Mechanisms of Endothelial Dysfunction and Cardiovascular System Adaptation

Alterations in cardiovascular (CV) system function contribute to the aetiology of CV disease (CVD) and the diminished capacity of adaptation to extreme environments, such as high altitude, hypoxia, or even intense physical activity. Endothelial dysfunction is characteristic of CVD, heart and blood vessel disorders with multifactorial causes, leading to coronary, cerebrovascular, peripheral arterial or congenital heart disease, among other complications, and its association with a diversity of factors is well documented [1].

The search for therapeutic strategies that preserve, protect and improve endothelial function is highly relevant in pathological conditions, including diabetes mellitus, diabetes in pregnancy, atherosclerosis, and hypertension. Several signalling mechanisms are involved in cardiovascular adaptation and function. These mechanisms include hormones, oxidative stress, specific molecules involved in cell homeostasis, heat-shock proteins, plasma membrane channels, and G-protein coupled receptors, among others. Other factors include those causing endothelial dysfunction altering angiogenesis and revascularization, post-ischemic injury, and hyperglycaemia [2]. The contributions published in this special issue consider mechanisms at a systemic and cellular level, addressing the CV system’s capacity to maintain its function.

CONTRIBUTIONS TO THIS ISSUE

This special issue includes selected contributions by researchers in the field of the CV system and its adaptation to different pathological conditions associated with alterations in the vascular response and endothelial function. The review by García et al. [3] addresses inflammation as a key and generalised phenomenon in CVD. Inflammation is also associated with vascular endothelial dysfunction in patients with diabetes mellitus, gestational diabetes, obesity, and hypertension, where CVD is highly prevalent. The authors of this review highlight the fact that approaches, such as antiplatelet, lipid-lowering, and antihypertensive therapies, have been implemented to prevent CV events. However, it is yet unclear whether the beneficial effect of applying these therapies was due to preventing or alleviating the CVD-associated inflammatory response. This review summarises the literature regarding the risk factors for developing CVD associated with endothelial cell dysfunction in hypertension (e.g. nitric oxide (NO), angiotensin II, oxidative stress, increased cytokines secretion, and upregulation of vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1)), obesity (e.g. higher level of tumour necrosis factor-α, interleukin-6 (IL-6), and leptin, and lower level of adiponectin), and diabetes mellitus (e.g. higher expression and maximal transport capacity, maximal transport velocity/Michaelis-Menten parameter ratio, $V_{\text{max}}/K_m$ [4], of sodium-glucose cotransporter 2 and a higher level of IL-6). The potential sequence of events from blood vessel inflammation resulting in CVD is depicted in Fig. (2) of this review.

The potential role in the vasculature of an anti-inflammatory cytokine, IL-10, is proposed in the review by Freitas et al. [5]. They describe the benefits of increasing the level of IL-10 in terms of alleviating inflammation and hypertension. The authors referred to the effects of IL-10 on vascular tone, providing detailed information regarding the intracellular pathways induced by this cytokine. One of the critical mechanisms addressed in this review is the potential action of IL-10 as an anti-inflammatory cytokine by inducing the expression of the suppressor of cytokine signalling-3, a negative regulator of cytokine signalling by inhibiting the Janus kinase-signal transducer and activator of transcription pathways [6], to block the IL-6 pro-inflammatory action (depicted in Fig. (1) of their review). Interestingly, it is reported that overexpression of IL-10 is associated with the generalised inflammatory response seen in the fetoplacental circulation in women with gestational diabetes mellitus (GDM) [7]. The inflammatory response seen in the fetoplacental vascular endothelium from women with pre-pregnancy obesity that developed GDM, i.e. gestational diabetes [8], is likely lowered by the diminished IL-10 release following activation of $A_2\alpha$ adenosine receptors by adenosine in the human vasculature [7]. Thus, mechanisms counteracting the importance of the equilibrium between the pro-inflammatory and anti-inflammatory responses in vascular endothelial cells are highlighted.

IL-10 may also result in vasodilation by lowering the expression of mitogen-activated protein kinases (MAPK), thus reducing the vasoconstriction caused, for example, by endothelin-1 [9] or angiotensin II [10]. A well-described synopsis of the therapeutic implications of IL-10 on vascular dysfunction is shown in Table 1 in this contribution, highlighting outcomes and intracellular mechanisms. The review summarises reports on human and animal models’ most significant physiological implications. The authors emphasise that several studies aimed at modulating the expression and biological actions of IL-10 as a strategy for preventing or treating vascular and inflammatory diseases in humans.

Adipokines and myokines play critical roles in attenuating CVD events associated with inflammation. The review by Luna-Cerón et al. [11] suggests that irisin, a cytokine considered an adipo-myokine released by the skeletal muscle cells and adipocytes [12], may protect against the deleterious effects of CVD. The authors show that clinical studies refer to this molecule as playing a dual role, i.e., increasing or reducing atherosclerosis. However, irisin-associated effects modulating metabolic and cell signalling mechanisms in the vascular endothelium are not well known. Along the few clinical studies on irisin and endothelial function are those describing a positive correlation between the plasma level of this molecule and CVD risk and systolic and diastolic blood pressure (Table 1 in this review).

