Journal of Advanced Veterinary Research Volume 8, Issue 1 (2018) 1-5

Journal of Advanced Veterinary Research

http://advetresearch.com/index.php/avr/index

Involvement of Oxidative Stress in Cardiovascular Diseases

Mahmoud Rushdi Abd Ellah

Department of Animal Medicine, Faculty of Veterinary Medicine, Assiut University, Egypt

ARTICLE INFO

Editorial

Keywords:

Antioxidants
Cardiovascular
Free radicals
Heart
Oxidative stress

ABSTRACT

Many research studies support the evidence that free radicals stress is involved in the pathogenesis of many diseases in human and animals. The current review aimed to throw the light on sources of free radicals in the cardiovascular system, involvement of oxidative stress in cardiovascular diseases and the role of the antioxidants in alleviating the damage produced by oxidative stress.

J. Adv. Vet. Res. (2018), 8 (1),1-5

Introduction

Cardiovascular diseases (CVD) are considered the principle cause of death in most countries (Hennekens, 1998). Elevated levels of oxidative stress markers were detected in numerous cardiovascular disorders in human including hypertension, ventricular hypertrophy, atherosclerosis and congestive heart failure (Carlos *et al*., 1998; Keith *et al*., 1998; Miller *et al*., 1998; Suzuki *et al*., 1998; Gokce *et al*., 1999; Harjai, 1999; Miwa *et al*., 1999; Buffon *et al*., 2000). In addition, many studies have shown increases in biomarkers of oxidant production and/or decreases in antioxidant potential in cardiovascular disorders in animals (Chintala *et al*., 1992 and Sagols and Priymenko, 2011).

Normally, oxygen is used by the mitochondria in the oxidative phosphorylation process and for the production of adenosine triphosphate (Abd Ellah, 2010). Lack of oxygen supply as in cases of hypoxia or ischemia upsets the mitochondrial electron transport chain, which consequently result in the accumulation of toxic metabolites, followed by cell death (Lemasters *et al*., 1997). Reactive oxygen species (ROS) formed during mitochondrial electron transport are removed by the antioxidant defense. The intracellular antioxidant defense chain can be overwhelmed by the generation of huge amounts of ROS, causing lipid peroxidation and DNA breaks (Ambrosio and Tritto, 1999).

Sources of free radicals

Under normal physiological conditions, ROS are produced in low concentrations, which are helpful in regulating vascular smooth muscle cell contaction, relaxation and growth. On the other hand, excess production of ROS could result in cardiac and vascular dysfunction.

Mitochondria represent the main source for ROS intracellularly under normal physiological conditions. Other sources include induction of cytosolic oxidases such as xanthine oxidase (XO), NADH/NADPH oxidase and nitric oxide synthase (NOS). XO generates superoxide anion, this enzyme is present mainly in the intestinal mucosa and in the liver. Thea activity of XO is enhanced during chronic hypoxia and in the presence of cytokines. It has been reported that activity of XO together with superoxide increased in the mesenteric tissue in animal model of hypertension, which may be responsible for intensifying vascular tone (Suzuki *et al*., 1998), this assumption was supported by the findings of Houston *et al*. (1999), who suggested that XO could be concentrated several fold in the vascular tissues and may play significant role in dysfunction of the endothelium in atherosclerotic humans and hypercholesterolemic rabbits.

Free radicals are produced by many immune cells, which used to kill ingested pathogen as a means of host defense. These immune cells act as a source for production of oxidants

*Corresponding author: Mahmoud Rushdi Abd Ellah
E-mail address: mrushdi@aun.edu.eg

ISSN: 2090-6277/2090-6269/

in an acute inflammatory response. Infiltration of tissues especially with neutrophils during post ischemic reperfusion is associated with cell death and tissue injury, which caused by the secreation of ROS and proteolytic enzymes. This assumption was supported by the findings of Buerke *et al.* (1994), who observed that reperfusion cardiac injury in feline is reduced after inhibition of neutrophils migration.

Phagocytic cells play an important role in defense against infection by the release of large amount of superoxide that is formed by the enzyme NADH/NADPH oxidase. This enzyme is established to be the source for superoxide production in the vascular tissues (Bayraktutan *et al*., 1998; Di Wang *et al*., 1999), under the effect of angiotensin II, higher production of superoxide has been involved in the pathogenesis of angiotensin II induced vascular hypertrophy and endothelial cell dysfunction (Griendling *et al*., 1994; Rajagopalan *et al*., 1996; Ushio-Fukai *et al*., 1998; Watta- napitayakul *et al*., 2000).

