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Brachial Artery Ultrasound: A Noninvasive Tool in the Assessment of Triglyceride-Rich Lipoproteins

ROBERT A. VOGEL, M. D., F.A.C.C.

Division of Cardiology, University of Maryland Hospital, Baltimore, Maryland, USA

Summary: In recent years, endothelial dysfunction has been identified as an early feature of atherosclerosis. Endothelial function can be measured noninvasively by using brachial artery ultrasound. A variety of factors associated with atherosclerosis also impair endothelial function. Some of these factors are lipoproteins such as various forms of low-density lipoproteins, postprandial chylomicron remnants, fasting triglyceride-rich particles, and free fatty acids. A high-fat diet also has an adverse effect on endothelial function. Several interventions can improve endothelial function and, at the same time, reduce cardiovascular events. Measuring endothelial function may eventually serve as a useful index to determine an individual's risk for coronary artery disease.

Key words: brachial artery, coronary artery disease, endothelium, high-density lipoprotein, low-density lipoprotein, ultrasound, very low-density lipoprotein

Introduction

In recent years, endothelial function has been used as a surrogate or intermediate biological marker for coronary atherosclerosis and cardiovascular events. Traditionally, atherosclerosis has been viewed as a disease of low-density lipoprotein (LDL) deposition in subintimal spaces. Through a sequence of events (platelet adherence, foam cell formation, collagen formation, etc.), there is eventual plaque formation and rupture leading to thrombosis and, ultimately, to a cardiovascular event. This process falls short, however, in the understanding of why so many different risk factors interact in a multiplicative fashion to yield exactly the same disease. This is true for lipids, dietary habits, and a number of environmental issues.

In the last two decades, a second atherosclerosis pathway has evolved that focuses on endothelial dysfunction. The basic tenet of this hypothesis is that all coronary risk factors (e.g., LDL, hypertension, smoking, triglyceride-rich particles, homocysteine, *Chlamydia*, etc.) lead to endothelial dysfunction. Such dysfunction then leads to a vasculopathy associated with the attraction of platelets and monocytes. Growth factors are subsequently released leading to smooth muscle cell migration and proliferation. This propsed pathway helps explain why the diverse risk factors lead to coronary artery disease (CAD).

Endothelium Function

The endothelium is the body's largest endocrine organ. It weighs approximately 1.5 kg and would cover two tennis courts with a surface area of 600 m^2. The endothelium carries out a number of functions. For example, it regulates vasoactivity, vascular cell growth, thrombotic and fibrinolytic properties, leukocyte and platelet adhesion to its surface, and vascular permeability. It also modulates lipid oxidation and mediates inflammatory and immune mechanisms. One of the most important endothelial functions is the maintenance of vascular tone and structure. Specifically, this is short-term vasodilation, predominately brought about by nitric oxide, prostacyclin, and hyperpolarizing factor. Vasoconstriction, on the other hand, is brought about by endothelin, thromboxane, angiotensin-II, oxygen free radicals, and other substances. Individuals constantly live in a balance between vasoconstriction and vasodilation, which are, respectively, proatherosclerotic and antiatherosclerotic. In addition to short-term factors, the endothelium elaborates a number of growth factors, thrombotic factors, thrombolytic factors, inflammatory factors, immune factors, and so forth. In conclusion, the endothelium is much more than the simple, semipermeable membrane it was originally thought to be.

Measuring Endothelial Function

Clinically, it is relatively easy to measure endothelial function using the vasodilator capacity of the endothelium. Most investigations have used vasodilation as an index of endothelial function. Figure 1 is an example of abnormal endothelial

Address for reprints:

Robert A. Vogel, M.D.
Division of Cardiology
University of Maryland Hospital
Room SB 306
22 S. Greene Street
Baltimore, MD 21201-1544, USA

