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Chapter

Intermittent Hypoxia and Obstructive Sleep Apnea: Mechanisms, Interindividual Responses and Clinical Insights

Lena Lavie

Abstract

Obstructive sleep apnea (OSA), a nightly respiratory condition, is characterized by recurrent upper airway collapse causing intermittent hypoxia (IH) resembling ischemia and reperfusion (I/R). Consequently, blood oxygenation levels are cyclically reduced; sleep fragmentation and sympathetic activation develop, thus invoking oxidative stress and inflammation. OSA is a major risk factor for cardio-/cerebrovascular morbidity and mortality. However, not all OSA patients develop cardio-/cerebrovascular disease, even if suffering from similar OSA severity. Possibly, this results from interindividual differences in responses to a given hypoxic stimulus involving gene polymorphism in oxygen-regulated transcription factors and downstream genes. The current review is aimed at highlighting potentially protective mechanisms induced by IH and OSA, rather than its well-established deleterious effects, while focusing on acute coronary syndromes. Therefore, protective mechanisms revealed in I/R biology and exhibited in vitro and in animal models utilizing IH followed by a severe ischemia are discussed and linked to acute myocardial infarction patients with concomitant OSA. The roles of endothelial progenitor cells, their proliferative and angiogenic properties, and collateral formation are emphasized in the clinical setting, as well as heterogenic interindividual responses to identical hypoxic stimuli. These findings might represent potential predictors to cardio-/cerebrovascular health, by identifying patients at higher or lower cardiovascular risk.

Keywords: intermittent hypoxia, hypoxia, endothelial progenitor cells (EPCs), endothelial cell colony-forming units (EC-CFUs), endothelial tube formation, hypoxia-inducible factor (HIF)-1α, vascular endothelial growth factor (VEGF), coronary collaterals

1. Introduction

Obstructive sleep apnea (OSA) is a nightly respiratory condition characterized by recurrent oropharyngeal upper airway collapse during sleep leading to multiple cycles of hypoxic episodes followed by blood reoxygenation. While blocking the respiratory system in OSA provokes hypoxic events, resuming respiration induces the reoxygenation phase. This intermittent respiration results in multiple cycles of

hypoxia and reoxygenation throughout the night which are termed intermittent hypoxia (IH). This intermittent respiration directly affects blood oxygenation/deoxygenation levels altering physiological biochemical and molecular pathways [1].

The significance of OSA to human health stems from its high prevalence worldwide, the complaints regarding the quality of life, and the association with cardiovascular and other comorbidities. It is identified by a loud and intermittent snoring, excessive daytime sleepiness, and polysomnographic respiratory findings. In the general population with classical complaints, as loud snoring and excessive daytime sleepiness, OSA affects 4 and 2% of adult men and women particularly after menopause, respectively. However, these values are much higher in the general population not having the classical complaints and are estimated to be as high as 24% in men and 9% in women. Moreover, in selected populations like the obese and the elderly, this value may rise up to 60% [1, 2]. Moreover, OSA is a well-established cardiovascular and cerebrovascular risk. It is currently implicated in the etiopathogenesis of cardiovascular comorbidities, arrhythmias, congestive heart failure, hypertension, atherosclerosis, and stroke [1].

Intermittent hypoxia is in fact the hallmark of OSA. Consequently, many physiological, cellular, and biochemical alternations occur due to the cyclically reduced blood oxygenation levels, sleep becomes fragmented, and sympathetic nerve activity develops [3]. The severity of the IH and the hypoxemia in OSA are determined by the number of the hypoxic events per hour of sleep, termed Apnea-Hypopnea Index (AHI). It mostly ranges from a cutoff point of 10 events per hour of sleep for normal breathing to mild (11–20), moderate (21–30), and severe OSA (>30 events per hour of sleep). In severe patients, blood oxygenation levels can intermittently drop to as low as 60%.