Oxidative stress in cardiovascular diseases

Oxidative stress was reported to be involved in the pathogenesis of many cardiovascular diseases, including myocardial infarction (MI), coronary disease, congestive heart failure (Mak and Weglicki, 1990; Belch *et al*., 1991; Kaul *et al*., 1993; McMurray *et al*., 1993; Nakamura *et al*., 2001; Serdar *et al*., 2001; Freeman *et al*., 2005; Giordano, 2005; Wojciechowska *et al*., 2014) and in the pathophysiology of atherosclerosis (Moreno and Fuster, 2004), diabetic cardiomyopathy (Bugger and Abel, 2010; Khullar *et al*., 2010), congestive cardiomyopathy (Pankuweit *et al*., 2004) and hypertensive heart disease (Shahbaz *et al*., 2010).

Reactive oxygen species have been implicated as a contributor to endothelial dysfunction, and reported to be a mojor cause of endothelial dysfunction in atherosclerosis (Cai and Harrison, 2000). Oxidative stress plays an important role in the pathogenesis of atherosclerosis through the production of ROS in the wall of the blood vessels, which could result in endothelial dysfunction (Channon and Guzik, 2002; Lee *et al*., 2012) and may produce damage to the cellular components of the vascular wall. An experimental study done by Liao *et al*. (1994) revealed that ROS involved in the development of atherosclerosis through the production of lipid peroxidation products and in another study by activation of matrix metalloproteinases (Rajagopalan *et al*., 1996)

Studies reported that increase the production of superoxide from the mitochondria in pathological conditions results in modification of mitochondrial DNA, which can lead to functional changes in the cell. Several studies have reported the presence of a correlation between DNA damage and atherosclerosis (Martinet *et al*., 2001). Reportedly, ROS can inhibit the sarcoplasmic reticulum Ca2+ pump in the cardiac contraction - relaxation cycle, which have direct impact on myocardial function (Matsubara and Dhalla, 1996; Temsah *et al*., 1999).

Myocardial infarction was reduced in dogs infused with SOD and catalase after coronary occlusion and reperfusion, which suggested the involvement of free radicals such as superoxide anion and hydroxyl radicals (Jolly *et al*., 1984), in ischemia–reperfusion injury (Bolli, 1988; Ferrari *et al*., 1998).

Ischemic reperfusion was reported to cause functional and structural alterations in the myocardium (Bolli *et al*., 1988). Moreover, Yasmin *et al*. (1997) demonstrated that reperfusion is associated with increased production of nitric oxide that interacts with superoxide anion to form peroxynitrite, which may play a role in the development of cardiac dysfunction. In addition, Randhawa and Singal (1992) documented the role of oxidative stress in myocardial stunning using spin-trap technique, where the production of free radicals was suppressed and myocardial stunning was attenuated after antioxidants therapy (Bolli, 1988).

Several studies proved that cytokines like interleukin, tumor necrosis factor and growth factors are pro-oxidants were elevated in plasma in patients with heart disease (Torre-Amione *et al*., 1996; Djurovic *et al*., 1999; Ueda *et al*., 1999; Ruotolo *et al*., 2000), and mediate cardiac dysfunction through the production of nitric oxide (NO) (Schulz *et al*., 1995; Wildhirt *et al*., 1995; Sawyer and Colucci, 1998).

Oxidative stress has been reported to contribute in the development of cardiac dysfunction in experimental animals (Chen *et al*., 2009; Ahmed *et al*., 2010). The pathogenesis of heart failure subsequent to myocardial infarction (MI) in rats was attributed to the involvement of free radicals, which resulted in changes in myocardial antioxidants with a state of oxidative stress, and lipid peroxidation in the early stage. In late stages of MI, the activities of glutathione peroxidase (GSH-Px), catalase, superoxide dismutase (SOD) and the vitamin E level in the myocardial tissues were decreased as reported by Hill and Singal (1996).

In an experimental study on animals, the levels of antioxidants were measured in the two ventricles during the sequelae of heart failure, oxidative stress was developed firstly in the left ventricle, followed by decrease antioxidants levels in the right ventricle in chronic stage of the disease (Hill and Singal, 1996, 1997). In vitro studies by Cheng *et al*. (1995) and Pimentel *et al*. (2001), ROS production was increased during overstretching of cardiomyocytes, which may be involved in in mediating contractile dysfunction. Furthermore, in an experimental induction of heart failure in guinea pigs, done by Dhalla *et al*. (1996), the authors observed that increased oxidative stress was occurred in the transition phase from myocardial hypertrophy to heart failure. In another study in a guinea pig model of heart failure subsequent to banding of the ascending aorta, myocardial antioxidant reserve in the form of SOD and GSHPx was decreased, which associated with increased oxidative stress (Randhawa and Singal, 1992), the authors added that, hypertrophy of the myocardial muscles was developed at ten weeks and heart failure at 20 weeks post surgery.

