ELSEVIER

Neurobiology of Aging 26 (2005) 303–307

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Cardiovascular risk factors in youth with implications for aging: The Bogalusa Heart Study

G.S. Berenson*, S.R. Srnivasan

For the Bogalusa Heart Study Group

Tulane Center for Cardiovascular Health, Tulane School of Public Health and Tropical Medicine, 1440 Canal Street, Suite 1829, New Orleans, LA 70112, USA

Received 19 December 2003; received in revised form 29 April 2004; accepted 19 May 2004

Abstract

Evidence that cardiovascular (C-V) risk factors are identifiable in childhood and are predictive of future C-V risk is now irrefutable. That levels of C-V risk factors track or persist over time is important, since such phenomenon confers a life-long burden of C-V risk and indicates subtle and progressive changes in the C-V system. C-V risk factors occur often in constellation and central obesity and the attendant insulin resistance/hyperinsulinemia underlie the comorbid conditions of dyslipidemia, hypertension, thrombosis, and inflammation, among others. Autopsy studies and non-invasive subclinical C-V imaging studies in youth clearly link the multiple risk factor burdens to adverse C-V system changes. The application of multiple risk factors profiling in young individuals in conjunction with non-invasive measurements of vascular changes can promote successful aging and encourage preventive cardiology beginning in early life.

Keywords: Risk factors; Atherosclerosis; Cardiovascular system; Aging

1. Introduction

Cardiovascular (C-V) risk factors are identifiable in childhood and are predictive of future C-V risk in adulthood [1–3,15]. The long-term burdens of C-V risk factors have implications for successful aging and longevity in contrast to premature morbidity and mortality. Although clinical heart disease occurs in middle age and in older individuals, evidence of atherosclerotic disease, and organ changes related to high blood pressure, and adult type two diabetes are evident in childhood. The precise environmental and genetic factors causing these diseases are still being investigated, but it is apparent that risk factors are expressed as genetic-environmental interactions leading to C-V disease. Identifying the earliest determinants of C-V risk and related risk factors can achieve a great deal in understanding the evolution of these complex traits. This remains important since heart diseases are common problems in adult medicine and result in the greatest cause of death.

The long-term burden of C-V risk factors and lifestyle behaviors in early childhood create a long-term burden on the C-V system, which ultimately results in C-V events. Unhealthy lifestyles, such as high fat–high calorie diet, tobacco use and physical inactivity represent strong environmental factors related to the latent “silent” C-V lesions developing in the C-V system. Advances in technology now provide opportunities to study by non-invasive methodology underlying C-V changes occurring in asymptomatic individuals. Application of such measures can be used to evaluate of progressive changes that are occurring throughout the C-V system.

The long-term Bogalusa Heart Study now has an opportunity using non-invasive methodology to evaluate silent changes of the C-V system and the effect of the risk factor burden.

* Corresponding author. Tel.: +1 504 988 7197; fax: +1 504 988 7194.
E-mail address: berenson@tulane.edu (G.S. Berenson).

0197-4580/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2004.05.009

2. Population

The Bogalusa Heart Study is a comprehensive long-term program investigating the early natural history of C-V disease in a population of children and young adults from a biracial (65% white, 35% black) semi-rural community [2,3]. The study began in 1973 and has continued with multiple cross-sectional and longitudinal surveys. Extensive C-V risk factor data have been collected on approximately 16,000 individuals now providing a database from birth to approximately 40 years of age. Many subjects have had multiple observations, an average of around six times over the past 30 years.