Events of IH in OSA and in animal models treated with IH were shown to elicit cell and tissue injury by increasing the formation of reactive oxygen species (ROS) and promoting inflammatory pathways. Both oxidative stress and inflammation are fundamental mechanisms in various pathologies, inducing vascular dysfunction, transcriptional reprograming, inflammation, and innate and adaptive immune activation, all of which are contributors of morbidity and mortality in a vast array of cardiovascular and other morbidities [4]. This sequence of events initiated by IH is illustrated in **Figure 1**, which was adapted from Lavie [3] and published by Levy et al. [1].

To date, the deleterious effects of OSA and IH on the cardio-/cerebrovascular system are well established, many of which result from the IH-associated oxidative stress, systemic inflammation, and sympathetic nerve activation. These fundamental components are largely responsible for inducing endothelial dysfunction and vascular comorbidities in these patients [1, 3]. Specifically, IH was shown to induce activation of various leukocyte subpopulations, by increasing their ROS and inflammatory cytokine production. Moreover, increased expression of adhesion molecules, increased avidly of OSA monocytes to endothelial cells, inhibition of neutrophil apoptosis, and increased cytotoxicity of CD8+ T lymphocytes and γδ T cells toward endothelial cells were also shown to contribute to endothelial cell damage, as illustrated in **Figure 1** [3, 5–7]. Thus, the multiple cycles of IH in OSA have been shown to resemble mechanisms of ischemia and reperfusion (I/R) injury by eliciting similar fundamental mechanisms, including increased ROS production, activated leukocytes, inflammation, transcriptional reprograming, and vascular dysfunction [5, 6, 8].

Importantly, although the most prominent and notable effects of I/R reveal tissue and organ injury leading to cardiovascular and cerebrovascular morbidity, I/R was also shown to confer cardioprotection by activating adaptive mechanisms such as ischemic preconditioning (IPC), post-conditioning, and remote-conditioning [9]. Thus, since not all OSA patients develop cardiovascular and other morbidities, it is feasible that in some instances IPC may occur in OSA as well. Apparently,

genetic polymorphism in HIF-1 and downstream genes as vascular endothelial growth factor (VEGF) and erythropoietin (EPO) might influence the individual responses to a given IH stimulus. However, also environmental- and lifestyle-related variables (diet, sports, air pollution) could affect these individual responses [1, 3].