In vitro studies revealed that exposure of isolated perfused hearts to free radicals resulted in decreased high energy phosphates, structural abnormalities and difficulty in myocardial contraction (Burton *et al*., 1984; Ytrehus *et al*., 1986; Gupta and Singal, 1989). Auto-oxidation of catecholamines was found to initiate the production of free radicals and the development of cardiac dysfunction (Meerson, 1980; Singal *et al*., 1982, 1983). Furthermore, the depression of calcium transport in the sarcoplasmic reticulum mediates the increased ROS in ischemia–reperfusion injury, as documented by Hess *et al*. (1983).

Several research studies had reported that exposure of cardiac preparations to free radical stress resulted in depressed cardiac contraction, diminishing of energy production and a state of lipid peroxidation (Mickelson *et al*., 1988; Gupta and Singal, 1989; Kaul *et al*., 1993,). In another study, reduction of contractile function was correlated with decrease in SOD, glutathione and alpha tocopherol in the myocardial tissues, and associated with increased hydrogen peroxide and lipid peroxidation products (Gupta and Singal, 1989; Vaage, 1997).

Markers of oxidative stress in cardiovascular diseases

Malondialdehyde (MDA), is one of the final products of lipid peroxidation, and mostly measured as a biomarker of oxidative stress (Valko *et al*., 2007; Abd Ellah *et al*., 2013). The degree of oxidative stress is evaluated by measuring the concentration of circulating oxidative products such as MDA

and oxidized low-density lipoproteins (oxLDL) (Betteridge, 2000; Braunwald, 2008). MDA is a mediator that produce the damaging effect of ROS on the cells of the cardiovascular system (Giordano, 2005), that was reported to increase in blood in case of heart failure in humans and animals (Mak and Weglicki, 1990; McMurray et a., 1990; Diaz-Velez *et al*., 1996; Freeman *et al*., 1999; Nakamura *et al*., 2001; Serdar, *et al*., 2001; Polidori *et al*., 2002; Boswood *et al*., 2008; Wojciechowska *et al*., 2014). A significant relationship between blood MDA level and heart disease was observed in dogs (Dhalla *et al*., 1996). In addition, the severity of heart failure was directly correlated with the increase in lipid peroxidation (Sobotka *et al*., 1993; Diaz-Velez *et al*., 1996). Moreover, increased MDA, SOD and glutathione levels were reported in congestive heart failure patients (Belch *et al*., 1991; McMurray *et al*., 1990; 1993).

Oxidized LDL (oxLDL) is known as a part of the atherosclerosis in humans (Witztum and Steinberg, 2001), which reported to increase in human patients with coronary artery disease. Moreover, oxLDL mediate apoptosis in human coronary smooth muscle cells (de Nigris *et al*., 2000; Sugamura and Keaney, 2011). Blood oxLDL level has been proposed as a useful predictor of coronary disease and of mortality in human patients (Tsutsui *et al*., 2002; Wu *et al*., 2006).

Role of antioxidants in cardiovascular diseases

Antioxidant vitamins, such as ascorbic acid, beta carotene and alpha tocopherol counteract the excess free radiclas and thus prevent lipid peroxidation and diminish atherogenesis and the risk of coronary heart disease. Alpha tocopherol acts to protect polyunsaturated fatty acids from oxidation by interfering with the chain reaction of lipid peroxidation in the membrane ((Singal *et al*., 1982; Packer, 1991). Furthermore, it has the ability to limite myocardial necrosis (Axford-Gatley and Wilson, 1991), and could protect the myocardium from infarction, when given in combination with vitamin C, as observed in an experimental study in pigs (Klein *et al*., 1989), and also, help to correct the depression of antioxidants that reported to occur during ischemia nad hypoxia (Dhaliwal *et al*., 1991; Kirshenbaum and Singal, 1992). Furthermore, Cardiac depression during ischemia/reperfusion was prevented by using vitamin E and superoxide dismutase (SOD) (Nagel *et al*., 1997; Carrasquedo *et al*., 1999).

Vitamin E levels has been decreased in patients with coronary artery bypass graft therapy, which was associated with increased blood free radical levels (Grech *et al*., 1993). Treatment of atherosclerotic patients with vitamin E reduced the rale of myocardial infarction (Stephens *et al*., 1996). Also, the risk of coronary artery disease in men and women was reduced after supplementing patients with vitamin E. On the other hand, the production of free radicals by thr neurophils was lowered after combined treatment of MI patients with vitamin C and E (Herbaczynska-Cedro etal., 1995). Furthermore, the infarct size was decreased, when a combination of vitamin A, C, E and Bet carotene administered to patients with MI (Singh *et al*., 1996). The protecting effect of vitamin E in case of MI, may be attributed to its antioxidants properties or due to its effect on smooth muscle cell proliferation that preserves endothelial function (Chatelain *et al*., 1993 and Ozer *et al*., 1995).

