Coffee and Caffeine Effects on Hypertension

Anna Vittoria Mattioli*

University of Modena and Reggio Emilia, National Institute of Cardiovascular Disease, Bologna, Italy

Abstract: In recent years, some epidemiological studies reported that coffee consumption was associated with increased serum cholesterol and blood pressure and subsequently increased cardiovascular risk.

Coffee is one of the most popular beverages consumed in a large amount in Western Countries. Coffee beverages contain several hundred different substances, but its effects of coffee on cardiovascular system have been mainly related to caffeine. Caffeine is present in a number of dietary sources consumed worldwide i.e. tea, coffee, cocoa beverages, chocolate bars and soft drinks. Caffeine exerts various effects on the autonomic nervous system and on blood vessels.

It is well-known that a dietary intake and lifestyle play an important role in hypertension. Meta-analyses of randomized control trials that examined the effects of coffee and caffeine intake on blood pressure presented conflicting results. Short term administration of caffeine in non-coffee drinkers increases blood pressure, plasma renin activity, and catecholamines. Heavy coffee drinkers seem to have negative effects mainly due to the activation of sympathetic system, i.e. rise in blood pressure, increase of risk of develop coronary artery disease. On contrary a moderate consumption shows no detrimental effects on cardiovascular system. In addition habitual coffee drinkers have less sympathetic response. Recent studies underline the antioxidants properties of coffee due to different compounds.

Coffee and Caffeine Effects on Hypertension

Anna Vittoria Mattioli*

University of Modena and Reggio Emilia, National Institute of Cardiovascular Disease, Bologna, Italy

Abstract: In recent years, some epidemiological studies reported that coffee consumption was associated with increased in serum cholesterol and blood pressure and subsequently increased cardiovascular risk.

Coffee is one of the most popular beverages consumed in a large amount in Western Countries. Coffee beverages contain several hundred different substances, but its effects of coffee on cardiovascular system have been mainly related to caffeine. Caffeine is present in a number of dietary sources consumed worldwide i.e. tea, coffee, cocoa beverages, chocolate bars and soft drinks. Caffeine exerts various effects on the autonomic nervous system and on blood vessels.

It is well-known that a dietary intake and lifestyle play an important role in hypertension. Meta-analyses of randomized control trials that examined the effects of coffee and caffeine intake on blood pressure presented conflicting results. Short-term administration of caffeine in non-coffee drinkers increases blood pressure, plasma renin activity, and catecholamines. Heavy coffee drinkers seem to have negative effects mainly due to the activation of sympathetic system, i.e. rise in blood pressure, increase of risk of develop coronary artery disease. On contrary a moderate consumption shows no detrimental effects on cardiovascular system. In addition habitual coffee drinkers have less sympathetic response. Recent studies underling the antioxidants properties of coffee due to different compounds.

Words: Coffee, caffeine, hypertension, inflammation.

INTRODUCTION

It is well-known that a dietary intake and lifestyle play an important role in hypertension.

From a variety of epidemiological studies on the effect of coffee consumption on blood pressure appear to be conflicting, demonstrating a positive relation, no relation or inverse relations [1,2]. Interestingly the JNC VII and the European Guidelines for the management of arterial hypertension do not mention coffee intake in lifestyle modification. A moderate consumption of coffee is included in the management of alcohol consumption is included [3,4].

Coffee is an infusion of ground, roasted coffee beans, is one of the most popular beverages consumed in Western Countries. Coffee contains several hundred different substances, including carbohydrates, lipids, vitamins, minerals, polyphenols and alkaloids [5]. Nevertheless effects of coffee on cardiovascular system have been mainly related to caffeine.

Coffee is the most widely consumed behaviorally active substance in the world and almost all caffeine comes from coffee and tea [6]. Caffeine is a naturally present alkaloid that is present in a number of dietary sources i.e. coffee, tea, chocolate bars and soft drinks. The caffeine content of these various food items ranges from 2 to 7 mg/150 ml for coffee to 24 to 50 mg/150 ml for cola, 2 to 7 mg/150 ml for

cocoa and 1 to 36 mg/28 mg for chocolate [5]. Caffeine concentration in coffee beverages can be variable. In a recent analysis of 14 different specialty coffees Mc Cusker and Golberger found that the amount of caffeine in 240 ml of brewed coffee ranged from 72 to 130 mg while caffeine in espresso coffee ranged from 58 to 76 mg in a single shot (28 ml) [7].

