The Role of Endothelial Dysfunction on Development and Progression of Atherosclerosis and Methods to Assess Vascular Function and Structure
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The Role of Endothelial Dysfunction on Development and Progression of Atherosclerosis and Methods to Assess Vascular Function and Structure

Abstract: The endothelium was originally thought to be just a semipermeable barrier between the vessel wall and the bloodstream, but today we now realize that it is actually a highly active autocrine, paracrine, and endocrine organ. Researchers have also begun to realize that the endothelium plays a key role in the development of atherosclerosis as well as other diseases. This increased recognition has resulted in considerable effort by both researchers and clinicians to develop accurate and reliable methods to measure and track changes in both vascular structure and function. In addition, research interest has focused on various cardiovascular risk factors (eg, age, gender, obesity, physical inactivity) and the effect they have on vascular structure and function. In this review, the authors discuss different research and clinical methods to assess vascular structure and function as well as the effect of various cardiovascular risk factors on the endothelium and the vascular system. They also discuss the ability to modify vascular structure and function through various lifestyle modifications such as weight loss and exercise.

Keywords: endothelial dysfunction; ultrasound imaging; cardiovascular disease risk factors; intima-media thickness

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in the United States and worldwide. During the past several decades, many risk factors have been reported to contribute to the development and progression of atherosclerosis and CVD. These include conventional risk factors such as age, gender, dyslipidemia, hypertension, diabetes, obesity, and tobacco smoking, as well as novel risk factors such as oxidative stress and inflammation. The conventional and novel risk factors have been demonstrated to induce endothelial dysfunction or injury. Endothelial dysfunction is considered to play a pivotal role in the etiology of CVD and is considered a marker of preclinical CVD. In this review article, we explore the various methods to measure vascular structure and function and the effect of certain CVD risk factors on vascular structure and function. In addition, we will explore various lifestyle modifications (eg, weight loss, exercise) and their effect on vascular structure and function. An in-depth review of the role of oxidative stress and inflammation on vascular structure and function appears in a companion article appearing in a later edition of this journal.

Definition of the Endothelium

Although the vascular system extends continuously throughout the body, its structure and function do change...
depending on its location. There is, however, one structural component that is common for the entire vascular system: the endothelial cell. In the vascular system, these endothelial cells form a single-celled layer commonly referred to as the endothelium. Although capillaries consist only of the endothelium, the large branches of the vascular system (ie, arteries, arterioles) also contain outer layers of connective tissue and smooth muscle. In addition to serving as a semipermeable barrier between the vessel wall and the bloodstream, the endothelium also functions as a highly active autocrine, paracrine, and endocrine organ that plays a crucial role in regulating blood flow, vascular tone, and vascular repair. A primary function of all vascular endothelium is the secretion of a wide variety of active molecules in the regulation of vascular homeostasis. One of the principal molecules that the endothelium secretes is nitric oxide (NO), which is responsible for vasodilation. NO has also been found to possess many antiatherogenic properties such as inhibition of leukocyte adhesion, platelet aggregation, and vascular smooth muscle proliferation, thereby conferring a protective effect on the human vasculature. Avoiding damage to the endothelium is imperative because of the prominent role it plays in the maintenance of both basal and dynamic vascular tone and vascular function.

Endothelial dysfunction of the arteries occurs early in the pathogenesis of atherosclerosis and may be the initial step in the development of CVD. Atherosclerosis is a systemic disorder associated with chronic inflammation, resulting from the uptake, entrapment, and deposition of lipids within the arterial walls. The processes that lead to atherosclerosis are not completely understood; however, many researchers think that damage is initiated by conventional and novel risk factors for CVD that injure the endothelium and the underlying smooth muscle, leading to an inflammatory and proliferative response. The innermost layer of the artery becomes markedly thickened by these accumulating cells and surrounding material. As the vessel wall thickens, the diameter of the artery is reduced, resulting in less blood flowing through the artery. This reduction in blood flow ultimately leads to a decrease in the oxygen supplied to the tissue. Although atherosclerosis takes many decades to develop, the initial process likely begins early in life. The fact that atherosclerosis begins early in life and develops over time has brought about the need to develop ways to measure and track its development. Because atherosclerosis is a disease that degrades both the structure and function of the artery, a number of invasive and non-invasive techniques for assessing arterial structure and function have been developed. The selection of which technique to be used is determined by such factors as population to be examined, cost, available equipment, and technician training.

