Autonomic innervation and circulating factors

The previously explored pathways are nowadays considered the major pathways of regulation of the vessel tone. However, other mechanisms may also come into play, such as the autonomic nervous system and circulating factors.

The innervation of the coronary circulation by the sympathetic and the parasympathetic divisions of the *autonomic nervous system* have been previously shown [70]. The endothelial production of vasoactive substances, namely NO, may be influenced by the stimulation of specific receptors in the endothelial cell membrane, such as muscarinic receptors for acetylcholine [41, 70]. Furthermore, the coronary circulation may also be regulated through adrenergic receptors (i.e. α- and β-adrenergic receptors) in both the endothelial cell and the VSMC membranes [70]. In general, the stimulation of the α-adrenergic stimulation seems to induce vasoconstriction, with the exception for the α_2 receptors which seem to elicit vasodilation. Moreover, the stimulation of β-adrenergic receptors generally induces vasodilation with β_2 receptors being the main population in the coronary microcirculation [19, 70, 71]. This autonomic innervation provides a mechanism for vessel tone regulation, particularly important during exercise. However, the role of the parasympathetic innervation remains debatable in the human coronary microcirculation [70].

Moreover, several *circulating factors* may also modulate the coronary blood flow through the regulation of the vessel tone, such as angiotensin II and other hormones (e.g. cortisol and tiroxine, among others), adipokines (particularly adiponectin) and growth factors among many others [19, 72].

4. Microcirculation pathophysiology

As previously discussed, the coronary microcirculation plays a key role in the myocardial perfusion. Therefore, the presence of functional and/or structural abnormalities of this circulatory pathway may impair the myocardial perfusion and be involved alone as the main mechanism of myocardial ischaemia. These abnormalities are normally designated as *coronary microvascular dysfunction* (CMD) [3]. The CMD may be assessed by several methods, though one of the most used methods is through the determination of the coronary flow reserve (CFR), which represents an integrated measure of coronary blood flow in both the macro- and microcirculation. The CFR involves the maximal vasodilation of a vessel in response to an endothelium-independent vasodilator, such as adenosine, thus reflecting the ratio of hyperaemic to baseline blood flow. This ratio may be measured through several methods, namely echocardiography and positron emission tomography (PET) [3].

CMD type	Clinical setting	Pathogenic mechanisms
In the absence of myocardial disease or obstructive CAD	Cardiovascular risk factors (e.g. ageing, arterial hypertension, smoking, diabetes) Microvascular angina	Endothelial dysfunction VSMC dysfunction Vascular wall remodeling
In the presence of myocardial disease	Cardiomyopathies (e.g. HCM, DCM) Aortic stenosis	Vascular wall remodeling VSMC dysfunction Extramural compression Luminal obstruction
In the presence of obstructive CAD	Acute coronary syndrome AMI	Endothelial dysfunction VSMC dysfunction Luminal obstruction
Iatrogenic microembolization	Coronary reperfusion procedures (e.g. PCI) Revascularization (i.e. CABG)	Luminal obstruction Autonomic dysfunction

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; PCI, percutaneous coronary intervention; VSMC, vascular smooth muscle cell. Adapted from Crea et al. [20].

Table 1. Classification of CMD according to the involvement of pathogenic mechanisms and the clinical setting.

CMD may present several pathogenic underlying mechanisms, depending on the source of the abnormality, namely structural and functional (**Table 1**), which will be discussed in this section. According to the underlying clinical setting, the CMD may also be classified into four types: type 1, in the absence of cardiomyopathies or obstructive CAD; type 2, in the presence of cardiomyopathies; type 3, in the presence of CAD; and type 4, iatrogenic [3, 20, 73, 74].

4.1. Functional abnormalities

The most common functional abnormalities are the *dysfunction of the endothelial cells and/or the VSMCs*, involving cardiovascular risk factors or cardiomyopathies, and the *autonomic nervous system dysfunction*, secondary to coronary reperfusion procedures.

4.1.1. Endothelial and/or VSMC dysfunction

As presented in **Table 1**, the traditional cardiovascular risk factors (i.e. ageing, gender, obesity, smoking, hypertension, dyslipidaemia and diabetes) may impair the endothelial function by several mechanisms, namely increased production of EDCFs and/or decreased production of EDRFs [3, 73]. Furthermore, this impairment may also contribute to the dysfunction of the VSMCs, which may also result from structural changes, derived from cardiomyopathies or arterial hypertension, described further below.