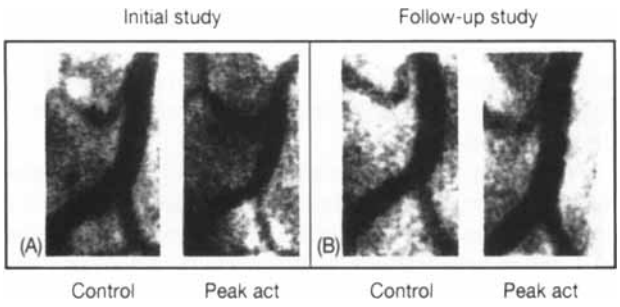

FIG. 1 Abnormal endothelial function in the coronary artery of a hypercholesterolemic patient. A vasoconstrictive response is shown to acetylcholine (A). After a cholesterol-lowering intervention, there is a mild vasodilator response to the same agonist (B). Reprinted from Ref. No. 1 with permission.

function based upon an arteriographic study using an artheriographic section of a coronary artery.[1] This in vivo vascular ring experiment shows a vasoconstrictive response (A) to an endothelium-dependent agonist, acetylcholine, in a hypercholesterolemic patient before cholesterol lowering. After a cholesterol-lowering intervention, there is now a mild vasodilator response to the same agonist at the same site (B). This shows that endothelial function is not a consequence of the atherosclerosis but vice versa. Endothelial function can be normalized, even in the face of significant atherosclerosis, by changing the risk factor milieu. Coronary narrowing is not simply a disease of fixed stenoses. In response to exercise, cold exposure, or emotional stress, patients may vasoconstrict if they have endothelial dysfunction in addition to atherosclerosis.

Another way to investigate endothelial function is to use an intrinsic stimulus, such as increased shear stress or blood flow. The endothelium regulates the linear velocity of blood to approximately 15–20 cm/s under basal conditions throughout the body. It has a shear receptor on the surface that can sense an increase in flow. Acute vasodilation and chronic vessel growth occur in response to increased shear. This is why all vessels turn out to have exactly the right dimensions under healthy conditions. When dysfunction is present, however, the response to the same increase in coronary blood flow is an absence of vasodilation and, perhaps, vasoconstriction.[2] One of the components of ischemia is a dysfunctional endothelium responding to increased flow inappropriately vasoconstricting the vessel.

Flow-mediated vasodilation is mostly nitric oxide dependent. Experiments conducted with nitric oxide synthase inhibitors show a reactive hyperemia with little vasodilation in response to this hyperemia (Fig. 2).[3] Of importance is the fact that nitric oxide availability reveals something about the antiatherosclerotic state of the vessel. In an experimental animal, inhibiting nitric oxide synthase with a specific eNOS inhibitor will result in about twice as much atherosclerosis compared with control.[4,5] When L-arginine, a precursor of nitric oxide, is given, there is approximately half as much atherosclerosis compared with control.

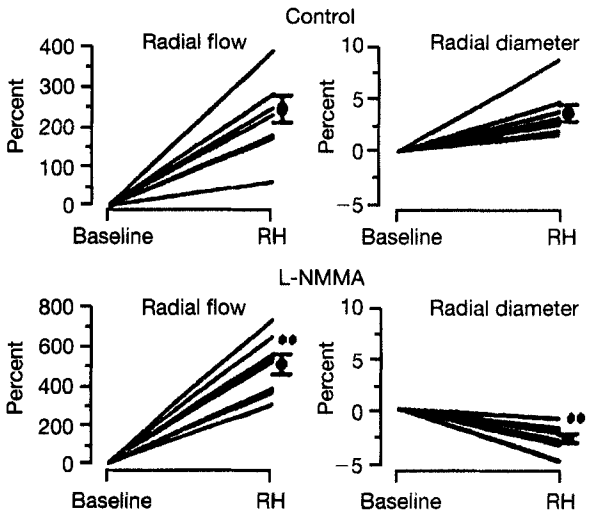

FIG. 2 The effect of a nitric oxide synthase inhibitor (L-NMMA) on flow-mediated vasodilation. There is a reactive hyperemia but no vasodilation in response to this hyperemia after the administration of L-NMMA. RH = reactive hyperemia. Reprinted from Ref. No. 3 with permission.

Factors and Interventions Affecting Endothelial Function

A variety of factors are clearly associated with endothelial dysfunction (Table I).[6] Every risk factor that is associated with atherosclerosis also impairs endothelial function. This observation is supporting evidence that the endothelium is also an important mediator of vascular and other diseases such as congestive heart failure and hypertension.

