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Coronary Microvascular Dysfunction in CAD: Consequences and Potential Therapeutic Applications

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1. Introduction

Substantial research and clinical effort has been directed toward the understanding, identification and management of coronary artery disease (CAD). As a result, the processes of cholesterol accumulation and inflammation that lead to large vessel occlusions have been fully elucidated. In contrast to those with CAD, many patients have symptoms of angina and reductions in coronary flow reserve despite normal coronary angiography of the large epicardial arteries. In this situation the vessels that limit flow to myocardium are the more distal epicardial prearterioles and intramyocardial arterioles – vessels typically too small to be directly visualized by conventional coronary angiography. These vessels comprise the coronary microcirculation. Coronary microvascular dysfunction (CMVD), in contrast to CAD, continues to be poorly understood and difficult to manage. In addition, the presence of CMVD can be a confounding factor in the management of patients with CAD.

2. Anatomy and physiology of the coronary microcirculation

The coronary arterial network is generally divided into three sequential morphological zones. The large epicardial coronary arteries decrease in diameter from 2-5 to 500 microns as they branch off of the aorta and travel distally along the epicardium. Distal to the large coronary arteries are epicardial pre-arterioles that decrease in diameter from 500 to 100 microns. Finally, the pre-arterioles give rise to intramyocardial arterioles that measure 100 microns or less in diameter. Coronary arterioles and pre-arterioles dilate and constrict in large part through feedback mechanisms in order to maintain a constant blood flow shear stress across the interior surface of the vessels (Camici & Crea, 2007).

Blood flow shear stress is the average laminar force per unit of cross sectional area of the vessel surface, applied parallel to the vessel wall. The interior surfaces of all blood vessels are lined with endothelial cells. Endothelial cells detect changes in blood flow shear stress and respond with signals to the surrounding smooth muscle cells to either relax in response

to an increase in shear stress or contract in response to a decrease in shear stress. It remains unclear exactly how endothelial cells are able to detect and respond to these fluctuations in shear stress. Some studies have identified the protein caveolin-1 (CAV-1, which forms caveolae) as a receptor in this process (Traub & Berk, 1998). Other evidence suggests that endothelial cells respond to an increase in shear stress by activating endothelial nitric oxide synthase (eNOS) which in turn catalyzes the production and release of nitric oxide (NO), a potent vasodilator (Traub & Berk, 1998). The roles of CAV-1 and of eNOS are examples of many different pathways involved in the process of arteriolar dilatation. Arterioles (500 microns or less) located deep within the myocardium are exposed to a complex milieu of hormones and cytokines, some of which also perform roles essential to the fine auto-regulation of vasoconstriction and vasodilatation.

Normal function of the microcirculation is dependent on the production and bioavailability of nitric oxide (NO) (Traub & Berk, 1998). NO is produced in the endothelium by nitric oxide synthase (NOS). There are three isoforms of NOS; endothelial NOS (eNOS), inducible NOS (iNOS) and neuronal NOS (nNOS). NOS converts L-arginine into nitric oxide (NO), which diffuses into surrounding vascular smooth muscle cells (VSMC) and induces relaxation. Relaxation of VSMC is caused by the binding of NO to guanylyl cyclase and subsequent activation of the enzyme. Guanylyl cyclase catalyzes the dephosphorylation of GTP to produce cGMP, which is a second messenger for many cellular functions. Cyclic GMP induces smooth muscle relaxation by suppressing intracellular entry of calcium through voltage-gated calcium channels, by activating (via phosphorylation) ATP-dependent potassium channels, or by activating the enzyme myosin light chain phosphatase, which dephosphorylates myosin light chains and relaxes smooth muscle (Traub & Berk, 1998). Subsequently, vasodilation occurs and blood flow is increased. The bioavailability of NO is critical to normal vascular function.