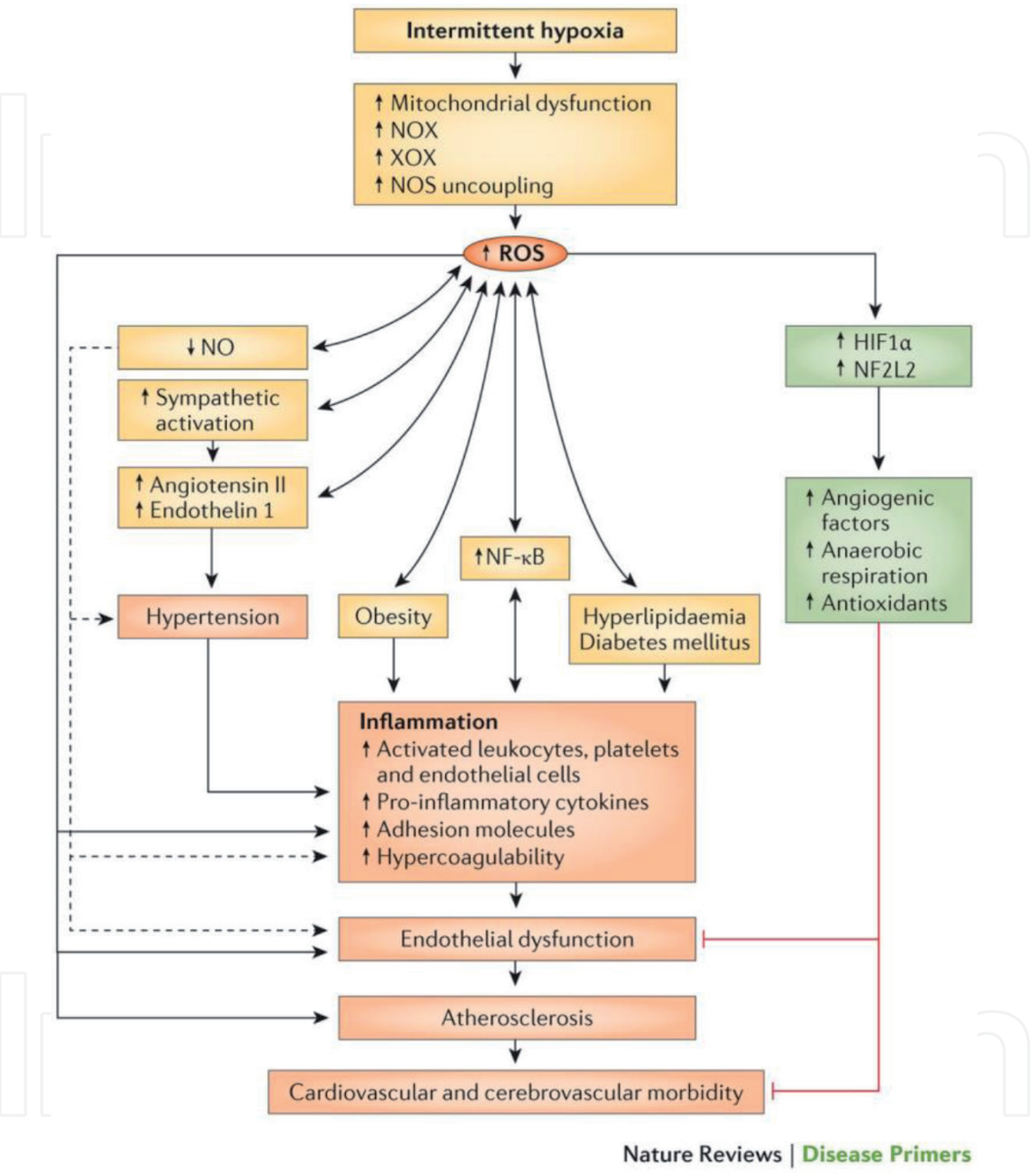


Figure 1.
Oxidative stress promotes sympathetic activation, cellular and systemic inflammation, and vascular comorbidities in OSA. Intermittent hypoxia induces the production of reactive oxygen species (ROS), resulting in oxidative stress by inducing mitochondrial dysfunction, activating NADPH oxidase (NOX) and xanthine oxidase (XOX), and inducing nitric oxide synthase (NOS) uncoupling. Interaction of ROS with nitric oxide (NO) further promotes oxidative stress while diminishing the bioavailability of NO and thus promoting hypertension, inflammation, endothelial dysfunction, hypercoagulability, and atherosclerosis. The ROS-dependent increase in sympathetic activation and in angiotensin II and endothelin 1 levels contribute to hypertension. Concomitantly, ROS can upregulate numerous redox-sensitive transcription factors, such as nuclear factor-κB (NF-κB), hypoxia-inducible factor-1α (HIF-1α), and nuclear factor (erythroid-derived 2)-like 2 (NF2L2). NF-κB orchestrates the various inflammatory processes that lead to endothelial dysfunction and atherosclerosis. By contrast, HIF-1α and NF2L2, which are also upregulated by ROS levels, are involved in protective mechanisms, which may counteract some of deleterious effects of ROS. Comorbidities and conditions associated with OSA, such as hypercholesterolemia, diabetes mellitus, and obesity, also have a ROS component and involve NF-κB activation and inflammation. Broken line, indirect pathway; red line, inhibition. Figure adapted from Ref. [3], Elsevier and published in Lévy et al. [1].

