ABSTRACT  Epidemiological studies suggest that tea consumption is associated with reduced cardiovascular disease risk, but the mechanisms for these observations have remained uncertain. In recent years, it has become apparent that the endothelium plays a central role in the regulation of vascular homeostasis and that endothelial dysfunction contributes to the pathogenesis and clinical expression of cardiovascular disease. This article reviews the evidence that human tea consumption has a beneficial effect on the vascular endothelium and the clinical implications of these findings. J. Nutr. 133: 3293S–3297S, 2003.

KEY WORDS: • tea • endothelium • coronary artery disease

The purpose of this presentation is to provide an overview of the relation between tea consumption and cardiovascular disease. I will briefly review some of the epidemiological evidence suggesting a relation between tea consumption and reduced risk for cardiovascular disease. I will then present a study from our laboratory that examined the effect of tea consumption on a surrogate marker for cardiovascular risk, endothelial function. I will also present findings from other studies that examined the effects of flavonoids on consumption on this endpoint. Finally, I will discuss the clinical implications of these findings and consider the possibility that a clinical trial of tea would be appropriate.

Epidemiological studies

In regard to the epidemiological evidence, a number of studies have examined the relation between tea and flavonoid consumption and cardiovascular risk (Fig. 1). For example, Hertog and colleagues examined the relation between cardiovascular disease and flavonoid consumption (tea, apples, onions) as assessed by a dietary questionnaire in 805 elderly men from the Zutphen Elderly Study (1). This prospective cohort study demonstrated a marked reduction in cardiovascular risk in the tertile of subjects with the highest flavonoid consumption compared with individuals in the lowest tertile. Specifically, they observed that individuals consuming >29 mg/d had a 68% reduction in cardiovascular risk, after adjustment for other known risk factors.

Another type of epidemiological study is a case-control study, which involves the identification of a number of individuals with the disease of interest and compares them with a matched group of subjects without the disease. Sesso and colleagues used this approach to examine the relation between tea and coffee consumption and myocardial infarction (2). They examined tea and coffee intake by questionnaire in 340 subjects and 340 matched controls from the Boston Area Health Study. They observed a 44% reduction in cardiovascular risk in the individuals drinking more than a cup of tea per day. There was no significant relation between coffee consumption and cardiovascular disease.

The two papers discussed in the preceding paragraphs examined the relation between tea consumption and first myocardial infarction. A recent study examined the effect of tea consumption on recurrent myocardial infarction in patients. Using a prospective cohort design, Mukamal and colleagues examined tea consumption in 1900 patients in the Myocardial Infarction Onset Study, a study that examined patients with myocardial infarction presenting to community hospitals in the United States (3). Tea consumption was assessed by questionnaire and the patients were followed for 3.8 y. This study demonstrated a 31 and 39% reduction in cardiovascular risk in moderate and heavy tea drinkers after adjustment for other risk factors.

Although these three studies all suggest a beneficial effect of tea on cardiovascular risk, a number of studies have failed to show such an association. Several of these neutral studies are...
would be a randomized study comparing tea consumption to placebo against a background of minimal flavonoid consumption. The remainder of this paper will focus on potential mechanisms of benefit of tea consumption in regard to the cardiovascular system.

**Potential mechanisms of benefit**

In recent years, there has been a shift in focus in regard to cardiovascular disease risk. In the past, the primary focus was the physical or anatomic stenosis that developed in atherosclerotic vessels and factors that led to progression or severity of obstruction. Novel approaches to treatment involved methods to relieve these stenoses. It is clear that angioplasty, by-pass surgery, and other more novel approaches such as drug-eluting stents have an important role in the treatment of patients with advanced disease who are unresponsive to medical therapy. However, the focus of research has shifted and has begun to emphasize the importance of the abnormal vascular biology of atherosclerotic vessels. It has become apparent that events like acute myocardial infarction occur after rupture of atherosclerotic plaques with subsequent platelet activation, thrombus formation and vasospasms of the vessel, and that such events often occur in lesions that are quite mild and do not obstruct the arterial lumen. Although all of the operative mechanisms remain uncertain, it is clear that these events represent a major loss of vascular homeostasis in the atherosclerotic vessel. Identifying the underlying factors that make lesions vulnerable to rupture and mechanisms that influence the severity of the thrombotic and vascular response have greater potential for the identification of new approaches for prevention and therapy for cardiovascular disease.