3. Clinical presentation of coronary microvascular dysfunction

In addition to occlusion of a coronary artery, myocardial ischemia may be caused by resistance to coronary blood flow related to increased vascular tone. In the healthy individual, epicardial coronary arteries contribute minimal resistance to blood flow as long as they are free of occlusive disease (Maseri, Beltrame, & Shimokawa, 2009). The pre-arterioles contribute about 20% of the total resistance to blood flow (Maseri et al., 2009), and the remainder of the coronary microcirculation collectively accounts for 60%-80% of the total resistance to blood flow (John F. Beltrame, Crea, & Camici, 2009). Dysfunction of a single arteriole would not affect overall cardiac function. However, an abnormal increase in resistance to blood flow through an entire network of coronary arterioles could cause ischemia in a large segment of myocardium. In some cases, coronary microvascular dysfunction can cause ischemia to a similar degree as that caused by large epicardial coronary artery occlusions. Indeed, up to 30% of patients who present with angina and myocardial infarction have patent epicardial coronary arteries at the time of cardiac catheterization (Romeo, Rosano, Martuscelli, Lombardo, & Valente, 1993; Vesely & Dilsizian). In some cases, cardiac angiography is able to detect a "slow blood flow phenomenon" based on delayed opacification of the microcirculation (J. F. Beltrame, Limaye, & Horowitz, 2002; Tambe, Zimmerma.Ha, Demany, & Mascaren.E, 1972), but in general the use of cardiac angiography is limited to the observation of only those vessels that are 500 microns or larger in size (Vesely & Dilsizian). Most studies suggest that

coronary microvascular dysfunction (CMVD) remains stable over time and is associated with a good overall prognosis in the majority of cases. Nonetheless, as many as 20-30% of patients with CMVD develop progressive symptoms of angina, sustain acute myocardial infarctions, and demonstrate reductions in cardiac function (G. A. Lanza & Crea, 2010). Some markers of ischemia in such patients include increased levels of plasma lactate and lipid peroxidase (both byproducts of anaerobic glucose metabolism), decreased oxygen saturation within the coronary sinus, and a shift in myocardial phosphate utilization on magnetic resonance spectroscopy (G. A. Lanza & Crea, 2010).

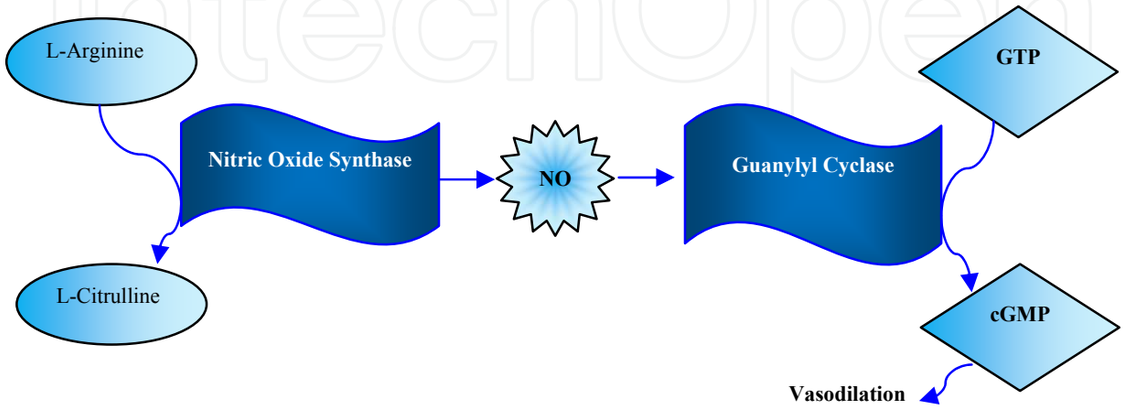

Fig. 1. Nitric oxide (NO) is produced in endothelial cells using L-arginine as a substrate. NO diffuses readily across plasma membranes to vascular smooth muscle cells. The synthesis of cyclic guanylyl monophosphate (cGMP) from guanylyl triphosphate (GTP) causes relaxation of vascular smooth muscle, and subsequent vasodilation.

4. Classification of coronary microvascular dysfunction

There are several broad categories of CMVD (Camici & Crea, 2007). The first category is classified as CMVD in the absence of obstructive large vessel CAD, based on the macroscopic findings at the time of coronary catheterization. The second category of microvascular dysfunction is defined as CMVD in the presence of cardiomyopathy. The third category is classified as CMVD in the presence of obstructive large vessel CAD. Clearly, in this subtype, the cardiac risk factors that induce the formation of occlusive disease within the large epicardial coronary arteries may also negatively impact blood flow through the small coronary arterioles.