The current review is aimed at highlighting potentially protective mechanisms induced by IH and OSA rather than the deleterious and well-established injurious effects described above while focusing on OSA patients with concomitant acute coronary syndromes. Thus, protective mechanisms revealed in I/R biology and also exhibited in animal models of IH after a global ischemic insult, as well as in patients with acute myocardial infarction (AMI) and concomitant OSA, are discussed and further elaborated in models of IH in vitro. A special emphasis is put on endothelial progenitor cells (EPCs), their proliferative and angiogenic properties, and their association with collateral formation. The significance of the heterogeneity in the proliferative and angiogenic functions of EPCs from healthy individuals exposed to a given identical IH stimulus is discussed with regard to potential collateral development and cardiovascular outcomes. Understanding individual differences to various forms of hypoxia and the associated molecular pathways can help in identifying patients at higher or lower cardiovascular risk.

2. Protective mechanisms associated with ischemia and reperfusion

The preconditioning effect is basically an experimental strategy. Applying brief ischemic episodes each followed by reperfusion—prior to a longer and potentially lethal duration of ischemia—can confer protection to an organ or a tissue. IPC of the heart is the best studied one. It demonstrates the heart's own self-preserving mechanism, by reducing infarct size and ventricular arrhythmias, and was shown in many of the models studied. In the first and seminal study demonstrating IPC [10], dog hearts were preconditioned by undergoing four circumflex coronary occlusions each lasting 5 min, separated each by 5 min of reperfusion (a total of 40 min), followed by a sustained 40 min occlusion and 4 days of reperfusion recovery. Control animals underwent only a single 40 min of occlusion and 4 days of reperfusion recovery after which infarct size was measured. In the controls, the infarcted area consisted 30% of the area at risk, whereas that of the preconditioned animals was only 7.5% of the area at risk (25% of the infarct size in the controls). This landmark study has paved the way to subsequent studies demonstrating the protective effects of IPC in the kidney, brain, liver, and intestine [11, 12]. Moreover, in various studies, the paradigms of IPC varied considerably ranging from intervals of minutes to seconds. Thus, when nonlethal sequential episodes of I/R—like those occurring in OSA nightly, prior to the occurrence of an acute lethal I/R episode—like in AMI or stroke, preconditioning may occur in those patients.

2.1 Mechanisms of ischemic preconditioning in animal models of intermittent hypoxia

The mechanisms involving IPC are complex and intricate, implicating various molecular, cellular, and paracrine pathways. Some of the triggers, mediators, and targets activated by I/R include Ca^{+2} ions, ROS, reactive nitrogen species, purinergic signaling, kinases, cytokines, and mitochondria. Transcriptional reprograming is affected as well. It involves upregulation of the redox-sensitive transcription factor hypoxia-inducible factor (HIF)-1α and its downstream genes VEGF and EPO and inducible nitric oxide synthase (iNOS) [4, 12]. The angiogenic VEGF promotes neovascularization and collateral vessel formation, while EPO is essential for protection against I/R injury. Nuclear factor kB (NF-κB) and some of its regulated inflammatory pathways are activated as well. Collectively, these transcriptional alterations invoke cellular and paracrine functions. In that context, a number of studies utilizing animal models of IH were shown to reduce infarct size in rat hearts

