The Causal Relationship between Reduced Vascular Compliance and Hypertension

Anjanette Ferris

A. Study Purpose and Rationale

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States. Coronary disease is the primary cause of death of all persons after age forty-five in the United States. The pathologic process for the development of CAD is atherosclerosis; defined as thickening and hardening of the wall of large arteries. The physiologic mechanism involves lipid deposition in intinial macrophages (foam cells) and proliferation of intimal smooth muscle cells. With progression, fibrous plaques develop Fibrous plaques are composed of a central core of extracellular lipid and necrotic cell debris covered by a fibromuscular layer (cap) containing smooth muscle cells, collagen, and macrophages (l). Ulceration of the cap leads to thrombus formation which causes occlusion of vessels; hence, ischemia. Development of atherosclerosis has a direct correlation with age (2). The pathogenesis is hypothesized to be related to repeated endothelial injury. Injury can be mechanical, as with the shear stress of hypertension, or metabolic, as with the advanced glycation end products of chronic diabetes. Repeated endothelial injury leads to the aggregation of monocytes, which subsequently accumulate lipids. The cascade leading to the development of the ulcerated fibrous cap then ensues.

Several risk factors, independent of age, have been shown to be associated with the development of atherosclerosis. By deduction, these risk factors are implicated in the development of coronary artery disease. Major risk factors include hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia, low level of high-density lipoprotein (HDL) family history of coronary disease (3). Additional associations with CAD include obesity, increased lipoprotein a, increased serum homocysteine, abnormalities of coagulation factors (3). The high morbidity and mortality associated with CAD has led to efforts in risk reduction either through lifestyle modification and/or pharmacological intervention.

Primary prevention offers opportunity for reducing the prevalence of coronary artery disease. The purpose of this study is to investigate one risk factor for development of atherosclerosis; hypertension. Atheromatous disease leads to decreased arterial elastic distensibility, which is measured by compliance. Compliance is defined as the change in area for a given change in pressure (4). Various investigational methods are used to evaluate arterial elasticity; direct angiography, ultrasound, magnetic resonance imaging, radionucleotide scanning. Angiography may be the best presumptive test for evaluation, however, it is invasive and introduces risk. Non-invasive techniques offer an alternative method of measurement. Using ultrasound, vascular compliance is reflected as pulse wave velocity (5). Pulse wave velocity increases as arterial wall stiffness increases (compliance decreases). Compliance has been studied in individuals with known risk factors for CAD. Direct correlation has been found between decreased compliance and hypertension (6). Arterial elasticity is under the influence of blood pressure. However, the decrease in arterial elasticity in hypertensive patients is considered to be due not solely to elevated blood pressure (shear force), but also to structural and functional changes in the arterial wall. What is still unknown is whether a decrease in compliance precedes or is a consequence of hypertension. This study will attempt to answer this question. If abnormal compliance is proven to occur prior to the clinical manifestation of hypertension, it may serve as a marker for identifying patients at risk, thereby allowing for primary prevention and early intervention. Early identification of vascular abnormalities may offer a tool for anticipation and possible prevention of clinical disease.

B. Literature Review

In 1954, GC Willis observed that on pathological study of the femoral and popliteal arteries of twenty hypertensive patients, sites of dilatation corresponded to the distribution of atherosclerotic plaques (7).

In 1971, Newman et al. studied aortic distensibility in cockerels fed an atherogenic crushed-egg diet. Distensibility was correlated with the severity of the atherosclerotic lesions using an atherosclerotic index ranging from I to 100. Increased distensibility was found up to an index value of 40. For index values greater than 60, distensibility progressively decreased to lower than normal values. Decreased distensibility was attributed to progressive calcification and fibrosis of the arterial wall. The authors postulated that the collagen-elastin interlamellar web was weakened possibly by infiltration of lipids into the arterial wall or by some change in proportion of elastin and collagen invoked by the diet (8).