The fourth category is classified as iatrogenic coronary microvascular dysfunction. This type of CMVD refers to the paradoxical "no re-flow phenomenon" associated with reperfusion injury. This occurs in the microcirculation, downstream of arteries recently made patent by thrombolysis, percutaneous angioplasty, stenting, or bypass grafting. This "no re-flow phenomenon" is identified based on persistent low blood flow (according to the TIMI flow scale (Antman et al., 1999)) after successful revascularization procedures. TIMI is an acronym for "thrombolysis in myocardial infarction" (Antman et al., 1999), and the flow scale measures the amount of time it takes (in seconds) for contrast dye to fill the length of a coronary artery during angiography (Camici & Crea, 2007).

One mechanism of reperfusion injury is distal embolization of plaque and thrombin in the small arterioles. Increased adrenergic tone following an acute cardiac event could cause vasoconstriction in the coronary microcirculation. However, in some cases, microvascular blood flow deficits have been measured in small vessels remote from the region of the infarct and revascularization (Gregorini et al., 1999), which are not explained by "no-reflow" or adrenergic stimulation. Moreover, microvascular reperfusion abnormalities can persist for as long as 3-6 months following the revascularization (John F. Beltrame et al., 2009). Myocardial ischemia initially causes a decrease in the level of intracellular ATP, a change from aerobic to anaerobic metabolism, a buildup of toxic byproducts of anaerobic metabolism, and a decrease in the pH. The restoration of oxygenated blood flow to recently ischemic tissue induces a cascade of toxic events. Some of these events might include, but are not limited to, abnormal leukocyte or platelet aggregation, complement activation, osmotic overloading of the mitochondria, and subsequent dysfunction of the microcirculation.

5. Cardiac Syndrome X

"Syndrome X" is the label used to describe an additional clinical phenomenon associated with CMVD. The label "syndrome X" typically refers to the presence of all of the following characteristics: angina or angina-like chest pain with exertion; ST- segment abnormalities during cardiac stress testing; absence of cardiac wall motion abnormalities during stress testing; and normal and patent coronary arteries without coronary artery vasospasm during cardiac catheterization (Bellamy et al., 1998). Therefore, "syndrome X" is a clustering of clinical signs and symptoms that indicate myocardial ischemia on exertion in the absence of evident coronary artery disease.

Most available evidence points to CMVD as the pathology responsible for "syndrome X". Zeiher et al (1995) found a suboptimal increase in coronary blood flow (CBF) in response to the endothelium-dependent vasodilator acetylcholine compared with an optimal increase in CBF in response to the endothelium-independent vasodilator papaverine, in patients with "syndrome X" (Zeiher, Krause, Schachinger, Minners, & Moser, 1995). In addition, a subsequent study of patients with "syndrome X" showed similar suboptimal CBF response to both endothelium-dependent and endothelium-independent vasodilators (Chauhan, Mullins, Taylor, Petch, & Schofield, 1997).

The central nervous system (CNS) has also been implicated in the process of microvascular angina, "syndrome X", and CMVD in general. Major CNS events such as massive strokes and subarachnoid hemorrhages sometimes lead to chest pain and diffuse ST- wave abnormalities on ECG thought to be induced in part by alterations in the autonomic adrenergic innervation of the coronary arteries (Kono et al., 1994). In one extreme but rare disease entity called "Stress-Related Cardiomyopathy" or Takotsubo (Japanese for "octopus trap") Disease, a single event of extreme physical or emotional stress by itself can induce cardiac ischemia characterized by ST- segment abnormalities on electrocardiogram (ECG) and segmental wall akinesis (typically the apical wall) on ECHO giving way to the "octopus trap" appearance of the heart muscle (Bybee & Prasad, 2008; Kume et al., 2005; Tsuchihashi et al., 2001). In addition, several cases of toxic pheochromocytoma have been observed to cause cardiac ischemia and ST- wave abnormalities (Shaw, Rafferty, & Tait, 1987; Yamanaka et al., 1994). Researchers have generally applied the terms "neurogenically-stunned myocardium" or "catecholamine myopathy" to these anectodal cases.