and improve focal ischemic injury in mice. In an acute model of IH, isolated rat myocardium was exposed to 4 h or 30 min of preconditioning by IH, using hypoxic episodes of either 10 or 5% oxygen, lasting 40 s and normoxia at 21% O_2 for 20 s (60 IH events per hour). After 24 h of recovery, sustained ischemia lasting 30 min was followed by 120 min of reperfusion. Only the paradigm of 4 h of IH at 10% oxygen induced a delayed preconditioning by reducing infarct size to more than 50% as compared to control hearts [13]. Moreover, besides reducing infarct size, also HIF-1α was stabilized and iNOS was activated. These effects were mediated through PKC and triggered by P38 MAPK and ERK1/ERK2 while inhibiting iNOS with aminoguanidine before the ischemic period abolished the IPC phenomenon [14]. In a chronic IH model investigating focal ischemic injury in mice, a dichotomous effect was noted. The mice were subjected to chronic IH at 10 or 6% O_2 for 35 days (8 h/day 20 hypoxic episodes/hour lasting 90 s at 90 s of intervals) or to room air (sham). Then the mice were treated for focal ischemic injury for 30–35 min. Only at 10% of O_2, EPO and VEGF were increased, while inflammatory markers were decreased compared to controls. At the more severe IH of 6% of O_2, inflammatory markers were increased as compared to control sham animals [15]. In both the acute and the chronic IH animal models described, the IH served as a nonlethal preconditioning effect before applying the lethal I/R stimulus. Acute as well as chronic IH displayed dichotomous effects, depending on the severity of the IH applied. Moreover, the molecular mechanisms described for IH-dependent IPC concur with classical IPC mechanisms in I/R (upregulation of HIF-1α, VEGF, EPO, and iNOS). Thus, the protective effects were dependent on the severity, the frequency, and the chronicity of the IH paradigms applied in these animal models of IH.

2.2 Potential involvement of IPC in OSA patients with acute MI and acute ischemic stroke

The involvement of IPC is potentially implicated in patients with OSA after an AMI or an acute ischemic stroke. For instance, peak cardiac troponin values were shown to be significantly higher in AMI patients without OSA than in AMI patients with OSA. This finding suggests that OSA might have a protective effect in the context of MI and that patients with OSA may experience less severe myocardial injury [16]. Additionally, the prevalence of non-ST-elevation myocardial infarction (NSTEMI) in AMI patients was associated with OSA and was shown to increase with the increasing severity of OSA. This finding may also suggest a cardioprotective role of OSA, which may attenuate the development of ST-elevation myocardial infarction (STEMI), perhaps through IPC [17]. In patients with OSA hospitalized because of an acute ischemic stroke, less severe neurological injury and lower unadjusted mortality rates were found than in those without a history of OSA [18]. Also, cardiac arrest survivors with OSA had better unadjusted survival rates and favorable adjusted neurological outcomes at discharge than those without OSA [19]. This latter study suggests that OSA patients may tolerate better acute brain ischemia due to preconditioning. Collectively, these recent studies favor the possibility that the presence of OSA may confer cardio-/neuroprotection in patients with AMI or acute ischemic stroke.

3. The role of endothelial progenitor cells in endothelial health

Blood-derived EPCs play a pivotal role in maintaining vascular homeostasis by providing an endogenous repair mechanism by replacing dysfunctional endothelium and enhancing tissue repair after an ischemic vascular insult [20, 21]. EPCs are mobilized by hypoxia or tissue ischemia, HIF-1α- and VEGF-dependent pathways [22].

In AMI patients, EPCs were shown to home at the ischemic myocardium and participate in vascular and cardiac repair, basically acting as an internal pool of endothelial cells (ECs). EPCs contribute up to 25% of ECs in newly developed vessels at ischemic sites. Hence, they promote coronary collateral formation while improving endothelial functions by integrating into newly developing capillaries or into injured blood vessels [20, 23]. Of note, low EPC numbers were shown to correlate with endothelial dysfunction, atherosclerosis, and poor cardiovascular outcome. Thus, they are currently considered in many studies to represent an independent predictor of endothelial dysfunction and long-term prognosis in patients with coronary artery disease [21, 24]. Therefore, circulating EPC levels might be used as a surrogate marker to assess clinical outcomes.

In most of the studies published thus far, EPCs were primarily identified by CD34 (primitive hematopoietic progenitors) and VEGF-R2 (a VEGF receptor) expressions [20]. Their proliferative and angiogenic capacities were demonstrated in vitro by two widely used assays: (1) the formation of endothelial colonies in culture—termed endothelial cell colony-forming units (EC-CFUs) [25]—and (2) the determination of the paracrine effects of these developed colonies on endothelial cells in culture [26].