Ageing is considered as one of the major cardiovascular risk factors that may influence the endothelial function. This influence seems to primarily involve both functional and structural changes, which will be discussed further below [42, 75]. Several mechanisms have been

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identified to mediate these changes and have been previously reviewed [55, 64, 76, 77]. In fact, the imbalance between vasoconstriction and vasodilation seems to be a key mechanism underlying ageing-induced vascular dysfunction.

Gender-associated differences related to hormones (i.e. oestrogens) have been previously described for the vascular reactivity in several vascular beds [42, 65]. The stimulation of G protein-coupled receptors by these hormones seems to promote an increased production of EDRFs, especially NO, which could elucidate the lower incidence of coronary disease and atherosclerosis in premenopausal women compared to men of the same age and postmenopausal women. In fact, impaired expression of eNOS was previously reported in postmenopausal women and suggested as a gender-specific risk factor in coronary surgery [78]. Moreover, Muir et al. [79] also showed differences in the endothelium-dependent vasodilation between males and females. In the coronary circulation, oestrogens seem to promote a decreased vascular tone, which promotes a reduced blood flow resistance and thus a higher coronary blood flow [80].

Obesity has also been considered an important cardiovascular risk factor; thus, a healthy diet and the regular practice of exercise have been proposed as important preventive measures. The influence of obesity in the vasoreactivity involves several mechanisms, namely an impaired regulation of vascular tone, a systemic chronic inflammation, induced by adipokines, which are involved in CMD, an altered lipidic profile (i.e. dyslipidaemia) and increased incidence of atherosclerosis and vascular oxidative stress [55, 80–82].

Cigarette smoking has been widely recognized as a major cardiovascular risk factor that induces endothelial dysfunction. In the peripheral circulation, this effect primarily involves the decreased production of EDRFs, namely NO, mainly through the impairment of eNOS activity [79, 83]. Interestingly, this downregulation of NO-mediated vasodilation seems to be exposure-dependent [84]. The ability to induce endothelial dysfunction may also manifest in the coronary circulation, particularly in long-term smokers, independently of the presence of atherosclerotic plaques [85]. Moreover, Kaufmann et al. [86] found CMD in asymptomatic smokers in the absence of CAD. These patients presented a reduction in 21% of the CFR, which could be restored with the short-term administration of vitamin C. These findings suggested that the smoking-associated CMD may involve an increase in oxidative stress in the coronary microcirculation [86].

Similarly to smoking, *arterial hypertension* is also considered a major cardiovascular risk factor. Previous studies suggested the increased production of EDCFs as the main mechanism underlying the hypertension-induced endothelial dysfunction [41]. This effect is primarily triggered by an increase in intracellular Ca^{2+}, stimulating a higher production of COX-derived prostanoids (e.g. TXA_2 and PGI_2) and ROS, namely $O_2\cdot^-$ [41]. The prostanoids may then diffuse to the VSMCs activating TP receptors, with subsequent influx of Ca^{2+}, creating the conditions to a predominant vasoconstriction [41]. The ROS may also influence the vascular function since they may react with NO, reducing its availability, or even stimulate the influx of Ca^{2+} [41].

The vascular effects of *dyslipidaemia*, namely hypercholesterolaemia, are dependent on the degree of atherogenesis. In fact, the accumulation and oxidation of low-density lipoproteins

(LDLs) are considered major steps in the development of the chronic inflammatory process that is atherosclerosis [87]. The accumulation of LDL in the subendothelial matrix depends on the circulating LDL levels as the LDLs diffuse from the lumen to the vessel wall through endothelial cell junctions [87]. Once in the subendothelial matrix, the LDLs may undergo oxidation by reacting with endothelium-derived ROS, producing oxidized LDLs [87]. These proinflammatory factors may mediate several effects on the vessel wall, mainly the impairment of NO-mediated vasodilation and the atherogenesis [64]. In fact, oxidized LDLs may (a) trigger the influx of asymmetric dimethyl-L-arginine (ADMA), which is a competitor substrate for eNOS, (b) downregulate the NO production through the Rho kinase and protein kinase C pathways and (c) promote the uncoupling of eNOS by upregulating the NADPH oxidase production of ROS [64]. Previous studies in the human coronary circulation have revealed a reduced CFR in asymptomatic patients with hypercholesterolaemia, which seems to be reversible with a cholesterol-lowering therapy [88–91].