### Measuring Arterial Structure

In recent years, advancements in imaging technology have allowed for improved abilities to measure and track changes in vascular structure in a variety of vascular beds and to quantify atherosclerosis. Currently, two modalities are frequently used to measure structure aspects of the arterial wall: computed tomography of the chest for evaluation of coronary artery calcification (CAC) and high-resolution ultrasound imaging of the carotid artery intima-media thickness (IMT).

### Computed Tomography

Computed tomography is a medical imaging method that generates a 3-dimensional image from a series of 2-dimensional radiographic images taken around a single axis of rotation. Using computed tomography, the quantity of CAC can be determined, which is thought to be a surrogate marker for coronary atherosclerotic plaque burden. The extent and density of CAC is frequently expressed using a simple scoring system developed by Agatston and colleagues. This simple scoring system involves creating a CAC score by multiplying the CAC area by the peak Hounsfield units (HU). A summed CAC score is then calculated by adding the scores of each coronary artery. Several guideline and consensus statements have suggested that screening for CAC by computed tomography imaging may be appropriate in individuals at intermediate risk for heart disease but not for lower risk general population screening. Also, the variability of coronary calcium measurements is high so repeated CAC measurements are not clinically useful. The radiation exposure as well as the cost of testing limits the use of this method to measure vascular structure in a number of populations.

### High-Resolution Ultrasound Imaging

High-resolution ultrasound imaging of the carotid IMT is the most widely used method to evaluate arterial structure. The IMT is often measured at the common carotid artery because this site has been linked to adverse cardiovascular events. High-resolution ultrasound imaging involves collecting a number of images of the far vessel wall, approximately 1 cm in length and 1 to 2 cm proximal to the bifurcation of the carotid. A mean value for these images of the IMT is then calculated, often using some type of automated wall-tracking software. Measures of carotid IMT can also be made of both the internal and external carotid artery as well as the bifurcation of the carotid artery. In addition, the IMT of other arteries (ie, abdominal aorta, femoral, brachial, etc) can also be used to determine the IMT because other arteries may actually demonstrate thickening of the IMT earlier than the carotid artery, or the IMT in these other arteries may be affected by interventions earlier than the carotid artery.

### Measuring Arterial Function

As previously mentioned, all arteries of the body are composed of a layer of endothelial cells. The large-conduit arteries of the body consist of an outer cylinder composed of smooth muscle surrounding the inner layer of endothelial cells. Therefore, the ability of the...
artery to dilate and constrict is controlled by both the endothelium’s ability to dilate the artery (endothelial-dependent dilation) as well as the smooth muscle’s ability to dilate the artery (endothelial-independent dilation). Although most research examining endothelial function and cardiovascular disease has focused on endothelial-dependent dilation, there is evidence that cardiovascular risk factors impair both endothelial-dependent dilation and endothelial-independent dilation.3,24 There are many techniques available for assessing endothelial function, depending on which vessel(s) are to be examined and the population that will be studied. These techniques can be either invasive or noninvasive and can determine endothelial-dependent dilation and/or endothelial-independent dilation.

**Endothelial-Dependent Dilation**

Endothelial-dependent dilation can be evaluated by measuring the arterial response to intra-arterial infusions of endothelium-dependent dilators such as acetylcholine, bradykinin, substance P, and adenosine.25 The arterial responses to these infusions are typically measured by strain gauge plethysmograph. This method involves placing an elastic strain gauge around the forearm or calf that will record the change in the volume of either the forearm or calf. High-resolution ultrasound imaging can also be used to measure diameter changes in brachial or femoral arteries and/or blood flow changes in response to the intra-arterial infusion. Although the intra-arterial infusion method is considered the gold standard to measure endothelial-dependent dilation, the invasiveness of this technique makes it impractical for measurement of endothelial function in children or other vulnerable populations.

A less invasive approach to measuring endothelial-dependent dilation is high-resolution ultrasound imaging of an artery’s response to reactive hyperemia.24 Briefly, a resting ultrasound image is captured and a hyperemic stimulus is created by inflating a blood pressure cuff placed on the forearm or calf to approximately 50 mm Hg or greater above systolic pressure, for 5 minutes. The cuff is rapidly deflated, creating an increase in blood flow and laminar shear stress, which causes the endothelium to release NO, resulting in dilation of the artery. The artery is imaged for 2 to 5 minutes after the release of the blood pressure cuff and evaluated for the peak dilation of the artery above the baseline measure. Because of differences in blood flow responses to the hyperemic stimulus, changes in artery diameter are sometimes adjusted for shear rates.26,27 This noninvasive method is a cost-effective way to measure endothelial-dependent dilation and has been used successfully in children and other vulnerable populations. The main drawback to this method is the fact that the method is dependent to some degree on the skill of the ultrasound sonographer.

