34-NON-INVASIVE IMAGING IN PEDIATRIC ATHEROSCLEROSIS

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ABSTRACT

Atherosclerosis is a lifelong process with the substrate beginning in childhood. However, in most children the manifestation is subclinical. There is a substantial body of evidence demonstrating the early phase of atherosclerosis is accelerated in the presence of acquired cardiovascular risk factors. In the adult population, conventional cardiovascular risk stratification is used to calculate the future lifetime risk of a cardiovascular event. A lifetime risk calculator in children with subclinical atherosclerosis does not exist. Therefore, the use of non-invasive imaging may have a role identifying "target organ damage" in asymptomatic children. Several non-invasive imaging modalities now make it possible to assess functional or structural end organ dysfunction. Our understanding of vascular dysfunction and cardiac remodeling has been enhanced by imaging technology. Initially reserved for research, imaging modalities are becoming useful adjunct for risk stratification and prevention strategies. Various medical societies are publishing consensus guidelines in an attempt to standardize non-invasive imaging as a reliable and valid clinical tool. The combination of traditional cardiovascular risk stratification and the use of non-invasive modalities are refining our ability to estimate future cardiovascular risk in subclinical pediatric atherosclerosis.

INTRODUCTION

Medical imaging is an important technique used to create visual representation of the body for clinical analysis and interventions. Recently, imaging has an important role in identifying subclinical disease for the purpose of risk stratification and prevention strategies. The traditional approach to cardiovascular assessment involves the identification and quantification of cardiovascular (CV) risk factors. Non-invasive imaging in the adult population has been established as a valid and reliable tool in defining cardiovascular risk. The use of non-invasive imaging in the pediatric population was reserved for research, but recently has transitioned to a practical clinical modality. Imaging is becoming a useful clinical adjunct to estimate future CV risks in addition to the traditional risk assessment.

BACKGROUND

Symptomatic atherosclerosis rarely occurs in children with the exception of children with homozygous familial hypercholesterolemia (1). Vascular progression in children with atherosclerosis is usually minor and clinically asymptomatic. However, several longitudinal studies have demonstrated that the atherosclerosis process can be accelerated in individuals

with multiple risk factors or high risk conditions. Identifying children with higher CV risk factors may allow the clinician to use early intervention to delay the process of atherosclerosis.

EARLY ANATOMICAL CHANGES IN ATHEROSCLEROSIS

Autopsy studies have demonstrated that the substrate of atherosclerosis begins in childhood with the formation of the fatty streak (2). Cohort studies have also suggested that nearly all children have some degree of fatty streak by 3 years of age.

The pathological substrate for vascular dysfunction is mediated by endothelial dysfunction. Endothelial integrity is insulted by a complex mechanism of oxidative stress, loss of vasoactive substrates, inflammatory substances and prothrombotic state. This cluster of harmful stimuli accelerates and compounds the mechanism of endothelial dysfunction (3).

VASCULAR FUNCTION

The arterial wall consists of three layers. The *tunical externa* (outermost layer) is composed of connective tissue and collagen. The *tunical media* (middle layer) is made up of smooth muscle cells and elastic tissues. This layer is thicker and differentiates arteries from veins. The pediatric arterial vessel is composed of more elastin than collagen. The *tunica intima* (innermost layer) consists of endothelial cells. The endothelium is a single cell layer lining the vascular lumen and has an important role in maintaining vascular integrity.

The endothelium has several protective mechanisms such as inhibition of platelet aggregation, inhibition of vascular smooth muscle proliferation, and anti-inflammatory molecules. Vascular homeostasis is balanced between vasoactive and vasoconstricting substances. Nitric oxide (NO) is the most important endothelial substance that stimulates vascular smooth muscle through a cascade enzyme process that results in an increased production of tissue cyclic-GMP. This mechanism results in vasodilation and smooth muscle relaxation.