Diabetes is a known cardiovascular risk factor responsible for several effects on the cardiac and peripheral vascular systems, which intermediate an increased morbidity and mortality [92]. In spite of the array of mechanisms involved, the relation between diabetes and CMD is not yet fully understood [93]. Previous studies suggested several mechanisms involved in the diabetes-induced vascular dysfunction, namely (a) impaired production of NO, due to BH_4 deficiency, increased arginase activity, increased ADMA influx or downregulation of the Akt phosphorylation pathway; (b) increased production of EDCFs, namely endothelin; and (c) other NO-independent mechanisms, such as hyperglycaemia [55]. Chronic hyperglycaemia has been previously suggested to play a key role in the diabetes-related CMD, as several mechanisms may be involved [55], namely the endothelial-protein glycation through the formation of advanced glycation end-products (AGEs) and subsequent stimulation of the respective receptors (RAGE). In fact, previous studies suggested that diabetic patients (both type 1 and type 2) present a marked reduction in the endothelium-dependent and endothelium-independent coronary vasodilation [94].

The impairment of the vasodilator response of the coronary microcirculation may also be present in patients with angina-like chest pain but without evidence of obstructive CAD or myocardial disease. This situation is usually known as *microvascular angina* or *coronary syndrome X*. The literature seems to be contradictory as some studies suggest no changes in the coronary blood flow and in the CFR [73], while others showed the presence of CMD through impairment of the endothelium-dependent and endothelium-independent vasodilation [95], reduction in the coronary blood flow and CFR [96] and evidence of myocardial ischaemia [97, 98]. However, the precise pathogenic mechanisms involved in these changes are not yet completely understood as this situation seems to be multifactorial [99].

4.1.2. Autonomic nervous system dysfunction

The autonomic nervous system dysfunction, following acute myocardial infarction (AMI) and/or coronary reperfusion procedures, may also contribute to the CMD. In fact, increased coronary vasoconstriction has been previously shown, after AMI and successful percutaneous

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coronary angioplasty, both at the site of stenosis and distal to it, suggesting abnormal coronary vasodilator response [73, 100].

After AMI, the CMD may result from autonomic dysfunction and luminal obstruction, discussed further below. The autonomic dysfunction in the AMI-associated CMD involves increased sympathetic activation with increased vasoconstriction. These findings were confirmed by Gregorini et al. [101], who showed this impaired autonomic function might be reverted with α-blockers, such as phentolamine (nonselective α-blocker) and urapidil (α_1-selective blocker), which may improve the recovery of myocardial perfusion after coronary stenting in patients with AMI [101–103]. Autonomic dysfunction secondary to percutaneous coronary angioplasty was also showed by Gregorini et al. [104] who linked the left ventricular macro- and microcirculatory dysfunction in patients with transient ischaemia. In this study, phentolamine and urapidil were similarly used to block the α-adrenergic neurotransmission and propranolol (nonselective β-blocker) and the β-adrenergic neurotransmission, and the results showed that the increased coronary vasoconstriction, secondary to percutaneous coronary angioplasty, may be prevented with α-adrenergic receptor antagonists as no effect was demonstrated for the β-adrenergic blockade. Moreover, this study suggested that CFR may still be decreased for 7 days to 3 months after the procedure [104]. In a similar study, Kozàkovà et al. [105] confirmed the potential usefulness of urapidil to improve the left ventricular function in the angioplasty follow-up. Moreover, persistent yet reversible CMD after coronary revascularization was also previously showed [106].

4.2. Structural abnormalities

In addition to functional abnormalities, structural abnormalities, namely vascular remodelling, vascular rarefaction, perivascular fibrosis, luminal obstruction and infiltration of the myocardium and vascular wall, may also contribute to CMD [3, 73].

4.2.1. Vascular wall remodelling

The remodelling of the vessel wall involves persistent modifications which may result from several *remodelling signals*, such as (a) the wall shear stress (which mechanisms have been previously discussed), (b) the circumferential wall stress (resulting from the stretch of the smooth muscle layer) and (c) specific metabolic signals [19, 107]. As mentioned above, the physiologic metabolic control of coronary blood flow mainly involves CO_2 and ROS. In a pathological setting (i.e. myocardial ischaemia) however, the metabolic control may involve several mediators, such as oxygen, adenosine, prostaglandins, nitric oxide and protons [28]. In the presence of myocardial ischaemia, the decreased pO_2 is detected by (a) the cardiomyocytes triggering the production of adenosine (which promotes the VSMC hyperpolarization through its receptors A_{2A} and A_{2B}) and NO, by (b) the endothelium, inducing the production of prostaglandins and by (c) the VSMCs, where K_{ATP} and Ca_V channels are activated leading to the hyperpolarization of these cells and to the vasodilation [28]. These remodelling signals promote, on one hand, the increase in the *luminal diameter* and, on the other hand, the *VSMC plasticity* and *matrix remodelling*, inducing the wall thickening [19, 108]. However, in the

presence of certain factors, such as ageing, arterial hypertension and cardiomyopathies, these mechanisms of adaptation may be impaired leading to pathogenic changes.