**Endothelial-Independent Dilation**

Endothelial-independent dilation can be evaluated using similar methods as used in the measurement of endothelial-dependent dilation. Intra-arterial infusions of sodium nitroprusside, which bypasses the endothelium and works directly on the smooth muscle of the artery, can be used to create endothelial-independent dilation. The response of the artery to sodium nitroprusside infusions is typically monitored by strain gauge plethysmography or high-resolution ultrasound imaging as previously described. This method suffers from the same limitations as intrainfusions of endothelial-dependent dilators.

Endothelial-independent dilation can also be determined via high-resolution imaging of an artery’s response to sublingual nitroglycerin administration. Briefly, a resting ultrasound image is made and sublingual nitroglycerin is administered. The artery is then imaged for 5 to 10 minutes after nitroglycerin administration. Typically, the endothelial-independent dilation is 3 times greater than endothelial-dependent dilation.28 As with the measurement of endothelial-dependent dilation, this noninvasive method has proven to be both cost-effective and reliable and has been used successfully in children and vulnerable populations.

A newer method of determining endothelial-dependent and endothelial-independent dilation involves measuring changes in the pulse wave amplitude in response to reactive hyperemia (endothelial-dependent dilation) or sublingual nitroglycerin (endothelial-independent dilation). Changes in the pulse wave amplitude are typically registered at the finger, so this method is sometimes referred to as finger-pulse plethysmography.29 Although the method is simple to use and is less dependent on technical skill than high-resolution ultrasound imaging, it does not account for differences in shear stress that are created during hyperemia. In addition, this method is limited to the finger and does not allow one to measure other vascular beds. It should also be noted that this method measures a resistance vessel rather than a conduit vessel, as is the case with the brachial or femoral arteries.

**Arterial Compliance**

Another way to determine vascular function is to measure the change in lumen diameter in response to diastole and systole (eg, arterial compliance).20 Arterial compliance can be measured using high-resolution ultrasound imaging. These high-resolution ultrasound images are typically captured at the carotid artery or the aorta, but they can also be made at other arteries (eg, brachial and femoral arteries). Although this measure is reasonably accurate, it is limited somewhat by the fact that it is best to have a direct measure of blood pressure at the artery where compliance is being determined.20

**Pulse Wave Velocity**

Measuring the arterial pulse wave velocity is another way to determine arterial function. The arterial pulse wave velocity can be measured using either Doppler ultrasound or a pressure-sensitive transducer. Both central (carotid to femoral artery) and peripheral (femoral to dorsalis pedis artery) pulse wave velocities can be determined. This method involves measuring the time for the pulse wave to travel the length of a particular arterial pathway; the higher the pulse wave velocity, the stiffer or less compliant the vessel. The
methodology used to measure pulse wave velocity is both simple to use and cost-effective, but it is important to measure blood pressure during the measurement of pulse wave velocity.

Factors Affecting of Vascular Structure and Function

When examining the various cardiovascular and metabolic risk factors that can affect vascular structure and function, researchers have employed two basic types of research designs: cross-sectional or longitudinal. When employing a cross-sectional research design, a cross-section of the population of interest is tested at one time and compared to a matched control group, and the differences between these groups are examined. With a longitudinal research design, the same participants are retested periodically over a period of time, or some type of intervention is employed in which the participants are tested prior to and at the end of the intervention. These two designs can be used to address the same question; however, the longitudinal research design is more powerful but takes more time to complete the data collection and resources than the cross-sectional research design.

A number of CVD factors can affect vascular health. Some of these factors, such as gender and age, cannot be modified, but other risk factors (eg, tobacco use, alcohol consumption, obesity, physical inactivity) can be modified. This next section explores the effect of these risk factors on both vascular structure and function.

Aging

As previously mentioned, atherosclerosis takes many decades to develop; therefore, it is not too surprising that both cross-sectional as well as longitudinal studies have reported an effect of aging on vascular structure and function. Cross-sectional research studies have reported an increase in the thickness of both carotid and femoral arteries’ IMT with increasing age.22,30,51 Although these age-related changes in IMT are well accepted, it should be pointed out that the IMT is affected by both obesity32,33 and physical inactivity.34,36 Therefore, whether the reported age-related increase in IMT is a result of aging or lifestyle choices needs to be further addressed in longitudinal research studies.