The arterial system is a dynamic and complex process that is maintained through a balanced relationship between vascular structure, cardiac output, and systemic vascular resistance. Central cardiac blood flow is pulsatile and then transitions to a continuous flow state in the peripheral arteries. Blood flow is determined by heart rate, stroke volume and vascular resistance. The concept of arterial stiffness can be described as compliance and distensibility. Vessel compliance is the intrinsic change of the local vessel capacity in response to changes in blood volume. Vessel distensibility is a measure of the artery to expand and contract with cardiac pulsations and relaxation. Distensibility is the marker of the arterial elastin properties (4, 5).

RISK FACTORS FOR ATHEROSCLEROSIS

Obesity

The prevalence of overweight and obese children has stabilized. However, the rate of morbid obesity continues to increase (6). The progression of cardiovascular dysfunction in children with obesity is not completely understood and is likely influenced by a variety of genetic and environmental factors. The presence of additional risk factors further compounds the complexity of understanding cardiovascular dysfunction in obese children. Obesity is associated with increased metabolic demand due to greater adipose tissue. Arterial stiffness is impacted by the metabolic demand of increased blood volume (preload) and alterations of afterload. Left ventricular hypertrophy is a marker of the increased cardiac work load. Several studies have reported greater LV mass in obese children compared to lean controls (7).

Greater epicardial fat has also been reported in children with obesity that further increases cardiac work load. Epicardial adipose tissue deposits around the heart between the pericardium and outer wall of the myocardium. Epicardial fat has been proposed as a surrogate CV risk predictor. Excessive epicardial fat deposition has been associated with insulin resistance, coronary artery disease, increased carotid intima-media thickness (CIMT) and arterial stiffness (8).

Several studies have reported that children and adolescents (ages 10 to 14 years) with obesity have greater CIMT compared to children and adolescents with a healthy BMI. A concept of vascular age has been proposed with the application of CIMT measurements. A study of 70 children (ages 6 to 19 years) with the obesity and additional risk factors (dyslipidemia, hypertension, insulin resistance, and tobacco exposure) reported that 75% of those children had evidence of an advance vascular age (9).

Greater arterial stiffness has been demonstrated in children with obesity by pulse wave velocity (PWV) technique. Arterial vessel compliance increases with age, but studies have reported an accelerated process in obese children with additional risk factors. Endothelial dysfunction has also been reported in obese children.

Hypertension

Chronic elevated blood pressure has an important role in vascular changes over time. Elevated blood pressure is a complex relationship that is affected by several factors including the sympathetic nervous system, renin-angiotensin-aldosterone system and stimulation of vascular smooth muscle proliferation (10). Children with hypertension have evidence of left ventricular hypertrophy (LVH), increased LV mass, carotid intima-medial thickening (CIMT), and vascular endothelial dysfunction. Increased LV mass is the most prominent clinical evidence of target-organ damage. A left ventricular mass index above 51 $g/m^{2.7}$ has been associated with a fourfold greater risk of adverse cardiovascular outcome in the adult studies. Ventricular remodeling occurs with chronic pressure afterload and alters the sarcomere arrangement. Geometric changes can be described as either concentric or eccentric hypertrophy. Concentric hypertrophy is associated with a poor prognostic cardiovascular outcome.

Diabetes

The combination of insulin resistance and hyperglycemia are linked with endothelial dysfunction and mediators of inflammation. Insulin resistance is the substrate of the obesity pattern of dyslipidemia that activates hepatic synthesis of very low density lipoprotein (VLDL). Therefore, the surrogate lipoprotein of plasma triglycerides is increased. The triglyceride rich lipoprotein utilizes cholesterol ester transfer protein (CETP) to exchange triglycerides and cholesterol esters molecule. This process leads to dysfunctional large low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The altered lipoproteins become triglyceride rich and cholesterol ester poor. VLDL lipoproteins become cholesterol ester rich. The dysfunctional lipoproteins upon exposure to hepatic lipase produce small dense LDL particles and smaller HDL particles. Smaller HDL particles are subject to catabolism and excreted by the kidneys. Thus, mixed dyslipidemia pattern is characterized by high Apo-B (increased small dense LDL particles and cholesterol ester rich VLDL remnants) and low Apo-A (low HDL particles) (11). The TG/HDL-c ratio is a measure of small density LDL-particle size that is a surrogate atherogenic index of the mixed dyslipidemic pattern. TG/HDL-c ratio was shown to be an independent determinant of arterial stiffness in obese adolescents using brachial artery distensibility (BrachD) and carotid-femoral pulse wave velocity (PWV)(12).