Growing EPCs on fibronectin in vitro can induce proliferation and differentiation into EC-CFUs which are characterized by a central core of round angiogenic T cells and outgrowing spindle-shaped cells. These colonies secret angiogenic growth factors such as VEGF inducing endothelial tube formation via paracrine pathways. Moreover, in AMI patients the expression of circulating EPCs (CD34+/VEGF-R2) was positively correlated with mean endothelial tube formation [27]. Also, EC-CFUs were shown to negatively correlate with the Framingham risk score, thus adequately representing circulating EPCs [25]. Both these two in vitro measures—the formation of EC-CFUs in culture and their paracrine effects on endothelial tube formation—might be considered as good surrogate markers for circulating EPCs [25, 27].

3.1 Endothelial progenitor cells and their proliferative and angiogenic properties in AMI patients with OSA

Acute MI can be a devastating I/R event and a frequent cause of sudden death. Sleep apnea is highly prevalent in AMI patients, ranging in various studies from 22 to 69%. However, in the setting of AMI, the presence of OSA is frequently not considered and therefore under diagnosed [28]. Evaluating circulating EPCs in patients diagnosed with OSA while recovering from an AMI revealed significantly higher EPC numbers than in AMI patients without OSA. Also the intracellular VEGF expression, EC-CFU numbers, and their angiogenic T cells in culture, and endothelial tube formation, were all significantly higher than those in AMI patients without OSA [27]. These findings suggest that the IH associated with OSA might have a crucial role in promoting these protective functions of EPCs in the setting of AMI. Subsequently, the development of EC-CFUs and their paracrine functions in healthy individuals were determined by exposure to IH in vitro. Indeed, the proliferative and paracrine abilities of EC-CFUs and endothelial tube formation were increased by IH, as compared to those that developed under normoxic conditions [27, 29]. Moreover, IH in vitro increased NADPH oxidase-dependent ROS production, protein carbonylation, and VEGF expression in EC-CFUs. Both EC-CFU numbers and endothelial tube formation in culture were increased by ROS-dependent mechanisms. Accordingly, ROS scavengers and NADPH oxidase inhibitors attenuated or completely abolished the formation of EC-CFUs treated by IH in vitro. It is therefore likely that IH and ROS are crucial contributors to increased EPC numbers and their proliferative and angiogenic functions [29].

4. Development of coronary collaterals in acute coronary syndromes

A number of studies demonstrate that coronary collaterals were increased in coronary artery disease patients with high EPC numbers. Conversely, inadequate coronary collateral development was associated with reduced numbers of circulating EPCs and impaired pro-angiogenic activity, as determined by the low values of EC-CFUs and tube formation in culture [30, 31]. Moreover, increased circulating EPC levels were also associated with collateral formation in patients with NSTEMI [32]. Furthermore, reduced circulating EPC numbers also predicted future cardiovascular events, emphasizing the clinical importance of endogenous vascular repair [30, 31, 33]. Therefore, circulating EPC numbers might represent a good prognostic marker for the outcomes in the clinical context of acute coronary syndrome [20].

Interestingly in OSA patients with total coronary occlusion, collateral development was significantly higher than in non-OSA patients with the same coronary occlusion (Rentrop score 2.4 ± 0.7 vs. 1.61 ± 1.2, $p = 0.02$, respectively) [34]. Similar finding supporting increased coronary collaterals in inaugural AMI patients with OSA was also reported more recently [35].