Gender

Generally speaking, men have a higher prevalence of CVD than premenopausal women.7 It has been reported that carotid IMT thickness values are not affected by gender up to 18 years of age. After the age of 18 years, carotid IMT increases sharply in men, whereas in premenopausal women, the IMT remains relatively constant.38 The Bogalusa Heart Study measured carotid IMT in 518 black and white men and women. These men and women were healthy except for being overweight. The authors reported that carotid IMT was significantly higher in men than in women.39 Recently, Juonala et al40 demonstrated that the gender difference in carotid IMT in young and middle-aged adults can be explained by differences in CVD risk factors between genders. It may well be that the gender difference in carotid IMT is driven to a large extent by gender differences in CVD risk factors.

Similar to carotid IMT, women have been found to have favorable differences in vascular function as compared to men. Previous studies32,41 have demonstrated that women have increased endothelial-dependent dilation compared to men. However, this difference can be accounted for by the greater brachial artery diameter observed in men.40,41 To date, few studies have examined the effect of gender on endothelial-independent dilation. Jensen-Urstad et al42 reported that gender had the greatest influence on endothelial-independent dilation in a population of healthy male and female 35-year-old participants. It is important to note the Jensen-Urstad et al42 did not correct for baseline brachial artery diameter, which was significantly greater in men. Similar to endothelial-dependent dilation, the gender differences in endothelial-independent dilation may be explained by gender differences in brachial artery diameter.

Obesity

Table 1 summarizes the relationship between vascular structure and function and obesity in cross-sectional studies. Kotis et al32 examined high-resolution ultrasound images from 536 individuals and divided them into 4 groups based

When examining vascular health, it is important to examine not only the structure of the vessel but also its function.
and overweight premenopausal women. However, there was no difference in endothelial-independent dilation between normal-weight, overweight, and obese women. Williams et al. reported that normal-weight (BMI <25 kg/m²) adults had significantly greater endothelial-dependent and endothelial-independent dilation than both overweight (BMI 26-30 kg/m²) and obese (BMI >30 kg/m²) adults.

The association between obesity and endothelial dysfunction has also been shown in children. Tounian et al. reported that both endothelial-dependent dilation and endothelial-independent dilation was significantly reduced in severely obese children when compared to normal-weight children. Woo et al. also reported that endothelial-dependent dilation was significantly reduced in obese children when compared to normal-weight children; however, there was no difference in endothelial-independent dilation.

Because both vascular structure and function are affected by obesity, it is reasonable to hypothesize that weight loss may result in improvements in vascular structure and/or function. Longitudinal research studies in both adults and children have examined the effect of weight loss on carotid IMT. Sarmento et al. reported no significant change in carotid IMT 3 months after bariatric surgery. However, 6 months following bariatric surgery, there was a significant reduction in carotid IMT, with a further reduction in carotid IMT after 12 months of follow-up. Mavri et al. reported a significant reduction in carotid IMT in obese premenopausal women with weight loss. The effect of weight loss on vascular structure has also been demonstrated in children. Wunsch et al. reported that a 1-year weight loss intervention in children significantly reduced carotid IMT.

Longitudinal weight loss studies examining vascular function in adults and children have also shown an improvement in vascular function with weight loss (Table 2). Williams et al. reported that weight loss induced by bariatric surgery resulted in a significant improvement in endothelial-dependent dilation but not endothelial-independent dilation after 6 months or a 10% reduction in body weight. Pierce et al. reported that a 3-month weight loss program in older men and women resulted in improvements in endothelial-dependent dilation but not in endothelial-independent dilation. We have previously reported that a 4-month weight loss program in children resulted in improvements in both endothelial-dependent dilation and endothelial-independent dilation. Raitakari et al. reported that a 6-week low-calorie diet resulted in improvements in endothelial-dependent dilation as well as endothelial-independent dilation. Raitakari et al. reported that a 6-week low-calorie diet resulted in improvements in endothelial-dependent dilation but not in endothelial-independent dilation. Clearly, weight loss can affect both vascular structure and function, however, the magnitude of the improvement is variable. Some of this variability may result from the amount of body mass or

