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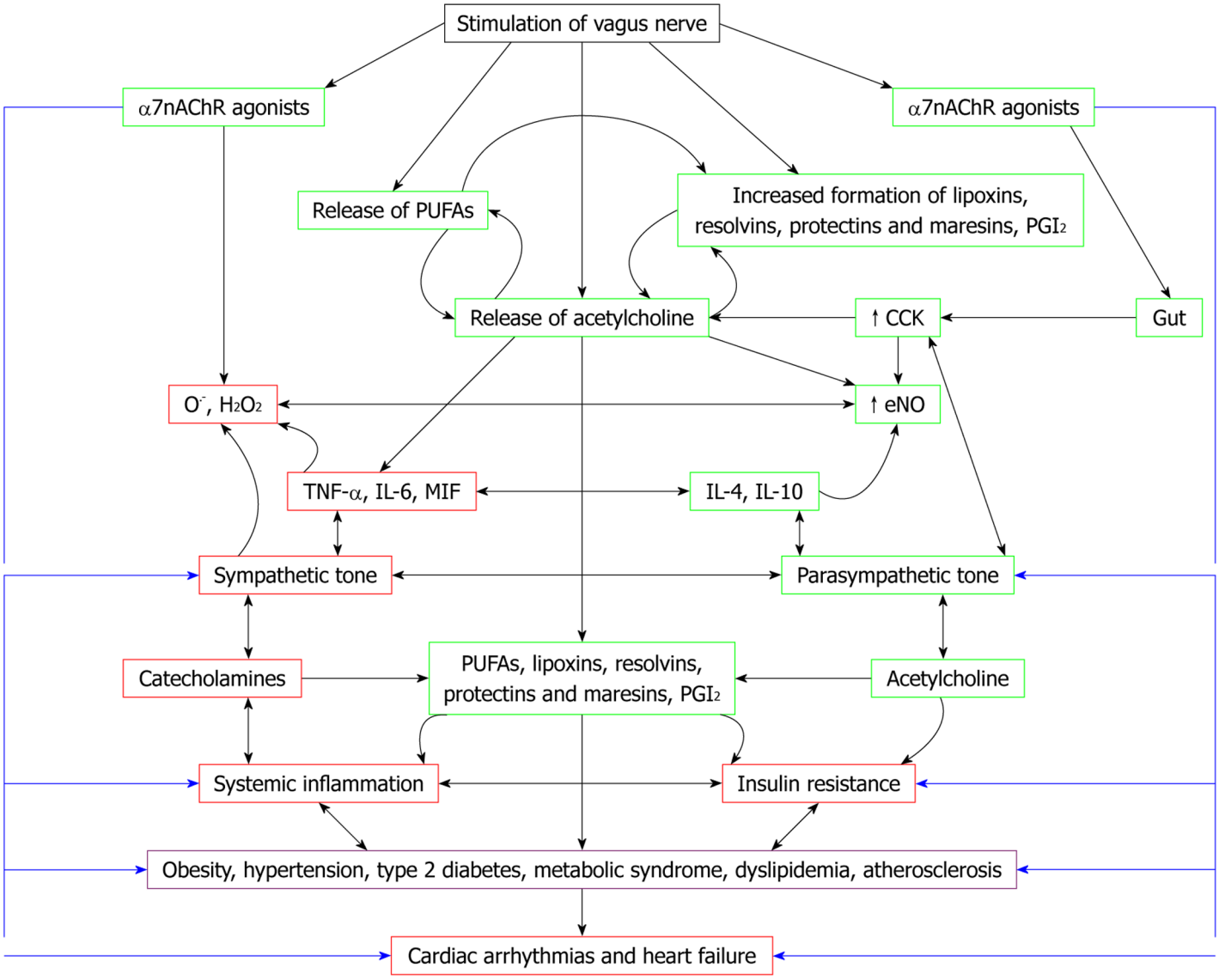

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EDITORIAL

Increased heart rate and atherosclerosis: Potential implications of ivabradine therapy

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Abstract

Despite all the therapeutic advances in the field of cardiology, cardiovascular diseases, and in particular coronary artery disease, remain the leading cause of death and disability worldwide, thereby underlining the importance of acquiring new therapeutic options in this field. A reduction in elevated resting heart rate (HR) has long been postulated as a therapeutic approach in the management of cardiovascular disease. An increased HR has been shown to be associated with increased progression of coronary atherosclerosis in animal models and patients. A high HR has also been associated with a greatly increased risk of plaque rupture in patients with coronary atherosclerosis. Endothelial function may be an important link between HR and atherosclerosis. An increased HR has been shown experimentally to cause endothelial dysfunction. Inflammation plays a significant role in the pathogenesis and progression of atherosclerosis. In the literature, there is data that shows an association between HR and circulating markers of vascular inflammation. In addition, HR reduction by pharmacological intervention with ivabradine (a selective HR-lowering agent that acts by inhibiting the pacemaker ionic current I_f in sinoatrial node cells) reduces the formation of atherosclerotic plaques in animal models of lipid-induced atherosclerosis. The aim of this editorial is to review the possible role of ivabradine on atherosclerosis.

Key words: Ivabradine; Heart rate; Atherosclerosis; Inflammation

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INTRODUCTION

Resting heart rate (HR) is an easily accessible clinical parameter. The initiation of the HR by spontaneous sinoatrial node depolarization is determined by voltage-sensitive membrane currents, particularly the hyperpolarization activated pacemaker current I_f, and by calcium release from the sarcoplasmic reticulum, leading to diastolic depolarization through activation of the sodium-calcium exchanger current[1].

Experimental data and clinical observations support the notion of the importance of HR in the pathophysiology of atherosclerosis and plaque rupture[2]. An elevated

HR enhances mechanical arterial wall stress and it prolongs the exposure of the coronary endothelium to systolic low and oscillatory shear stress. All these processes induce structural and functional changes in endothelial cells, which accumulate over time in atherosclerosis-prone regions, promoting atherosclerosis[2]. Furthermore, elevated HR caused by mechanical stress may promote weakening of the fibrous cap, ultimately increasing the risk of plaque disruption and the onset of an acute coronary syndrome[3].

Ivabradine, a selective inhibitor of the I_f channel, reduces resting and exercise HR without affecting cardiac contractility or blood pressure[4-6]. Clinical trials have revealed an improved exercise tolerance, an increased time to exercise-induced ischemia, and a reduced frequency of ambient angina attacks after I_f channel inhibition[7,8]. This editorial summarizes the possible role of ivabradine on atherosclerosis.

THE ROLE OF HR IN CARDIOVASCULAR DISEASE

A large number of studies in healthy and asymptomatic subjects as well as in patients with already established coronary artery disease (CAD) have demonstrated that HR is a very important and major independent cardiovascular risk factor for prognosis[9]. In the general population, life expectancy is associated inversely with elevated HR[10-12]. This association is independent of gender and genetic background. An increase in risk is derived from data comparing individuals with HR < 60 beats per minute with those with HR of 90-99 beats per minute[13]. In particular, there is an increase in CAD mortality and there is also an increase in sudden cardiac death[11]. The contribution of HR reduction to the clinical effects of β-blockers and calcium-channel blockers has been analyzed in several studies[14,15].

In the Framingham study, cardiovascular and coronary mortality increased progressively with resting HR in a cohort of 5070 subjects free from cardiovascular disease at the time of entry into the study. The effect of HR on mortality was independent of traditional cardiovascular risk factors[2,16-18].

The analysis of a pre-specified subgroup of the BEAUTIFUL (morbidity-mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) trial demonstrated that, in patients with CAD and left ventricular systolic dysfunction, a resting HR > 70 beats per minute is associated with an increased cardiovascular mortality as well as increased risk for hospitalization due to heart failure, myocardial infarction, or the need for coronary revascularization[19]. Recently, the systolic heart failure treatment with I_f inhibitor ivabradine trial, demonstrated that patients with HR ⩾ 87 beats per minute, had a two-fold higher risk of the primary composite endpoint (cardiovascular death or hospital admission for worsening heart failure) than patients with the lowest HR (70 to < 72 beats per minute). The risk of primary composite endpoint events increased by 3% with every beat increase from baseline HR, and 16% for every 5 beats per minute increase. Thus, the authors conclude that high HR is a risk factor in heart failure and therefore, it should be an important target for treatment of heart failure[20]. Taken together, there is compelling epidemiologic evidence that elevated resting HR is predictive of cardiovascular risk, independently of the other currently accepted risk factors.

ATHEROSCLEROSIS, INCREASED HR AND IVABRADINE

HR is influenced by a variety of physiological processes mainly *via* effects on the balance of sympathetic and vagal tone. The factors and conditions which influence HR are summarized in Figure 1. The importance of an increased HR in cardiovascular prognosis can be explained by its relationship with major pathophysiological determinants: (1) greater myocardial oxygen consumption; (2) decreased myocardial perfusion; (3) increased severity and progression of coronary atherosclerosis; (4) less development of collaterals; (5) increased risk of coronary plaque disruption; (6) increased arterial rigidity; and (7) a marker and possible mediator of sympathetic overactivity[21].

Experimental and clinical evidence also suggests that sustained elevations in HR may also play a direct role in the pathogenesis of coronary atherosclerosis and its complications[2]. Accelerated atherogenesis resulting from increased HR may be due to both mechanical and metabolic factors. Increased vascular wall stress may contribute to endothelial injury, potentially promoting the complex cascade of events leading to increased atherosclerosis[21]. Experimental data also show that a reduction in HR can delay the progression of coronary atherosclerosis in monkeys[22]. Additionally, in young patients with myocardial infarction, there is a strong positive relationship between higher HR and the extent of atherosclerotic coronary lesions[23].

In apolipoprotein E knockout mice, cholesterol-induced atherosclerosis was inhibited by HR reduction with ivabradine[24]. In this study, ivabradine also markedly reduced vascular oxidative stress, nicotinamide adenine dinucleotide phosphate oxidase activity, superoxide production, and lipid peroxidation[24]. Ivabradine also prevented atherogenesis when given simultaneously with a high cholesterol diet, but it was also effective in reducing plaques size when given to animals 4 wk after initiation of a high-cholesterol diet[25]. Presumably, therefore, mechanical load on the vessel wall caused by higher HR might lead to endothelial dysfunction, increased oxidative stress, and enhanced plaque formation, which can be reversed or prevented by the inhibition of I_f channels and consequent HR reduction with ivabradine[26].

