World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v2.i12.421

World J Cardiol 2010 December 26; 2(12): 421-427
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

Cuihua Zhang, MD, PhD, FAHA, Associate Professor, *Series Editor*

Corruption of coronary collateral growth in metabolic syndrome: Role of oxidative stress

Yuh Fen Pung, William M Chilian

Yuh Fen Pung, William M Chilian, Department of Integrative Medical Sciences, Northeastern Ohio Universities College of Medicine and Pharmacy, Rootstown, OH 44272, United States
Author contributions: Pung YF and Chilian WM contributed to the manuscript equally.
Supported by National Institute of Health Grants No. HL32788, R01 83366, RC1HL100828 (to Chilian WM); and an American Heart Association Post-doctoral Fellowship, No. 09POST2290021 (to Pung YF)
Correspondence to: William M Chilian, PhD, Department of Integrative Medical Sciences, Northeastern Ohio Universities College of Medicine and Pharmacy, Rootstown, OH 44272, United States. wchilian@neoucom.edu
Telephone: +1-330-3255912 Fax: +1-330-3255912
Received: August 2, 2010 Revised: October 23, 2010
Accepted: October 30, 2010
Published online: December 26, 2010

Abstract

The myocardium adapts to ischemic insults in a variety of ways. One adaptation is the phenomenon of acute preconditioning, which can greatly ameliorate ischemic damage. However, this effect wanes within a few hours and does not confer chronic protection. A more chronic adaptation is the so-called second window of preconditioning, which enables protection for a few days. The most potent adaptation invoked by the myocardium to minimize the effects of ischemia is the growth of blood vessels in the heart, angiogenesis and arteriogenesis (collateral growth), which prevent the development of ischemia by enabling flow to a jeopardized region of the heart. This brief review examines the mechanisms underlying angiogenesis and arteriogenesis in the heart. The concept of a redox window, which is an optimal redox state for vascular growth, is discussed along with signaling mechanisms invoked by reactive oxygen species that are stimulated during ischemia-reperfusion. Finally, the review discusses of some of the pathologies, especially the metabolic syndrome, that negatively affect collateral growth through the corruption of redox signaling processes.

Key words: Angiogenesis; Arteriogenesis; Redox-dependent signaling; Mitochondria

Peer reviewer: Qinglin Yang, MD, PhD, Associate Professor, Department of Nutrition Sciences, University of Alabama at Birmingham, 1675 University Blvd, Birmingham, AL 35294, United States

Pung YF, Chilian WM. Corruption of coronary collateral growth in metabolic syndrome: Role of oxidative stress. *World J Cardiol* 2010; 2(12): 421-427 Available from: URL: http://www.wjgnet.com/1949-8462/full/v2/i12/421.htm DOI: http://dx.doi.org/10.4330/wjc.v2.i12.421

INTRODUCTION

Recently, there has been a rapid increase in the incidence of metabolic syndrome, a term used to describe a condition characterized by abdominal obesity, hyperglyceridemia, insulin resistance and hyperinsulinemia, to near epidemic levels. People with metabolic syndrome are particularly at increased risk for ischemic heart disease (IHD) and approximately 30% to 40% of these patients show little to no coronary collateral growth. Importantly, patients with well-developed coronary collaterals have a better prognosis in recovering from a myocardial infarction than those with poorly developed collaterals[1]. Because collateral growth is a chronic event, patients without collaterals that have an acute coronary occlusion have a poor prognosis because the wavefront of necrosis proceeds faster (minutes to hours) than vascular growth (days

Table 1 Differences in the underlying mechanisms of induction, as well as mediator and growth factor involvement in angiogenesis and arteriogenesis[8,9]

	Angiogenesis	Arteriogenesis
Inducer	Ischemia	Shear stress, inflammation, ishemia
Promoter	Hypoxia inducible factor (TACGTGCT)	Hypoxia inducible factor (TACGTGCT) Shear stress responsive element (GAGACC)
Substrate	Pre-existing capillaries	Pre-existing arterioles
Cell type	Endothelial cells	Endothelial and smooth muscle cells; likely fibroblast
Result	Increase capillaries density	Remodeling of arteries into collateral arterioles
Duration	Days	Days to weeks
Growth factors	VEGF, bFGF, PDGF, PIGF, MCP-1, MMPs, GM-CSF, *etc.*	VEGF, bFGF, PDGF, PIGF, MCP-1, MMPs, GM-CSF, *etc.*