The variability in caffeine content may be due to many factors: modality of preparation i.e. espresso or percolation, different quality of coffee bean, roasting method and the length of brewing time [7,8]. In decaffeinated coffee the caffeine content ranges from none to 13.9 mg per 16-oz. In espresso decaffeinated coffee the range was wider, from 3.0 to 15.8 mg of caffeine per shot, due to human manipulation involved in the production of the espresso extraction [8]. The estimated caffeine from coffee consumption is 210 mg/day per person in U.S.A. and 198 mg/day per person in Italy [6].

Caffeine exerts various effects on the autonomic nervous system and on blood vessels. Caffeine is a non-selective competitive antagonist of adenosine receptors, A1 and A2A subtypes. The plasmatic concentration reached after coffee consumption is within concentration range that is needed to antagonize adenosine receptors. Other mechanisms of action of caffeine, such as inhibition of phosphodiesterase or calcium release from intracellular stores, occur at higher concentrations [6]. All tissues with adenosine receptors may be influenced by caffeine assumption.

Effects of caffeine include central nervous system stimulation, increased metabolic rate, gastric acid secretion stimulation, coronary vessel dilation, diuresis. Caffeine stimulates fat oxidation in muscle. Caffeine stimulates

*Corresponding author. Address: Department of Biomedical Sciences, University of Modena and Reggio Emilia, Modena, Italy. Tel: +39/59/422 4043; Fax: +39/59/422 4044; Email: annavittoria.mattioli@unimore.it

courage people to drink coffee [10]. Caffeine withdrawal induces a variety of symptoms: apathy, weakness, headaches, anxiety, increased heart rate and decreased motor behavior [11]. Heavy caffeine drinkers would experience stronger withdrawal symptoms than light drinkers.

EPIDEMIOLOGICAL STUDIES.

Data on the effect of coffee and caffeine on blood pressure are controversial. Much of the currently available information on cardiovascular effects of coffee is derived from epidemiological research. Coffee exposure is often assessed using food frequency questionnaires that collect information regarding the number of cups of coffee consumed daily or weekly. However caffeine content may vary considerably (see above) and this could affect the results. Recent studies found that a genetic polymorphism in the NAT2 gene, which results in "fast acetylators" and "slow acetylators", influence individual exposure to caffeine metabolites [12]. In addition, smoking increase increases the metabolism of caffeine by inducing CYP1A2 activity [13]. Smokers metabolize caffeine by approximately 50% more rapidly than nonsmokers [14]. A positive correlation between drinking coffee and smoking is reported [15] and it is well known that smokers are particularly liable to smoke when drinking coffee. There are also a larger proportion of patients who do not consume caffeine among nonsmokers than among smokers. Most analysis are adjusted for the effect of smoking. All these variables are potential confounders that should be considered when analyzing the results of epidemiological studies on coffee.

Meta-analyses of randomized control trials that examined the effects of coffee and caffeine intake on blood pressure presented conflicting results [2, 16].

In the meta-analysis performed by Noordzij and coworkers, evaluating coffee and caffeine trials separately, blood pressure elevation in caffeine trials appeared to be larger for systolic and diastolic blood pressure when compared to coffee trials [2]. The effect of coffee on blood pressure could depend on brewing methods, the strongest effect was found for boiled coffee, filtered coffee caused a moderate elevation in blood pressure, whereas only a small change was observed for instant coffee (Table 1).

A meta-analysis of 11 trial estimated the effect of coffee on blood pressure as 2-4 mmHg for systolic and 1-2 mmHg for diastolic blood pressure compared with the non-coffee drinkers [16] (Table 1).