Subclinical inflammation and the concentration of inflammatory markers have shown in many studies to correlate strongly with cardiovascular mortality and morbidity in both healthy subjects and in subjects with known

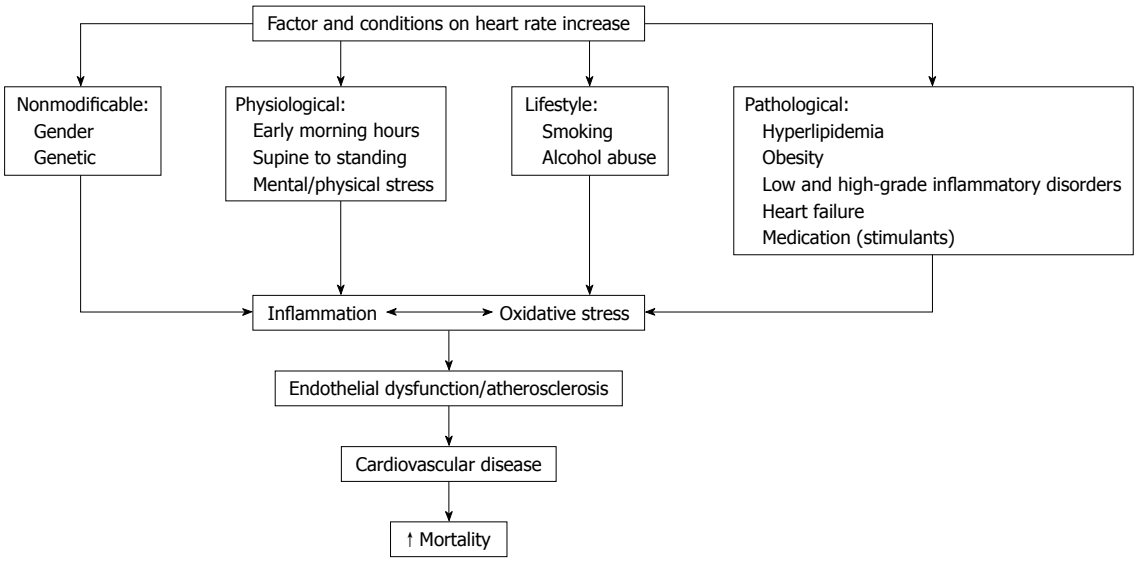

Figure 1 The role of heart rate in the pathophysiology of cardiovascular disease.

CAD[27,28]. Two population-based studies reported a positive correlation between increased resting HR and markers of inflammation in apparently healthy subjects[29,30]. Thus, increased HR may contribute to endothelial dysfunction by upregulation of inflammatory cytokines[2]. In summary, the data show an association of HR with circulating markers of vascular inflammation.

These observations support the rationale for HR reduction with ivabradine as an intervention to improve endothelial function and to attenuate the progression of atherosclerosis and cardiovascular event prevention[2]. In this respect, the RIVIERA study (randomized, double-blind, placebo-controlled trial of ivabradine in patients with acute coronary syndrome: effects of the I_f current inhibitor ivabradine on reduction of inflammation markers in patients with acute coronary syndrome), is the first opportunity to investigate whether a pure HR-lowering agent reduces vascular inflammatory stress in patients with acute coronary syndrome[31]. The importance of this study will explore potentially new cardiovascular effects of ivabradine that may be useful for management of these patients. In addition, the use of ivabradine can be further expanded by investigating its mechanism of action in high grade inflammatory disorders in models of inflammation-induced accelerated atherosclerosis leading to a substantial cardiovascular burden[32].

Likewise, the effect of ivabradine had been demonstrated in various clinical trials. In the international trial on the treatment of angina with ivabradine *vs* atenolol (INITIATIVE), ivabradine was compared with atenolol in a double-blind trial in 939 patients with stable angina randomized to receive ivabradine 5 mg *bid* for 4 wk and then either 7.5 or 10 mg *bid* for 12 wk or atenolol 50 mg *od* for 4 wk and then 100 *od* for 12 wk. Patients underwent treadmill exercise tests at randomization and after 4 and 16 wk of treatment. Increases in total exercise duration and other exercise test parameters at trough of drug activity were not inferior with ivabradine, suggesting that ivabradine is as effective as atenolol in patients with stable angina[7].

The ASSOCIATE (evaluation of the antianginal efficacy and safety of the association of the I_f current inhibitor ivabradine with a β-blocker) study was an international, double blind, placebo-controlled trial which investigated the effects of ivabradine in patients with stable angina receiving atenolol[33]. This study clearly demonstrates that ivabradine in patients with stable angina receiving the β-blocker atenolol had a significant long-term improvement in total exercise duration in standardized Bruce protocol exercise testing.

Regarding ivabradine-associated adverse effects, the most frequently encountered (sinus bradycardia and visual disturbances) are related to the drug's mechanism of action; e.g. inhibition of sinus node I_f channels and inhibition of *h* channels in retinal rods and cones, though their density is low[19]. In BEAUTIFUL, the incidence of symptomatic sinus bradycardia was 3%. The rate of visual symptoms (phosphenes, blurred vision, and visual disturbances) was also very low and led to discontinuation in only 0.5% of patients receiving ivabradine *vs* 0.2% of patients receiving placebo[19].

CONCLUSION

HR should become a significant cardiovascular parameter for predicting complications because it is an integral sign of cardiovascular function and is related to several complications at different stages of the cardiovascular continuum. Therefore, in all future cardiovascular studies, HR should be carefully monitored in order to improve our knowledge of this important physiological risk marker, or even risk factor. HR reduction by the HR-lowering agent, ivabradine, should prevent atherosclerosis and hence cardiovascular events. All observations commented here constitute a strong rationale for further clinical investigation of the cardioprotective effects of pure HR reduction.

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REVIEW

Vagal nerve stimulation in prevention and management of coronary heart disease

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Abstract

Coronary heart disease (CHD) that is due to atherosclerosis is associated with low-grade systemic inflammation. Congestive cardiac failure and arrhythmias that are responsible for mortality in CHD can be suppressed by appropriate vagal stimulation that is anti-inflammatory in nature. Acetylcholine, the principal vagal neurotransmitter, is a potent anti-inflammatory molecule. Polyunsaturated fatty acids (PUFAs) augment acetylcholine release, while acetylcholine can enhance the formation of prostacyclin, lipoxins, resolvins, protectins and maresins from PUFAs, which are anti-inflammatory and anti-arrhythmic molecules. Furthermore, plasma and tissue levels of PUFAs are low in those with CHD and atherosclerosis. Hence, vagal nerve stimulation is beneficial in the prevention of CHD and cardiac arrhythmias. Thus, measurement of catecholamines, acetylcholine, various PUFAs, and their products lipoxins, resolvins, protectins and maresins in the plasma and peripheral leukocytes, and vagal tone by heart rate variation could be useful in the prediction, prevention and management of CHD and cardiac arrhythmias.

INTRODUCTION

Coronary heart disease (CHD) is usually due to underlying atherosclerosis and is the leading cause of death in the United States and elsewhere. Both heart failure and cardiac arrhythmias are the common causes of death due to CHD. It is interesting to note that both CHD and atherosclerosis are associated with low-grade systemic inflammation[1,2]. Diseases that predispose to the development of atherosclerosis and CHD, such as obesity, hypertension, type 2 diabetes mellitus and the metabolic syndrome, are also considered as low-grade systemic inflammatory conditions[3-8]. Thus, inflammation plays a significant role in CHD and cardiac arrhythmias and conditions that predispose to its development. Vagal stimulation has an antifibrillatory effect and is beneficial in animal models of heart failure[9]. I propose that inflammation plays a role in cardiac arrhythmias, and that vagal stimulation is beneficial because of its anti-inflammatory actions.

Previously, it has been reported that increasing heart rate within a physiological range by diminishing vagal tone during myocardial ischemia decreases ventricular electrical stability by increasing ischemia consequent to the rate-induced increase in myocardial oxygen require-

ments, and a direct electrophysiological action of the vagus on the ventricular myocardium[10]. The incidence of ventricular arrhythmias is significantly higher and ventricular fibrillation tends to occur more frequently in the atropine-treated group, while vagally mediated bradycardia exerts a protective effect, which indicates that vagal stimulation per se (independent of heart rate) increases ventricular electrical stability in non-ischemic and ischemic hearts[11]. In addition, acetylcholine, the principle vagal neurotransmitter, depresses the slope of diastolic depolarization, and increases the rise time, amplitude, and conduction velocity of action potentials recorded in the proximal portion of the His-Purkinje system of the canine ventricle[12], and thus, in addition to its heart-rate-mediated effects, atropine increases the incidence of arrhythmia by attenuating a stabilizing vagal influence. These and other studies have suggested that vagal nerve stimulation (VNS) could prevent or even abrogate cardiac arrhythmias[13-15].

VNS FAVORABLY INFLUENCES ENERGY PROVISION TO THE ISCHEMIC MYOCARDIUM

Vagal stimulation increases coronary resistance and decreases regional myocardial blood flow (RMBF) in non-ischemic myocardium, while increasing endocardial RMBF, endo/epicardial ratio and ischemic/non-ischemic areas flow ratio, thus inducing a "reverse coronary steal phenomenon" in the ischemic myocardium. These effects are independent of the induced bradycardia because they persist during atrial pacing, but result from muscarinic receptor activation because they are abolished by atropine[16]. Vagal stimulation results in decreased collateral resistance in the ischemic area and a marked reduction of myocardial oxygen requirement in non-ischemic and border zone myocardium, when myocardial ischemia produced by acute coronary occlusion during β-receptor blockade is examined[17]. This suggests that the provision of energy to the ischemic myocardium is favorably balanced with its actual demand during vagal stimulation.

Low-frequency electroneurostimulation (ENS) of the efferent vagus endings and brainstem structures *via* transauricular electroacupuncture increase the parasympathetic tone of the autonomic nervous system. ENS has a central vagotonic/sympatholytic influence on the heart, which leads to relief of anginal symptoms, diminution of biochemical myocardial signs of disease, in the form of a decrease in heat shock protein 70 and myocardial ATP content, and an increase in cardiac tolerance of operative reperfusion damage in patients with coronary artery disease (CAD) who underwent coronary artery bypass grafting[18]. These results are supported by the observation that CAD is characterized by overactivity of sympathetic cardiac tone, whereas vagal stimulation reduces sympathetic inflow to the heart *via* inhibition of norepinephrine release from sympathetic nerves. It has been noted that VNS induces sympatholytic/vagotonic dilation of cardiac microcirculatory vessels and improves left ventricular (LV) contractility in patients with severe CAD[19].

VNS PREVENTS CARDIAC ARRHYTHMIAS

VNS exerts anti-arrhythmogenic effects by preventing the loss of phosphorylated connexin (CX)43 during acute myocardial infarction[20], and ameliorates LV remodeling in heart failure by inducing tissue inhibitor of matrix metalloproteinase (TIMP) expression and reducing matrix metalloproteinase (MMP)-9 in cardiomyocytes[21]. Cardiac microdialysis has demonstrated that topical perfusion of acetylcholine has similar actions on CX43, TIMP expression and MMP-9 protein level, which is suppressed by co-perfusion of atropine. The protective action of VNS in CAD appears to be mediated by a vagus-nerve-mediated, brain cholinergic protective mechanism that is activated by melanocortin peptides[22], which suggests that melanocortins and pertinent compounds able to activate such a pathway may form a novel approach to management of ischemic heart disease.