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Measure of Arterial Structure or Function</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotsis et al.</td>
<td>536 adults</td>
<td>Ultrasound IMT</td>
<td>Carotid IMT higher in obese compared to normal weight</td>
</tr>
<tr>
<td>Burke et al.</td>
<td>6814 adults</td>
<td>Ultrasound IMT</td>
<td>Carotid IMT higher in obese compared to normal weight</td>
</tr>
<tr>
<td>Steinberg et al.</td>
<td>25 adults</td>
<td>Intrafemoral artery infusions</td>
<td>Lower EDD in obese compared to normal weight; no difference in EID</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>73 adults</td>
<td>Ultrasound EDD, EID</td>
<td>Lower EDD and EID in obese and overweight compared to normal weight</td>
</tr>
<tr>
<td>Olson et al.</td>
<td>59 adults</td>
<td>Ultrasound EDD, EID</td>
<td>Lower EDD in obese compared to normal weight; no difference in EID</td>
</tr>
<tr>
<td>Tounian et al.</td>
<td>69 children</td>
<td>Ultrasound EDD, EID</td>
<td>Lower EDD and EID in obese and overweight compared to normal weight</td>
</tr>
<tr>
<td>Woo et al.</td>
<td>72 children</td>
<td>Ultrasound EDD, EID</td>
<td>Lower EDD in obese compared to normal weight; no difference in EID</td>
</tr>
</tbody>
</table>

IMT, intima-media thickness; EDD, endothelial-dependent dilation; EID, endothelial-independent dilation.
fat mass lost, the length of the weight loss program, the population examined (ie, children, adults, obese, overweight, or with overt disease), and change in nutrient content of the weight loss program. Future studies are needed to address such questions as the length of the weight loss intervention or the amount of weight loss needed to improve both vascular structure and function.

**Physical Activity**

Cross-sectional population studies examining the influence of leisure time physical activity and TV watching have reported no associations between physical activity and carotid IMT. In addition, cross-sectional studies examining the effects of physical activity on carotid IMT have reported no difference in carotid IMT among sedentary, active, and endurance-trained adults. Cross-sectional studies examining the effect of physical activity on vascular function have produced mixed results. DeSouza et al. examined only men in their study, whereas Taddei et al. examined both men and women. Another difference in study design is level of cardiorespiratory fitness in the population examined. Taddei et al. required all athletes to have a minimum maximal oxygen uptake (VO\(_2\)max) of least 60 mL/kg/min. In this study, there was no difference in VO\(_2\)max between the young and older endurance-trained athletes examined. In the study by DeSouza et al., the VO\(_2\)max in the young endurance-trained athletes was 58.4 mL/kg/min, whereas the VO\(_2\)max in the older endurance-trained athletes was 42.6 mL/kg/min. Therefore, endurance-trained athletes studied by Taddei et al. may have been more on the elite level, and this may have contributed to the differences between the young and old endurance-trained athletes. To date, cross-sectional studies examining the effect of physical activity on vascular structure and function have produced inconclusive results.

Given that cross-sectional designed research studies have found no relationship between physical activity and vascular

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**Table 2.**

Summary of Studies Assessing the Effects of Weight Loss on Vascular Structure and Function

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Intervention</th>
<th>Measure of Arterial Structure or Function</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavri et al.</td>
<td>30 women</td>
<td>Caloric restriction and exercise</td>
<td>Ultrasound IMT</td>
<td>Weight loss resulted in carotid IMT reduction</td>
</tr>
<tr>
<td>Sarmento et al.</td>
<td>18 women</td>
<td>Bariatric surgery</td>
<td>Ultrasound IMT</td>
<td>Decrease in carotid IMT 6 and 12 months postsurgery</td>
</tr>
<tr>
<td>Wunsch et al.</td>
<td>56 children</td>
<td>Caloric restriction and exercise</td>
<td>Ultrasound IMT</td>
<td>Carotid IMT decreased significantly over non-weight loss</td>
</tr>
<tr>
<td>Pierce et al.</td>
<td>40 adults</td>
<td>Caloric restriction</td>
<td>Ultrasound EDD, EID</td>
<td>Weight loss resulted in increase in EDD but not EID</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>8 adults</td>
<td>Bariatric surgery</td>
<td>Ultrasound EDD, EID</td>
<td>EDD normalized by weight loss, although still significantly overweight</td>
</tr>
</tbody>
</table>

IMT, intima-media thickness; EDD, endothelial-dependent dilation; EID, endothelial-independent dilation.
structure, it is not too surprising that a number of intervention studies have observed no effect of exercise training on carotid IMT (Table 3).35,36,57 However, unlike carotid IMT, exercise training has been shown to reduce femoral IMT in adults.21 It is possible that the effect of exercise training on vascular structure may be influenced by the artery bed being examined. Exercise training (eg, femoral) may affect those vascular beds distal to the muscles involved in the exercise training. In one of the few studies examining children and the effect of exercise training on carotid IMT, Meyer et al58 demonstrated that 6 months of exercise training in obese children resulted in a significant reduction in carotid IMT. It may be that the age of the population being examined may have an effect on the ability of exercise training to alter carotid IMT.