In addition to the functional changes, *ageing* may induce these structural modifications, namely the proliferation of VSMCs and increase the inflammation status in the vascular wall, which is linked to atherogenesis, leading to the remodelling of the vessel wall and to the decrease in the luminal diameter [75].

Other situations may also contribute to the vascular remodelling, especially arterial hypertension and cardiomyopathies. Previous studies have suggested that *arterial hypertension* may promote the thickening of the smooth muscle layer, by stimulating the proliferation of VSMCs and collagen fibres [3, 73].

Furthermore, *cardiomyopathies* (especially hypertrophic cardiomyopathy) may also contribute to the vascular remodelling. According to Maron et al. [109], "cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability". The cardiomyopathies are usually classified into primary and secondary, based on the American Heart Association classification [109]. On the basis of the management of cardiomyopathy with a morphofunctional phenotype, the European Society of Cardiology proposed in 2008 the classification of cardiomyopathies into the hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhytmogenic right ventricular (ARVC) and unclassified varieties [110]. Each of these groups was subdivided into familial or genetic and nonfamilial or nongenetic forms [110]. In 2014, another classification was proposed by the World Heart Federation, involving a descriptive genotype-phenotype nosology system, the MOGE(S) classification [111]. Vascular remodelling in coronary arterioles has been previously associated with both HCM and DCM [73]. Similarly to arterial hypertension, the remodelling of these vessels also involves the thickening of both the smooth muscle layer and the intimal layer. These morphological changes may contribute to the CMD associated with HCM, as patients with this cardiomyopathy showed a marked decrease in vasodilator response in the endocardium, proportional to the degree of hypertrophy [3, 73]. Relatively to DCM, the degree of CMD may be considered an independent prognostic factor for cardiac events [73, 112, 113].

4.2.2. Vascular rarefaction and perivascular fibrosis

The coronary microvascular function may also be influenced by modifications in the vascular density, particularly by vascular rarefaction, that is the reduction in the number of microcirculatory vessels, which may also be recognized as hypotrophic remodelling [19]. The presence of arterial hypertension and the extravascular compression, observed in aortic stenosis and cardiomyopathies, induces vascular rarefaction leading to the reduction in the CFR. In addition to the vascular rarefaction, both situations may also induce perivascular fibrosis promoting structural modifications of the vessel wall [73, 114].

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4.2.3. Luminal obstruction

CMD may also be characterized by luminal obstruction originated from (a) obstructive CAD or (b) iatrogenic microembolization [73].

According to the mechanisms underlying the associated CMD as well as the clinical findings, the *obstructive CAD* may be divided into stable CAD, unstable CAD and AMI [73]. Changes in the CFR were previously showed in patients with both stable CAD and acute coronary syndromes.

In patients with *stable CAD*, the CMD distal to a coronary stenosis seems to be triggered through two main pathways: (a) increased prearteriolar and arteriolar constriction, increasing the blood flow resistance and decreasing the myocardial perfusion and (b) impaired prearteriolar dilation in the presence of increased myocardial oxygen demands [73]. Although in the presence of coronary stenosis (for example during exercise), the transmural myocardial perfusion tends to be redistributed, with an increase in the subendocardial perfusion. The impairment of this mechanism in patients with stable CAD may lead to increased microvascular vasoconstriction, which might promote a critical stenosis and thus capillary derecruitment distal to the stenosis, ultimately contributing to CMD [73].

Similarly to stable CAD, *unstable CAD* (i.e. acute coronary syndromes without ST-segment elevation) may also involve a CMD distal to a critical stenosis which might play a role in the severity of the myocardial ischaemia. In addition to the mechanisms described for stable CAD, this type of acute coronary syndromes also involves other mechanisms, such as thrombogenesis [73]. In fact, Marzilli et al. [115] suggested that the blockade of the platelet glycoprotein IIb/IIIa receptor with abciximab might improve the microvascular function in patients with unstable CAD. Moreover, the inflammation status may also come into play as suggested by previous studies that showed a direct relation between CMD and the systemic levels of C-reactive protein, a marker of inflammation independent of the cardiovascular risk factors [116, 117]. Both of these factors may contribute to the luminal obstruction observed in patients with unstable CAD.