There are interventions which can improve endothelial function (Table I). Some of these interventions have been shown to reduce cardiovascular events, while some, such as

TABLE I Factors associated with endothelial dysfunction and interventions demonstrated to improve endothelial function

Factors associated with endothelial dysfunction	Interventions improving endothelial function
Increased age	L-arginine
Male sex	Estrogen
Family history of CAD	Antioxidants
Smoking	Smoking cessation
Increased cholesterol	Cholesterol lowering
Low HDL cholesterol	ACE inhibitors
Hypertension	Exercise
Diabetes mellitus	Homocysteine lowering
Obesity	
High-fat meal	
Increased homocysteine	

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Abbreviations: CAD = coronary artery disease, HDL = high-density lipoprotein, ACE = angiotensin-converting enzyme.

lowering homocysteine, have not yet been verified. Estrogen, on the other hand, has been clearly shown to improve endothelial function. Hormone replacement therapy, in the form of estrogen and progestin, however, may not improve endothelial function.

The Effect of Age on Endothelial Function

Endothelial cells live about 30 years. Rejuvenated endothelial cells do not elaborate as much nitric oxide as the original cells. As men and women approach the ages of 40 and 50, there is a progressive decline in endothelial function.[7] At age 40, there is a slow decline in men in endothelial function. In women, function is preserved on the basis of estrogen availability. This results in a longer plateau but a steeper decline.

There are increasing data, however, to suggest that age is not an immutable risk factor. At age 50 or 60, however, individuals can no longer tolerate this risk-factor burden that they were once able to tolerate at age 10 or 20. For example, aging data from Australia and China show that Caucasians in Australia have a progressive decline in endothelial function (endothelial-dependent dilation).[8] In the Chinese population studied, this progressive decline in endothelial function is not observed.

At our institution, work has also been conducted on master athletes. These are defined as individuals over the age of 65 who run marathons. One of these individuals studied was an 80-year-old male marathon runner who had CAD. He was placed on an aggressive exercise, lipid reduction, and antioxidant program. After this program, he showed normal endothelial function. This demonstrates that it is not the atherosclerosis that causes causing endothelial dysfunction, but rather the risk factors, which can be reversed even at this advanced age.

The Effect of Smoking

Cigarette smoking is a potent risk factor for atherosclerosis. Endothelial function data look much the same. Short-term changes in endothelial function have been measured immediately following cigarette smoking.[9] Within 5 min of smoking one cigarette, there is no nitric oxide availability (Fig. 3). This is quite interesting, since cigarette smoke contains nitric oxide; something must break this nitric oxide down very quickly. This effect lasts upward of an hour to an hour and a half. It also occurs whether the person is a smoker or is simply breathing in secondhand smoke.

Lipoproteins and Endothelial Dysfunction

A number of lipoproteins produce endothelial dysfunction. Endothelial dysfunction can be used as biological markers to identify the lipoproteins which are predominantly atherogenic. Lipoproteins which have been identified as depressing endothelial function include LDL, oxidized LDL, lipoprotein(a), small dense LDL, postprandial chylomicron remnants, very low-density lipoprotein (VLDL) remnants, free fatty acids, and low levels of high-density lipoprotein (HDL). The data for total and LDL cholesterol are scattered but statistically significant. Correlations tend to be 0.3 to 0.4 in most studies, suggesting individual biological variability.[10] These data also suggest a biological ideal LDL cholesterol to be in the range of 50–75 mg/dl.

There is an inverse association between HDL and endothelial function: the higher the HDL cholesterol, the better the endothelial function.[11] There is also an association between LDL and endothelial function. We conducted a study on medical school faculty members who were about 50 years of age.[12] An LDL of 125 mg/dl was associated with an impairment in endothelial function, which was a value roughly equivalent to that of a cigarette smoker. When the LDL was lowered to slightly below 100 mg/dl, endothelial function improved. When it was lowered to the range of 75–80 mg/dl, it improved even further.

The Effect of Diet on Endothelial Function

The contribution of diet to endothelial function has also been examined. Around the world, there is a very different incidence of heart disease depending on factors much more complex than total or LDL cholesterol. For example, a Japanese person with a cholesterol of 200 mg/dl has far less disease than a Scandinavian person also with a cholesterol of 200 mg/dl. Several questions have been asked in this regard. Is there an immediate effect of a high-fat diet on the endothelium? Is there a direct association between diet and endothelial function?

