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Beyond the French paradox: the impact of moderate beverage alcohol and wine consumption in the prevention of cardiovascular disease

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Cardiovascular disease (CVD) is the leading cause of death and disability in the United States and is responsible for 53% of deaths in women and 46% of deaths in men. [1] CVD is a primary or contributing cause in 60% of all deaths, and claims as many lives as the next leading causes of death including cancers, accidents, infections, and pulmonary disease. Coronary heart disease (CHD) affects 12 million people in the United States of which 1.1 million have a myocardial infarction annually and about one third die. Worldwide, CVD is the foremost cause of death, accounting for 57% of deaths among developing nations, and the second most cause of disability [2].

Over the past two decades, studies have consistently demonstrated an inverse relationship between alcohol consumption and the occurrence of myocardial infarction and cardiac death, with a J-shaped curve relating alcohol intake to mortality, favoring moderate alcohol drinkers compared with non-drinkers or heavy drinkers [3–5]. Millions of persons living in the United States drink alcohol; most consume fewer than three alcoholic drinks per day [4]. The American Heart Association's Science Advisory on alcohol and health cites the widely acknowledged harmful effects of heavy drinking [6]. This report underemphasizes, however, the risk reduction for cardiac and all cause mortality that has been associated with moderate alcohol consumption. Plausible biologic mechanisms for vascular protection from beverage alcohol is discussed in this article. The medical community has been cautioned not to expound the health benefits of alcohol, and particularly wine. In a letter, Ellison countered that, "telling people to avoid any alcohol consumption, because of the potential dangers of heavy use may not be in the best health interest of the public" [7]. Most agree that in the absence of a well-executed, randomized, double-blinded, intervention trial, controlled for confounding variables, the debate as to the health benefits of wine and beverage alcohol, as a part of a healthy lifestyle, will undoubtedly continue.

Prevention

In our society, CVD is the leading cause of death and prevention is vital to longer life and better health. Encarta World English Dictionary defines prevention as, "an action that stops something from happening" [8]. Although patients with CHD typically become symptomatic after age 40 years, studies indicate that CHD begins very early in life, such that by the age risk management and prevention is emphasized, many patients already have established vascular disease. In a study of cardiac transplant donors examined for the prevalence of CHD, 17% of victims aged less than 20 years, 39% of victims ages 20 to 29 years, and 85% in those aged greater than 50 years, had demonstrable lesions of coronary atherosclerosis [9]. Many epidemiologic and

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observational studies indicate that a healthy lifestyle including cigarette avoidance, low fat high fiber diet, lean body weight, regular exercise, and small amounts of daily beverage alcohol, is protective against CHD [10].

The prior study, however, suggests that one in six American teenagers, already have lesions of CHD, and the opportunity for prevention in these young people, has been lost [9].

History of alcohol and health

Through the ages, beverage alcohol, particularly wine, has been touted as an elixir for better health. Records of civilization spanning over thousands of years show evidence of fermentation and winemaking [11]. Fermentation was exploited for preserving foods and making food more nutritious. Accounts of ancient societies show evidence of wine consumption in moderation, and noted these earliest wine consumers to be better nourished and less prone to sickness [12]. Judaic records described "wine to be at the head of all medicines," and, "where wine is lacking, drugs are necessary." Hippocrates illustrated the value of wine as a medicine, and considered wine to be vital to a healthy diet. Paracelsus, a German physician of the 16th century wrote, "whether wine is a nourishment, medicine, or poison, is a matter of dosage." Thomas Jefferson noted the health benefits of wine, and wrote, "wine of long habit has become indispensable to my health," and, "I think it a great error to consider a heavy tax on wine as a tax on luxury. On the contrary, it is a tax on the health of our citizens." Louis Pasteur, the noted French biologist, recorded, "wine to be the most healthful and hygienic of beverages." William Heberden's classic description of angina pectoris in 1786 included the statement, "wines and spirituous liquors afford considerable relief," and postulated that alcohol was a coronary vasodilator [13].