Luminal obstruction is a key characteristic of the *AMI*. Early after a myocardial infarction, patients may present a marked reduction in the CFR that could significantly impair the contractility of the myocardium in the infarction region [73]. In addition to the autonomic dysfunction (previously explored), this impaired myocardial contractility might also be reverted with α-blockers [73, 101]. Even after reperfusion procedures, the CMD involving luminal obstruction in the stenotic and poststenotic areas may be responsible for the failure of the reperfusion, situation usually known as *"no-reflow" phenomenon*. This phenomenon is characterized by the lack of morphological and functional integrity in the microcirculation, in spite of successful reperfusion procedures [12, 73, 118, 119] and is associated with clinically significant decreased prognosis. The pathogenesis of the "no-reflow" phenomenon seems to be multifactorial; thus, a classification has been previously proposed which divides this phenomenon into (a) structural and (b) functional types. The structural type involves irreversible changes in the wall of the microvessels, while the functional type includes morphologically intact yet functionally compromised microvessels. The functional changes include

impairment of the endothelium-dependent vasodilation, autonomic nervous system dysfunction and extravascular compression due to interstitial oedema, among others [73, 120, 121]. Recently, O'Farrell et al. [12] proposed a key role of pericytes in the pathogenesis of this phenomenon (**Figure 8**), suggesting that these cells irreversibly constrict the coronary microcirculation impeding the adequate reperfusion after AMI.

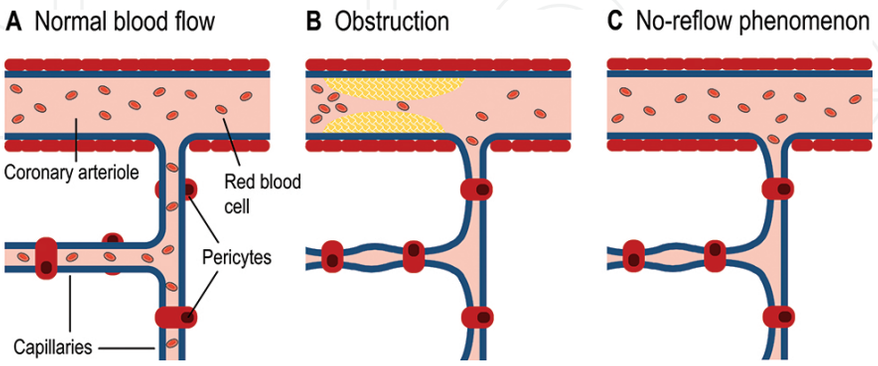

Figure 8. Role of pericytes in healthy and ischaemic microvessels: (a) normal blood flow in coronary arterioles and capillaries covered with pericytes; (b) in ischaemia, the pericytes may constrict the coronary microcirculation compromising the coronary blood flow and leading to coronary microvascular dysfunction; (c) after reperfusion procedures, the coronary microvascular dysfunction may block the re-establishment of the normal blood flow, situation usually known as no-reflow phenomenon.

As previously mentioned, CMD may also be originated from *iatrogenic microembolization* after coronary reperfusion procedures or coronary artery bypass grafting. During or after these procedures, plaque rupture may occur thus releasing plaque content into the blood which in turn might lead to luminal obstruction in the microcirculation [73].

4.2.4. Vascular wall infiltration

In addition to the previous explored structural changes, the infiltration of the vessel wall with metabolic deposits may also be found. This infiltration is commonly found in infiltrative diseases, such as Anderson-Fabry disease and other metabolic disorders. The Anderson-Fabry disease involves a genetically linked (X chromosome) deficiency of lysosomal α-galactosidase A, which leads to damages in several organs, namely the heart, through the deposition of glycosphingolipid in cardiomyocytes and in the vascular wall [73]. In turn, this infiltration promotes the hypertrophy and fibrosis of cardiomyocytes as well as CMD and perivascular fibrosis [73]. In fact, Elliott et al. [122] demonstrated these patients present a marked decrease in CFR, confirming the presence of CMD in the pathogenesis of the cardiomyopathy induced by this disease.

5. Conclusions

This review provides an insight on the morphology, physiology and pathophysiology of the cardiac microcirculation. As discussed, the heart is one of the most nutrient and oxygen

demanding organs as this demand needs to be satisfied with an adequate vascularization of the myocardium through an extensive macro- and microvascular network. Although most of the cardiac diseases, such as the acute coronary syndrome, are commonly associated with the coronary macrocirculation (i.e. epicardial coronary arteries), the coronary microcirculation also seems to play a key role in the coronary pathophysiology. This role involves both molecular and clinical aspects that should not be overlooked and that constitute potential diagnostic and therapeutic targets, particularly important in the early pathogenesis of these diseases.

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