In 1990, Shanker and Bond compared non-invasive arterial compliance using plethysmography with post-mortem pathologic atherosclerotic changes in the peripheral arteries of fifteen cynomolgus, monkeys. The authors concluded that change in compliance was the mechanical parameter that correlated most with progressive atherosclerosis (9).

In 1993, Kupari et al. investigated factors responsible for increasing aortic stifffiess. Fifty-five healthy individuals (31 men, 24 women) born in Helsinki in 1954 were evaluated. The study collected a two-month chronicle of each subject's physical activity level, alcohol consumption, tobacco use, and dietary intake. At completion of the two months, subjects underwent an MRI of the thoracic aorta for measurement of elastic modulus. The study concluded that the stiffness of the thoracic aorta was increased with elevated blood pressure, low level of physical activity, and increased levels of insulin in individuals homogeneous for age and with prior undetectable cardiovascular risk factors. Implication was that aortic distensibility may be susceptible to lifestyle modification(l 0).

Prior studies have failed to establish the causal relationship between arterial compliance and risk factors for atherogenesis. This investigation will attempt to determine if change in compliance precedes or is a consequence of hypertension.

C. Study Design and Statistical Analysis

This cross sectional study will be composed of four anns. The first group of subjects will consist of normotensive patients with a high risk profile for hypertension. Qualification for high risk includes having one or both parents with an established diagnosis of hypertension. The second group will include normotensive patients with a low risk profile for hypertension. Qualification for low risk includes having neither parent with an established diagnosis of hypertension. Normotensive high risk will be compared to normotensive low risk subjects to assess for difference in vascular compliance. The normotensive low risk subjects will serve as controls. Normotensive subjects, both high and low risk, will range in age from 20 to 29 years old. The third group of subjects will include newly diagnosed hypertensives; diagnosed within three months prior to recruitment. The fourth group of subjects will include longstanding hypertensives. Qualification is having hypertension for greater than or equal to three years prior to recruitment. Hypertensive patients, both newly diagnosed and longstanding, will range in age from 40 to 49 years old. Newly diagnosed hypertensives will be compared to longstanding hypertensives to assess for difference in vascular compliance.

This study proposes two hypotheses: Hypothesis 4 1 - Decreased vascular compliance occurs prior to the onset of hypertensive disease. Hypothesis # 2 - Decreased vascular compliance occurs as a consequence of hypertensive disease.

Study subjects and controls will be matched by gender, race, and area of residence. Subjects will not be crossed over from one group to the other. Hypertension will be defined as having a systolic blood pressure of greater fl= 140 mmHg and/or a diastolic blood pressure greater than 90 mmHg. Criteria must be satisfied by readings on three separate visits to the subject's primary care provider or upon visit to the study center. Criteria of hypertension will apply to study subjects and to the parents of the study subjects.

Subjects will be assigned to groups based upon age, presence or absence of risk factors for hypertension, and the duration of hypertension. Subjects will be recruited from Columbia Presbyterian

outpatient clinics, Harlem Hospital, and Cornell Medical Center. The number of subjects for each group will be 48 calculated from the unpaired ttest for 90 % power, testing at p = 0.05. Study outcome is vascular compliance. The proposed method of statistical analysis will include use of the unpaired t-test.

D. Study Procedures

Study procedures include venipuncture at the antecubital fossa to obtain approximately 10 ml of blood. A sterile 23-gauge butterfly needle will be used. The blood will be placed into two tubes and analyzed for fasting lipid profile (5ml) and fasting glucose (5 ml) using an Olympus analyzer. The procedure is estimated to take five to ten minutes and will be perfon-ned after consent is obtained. Study procedure also includes use of a Doppler ultrasound machine. Each subject will rest supine for an estimated fifteen minutes. A blood pressure cuff will be placed on either arm for monitoring. One continuous wave Doppler ultrasound transducer will be placed at the level of the umbilicus just proximal to the aorto-iliac bifurcation (2). Emitted signals will be converted to pulse wave velocities using a spectral analyzer. Pulse wave velocity will then be converted to compliance using the equation C = 0.667 x (I/PWV)2, where C = compliance and PW = pulse wave velocity (2) . One ultrasonographer will perform each of the studies to limit variation in technique. The ultrasonographer will be blinded to the hypertensive status of the subjects.