The 20th century gave rise to tantalizing epidemiologic reports showing an inverse relationship between alcohol consumption and atherosclerotic disease. Early data suggested that heavy drinkers had the highest mortality; likewise abstainers were also prone to a higher mortality and moderate drinkers had the lowest mortality [13]. An observation in cirrhotic patients, showing the sparing of the vascular intima from atherosclerosis, particularly in the coronary circulation, suggested an anti-atherosclerotic effect of alcohol and a salutary effect on the endothelium [14].

Epidemiology

St. Leger and colleagues [15], studied variables associated with cardiovascular death in 18 developed countries. There was a strong and specific negative association between cardiac deaths and alcohol consumption, and the association seemed to be entirely because of wine consumption. Cigarette consumption, a strong cardiac risk factor, and total fat and caloric food intake, were positively associated with cardiac death. Gross national product per capita, an indicator of affluence and social maturity, was negatively associated with cardiac death. Other variables, such as the availability of medical professionals within a population, showed little association. The negative association between cardiac death and alcohol consumption was robust, and the strongest of predictors for mortality.

Important population studies that followed the initial observations of the past century provide a foundation for our current understanding of the association between alcohol consumption, CVD, and mortality.

Fig. 1 shows relative mortality, from all causes, with respect to alcohol consumption in pooled data from the Copenhagen Center for Population Studies [16]. Pooling data from three study samples including 13,064 men and 22,459 women of the Copenhagen City Heart Study, the Glostrup Population Study, and the Copenhagen Male Study, Groenbaek and colleagues [17] examined the relationship between intake of different alcohol beverages and death from all causes and CHD. All cause mortality is depicted as a J-shaped curve for non-wine drinkers. Compared with non-drinkers, light drinkers who avoided wine had a relative risk for death from all causes of 0.90 (CI, 0.82–0.99), and light drinkers who drank wine had a relative risk of 0.66 (CI, 0.55–0.77). At all levels of alcohol intake, wine drinkers were at significantly lower risk than non-wine drinkers for all cause mortality ($P < 0.001$). Wine drinkers had a significantly lower risk for death from CHD than did non-wine drinkers at all levels of alcohol intake. Compared with non-drinkers, light drinkers who avoided wine had a relative risk for death from CHD of 0.76 (CI, 0.47–0.72), and those who drank wine had a risk of 0.58 (CI, 0.47–0.72). Among the 6051 men and 7234 women aged 30 to 70 of the Copenhagen City Heart Study, the risk for dying steadily decreased with an increasing intake of wine, from a relative risk of 1.00 for subjects who never drank