Conclusion

Oxidative stress may be involved in many cardiovascular diseases including hypertension, ventricular hypertrophy, atherosclerosis, congestive heart failure, myocardial infarction, ischemic reperfusion injury, coronary diseases and diabetic cardiomyopathy. Antioxidants play an important role in releaving the damage produced by free radical stress in the cardiovascular tissues.

References

Abd Ellah, M.R., 2010. Involvement of Free Radicals in Animal Diseases. Comparative Clinical Pathology 19, 615-619.

Abd Ellah, M.R., Okada, K., Goryo, M., Yasuda, J., 2013. Levels of malondialdehyde and 4-hydroxyalkenals in bovine liver biopsy. Comparative Clinical Pathology 22, 823-827.

Ahmed, M.I., Gladden, J.D., Litovsky, S.H., Lloyd, S.G., Gupta, H., Inusah, S., Denney, T.Jr., Powell, P., McGiffin, D.C., Dell'Italia, L.J., 2010 Increased oxidative stress and cardiomyocyte myofibrillar degeneration in patients with chronic isolated mitral regurgitation and ejection fraction >60%. J. Am. Coll. Cardio. 55, 671–679.

Ambrosio, G., Tritto, I., 1999. Reperfusion injury: experimental evidence and clinical implications. Am. Heart J. 13, S69 - S75.

Axford-Gatley, R.A., Wilson, G.J., 1991. Reduction of experimental myocar dial infarct size by oral administration of alpha tocopherol. Cardiovasc. Res. 25, 89–92.

Bayraktutan, U., Draper, N., Lang, D., Shah, A.M., 1998. Expression of functional neutrophil-type NADPH oxidase in cultured rat coronary microvascular endothelial cells. Cardiovasc. Res. 3, 256-262.

Belch, J.J., Bridges, A.B., Scott, N., Chopra, M., 1991. Oxygen free radicals and congestive heart failure. Br. Heart J. 65, 245–248.

Betteridge, D.J., 2000. What is oxidative stress? Metabolism 49, 3–8.

Bolli, R., 1988. Oxygen-derived free radicals and postischemic myocardial dysfunction (stunned myocardium). J. Am. Coll. Cardiol. 12, 239–249.

Bolli, R., Patel, B.S., Jeroudi, M.O., Lai, E.K., McCay, P.B., 1988. Demonstration of 'free radical' generation in 'stunned' myocardium of intact dogs with the use of the spin trap a-phenyl N tert-butyl nitrone. J. Clin. Invest. 82, 476–485.

Boswood, A., *et al*. 2008. The diagnostic accuracy of different natriuretic peptides in the investigation of canine cardiac disease. J. Small Anim. Pract. 49, 26–32.

Braunwald, E., 2008. Biomarkers in heart failure. N. Engl. J. Med. 358, 2148–2159.

Buerke, M., Weyrich, A.S., Murohara, T., Queen, C., Klingbeil, C.K., Co, M.S., Lefer, A.M., 1994. Humanized monoclonal antibody DREG-200 directed against I-selectin protects in feline myocardial reperfusion injury. Pharmacol. Exp. Ther. 271, 134 - 142.

Buffon, A., Santini, S. A., Ramazzotti, V., Rigattieri, S., Liuzzo, G., Biasucci, L. M., Crea, F., Giardina, B., Maseri, A., 2000. Large, sustained cardiac lipid peroxidation and reduced antioxidant capacity in the coronary circulation after brief episodes of myocardial ischemia. J. Am. Coll. Cardio. 3, 633 - 639.

Bugger, H., Abel, E.D., 2010. Mitochondria in the diabetic heart. Cardiovascular Research 88, 229–240.

Burton, K.P., McCord, J.M., Ghai, G., 1984. Myocardial alterations due to free radical generation. Am. J. Physiol. 246, H776–H783.

Cai, H., Harrison, D.G., 2000. Endothelial dysfunction in cardiovascular diseases: the role of oxidative stress. Circ. Res. 87, 840-844.

Carlos, D.M., Goto, S., Urata, Y., Iida, T., Cho, S., Niwa, M., Tsuji, Y., Kondo, T., 1998. Nicardipine normalizes elevated levels of antioxidant activity in response to xanthine oxidase-induced oxidative stress in hypertensive rat heart. Free Radic. Res. 2, 143-150.

Carrasquedo, F., Glanc, M., Fraga, C.G., 1999. Tissue damage in acute myocardial infarction: selective protection by vitamin E. Free Radic. Biol. Med. 26, 1587-1590.

Channon, K.M., Guzik, T.J., 2002. Mechanisms of superoxide production in human blood vessels: relationship to endothelial dysfunction, clinical and genetic risk factors. Journal of Physiology and Pharmacology 53, 515–524.

Chatelain, E., Boscoboinik, D.O., Bartoli, G.M., Kagan, V.E., Gey, F.K., Packer, L., Azzi, A., 1993. Inhibition of smooth muscle cell proliferation and protein kinase C activity by tocopherols and tocotrienols. Biochim. Biophys. Acta 1176, 83–89.