5. Interindividual responses to hypoxic conditions

Interindividual differences are fundamental to the development of personalized medicine. Different individuals respond in a distinctively different manner to an identical hypoxic stimulus. Such diverse responses can result from a number of reasons. Specifically, however, genetic variations in the expression of oxygen-regulated genes are of a particular interest in this growing field of personalized and regenerative medicine, as EPCs and their proliferative and angiogenic functions are [3]. For instance, the expression of the transcription factor HIF-1α and some of its downstream genes as VEGF and aldolase C was determined in lymphocytes from healthy adults exposed to eight different hypoxic treatments ranging from 0.1 to 20% oxygen. The sensitivity of HIF-1α expression to hypoxia varied considerably between individuals. HIF expression in the "low responders" was upregulated at 0.1% oxygen, whereas "high responders" upregulated HIF already at 5% oxygen. Moreover, also the HIF-regulated downstream genes responded in the same manner in each individual, suggesting that the source of this variation resides within the HIF system itself [36]. Furthermore, in patients with ischemic heart disease, DNA was genotyped for single-nucleotide polymorphism (C or T changes at residue 582 of HIF-1α, from proline to serine). HIF-1α polymorphism was associated with the development of collaterals in those patients and was dependent on the frequency of the T alleles. Its frequency was higher in patients without collaterals than in patients with collaterals (the presence of CT or TT was a negative predictor). Thus, variations in HIF-1α genotype may influence the development of collaterals in patients with significant coronary artery disease perhaps regardless of the severity of the ischemia they encounter [37]. In an earlier study, interindividual responses to hypoxia were also shown in coronary artery disease patients undergoing angiography. Their monocytes were harvested and exposed to an identical hypoxic stimulus. Then, mRNA levels of VEGF were determined and correlated with the presence of collaterals. Patients with no collaterals had significantly lower hypoxic induction of mRNA VEGF levels, whereas high mRNA VEGF levels were correlated with high collateral formation [38]. Collectively, these latter studies emphasize the heterogenic responses observed between different individuals exposed to an identical hypoxic stimulus, due to a different genetic background. Moreover, the significance of collateral development in the context of individual responses and clinical outcomes is further emphasized.