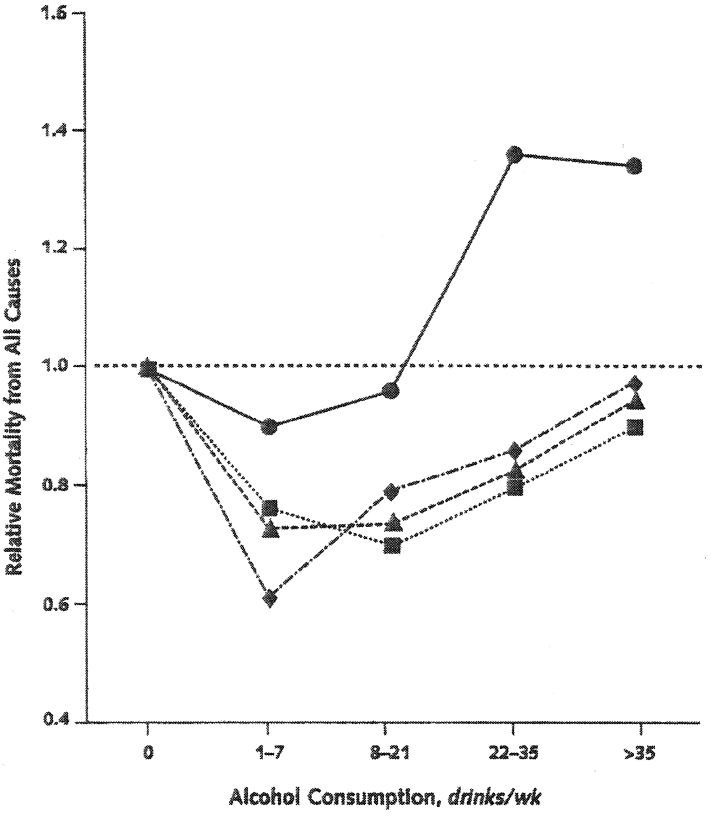

Fig. 1. Data pertain to non-wine drinkers (*circles*), wine drinkers (*triangles*), drinkers for whom wine made up 1% to 30% of their total alcohol intake (*diamonds*), and drinkers for whom wine made up more than 30% wine of their total alcohol intake (*squares*). Relative risk is set at 1.00 among nondrinkers (< 1 drink/wk). Estimates were adjusted for age, sex, educational level, smoking status, physical activity, and body mass index. (*From* Gronbaek M, Becker U, Johansen D, Gottschau A, Schnohr P, Hein HO, et al. Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. Ann Intern Med 2000;133:411–9; with permission.)

to 0.51 (CI, 0.32–0.81) for those who drank 3 to 5 glasses a day. Neither beer nor spirits was associated with a reduced risk.

The association between alcohol intake and CHD was studied prospectively among 51,529 male health professionals [18]. Alcohol consumption was consistently associated with a reduced risk for fatal and non-fatal myocardial infarction, and the need for coronary bypass surgery (CABG) or percutaneous coronary intervention (PCI). Risk reduction was comparable among subjects regardless of baseline cardiovascular risk. Increasing consumption of beverage alcohol was inversely related to CHD risk, with the strongest association seen for spirits. The multivariate relative risk for CHD was 0.55 (CI 0.39–0.77) for men who drank 2 drinks a day compared with men who did not drink ($P = 0.0004$).

In a prospective study of 87,526 female nurses studied for effects of alcohol consumption on the risk for CHD and stroke, drinking alcohol was associated with a profound risk reduction for CHD with a relative risk of 0.4 (CI, 0.2–0.8) for two drinks per day, and ischemic stroke relative risk of 0.3 (CI, 0.1–0.7) with up to one drink per day [19]. However, an increased relative risk of hemorrhagic stroke (RR = 4.4; CI, 1.2–15.2) suggests a compelling adverse hemostatic effect, and supports a causal relationship.

A meta-analysis of studies involving 209,413 persons on the relationship between wine and beer consumption and risk for fatal and non-fatal vascular events, support a significant inverse

relationship between wine consumption and vascular risk [20]. The relative risk for vascular endpoints among wine drinkers was 0.68 (CI, 0.59–0.77) relative to non-drinkers, with a dose-dependent relationship supporting a J-shaped curve. A significant inverse relationship was found at a daily intake of 150 mL. of wine; however a maximum risk reduction was predicted at 750 mL/day (Fig. 2). A risk reduction in favor of beer drinkers was also noted with a RR of 0.78 (CI, 0.70–0.86), however, there was no observed dose relationship.

Biology of alcohol and wine

Classically, the mechanism of CVD risk reduction for alcohol drinkers has been believed to be caused by the significant rise in HDL-C associated with alcohol consumption; At least 50% of the benefit has been attributed to HDL-C rise, an effect not unique to wine [21]. With the increasing interest in the protective role that HDL-C plays in the prevention of CVD, there is good reason to consider the effects that moderate alcohol consumption can add to current preventative and therapeutic strategies for CVD. At present, lifestyle factors, such as aerobic exercise, and lipid lowering drugs, produce only small increases in HDL-C. Alcohol intake may be the strongest positive predictor for an increased HDL-C in men and women [22].