The discrepancy between the two analysis can be explain by the different dosage of caffeine. Jee included trials with a high caffeine dose (greater than 410 mg/day) in which the rise in systolic blood pressure was larger than in trial with a lower caffeine dose [16]. In addition Jee and coworkers included short term trial that were excluded from the analysis performed by Noordzij. The smaller effects of coffee in studies lasting more than 2 weeks could reflect the adaptation to cardiovascular effects of coffee drinking [17]. Both review suggest that coffee consumption is associated with increase in both systolic and diastolic blood pressure, nevertheless results from observational studies failed to identify a pressor effect of habitual coffee consumption.

Winkelman and coworkers found no relation between coffee intake and incident hypertension in a cohort of 155,594 women followed for more than 10 years [18]. Caffeine intake was correlated positively with alcohol consumption and smoking habits. The risk of incident hypertension was increased by 14% and 15% for those in the third quintile as compared with lowest quintile whereas those in the highest quintile did not show an increased risk of hypertension. The Authors were not able to explain this modest inverse U-shaped association between caffeine intake and hypertension.

On contrary, in a study group of 1017 men followed up over 33 years, a greater incidence of hypertension was found in coffee drinkers [19]. Although the association with blood pressure level was significant in multivariate analyses, a nonsignificant 40% increase in the risk of incident diagnosis of hypertension for 3-4 cups/day and a 43% increase for 5 or more cups/day versus non drinkers was found and suggested that coffee drinking plays only a minor role.

The hypothesis that coffee may cause hypertension was supported by several small experiments over short follow-up. If short term effects of caffeine on blood pressure persist, then habitual coffee drinking might contribute to an excess risk of hypertension, but it is known that but the time, attenuation of these effects does occur.

Table 1.

	Systolic Blood Pressure (95% CI)	Diastolic Blood Pressure
Total coffee (16)	2.4 (1.0-3.7)	1.2 (0.4-2.1)
Total coffee (2)	2.04 (1.10-2.99)	0.73 (0.14-1.31)
Boiled coffee (2)	4.75 (2.33-7.17)	1.85 (-0.10-3.80)
Filtered coffee (2)	2.07 (0.95-3.18)	0.44 (-0.52-1.38)
Filtered coffee (16)	2.0 (0.4-3.6)	1.5 (0.5-2.5)
Instant coffee (2)	1.07 (-0.68-2.82)	0.19 (-1.04-1.41)
Instant coffee (16)	1.5 (-1.2-4.1)	0.5 (-1.5-2.6)

Short-term administration of caffeine in non-coffee drinkers increases blood pressure, plasma renin activity, and catecholamines [20]. These effects were observed in young non-coffee drinker subjects after the administration of a single dose equivalent to 2/3 cups of coffee. It is possible that these effects of caffeine were related to ideal laboratory conditions, and do not reflect the pressor response to regular daily drinking.

Corti and coworkers found that in non-habitual coffee drinkers, systolic blood pressure increased markedly after coffee consumption (+12.6 mmHg), while in habitual coffee drinkers this effect was small and non significant (+2.3 mmHg). Elevation of diastolic blood pressure was also more pronounced in nonhabitual drinkers (+7.1 mmHg) as compared with habitual coffee drinkers (+0.7 mmHg). A similar effect was observed after administration of caffeine. They also found that coffee and caffeine induced increases in muscle sympathetic nervous activity in non-habitual coffee drinkers, whereas habitual coffee drinkers exhibited lack of blood pressure increase despite sympathetic activation to coffee [21]. In nonhabitual coffee levels, nevertheless coffee did not increase plasma caffeine levels, nevertheless systolic blood pressure increase suggesting the hypothesis that substances other than caffeine may be responsible for the stimulating effect of coffee on cardiovascular system. This study demonstrates an activation of the sympathetic nervous system by caffeine and coffee as well as decaffeinated coffee. The effect in nonhabitual coffee drinkers must be related to a central or a peripheral nervous activation. So far the cardiovascular effects of coffee have been related to sympathetic nerve activation by caffeine. In habitual coffee drinkers the ingestion of a triple espresso did not cause any increase in blood pressure, probably because of induced tolerance. On contrary, administration of intravenous caffeine induced similar changes in sympathetic activity in both group. Thus, tolerance to coffee also does not appear to be related to caffeine. The impact of habitual versus nonhabitual coffee drinking is so important that appropriate stratification of patients is needed when analyzing data in this field.