On the other hand, a negative correlation of plasma irisin level was found for carotid intima-media thickness. However, the clinical studies demonstrated results for relatively few numbers of subjects (17-810 subjects) and with different health statuses (patients studied had metabolic syndrome, acute ischemic stroke, coronary artery disease, obesity, or even children with obesity or type 2 dia-
betes mellitus (T2DM)). The latter raises the question of whether the irisin biological actions (positive or negative) will be homogeneous in patients with similar health status, age, sex, and other characteristics.

Fig. (1). Cardiovascular disease (CVD) and endothelial function. CVD is characterised by generalised inflammation with a dysregulation of the interleukin 6 (IL-6) and 10 (IL-10) ratio (high IL-6, low IL-10), impacting endothelial cell function in the blood vessels. The vascular endothelium shows reduced (red arrows) generation of nitric oxide, resulting in cerebrovascular dysfunction and pulmonary hypertension, and may relate to ageing-associated inflammation (Inflammating “Inflamm-ageing”). Hypoxia and ischaemia/reperfusion injury also results in reduced nitric oxide generation. The brain may be protected by glycine. Improving endothelial function in CVD-associated inflammation may result in restoring nitric oxide generation (green arrows) due to, among others, elevated levels of Irisin, which is released by adipose and skeletal muscle tissues. Also, intermittent fasting may restore the regular release of nitric oxide by reducing inflammation protecting against cardiac diseases and improving myocardial circulation. The numbers in square brackets refer to contributions in this issue. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

This review also shows the limited literature addressing cell signalling mechanisms involved in the biological actions of adipokines. However, even when there is no clear proposal about the irisin receptor(s) in human tissues, a member of the integrin heterodimer αVβ5 family has been proposed. Activating these proteins by irisin may increase NO generation, likely because of increased calcium entry due to the activation of vanilloid transient receptor potential calcium channels. Irisin also activates MAPK, which may result in increased angiogenesis mediated by miRNA126-5p and reduced inflammation by inhibiting the activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB). The latter limits the expression of VCAM-1 and ICAM-1. In the general conclusion, the authors suggest that the role of irisin in causing endothelial damage is unclear regarding the cell signalling mechanisms described in clinical (and pre-clinical) studies.

Hypoxia causes several alterations in tissues and organs, including the human vasculature. Reduced synthesis of vasodilators, such as NO, is reported in response to low oxygen levels [13, 14]. Reduced oxygen delivery from the placental circulation to the fetus is associated with intrauterine growth restriction, likely due to a reduced NO synthesis and uptake of the endogenous nucleoside adenosine by the human umbilical vein endothelium [15]. Therefore, hypoxia is a crucial regulator of human vascular tone and endothelial function.

The contribution by Castillo-Galán et al. [16] summarises the findings addressing intermittent hypoxia as a factor causing hypertension in the lung. Intermittent hypoxia is an alteration that, when recurrent, such as in obstructive sleep apnoea in humans, may result in pulmonary hypertension. In this review, the contribution of stromal interaction molecule (STIM)-activated transient receptor potential channels (TRPC) and calcium release-activated calcium channel protein (ORAI) channels (STOC) to intermittent hypoxia-induced pulmonary hypertension is discussed. However, the latter is a less clear phenomenon in clinical studies. It is proposed that oxidative stress and hypoxia-inducible factors are overexpressed by intermittent hypoxia involving the activation of the channels mentioned above. This review highlights findings that intermittent or sustained hypoxia may result in the upregulation of different genes associated with the development and progression of pulmonary hypertension.

Tissues targeted by a reduced blood flow may present a degree of hypoxia. If the oxygen level is re-established, several signaling mechanisms are triggered, i.e., the ischaemia/reperfusion response. This response results in microvascular endothelial dysfunction linked to clinical manifestations, such as cerebral dysfunction, acute heart failure, systemic inflammatory response syndrome, and multiple organ dysfunction syndromes [17].

The review by Valdés-Jorquera et al. [18] addresses the potential role of the non-essential amino acid glycine as protective of vascular endothelial dysfunction caused by ischaemia/reperfusion injury. The mechanisms considered in this review include glycine activation of glycine receptors, likely the homopentamer glycine receptor α2, whose expression seems to be induced by glycine in the cerebrovascular endothelium. Glycine receptors are also discussed in terms of increasing mitochondrial activity favouring angiogenesis and endothelial cell survival as a protective role in ischaemia/reperfusion injury.
The contribution by Garza-González et al. [19] covered whether alterations in the regular pattern of food consumption are associated with CVD and related conditions, such as obesity, insulin resistance, and T2DM. Their review shows evidence that intermittent fasting protects against the development of heart failure and other CVD. Ketone bodies regulate the expression of oxidative stress protection-associated genes, lipid metabolism, and glucose metabolic rate. The authors also discussed the involvement of signalling molecules, such as protein kinase B/Akt and vascular endothelial growth factor, molecules that activate the endothelial NO synthase [20], in modulating angiogenesis in pre-clinical studies performed on heart failure-induced experimental animals.