3. Predictability of childhood risk factors for adult risk

Levels of risk factor variables for an individual tend to remain over time in a given rank within the distribution of the population. This "Tracking" based on findings beginning in early life is important, since childhood risk factors predict adult levels and clinical C-V disease. Tracking has significant implications for the life-long burden of C-V risk because this burden identifies with underlying disease of the C-V system. Risk factors track to varying degrees, with measures of obesity tracking the most [25]. Obesity, which begins in infancy and childhood, persists into adulthood and levels in childhood are strongly predictive of adult obesity. Serum total cholesterol and low-density lipoprotein cholesterol (BDL) track almost as well. The magnitude (LDL) of tracking of triglycerides, high-density lipoprotein (HDL) cholesterol and blood pressure is somewhat lower, due to the biologic changes and measurement variability. Although tracking of individual risk factors occurs, more important is that clusters or aggregation of multiple risk factors persist strongly from childhood to adulthood. This is especially true among individuals with increased body fatness [8]; and it is unfortunate there has been a secular trend of obesity across the nation, as documented in Bogalusa [13,21]. Overweight and obese subjects are likely to have three or four additional risk factors. Adiposity in childhood precedes hyperinsulinemia, which becomes more marked at the adult age, independent of race, sex, and baseline insulin levels. Adiposity is an independent predictor of the risk of developing the cluster of risk variables consistent with the metabolic syndrome or insulin resistance and, importantly, it begins in childhood [26]. This persistence of multiple risk factors with excessive weight reflects a life-time burden that relates to the development of atherosclerosis and hypertensive C-V disease target organ changes.

Individual risk factors correlate with other risk factors in both childhood and adulthood alike. For example, obesity is associated with higher blood pressure levels, especially in white children. It is of additional interest that there is the coexistence of the multiple risk factors beginning in childhood and persisting into adulthood indicating the trend for a life long burden. The degree of clustering of risk variables increases with age, particularly after the adolescent age following dramatic changes at puberty with growth spurts. A striking change of serum lipoproteins occurs in white males who show a decrease of HDL cholesterol starting at 65 ml/dL in childhood and decreasing to approximately 45 ml/dL around age 16 [4]. In addition, white males show a more accelerated increase of LDL-cholesterol, which is associated with a marked increase of the total cholesterol/HDL cholesterol ratio. In blacks, girls at the 85th percentile level begin to show a marked increase of obesity beginning around 9 years of age. Yet, black boys tend to be thin, muscular, have slower heart rates and higher peripheral resistance and higher blood pressure levels. These latter findings are consistent with the increased prevalence of hypertension in black adults. It is of further interest that the degree of clustering of risk factors increases with age and likely has a strong relation to limiting longevity.

The coexistence and high prevalence of multiple risk factors in young individuals has implications for the common occurrence of adult heart disease. From epidemiologic studies in older individuals such as the Framingham Study and Multiple Risk Factor Intervention Trial (MRFIT) a coexistence of multiple risk factors has a strong relationship to C-V events. Although individuals in the Bogalusa Heart Study are not old enough to manifest clinical symptomatology, the degree of clustering of risk factors, as seen in the Framingham Study, are essentially similar. Central obesity and the attendant insulin resistance/hyperinsulinemia underlie the constellation of metabolic, hemodynamic, thrombotic and inflammatory disorders already evident in young individuals.

4. Evidence of underlying cardiovascular disease

4.1. Autopsy studies

The burden of multiple C-V risk factors from childhood on the C-V system can be evaluated by various types of studies. Most important are autopsy studies of young individuals. In the Bogalusa Heart Study an unusually high prevalence (90%) of coronary atherosclerosis is seen by the third decade of life in the general population. Several autopsy studies have supported this distressing high occurrence of atherosclerosis: the International Atherosclerosis Study [17], soldiers killed in the Korean and Vietnamese wars [11,19] and Pathobiologic Determinants of Atherosclerosis in Youth (PDAY) [18]. In life, observations by intravascular ultrasonic studies (IVSS) provide further evidence that the general occurrence of atherosclerosis really greater than appreciated by coronary arteriography [24]. Autopsy studies in Bogalusa further demonstrate race and sex differences. A lag of lesions occur in females and blacks show more aorta fatty streaks and white males more coronary artery fibrous plaques in early life [5,12]. Further studies even indicate changes may be influenced by gestational effects [22] and vary at different vascular sites [16,27].