CARDIAC ARRHYTHMIAS ARE DUE TO LOCAL INFLAMMATION

Recent studies have suggested that cardiac arrhythmias are due to local inflammation, oxidative injury, altered myocyte metabolism, extracellular matrix remodeling, and fibrosis. This is because myeloperoxidase (MPO)-deficient mice pretreated with angiotensin-Ⅱ have lower atrial tissue MPO, reduced activity of MMPs, blunted myocardial fibrosis, and markedly reduced incidence of arrhythmias. Patients with cardiac arrhythmias had higher plasma concentrations of MPO and larger MPO content in the myocardial tissue compared to the controls. These data support the mechanistic involvement of MPO in the pathogenesis of cardiac arrhythmias and suggest a strong association between cardiac arrhythmias and inflammation[22-24], and have led to the suggestion that the activation state of leukocytes[25] (activation of leukocytes leads to excess production of MPO) could be secondary to a deficiency of lipoxin A_4 (LXA_4), a potent anti-inflammatory, organ-protective and antifibrotic molecule[24,25] and prostacyclin (PGI_2), another anti-arrhythmic and anti-inflammatory molecule[24,26].

POLYUNSATURATED FATTY ACIDS, PGI_2 AND LIPOXINS HAVE ANTIARRHYTHMIC ACTIVITY

Free polyunsaturated fatty acids (PUFAs) (10-15 μmol/L) eicosapentaenoic acid (EPA, 20:5 n-3), docosahexaenoic acid (DHA, 22:6 n-3), α-linolenic acid (18:3 n-3), arachidonic acid (AA, 20:4 n-6) and linoleic acid (18:2 n-6) effectively prevent and terminate lysophosphatidylcholine- or acylcarnitine-induced arrhythmias of cultured,

spontaneously beating, neonatal rat cardiomyocytes, while monounsaturated oleic acid (18:1 n-9) and saturated stearic acid (18:0) are not effective[27]. Such antiarrhythmic actions of n-3 PUFAs have been described in experimental animals and humans[28-31]. Among elderly adults, consumption of EPA/DHA-rich, fish-based diet lowers the incidence of cardiac arrhythmias[32,33].

In adult dogs, intravenous infusion of n-3 PUFAs (EPA 1.25-2.82 g /100 mL, DHA 1.44-3.09 g /100 mL) significantly reduces cardiac arrhythmias[34]. It is particularly interesting that CX40 and CX43 levels are lower[35] in n-3 PUFA-treated dogs, which suggests that n-3 PUFAs reduce vulnerability to induction of cardiac arrhythmias by modulating cardiac CXs. Supplementation with n-3 PUFAs not only reduces all-cause mortality and cardiac arrhythmias in patients with post-myocardial infarction[36], but also downregulates protein kinase B (Akt), epidermal growth factor, JAM3, myosin heavy chain α and CD99, and significantly decreases levels of Smad6 compared with controls. This suggests that PUFA-mediated prevention of cardiac arrhythmias is due to attenuation of fibrosis, hypertrophy, and inflammation-related genes in response to mechanical stress[37].

MPO could mediate cardiac arrhythmias by augmenting myocardial fibrosis[23]. It is noteworthy that AA, EPA and DHA form precursors to anti-inflammatory products PGI_2, lipoxins, resolvins, protectins and maresins[24], which stop leukocyte entry into the exudates as well as counter-regulate the signs of inflammation. Leukocytes that enter an exudate interact with other cells such as monocytes, platelets, endothelial cells, mucosal epithelial cells, fibroblasts and myocardial cells in their immediate vicinity, and are able to perform transcellular biosynthesis of these anti-inflammatory compounds, especially lipoxins. During the course of inflammation and resolution, mediator switching occurs between families of lipid mediators, namely from eicosanoids to lipoxins, resolvins as well as protectins; a process that depends on the availability of substrate within the evolving exudates. Thus, resolution of inflammation involves the appearance of EPA and DHA, which follows the appearance of unesterified AA that is transformed *via* enzymatic mechanisms to bioactive compounds such as lipoxins, resolvins and protectins that regulate the duration and magnitude of inflammation. Lipoxins, resolvins and protectins also increase the expression of CCR5 receptors on T cells and aging leukocytes, which help clear local chemokine depots from the inflammatory site[24]. Lipoxins stimulate PGI_2 generation by endothelial cells and nitric oxide production by vascular endothelial cells[38]; lipoxins and resolvins reduce neutrophil transendothelial migration, interleukin (IL)-12 production, block tumor necrosis factor (TNF)-α, IL-8, interferon-γ, and IL-6 production, signal transduction by nuclear factor-κB, as well as intercellular adhesion molecule-1 expression[39-41]. Intravenous, oral and topical application of LXA_4, lipoxin B_4 and their synthetic analogs suppresses inflammation and lung and leukocyte MPO activity[42,43]. Furthermore, statins and thiazolidinediones that have anti-inflammatory properties increase the myocardial content of LXA_4 and 15-epi-LXA_4, which demonstrates that myocardial cells are capable of producing anti-inflammatory and antiarrhythmic lipid mediators[44].

These results suggest that inflammation plays a key role in the pathobiology of cardiac arrhythmias. VNS also suppresses cardiac arrhythmias, therefore, it is likely that it has anti-inflammatory actions.

VAGUS STIMULATION SUPPRESSES INFLAMMATION

Wang *et al*[45] have shown that the vagus nerve can inhibit significantly and rapidly the release of macrophage TNF, and attenuate systemic inflammatory responses, and have termed it as the "cholinergic anti-inflammatory pathway". The essential macrophage acetylcholine-mediated (cholinergic) receptor that responds to vagus nerve signals has been identified as the nicotinic acetylcholine receptor α7 subunit that is required for acetylcholine inhibition of macrophage TNF release. Electrical stimulation of the vagus nerve inhibits TNF synthesis in wild-type mice, but fails to do so in α7-deficient mice. It has been reported that stimulation of cholecystokinin receptors leads to attenuation of the inflammatory response by way of the efferent vagus nerve and nicotinic receptors[46]. Even the functional relationship between the cholinergic anti-inflammatory pathway and the reticuloendothelial system has been found to be mediated *via* the vagus nerve. VNS fails to inhibit TNF production in splenectomized animals during lethal endotoxemia, whereas selective lesioning of the common celiac nerve abolishes TNF suppression by VNS, which suggests that the cholinergic pathway is functionally hard wired to the spleen *via* this branch of the vagus nerve[47]. These results indicate that electrical VNS or administration of α7 agonists inhibits proinflammatory cytokine production. VNS strongly inhibits lipopolysaccharide (LPS)-induced procoagulant responses, attenuates the fibrinolytic response, and LPS-induced increases in plasma and splenic concentrations of the proinflammatory cytokines TNF-α and IL-6, while not influencing the release of the anti-inflammatory cytokine IL-10[48]. On the other hand, spleen vagal denervation inhibits the production of antibodies to circulating antigens[49]. Transcutaneous VNS dose-dependently reduces systemic TNF levels, inhibits high mobility group protein B1 (HMGB1) levels, and improves survival in mice with polymicrobial sepsis[50]. These observations attest to the fact that VNS suppresses inflammation.

CONCLUSION

The observation that vagal tone is decreased, sympathetic tone is enhanced, production of IL-6, TNF-α, migration inhibitory factor and HMGB1 is increased, and plasma and tissue concentrations of AA and DHA and their products PGI_2, lipoxins, resolvins, protectins and maresins are decreased in CHD, atherosclerosis and cardiac ar-