In a study of 340 patients with myocardial infarction and age matched controls, the relative risk of myocardial infarction for subjects consuming three or more alcohol drinks a day was 0.45 (CI, 0.26– 0.80), compared with non-drinkers ($P < 0.001$) [23]. The levels of total HDL-C and anti-atherosclerotic sub-fractions, HDL-2 and HDL-3, were highest in the alcohol group ($P < 0.001$). Using a multivariate model, correcting for the increased HDL-C in alcohol drinkers substantially reduced the inverse association between alcohol intake and myocardial infarction and attenuated the benefit, supporting the position that the alcohol benefit is mediated, in large part, by increases in HDL-C.

In 1992, Renaud and DeLongeril [24] presented the discovery of the French Paradox, enhancing an interest in wine worldwide. Mortality rate for CHD in France was paradoxical and unexpectedly lower than other industrialized countries, such as the United States and the United Kingdom, despite similarly high dietary intake of saturated fat. Using a regression equation, adding the protective effect of wine in accord with previous reports, the paradox for CHD

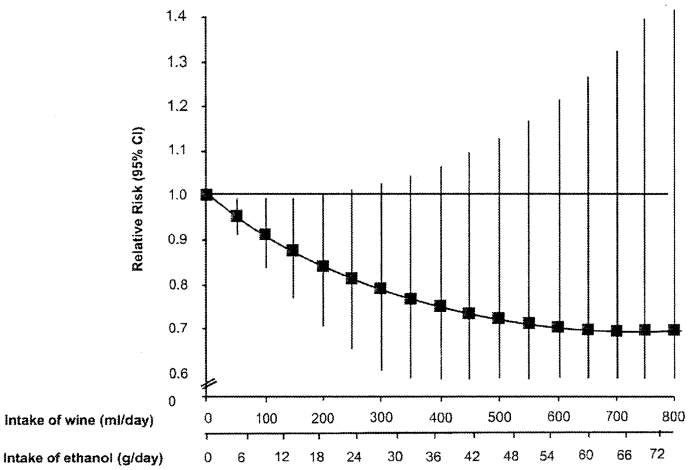

Fig. 2. Best-fitting model for wine effect ($R^2 = 0.54$ versus $R^2 = 0.27$ for the linear model with a positive linear term; $P = 0.34$) using dose-response curves in 7 prospective studies. Parameters of the model were $\beta_1 = -9.9 \pm 4.4 \times 10^{-4}$($P = 0.042$) and $\beta_2 = 0.0067 \pm 0.0023 \times 10^{-4}$($P = 0.013$). The best fitting model using data from the 3 case-control studies was a quadratic model that was not statistically significant with positive linear term ($P = 0.16$) and a negative quadratic term ($P = 0.091$). Horizontal lines represent the 95% CI. (*From* Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, de Gaeteno G. Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation 2002;105:2836–44; with permission.)

mortality was corrected and subsequently compared with other countries. This strongly supported the view that in France, the untoward effects of saturated fats are counteracted by the intake of wine. Serum concentrations of HDL-C were seen, however, to be no higher in France than other European countries, and therefore primary protection through alcohol consumption by the anti-atherosclerotic effect of HDL-C, would seem to be nearsighted. Alcohol can prevent myocardial infarction, but have little effect on stable angina [25]; Ex-drinkers have rapid loss of protection from CHD after ceasing alcohol intake [25], and whereas ischemic stroke is reduced, alcohol drinking increases the risk of hemorrhagic stroke [26]. A critical effect on hemostasis at levels of moderate alcohol intake is associated with a decrease in platelet reactivity and aggregability in humans [27]. Experimental models have shown that alcohol can produce a dramatic and significant decrease in intravascular platelet deposition in a normal laminar flow state, and high shear flow states, as one would encounter across a stenotic atherosclerotic lesion [28]. In human subjects, the effect of a single alcohol beverage on the bleeding time, a sensitive measure of platelet function, is increased and lengthened, when consumed with aspirin or within thirty six hours after aspirin ingestion. Because aspirin is commonly prescribed in patients with CHD, the intensified effect on bleeding time, with alcohol, may be a noteworthy mechanism of protection in patients with CHD [29].