Chen, M.C., Chang, J.P., Liu, W.H., Yang, C.H., Chen, C.J., Fang, C.Y., Hsieh, Y.K., Wang, Y.H., Chang, H.W., 2009. Increased serum oxidative stress in patients with severe mitral regurgitation: A new finding and potential mechanism for atrial enlargement.

Clin. Biochem. 42, 943–948.
Cheng, W., Li, B., Kajstura, J., Li, P., Wolin, M.S., Sonnenblick, E.H., Hintze, T.H., Olivetti, G., Anversa, P., 1995. Stretch-induced programmed myocyte cell death. J. Clin. Invest. 96, 2247–2259.
Chintala, M.S., Severina M. Jacinto, Bhagavan S.J., 1992. Studies on the eleterious effects of free radicals on myocardial contractility and hemodynamics in dogs: Protection by felodipine, a dihydropyridine calcium antagonist. Drug Development Research 27, 287–295.
de Nigris, F., Franconi, F., Maida, I., Palumbo, G., Anania, V., Napoli, C., 2000. Modulation by alpha- and gamma-tocopherol and oxidized low-density lipoprotein of apoptotic signaling in human coronary smooth muscle cells. Biochem. Pharmacol. 59, 1477–1487.
Dhaliwal, H., Kirshenbaum, L.A., Randhawa, A.K., Singal, P.K. 1991. Correla tion between antioxidant changes during hypoxia and recovery on reoxygenation. Am. J. Physiol. 261, H632–H638.
Dhalla, A., Hill, M., Singal, P., 1996. Role of oxidative stress in transition of hypertrophy to heart failure. J. Am. Coll. Cardiol. 28, 506–514.
Di Wang, H., Hope, S., Du, Y., Quinn, M.T., Cayatte, A., Pagano, P.J., Cohen, R.A., 1999. Paracrine role of adventitial superoxide anion in mediating spontaneous tone of the isolated rat aorta in angiotensin II- induced hypertension. Hypertension 33, 1225-1232.
Diaz-Velez C.R., Garcia-Castineiras, S., Mendoza-Ramos, E., Hernan dez-Lopez, E., 1996. Increased malondialdehyde in peripheral blood of patients with congestive heart failure. Am. Heart J. 131, 146–152.
Djurovic, S., Thelle, D.S., Ringstad, J., Christensen, B., Berg, K., 1999. Altered serum concentrations of TGF-beta 1 and Lp(a) lipoprotein and their correlation in patients with first acute myocardial infarction. Nutr. Metab. Cardiovasc. Dis. 9, 250-254.
Ferrari, R., Agnoletti, L., Comini, L., Gaia, G., Bachetti, T., Cargnoni, A., Ceconi, C., Curello, S., Visioli, O., 1998. Oxidative stress during myocardial ischemia and heart failure. Eur. Heart J. 19, B2–B11.
Freeman, L.M., Brown, D.J. Rush, J.E., 1999. Assessment of degree of oxidative stress and antioxidant concentrations in dogs with idiopathic dilated cardiomyopathy. J. Am. Vet. Med. Assoc. 215, 644–646.
Freeman, L.M., Rush, J.E., Milbury, P.E., Blumberg, J.B., 2005. Antioxidant status and biomarkers of oxidative stress in dogs with congestive heart failure. J. Vet. Intern. Med. 19, 537–541.
Giordano, F.J., 2005. Oxygen, oxidative stress, hypoxia and heart failure. J. Clin. Invest. 3, 500–508.
Gokce, N., Keaney, J.F.J., Frei, B., Holbrook, M., Olesiak, M., Zachariah, B.J., Leeuwenburgh, C., Heinecke, J.W., Vita, J.A., 1999. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 99, 3234-3240.
Grech, E., Jack, C.I., Bleasdale, C., Jackson, M.J., Baines, M., Faragher, E.B., Hind, C.R., Perry, R.A., 1993. Differential free radical activity after successful and unsuccessful thrombolytic reperfusion in acute myocardial infarction. Coron. Artery Dis. 4, 769–774.
Griendling, K.K., Minieri, C.A., Ollerenshaw, J.D., Alexander, R.W., 1994. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ. Res. 74, 1141 - 1148.
Gupta, M., Singal P.K., 1989. Time course of structure, function and metabolic changes due to an exogenous source of oxygen metabolites in rat heart. Can. J. Physiol. Pharmacol. 67, 1549–1559.
Harjai, K.J., 1999. Potential new cardiovascular risk factors: left ventri- cular hypertrophy, homocysteine, lipoprotein (a), triglycerides, oxidative stress, and fibrinogen. Ann. Intern. Med. 131, 376 - 386.
Hennekens, C.H., 1998. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation 7, 1095-1102.
Herbaczynska-Cedro, K., Ktosiewicz-Wasek, B., Cedro, K., Wasek, W., Panczenko-Kresowska, B., Wartanowicz, M., 1995. Supplementation with vitamins C and E suppresses leukocyte oxygen free radical production in patients with myocardial infarction. Eur. Heart J. 16, 1044–1049.