6. Measurement of coronary microvascular function

Investigators have been using a variety of direct and indirect methods to measure blood flow through the small coronary arterioles in order to facilitate the study of the coronary microcirculation. One direct method for measurement is the passage of a guide wire tipped with a thermistor probe and pressure sensor into the epicardial arteries to measure blood flow by thermodilution (Vesely & Dilsizian). Indirect methods of measurement have included transthoracic echocardiography with doppler flow analysis (TTE-DR), contrast stress echocardiography, thallium scintigraphy, positron emission tomography using ^{82}rubidium as a marker, and cardiovascular magnetic resonance (CMR) using gadolinium as a flow tracer. Many of these tests are expensive, time-consuming, expose patients to radioactivity, and provide limited information on the microvasculature. Still, the ultimate goal of each modality is to measure coronary perfusion based on several mathematic equations. Coronary blood flow (CBF) is the measurement of the amount of blood that passes through a cross section of the artery per unit of time. Coronary flow reserve (CFR) is a calculation of the ratio of maximally-stimulated CBF within a particular coronary artery to the CBF through the same artery at rest. Flow is maximized using physical or chemical stimuli to cause vasodilation. A ratio of less than 2 – 2.5 is considered abnormal (G. A. Lanza & Crea, 2010). Regional myocardial blood flow (MBF), which equals the amount of blood flow (milliliters/minute/gram) through a segment of myocardium, can also be measured (Vesely & Dilsizian). A normal resting MBF is usually 0.6 – 1.3 ml/min/g and should increase 3 – 4 fold during the peak response (Vesely & Dilsizian). In thallium scintigraphy, the injection of a vasodilator simulates an increase in cardiac stress by preferentially dilating normal vessels that in turn potentially divert blood flow from diseased vessels. A post-stress disparity in blood flow will appear in the form of an abnormal redistribution of thallium, the radioactive marker. Large vessel occlusions typically appear as segmental areas of decreased blood flow corresponding to the perfusion territories of one or more of the main epicardial coronary arteries with or without associated cardiac wall motion abnormalities. By comparison, microvascular disease often appears as patchy isolated areas of decreased blood flow, most often with no evidence of associated wall motion abnormalities (G. A. Lanza & Crea, 2010). All of these imaging modalities carry a certain margin of error, and, while they can be instrumental in locating a large coronary vessel occlusion, they often do not provide helpful information in cases of CMVD (Maseri et al., 2009).

7. Treatment

The various etiologies of CMVD as well as the lack of data from clinical trials preclude a definitive treatment regimen. As a result, multiple pharmacologic attempts have been made to limit CMVD induced morbidity and mortality. CMVD is typically treated similarly to coronary artery disease. Beta-blockers, nitrates and calcium channel blockers have long been used for CMVD, but only beta-blockers have shown beneficial effects in clinical trials. Additional agents such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have also been considered for persistent symptoms despite optimal anti-ischemic drug therapy. Alpha adrenergic antagonists, statins, estrogens, xanthine derivatives, adenosine and tricyclic antidepressants have also been investigated for treatment of CMVD-induced angina. Other experimental therapies include GLP-1, L-arginine, nicorandil, tetrahydrobiopterin and nitrite. This section will examine the evidence in support of the pharmacologic treatment of CMVD.

7.1 Anti-anginals

Beta blockers, nitrates and calcium channel blockers are the conventional anti-anginal drugs used most often for ischemic chest pain with associated ECG changes in the presence or absence of coronary artery lesions. There are no definitive trials indicating a superior anti-anginal therapy for the treatment of CMVD. However, beta blockers seem to be the most effective at decreasing the severity and frequency of chest pain and they are considered first line therapy. One randomized, double-blinded prospective trial found that beta blockers, but not calcium channel blockers or nitrates, significantly reduced chest pain episodes in patients diagnosed with cardiac "syndrome X" (Gaetano Antonio Lanza, Colonna, Pasceri, & Maseri, 1999). Similarly, in 16 patients with transient myocardial ischemia and normal coronary angiography randomized to treatment with propanolol, verapamil or placebo, those patients receiving propanolol had significantly fewer episodes of ischemic chest pain when compared to placebo (Bugiardini, Borghi, Biagetti, & Puddu, 1989).