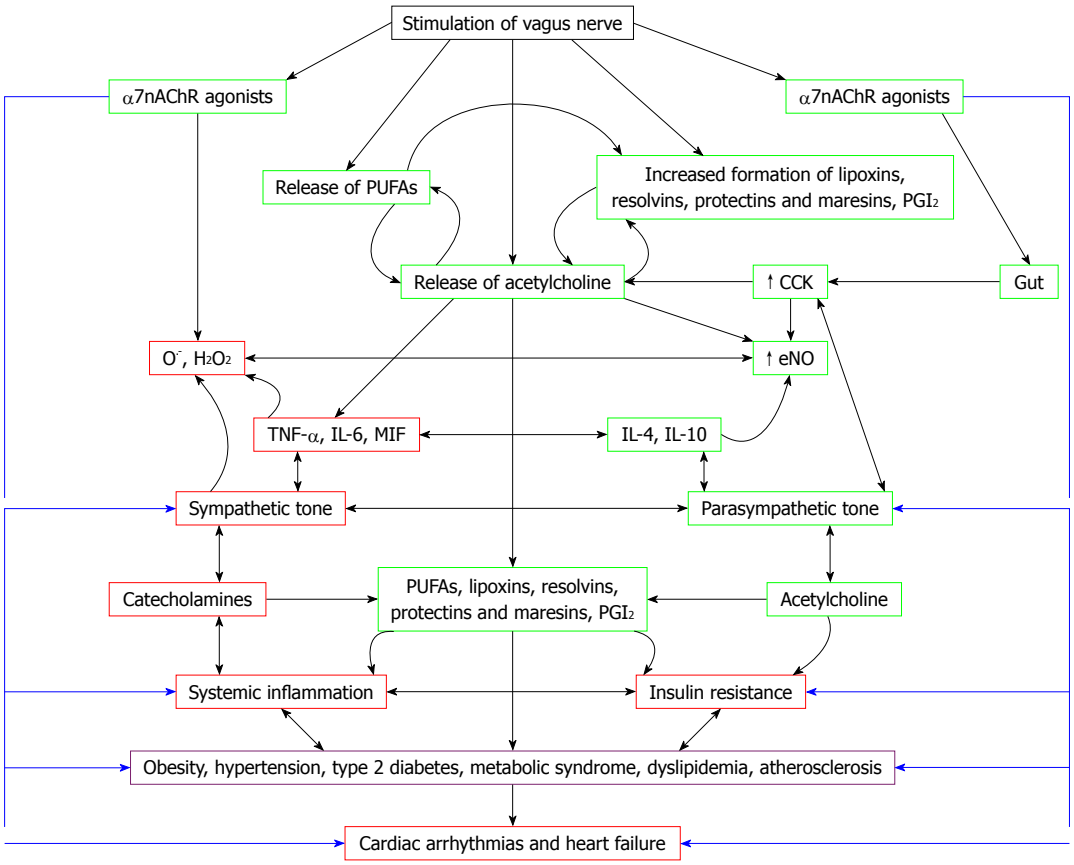

Figure 1 Scheme showing relationship between vagal nerve stimulation, autonomic nervous system, inflammation, insulin resistance, metabolic syndrome and cardiac arrhythmias and cardiac failure. Inflammation plays a significant role in coronary heart disease (CHD) and cardiac arrhythmias and conditions that predispose to its development such as atherosclerosis. In contrast, vagal nerve stimulation (VNS) has anti-inflammatory activity, an antifibrillatory effect, and is beneficial in heart failure. Cardiac arrhythmias are due to local inflammation, oxidative injury, altered myocyte metabolism, extracellular matrix remodeling, and fibrosis. Myeloperoxidase (MPO)-deficient mice show reduced activity of matrix metalloproteinases (MMPs), blunted myocardial fibrosis, and markedly reduced incidence of arrhythmias. Patients with cardiac arrhythmias have higher plasma and myocardial concentrations of MPO compared to controls. Activation of leukocytes occurs in cardiac arrhythmias and congestive heart failure (CHF) that leads to excess production of MPO. Increased production of leukocyte MPO could be secondary to a deficiency of lipoxin A_4 (LXA_4) and prostacyclin (PGI_2), which are potent anti-inflammatory, organ-protective, antifibrotic, and antiarrhythmic molecules. Thus, under normal physiological conditions, a delicate balance exists between proinflammatory molecules such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, macrophage migration inhibitory factor (MIF), MPO and anti-inflammatory molecules such as IL-4, IL-10, NO, lipoxins, resolvins, protectins and maresins. Similarly, a balance exists between sympathetic tone and parasympathetic tone. Catecholamines (the neurotransmitters of the sympathetic nervous system) have proinflammatory actions, whereas acetylcholine (the principal neurotransmitter of the vagus nerve) has anti-inflammatory actions. Acetylcholine and VNS might augment the production of anti-inflammatory molecules lipoxins, resolvins, protectins and maresins. Thus, VNS is beneficial in cardiac arrhythmias, CHF and in other low-grade systemic inflammatory conditions such as obesity, hypertension, type 2 diabetes, metabolic syndrome, dyslipidemia, atherosclerosis and insulin resistance. Hence, measurement of plasma/leukocyte content of acetylcholine, catecholamines, IL-6, TNF-α, MIF, IL-4, IL-10, various PUFAs, lipoxins, resolvins, protectins, maresins and vagal tone could be used for prediction of disease progression, and assessing prognosis and response to treatment of CHF and cardiac arrhythmias.

rhythmias has important therapeutic implications. If this is true, it implies that blockade of α_2-adrenoreceptors (blocking these receptor inhibits inflammation injury due to catecholamines[51]), stimulation of the vagus nerve[52] and the nicotinic acetylcholine receptor α7 subunit[45], and administration of AA, DHA, PGI_2, lipoxins, resolvins, protectins and maresins, or their stable synthetic analogs, could be of significant benefit in the prevention and management of CHD and cardiac arrhythmias (Figure 1). It is also likely that acetylcholine and VNS enhance the production of anti-inflammatory molecules such as lipoxins, resolvins, protectins and maresins by inducing the release of PUFAs (such as AA, EPA and DHA) from the cell membrane lipid pool.

VNS is already in clinical use as an adjunctive treatment for certain types of intractable epilepsy and major depression[53-56]. VNS uses an implanted stimulator that sends electric impulses to the left vagus nerve in the neck *via* a lead wire implanted under the skin. The advantage of VNS is that it can be performed as an outpatient procedure. It is possible to target pharmacologically the nicotinic acetylcholine receptor α7 subunit-dependent control of cytokine release in CHD, cardiac arrhythmias and atherosclerosis. It is also likely that in future, the currently available treatment regimens for CHD, cardiac arrhythmias and atherosclerosis could be combined with VNS and nicotinic acetylcholine receptor α7 subunit agonists. Another exciting possibility is that VNS might potentially enhance myocardial stem cell (progenitor cell) proliferation and thus augment myocardial healing and function in patients with CHD, as has been shown for hippocampal progenitor proliferation[57].

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BRIEF ARTICLE

Chronic cola drinking induces metabolic and cardiac alterations in rats

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Abstract

AIM: To investigate the effects of chronic drinking of cola beverages on metabolic and echocardiographic parameters in rats.

METHODS: Forty-eight male Wistar rats were divided in 3 groups and allowed to drink regular cola (C), diet cola (L), or tap water (W) *ad libitum* during 6 mo. After this period, 50% of the animals in each group were euthanized. The remaining rats drank tap water *ad libitum* for an additional 6 mo and were then sacrificed. Rat weight, food, and beverage consumption were measured regularly. Biochemical, echocardiographic and systolic blood pressure data were obtained at baseline, and at 6 mo (treatment) and 12 mo (washout). A complete histopathology study was performed after sacrifice.

RESULTS: After 6 mo, C rats had increased body weight (+7%, $P < 0.01$), increased liquid consumption (+69%, $P < 0.001$), and decreased food intake (-31%, $P < 0.001$). C rats showed mild hyperglycemia and hypertriglyceridemia. Normoglycemia (+69%, $P < 0.01$) and sustained hypertriglyceridemia (+69%, $P < 0.01$) were observed in C after washout. Both cola beverages induced an increase in left ventricular diastolic diameter (C: +9%, L: +7%, $P < 0.05$ *vs* W) and volumes (diastolic C: +26%, L: +22%, $P < 0.01$ *vs* W; systolic C: +24%, L: +24%, $P < 0.05$ *vs* W) and reduction of relative posterior wall thickness (C: -8%, L: -10%, $P < 0.05$ *vs* W). Cardiac output tended to increase (C: +25%, $P < 0.05$ *vs* W; L: +17%, not significant *vs* W). Heart rate was not affected. Pathology findings were scarce, related to aging rather than treatment.

CONCLUSION: This experimental model may prove useful to investigate the consequences of high consumption of soft drinks.

Key words: Cola beverages; Echocardiography; Metabolic syndrome; Soft drinks

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INTRODUCTION

Metabolic syndrome has been linked to an increased risk of type 2 diabetes, cardiovascular disease, stroke and premature death[1]. Soft drinks are the leading source of added sugar worldwide, and their consumption has been linked to obesity, diabetes, and metabolic syndrome[2-4]. Epidemiological and experimental evidence indicate that a greater consumption of sweet carbonated beverages is associated with overweight and obesity by virtue of the high sugar content, low satiety, and incomplete compensation for total energy in subsequent meals[5]. The health impact of soft drink consumption is becoming alarming, particularly among adolescents. A recent survey on the dietary habits and nutritional status of 4 to 18 years olds in Great Britain showed that on average 56% of total fluid intake was in the form of soft drinks[2].

Recently, we have demonstrated that most features of metabolic syndrome can be replicated in an experimental model of soft drink consumption. Body weight gain, hypertension, decreased food intake, hyperglycemia, hypertriglyceridemia, and a tendency to hypercholesterolemia were found after chronic consumption of regular (sucrose-sweetened) cola beverage in rats[6].

As a logical extension to that earlier report, the present paper aimed to investigate possible biochemical, echocardiographic and pathological alterations associated with chronic consumption of cola beverage in rats. This experimental model has the advantage of being able to dissect out potentially confounding factors usually associated with soft drinks consumption in human subjects, such as increased smoking, increased junk food consumption, and sedentary lifestyle, which might all indirectly contribute to development of metabolic syndrome. Furthermore, compared with previous animal models of metabolic syndrome[7], this approach has the potential advantage that it lends itself well to a direct comparison with the situation commonly found in real life.

MATERIALS AND METHODS

Experimental protocol

Forty-eight male Wistar rats were randomly assigned to 3 groups, receiving 3 different beverages *ad libitum* as the only liquid source for 6 mo: water (W), regular cola (C) (commercially available sucrose-sweetened carbonated drink, Coca-Cola™, Argentina), and Light Cola™ (L) (commercially available low calorie -aspartame-sweetened carbonated drink, Coca-Cola light™, Argentina). The soft drinks had carbon dioxide content largely removed by vigorous stirring using a stirring plate and placing a magnetic bar in a container filled with the liquid prior to being offered to the animals at room temperature.

After 6 mo, 50% of the animals in each group (C, L and W) were randomly chosen to be euthanized. The remaining C and L rats were switched to tap water *ad libitum,* while the W group continued to drink tap water as usual for another 6 mo (washout period; end of study: 12 mo after the start). Rats were weighed weekly, while food and drink consumption were assessed twice a week. Biochemical, echocardiographic and systolic blood pressure (SBP) measurements were obtained at baseline, and at 6 mo (treatment) and 12 mo (washout); histopathological data were obtained at the time of sacrifice.

According to company specifications, Coca Cola™ is a carbonated water solution containing (for each 100 mL): carbohydrate 10.6 g, sodium 7 mg, caffeine 11.5 mg, caramel, phosphoric acid, citric acid, vanilla extract, natural flavorings (orange, lemon, nutmeg, cinnamon, coriander, *etc.*), lime juice and fluid extract of coca (*Erythroxylon novogranatense*). As far as nutritional information is concerned, the only difference between regular and light cola is the replacement of carbohydrates with non-nutritive sweeteners (aspartame + acesulfame K) in the latter.

Animals were housed at the ININCA facilities under controlled temperature (21 ± 2℃) and 12-h light-dark cycles (7 am to 7 pm). Rats were fed a commercial chow (16%-18% protein, 0.2 g% sodium (Cooperación, Buenos Aires, Argentina) *ad libitum*.

Animal handling, maintenance and euthanasia procedures were performed according with international recommendations[8]. This study was approved by the Ethics Committee for Scientific Research of the ININCA.

Biochemical determinations

Plasma levels of glucose, triglycerides and uric acid were determined by enzymatic conventional assays in blood samples collected from the tail vein after 4-h fasting[9]. Plasma concentrations of coenzyme Q_{10} and α-tocopherol were determined by HPLC-RP with UV detection using Waters 1500 Series, HPLC binary pump, Waters 717 plus Autosampler, Symmetry C_{18} 4.6 mm × 150 mm and 5 μm particle size column, guard column 4 mm × 4 mm (5 μm), Waters 2487 Dual λ Absorbance Detector, and Waters 2465 Electrochemical Detector. Waters Breeze™ Chromatography Data System software version for Windows NT was used for data acquisition and storage[6].

Blood pressure determination

SBP was measured by tail cuff plethysmography in unanesthetized rats restrained in a plastic chamber. The average of at least 3 readings per session was recorded. A pneumatic pulse transducer positioned on the ventral surface of the tail, distal to the occlusion cuff, detected the return of the pulse following a slow deflation of the cuff. Cuff pressure was determined by a pneumatic pulse transducer, using a programmed electro-sphygmomanometer PE-300 (Narco Bio-Systems, Austin, Texas). Pulses were recorded on a Physiograph MK-IIIS (Narco Bio-Systems, Austin, Texas).

Echocardiographic evaluation

Transthoracic echocardiograms were obtained in unanesthetized, gently restrained rats using an ATL 3000 HDI (Bethold, WA, USA) echocardiographic system equipped with a 10.5 MHz transducer. M-mode and 2-dimensional echocardiography images were acquired in short axis views at the level of the papillary muscle. Interventricular

septal end diastolic dimension (IVSd) and left ventricular end diastolic posterior wall dimension (LVPWd) were determined at the parasternal long axis at the midchordal level. Left ventricular diastolic dimension (LVDD) and left ventricular end-systolic posterior wall dimension (LVPWs) were measured perpendicularly to the long axis of the ventricle also at the midchordal level. Shortening fraction (Sf) was calculated by the following formula: 100 × (LVPWd - LVPWs)/LVDD. LV mass (LVM) was determined using the standard cube method[10] according to LVM = (LVDD + RWTh + LVPWd)^3 - (LVDD)^3 × 1.04. Other parameters were calculated as follows:

Relative posterior wall thickness (RWTh) = (LVPWd + IVSd)/LVDD; end diastolic volume (EDV) = 0.85 × (LVDD)^3; end systolic volume (ESV) = 0.85 × (LV systolic dimension)^3; cardiac output = (EDV - ESV) × heart rate (HR); systolic volume (SV) = EDV - ESV. Echocardiographic images and HR were simultaneously recorded.