Dyslipidemia

It has been established that the precursor of the atherosclerosis process is developed in childhood by the formation of the fatty streak. The natural process of atherosclerosis is understood by the biological model of Familial Hypercholesterolemia. Atherosclerosis in childhood is subclinical before manifesting clinical symptoms of cardiovascular heart disease in adulthood.

The relationship between the number of identified CV risk factors and pathological atherosclerotic lesions have been demonstrated by autopsy studies. The study concluded that multiple CV risk factors are associated with accelerated and premature atherosclerosis (13). Imaging studies, such as CIMT have demonstrated the correlation of CV risk factors and premature atherosclerosis. Imaging (CIMT) has been used as a surrogate marker tracking the relationship of LDL-c measured in childhood into adulthood (14).

Metabolic Syndrome

Metabolic syndrome (MS) has been well established in the adult population, described as a cluster of CV risk factors including hypertension, overweight/obesity, dyslipidemia (high triglycerides, low HDL), and insulin resistance. The components of MS as independent risk factors have been associated with vascular dysfunction; however cross-sectional studies of the relationship between metabolic syndrome and vascular dysfunction have been unclear in the pediatric population. The NHLBI guidelines for integrative CV health in pediatrics did not consider MS as a separate risk factor in childhood due to the paucity of evidence (15). The International Diabetes Federation has developed a definition of MS in children and adolescents.

NON-INVASIVE IMAGING MODALITIES

Carotid Intima-Media Thickness (CIMT)

CIMT is a non-invasive, non-radiation test that utilizes ultrasound imaging to assess atherosclerosis. CIMT has been useful as a surrogate imaging modality demonstrating the relationship between CV risk factors and vascular changes. Early atherosclerosis in children is usually manifested as diffuse thickening of the intima-media space rather than discrete lipid core or fibrous cap progression.

An abnormal CIMT is a thickened sub-intimal (tunica intima and tunica media) layer due to the complex atherosclerotic process of atherogenic particle deposition and inflammatory process. Imaging acquisition is obtained with 2D grayscale imaging along the longitudinal axis of the artery. The ultrasound beam is perpendicular to the vessel of interest. The segment of the artery clearly defines the intimal-luminal interface showing the anterior and posterior wall of the vessel. Images are obtained using a high definition transducer with linear frequencies of at least 8 MHz (8-12 MHz). Using a minimum of at least 10mm of arterial vessel segment, measurements are obtained by edge-detection system or manual cursor placement. Measurement values should be a mean IMT measurement with standard deviation (SD). Normative values and reference charts have been developed for pediatric and adolescent populations (16). The American Society of Echocardiography (ASE) has published a consensus statement to address the recommendations and standardization of CIMT use in clinical practice (17). The use of CIMT modality in asymptomatic adults is considered reasonable for CV risk assessments that are categorized intermediate risk (Class IIa; level of evidence B)(18).

Echocardiography-Transthoracic

Traditionally transthoracic echocardiography is an image modality that utilizes an ultrasound beam to acquire anatomical images through m-mode imaging and 2D imaging. Doppler technique is an addition tool to acquire information about blood flow and pressure differences. Assessment of left ventricular hypertrophy (LVH) secondary to increased afterload (hypertension) is best obtained by echocardiography. Left ventricular hypertrophy is defined as an increased in the LV mass, which can be secondary to an increase in wall thickness with or without an increase in cavity size. The estimation of the LV mass is derived from LV measurements obtained by 2D echocardiography. The standardized LV mass measurement is normalizing LV mass to body size that is $g/m^{2.7}$. Pediatric normative reference values have been published (19). Left ventricular index mass greater than 51 $g/m^{2.7}$ is consider probable left ventricular hypertrophy that has been associated with increased CV morbidities in the adult studies. In addition, geometric changes of the LV geometry can be described as eccentric or concentric hypertrophy. In asymptomatic adults with hypertension, the clinical use of transthoracic echocardiography can be considered for CV risk assessment (Class IIb; level of evidence B)(18).