Nitrates are frequently used to treat chest pain but their effectiveness in coronary microvascular dysfunction is unclear. Radice et al (1994) showed that exercise duration and time to 1-mm ST-segment depression in patients with CMVD improved with nitroglycerin administration, albeit significantly less than in patients with CAD (Radice, Giudici, Albertini, & Mannarini, 1994). Similarly, another study showed an improvement in time to angina and peak ST-segment depression with nitroglycerin administration (Bugiardini et al., 1993). However, approximately 50% of patients CMVD taking sublingual nitrates for chest pain experience minimal relief (J. Kaski et al., 1995) and exercise tolerance tests for patients with CMVD worsened with nitrate use (G. Lanza, Manzoli, Bia, Crea, & Maseri, 1994; Radice et al., 1996).

Similarly, calcium channel blockers (CCB) have limited effectiveness in the treatment of CMVD. A 4 week treatment with nisoldipine (a dihydropyridine CCB) significantly increased exercise duration and time to angina in patients with CMVD (Özçelik, Altun, & Özbay, 1999). Similarly, a 4-week trial of nifedipine or verapamil (a non-dihydropyridine CCB) showed a significant improvement in exercise tolerance and angina (Cannon, Watson, Rosing, & Epstein, 1985). Montorsi et al (1990) showed improvement in ST-segment depression during exercise in patients with CMVD treated with nifedipine for 4 weeks (Montorsi et al., 1990). In contrast, Lanza et al (1999) demonstrated that calcium channel blockers did not decrease the number of episodes of chest pain (Gaetano Antonio Lanza et al., 1999). In addition, a 7-day treatment with verapamil made no difference in the frequency of episodes of ST-segment depression, measured by continuous ECG monitoring over 2 days (Bugiardini et al., 1989).

7.2 Statins

The role of statins in the primary and secondary prevention of cardiovascular events has been well established, as has the improvement of endothelial function via non-cholesterol lowering effects (Rosenson & Tangney, 1998). Statins are beneficial in patients with CMVD and they are commonly used in patients with hypercholesterolemia. In a randomized, placebo-controlled study, pravastatin improved exercise duration and time to ST-segment depression in patients with CMVD (Kayikcioglu et al., 2003). Similar results were reported by Fabian et al (2004) using simvastatin (Fábián et al., 2004). Pizzi et al (2004) found that a 6-

month trial of atorvastatin and ramipril significantly improved exercise tolerance and symptoms of chest pain secondary to CMVD, possibly through the reduction of oxidative stress (Pizzi, Manfrini, Fontana, & Bugiardini, 2004).

7.3 Angiotensin converting enzyme inhibition

As mentioned above, angiotensin converting enzyme inhibitors (ACE-I) have been associated with improvement of chest pain and ECG-findings in patients with CMVD (Pizzi et al., 2004). Kaski et al (1994) found an increase in exercise time and time to ST-segment depression in patients with reduced coronary flow taking enalapril (Juan Carlos Kaski, Rosano, Krzyzowska-Dickinson, Martuscelli, & Romeo, 1994). Evidence from Nalbantgil et al (1998) further supported these findings in patients with CMVD taking cilazapril (Nalbantgil et al., 1998). Long-term inhibition of ACE is associated with improved nitric oxide bioavailability (Chen, Hsu, Wu, Lin, & Chang, 2002), which may be one mechanism by which ACE-Is reduce episodes of chest pain in patients with CMVD.

7.4 Metformin

Metformin has been shown to have vasculoprotective properties and can improve endothelial function (Mather, Verma, & Anderson, 2001). These vascular effects have proven to be beneficial for patients with CMVD. In a randomized, double blinded, placebo controlled study, Jadhav et al (2006) found that metformin improved vascular function and decreased myocardial ischemia in non-diabetic women with chest pain and angiographically normal coronary arteries (Jadhav et al., 2006). This study found a significant reduction in the incidence of chest pain and ST-segment depression during exercise treadmill testing. Similarly, Kapinya et al (2008) conducted a retrospective, observational study investigating cardiac stress test results in patients with chest pain without cardiac biomarker rise. These investigators found that patients previously taking metformin had significantly less ischemia and infarction compared to patients previously taking insulin or insulin secretagogues (Kapinya, Nijjar, Stanek, & Amanullah, 2008).