VEGF: Vascular endothelial growth factor; bFGF: Basic fibroblast growth factor; PDGF: Platelet-derived growth factor; PIGF: Placenta growth factor; MCP-1: Monocyte chemoattractant protein-1; MMPs: Matrix metalloproteinases; GM-CSF: Granulocyte-macrophage colony-stimulating factor.

to months). Coronary collaterals carry insufficient flow to completely prevent infarction in most cases, although their presence is known to limit the damage and reduce infarct size[2]. Thus, the growth of coronary collaterals has earned the name "mother nature's by-pass". The complex mechanisms mediating the enlargement and/or development of new blood vessels in the heart are not well-understood. In this review, we discuss redox-sensitive mechanisms that lead to coronary collateral growth and how redox-dependent signaling should be considered in therapies designed to stimulate the growth of blood vessels in the heart, particularly in patients with metabolic syndrome.

MECHANISMS OF CORONARY COLLATERAL FORMATION IN THE HEART

Coronary collateral growth is the enlargement of arterial-arterial connections in the heart. It is a chronic coronary adaptation to myocardial ischemia that helps to restore the coronary flow and prevent or minimize myocardial ischemic injury[3]. Under physiological conditions, collateral vessels are very small and thus resistance to net blood flow is high[4]. However, collaterals can greatly expand their calibers and serve as conduits offering little resistance to blood flow if challenged with appropriate stimuli[5]. The stimuli that trigger this physiologic remodeling in an outward direction, rather than pathologic remodeling in which cell proliferation is involved in the development of a neointima and atherosclerotic plaque formation, remain unknown[4].

Vascular growth is usually categorized as angiogenesis (the tightly regulated sprouting of new capillaries from pre-existing ones) or vasculogenesis (the *in situ* development of vessels from angioblasts, which is normally confined to the embryonic phase of development)[6]. Arteriogenesis, formerly regarded as a variant of angiogenesis, is a relatively new term that was introduced to distinguish it from other mechanisms of vascular growth; i.e. angiogenesis and vasculogenesis[7-9]. Arteriogenesis describes the formation of mature arteries from pre-existent interconnecting arterioles after an arterial occlusion. According to Cai *et al*[10], the fundamental difference between the two types of vascular growth is that arteriogenesis occurs in a normoxic environment; whereas angiogenesis depends on tissue hypoxia/ischemia that leads to the activation of the transcription factor hypoxia-inducible factor-1α (HIF-1α). However, these generalizations are far too simplistic because, in the heart, arteriogenesis or collateral growth is initiated by ischemia/tissue hypoxia. Several years ago, Chilian *et al*[11] attempted to resolve the contributions of shear stress from ischemia in the coronary circulation by distally embolizing the microcirculation of the heart with microspheres (thus producing ischemia, but without pressure gradients across upstream collaterals). Under these conditions, initiation of collateral growth was observed, but the magnitude of collateral growth was not nearly as robust as with other models. Importantly, Toyota *et al*[3] further demonstrated that neutralizing antibodies to vascular endothelial growth factor (VEGF) prevented coronary collateral growth. Because VEGF has an HIF responsive element in the promoter, such an observation is consistent with the early initiation of collateral growth being regulated by ischemia (tissue hypoxia). As collaterals develop, tissue hypoxia is ameliorated because the collaterals enable the delivery of oxygenated blood. Thus, at least in the heart, ischemia can be thought of as an initiating factor for collateral development, but shear stress is likely a factor that contributes to remodeling during the continuation of this process as the tissue hypoxia is abated[4].

Whether the growth and enlargement of coronary collaterals is due to the enlargement of pre-existent vessels, *de novo* arteriogenesis, or both, remains a controversy. In our opinion, we think that repetitive occlusions in the heart may give rise to a mixed arteriogenic/angiogenic adaptation due to the close proximity of the stenosing vessel and the downstream region at risk. Indeed, we previously found an increase in capillary density in a canine model of collateral growth induced by episodic ischemia[12]. However, what is not resolved is whether these capillaries can arterialize and contribute to the formation of the collateral network. Obviously, the underlying mechanisms of this "natural process" of coronary collateral growth/arteriogenesis are a complex orchestration of the expression of numerous growth factors and signaling cascades that have not been well elucidated, as illustrated in Table 1 and Figure 1. Figure 1 summarizes how both