Other studies found the same impact on blood pressure in nonhabitual drinkers and after a prolonged abstinence [20, 21]. It is possible that the negative effects adjudicated to coffee could be significantly less when coffee is consumed regularly.

TOLERANCE TO COFFEE AND CAFFEINE

In a later study Sudano and Corti found that the stress-induced response of systolic blood pressure was preserved after drinking a triple espresso in nonhabitual drinkers, whereas it was blunted in habitual coffee drinkers. Caffeine alone did not exert any potentiating effect in habitual and nonhabitual coffee drinkers, suggesting that ingredients other than caffeine are responsible for the effect on cardiovascular system [23].

The mechanism of tolerance were analyzed in several paper leading to different conclusions. Livallo and coworkers found a partial, but not complete, tolerance after regular caffeine intake and the degree of tolerance varied considerably from person to person [24].

Many different factors could influence incomplete tolerance to blood pressure effects of caffeine in habitual consumers.

Data from different reports found a continued effect of acute caffeine in regular users, i.e. consistent blood pressure responses to caffeine after overnight abstinence effect [25, 26]. Also the meta-analysis from Jee and coworkers concluded that the effect of caffeine persist with regular use [16]. Caffeine withdrawal can lower blood pressure acutely and over a period of weeks, suggesting sustained pressure elevation [27, 28]. In the study from Livallo the high- and low-tolerance groups did not appear to differ in caffeine metabolism so it is possible that adenosine receptor density or dynamics may influence the tolerance. Another explanation is the selection of young subjects, it is well known that ingestion of caffeine after chronic use is more likely to increase blood pressure in younger subjects [16]. Even in this case, study in laboratory tended to maximize the likelihood of caffeine effects on blood pressure [29]. Having found a very small change in blood pressure after acute ingestion of caffeine Livallo and coworkers divided subjects according to the median change in blood pressure so that the mean increase of systolic and diastolic blood pressure was only 2 and 3 mmHg in the low-tolerance subgroup. The magnitude of variation is low and we still don't know which levels of coffee consumption increase blood pressure in the daily living.

Caffeine affects persons to a progressively greater degree according to their blood pressure classification. Chronic elevations in blood pressure associated with a greater risk for hypertension are accompanied with increasingly large blood pressure responses to acute doses of caffeine. This finding suggest that caffeine may exert greater blood pressure effects in those with a greater risk of hypertension [30].

The pressor effect of caffeine is due to the elevation of peripheral vascular resistance rather than enhancement of cardiac output [31]. The ability of caffeine to increase vascular resistance raises the question of its effect in hypertension development.

COFFEE AND CAFFEINE AND VASCULAR FUNCTION

The effect of caffeine and coffee on vascular function has been examined as a mechanism of hypertension risk [32]. Umemura and coworkers found that acute administration of caffeine augments endothelium-dependent vasodilatation in healthy young men through an increase in nitric oxide production [33]. The same mechanism is involved in blood pressure lowering effects of tea and cocoa [34]. The reduction of blood pressure have been attributed to the polyphenols. A recent meta-analysis of controlled trials found that diets rich in cocoa were associated with a significant reduction in both systolic and diastolic pressure [34]. Interestingly black or green tea did not lead to evident changes in blood pressure even if tea contains polyphenols. Explanation of the lack of effects of tea on blood pressure could be the different composition of polyphenols, the main cocoa polyphenols are procyanidins [35,36] while the main polyphenols in tea are flavan-3-ols, gallic acid and condensed catechins. Cocoa

tributed by antioxidants such as other carotenoids, flavonoids and lignans.