Epicardial fat thickness can be visualized using standard parasternal long-axis and short-axis imaging planes of the right ventricle. The epidcardial fat is the echo-free space between the outer wall of the myocardium and visceral layer of the pericardium. The thickness is measured perpendicularly on the free wall of the right ventricle at end-systole (20). Normative reference values for pediatrics have not been published. Studies have reported a value > 7mm is associated with subclinical atherosclerosis and coronary artery disease.

Echocardiography may also be helpful in detecting advance coronary artery disease (CAD) secondary to atherosclerosis. Advance CAD can be visualized as valvular thrombus formation causing valvular regurgitation. Ventricular wall motion abnormalities secondary to poor coronary flow can also be detected.

Pulse-Wave Velocity (PWV)

Pulse-Wave Velocity (PWV) is a surrogate technique used to assess arterial stiffness. The modality measures the velocity of the pulse wave (indicator of blood flow) to travel a given distance between 2 sites of the arterial system. The velocity of this movement between the 2 time points gives an estimated measure of arterial compliance. PWV velocity is increased with arterial stiffness and vascular damage secondary to hypertension, obesity and atherosclerosis. Pulse-Wave Velocity technique is a valuable clinical research tool; however the technique has not transitioned to daily practical clinical use. Several studies have published pediatric normal values. Outside the setting of research, the use of PWV in asymptomatic adults is not recommended and has no clinical benefit (Class III, Level of Evidence C)(18).

Flow-Mediated Dilation (FMD)/EndoPat^{TM}

Flow-mediated dilation (FMD) is a technique used to assess endothelial function. The technique measures the nitric oxide-mediated vasodilation produced by increased blood flow after a period of ischemia (Reactive hyperemia). There are 2 basic methods to assess endothelial function either by infusion of endothelial dependent vasodilator or the technique of reactive hyperemia.

A practical medical device (Endopat) has been made available to clinicians for the assessment of endothelial function. EndoPat ^{TM} utilizes the reactive hyperemia method and generates signal amplitude. The technique involves a 5 minute occlusion of the brachial artery (standard blood pressure cuff) and then measures the surge of blood after release of the blood pressure cuff. A post-occlusion and pre-occlusion ratio is calculated by computer software that provides an EndoPAT^{TM} index. A lower EndoPAT^{TM} index score indicates poor endothelial function. Reproducibility studies have been performed on a group of healthy adolescents, demonstrating the clinical feasibility and practical use in the pediatric population (21). However, FMD is not recommended for CV risk assessment in asymptomatic adults (Class III, Level of Evidence B)(18).

Advance Imaging Modalities

Advance imaging modalities such as cardiac magnetic resonance imaging (C-MRI) and computed tomography (CT) imaging are useful methods in understanding anatomical anatomy and tissue characterization. Clinical decision to utilize CT or MRI is debated on the risk of radiation exposure (CT imaging) and the imaging resolution limitations of each modality. In asymptomatic adults, the use of CT imaging and MRI is not recommended for low CV risk assessment (Class III, Level of Evidence C).

In the adult population, MRI utilized as an imaging assessment for plaque formation in the aorta, femoral and carotid arteries. Early plaque formation in the pediatric population is extremely rare.

Cardiac CT for calcium scoring is a method used to assess the presence and extent of calcified plaque in the coronary arteries that is associated with atherosclerosis. The coronary artery calcium (CAC) score is a helpful prognostic tool. CAC scoring is used as a method to assess risk classification for adult atherosclerosis cardiovascular disease (ASCVD). The use of CAC scoring is not recommended as a surrogate pediatric risk marker.

Myocardial perfusion imaging is reserved for adults with advance cardiovascular risk, however the use of perfusion imaging in children is not recommended as a risk assessment marker.

The use of coronary advance imaging in Kawasaki disease and transplant coronary vasculopathy may be a helpful imaging adjunct to traditional angiography (22).

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