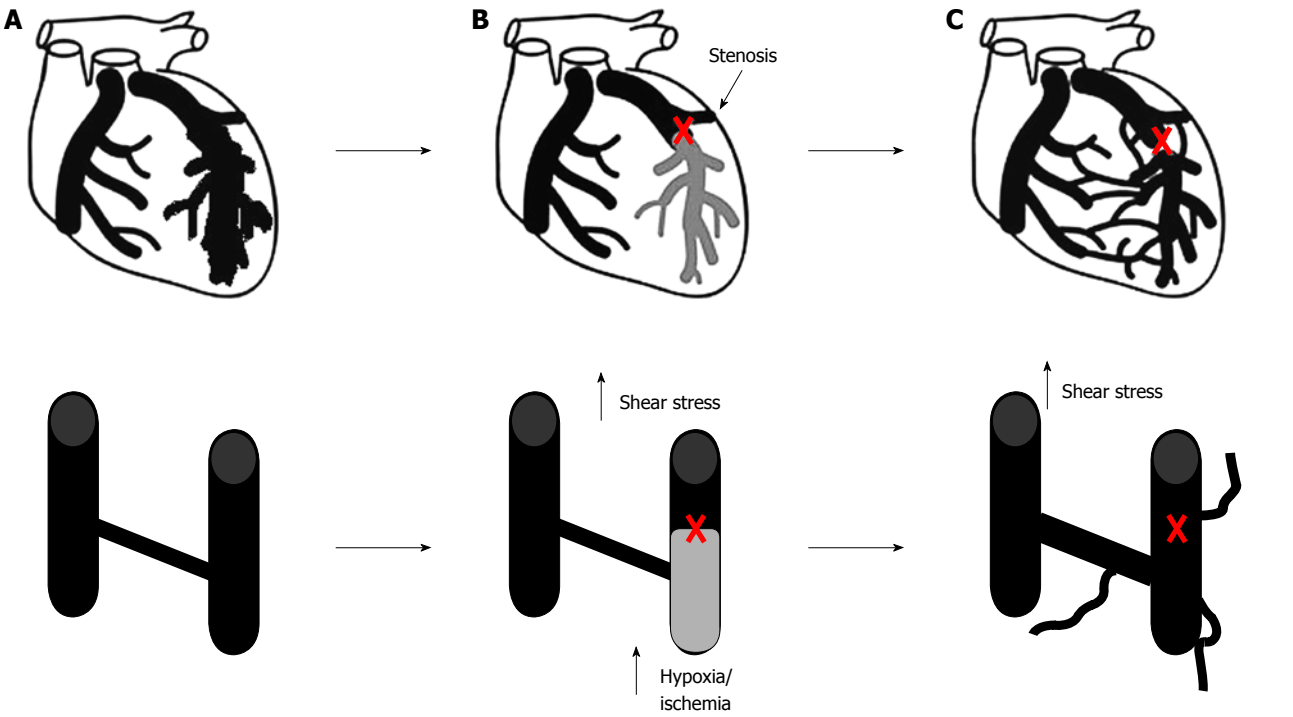

Figure 1 Compensatory mechanism of coronary collateral growth/arteriogenesis. A: A non-functioning collateral between parallel circuits in the absence of flow obstruction; B: Following proximal occlusion, there is a pressure drop across the pre-existing collateral stimulated by shear stress-driven redirection of flow; C: A complex intracellular signaling cascade involving various growth factors act in a coordinated manner to facilitate migration and proliferation of endothelial and smooth muscle cells (likely fibroblasts), leading to enlargement/ formation of arteries, arterioles and capillaries.

tissue hypoxia/ischemia and shear stress can contribute to coronary growth. In this figure, an acute occlusion produces ischemia and increases shear stress across collaterals. As the collaterals grow, ischemia is absolved but shear stress may still be elevated compared to the normal state. Table 1 summarizes key aspects, regulators and components of growth of a collateral vessel (arteriogenesis) and growth of new vessels (angiogenesis). This table shows that the two processes overlap in various categories.

ISCHEMIA-REPERFUSION INJURY

In the heart, ischemia or ischemia-reperfusion (IR) is the initiating stimulus for collateral growth and angiogenesis. IR injury in the myocardium is a biphasic process, in which exposure of the myocardium to prolonged reduction in blood flow (ischemic phase) produces a variety of events including hypoxia, which initiates cell injury or even death in the affected region of the heart. This is then followed by further injury commencing upon reestablishment of blood flow (reperfusion phase), which furthers cellular destruction, including stunning and death[3,13]. Massive amounts of reactive oxygen species (ROS) released during reperfusion have been shown to be the major cause of death of myocardial tissue that was still alive before the onset of reperfusion. Treatment with superoxide dismutase-1 (SOD-1), catalase (cat) and nitric oxide synthase (NOS) inhibitors at the onset of reperfusion have been shown to be cardioprotective[3,14]. The caveat to IR is that if the period of occlusion is brief, then instead of inducing cell death, adaptive processes of cardio-protection and collateral growth are initiated.