Svilaas and coworkers found that coffee was a major contributor to total antioxidant intake. The intake of coffee contributed 64% of the total antioxidant intake, followed by fruits and berries [48]. Green and black coffee beans contain different quantity of antioxidant, 15.9 and 22.6 mmol tot antioxidant/100 g, respectively. This difference depends on the roasting process that damages some antioxidants [49]. Coffee consumption is associated with a reduction of plas-matic gamma-glutamyl transpeptidase, a marker of early oxidative stress [50].

Thus, coffee contains several bioactive substances, some of which may be beneficial, while others may increase the risk of cardiac disease.

CONCLUSIONS

In conclusion, the effects of coffee consumption on cardiovascular system remain largely unknown, while more information are available on caffeine effects. A moderate consumption shows no detrimental effects on cardiovascular system. On the basis of epidemiological studies it seems that in normotensive individuals without a genetic background for hypertension, coffee consumption cannot be considered a risk factor for hypertension. In habitual coffee drinkers have less sympathetic activity. Recent studies underling the antioxidants properties of coffee due to different compounds, it is well known that coffee beverage contains several hundred different substances and caffeine is only one of the coffee compounds.

In the future, it likely that we will determine beneficial and detrimental properties of coffee consumption, having in mind that coffee is an infusion that contains many different compound including caffeine. Future developments will identify substances, other than caffeine, responsible for cardiovascular activation.

REFERENCES

- [1] Nurminen ML, Nittymä L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. *Eur J Clin Nutr* 1999; 53:831-839.
- [2] Noordzij M, Utevaal CS, Arends LR, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. *J Hypertens* 2005; 23: 921-928.
- [3] Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003; 289: 2560-2572.
- [4] Guidelines for the management of arterial hypertension. The task force for the management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology. *J Hypertens* 2007; 25: 1105-1187.
- [5] Mattioli AV. Effects of coffee consumption in the developments of cardiac disease and arrhythmias. *Future Cardiol* 2007; 3:203-212.
- [6] Fredholm BB, Battie K, Holmen J, Nehlig A, Zwartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999; 61: 83-133.
- [7] McCusker RR, Goldberger BA, Cone EJ. Caffeine content of specialty coffees. *J Anal Toxicol* 2003; 27: 520-522.
- [8] McCusker RR, Fuehrlein B, Goldberger BA, Gold MS, Cone EJ. Caffeine content of Decaffeinated Coffee. *J Anal Toxicol* 2006; 30: 611-613.

Flavonoids induced vasodilation by increasing endothelial production of nitric oxide [37]. They also improve endothelial function and platelet inhibition [36, 38]. Beneficial effects on arterial function seems to be not mediated by a effect on antioxidant status, and can be attribute to improved bioavailability and prostacyclin increase [39]. It was demonstrated that the lowering effects of polyphenols are out-weighed by pressor effects of tea caffeine [34]. Long-term epidemiological studies of tea intake and blood pressure re-ported either non lowering effects in habitual tea consumers [40] or a small reduction, consistent with the nonsignificant effects found in short-term trials [41].

The effect on caffeine on vascular function is the result of the balance of the vasodilatory effect of caffeine as an endothelium-dependent vasodilator and the vasoconstrictive effect of caffeine as an adenosine receptor antagonist.

COFFEE AND CAFFEINE AND INFLAMMATION

The relation between coffee consumption and inflammatory markers has been evaluating in different studies [42-44].

The ATTICA study found a linear dose-response relation between coffee consumption and increase of inflammatory markers. Is it interesting that the difference was significant only when the consumption of coffee exceed 200 mL/day compared with subjects who did not drink coffee [42]. A possible explanation is the inclusion of unfiltered coffee in the coffee consumption analysis, and it is plausible that compounds in this kind of coffee that increase cholesterol concentration also contribute to increased inflammation and endothelial dysfunction [42].

In contrast many other reports underline anti-oxidant properties of coffee mediated by flavonoids, potassium, magnesium and other components that could have anti-inflammatory effects [43].