**Endothelial function and cardiovascular risk**

One area of interest in cardiovascular disease research is the function of endothelial cells, one of the primary regulatory cells within the blood vessel wall. Endothelial cells are now recognized as playing a central role in vascular homeostasis, and they produce factors that act locally in the vessel wall and lumen. One such factor was initially termed endothelium-derived relaxing factor (EDRF). Subsequent work identified this factor as nitric oxide or a closely related substance. Although nitric oxide was first described in regard to its vasodilator effects, it is now clear that it has other very important functions. EDRF is a gaseous molecule that can diffuse into the vessel wall and act on smooth muscle cells to cause relaxation. In recent years, there has been a shift in focus in regard to cardiovascular disease risk. In the past, the primary focus was the physical or anatomic stenosis that developed in atherosclerotic vessels and factors that led to progression or severity of obstruction. Novel approaches to treatment involved methods to relieve these stenoses. It is clear that angioplasty, by-pass surgery, and other more novel approaches such as drug-eluting stents have an important role in the treatment of patients with advanced disease who are unresponsive to medical therapy. However, the focus of research has shifted and has begun to emphasize the importance of the abnormal vascular biology of atherosclerotic vessels. It has become apparent that events like acute myocardial infarction occur after rupture of atherosclerotic plaques with subsequent platelet activation, thrombus formation and vasospasms of the vessel, and that such events often occur in lesions that are quite mild and do not obstruct the arterial lumen. Although all of the operative mechanisms remain uncertain, it is clear that these events represent a major loss of vascular homeostasis in the atherosclerotic vessel. Identifying the underlying factors that make lesions vulnerable to rupture and mechanisms that influence the severity of the thrombotic and vascular response have greater potential for the identification of new approaches for prevention and therapy for cardiovascular disease.

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and relevant effects on vascular homeostasis. Nitric oxide is an anti-inflammatory compound that prevents adherence of leukocytes to the endothelial surface. It is an antithrombotic compound in that it prevents platelet adhesion and platelet aggregation. Nitric oxide inhibits the proliferation of vascular smooth muscle cells and the formation of other noncellular components that comprise the matrix of the vascular wall and, thus, is relevant to lesion formation and vascular compliance. Nitric oxide not only affects conduit arteries where lesions develop, but also affects microvessels that regulate blood flow to tissues. It is clear that an impairment of nitric oxide formation would have adverse effects on the cardiovascular system. When produced in appropriate amounts, nitric oxide is an antiatherosclerotic antithrombotic and is a vasodilator molecule.

The endothelium produces a number of other very important regulatory factors, and loss of nitric oxide is paralleled by impairment of these other regulatory mechanism. These observations have led to the concept that the endothelium may be a barometer for vascular health (10). A number of risk factors for cardiovascular disease may adversely impact the endothelium. These risk factors include the traditional factors such as dyslipidemia, hypertension, diabetes, smoking and the aging process, and those more recently identified including physical inactivity, systemic inflammation and infectious processes, hyperhomocysteinemia and the postmenopausal state. The endothelium may have both intrinsic or extrinsic mechanisms that affect the its ability to resist the effects of risk factors. For example, genetic factors might influence the activity of antioxidant enzymes or nitric oxide synthase. Environmental factors such as diet (including tea consumption) might also influence the ability of the endothelium to resist the adverse effects of risk factors. If the defense mechanisms are unable to compensate for the adverse effects of risk factors, the endothelium will then develop a pathological phenotype. This situation leads to a state of endothelial dysfunction that is characterized by a loss of nitric oxide. In addition, endothelial dysfunction may also be associated with dysregulation of the fibrinolytic and inflammatory systems in a manner that promotes lesion development and progression and the clinical expression of atherosclerosis. These mechanisms may increase the risk of cardiovascular events and stroke.

This hypothesis is well supported by prospective studies suggesting that endothelial dysfunction is associated with an increased risk of cardiovascular events. There have been at least eight studies involving over 1500 subjects that have examined this issue, and all indicate that endothelial dysfunction has prognostic value (11–18). The presence of endothelial dysfunction is predictive of adverse cardiovascular events and appears to have utility as a biomarker or surrogate marker of cardiovascular risk. Endothelial dysfunction has evolved into a marker that may be used to identify potential interventions for the prevention or treatment of cardiovascular disease (10).

Noninvasive assessment of endothelial function

A number of methods have evolved for the assessment of endothelial function in human subjects, but study of the effects of tea on endothelial function has used a noninvasive ultrasound-based method developed by several investigators (19–21). This methodology examines endothelium-dependent flow-mediated dilation of the conduit brachial artery. Although it is clear that study of endothelial function in the arm is less relevant than studies in the coronary circulation, a number of studies has shown that responses in the arm are clinically relevant. Anderson and colleagues showed that endothelial dysfunction in the brachial artery has a high predictive value for abnormal endothelial function in the coronary circulation, as assessed by intracoronary acetylcholine infusion (22). Importantly, several recent studies have shown that impaired brachial artery flow-mediated dilation identifies patients at increased risk for cardiovascular disease events (17,18).

The methodology has been described in detail in a recent review (23). Briefly, the brachial artery is imaged by two-dimensional ultrasound. A cuff on the arm is inflated for 5 min and then released. This procedure produces a state of reactive hyperemia, and this high flow stimulates nitric oxide production by the endothelium because shear stress is increased at the endothelial surface. If one images the brachial artery 1 min after cuff release, flow-mediated dilation is readily detectable. Doppler recordings before and after cuff release are used to assess the extent of reactive hyperemia. In normal subjects, the conduit brachial artery dilates ~12% in response to increased flow induced in this manner. Patients with risk factors for cardiovascular disease and patients with angiographically evident disease have blunted responses (Fig. 3). For example, patients with coronary disease dilate about 6%, and this reduction is readily measurable despite the limitations of ultrasound resolution.