OXIDATIVE STRESS

ROS are a family of molecules, including molecular oxygen and its derivatives, produced in all aerobic cells. Many ROS possess unpaired electrons and thus are free radicals. These include superoxide anion (O_2^-), hydroxyl radical (HO^-), nitric oxide (NO^-) and lipid radicals. Other ROS, such as hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl), are not free radicals *per se*, but have potent oxidizing effects that contribute to oxidative stress[15]. As stated previously, there is a burst in the production of ROS during the reperfusion phase of IR, which has been implicated in the regulation of intracellular signaling pathways and biological functions of the cells[14,16]. Superoxide is rapidly converted to the more stable H_2O_2 by the actions of superoxide dismutase 1 and 2 (SOD-1 and -2). Catalase (cat) then converts H_2O_2 into water and O_2. Peroxynitrite is formed by the reaction of O_2^- and NO, and has been implicated in the disruption of intracellular signaling by nitration of tyrosine residues[17-19]. However, if there is an imbalance between pro-oxidant generation and anti-oxidant defenses, oxidative stress may ensue. Oxidative stress can result in oxidation of biological macromolecules, such as DNA, protein, carbohydrates and lipids. Oxidative modification of lipids, tyrosine residues, nucleotides, and a shift in the ratio of

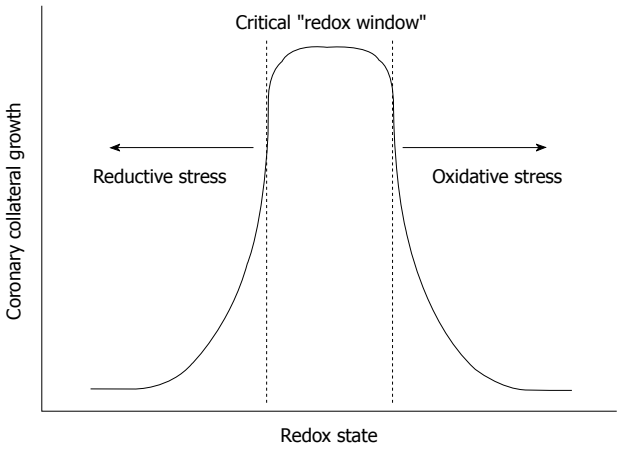

Figure 2 "Redox-window" hypothesis on coronary collateral growth. Existence of a critical "redox-window" is required; either reductive or oxidative stress will corrupt collateral growth and redox-dependent growth-factor signaling. The figure illustrates the principal measure in our system-collateral growth-as a function of the redox state in cells. The summary of this concept is best described as, in situations where there is reductive stress or oxidative stress, collateral growth is corrupted because of either too many neutral or oxidized thiol groups.

reduced to oxidized thiols are all standard measurements to evaluate oxidative stress. However, when does the shift to an oxidative state become a stress and therefore is outside the bounds of the norm? This question is difficult to answer, but in fact is the most important, and we pose it in a different venue, as shown in Figure 2 where we illustrate a "redox window". In Figure 2, the outcome of redox-dependent signaling is coronary collateral growth. However, we emphasize that there are many surrogates for the effects of oxidative or reductive stresses. In our model, the final measure of redox signaling is coronary collateral growth and, accordingly, we plotted this variable as the outcome for redox signaling in the heart. In some instances oxidative stress should be confined to a situation where the normal metabolism or biology of a cell is altered by excess production of oxidants or inadequate antioxidant defenses. Alternatively, reductive stress occurs with insufficient production of ROS, excessive amounts of free radical scavengers or enhanced levels of NADPH or NADH (because of inadequate oxidation of these substrates). Although oxidative stress is generally perceived as being more important than reductive stress, the latter is known to corrupt growth factor signaling[20] and also induce cardiomyopathy[21]. The likely mechanism of reductive stress relates to the incomplete oxidation of protein thiols on cysteine residues that, when oxidized, produce the negatively charged sulfenic acid. If too many (oxidative stress) or too few (reductive stress) thiol groups are oxidized into sulfenic acid, the activity of the enzyme is affected *via* conformational changes in tertiary structure that is determined by either neutrality or negatively charged thiols.