Alcohol and wine in vascular biology

Possibly, the most interesting effect of alcohol consumption, and wine, is its effects on vascular biology and atherogenic mechanisms. As we have seen, alcohol has fundamental benefits on HDL-C, and platelets and hemostasis, and these effects are significant. For this reason, differentiating benefits unique to wine, compared with other alcohol beverages has been difficult and inconsistent. Furthermore, wine drinkers tend to be higher educated, belong to a higher socioeconomic class, are leaner and more adherent to a healthy diet, and less likely to smoke, confounding appreciation of a greater benefit for wine than from other alcohol beverage choices [30]. Wine is a particularly rich source of flavonoid phenolics such as resveratrol. The phenolic compounds in wine are well known to enologists for their sensory properties, and for this reason their chemistry has been investigated for decades. These substances give wine its astringency and bitterness, and are the foundation of long aging, since they are effective antioxidants. Red wines, unlike white wines, are high in concentrations of these substances and age gracefully. These complex chemical compounds, derived from the skins and seeds of red wine grapes are potent antioxidants and are of keen interest in health and CVD prevention.

Moderate wine consumption increases measurable plasma antioxidant activity, and inhibits the oxidation of LDL-C, an important event in atherogenesis. Maxwell measured serum antioxidant capacity in 10 healthy volunteers fed a standard meal alone and with 5.7 mL/kg of a red Bordeaux wine [31]. Serum antioxidant activity peaked in 90 minutes and remained elevated for more than 4 hours after wine was consumed with the meal. Whitehead [32] reported an 18% increase in serum antioxidant capacity in subjects who drank 300 mL of red wine, compared with a 4% increase for the same amount of white wine. Frankel [33] incubated human LDL with phenolics prepared from a California red wine after removal of all ethanol by distillation. Oxidative susceptibility of LDL was tested in vitro, and demonstrated a 60% and 98% reduction of LDL peroxidation by adding 3.8 and 10.0 μm/L of polyphenols from red wine. Reduced oxidation of lipoproteins and reduced oxidative stress on the human endothelium, a common pathway of vascular disease, may lessen the expected morbidity and mortality from CVD.

Risk factor intervention, such as serum cholesterol reduction, has salutary effects on endothelial function. Anderson had demonstrated that the addition of a potent antioxidant to a regimen of aggressive lipid lowering produced enhanced endothelial-dependent vasodilatation in subjects with impaired endothelial function [34]. Red wine, and de-alcoholized red wine, and purple grape juice have been shown to similarly enhance endothelial mediated vasodilatation of human arteries both in vitro and in vivo, by increasing endothelial nitric oxide synthesis. Leikert and colleagues [35] demonstrated an increase in endothelial nitric oxide synthase (eNOS) protein and eNOS promoter activity consistent with enhanced transcription of the eNOS gene in human endothelial cells exposed to alcohol-free red wine polyphenol extract. This data suggests that red wine contains unique polyphenolic constituents that may antagonize the earliest of vascular pathology and enhance endothelial

function by increasing endothelial nitric oxide output. This effect may not be common to all red wines, as suggested by Wallerath and colleagues [36] who reported that French red wines, not German red wines, increase endothelial nitric oxide mRNA protein and eNOS activity in cultured human endothelial cells.

Endothelin-1(ET-1), a potent vasoconstrictor derived from endothelial cells, has been shown to play a pivotal role in atherosclerotic lesion formation. Hereto, red wine and red wine polyphenols may have protective actions. Kahn, and associates [37], showed a concentration dependent inhibition of ET-1 synthesis from endothelial cells exposed to wine polyphenols from a cabernet sauvignon wine. When individual phenolic compounds, such as resveratrol and other anthocyanins, were tested, they had little or no independent effect on ET-1 synthesis. This suggests a mechanistic effect that is dependent on the composite activities of non-alcohol wine components.