Hess, M.L., Krause, S., Kontos, H.A., 1983. Mediation of sarcoplasmic reticulum disruption in the ischemic myocardium: proposed mechanism by the interaction of hydrogen ions and oxygen-free radicals. Adv. Exp. Med. Biol. 161, 377–389.
Hill, M.F., Singal, P.K., 1997. Right and left myocardial antioxidant responses during heart failure subsequent to myocardial infarction. Circulation 96, 2414–2420.
Houston, M., Estevez, A., Chumley, P., Aslan, M., Marklund, S., Parks, D.A., Freeman, B.A., 1999. Binding of xanthine oxidase to vascular endothelium. Kinetic characterization and oxidative impairment of nitric oxide-dependent signaling. J. Biol. Chem. 274, 4985-4994.
Jolly S.R., Kane W.J., Bailie M.B., Abrams G.D., Lucchesi B.R., 1984. Canine myocardial reperfusion injury: its reduction by the combined administration of superoxide dismutase and catalase. Circ. Res. 54, 277–285.
Kaul, N., Siveski-Iliskovic, N., Hill, M., Slezak, J., Singal, P.K., 1993. Free radicals and the heart. J. Pharmacol. Toxicol. Methods 30, 55–67.
Keith, M., Geranmayegan, A., Sole, M.J., Kurian, R., Robinson, A., Omran, A.S., Jeejeebhoy, K.N., 1998. Increased oxidative stress in patients with congestive heart failure. J. Am. Coll. Cardiol. 31, 1352 - 1356.
Khullar, M., Al-Shudiefat, A.R.S., Ludke A., Binepal G., Singal P.K., 2010. Oxidative stress: a key contributor to diabetic cardiomyopathy. Canadian Journal of Physiology and Pharmacology 88, 233-240.
Kirshenbaum, L.A., Singal, P.K., 1992. Antioxidant changes in heart hypertrophy: significance during hypoxia reoxygenation injury. Can. J. Physiol. Pharmacol. 70, 1330–1335.
Klein, H.H., Pich, S., Lindert, S., Nebendahl, K., Niedmann, P., Kreuzer, H., 1989. Combined treatment with vitamin E and C in experimental myocardial infarction in pigs. Am. Heart J. 118, 667–673.
Lee, R., Margaritis, M., Channon, K.M., Antoniades, C., 2012. Evaluating oxidative stress in human cardiovascular disease: methodological aspects and considerations. Current Medicinal Chemistry 19, 2504–2520.
Lemasters, J.J., Nieminen, A.L., Qian, T., Trost, L.C., Herman, B., 1997. The mitochondrial permeability transition in toxic, hypoxic and reperfusion injury. Mol. Cell Biochem. 174, 159-165.
Liao F., Andalibi, A., Qiao, J.H., Allayee, H., Fogelman, A.M., Lusis, A.J., 1994. Genetic evidence for a common pathway mediating oxidative stress, inflammatory gene induction, and aortic fatty streak formation in mice. Journal of Clinical Investigation 94, 877–884.
Mak, I.T., Weglicki, W.B., 1990. Comparative antioxidant activities of propranolol, nifedipine, verapamil and diltiazem against sarcolemmal membrane lipid peroxidation. Circ. Res. 66, 1449–1452.
Martinet, W., Knaapen, M.W., De Meyer, G.R., Herman, A.G., Kockx, M.M., 2001. Oxidative DNA damage and repair in experimental atherosclerosis are reversed by dietary lipid lowering. Circ. Res. 88, 733-739.
Matsubara, T., Dhalla, N.S., 1996. Relationship between mechanical dysfunction and depression of sarcolemmal Ca (2+)-pump activity in hearts perfused with oxygen free radicals. Mol. Cell Biochem. 160 -161, 179 - 185.
McMurray, J., Chopra M., Abdullah I., Smith W.E., Dargie H.J., 1993. Evidence of oxidative stress in chronic heart failure in humans. Eur. Heart J. 4, 1493–1498.
McMurray, J., Mclay, J., Chopra, M., Bridges, A., Belch, J.J.F., 1990. Evidence for enhanced free radical activity in chronic congestive heart failure secondary to coronary artery disease. Am. J. Cardiol. 65, 1261–1262.
Meerson, F.Z., 1980. Disturbance of metabolism and cardiac function under the action of emotional painful stress and their prophylaxis. Res. Cardio.l 75, 479–500.
Mickelson, J.K., Simpson, P.J., Jacson, C.V., Lucchesi, B.R., 1988. Protection of myocardial function and coronary vasculature by streptokinase. J. Cardiovasc. Pharmacol. 12, 186–195.
Miller, F.J.J., Gutterman, D.D., Rios, C.D., Heistad, D.D., Davidson, B.L., 1998. Superoxide production in vascular smooth muscle contributes to oxidative stress and impaired relaxation in atherosclerosis. Circ. Res. 2, 1298-1305.
Miwa, K., Igawa, A., Nakagawa, K., Hirai, T., Inoue, H., 1999. Consumption of vitamin E in coronary circulation in patients with variant angina. Cardiovasc. Res. 41, 291-298.
Nagel, E., Meyer, Z.U., Vilsendorf, A., Bartels, M., Pichlmayr, R., 1997.