Despite many potential enzymatic sources of ROS, only xanthine oxidase, NADH/NADPH oxidase and NO synthase, have been studied extensively in the cardiovascular system[15]. In recent years, more studies have revealed several important mechanistic details of mitochondrial ROS production in the heart. Mitochondria, which encompass 40% to 50% of a cardiac myocyte volume, are densely packed with various protein electron carriers (mitochondrial complexes) that, instead of transferring electrons for the production of energy, have electrons inadvertently leak from the complexes and reduce oxygen to form the superoxide anion. Superoxide anion then serves as a ROS progenitor to induce a positive feedback loop ('vicious cycle') wherein ROS-mediated oxidative damage to cells favors further elevated ROS production[22]. Many cell types have been proposed to contribute to the enzymatic production of ROS during IR, namely infiltrating neutrophils, cardiac myocytes and endothelial cells[23]. However, potential roles for both cardiac and vascular fibroblasts and vascular smooth muscle cells have also been reported[23].

REDOX-DEPENDENT SIGNALING IN CORONARY COLLATERAL GROWTH

Studies have shown that ROS modulate cellular function *via* intricate mechanisms. Ambient production of O_2^- and H_2O_2, maintained by basal activity of pre-assembled NADPH oxidases or mitochondrial respiration, is necessary for the growth, proliferation and migration of vascular cells. Under pathological conditions, activation of vascular NADPH oxidase, xanthine oxidase, uncoupled from eNOS and even mitochondrial dysfunction, lead to detrimental consequences. The functions of some ROS, particularly H_2O_2, are often viewed in a dichotomous manner as an important physiological mediators in certain concentrations (e.g. endogenous vasodilator[24,25]) but harmful in large amounts (e.g. anti-microbial and apoptotic[15]).

The likely actions of H_2O_2 are mediated *via* its effects on cellular thiols, in which oxidation of a free thiol by H_2O_2 produces sulfenic acid. The conference of a negative charge *via* oxidation of a free thiol to sulfenic acid performs a similar action as when a protein is phosphorylated by a kinase; the introduction of the negatively charged phosphate induces a change in the tertiary structure of the protein causing an alteration in function; e.g. activation, docking and inhibition. However, one critical issue related to ROS signaling is that a little is "good", but a lot seems to be "bad". Perhaps there are critical thiol residues that are normally subjected to oxidation by ROS, but if there are too many ROS, then additional thiols may be converted into sulfenic acids, which could result in improper tertiary changes in structure. An observation supporting this contention is that different thiols show varying sensitivity to oxidative modification[26] and, therefore, it is not unreasonable to assume that oxidative stress can induce a very different effect on protein structure than physiological levels of ROS.

Rocic *et al*[20] demonstrated that too many or too few

ROS have a negative effect on endothelial tube formation *in vitro*, which may be a shared common mechanism with angiogenesis and collateral growth. These investigators showed that there was robust tube formation induced by VEGF when endothelial cells were seeded on two-dimensional Matrigel. However, tube formation was inhibited when the cultures were treated with either diphenylene iodonium (DPI) to block O_2^- formation or diethyldithiocarbamic acid (DETC) to inhibit SODs[20]. The former shifted the redox state to a more reductive condition and the latter to a more oxidative environment. To further establish the physiological relevance of the impact of the critical "redox window" in mediating the angiogenesis process, the study was extended to an *in vivo* coronary collateral growth model. Healthy, lean rats were subjected to a 10-d protocol of brief episodic ischemia, a sham group with the surgical procedure but without repetitive ischemia, and two experimental groups in which O_2^- production was decreased by administration of DPI or increased by DETC, respectively. The desired redox state induced by drug treatment was monitored and confirmed using X-band electron paramagnetic resonance spectroscopy. Compared to the sham group, the experimental group produced an increase in O_2^-, which was blocked by DPI and augmented by DETC. Robust growth of coronary circulation (ratio of flow to the collateral relative to normal zones) was observed as opposed to abrogated growth by either too little or too much O_2^-[20]. This *in vivo* study again emphasized the existence and importance of redox-dependent signaling in coronary collateral growth.