Endothelial function has been studied in relationship to diet. In one study, participants received one of two meals.[13] The first was a high-fat, fast-food breakfast consisting of 900 calories and 50 g of fat. The other meal consisted of a cereal-type breakfast containing 900 calories and 0 g of fat. Endothelial function was examined hourly for 6 h after ingestion of the breakfast. Within 2 h, there was a significant decrease in nitric

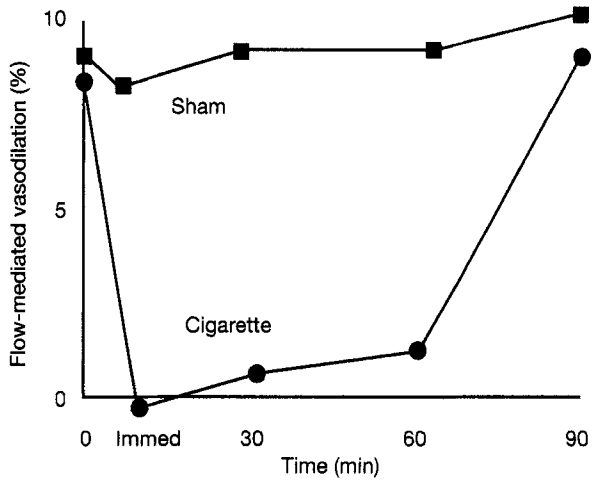

FIG. 3 The effect of cigarette smoking on endothelial function. Within 5 min of smoking one cigarette, no nitric oxide is available. Reprinted from Ref. No. 9 with permission.

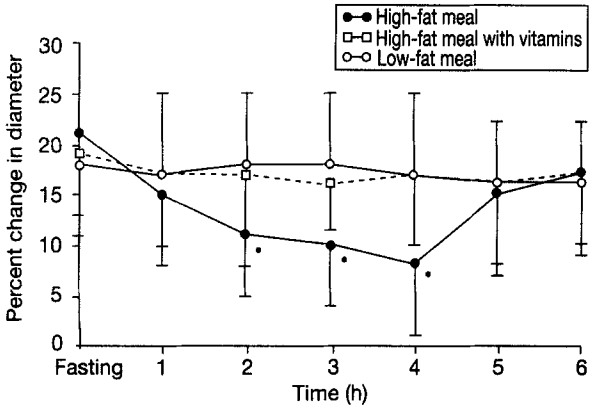

FIG. 4 The effect of a high-fat breakfast on endothelial function. Within 2 h, there was a significant decrease in nitric oxide availability. After supplementation with vitamins E and C, there was a significant reduction in the impairment. Reprinted from Ref. No. 15 with permission.

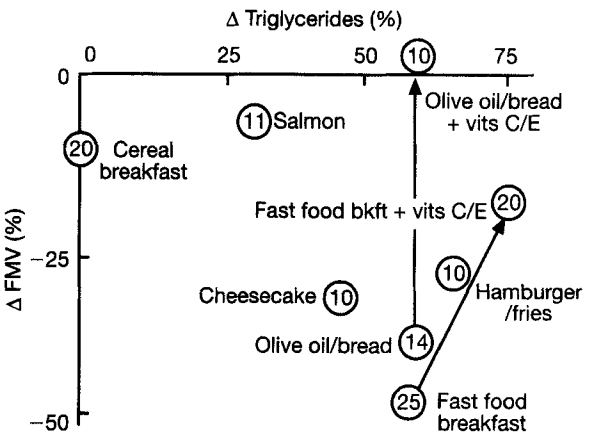

FIG. 5 Three-hour postprandial changes in triglycerides and flow-mediated vasodilation (FMV) to specific meals. Vits = vitamins, Bkft = breakfast.

oxide availability based on one meal (Fig. 4). This concept has been supported by other studies. For example, trans-species studies from Japan have looked at VLDL and chylomicron remnants using postprandial human serum and vascular ring studies in the rabbit.[14] Lipid-rich particles were found to reduce nitric oxide availability in a dose-dependent fashion.