Endothelial-dependent vasodilatation in response to red wine can be shown to be dose-dependent and caused by endothelial production of nitric oxide [38]. The effect of red wine on vascular tone can be inhibited by endothelial denuding, or pre-treatment of the vessel with a nitric oxide antagonist such as L-NMMA [38]. Flow mediated dilatation can be enhanced in healthy and diseased vascular models by red wine, de-alcoholized red wine [39], and purple grape juice [40]. One investigator suggested that differences in grape variety, regions of production, cultivation, and method of post fermentation processing may be important variables for health benefits. Flesch and colleagues [41] showed that red wines produced "en barrique," that is, in small barrels, typical of French Bordeaux produced a particularly pronounced vasodilatory effect compared with other red wines. These effects were endothelial dependent, and specific for some red wines, such as Châteauneuf du Pape and Bordeaux, and not others, such as Valpolcella and Rioja (Fig. 3).

Inflammation and vascular remodeling

C-Reactive protein is an emerging marker for acute CHD and has been associated with a significantly higher mortality in patients presenting with acute ischemic coronary syndromes [42]. Moderate red wine consumption has anti-inflammatory properties, and is associated with a lowered level of CRP. In a study of 2008 men and women, ages 18 to 88 years, alcohol consumption showed a U-shaped association with mean values of CRP [43]. Paralleling the J or U-shaped curves for total and coronary mortality, an anti-inflammatory action of beverage alcohol may contribute to the link between moderate consumption and lower mortality.

Data further support an effect of red wine on vessel wall remodeling including neointimal hyperplasia [44], monocyte recruitment and adhesion to the endothelium [45], inhibition of intracellular adhesion molecules [46], foam cell accumulation [44], smooth muscle cell (SMC) proliferation and migration [47,48], and abnormal expression of intracellular tissue factor [49].

Feng and colleagues [44] showed a significant reduction in Monocyte Chemotactic Protein (MCP-1) expression and reduced neointimal thickening in rabbits fed a high cholesterol diet with red wine, after balloon injury. Monocyte recruitment and macrophage accumulation promote intimal hyperplasia and lead to atherogenesis. After balloon injury, these actions contribute to restenosis, such as seen in many patients after PCI. In a study of 247 patients undergoing PCI, nondrinkers compared with alcohol drinkers had a 5-fold increase in risk of cardiac death, non-fatal MI, and other adverse end points possibly by inhibition, in some part by, these pathologic remodeling mechanisms [50].

Resveratrol, a red wine polyphenol, inhibits a number of polymorphonuclear leukocyte (PMN) functions considered to contribute to the pathogenesis and evolution of acute and chronic CHD [45]. These include inhibiting toxic reactive oxygen species produced by activated PMNs, and B-glucuronidase and elastase release, proteolytic enzymes responsible for acute vascular damage. Resveratrol inhibits the production of 5-lipooxygenase derived metabolites, which are chemotactic for neutrophils, eosinophils, and monocytes and increase neutrophil adherence. This effect blunts the inflammatory responses of neurophil aggregation, degranulation, and superoxide production. Resveratrol inhibits the expression and activation of the cell surface integrin MAC-1, blocking the formation of mixed cell conjugates between PMN and thrombin-stimulated platelets. These specific actions on the inflammatory cells of early CVD contribute to the protective effect of red wine consumption [45].

Red wine polyphenols have potent anti-proliferative properties, and inhibit SMC proliferation and migration, which is critical to atherosclerosis