OXIDATIVE STRESS IN METABOLIC SYNDROME AND CORONARY COLLATERAL GROWTH

Metabolic syndrome is associated with overproduction of ROS, leading to the concept that the amelioration of risk factors of metabolic syndrome, including insulin resistance, elevated blood pressure, elevated lipid levels, inflammation and endothelial dysfunction, may reduce oxidative damage and curtail the progression of IHD[27]. As mentioned, enzymatic sources of ROS production under pathological conditions, including activation of vascular NADPH oxidase, xanthine oxidase and uncoupling of eNOS, are well characterized in cardiovascular diseases. In our opinion, cardiac mitochondrial dysfunction is the major cause and/or effect of mitochondrial ROS generation, leading to a vicious cycle of "ROS-induced, ROS-released" in the diabetic myocardium. Supporting this argument are many observations showing alterations in mitochondrial structure and function in the metabolic syndrome[28-33], with some of these manifestations ameliorated by scavenging ROS in mitochondria.

Mitochondria are the principal source of high energy phosphate (ATP) production. Tissues that have high energy requirements, such as the heart, have a higher density of mitochondria and are reliant on mitochondrial aerobic metabolism to produce energy to maintain contractile function. In addition to energy production, mitochondria continuously produce ROS as a by-product of electron transfer. This is because the transfer of e^- through the mitochondrial electron transport chain is not 100% efficient, and a small percentage of e^- leak out and react with O_2 to produce O_2^-. Although the heart is able to oxidize a broad variety of substrates for ATP production, the normal heart generates ATP mainly from the mitochondrial oxidation of fatty acid (60% to 70% of ATP generated) and to a lesser extent from glucose, lactate and other substrates (30% to 40%). In contrast, hearts of diabetic and obese animals use relatively more fatty acids to generate ATP, while glucose oxidation rates are decreased in isolated working heart perfusions of *db/db* and *ob/ob* mice, as shown by Andreyev *et al*[22] and Buchanan *et al*[34]. Similarly, increased fatty acid oxidation has also been observed in Zucker Diabetic Fatty rats (ZDF)[35]. The resulting increase in reducing equivalent delivery to the respiratory chain may increase chances of e^- leakage, leading to mitochondrial oxidative stress. In addition, studies have shown that fatty acids are less efficient fuel when compared to glucose in terms of the yield of ATP per oxygen atom consumed. Substrate switched from 100% palmitate to 100% glucose would increase the ATP yield per oxygen atom by 12% to 14%[36]. Thus increased fatty acid utilization in the diabetic myocardium may be energetically detrimental because of the higher cost to produce ATP to keep up with increased cardiac work. Importantly, reduction in ATP would also prevent a phenotypic switch of endothelial and smooth muscle cells (likely fibroblasts) from quiescent to proliferating and migrating phenotypes, which is essential for angiogenesis and collateral growth.

To understand whether amelioration of oxidative stress would confer a positive effect on VEGF gene therapy, we studied coronary collateral growth in Zucker Obese Fatty rats (ZOF). ZOF rats are a rat model of human metabolic syndrome because these rats share many of the same afflictions including obesity, insulin resistance, hyperlipidemia, hyperinsulinemia and hyperphagia. The ZOF rats also demonstrated endothelial dysfunction and oxidative stress[37]. We first observed that coronary collateral growth was markedly compromised in response to episodic ischemia in the obese rats[38]. VEGF gene therapy was administered *via* transfected smooth muscle cells that were introduced into the coronary circulation. There was no significant improvement in coronary blood flow to the ischemic zone. However, correction of oxidative stress with ecSOD (SOD-3), using the same smooth muscle-based gene delivery system as for VEGF, partially restored coronary collateral development[38]. Importantly, this observation was also confirmed in a different model of MS; i.e. JCR rats[39]. These results argue that amelioration of oxidative stress in diabetic/pre-diabetic myocardium will restore growth-factor redox-dependent signaling and thus enable the VEGF gene therapy to stimulate collateral growth. Clearly, redox-dependent signaling plays a critical role in collateral growth in the heart, and corruption of

this signaling by either reductive or oxidative stress can have negative influences and actions of growth factors on collateral growth.

CONCLUSION

The metabolic syndrome compromises vascular adaptations to ischemia[40-42] resulting in impaired coronary collateral growth. Central to this inadequate adjustment, are impairments in endothelial function produced by oxidative stress, which also corrupts the signal transduction of growth factors. These issues represent a major challenge for clinical application of any therapeutic strategy, because the presence of oxidative stress prevents the actions of growth factors administered as gene therapy or recombinant protein. The correction of oxidative stress to restore redox-dependent signaling is imperative to enable realization of therapies designed to stimulate collateral growth.