An additional investigation was conducted to see whether this phenomenon is oxidatively stress modified in the same way that we assume hypercholesterolemia, cigarette smoking, and other risk factors that injure the endothelium are oxidatively stressed modified. The study involved the same 20 subjects who ate in fast-food restaurants and the 20 subjects who ate a cereal-based breakfast.[15] The subjects eating a fast-food breakfast were pretreated with 800 U of vitamin E and 1 g of vitamin C. A significant reduction in nitric oxide availability impairment was noted in the group receiving the supplements (Fig. 4).

The Impact of Specific Foods

The direct impact of specific meals on triglycerides and endothelial function was also studied. Three-hour rises in triglycerides and 3-h declines in flow-mediated vasodilation have been observed with a traditional meal of a hamburger and fries, as well as with cheesecake (Fig. 5). Olive oil was also found to have the same impairment to endothelial function as the rest of these high-fat meals. This impairment, however, was also totally eliminated when vitamins C and E were given. As with antioxidant vitamin supplementation, olive oil, eaten with vinegar on a salad, did not impair endothelial function. Some societies that use the Mediterranean diet may have learned to provide the natural antioxidants which buffer the oxidative stress of these fatty meals. An exception to fats that impair endothelial function is fish oil. Salmon (50g) does not confer any impairment on endothelial function; it also results in half the rise in triglycerides. Other studies show that Omega-3 fatty acids improve endothelial function.

There has been additional study of the effect of two high-fat meals on coagulation factor VIIa.[16] Both olive oil and butter show, in essence, the same increase in factor VIIa. The coagulant effects of fat are the same; they only differ in the way they elevate LDL cholesterol.

Other studies have looked at links between various foods and CAD. For example, an association has been demonstrated in different countries between animal fat and the incidence of CAD.[17] This study showed a rise in the incidence of CAD with an increased intake of animal fat. The clinical community has used these observations to convey the message about stopping excessive fat intake. In the same study, fruit showed an inverse relationship with CAD; this may be due to the antioxidant capacity of fruit. There is a stronger inverse relationship between fruit intake and CAD compared with the adverse effect of fat. Both of these phenomena are based on the balance between the direct impairment of fat on the endothelium and the protection given by concomitant antioxidant-rich foods.

The Effect of Transient Triglycerides on Vascular Reactivity

Another study has looked at the effect of transient triglycerides and vascular reactivity.[18] Plasma concentrations of triglyceride, cholesterol, and free fatty acids were measured before and during an infusion of 0.15 g/kg body weight^{-1}/h^{-1} of intralipid. A profound decrease was observed in flow-dependent vasodilation, as was a significant decrease in flow-independent vasodilation. Such data support the cautious use of parenteral nutrition with lipids in acute settings where endothelial or vascular dysfunction may be an issue (e.g., shock lung).

In addition to postprandial chylomicron remnants being injurious to the endothelium, VLDL remnants have also been found to cause injury. Data obtained from research in Japan demonstrate that non-apo A, non-apo B VLDL remnants impair endothelial function.[19] This remnant fraction has the strongest association with endothelial dysfunction of any par-

ticle or of any other risk factor described to date, including LDL, age, and smoking.

Pathophysiologic Mechanisms of Nitric Oxide Availability

Endothelial dysfunction may be associated with increased nitric oxide destruction or impaired synthesis as occurs with hypercholesterolemia or hypertriglyceridemia. Experimental atherosclerosis is associated with increased superoxide production and increased nitric oxide production. Superoxide deactivates nitric oxide more rapidly than does superoxide dismutase. In human advanced atherosclerosis, the prevailing data at the moment, however, show that there is decreased, not increased, nitric oxide production. This may be an advanced stage of atherosclerosis. Oxidized LDL has been shown to impair endothelium nitric oxide synthase directly, and L-arginine may have decreased microdomain availability in hypercholesterolemia. Inhibitors of nitric oxide synthesis, such as ADMA and caveolin, are also increased in hypercholesterolemia.

Conclusion

Westernized individuals live in a world of coronary risk factors. Oxidative stress, among others, contributes to endothelial dysfunction. Since endothelial function is relatively easy to measure, it is hoped that it will serve as a useful intermediate index. Such endothelial dysfunction may eventually lead to atherosclerosis and subsequent cardiovascular events.