Histopathological study

At the above indicated times euthanasia was performed by subtotal exsanguination under anesthesia (sodium thiopental 40 mg/kg, ip) of 50% of the animals (all 3 groups). The abdominal aorta was cannulated to perfuse with isotonic saline solution until the blood was washed out and the liver parenchyma presented a pale appearance. Complete autopsies were performed. Heart, liver, thoracic and abdominal aorta, kidneys, pancreas and muscle were excised and harvested for light microscopy. Tissues were immersed in 10% formalin at pH 7.4. After 48 h fixation, tissues were dehydrated in alcohol, cleared in xylene, and embedded in paraffin. Sections (3-5 μm thick) were cut and stained with hematoxylin and eosin, Masson's trichrome, or periodic acid-Schiff. Two independent evaluators (blinded to group assignment) examined the slices under a light microscope (Leitz Laborlux S) for histopathological changes.

Statistical analysis

Data were analyzed by two-way analysis of variance followed by *post hoc* tests (Bonferroni multiple comparison *t*-test) in order to evaluate selected pairs of groups. $P < 0.05$ was considered significant. SPSS™ version 15.0 software was used to analyze data.

RESULTS

Nutritional aspects

At baseline, experimental groups were comparable to each other with respect to all variables measured (Table 1). Table 2 shows the effects of regular cola and diet cola drinking on body weight and daily intake of food, liquid, sodium and calories, after treatment and following washout (6 and 12 mo, respectively, from the beginning of the study). Liquid and caloric consumption increased (by 70%, $P < 0.001$ and 11%, $P < 0.05$ respectively) and food intake decreased (31%, $P < 0.001$) after 6 mo of regular cola drinking (C_6). After washout, liquid intake normalized only partially (59% increase, $P < 0.05$ *vs* W_{12}; 11% reduction, $P < 0.05$ *vs* C_6). A sustained reduction in food intake was observed (by 38%, $P < 0.05$ *vs* W_{12}); caloric and sodium intake were accordingly reduced to a similar extent (31%, $P < 0.05$ *vs* W_{12}) in group C. Drinking diet cola did not affect food intake but a decrease in food intake was observed during washout (by 11%, $P < 0.05$).

Table 1 Body weight, systolic blood pressure, biochemical and echocardiographic data of rats at baseline (n = 16) (mean ± SD)

	W	C	L
Body weight (g)	390 ± 6	393 ± 6	395 ± 5
SBP (mmHg)	127 ± 7	127 ± 10	120 ± 11
Glucose (mg/dL)	110 ± 3	112 ± 3	111 ± 3
Triglycerides (mg/dL)	72 ± 9	70 ± 10	72 ± 8
LVDD (mm)	6.2 ± 0.5	6.3 ± 0.6	6.8 ± 0.5
RWTh	0.34 ± 0.06	0.37 ± 0.03	0.34 ± 0.06
ESD (mm)	2.7 ± 0.5	2.7 ± 0.5	3.3 ± 0.5
IVSd (mm)	0.84 ± 0.15	0.93 ± 0.09	0.91 ± 0.12
LVPWd (mm)	1.2 ± 0.2	1.4 ± 0.1	1.4 ± 0.3
LVPWs (mm)	2.6 ± 0.4	2.6 ± 0.4	2.6 ± 0.3
HR (bpm)	447 ± 45	421 ± 69	425 ± 49
Aorta (mm)	2.7 ± 0.1	2.9 ± 0.3	2.8 ± 0.4
LA (mm)	2.5 ± 0.3	2.7 ± 0.6	2.8 ± 0.4
Sf (%)	55.6 ± 6.9	56.8 ± 8.8	51.7 ± 4.9
EDV (mL)	0.21 ± 0.05	0.22 ± 0.06	0.27 ± 0.06
ESV (mL)	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Ef (%)	90.7 ± 3.7	91.0 ± 5.5	88.4 ± 3.5
SV (mL)	0.19 ± 0.05	0.20 ± 0.06	0.24 ± 0.05
CO (mL/min)	83.2 ± 20.1	85.5 ± 32.22	88.6 ± 23.8

SBP: Systolic blood pressure; LVDD: Left ventricular diastolic dimension; RWTh: Relative wall thickness; ESD: End-systolic dimension; IVSd: Interventricular septal end-diastolic dimension; LVPWd: Left ventricular end-diastolic posterior wall dimension; LVPWs: Left ventricular end-systolic posterior wall dimension; HR: Heart rate; Aorta: Aorta diameter; LA: Left atrial dimension; Sf: Shortening fraction; EDV: End diastolic volume; ESV: End systolic volume; Ef: Ejection fraction; CO: Cardiac output; SV: Systolic volume.

Plasma biochemistry

Regular cola drinking led to mild hyperglycemia (15% increase, $F_{2,18} = 3.611$, $P < 0.05$), and hypertriglyceridemia (3-fold, $F_{2,18} = 5.998$, $P < 0.01$) (Table 2). Normoglycemia and sustained hypertriglyceridemia were observed in group C after washout. Diet cola drinking caused only a trend to hypertriglyceridemia (2-fold, NS) (Table 3).

At the end of 6 mo, plasma levels of CoQ_{10} were reduced by 52% in the C group compared with the levels in W rats ($F_{2,18} = 3.576$, $P < 0.05$). No differences in plasma CoQ_{10} concentration were found across groups after washout ($F_{2,16} = 2.379$, NS), though W rats had 46% lower levels compared with those at baseline ($F_{1,34} = 5.197$, $P < 0.03$)[6].

Treatment did not modify plasma levels of α-tocopherol at any time ($F_{1,34} = 2.018$, NS) although, similar to that observed for CoQ_{10}, plasma levels of α-tocopherol decreased by 48% ($F_{1,34} = 4.532$, $P < 0.04$) in the W group at the end of the washout period compared with levels found in the same group at baseline[6].

Consumption of cola drinks had no significant effect on uricemia (data not shown).

Table 2 Body weight and nutritional facts (food, liquid, calories and sodium daily intake per 100 g body weight) after treatment and washout periods (mean ± SD)

	Treatment (6 mo)			Washout (12 mo)		
	W6 (n = 15)	C6 (n = 14)	L6 (n = 15)	W12 (n = 7)	C12 (n = 6)	L12 (n = 8)
Body Weight (g)	626 ± 8	669 ± 9[b]	630 ± 9	689 ± 10[d]	703 ± 27	699 ± 61
Intake (mL or g/100 g BW)						
Liquid	8.7 ± 1.2	14.7 ± 2.8[c]	8.5 ± 1.7	7.1 ± 1.1	11.3 ± 1.8[c,d]	6.5 ± 1.5
Solid	4.9 ± 0.6	3.4 ± 0.6[c]	5.1 ± 0.4	5.5 ± 0.6	3.8 ± 0.6[a]	4.9 ± 0.6[a]
Energy (Kcal/100 g BW)						
Liquid	0	6.17 ± 0.5[c]	0.09 ± 0.00	0	0	0
Solid	14.7 ± 1.1	10.2 ± 1.3	15.3 ± 0.9	16.5 ± 1.0	11.4 ± 0.9	14.7 ± 0.9
Total	14.7 ± 1.1	16.4 ± 1.2[b]	15.4 ± 0.9	16.5 ± 1.5	11.4 ± 1.1[d]	14.7 ± 0.9
Sodium (mg/100 g BW)						
Liquid	0	0.59 ± 0.2[c]	0.34 ± 0.1[c]	0	0	0
Solid	9.8 ± 1.0	6.8 ± 0.7[a]	10.2 ± 0.9	11.0 ± 0.1	7.6 ± 0.7	9.8 ± 1.0
Total	9.8 ± 1.0	7.4 ± 1.2	10.5 ± 1.0	11.0 ± 0.1	7.6 ± 0.7[a]	9.8 ± 1.0

Calculations based on: (1) kcal/g or mL: 3 (food), 0.42 (Coke) and 0.01 (Light coke); (2) Na^+ mg/g or mL: 2 (food), 0.075 (Coke or Light coke). [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ *vs* W for the same period (i.e. treatment or washout); [d]$P < 0.01$ *vs* respective group after treatment.

Table 3 Systolic blood pressure and biochemical data at 6 and 12 mo (mean ± SD)

	Treatment (6 mo)			Washout (12 mo)		
	W (n = 15)	C (n = 14)	L (n = 15)	W (n = 7)	C (n = 6)	L (n = 8)
SBP (mmHg)	134 ± 2	145 ± 3[b]	135.5 ± 2	131 ± 9	142.5 ± 15	144 ± 8
Glycemia (mg/dL)	128 ± 3	139 ± 3[a]	126 ± 3	128 ± 10.5	127 ± 34	119 ± 16
Triglyceridemia (mg/dL)	90 ± 9[c]	196 ± 24[b]	107 ± 20	132 ± 73	206.5 ± 77[a]	149 ± 60

[a]$P < 0.05$, [b]$P < 0.01$ *vs* W group; [c]$P < 0.05$ *vs* same group after washout. SBP: Systolic blood pressure.