REFERENCES

1 **Schaper W**, De Brabander M, Lewi P. DNA synthesis and mitoses in coronary collateral vessels of the dog. *Circ Res* 1971; **28**: 671-679
2 **Wolf C**, Cai WJ, Vosschulte R, Koltai S, Mousavipour D, Scholz D, Afsah-Hedjri A, Schaper W, Schaper J. Vascular remodeling and altered protein expression during growth of coronary collateral arteries. *J Mol Cell Cardiol* 1998; **30**: 2291-2305
3 **Toyota E**, Warltier DC, Brock T, Ritman E, Kolz C, O'Malley P, Rocic P, Focardi M, Chilian WM. Vascular endothelial growth factor is required for coronary collateral growth in the rat. *Circulation* 2005; **112**: 2108-2113
4 **Yun J**, Rocic P, Pung YF, Belmadani S, Carrao AC, Ohanyan V, Chilian WM. Redox-dependent mechanisms in coronary collateral growth: the "redox window" hypothesis. *Antioxid Redox Signal* 2009; **11**: 1961-1974
5 **Schaper W**, Görge G, Winkler B, Schaper J. The collateral circulation of the heart. *Prog Cardiovasc Dis* 1988; **31**: 57-77
6 **Schaper W**, Ito WD. Molecular mechanisms of coronary collateral vessel growth. *Circ Res* 1996; **79**: 911-919
7 **Schaper W**, Buschmann I. Arteriogenesis, the good and bad of it. *Eur Heart J* 1999; **20**: 1297-1299
8 **van Royen N**, Piek JJ, Buschmann I, Hoefer I, Voskuil M, Schaper W. Stimulation of arteriogenesis; a new concept for the treatment of arterial occlusive disease. *Cardiovasc Res* 2001; **49**: 543-553
9 **Van Royen N**, Piek JJ, Schaper W, Bode C, Buschmann I. Arteriogenesis: mechanisms and modulation of collateral artery development. *J Nucl Cardiol* 2001; **8**: 687-693
10 **Cai W**, Schaper W. Mechanisms of arteriogenesis. *Acta Biochim Biophys Sin* (Shanghai) 2008; **40**: 681-692
11 **Chilian WM**, Mass HJ, Williams SE, Layne SM, Smith EE, Scheel KW. Microvascular occlusions promote coronary collateral growth. *Am J Physiol* 1990; **258**: H1103-H1111
12 **Matsunaga T**, Warltier DC, Weihrauch DW, Moniz M, Tessmer J, Chilian WM. Ischemia-induced coronary collateral growth is dependent on vascular endothelial growth factor and nitric oxide. *Circulation* 2000; **102**: 3098-3103
13 **Park JL**, Lucchesi BR. Mechanisms of myocardial reperfusion injury. *Ann Thorac Surg* 1999; **68**: 1905-1912
14 **Fujita M**, McKown DP, McKown MD, Franklin D. Changes in coronary flow following repeated brief coronary occlusion in the conscious dog. *Heart Vessels* 1986; **2**: 87-90
15 **Cai H**, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000; **87**: 840-844
16 **Griendling KK**, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res* 2000; **86**: 494-501
17 **Ischiropoulos H**, al-Mehdi AB. Peroxynitrite-mediated oxidative protein modifications. *FEBS Lett* 1995; **364**: 279-282
18 **Ischiropoulos H**, Zhu L, Chen J, Tsai M, Martin JC, Smith CD, Beckman JS. Peroxynitrite-mediated tyrosine nitration catalyzed by superoxide dismutase. *Arch Biochem Biophys* 1992; **298**: 431-437
19 **Koppenol WH**, Moreno JJ, Pryor WA, Ischiropoulos H, Beckman JS. Peroxynitrite, a cloaked oxidant formed by nitric oxide and superoxide. *Chem Res Toxicol* 1992; **5**: 834-842
20 **Rocic P**, Kolz C, Reed R, Potter B, Chilian WM. Optimal reactive oxygen species concentration and p38 MAP kinase are required for coronary collateral growth. *Am J Physiol Heart Circ Physiol* 2007; **292**: H2729-H2736
21 **Zhang X**, Min X, Li C, Benjamin IJ, Qian B, Zhang X, Ding Z, Gao X, Yao Y, Ma Y, Cheng Y, Liu L. Involvement of reductive stress in the cardiomyopathy in transgenic mice with cardiac-specific overexpression of heat shock protein 27. *Hypertension* 2010; **55**: 1412-1417
22 **Andreyev AY**, Kushnareva YE, Starkov AA. Mitochondrial metabolism of reactive oxygen species. *Biochemistry* (Mosc) 2005; **70**: 200-214
23 **Lefer DJ**, Granger DN. Oxidative stress and cardiac disease. *Am J Med* 2000; **109**: 315-323
24 **Saitoh S**, Kiyooka T, Rocic P, Rogers PA, Zhang C, Swafford A, Dick GM, Viswanathan C, Park Y, Chilian WM. Redox-dependent coronary metabolic dilation. *Am J Physiol Heart Circ Physiol* 2007; **293**: H3720-H3725
25 **Saitoh S**, Zhang C, Tune JD, Potter B, Kiyooka T, Rogers PA, Knudson JD, Dick GM, Swafford A, Chilian WM. Hydrogen peroxide: a feed-forward dilator that couples myocardial metabolism to coronary blood flow. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2614-2621
26 **Di Simplicio P**, Franconi F, Frosalí S, Di Giuseppe D. Thiolation and nitrosation of cysteines in biological fluids and cells. *Amino Acids* 2003; **25**: 323-339
27 **Roberts CK**, Sindhu KK. Oxidative stress and metabolic syndrome. *Life Sci* 2009; **84**: 705-712
28 **Abdul-Ghani MA**, DeFronzo RA. Mitochondrial dysfunction, insulin resistance, and type 2 diabetes mellitus. *Curr Diab Rep* 2008; **8**: 173-178
29 **Fisler JS**, Warden CH. Uncoupling proteins, dietary fat and the metabolic syndrome. *Nutr Metab* (Lond) 2006; **3**: 38
30 **Hampton T**. Mitochondrial defects may play role in the metabolic syndrome. *JAMA* 2004; **292**: 2823-2824
31 **Minamino T**, Komuro I. Vascular cell senescence: contribution to atherosclerosis. *Circ Res* 2007; **100**: 15-26
32 **Nicolson GL**. Metabolic syndrome and mitochondrial function: molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. *J Cell Biochem* 2007; **100**: 1352-1369
33 **Nilsson MI**, Greene NP, Dobson JP, Wiggs MP, Gasier HG, Macias BR, Shimkus KL, Fluckey JD. Insulin resistance syndrome blunts the mitochondrial anabolic response following resistance exercise. *Am J Physiol Endocrinol Metab* 2010; **299**: E466-E474
34 **Buchanan J**, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC, Litwin SE, Abel ED. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology* 2005; **146**: 5341-5349
35 **Wang P**, Lloyd SG, Zeng H, Bonen A, Chatham JC. Impact of altered substrate utilization on cardiac function in isolated