Adults are not the only ones who can improve vascular function with exercise training. We previously have demonstrated in adolescents that an 8-week aerobic exercise training program improves endothelial-dependent dilation but not endothelial-independent dilation. To date, the evidence provided by cross-sectional and longitudinal research studies demonstrates the effectiveness of exercise on vascular health in a variety of populations. Future studies need to address the exercise prescription (eg, intensity, frequency, duration) necessary to not only maintain vascular health but also improve it.

Smoking

The effect of smoking on vascular structure and function is presented in Table 4. It is well known that smoking is a risk factor for CVD; therefore, it is not too surprising that smoking is associated with negative effects on both vascular structure and function.54 A number of cross-sectional studies have reported a significant relationship between chronic tobacco use and increased carotid IMT.64,68 Tobacco use is responsible for alterations in not only vascular structure but also vascular function. Celemajer et al40 compared endothelial-dependent dilation and endothelial-independent dilation in 120 smokers and 80 non-smoker controls and reported that both endothelial-dependent dilation and endothelial-independent dilation were significantly lower in smokers than in non-smokers. Zeiher et al70 reported similar

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**Table 3.**

Summary of Studies Assessing the Effects of Exercise Training on Vascular Structure and Function

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Intervention</th>
<th>Measure of Arterial Structure or Function</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kronenberg et al34</td>
<td>1778 adults</td>
<td>Self-reported leisure-time physical activity</td>
<td>Ultrasound IMT</td>
<td>Leisure-time physical activity and time watching TV was not associated with IMT</td>
</tr>
<tr>
<td>Taddei et al56</td>
<td>49 adults</td>
<td>Athletes, sedentary participants</td>
<td>Intrabrachial artery infusions</td>
<td>Sedentary participants had decreased EDD</td>
</tr>
<tr>
<td>Sugawara et al57</td>
<td>15 postmenopausal women</td>
<td>12-week aerobic exercise</td>
<td>Ultrasound IMT</td>
<td>Overall increase in arterial compliance but no significant difference between groups</td>
</tr>
<tr>
<td>Meyer et al58</td>
<td>67 children</td>
<td>6-month aerobic exercise</td>
<td>Ultrasound EDD, IMT</td>
<td>Exercise group showed significant improvement in IMT and EDD</td>
</tr>
</tbody>
</table>

IMT, intima-media thickness; EDD, endothelial-dependent dilation.
results in 46 smokers and 50 nonsmokers, with both endothelial-dependent dilation and endothelial-independent dilation being significantly lower in the smokers. Barua et al also reported lower endothelial-dependent dilation in a group of smokers when compared to a group of nonsmokers. However, there were no differences in endothelial-independent dilation between smokers and nonsmokers. It should be pointed out that this study involved only 15 smokers and 8 nonsmokers. Therefore, it is possible that this study is underpowered.

Not only does chronic tobacco use have an effect on vascular function, but studies examining the acute effects of tobacco use have also demonstrated that smoking 1 cigarette is enough to cause a temporary decline in endothelial-dependent dilation. This decrease in endothelial-dependent dilation from acute smoking has been reported to be as high as 50%. Lekakis et al reported that a decline in endothelial-dependent dilation due to smoking 1 cigarette remains for up to 90 minutes after smoking. Although acute tobacco use affects endothelial-dependent dilation, there does not appear to be any effect on endothelial-independent dilation.

The direct inhalation of tobacco smoke, either chronically or acutely, is not the only way tobacco smoke affects vascular structure and function. Passive exposure to tobacco smoke has also been shown to affect both vascular structure and function. Knoflach et al recently reported a dose-response relationship between passive exposure to tobacco smoke and carotid IMT thickening. The greater the passive exposure to tobacco smoke, the greater the thickening of the carotid IMT. Besides vascular structure, passive smoke inhalation can also alter vascular function. Raitakari et al examined endothelial-dependent dilatation and endothelial-independent dilatation in 20 lifelong nonsmokers who had never been regularly exposed to tobacco smoke, 20 individuals who had a history of being passively exposed to tobacco smoke at least 1 hour per day for 2 or more years, and 20 individuals who had been passively exposed to tobacco smoke at least 1 hour per day for 2 or more years and this passive exposure had ceased for at least 1 year. Endothelial-dependent dilatation was significantly lower in both current passively exposed smokers compared to current passive smokers; smokers had lower EDD compared to nonsmokers.