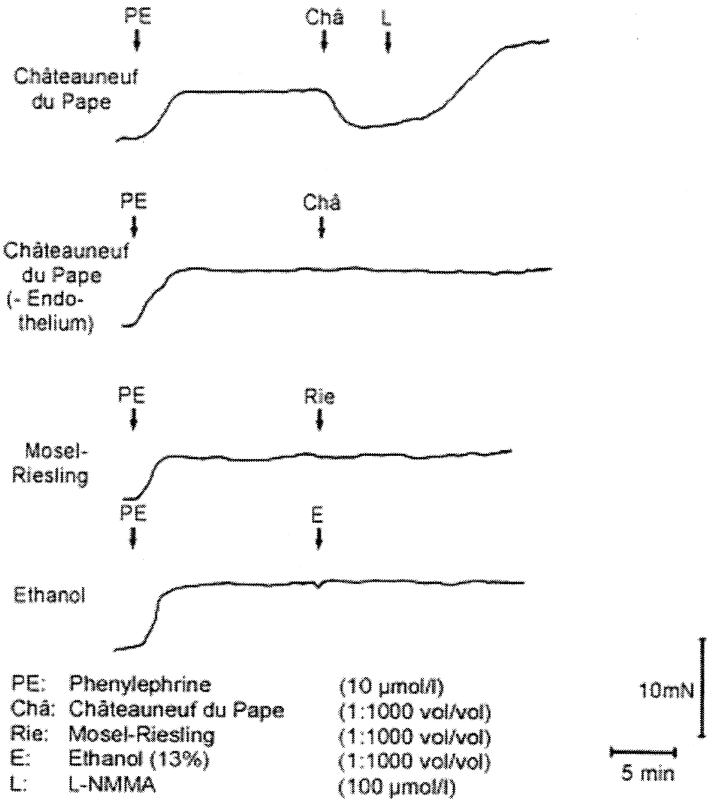

Fig. 3. Original recordings demonstrating response of human coronary arteries precontracted with phnylephrine to Châteauneuf du Pape, Mosel-Riesling, and ethanol. First trace, effect of Châteauneuf de Pape; second trace, effect of Châteauneuf du Pape after endothelial denudation; third trace, effect of Mosel-Riesling; fourth trace, effect of ethanol in same concentration as in tested wine. Notice that ethanol itself had no effect on vascular tone and that vasodilatory effect of Châteauneuf de Pape was dependent on integrity of endothelium and could be attenuated by addition of nitric oxide synthase inhibitor L-NMMA into organ bath. (*From* Flesch M, Schwarz A, Bohm M. Effects of red and white wine on endothelium-dependent vasorelaxation of rat aorta and human coronary arteries. Am J Physiol 1998;275:H1183–90; with permission.)

formation. Through cell cycle interference, mitigated by down-regulation of cyclin A mRNA and cyclin A promoter activity, DNA synthesis and SMC proliferation are inhibited [47]. Through the inhibition of signaling pathways in serum stimulated SMC's, red wine polyphenols inhibited SMC migration in serum stimulated cultures [48]. The effect that red wine polyphenols express on SMC migration and proliferation, in the context of atherogenesis, lend further insight into the mechanisms of the French Paradox.

Summary

Alcohol beverages, particularly red wine, when consumed in moderation reduce the risk of acute CVD and death. Important questions and issues, however, still remain, including the role of beverage type, pattern of drinking, and the risk that moderate drinking can lead to problem drinking.

The mechanism for alcohol beverage benefit is complex, and includes an independent benefit of ethyl alcohol. The multiplicity of effects identified for the non-alcohol components of red wine, play a role in improved endothelial physiology and enhance vascular homeostasis.

CAD begins in early life, and it progresses over decades. As the complexity of vascular pathology changes with time, so may the healthful effects of alcohol and non-alcohol wine components also vary. Prospective studies of alcohol or wine

consumption in the young, middle, and older aged persons would be interesting, but they are laden with obvious sociologic complexities.

Meanwhile, it is prudent for physicians to discuss the harmful effects of alcohol with their patients, while at the same time, not discourage a potentially healthy practice of wine in moderation (eg, with meals). The current literature is consistent in that heavy drinkers would be better off to reduce drinking or abstain, and abstainers or light drinkers, should be advised to avoid heavy drinking [13].

Whether moderate alcohol consumption can be characterized as a pharmacologic intervention or a dietary intercession may be a matter of opinion. I would rather like to believe that the growing scientific interest in wine and better health is a part of adopting a healthy lifestyle that connects our society with nature, to sustain and enhance human life.

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