hearts from Zucker diabetic fatty rats. *Am J Physiol Heart Circ Physiol* 2005; **288**: H2102-H2110
36 **Bugger H**, Abel ED. Molecular mechanisms for myocardial mitochondrial dysfunction in the metabolic syndrome. *Clin Sci* (Lond) 2008; **114**: 195-210
37 **Picchi A**, Gao X, Belmadani S, Potter BJ, Focardi M, Chilian WM, Zhang C. Tumor necrosis factor-alpha induces endothelial dysfunction in the prediabetic metabolic syndrome. *Circ Res* 2006; **99**: 69-77
38 **Hattan N**, Chilian WM, Park F, Rocic P. Restoration of coronary collateral growth in the Zucker obese rat: impact of VEGF and ecSOD. *Basic Res Cardiol* 2007; **102**: 217-223
39 **Reed R**, Kolz C, Potter B, Rocic P. The mechanistic basis for the disparate effects of angiotensin II on coronary collateral growth. *Arterioscler Thromb Vasc Biol* 2008; **28**: 61-67
40 **Rivard A**, Fabre JE, Silver M, Chen D, Murohara T, Kearney M, Magner M, Asahara T, Isner JM. Age-dependent impairment of angiogenesis. *Circulation* 1999; **99**: 111-120
41 **Rivard A**, Berthou-Soulie L, Principe N, Kearney M, Curry C, Branellec D, Semenza GL, Isner JM. Age-dependent defect in vascular endothelial growth factor expression is associated with reduced hypoxia-inducible factor 1 activity. *J Biol Chem* 2000; **275**: 29643-29647
42 **Abaci A**, Oğuzhan A, Kahraman S, Eryol NK, Unal S, Arinç H, Ergin A. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999; **99**: 2239-2242

S- Editor Cheng JX **L- Editor** Lutze M **E- Editor** Zheng XM