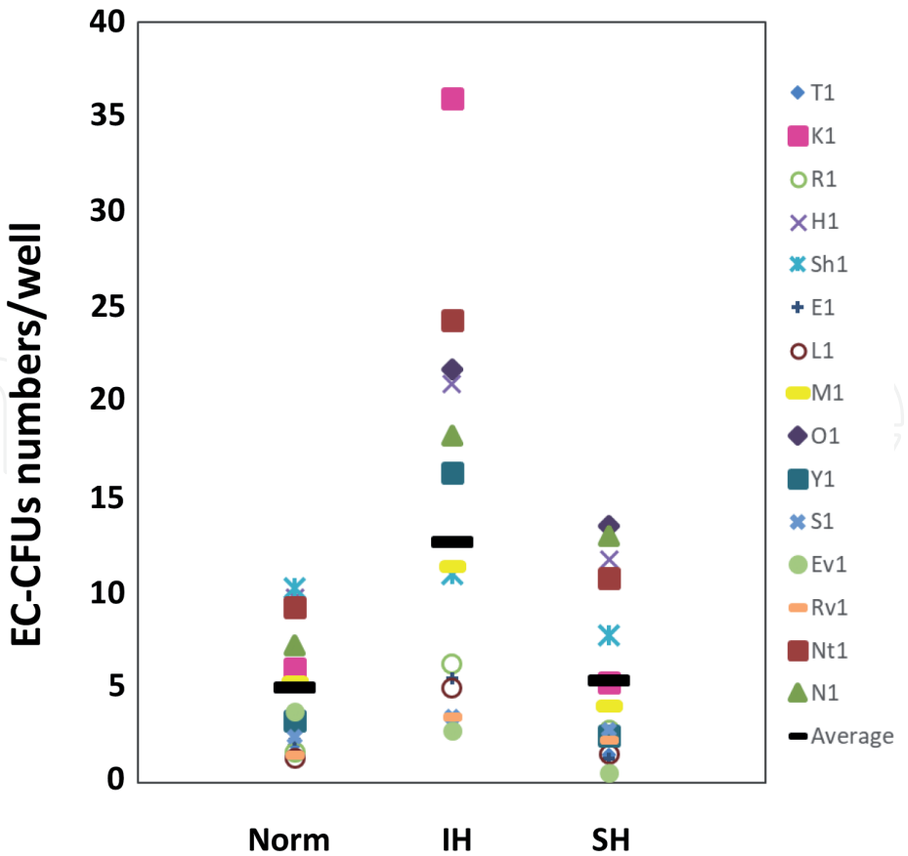


Figure 2.
Individual and mean EC-CFU numbers were determined on the 7th day in culture in 15 healthy donors. Cells were exposed to intermittent hypoxia (IH) and to sustained hypoxia (SH) and compared to normoxia (Norm). Each symbol represents a different donor. The horizontal black bar represents the average value for each treatment. (IH 12.7 ± 10.0 vs. Norm 5.0 ± 3.3 EC-CFUs/well, $p < 0.017$; SH 5.4 ± 4.7 vs. Norm EC-CFUs/well, p = NS). These data were published in Avezov et al. [29].

Since high levels of EC-CFUs and endothelial tube formation were correlated with high collateral formation [30, 31], we investigated the effects on EC-CFUs, endothelial tube formation, and VEGF levels in young healthy adults by applying IH in vitro. As aforementioned, IH increased the formation of EC-CFUs and their paracrine activity by increasing endothelial tube formation via higher VEGF expression in culture [29]. However, there was also a significant variation within the cellular responses to the hypoxic stimuli between individuals as depicted in **Figure 2**. This latter finding emphasizes again the importance of the interindividual heterogeneity observed in the hypoxic responses to a specific stimulus as described earlier for the HIF system and the downstream genes in cardiovascular patients as well as in healthy individuals [36–38].

6. Conclusions

Intermittent hypoxia is the hallmark of obstructive sleep apnea. However, many of the molecular pathways activated in OSA and in response to IH in vivo and in vitro resemble pathways activated by ischemia and reperfusion (I/R). This is evident in injurious as well as in protective mechanisms. IH, similar to I/R, promotes fundamentally injurious mechanisms as oxidative stress and inflammation which invoke atherosclerotic processes rendering OSA a major risk factor for cardio- and cerebrovascular disease. Yet, not all OSA patients develop these morbidities. Importantly, also, similar to I/R, some OSA patients with concomitant acute MI respond to the harsh effects of IH by activating akin molecular pathways

which promote protective mechanisms as ischemic preconditioning. It is therefore likely that OSA promotes IPC in some instances as well. This is particularly evident in patients recovering from AMI.

Both IH and ROS were shown to play a major role in increasing EPC and EC-CFU numbers and angiogenic functions. All in all, circulating EPC numbers and their angiogenic functions were shown to represent a good surrogate marker as well as a prognostic marker to assess the outcomes in the clinical context of acute MI. This is emphasized by their association and significance to collateral development and clinical outcome. Moreover, the heterogenic responses observed between individuals, implicating a specific personal response to a given particular stimulus, based on genetic variants, might be considered as the foundation for developing personalized medicine for acute MI patients. Thus, IH might be considered as a new modality for the upregulation of angiogenic processes to induce collateral formation in the clinical setting. However, the severity, the frequency, and the chronicity of the IH paradigms should be determined in order to identify and harness IH patterns possessing protective effects. Collectively, based on the studies presented in this review, it is clearly evident that determination of collateral formation, EPC numbers (and possibly their proliferative and angiogenic properties), HIF polymorphism, downstream genes as VEGF, and additional markers, yet to be unraveled, represent an important tool to identify patients at higher or lower risk for outcomes of acute coronary syndromes. However, no less important is the identification of IH patterns possessing protective effects toward elevating EPC numbers in the circulation of acute MI patients with low or unfavorable HIF polymorphism.

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Conflict of interest

None to declare.

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