Antioxidative vitamins in prevention of ischemia/reperfusion injury. Int. Vitam. Nutr. Res. 67, 298 - 306.

Nakamura, K., Murakami, M., Miura, D., Yunoki, K., Enko, K., Tanaka, M., Saito, Y., Nishii, N., Miyoshi, T., Yoshida, M., Oe, H., Toh, N., Nagase, S., Kohno, K., Morita, H., Matsubara, H., Kusano, K.F., Ohe, T., Ito, H., 2001. Beta-blockers and oxidative stress in patients with heart failure. Pharmaceuticals 4, 1088–1100.

Ozer N.K., Boscoboinik D., Azzi A., 1995. New roles of low density lipoproteins and vitamin E in the pathogenesis of atherosclerosis. Biochem. Mol. Biol. Int. 35, 117–124.

Packer, L., 1991. Protective role of vitamin E in biological systems. Am. J. Clin. Nutr. 53, 1050–1055.

Pankuweit, S., Ruppert, V., Maisch, B., 2004. Inflammation in dilated cardiomyopathy. Herz 29, 788–793.

Pimentel, D.R., Amin, J.K., Xiao, L., Miller, T., Viereck, J., Oliver-Krasinski, J., Baliga, R., Wang, J., Siwik, D.A., Singh, K., Pagano, P., Colucci, W.S., Sawyer, D.B., 2001. Reactive oxygen species mediate amplitude-dependent hypertrophic and apoptotic responses to mechanical stretch in cardiac myocytes. Circ. Res. 89, 453–460.

Polidori, M.C., Savino, K., Alunni, G., Freddio, M., Senin, U., Sies, H., Stahl, W., Mecocci, P., 2002. Plasma lipophilic antioxidants and malondialdehyde in congestive heart failure. Free Radic. Biol. Med. 32, 148–152.

Rajagopalan, S., Kurz, S., Munzel, T., Tarpey, M., Freeman, B.A., Griendling, K.K., Harrison, D.G., 1996. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to altera- tions of vasomotor tone. J. Clin. Invest. 7, 1916 - 1923.

Randhawa, A.K., Singal, P.K., 1992. Pressure overload induced cardiac hypertrophy with and without dilation. J. Am. Coll. Cardiol. 20, 1569–1575.

Ruotolo, G., Bavenholm, P., Brismar, K., Efendic, S., Ericsson, C.G., de Faire, U., Nilsson, J., Hamsten, A., 2000. Serum insulin-like growth factor-I level is independently associated with coronary artery disease progression in young male survivors of myocardial infarction: benefi- cial effects of bezafibrate treatment. J. Am. Coll. Cardiol. 3, 647-654.

Sagols, E., Priymenko, N., 2011. Oxidative stress in dog with heart failure: the role of dietary fatty acids and antioxidants. Vet. Med. Int. 6, 180-206.

Sawyer, D. B., Colucci, W.S., 1998. Nitric oxide in the failing myocardium. Cardiol. Clin. 16, 657-664.

Schulz, R., Panas, D. L., Catena, R., Moncada, S., Olley, P.M., Lopaschuk, G.D., 1995. The role of nitric oxide in cardiac depression induced by interleukin-1 beta and tumour necrosis factor-alpha. Br. J. Pharmacol 114, 27-34.

Serdar, A., Yesilbursa, D., Serdar, Z., Dirican, M., Turel, B., Cordan, J., 2001.*et al*. Relation of functional capacity with the oxidative stress and antioxidants in chronic heart failure. Congest. Heart Fail. 7, 309–311.

Shahbaz, A.U., Sun, Y., Bhattacharya, S.K., Ahokas, R.A., Gerling, I.C., McGee, J.E., Weber, K.T., 2010. Fibrosis in hypertensive heart disease: molecular pathways and cardioprotective strategies. Journal of Hypertension 28, S25–S32.

Singal, P.K., Beamish R.E., Dhalla, N.S., 1983. Potential oxidative pathways of catecholamines in the formation of lipid peroxides and genesis of heart disease. Adv. Exp. Med. Biol. 161, 391–401.