Table 4 Echocardiographic parameters at 6 and 12 mo (mean ± SD)

	Treatment (6 mo)			Washout (12 mo)		
	W (n = 15)	C (n = 14)	L (n = 15)	W (n = 7)	C (n = 6)	L (n = 8)
LVDD (mm)	6.8 ± 0.4	7.4 ± 0.3[a]	7.3 ± 0.5[a]	7.2 ± 0.5	7.4 ± 0.4	7.8 ± 0.6
RWTh	0.40 ± 0.03[c]	0.37 ± 0.03[a]	0.36 ± 0.05[a]	0.35 ± 0.04	0.36 ± 0.02	0.35 ± 0.04
ESD (mm)	2.7 ± 0.5[c]	3.1 ± 0.6	3.1 ± 0.5	3.4 ± 0.4	3.4 ± 0.4	3.2 ± 0.3
IVSd (mm)	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
LVPWd (mm)	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.2	1.4 ± 0.1	1.6 ± 0.2	1.6 ± 0.1
LVPWs (mm)	3.6 ± 0.6	3.6 ± 0.6	3.1 ± 0.6	3.7 ± 0.4	3.1 ± 0.5	3.7 ± 0.5
HR (bpm)	469 ± 36	470 ± 46	457 ± 44	469 ± 23	472 ± 26	452 ± 52
Aorta (mm)	3.5 ± 0.3	3.5 ± 0.3	3.5 ± 0.3	3.4 ± 0.2	3.4 ± 0.2	3.6 ± 0.1
LA (mm)	3.3 ± 0.3	3.4 ± 0.4	3.2 ± 0.4	3.3 ± 0.3	3.4 ± 0.5	3.3 ± 0.2
Sf (%)	59.9 ± 7.2	58.5 ± 8.6	57.2 ± 7.4	52.1 ± 4.6	54.3 ± 6.3	58.9 ± 2.9
EDV (mL)	0.27 ± 0.04	0.34 ± 0.04[b]	0.33 ± 0.06[a,c]	0.32 ± 0.06	0.34 ± 0.06	0.41 ± 0.09[b]
ESV (mL)	0.02 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Ef (%)	93.0 ± 4	92.0 ± 4.9	91.5 ± 3.8	88.8 ± 2.9	90.1 ± 3.7	92.9 ± 1.4
SV (mL)	0.25 ± 0.04	0.31 ± 0.04[a]	0.31 ± 0.07[a]	0.28 ± 0.06	0.31 ± 0.07	0.37 ± 0.08[a]
CO (mL/min)	118 ± 21	148 ± 21[a]	138.5 ± 33	132 ± 26	146 ± 29	172 ± 46

[a]$P < 0.05$, [b]$P < 0.01$ *vs* W; [c]$P < 0.05$ *vs* same group after washout. LVDD: Left ventricular diastolic dimension; RWTh: Relative wall thickness; ESD: End-systolic dimension; IVSd: Interventricular septal end-diastolic dimension; LVPWd: Left ventricular end-diastolic posterior wall dimension; LVPWs: Left ventricular end-systolic posterior wall dimension; HR: Heart rate; Aorta: Aorta diameter; LA: Left atrial dimension; Sf: Shortening fraction; EDV: End diastolic volume; ESV: End systolic volume; Ef: Ejection fraction; CO: Cardiac output; SV: Systolic volume.

Echocardiographic evaluation

Chronic drinking of either cola beverage induced an increase in LVDD (C: +9%, L: +7%, $P < 0.05$ *vs* W) and LV volume (diastolic C: +26%, L: +22%, $P < 0.01$ *vs* W; systolic C: +24%, L: +24%, $P < 0.05$ *vs* W), and a reduction in RWTh (C: -8%, L: -10%, $P < 0.05$ *vs* W). An increase in cardiac output was also observed, which became significant in group C rats (C: +25%, $P < 0.05$ *vs* W; L: +17%, $t = 1.985$, NS *vs* W). Heart rate was not affected (Table 4).

After the washout period a regression of most alterations was observed with the exception of end diastolic

and systolic volumes in group L, which remained elevated compared with W (Table 4).

Histopathological study

Necropsy findings in heart, aorta, pancreas and skeletal muscle were scarce, and mainly due to the aging process. In liver, different degrees of hepatic steatosis were found as described by Kleiner *et al*[11], and were related to aging in all washout groups. A few animals showed kidney lesions attributable to the aging process, which were consistent with chronic progressive nephropathy.

DISCUSSION

In the present study, long-term drinking of regular cola beverage resulted in weight gain, mild hyperglycemia and marked hypertriglyceridemia. Changes in plasma triglycerides were also associated with the consumption of diet cola. Importantly, reversal of most parameters was observed after switching back from cola to water. Both cola beverages induced increases in diastolic and systolic volumes, and thinning of the left ventricular posterior wall, resulting in greater cardiac output without a change in HR.

The hypothesis that regular cola drinking could induce weight gain because of solid food overeating, which would be secondary to perceived low satiety (due to the fact that calories were mostly provided as liquid)[5] was not confirmed in this study. Actually, weight gain observed after regular cola drinking occurred in spite of a net decrease in solid food consumption. This was likely the result of drinking large volumes of regular cola which provided excess caloric intake.

Regarding the diet cola group, the biochemical profile induced by low-calorie sweet beverage drinking revealed only mild changes in triglycerides and total cholesterol, which were not different from those found in the other experimental group.

A review of the literature suggests that consumption of non-nutritive sweeteners may heighten appetite[12]. Interestingly, in this study diet cola drinking did not increase food intake, suggesting that an increase in food consumption associated with aspartame-sweetened drinks in man might be due to other, non-nutritional factors. Indeed, it is appreciated that overeating may also be subject to psychological influences. Also, awareness of fewer calories provided by drinking light beverages might induce individuals to eat in excess. As mentioned above, this apparently did not occur in our rats.

Sustained hypertriglyceridemia observed 6 mo after washout could not be accounted for by the increase in triglycerides with time (i.e. W_{12} *vs* W_6). As observed previously in relation to the antioxidant concentration in plasma, long-term hypercaloric consumption resulted in changes similar to those found as a result of normal aging[6].

Both cola beverages induced an increase in LVDD, EDV and ESV, accompanied by a reduction in relative wall thickness. These ventricular changes induced a concomitant increase in cardiac output, without significant changes in HR. These cardiac ventricular changes could be likely related to the effect of increased fluid load associated with drinking larger volumes. Of note, a regression of these alterations was observed in both groups following washout.

Regular cola is a hypertonic solution (493 mOsm/L) due to its high carbohydrate content, while both tap water (3 mOsm/L) and light cola (38 mOsm/L) are hypotonic solutions compared with plasma (285-295 mOsm/L). Ingestion of regular cola is supposed to stimulate antidiuretic hormone secretion causing hypervolemia so as to maintain plasma osmolarity within normal values.

Decreased CoQ_{10} levels have been suggested to be a useful biomarker of oxidative stress[13]. CoQ_{10} mainly accumulates in the liver and in cell membranes, where it acts as an endogenous antioxidant[14], and plasma levels of CoQ_{10} are well correlated with liver stores. It is conceivable that reduced plasma levels of CoQ_{10} found after 6 mo of cola drinking in our rats might reflect the exhaustion of the protective response mechanism to sustained oxidative stress induced by chronic carbohydrate ingestion. Long-term ingestion of a hypercaloric hyperglycemic diet (as in C rats) leads to obesity and increased lipid peroxidation and induces oxidative stress by compromising the mitochondrial redox metabolism[14]. Considering that ubiquinone allows regeneration of α-tocopherol[15], and that α-tocopherol levels did not show substantial variations among treatments in our study, it seems reasonable to assume that α-tocopherol was preserved as the main antioxidant source at the expense of CoQ_{10} consumption, so that α-tocopherol levels remained largely unchanged while CoQ_{10} levels substantially decreased.

Interestingly, there is evidence that decreases in CoQ_{10} and α-tocopherol levels may cause impairment of LV function[14,16]. This is in agreement with our echocardiographic findings of LV dilation and remodeling in this model.

Systolic hypertension might result from an increase in adrenergic activity elicited by caffeine. However this is unlikely in the present study, as the calculated caffeine doses provided by the cola drinks were in the order of 2.5 μg/kg (regular cola) and 1.6 μg/kg (diet cola), which was far below (1/1000th) pharmacologically effective levels in male rats[17].

In summary, in this animal model, oxidative stress, overweight, hypertriglyceridemia, mild hyperglycemia, systolic hypertension and echocardiographic alterations occurred as a consequence of chronic drinking of cola beverages in rats. Most of these changes reversed after washout to tap water. This model may be useful in view of its clinical significance in relation to the high consumption of cola beverages.

COMMENTS

Background

Epidemiological and experimental evidence indicate that excessive consumption of sweet carbonated beverages is associated with overweight and obesity

by virtue of the high sugar content, low satiety, and incomplete compensation for total energy in subsequent meals. The health impact of soft drink consumption is becoming alarming, particularly among adolescents. The present paper aims at investigating possible biochemical, echocardiographic and pathological alterations associated with chronic consumption of cola in rats.

Research frontiers

This experimental model has the advantage of being able to dissect out potentially confounding factors usually associated with soft drinks consumption in human subjects, such as increased smoking, increased junk food consumption, and sedentary lifestyle, which might all indirectly contribute to development of metabolic syndrome. Furthermore, compared with previous animal models of metabolic syndrome, this approach has the potential advantage that it lends itself well to a direct comparison with the situation commonly found in real life.

Innovations and breakthroughs

In spite of the existence of multiple experimental data with fructose-induced model of metabolic syndrome, there are few reports on the effects of cola drinking in animal models. We are well aware that soft drinks are compound substances, making difficult the assertion of the effect of each component. However, soft drink consumption has increased by 300% in the past 20 years, and 56%-85% of children in school consume at least one soft drink daily. In this regard, our aim was to study the effect of chronic cola beverage drinking taking into account the major public health issue involved.

Applications

This model could be used not only to study metabolic syndrome but to raise awareness of the serious problems that high consumption of soft drinks can generate, especially in children and young people.

Terminology

Metabolic syndrome: A cluster of risk factors for developing cardiovascular disease and diabetes comprising obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia. Cola beverage: A carbonated soft drink flavored with caramel and frequently containing caffeine. It also contains sugar or non-nutrient sweeteners, phosphoric or citric acids and a combination of flavoring substances and preservatives. Chronic progressive nephropathy: A progressive disease of the renal tissue that results in degeneration and regeneration of the epithelium lining the tubules, a thickening of basement membranes in the capsule, interstitial inflammation and fibrosis, and lesions which may be found in the glomeruli that tend to be generalized with variability in the amount present. It is commonly an age-related disease in rats. Coenzyme Q10: Also known as ubiquinone, ubidecarenone, coenzyme Q, is found in all membranes, particularly in mitochondria and acts as an important antioxidant in the body. α-tocopherol: is the form of vitamin E that is preferentially absorbed and accumulated in humans. Vitamin E may help prevent or delay coronary heart disease by limiting the oxidation of LDL-cholesterol, and also may help prevent the formation of blood clots.

Peer review

The study is very interesting, however there are still some questions to be answered.

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CASE REPORT

Percutaneous approach to treatment of coronary disease in a patient with uremic cardiomyopathy

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Abstract

Uremic cardiomyopathy is chronic ischemic left ventricular dysfunction characterized by heart failure, myocardial ischemia, hypotension in dialysis and arrhythmia. This nosologic entity represents a leading cause of morbidity and mortality among patients with end-stage renal disease receiving long-term hemodialysis. It is intuitive that revascularization in the presence of coronary artery disease in these patients represents an effective option for improving their prognosis. Although the surgical option seems to be followed by the best clinical outcome, some patients refuse this option and others are not good candidates for surgery. The present report describes the case of a patient affected by uremic cardiomyopathy and severe coronary artery disease in whom revascularization with percutaneous coronary angioplasty was followed by a significant improvement in quality of life.

Key words: Coronary artery disease; Heart failure; Percutaneous coronary intervention; Uremic cardiomyopathy

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INTRODUCTION

Uremic cardiomyopathy is chronic ischemic left ventricular (LV) dysfunction characterized by heart failure (HF), myocardial ischemia, hypotension in dialysis and arrhythmia[1]. This nosologic entity represents a leading cause of morbidity and mortality among patients with end-stage renal disease receiving long-term hemodialysis[1,2].