7.5 Hormone replacement therapy/estrogen

The high proportion of peri- and post-menopausal women with CMVD raises questions about the lack of estrogen as a pathophysiologic cause of CMVD and its replacement as a potential therapy. Hormone replacement therapy has been shown to improve endothelial function (J C Kaski, 2006; Roque et al., 1998; Sitges et al., 2001) as well as decrease episodes of angina (Rosano et al., 1996) and increase exercise tolerance (Albertsson, Emanuelsson, & Milsom, 1996). However, the risk of breast cancer and thromboemoblic disease has limited the possibilities of hormone replacement therapy for CMVD (Committee, 2004; Investigators, 2002).

7.6 Other pharmacologic therapies

7.6.1 Imipramine

Imipramine, a tricyclic antidepressant, has been shown to improve chest pain symptoms but not quality of life in patients with CMVD (Cox, Hann, & Kaski, 1998). The hypothesized

mechanism of this effect is not through vasoactive pathways, but through its visceral analgesic effects (Cannon et al., 1994). The American College of Cardiology recommends imipramine for treatment of CMVD in patients who have failed treatment with risk factor reduction, beta blockers, calcium channel blockers or nitrates (Wright et al., 2011).

7.6.2 L-arginine

L-arginine is a substrate for the production of NO by NOS (Palmer, Ashton, & Moncada, 1988). In patients with angina and normal coronary arteries, intravenous infusion of L-arginine restored nitric oxide activity and resulted in the improvement of endothelial function (Piatti et al., 2003). In addition, chronic L-arginine supplementation enhanced NO synthesis in diabetic animals (Kohli et al., 2004), and improved coronary microvascular endothelial function in humans (Lerman, Burnett, Higano, McKinley, & Holmes, 1998). These findings demonstrate a potential role for L-arginine in the treatment of CMVD.

7.6.3 Tetrahydrobiopterin

Tetrahydrobiopterin (BH_4) is a co-factor required for the production of NO from L-arginine and molecular oxygen (Scott-Burden, 1995), and BH_4 deficiency causes decreased NO production by diabetic coronary endothelium (Meininger et al., 2000). In addition, intracoronary BH_4 improved acetylcholine-induced microvascular dilator responses in patients with endothelial dysfunction *in vivo*. Thus, supplementation with BH_4 may be a novel therapeutic means to increase NO availability for patients with coronary microvascular disease (Setoguchi, Mohri, Shimokawa, & Takeshita, 2001).

7.6.4 Alpha antagonists

Alpha adrenergic antagonists decrease alpha-mediated vasoconstriction and have been hypothesized to improve CMVD symptoms. However, a study by Bøtker et al (1998) proved disappointing. Doxazosin did not increase exercise tolerance or time to ST-segment depression during exercise versus placebo (Bøtker, Sonne, Schmitz, & Nielsen, 1998).

7.6.5 Xanthine derivatives

Xanthine derivatives such as theophylline, bamiphylline and aminophylline have been used to reduce chest pain symptoms related to CMVD. Emdin et al (1989) found that aminophylline had a beneficial effect on exercise induced chest pain and ischemic ECG changes in patients with CMVD (Emdin, Picano, Lattanzi, & L'Abbate, 1989). The proposed mechanism for this is through the inhibition of pain transmission through adenosine receptor blockade. In addition, myocardial flow maldistribution (elicited by inconsistent adenosine release in the presence of increased coronary arteriolar resistance) may also have been prevented, but this was not measured directly (Emdin et al., 1989).

7.6.6 Nicorandil

Nicorandil (nicotinamide nitrate) is a hybrid between a nitrate and an activator of ATP-sensitive potassium channels. Its vasodilatory mechanisms include guanylyl cyclase activation and hyperpolarization (Akai et al., 1995) which preferentially relaxes VSMC in the

microcirculation (Akai et al., 1995). Ito et al demonstrated preservation of microvascular integrity by intravenous nicorandil after coronary ischemia and reperfusion (Ito et al., 1999). Ikeda et al (1994) found that post-angiography treatment with nicorandil improved coronary microvascular function and was associated with earlier recovery of ST segment elevation and greater regional wall motion in the infarcted area after reperfusion (Ikeda et al., 2004). In addition, in a prospective study, patients with end-stage renal disease who were taking oral nicorandil prior to an ischemic coronary event had improved outcomes after revascularization (Ishii et al., 2007).