Discussion

Rackley: Endothelial interaction offers the opportunity to bring the metabolic aspects of cardiovascular disease into the hemodynamic aspect. One major challenge is how to explain some of the acute events based on chronic metabolic and physiologic abnormalities. About a year ago, the Indianapolis group showed that the infusion of free fatty acids, first in diabetics and then in normal, lean, nondiabetic individuals, induces the same vasoconstriction rate as observed with various lipid components. The source of free fatty acids is triglyceride. We monitored this by giving glucose and potassium in solution. As a metabolic measure, we discovered that solution suppressed the free fatty acids so low that it changed the respiratory quotient at the myocardium. It actually could be shown to increase coronary blood flow. If one wants to elevate free fatty acids, one has to elevate the triglycerides or provide an adrenergic stress. This is what cigarettes do. After a cigarette is smoked, free fatty acids and circulating catecholamines increase. Another way to raise free fatty acids is to give a heparin dose. On the other hand, a way to lower free fatty acids is by using nicotinic acid. Now we have the opportunity to look at some exciting metabolic interventions that may tie in some of these chronic lipid and metabolic disturbances with acute events. These interventions may call into the forefront triglycerides and free fatty acids.

Vogel: We are always interested in why metabolic syndrome factors track together. One of the mechanisms may be that free fatty acids and triglyceride-rich particles impair endothelial function, decrease nitric oxide availability, and produce hypertension among other actions. A number of investigators are showing a direct association between hypertension and endothelial impairment.

Georgopoulos: Were the antioxidants given on an acute or chronic basis?

Vogel: They were all acute studies. Giving antioxidant vitamins chronically is a very complex issue for understanding what the redox state really will do since superoxide dismutase and other intrinsic antioxidant levels will change. The experimental world is rather mixed on documentation of whether you can chronically improve endothelial function by giving antioxidant vitamins; some studies say yes while others say no. Much of it is stimulus and model dependent. Recent work has shown that a combination of lipid-lowering medication and chronic administration of vitamin E shows a benefit.

Criqui: What experimental work has been conducted on the consumption of alcohol or red wine solids and their effect on endothelial function?

Vogel: The best data show that a modest intake of alcohol (defined as one drink/day) is probably optimal. In Europe, the data suggest that red wine may have an event advantage over other alcohol. In the United States, the data show no predominance as to alcohol type. The data on endothelial function are far less clear with regard to alcohol. Alcohol has a lot of effects, including changing lipids and coagulation. The direct vasoactive properties of alcohol confound these measurements when it comes to studying endothelial function. Preliminary data suggest that red wine extracts are favorable to the endothelium, but alcohol is not.

Ferdinand: Is the use of brachial ultrasound a clinical tool at this point? If we have a transducer, should we start doing brachial studies to see endothelial function in our patients?

Vogel: Absolutely not. This is a research tool. Reproducibility depends on many factors in the laboratory and a lot of dedication. The question that really is behind your question is: Is endothelial function an independent predictor of events or atherosclerosis? Early data suggest that endothelial dysfunction is a predictor of future cardiovascular events. The NIH is also looking at different predictors of events. We are also conducting two trials. One is a hormone replacement study and the other is a statin trial. The hormone trial is comparing endothelial function through the use of quantitative arteriography. The statin trial is using intravascular ultrasound. In the future, this will help determine whether this is an appropriate intermediate biological marker.

Conti: Does activity in the brachial artery reflect what is going on in the coronary circulation? As far as I know, we don't have an answer yet. We have given a lot of acetylcholine into people's coronary arteries. Constriction has been seen in one part and dilation in another. While we know what is happening in the coronary circulation with acetylcholine, we have not looked at what is happening in the brachial artery.

Vogel: There has been reported an approximate 0.4 correlation that is statistically significant concerning acetylcholine in the coronary circulation versus flow-dependent vasodilation in the brachial artery. The correlation between flow-dependent in the coronary circulation and flow- dependent in the arm is better, in the range of 0.8. This would suggest a reasonable association. At a recent NIH conference, there is some consensus that flow-dependent would be the endothelium index of choice. Clearly, it is wholly endothelium-dependent. It is not yet known, however, whether or not improving endothelial function will lessen cardiovascular events.

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