We have recently been interested in the mechanisms of endothelial dysfunction in patients with atherosclerosis and have focused on the importance of oxidative stress in this regard. As part of these investigations, we recently collabo rated with Dr. Balz Frei to examine the effect of the antioxidant vitamin ascorbic acid (vitamin C) and brachial artery flow-mediated dilation. In this study, we examined the effects of ascorbic acid treatment on endothelial function in 48 patients who had angiographically proven coronary disease, but were not taking antioxidant supplements (24). These subjects were randomized in a double-blind placebo-controlled manner to treatment with vitamin C or placebo. We examined the acute (2 h after a 2-g oral dose) and chronic effects (500 mg/d for 30 d) of ascorbic acid on brachial artery flow-mediated dilation. We observed a significant improvement in flow-mediated dilation at both time points. Studies in vitro using a cell culture model by Dr. John Keaney have suggested that some of this benefit may be related to an effect of ascorbic acid to increase the activity of endothelial nitric oxide synthase by stabilizing its cofactors tetrahydrobiopterin (25).

This work with the water-soluble antioxidant ascorbic acid prompted us to consider that tea might have a beneficial effect

![Figure 3](https://example.com/figure3.png)

**FIGURE 3** Effects of risk factors and coronary artery disease (CAD) on brachial artery flow-mediated dilation (FMD). Compared to control patients (CTR), patients with hypertension (HTN), diabetes mellitus (DM), and CAD demonstrate significant lower flow-mediated dilation. The data for are drawn from the author’s database of over 1500 subjects (mean ± SD).
on endothelial function because tea contains antioxidant flavonoids, which are also water soluble. In a placebo-controlled crossover study, we examined the effects of acute and chronic tea consumption on brachial artery flow-mediated dilation in 50 subjects with angiographically proven coronary disease (26). These subjects were taking no antioxidant supplements, and they were asked to refrain from drinking tea and red wine during the period of study. These patients were taking other standard medications for coronary disease including lipid-lowering therapy (77%). In this study, we used a standard blend of black tea that contained 1 g/L of total flavonoids. The subjects consumed 450 mL of this freshly brewed tea and we measured brachial artery flow-mediated dilation before and 2 h after tea consumption. We also examined endothelial function after subjects consumed 900 mL of this tea (reconstituted from a freeze-dried powder) for 4 wk. The study had a crossover design with water as a control beverage, and the beverage order was randomized.

The results of the study are presented in Figure 4. As shown, both acute and chronic tea consumption was associated with improved endothelial function. There were no effects on nitroglycerin-mediated dilation, confirming that tea consumption affected endothelial function rather than that of vascular smooth muscle. There also was no effect of a comparable dose of caffeine on endothelial function. Tea consumption had no effect on blood pressure, serum glucose or serum lipids. Total catechins were increased ~20% following tea consumption; however, we observed no effects of tea consumption on plasma antioxidant capacity. There also was no effect on plasma F2 isoprostanes, a marker of systemic lipid peroxidation. Finally, we observed no effect of tea consumption on platelet aggregation in response to ADP or thrombin-related activated peptide (27). Others have suggested that collagen-induced aggregation might be affected by tea selectively, but unfortunately we didn’t look at collagen as one of our stimuli.

Our findings are consistent with several other studies. For example, Hodgson and colleagues examined the effect of tea consumption on brachial artery flow-mediated dilation in a group of otherwise healthy subjects with modest hypercholesterolemia (28). These investigators also observed a beneficial effect of tea. In that study, tea consumption also reduced plasma levels of P-selectin, a marker of in vivo platelet aggregation, but had no effect on other adhesion molecules, and saw similar effects of tea consumption (29). Finally, one other study examined the effects of another flavonoid-containing beverage, purple grape juice. In this study, Stein and colleagues observed that brachial artery flow-mediated dilation was improved with a 14-d period of grape juice consumption (30).

**CONCLUSIONS**

In summary, this presentation has reviewed several epidemiological studies that suggested a beneficial effect of flavonoids and tea consumption. I also reviewed several studies that suggested no beneficial effect and discussed a number of possible explanations for these conflicting results. One mechanism that might explain a beneficial effect of tea on the cardiovascular system is that it improves the vascular endothelium. Endothelial function, including brachial artery flow-mediated dilation, is gaining increasing acceptance as a clinically relevant surrogate endpoint for cardiovascular disease risk. Although these findings cannot be interpreted as meaning that tea consumption should be recommended for the prevention or treatment of cardiovascular disease, they provide mechanistic insight and certainly suggest that tea consumption has a beneficial effect. Furthermore, the studies do fit well with the American Heart Association recommendation that Americans should increase their consumption of fruits and vegetables, including a vegetable-based beverage, such as tea.

**LITERATURE CITED**

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