7.6.7 Nitrite

Until recently, nitrite was typically thought of as a biologically inactive metabolite of nitric oxide metabolism. However, more recent findings have determined that the generation of NO from the reduction of nitrite can occur *in vivo,* under a variety of physiologic and pathophysiologic conditions (Vitturi & Patel, 2011). Nitrite is cardioprotective after episodes of ischemia and reperfusion in a variety of experimental models, and clinical trials are underway to determine the vasculoprotective and cardioprotective actions of nitrite therapy in patients with cardiovascular disease (Calvert & Lefer, 2009).

7.6.8 Glucagon-like peptide-1 (GLP-1)

GLP-1 is an incretin hormone that regulates post-prandial metabolism and blood glucose concentration. GLP-1 is also biologically active in the cardiovascular system. GLP-1 improves endothelial function *in vivo* (Basu et al., 2007; T. Nystrom, 2008; Thomas Nystrom et al., 2004), attenuates the expression of pro-inflammatory cytokines (Liu, Hu, Simpson, & Dear, 2008) and adhesion molecules (Liu, Dear, Knudsen, & Simpson, 2009) in cultured endothelial cells, decreases inflammatory injury in intact endothelium (Dozier et al., 2009), and protects myocardium from ischemia/reperfusion injury in isolated heart models and *in vivo* (Ban et al., 2008; Bose, Mocanu, Carr, Brand, & Yellon, 2004, 2005; Bose, Mocanu, Carr, & Yellon, 2007; B. B. Dokken, Labonte, Davis-Gorman, & McDonagh, 2007; Huisamen, Genade, & Lochner, 2008; Sonne, Engstrom, & Treiman, 2008; Timmers et al., 2009). The mechanisms of GLP-1 in the vasculature are not well-understood, but preliminary findings suggest that it may decrease endothelial production of ROS (Bloomgarden; Brownlee, 2006) and enhance endothelium-dependent vasodilation through nitric oxide (NO) signaling (Ban et al., 2008; Basu et al., 2007; Tesauro et al., 2009). We recently reported that GLP-1 prevents coronary microcirculatory dysfunction in swine when administered after cardiac arrest and resuscitation (Betsy B Dokken et al., 2009). Endogenous GLP-1 is decreased in patients with type 2 diabetes, who incidentally are more likely to have CMVD. GLP-1-receptor agonists are currently FDA approved for the treatment of hyperglycemia in patients with type 2 diabetes. Substantial effort is currently underway to determine the mechanisms of the protective effects of GLP-1 and its related peptides.

In summary, the optimal therapy for CMVD is far from defined. In a recent study investigating the long-term prognoses of patient's with CMVD, Lamendola et al (2010) found that chest pain episodes remained unchanged in one-third of patients and worsened significantly in 14% despite treatment with either beta-blockers, calcium channel blockers, nitrates, ACE inhibitors or statins (Lamendola et al., 2010).

8. Conclusion

The coronary microcirculation modulates blood flow throughout the heart, and thus is of major importance in both health and disease. The presence of CMVD complicates the presentation and management of patients with CAD. Due to the multifactorial nature of CMVD and to the difficulty associated with accurately measuring its function, the coronary microcirculation has received limited attention. In order to determine appropriate strategies for the diagnosis and management of CMVD, the physiology, pathophysiology and pharmacology of the coronary microcirculation demands further investigation.

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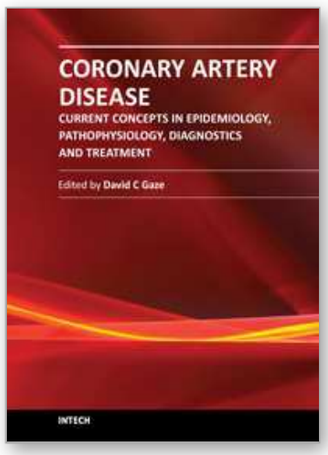

Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment

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Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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