The contribution by Howlett et al. [21] refers to the effect of ageing as a cause of changes in the heart’s structure and vasculature, leading to an increased incidence of CVD. The authors described a series of factors or conditions that associate CVD with ageing, which could be modified to reduce the incidence of these alterations. Cardiac hypertrophy linked to deficient intracellular calcium handling is proposed to result from the activation of calcium/calmodulin-dependent protein kinase II and the renin-angiotensin-aldosterone system pathway. This review also mentioned endothelial dysfunction as an alteration associated with ageing due to the loss of endothelial-dependent vasodilation. The latter is proposed to result from a reduction in NO generation and higher oxidative stress. Several other mechanisms are discussed regarding the effect of ageing in the adventitia, vascular media, intima, and endothelial layer, highlighting the involvement of inflammation, extracellular matrix remodelling, calcification, and vascular smooth muscle contraction. Different pharmacological agents and their potential effects on vasculature are also included in their review. The potential role of metformin, resveratrol, beta-blockers, and angiotensin-converting enzyme inhibitors are also discussed in terms of their anti-ageing effect, thus resulting in CV protective actions. Interestingly, exercise training is proposed as a condition that may decrease age-related CVD, impacting an apparent ‘rejuvenation’ of cardiac and vascular function. However, the mechanisms explaining this potential phenomenon are yet unknown. It is unclear if high physical activity-associated tissue transient hypoxia or modulation of vascular reactivity by vascular tone regulators, such as adenosine, is involved.

Hypoxia may also result in restricting venous outflow in humans. The effect of hypobaric hypoxia is addressed in the original contribution by Alcantara-Zapata et al. [22]. Hypobaric hypoxia was the environmental condition to which 492 Chilean miners were exposed at different altitudes (up to ~4000 m) in the Chilean Andes. The authors studied whether exposure to hypobaric hypoxia at high altitude was the cause of varicocele, venous congestion due to poorly functioning valves at the pampiniform plexus in humans. This study showed that high altitude was associated with a 4-fold increase in the positive cases found in these subjects compared to miners at low altitude (800-2370 m). Therefore, the reduced adequate amount of oxygen in the air (hypoxia) at high altitude (hypobaric) to which the subjects of this study were exposed may have reached only ~12.5% oxygen (~40% reduced from sea level) compared to the individuals kept at low altitude (~19-16% oxygen, ~9-23% reduced from sea level). Therefore, hypoxia may favour the characteristic abnormal venous response seen in subjects with varicocele.

FINAL THOUGHTS

This special issue highlights recent work addressing mechanisms involved in the alterations of the CV system and the potential role of the vascular endothelium in this phenomenon. CVD is associated with different systemic and local modifications due to a generalized inflammation, which has been demonstrated in other metabolic diseases linked to CVD, such as obesity and diabetes mellitus. Along with the involvement of the pro-inflammatory IL-6 and the anti-inflammatory IL-10 cytokines, it is clear that NO generation and its bioavailability are reduced in CVD-affected tissues. A greater generation of free radicals and their potential effects as NO scavengers is a possible mechanism altered in vascular endothelium, leading to a higher risk of developing CVD.

Other mechanisms include the potential role of molecules, such as irisin, that may protect the damaged endothelium in CVD, reducing, for example, the risk of developing atherosclerosis. Other conditions, such as intermittent or sustained hypoxia and ischaemia/reperfusion injury, are also associated with an increased risk of developing CVD. Hypoxia and ischaemia/reperfusion induce the expression of a battery of genes associated with protecting the lung vasculature, leading to decreased pulmonary hypertension. Ischaemia/reperfusion injury is also counteracted by activating glycine receptors in the brain. Glycine acting on glycine receptors may have a protective effect in the brain by increasing mitochondria activity-dependent angiogenesis.

The risk of developing CVD also includes lifestyle in terms of the regular feeding patterns. Intermittent fasting may be beneficial against heart failure, with ketone bodies playing a vital role in this potential protective mechanism. However, these mechanisms may be bypassed or worsened when getting older. Ageing is a substantial risk factor for CVD leading, for example, to cardiac hypertrophy and endothelial dysfunction likely associated with reduced NO generation and increased oxidative stress.

Specific pathologies may be associated with hypoxia, including varicocele, as reported in a group of subjects exposed to environmental very high altitude-associated hypoxia. Thus, hypoxia results in vascular endothelial dysfunction and a higher risk of CVD. Ageing is a natural phenomenon that results in or from inflammaging (or “inflamm-ageing”). The latter is a concept proposed early in the 2000s, essentially referring to the low-grade, chronic inflammation seen in ageing [23]. Several studies to understand the mechanisms associated with this phenomenon are now available. Interestingly, some of these studies aim for “rejuvenation”, if possible, of the vascular endothelium and cardiac and other vascular beds in the human body. Thus, reducing the risk factors for developing inflammation might result in better control of CVD prevalence with a potentially positive outcome for inflamm-ageing.

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CONFLICT OF INTEREST

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