The anticipated duration for study procedures is thirty minutes. The anticipated duration of each subject's participation in the study is two weeks. Two weeks will be accounted for by repeated blood pressure readings, if required, and for confirmation of laboratory tests. Subject visits may range from two required (phlebotomy and ultrasound) to a maximum of five (including three visits for blood pressure measurements

E. Study Drugs

None

F. Medical Devices

Medical devices are not under investigation in this study.

G. Study Questionnaires

Once recruited, patients will be asked relevant questions. No questionnaires will be distributed.

H. Study Subjects

Study subjects will be divided into four groups. The first arm will include normotensive patients with a high risk profile for hypertension. High risk is defined as having one or both parents with an established diagnosis of hypertension. The second arm will include normotensive individuals with a low risk profile for hypertension. Low risk is defined as having neither parent with an established diagnosis of hypertension. The third arm of the study will include longstanding hypertensives; individuals with a diagnosis of hypertension for greater than or equal to three years. The fourth arm of the study will include newly diagnosed hypertensive patients; those individuals diagnosed with hypertension three months prior to recruitment. Exclusion criteria for all subjects will include a personal history of diabetes mellitus, hyperlipidemia, cigarette smoking (present or past). Normotensive patients will range in age from twenty to twenty-nine. Hypertensive patients will range in age from forty to forty-nine. Additional exclusion criteria for normotensive sub ects, both low and high risk, include a history of diabetes mellitus and/or hyperlipidernia in either or both parents. Fasting glucose and lipid profiles will be measured on all subjects. Subjects will be excluded if a fasting glucose greater than or equal to 126 mg/dl and/or a fasting

cholesterol of greater than 200 mg/dl is obtained. Women and minorities will be included in the study. Subjects will be matched for gender, race, and area of residence.

I. Recruitment of Subjects

Subjects will primarily be recruited from Columbia Presbyterian Medical Center Internal Medicine clinics. Additional recruitment will occur at Harlem Hospital and Cornell Medical Center in an effort to diversify the subject population. Primary physicians will be made aware of the study and would refer patients based upon their hypertensive status and age. Younger subjects (ages 20 -29) will be recruited from the clinic. To increase the number of subjects in this age group, older subjects (40 - 49) will be asked about the possible enrollment of their children if age criteria are satisfied. Flyers describing the study will also be posted throughout the aforementioned locations to serve as further means of recruitment.

J. Confidentiality of Study Data

Subject names will not be used. Once entered into the study, subjects will be identified by a designated number. Data containing both the subject name and number will be kept confidential by the principal investigators.

K. Potential conflict of Interest

None

L. Location of Study

Columbia Presbyterian Medical Center

M. Potential Risks

Risks of venipuncture include development of a hematoma, excessive bleeding from site, discomfort at site. Doppler study is non-invasive and introduces minimal if no risk. Discomfort may be experienced with inflation and deflation of the blood pressure cuff used for monitoring and with the application of transducer gel to the skin of the abdomen.

N. Potential Benefits

If a statistically significant decrease in vascular compliance is found between the low and high risk normotensive patients, evidence would support change in compliance as a marker for identification of patients who may later go on to develop clinical disease. Primary prevention is the goal. With lifestyle modification and vigilant clinical monitoring, it may be possible to prevent clinical disease. This study will also give impetus to other studies investigating additional high risk factors for coronary disease.

O. Alternative Therapies

Not applicable

P. Compensation to Subjects

Each participant will be compensated for his/her time and effort. Twenty dollars cash will be distributed to each subject at the conclusion of his/her participation in the study. If the subject chooses not to complete the study, payment will be pro-rated.

Q. Costs to Subjects

None

R. Minors as Research Subjects

None

S. Radiation or Radioactive Substances

None

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