Singal, P.K., Kapur, N., Dhillon, K.S., Beamish, R.E., Dhalla, N.S., 1982. Role of free radicals in catecholamine-induced cardiomyopathy. Can. J. Physiol. Pharmacol. 60, 1390–1397.

Singh, R.B., Niaz, M.A., Rastogi, S.S., Rastogi, S., 1996. Usefulness of antioxidant vitamins in suspected acute myocardial infarction (the Indian experiment of infarct survival-3). J. Am. Coll. Cardiol. 77, 232-236.

Sobotka, P.A., Brottman, M.D., Weitz, Z., Birnbaum A.J., Skosey J.L., Zarling E.J. 1993. Elevated breath pentane in heart failure reduced by free radical scavenger. Free Radic. Biol. Med. 14, 643–647.

Stephens, N.G., Parsons, A., Schofield, P.M., Kelly, F., Cheeseman, K., Mitchinson, M.J. 1996. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 347, 781-786.

Sugamura, K., Keaney, J.F.Jr., 2011. Reactive oxygen species in cardiovascular disease. Free Radic. Biol. Med. 51, 978–992.

Suzuki, H., DeLano, F.A., Parks, D.A., Jamshidi, N., Granger, DN., Ishii, H., Suematsu, M., Zweifach, B. W., Schmid-Schonbein, W., 1998. Xanthine oxidase activity associated with arterial blood pressure in spontaneously hypertensive rats. Proc. Natl. Acad. Sci. USA 95, 4754 - 4759.

Temsah, R. M., Netticadan, T., Chapman, D., Takeda, S., Mochizuki, S., Dhalla, N.S., 1999. Alterations in sarcoplasmic reticulum function and gene expression in ischemic-reperfused rat heart. Am. Physiol. 277, H584 - H594.

Torre-Amione, G., Kapadia, S., Benedict, C., Oral, H., Young, J.B., Mann, D.L., 1996. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J. Am. Coll. Cardiol. 27, 1201-1206.

Tsutsui, T., Tsutamoto, T., Wada, A.., Maeda, K., Mabuchi N., Hayashi, M.., Ohnishi, M., Kinoshita, M., 2002. Plasma oxidized low-density lipoprotein as a prognostic predictor in patients with chronic congestive heart failure. J. Am. Coll. Cardiol. 39, 957–962.

Ueda, K., Takahashi, M., Ozawa, K., Kinoshita, M., 1999. Decreased soluble interleukin-6 receptor in patients with acute myocardial infarction. Am Heart J. 13, 908-915.

Ushio-Fukai, M., Alexander, R.W., Akers, M., Griendling, K.K., 1998. p38 mitogen-activated protein kinase is a critical component of the redox-sensitive signaling pathways activated by angiotensin II. Role in vascular smooth muscle cell hypertrophy. J. Biol. Chem. 273, 15022-15029.

Vaage, J., Antonelli, M., Bufi, M., Irtun, O., DeBlasi, R.A., Corbucci, G.G., Gasparetto, A., Semb, A.G., 1997. Exogenous reactive oxygen species deplete the isolated rat heart of antioxidants. Free Radic. Biol. Med. 22, 85–92.

Valko, M., Leibfritz D, Moncol J, Cronin, M.T., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39, 44–84.

Wattanapitayakul, S.K., Weinstein, D.M., Holycross, B.J., Bauer, J.A., 2000. Endothelial dysfunction and peroxynitrite formation are early events in angiotensin-induced cardiovascular disorders. FASEB 14, 271 - 278.

Wildhirt, S.M., Dudek, R.R., Suzuki, H., Bing, R.J., 1995. Involvement of inducible nitric oxide synthase in the inflammatory process of myocardial infarction. Int. J. Cardiol. 50, 253-261.

Wojciechowska, C., Romuk, E., Tomasik, A., Skrzep-Poloczek, B., Nowalany-Kozielska, E., Birkner, E., Jacheć, W., 2014. Oxidative stress markers and C-reactive protein are related to severity of heart failure in patients with dilated cardiomyopathy. Mediators Inflamm. 2014, 147040.

Wu, T., Willett, W.C., Rifai, N., Iris Shai, JoAnn E. Manson, Eric B.R., 2006. Is plasma oxidized low density lipoprotein, measured with the widely used antibody 4E6, an independent predictor of coronary heart disease among U.S. men and women? J. Am. Coll. Cardiol. 48, 973–979.

Yasmin, W., Strynadka, K.D., Schulz, R., 1997. Generation of peroxynitrite contributes to ischemia–reperfusion-injury in isolated rat hearts. Cardiovasc. Res. 33, 422–432.

Ytrehus, K., Myklebut, R., Mjos, O.D., 1986. Influence of oxygen radicals generated by xanthine oxidase in the isolated perfused rat heart. Cardiovasc. Res. 20, 597–603.