Table 4.
Summary of Studies Assessing the Effects of Smoking on Vascular Structure and Function

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Measure of Arterial Structure or Function</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raitakari et al</td>
<td>2229 adults</td>
<td>Ultrasound IMT</td>
<td>Cigarette smoking at ages 12 to 18 years was associated with increased IMT but not when adjusted for adult smoking</td>
</tr>
<tr>
<td>Juonala et al</td>
<td>2109 adults</td>
<td>Ultrasound IMT, EDD</td>
<td>Number of cigarettes/day and years of smoking correlated with an increase in IMT</td>
</tr>
<tr>
<td>Celermajer et al</td>
<td>200 adults</td>
<td>Ultrasound EDD, EID</td>
<td>Lifetime dose smoked was inversely related to EDD</td>
</tr>
<tr>
<td>Zeiher et al</td>
<td>96 adults</td>
<td>Ultrasound EDD, EID</td>
<td>EDD blunted in smokers and was compounded with presence of atherosclerosis</td>
</tr>
<tr>
<td>Barua et al</td>
<td>23 adult men</td>
<td>Ultrasound EDD, EID</td>
<td>Smokers had decreased EDD compared to nonsmokers</td>
</tr>
<tr>
<td>Kiowski et al</td>
<td>35 adults</td>
<td>Intrabrachial artery infusions</td>
<td>EDD lower in smokers</td>
</tr>
<tr>
<td>Lekakis et al</td>
<td>10 adults</td>
<td>Ultrasound EDD</td>
<td>Acute smoking results in impairment of EDD</td>
</tr>
<tr>
<td>Raitakari et al</td>
<td>60 adults</td>
<td>Ultrasound EDD, EID</td>
<td>EDD higher in former passive smokers compared to current passive smokers; smokers had lower EDD compared to nonsmokers</td>
</tr>
</tbody>
</table>

IMT, intima-media thickness; EDD, endothelial-dependent dilation; EID, endothelial-independent dilation.
Cross-sectional as well as longitudinal research studies have clearly demonstrated the negative effects of tobacco use on vascular structure and function. More important, research studies have demonstrated the negative effects of passive or second-hand tobacco smoke on vascular health. The damage done by both direct and indirect inhalation of tobacco smoke is permanent, and removal of tobacco smoke does not appear to result in an improvement in vascular structure or function.

**Alcohol**

The role of alcohol on vascular health is controversial. The effects of alcohol on vascular structure and function are presented in Table 5. Cross-sectional research studies have reported a positive relationship between moderate alcohol consumption and vascular health, whereas heavy alcohol consumption is related to decrements in vascular health. In addition to differences in consumption, there appears to be gender differences in the effects of alcohol consumption on vascular health. Cross-sectional studies examining the effect of alcohol consumption on carotid IMT have reported a variety of results. In a study of 1230 men and 1190 women, aged 20 to 79 years, a J-shaped association was observed between alcohol consumption and carotid IMT in men after controlling for major confounders. There was a decrease in carotid IMT up to a daily intake of 80 g of alcohol per day, after which the intake of alcohol was observed to increase carotid IMT in men. In this study, there was no association between alcohol consumption and carotid IMT in women. Kawamoto et al reported similar findings in that increased alcohol consumption was significantly related to thickening of the carotid IMT in men aged 70.3 years (range, 14-97 years) but not in women aged 75.6 years (range 19-103 years). In a study of 5888 adults aged 65 years and older, consumption of 1 to 6 drinks per week had an inverse association with carotid IMT, whereas consumption of 14 or more drinks per week had a positive association with carotid IMT. This positive association was found in both men and women. This study would suggest that there is a dose-dependent relationship between alcohol consumption on carotid IMT in men and also in women after the age of 65 years.

Cross-sectional studies examining the long-term effects of alcohol consumption on vascular function have typically reported a reduction in endothelial-dependent dilation in those individuals who were heavy users of alcohol but not in moderate drinkers. The damage caused by years of heavy alcohol consumption on endothelial-dependent dilation appears to be permanent, even when alcohol consumption is reduced or stopped entirely. There appears to be little if any effect of heavy alcohol use on endothelial-independent dilation.