The association between coffee consumption and lower plasma concentrations of several markers of inflammation and endothelial dysfunction was reported in both healthy and diabetic women [44]. Regular coffee ingestion reduced LDL oxidation susceptibility. Coffee may favorably affect endothelial atherosclerotic plaques through this pathway. In addition, the phenolic compounds of coffee, chlorogenic acid and caffeic acid, have a strong protective antioxidant effect in the endothelium [44]. Chlorogenic acid and caffeic acid have antioxidant activity *in vitro*, but it is unclear how much antioxidant activity they contribute *in vivo* because they are extensively metabolized, and the metabolites often have lower antioxidant activity [45].

Epidemiologic studies suggest that regular consumption of food and beverages rich in flavonoids is associated with a decreased risk of cardiovascular disease [46]. The protective effect could be related to bioactive compounds in food and beverages that reduce oxidative stress. A condition that promotes when the formation of reactive oxidants outstrips the antioxidant defense and the oxidative damage occur [47].

The well-known antioxidant (i.e. vitamin C and beta-carotene) contribute a relatively small part of the total antioxidants in most dietary plants, whereas the majority is con-

- [9] Van Soeren MH, Graham TE. Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal. *J Appl Physiol* 1998; 85: 1493-1501.
- [10] Richardson NJ, Rogers PJ, Elliman NA, O'Dell RJ. Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. *Pharmacol Biochem Behav* 1995; 52: 313-320.
- [11] Nikolajsen L, Larsen KM, Kierkegaard O. Effect of previous caffeine deprivation. *Pharmacol Biochem Behav* 1995; 52: 295-297.
- [12] Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet* 2000; 39: 127-153.
- [13] Cornelis MC, El-Sohemy A, Katagambé EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA* 2006; 295: 1135-41.
- [14] Benowitz NL, Hall SM, Modin G. Persistent increase in caffeine concentrations in people who stop smoking. *BMJ* 1989; 298: 1075-76.
- [15] Swanson JA, Lee JW, Hopp JW. Caffeine and nicotine: A review of their joint use and possible interactive effects in tobacco withdrawal. *Addict Behav* 1994; 19: 229-256.
- [16] Jee SH, He J, Whelton PK, Suh I, Klag MJ. The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension* 1999; 33: 647-652.
- [17] Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. *J Clin Invest* 1981; 67: 1111-1117.
- [18] Winkelmayr WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA* 2005; 294: 2330-2335.
- [19] Kiang MJ, Wang NY, Meoni LA, et al. Coffee intake and risk of hypertension: the John Hopkins precursors study. *Arch Intern Med* 2002; 162: 657-662.
- [20] Robertson D, Frolich JC, Carr RK, et al. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. *N Engl J Med* 1978; 298: 181-186.
- [21] Corti R, Binggeli C, Sudano I, et al. Coffee acutely increases sympathetic activity and blood pressure independently of caffeine content. Role of habitual versus nonhabitual drinking. *Circulation* 2002; 106: 2935-2940.
- [22] Rakic V, Burke V, Beilin LJ. Effects of coffee on ambulatory blood pressure in older men and women: a randomized controlled trial. *Hypertension* 1999; 33: 869-873.
- [23] Sudano I, Spieker L, Binggeli C, et al. Coffee blunts mental stress-induced blood pressure increase in habitual but not in nonhabitual coffee drinkers. *Hypertension* 2005; 46: 521-526.
- [24] Lavallo WR, Wilson MF, Vincent AS, Sung BH, McKey BS, Whitsett TL. Blood pressure response to caffeine shows incomplete tolerance after short-term regular consumption. *Hypertension* 2004; 43: 760-765.
- [25] Sung BH, Whitsett T, Lavallo WR, al'Abisi M, Pincomb GA, Wilson MF. Prolonged increase in blood pressure by a single oral dose of caffeine in mildly hypertensive men. *Am J Hypertens* 1994; 7: 755-758.