Revascularization in the presence of coronary artery disease in these fragile patients might represent an effective option in order to improve their poor prognosis. Although the surgical option seems to be followed by the best clinical outcome, some patients refuse this option and others are not good candidates for surgery. In these patients percutaneous approach may be a valid alternative. Treatment of uremic patients with ischemic LV dysfunction is nowadays still debated.

CASE REPORT

A 55-year-old male patient with a history of uremic cardiomyopathy was admitted to our Department because,

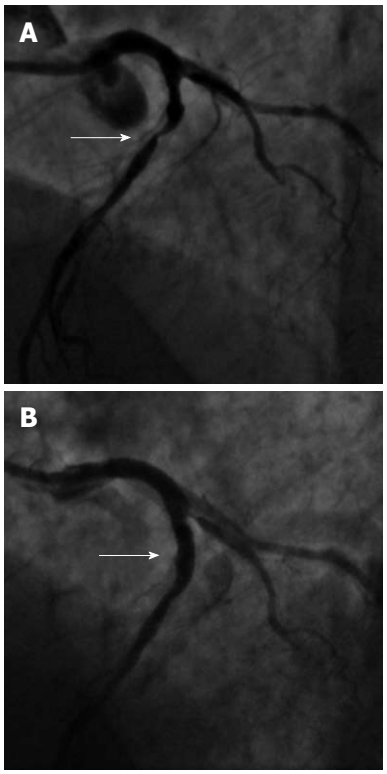

Figure 1 Angiography before and after percutaneous coronary intervention. A: Angiogram showing severe stenosis of the proximal left anterior descending artery; B: Final result after percutaneous coronary intervention.

during dialysis, severe hypotension associated with chest pain occurred. An electrocardiogram recorded during chest pain showed significant depression of the ST segment in the anterior leads. His clinical history was notable for several episodes of decompensated HF.

An echocardiogram showed severe reduction of LV ejection fraction (33%, biplane Simpson's method) with akinesis of the apex, inferior wall and basal segment of the interventricular septum, hypokinesis of the lateral, anterior and postero-lateral walls and of the medium segment of the interventricular septum [wall motion score index (WMSI): 2.375]. In addition, a severe regurgitation of the mitral valve was reported. As this patient was suspected of having coronary artery disease, we decided to perform a coronary angiography. After placing a 6-French sheath in the right femoral artery, coronary angiography revealed atherosclerotic lesions of the 3 main coronary vessels. Specifically, he had a subocclusive calcific stenosis in the proximal left anterior descending artery (LAD) (Figure 1A), and borderline stenosis in the medium segment of the circumflex coronary artery (CX) and of the distal right coronary artery (RCA).

After consultation with the cardiac surgeon, who suggested performing complete coronary revascularization of LAD, CX and RCA with coronary artery bypass surgery, the patient refused this treatment option. Thus, we decided to treat LAD by performing percutaneous coronary intervention (PCI) as the best choice of revascularization.

Table 1 Echocardiographic data before and after percutaneous coronary intervention

	Pre-PCI	Post-PCI
LVIDd (mm)	50	45
LVIDs (mm)	39	37
LVIDs/BSA (mm/m^2)	35	32
EFS (%)	22	18
EF, Simpson Biplane (%)	33	45
LA volume/BSA (mL/m^2)	42	23

PCI: Percutaneous coronary intervention; LVIDd: Left ventricular internal dimension, diastole; LVIDs: Left ventricular internal dimension, systole; EFS: Endocardial fractional shortening; EF: Ejection fraction; LA: Left atrium; BSA: Body surface area.

Acetylsalicylic acid (ASA) 500 mg iv, heparin (4500 IU iv), and a loading dose of 300 mg of clopidogrel were administered, after which the LAD lesion was treated with (PCI) and stenting resulting in a good angiographic result with TIMI 3 flow (Figure 1B). To reduce the risk of bleeding at the arterial puncture site, it was sealed with an Angio-Seal™ (St. Jude Medical, St. Paul, MN, USA) vessel closure device. He was discharged on ASA 100 mg/d and clopidogrel 75 mg/d for 1 mo followed by ASA monotherapy (100 mg/d).

After discharge, the patient reported a significant improvement in his clinical status. Specifically, hypotension episodes or chest pain with electrocardiographic changes during dialysis did not occur again. Of note, the echocardiogram showed improvement of the ejection fraction (45%, biplane Simpson's method) and of segmental wall motion (normal kinesis of the basal and medium segments of interventricular septum, lateral, anterior and postero-lateral walls. The apex became hypokinetic while akinesis of the inferior wall persisted; WMSI: 1.5). Moreover, an improvement in mitral valve regurgitation was reported (Table 1).

At 1-year follow-up, the patient had no cardiovascular events and showed no instrumental or clinical signs of ischemia. Of note, in his "new" clinical history he did not display any episodes of decompensated HF.

DISCUSSION

In the present report we describe the case of a patient affected by uremic cardiomyopathy and with angiographic evidence of coronary disease involving more than one vessel in which the clinical outcome was significantly improved by revascularization obtained by PCI.

Cardiovascular disease is the leading cause of death among patients with end-stage renal disease receiving long-term hemodialysis[1]. HF is one of the most frequent cardiac complications in this type of patient and is associated strongly with a poor prognosis[2]. The pathophysiology of cardiovascular disease in dialysis patients is characterized by disorders of perfusion (coronary artery disease, CAD) and disorders of structure and function (LV hypertrophy with subsequent dysfunction)[3]. Specifi-

cally, one-third of patients beginning dialysis has a history of symptomatic CAD and congestive HF[4]. Noteworthy, a close relationship exists between these 2 clinical entities because the clinical impact of CAD is mediated through changes in LV function. In this clinical setting, this specific type of chronic ischemic LV dysfunction is known as uremic cardiomyopathy.

Treatment of high risk patients, such as uremic patients, with ischemic LV dysfunction has been strongly debated. The benefits of pharmacologic management are strongly evidence-based, and all patients should be placed on medical management with recommended agents according to the 2005 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines Update for the Diagnosis and Management of Chronic Heart Failure[5]. On the contrary, clinicians have challenged with decisions about the unclear benefits of revascularization in these high-risk patients.

Percutaneous coronary intervention with stenting is the most widespread revascularization method for coronary disease which can be safely performed also in patients with low LV ejection fraction obtaining, in addition, acceptable late major adverse cardiac event rates[6]. The ACC/AHA guidelines provide several recommendations on the role of coronary angiography. A class I recommendation is given to patients presenting with chronic HF and angina or significant ischemia[5]. Coronary angiography is a class IIa recommendation in patients with HF who have chest pain that may or may not be of cardiac origin, whose coronary anatomy is unknown. Moreover, in spite of the concerns in the guidelines about the effectiveness of revascularization, coronary angiography is also a class IIa recommendation in patients with HF and known or suspected CAD but who do not have angina. In practice, if not previously performed, cardiac catheterization is reasonable in all patients who present with HF and are potential candidates for revascularization. In addition, when perfusion deficits and segmental wall-motion abnormalities identified on noninvasive testing cannot reliably distinguish patients with ischemic LV dysfunction from those with nonischemic cardiomyopathy, coronary angiography is usually required to reliably demonstrate or exclude the presence of CAD.

Coronary angiography plays an important role not only in determining which patient with HF is a candidate for revascularization but also to make decisions about the appropriate medical therapy. Use of aspirin is not recommended in patients without obstructive coronary disease and HF except for other indications. In contrast, patients with CAD should be treated with vasculoprotective medications including therapy with statins.

The 2005 ACC/AHA guidelines also provide recommendations for revascularization[5]. Revascularization in patients who have HF symptoms and angina pectoris is a class I recommendation. Despite theoretical arguments that support revascularization, the benefit is unproven in patients with HF but no angina.

The 2004 ACC/AHA Guidelines for Coronary Artery Bypass Graft (CABG) paid attention to patients with poor LV function, and specifically considered the number of vessels responsible for CAD. These guidelines assigned a class I recommendation for patients with LV dysfunction and left main, left main equivalent, and proximal LAD CAD with 2- or 3-vessel disease without regard to symptoms or viability[7]. A class IIa recommendation was given to patients with LV dysfunction with a myocardium that could be significantly revascularized without the class I anatomical patterns, but again, without regard to symptoms. The last version of the guidelines for PCI did not contain any recommendation for patients with clinical HF or LV dysfunction[8]. In practice, HF patients with ischemic dysfunction and angina are considered as potential PCI candidates if revascularization is feasible.

In this complex dispute between surgery and percutaneous intervention in patients receiving dialysis, a recent meta-analysis has pointed out that short-term mortality was higher after CABG compared with that after PCI. However, the PCI mortality rate significantly increased after the first year following the procedure, finally cancelling any difference between the 2 kinds of treatment[9]. More recently, Sunagawa *et al*[10] have reported that CABG is superior to PCI in patients with chronic renal failure on hemodialysis in terms of long-term outcomes for cardiac death, major adverse cardiac events, and target lesion revascularization.

In conclusion, patients with uremic cardiomyopathy are characterized by clinical complexity and, in addition, they often present CAD involving more than one vessel. Thus, surgery appears as the best treatment especially when chronic LV dysfunction is associated with CAD. However, this treatment could not always have been applied: some patients are too critical to be surgically treated and some others refuse this option. Anyway, these patients need revascularization. Here, we point out that the percutaneous approach may be considered as a valid alternative to surgery, with the ability to significantly improve the patient's quality of life.

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Molecular biology of heart disease

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Abstract

Dr. Robert Roberts is currently Professor of Medicine and Director of the Ruddy Canadian Cardiovascular Genetics Centre along with being President and CEO of the University of Ottawa Heart Institute. Prior to this appointment, he was Chief of Cardiology for 23 years at Baylor College of Medicine, Houston, Texas. His original research was in cardiac enzymology which led to the development of the MBCK test which was the standard diagnostic assay for myocardial infarction for more than 3 decades. In the late 1970s, his research interests switched to molecular biology and the genetics of cardiomyopathies. He is regarded as one of the founders of molecular cardiology and has identified and sequenced more than 20 genes responsible for cardiovascular disorders. In the past 6 years, he has pursued genome-wide association studies to identify genes predisposing to coronary artery disease (CAD) and myocardial infarction. The first genetic variant for CAD, 9p21, was identified by Dr. Robert's laboratory and, in collaboration with the international consortium, CARDIoGRAM, has identified 13 novel genes for CAD.

Figure 1 Robert Roberts, MD, FRCPC, MACC, President and CEO, Professor of Medicine and Director, Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y 4W7, Canada.

Key words: Molecular biology; Genetics; Heart disease; Genome wide association studies; Genetic linkage; Creatine kinase

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Robert Roberts (Figure 1) received his MD from Dalhousie University and completed his residency in Internal Medicine and Fellowship in Cardiology at the University of Toronto. Funded by a Canadian Heart Foundation Scholarship he pursued research in enzymology and cardiac metabolism at the University of California, San Diego, following which he was Director of the Cardiac Care Unit at Barnes Hospital and Associate Professor of Medicine, Washington University. In 1982, he accepted a position as

Chief of Cardiology at Baylor College of Medicine and became Professor of Medicine with joint appointments in the departments of Cell Biology and Molecular Physiology and Biophysics. On April 1, 2004, Dr. Roberts was appointed President and CEO of the University of Ottawa Heart Institute and Director of The Ruddy Canadian Cardiovascular Genetics Centre. He is also an adjunct Professor of Medicine at Baylor College of Medicine.