**Table 5.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Measure of Arterial Structure or Function</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maiorano et al</td>
<td>20 adult alcoholics</td>
<td>Ultrasound EDD, EID</td>
<td>Alcoholics displayed significantly less EDD than control</td>
</tr>
<tr>
<td>Di Gennaro et al</td>
<td>42 adult recovered alcoholics</td>
<td>Ultrasound EDD, EID</td>
<td>EDD reduced in detoxified alcoholics</td>
</tr>
<tr>
<td>Zilkens et al</td>
<td>16 adult men</td>
<td>Ultrasound EDD, EID</td>
<td>Reduction in alcohol intake had no effect on EDD</td>
</tr>
<tr>
<td>Bau et al</td>
<td>100 adult men</td>
<td>Ultrasound EDD, EID</td>
<td>EDD increased 4 hours after alcohol consumption</td>
</tr>
<tr>
<td>Vlachopoulos et al</td>
<td>12 adult men</td>
<td>Ultrasound EDD, EID</td>
<td>Pure alcohol induces significant vasodilation but no effect on EDD</td>
</tr>
<tr>
<td>Hashimoto et al</td>
<td>11 adult men</td>
<td>Ultrasound EDD, EID</td>
<td>EDD increased for both regular red wine and de-alcoholized red wine consumption</td>
</tr>
<tr>
<td>Agewall et al</td>
<td>12 adults</td>
<td>Ultrasound EDD, EID</td>
<td>EDD increased after ingestion of red wine and de-alcoholized red wine</td>
</tr>
<tr>
<td>Papamichael et al</td>
<td>16 adults</td>
<td>Ultrasound EDD, EID</td>
<td>Consumption of alcohol did not change EDD</td>
</tr>
</tbody>
</table>

EDD, endothelial-dependent dilation; EID, endothelial-independent dilation.
The effects of acute alcohol consumption on vascular function have produced mixed results, with Bau et al reporting a decrease in both endothelial-dependent dilation and endothelial-independent dilation 4 hours after consumption of a single drink (eg, 60 g of ethanol), whereas Vlachopoulos et al reported no change in either endothelial-dependent dilation and endothelial-independent dilation 30 minutes after consumption of a single drink (eg, 1 ounce of pure alcohol). The differences between these studies may be a result of the different times after the consumption of alcohol that the vascular measures were done or in the type of alcohol consumed. Hashimoto et al reported that consuming 500 mL of vodka decreased endothelial-dependent dilation, whereas either alcoholized red wine or de-alcoholized red wine increased endothelial-dependent dilation. Other studies have also reported that alcoholized and de-alcoholized red wine improves endothelial-dependent dilation. The difference in studies may be a result of not only the type of alcohol consumed but also the population studied. Karatzi et al examined patients with coronary artery disease, and Papamichael et al examined healthy smokers. These 2 populations may have had other underlying health conditions that could have ultimately affected the overall results.

In summary, long-term chronic alcohol abuse is associated with both vascular structural and functional decrements. Research suggests that moderate amounts of alcohol may actually have a beneficial effect on carotid IMT as well as endothelial-dependent dilation. Acutely, alcohol consumption has resulted in no effect or, in some studies, an improvement in endothelial-dependent dilation. Differences between study results may be a result of the populations studied as well as the type of alcohol (eg, pure alcohol, wine) consumed. Future studies are needed to ultimately determine the effects of volume of alcohol consumed as well as the effects of different types of alcohol on vascular structure and function.

### Conclusions and Future Directions

When examining vascular health, it is important to examine not only the structure of the vessel but also its function. There are a number of invasive and non-invasive methods currently available for measuring both vascular structure and function. To date, there have been a number of studies describing both decrements and improvements in vascular structure and function. Obviously, CVD risk factors such as age, obesity, physical inactivity, tobacco use, and alcohol consumption can negatively affect vascular health. Lifestyle modifications such as weight loss or exercise, which result in decreases in body mass or fat mass or increases physical activity, have proven successful in improving vascular structure and function in both children and adults. Although research in the past decade has increased our overall knowledge about vascular structure and function, little is known regarding the mechanisms that result in improvements in vascular structure and function following exercise training or weight loss or other lifestyle modifications. In addition, information is lacking regarding whether there is a particular level of weight or fat mass that must occur or an particular exercise prescription (ie, duration, frequency, intensity) that must be attained before improvements in vascular structure and function. Future studies need to focus on the mechanisms as well as the exact lifestyle prescription that are necessary to bring about vascular health.

### References