- [26] Lane JD, Adcock RA, Williams RB, Kuhn CM. Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual caffeine consumption. *Psychosom Med* 1990; 52: 320-336.
- [27] James JE. Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels. *J Cardiovasc Risk* 1994; 1: 159-164.
- [28] van Dusseldorp M, Smits P, Thien T, Katan MB. Effect of decaffeinated versus regular coffee on blood pressure. A 12-week, double-blind trial. *Hypertension* 1989; 14: 563-569.
- [29] Myers MG. Effect of caffeine on blood pressure beyond the laboratory. *Hypertension* 2004; 43: 724-725.
- [30] Hartley TR, Sung BH, Pincomb GA, Whitsett TL, Wilson MF, Lavallo WR. Hypertension risk status and effect of caffeine on blood pressure. *Hypertension* 2000; 36: 137-141.
- [31] Pincomb GA, Lavallo WR, Passey RB, Whitsett TL, Silverstein SM, Wilson MF. Effects of caffeine on vascular resistance, cardiac output and myocardial contractility in young men. *Am J Cardiol* 1985; 56: 119-122.
- [32] Hibino G, Moritani T, Kawada T, Fushiki T. Caffeine enhances modulation of parasympathetic nerve activity in humans: quantification using power spectral analysis. *J Nutr* 1997; 127: 1422-1427.
- [33] Umemura T, Ueda K, Nishioka K, et al. Effects of acute administration of caffeine on vascular function. *Am J Cardiol* 2006; 98: 1538-1541.
- [34] Taubert D, Roessen R, Schomig E. Effect of cocoa and tea intake on blood pressure. A meta analysis. *Arch Intern Med* 2007; 167: 626-634.
- [35] Lee KW, Kim YJ, Lee HJ, Lee CY. Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. *J Agric Food Chem* 2003; 51: 7292-7295.
- [36] Natsume M, Osakabe N, Yamagishi M. Analyses of polyphenols in cacao liquor, cocoa, and chocolate by normal-phase and reversed-phase HPLC. *Biochem Biotechnol* 2000; 64: 2581-2587.
- [37] Karim M, McCormick K, Kappagoda CT. Effects of cocoa extracts on endothelium-dependent relaxation. *J Nutr* 2000; 130: 2105S-2108S.
- [38] Holt RR, Schramm DD, Keen CL, Lazarus SA, Schmitz HH. Chocolate consumption and platelet function. *JAMA* 2002; 287: 2212-2213.
- [39] Vlachopoulos C, Aznaouridis K, Alexopoulos N, Economou E, Andreadou I, Stefanadis C. Effect of dark chocolate on arterial function in healthy individuals. *Am J Hypertens* 2005; 18: 758-791.
- [40] Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. *Ann Epidemiol* 1993; 3: 375-381.
- [41] Yang YC, Lu FH, Wu JS, Wu CH, Chang CJ. The protective effect of habitual tea consumption on hypertension. *Arch Intern Med* 2004; 164: 1534-1540.
- [42] Zampelas A, Panagiotakos DB, Pitsavos C, Chrysoschoou C, Stefanadis C. Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am J Clin Nutr* 2004; 80: 862-867.
- [43] Svilaas A, Sakhi AK, Andersen LF, et al. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. *J Nutr* 2004; 134: 562-567.
- [44] Lopez-Garcia E, van Dam RM, Qi L, Hu FB. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. *Am J Clin Nutr* 2006; 84: 888-93.
- [45] Iwai K, Kishimoto N, Kakino Y. *In vitro* antioxidative effects and tyrosinase inhibitory activities of seven hydroxycinnamoyl derivatives in green coffee beans. *J Agric Food Chem* 2004; 52: 4893-4898.
- [46] Knecht P, Ritz J, Pereira MA, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. *Am J Clin Nutr* 2004; 80: 1508-1520.
- [47] Beckman KB, Ames BN. The free radical theory of aging mature. *Physiol Rev* 1998; 78: 54-581.
- [48] Svilaas A, Sakhi AK, Andersen LF, et al. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. *J Nutr* 2004; 134: 562-567.
- [49] Daglia M, Papetti A, Gregotti C, Berte F, Gazzani G. *In vitro* antioxidant and ex vivo protective activities of green and roasted coffee. *J Agric Food Chem* 2000; 48: 1449-1454.
- [50] Wild AC, Mulcahy RT. Regulation of gamma-glutamylcysteinyl synthetase subunit gene expression: insight into transcriptional control of antioxidant defenses. *Free Radic Res* 2000; 32: 281-301.