ACADEMIC STRATEGIES AND GOALS

Dr. Roberts, in addition to his role as clinician, educator and academic leader has been a very productive scientist. His early research focused on quantification and diagnosis of ischemic heart disease. He developed the first quantitative assay for the plasma MB isoenzyme of creatine kinase (MBCK) in 1974[1,2] and the first radioimmunoassay (RIA) for MBCK[3], based on an antibody to the B-subunit in 1976, which was also the first RIA for an isoenzyme. MBCK remained the standard for the diagnosis of myocardial infarction throughout the world for more than three decades[4-12]. He was the first to purify mitochrondrial CK[13,14] and clone the cytosolic CK genes[7,15]. Today all markers for myocardial infarction, including the troponins, are antibody-based. He isolated and purified the plasma MM and MB CK subforms[8,16], elucidated the mechanism responsible for their generation, and utilized them to develop an assay for the early diagnosis of infarction[8]. His laboratory played a pivotal role in the quantification of the extent of damage associated with myocardial infarction[4,6,14] and the effect of therapies on experimental infarction[17-19] in clinical trials, including β blockers[20] and thrombolytic therapy[20-27]. Notably, the Diltiazen on Non-Q-wave Infarction Study was directed by Dr. Roberts and showed diltiazen to be an effective therapy for non-Q-wave infarction which remains the mainstay of therapy 25 years later[28].

On moving to Baylor, Dr. Robert's basic research effort focused on the application of the techniques of recombinant DNA to cardiac growth[19,29-32] and molecular genetics. These efforts would subsequently earn him the title of one of the founders of molecular cardiology. He edited and co-authored the first textbook on Molecular Basis of Cardiology in 1993[33], and continues to author the section on Molecular Cardiology in numerous text books including Hurst's The Heart for the past two decades[34-36]. In the early 1980s, he cloned the genes for all three human creatine kinases[7]. His achievements were sufficiently recognized by the mid-1980s, that he was chosen by the American Heart Association to direct one of the three initial Bugher Training Programs for molecular biology of the cardiovascular system. Dr. Roberts' research has since been devoted to molecular genetics of cardiovascular disease.

ACADEMIC ACHIEVEMENTS

He has made many contributions in the field of molecular genetics on hypertrophic cardiomyopathy[37-48], familial dilated cardiomyopathy[49,50], muscular dystrophies[51,52], atrial fibrillation[45,53-56], Wolf Parkinson White Syndrome[57,58], Human eHAND[59], and arrhythmogenic right ventricular cardiomyopathy[60-62], and accomplished the following: (1) mapped the first locus for familial dilated cardiomyopathy; (2) mapped the first locus for atrial fibrillation; (3) mapped the first locus for arrhythmogenic right ventricular dysplasia in North America; (4) cloned and sequenced the desmin gene responsible for familial dilated cardiomyopathy; (5) identified the first gene for Wolff-Parkinson-White syndrome; (6) identified the troponin T mutation responsible for dilated cardiomyopathy; and (7) identified a novel family of proteins that bind specifically to triplet repeats and are responsible for myotonin mRNA nucleocytoplasmic transport[51,63-65]. He developed the only transgenic rabbit[66] with a phenotype of hypertrophic cardiomyopathy and together with transgenic mice has elucidated the pathogenesis of familial hypertrophic cardiomyopathy. Utilizing these transgenic animal models, he and his colleagues identified that statins, angiotensin Ⅱ blockers and aldosterone inhibitors could reverse the phenotype[44,67,68]. In 2005, he showed that the hypertrophic cardiomyopathy phenotype in the transgenic rabbit could be prevented with atorvastatin therapy[36]. The pioneering application of genetics in research and clinical management of cardiomyopathies developed Baylor Cardiology into a major referral center for inherited cardiovascular disease.

On moving to the University of Ottawa Heart Institute, he founded The Ruddy Canadian Cardiovascular Genetics Centre. This was initiated by a $5 million donation from John and Jennifer Ruddy followed by two endowed Fellowships of $1 million each by Doug Arand and Michael Potter and Family. While his research up to this time had been on single gene disorders he now focused on genetics of common cardiovascular disorders, namely coronary artery disease (CAD). The Ottawa Heart Genomics Study was initiated in 2004 in pursuit of genes responsible for CAD and myocardial infarction. It was the first genome-wide association study (GWAS) to utilize the 500 000 DNA chip to genotype for CAD. This led to the mapping of the first locus 9p21 for CAD[69]. The risk imparted by this locus is independent of known risk factors for CAD and was published in Science on May 3, 2007[70]. The Ruddy Canadian Cardiovascular Genetics Centre, under the direction of Dr. Roberts, rapidly acquired an international reputation and the capacity to perform high throughput genotyping (> 300 million genotypes per day) and DNA sequencing. In recognition of his scientific contributions he became a member of the International Consortium, CARDIoGRAM[71], which subsequently led to the discovery of over 95 genetic risk variants regulating lipids[72], and most recently a landmark study of over 23 genetic variants with increased risk for CAD and myocardial infarction[73]. These studies have led to numerous investigations regarding the mechanism of action of 9p21, including studies in Dr. Roberts' laboratory[74-77]. Utilizing the 9p21 gene, studies were performed which showed it could predict the severity and progression of CAD[77-79]. In a collaborative genome-wide study,

his lab recently identified the first gene in the ABO group that predisposes to myocardial infarction, and ADAMTS7 which predisposes to coronary atherosclerosis without infarction[80]. He is currently involved with a GWAS to map genes predisposing to hypertension[81]. In recognition of this effort, Dr. Roberts as Principal Investigator along with his co-investigators were awarded a $12 million grant for genetic research by the Canadian Foundation for Innovation in 2006 and another 5-year grant from the Canadian Institutes of Health Research.

Dr. Roberts is world renowned as an educator, particularly in bringing the techniques of molecular biology and genetics to the cardiovascular community. He has supported this mission through several venues including national and international academic and government committees. Dr. Roberts is currently a member of the Medical Advisory Committee to the Leducq Foundation (2010-2013) and the Gairdner Foundation (2010-2013). He is also on the Board of Directors for Fields Institute. He serves on the Grant Review Committees for the Canadian Institute for Health Research (CIHR), Genome Canada, Genome Quebec, the National Heart, Lung and Blood Institute (NHLBI) and the Heart and Stroke Foundation of Ontario. Dr. Roberts chairs the Safety Monitoring of the RAMICAT clinical trial. He is the editor of Current Opinion in Cardiology and is on the editorial board of several journals. Dr. Roberts served on the Cardiovascular Study Section of the National Institutes of Health (1979-1982), the Cardiology Advisory Committee of the NHLBI (1984-1988) and subsequently the Advisory Council of the NHLBI (2000-2001). He was Chairman of the Study Section for the Cardiovascular Physiology and Pathophysiology Committee of the American Heart Association (1990-1993) and a member of the Central Research Review Committee (1990-1995). He served on the American Heart Association (AHA) Scientific Sessions Committee from 1986-1990. He became a member of the Research Planning Evaluation Committee for the AHA (1994-2001), and served as Vice-Chairman (1997-1999) and Chairman (1999-2001), and during this time, he also served on the Board of Directors for the AHA. He served as Vice President of the AHA (2001-2002). In 1991, he served as Chairman of the Scientific Sessions for the American College of Cardiology (ACC) and served on the Board of Trustees (1996-2001), Young Investigators' Awards Committee (1988-1990), Member of Budget, Finance and Investment Committee (1997-2003), Nominating Committee (1998-2000) and Chairman of the Advisory Committee for Merck/Pfizer/ACC Foundation (2000-2006), and Member, CIHR Team Grant A (2007-Present). Dr. Roberts has lectured throughout the world and has been the plenary speaker at many national meetings including the American College of Chest Physicians Simon Rodbard Lecturer, 61st Annual Scientific Meeting of the Japanese Circulation Society, Mikamo Lecturer, Tokyo, Japan 1997, opening Plenary Speaker for the Japanese College of Cardiology 1995, Japanese Cardiology, the Secondary International Symposium on Heart Failure in Geneva, Switzerland, Simon Dack Presidential Address at the ACC Scientific Sessions (2002) and the State-of-the-Art Lecture, Canadian Cardiovascular Society (2005).

In recognition of his contributions, he has received several national and international awards. Dr. Roberts received the Distinguished Scientist Award from the ACC in 1998, the Award of Meritorious Achievement from The American Heart Association (2001), Master of the ACC (2007), and recently was awarded the McLaughlin Award from the Royal Society of Canada (2008). He was awarded the Robert Beamish Leadership Award in 2005. He has over 800 publications including Associate Editor of Hurst's The Heart, (1989-present) and was awarded the Most Highly Cited Researcher (2002).

CONCLUSION

Dr. Roberts is a major national and international educator for molecular genetics throughout the cardiac community. He chaired and participated in a core curriculum course of molecular biology for the clinician at the AHA and ACC Annual Scientific Sessions each year for over 15 years. He has participated in the fellowship program sponsored by AHA, ACC and NHLBI annually for over 20 years. As the Director of the Bugher and NHLBI training programs, he trained more than 40 molecular cardiologists, held leadership positions in the AHA and ACC and has been recognized as an important leader in the research and practice of cardiology worldwide. Several of his fellows are Chiefs of Cardiology in the USA, Canada, Japan and several other countries.

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January 25
Moving towards a national strategy for Chronic Obstructive Pulmonary Disease
London, United Kingdom

Februrary 24-26
Abdominal Obesity 2011 - 2nd International Congress on Abdominal Obesity
Buenos Aires, Argentina

Februrary 25-27
CardioRhythm 2011
Hong Kong, China

March 19-26
Cardiology Update: Caribbean Cruise
San Diego, CA, United States

March 25
Cardiology for General Practice
London, United Kingdom

April 1-2
11th Annual Spring Meeting on Cardiovascular Nursing
Brussels, Belgium

April 14-16
EuroPRevent 2011
Genova, Switzerland

April 30-May 4
ATC 2011 - 2011 American Transplant Congress
Philadelphia, United States

May 11-14
3th Radiochemotherapy and Brachitherapy Congress & 6th Medical Physycs Meeting
Córdoba, Argentina

May 15-18
ICNC10 - Nuclear Cardiology and Cardiac CT
Amstedan, The Netherlands

May 19-20
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
Gothenburg, Sweden

June 2-5
CODHy 2011 - The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 26-29
EHRA EUROPACE 2011
Madrid, Spain

June 29-July 1
Hands-on Cardiac Morphology - Summer Edition
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August 27-31
ESC 2011 - European Society of Cardiology Congress 2011
Paris, France

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9th International Congress on Coronary Artery Disease
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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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