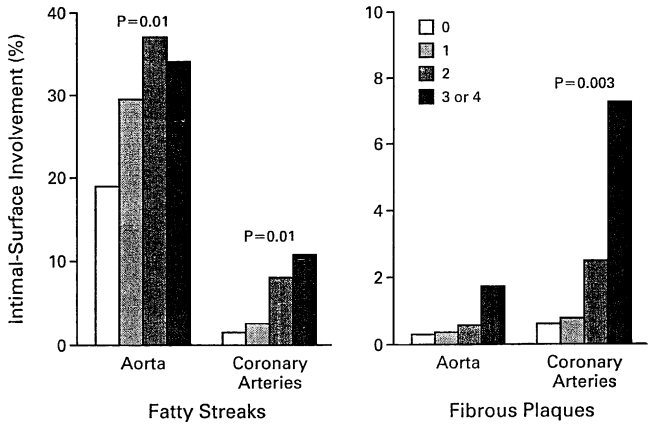

Fig. 1. The effect of multiple risk factors on the extent of atherosclerosis in the aorta and coronary arteries in children and young adults. Values shown are the percentages of the intimal surface covered with lesions in subjects with 0, 1, 2, and 3 risk factors. Risk factors were elevated values for body-mass index, systolic blood pressure, and serum triglycerides and LDL cholesterol concentrations, defined as values above the 75th percentile for the study group (specific for study period, race, sex, and age). There were 52 subjects with no risk factors, 20 with one, 14 with two, and 7 with three or four. The *P* value is based on the analysis of trend. A marked increase in the percentage of the intimal surface covered by fibrous plaques is evident in the coronary vessels of subjects with multiple risk factors (Berenson, Ref. [21]).

Notably, the importance of multiple risk factors has been documented in the autopsy studies conducted in the Bogalusa Heart Study. Fig. 1 shows the severity of atherosclerotic disease related to none or increasing number of risk factors. It might be noted that both fatty streaks and fibrous plaques accelerate markedly in the coronary vessels with increasing multiple risk factors [6]. This finding alone emphasizes the early origin of atherosclerosis and why the assessment of clinical risk factors in early life is important.

4.2. Non-invasive studies of the cardiovascular system

Although a profile of C-V risk factors is useful in predicting C-V events, inclusion of measurements of subclinical atherosclerosis by non-invasive imaging techniques can be a powerful approach to determine the extensiveness and severity of asymptomatic disease and potential future risk. Recently there has been considerable interest in imaging for calcification of coronary arteries, but these observations are often limited in determining the extensiveness of coronary atherosclerosis in non-calcified lesions, even in individuals with known coronary artery disease. The Muscatine Study has shown a relation of obesity from childhood to coronary calcification, even though coronary calcification showed a limited relationship to C-V risk factors [20]. While high technologic advances are expanding imaging capability of underlying C-V disease, these are costly and may not be practical for studies of large number of individuals. There are more accessible methods now available and these are discussed.

4.3. Echo-Doppler studies

Perhaps the most viable approach is the use of echo-Doppler measurements. With regards to hypertension, a number of studies have shown cardiac hypertrophy and increased left ventricular mass associated with higher levels of blood pressure in young individuals. It is to be stressed that blood pressure levels in children and adolescents are much lower than advocated as abnormal by the Joint National Commission VI. Essentially levels at the 80th percentile of blood pressure distributions show some evidence of cardiac hypertrophy [9]. It is well known that increased left ventricular mass has been shown to be an independent risk factor for future C-V events in adults, such as heart failure and strokes. It is unfortunate that primary care physicians caring for young individuals are not sufficiently aggressive to detect young individuals with hypertension, monitor the course and encourage treatment. Based on tracking, high blood pressure levels are predictive of future hypertension at the recommended abnormal clinical levels; but target organ C-V and renal disease are already present in youth.

Echo-Doppler studies of the carotid arteries provide a non-invasive and readily available tool for evaluating large numbers of asymptomatic individuals. We measured intima-media thickness (IMT) of carotid arteries by B-mode duplex ultrasonography in 517 black and white subjects, aged 20–38 years, enrolled in the Bogalusa Heart Study. Observations of the carotid IMT related to multiple risk factors which including parental history, blood pressure, obesity measures, lipoproteins, insulin, glucose and cigarette smoking [28]. Measurements were obtained on the common, the bulb or bifurcation area, and internal carotid segments. In general, IMT in the common carotid and bulb segments were significantly greater in blacks, males and older individuals. As might be expected, age remains a major determinant of vascular changes. Marked individual differences were noted to occur in IMT. Studies of the top 5% of carotid artery IMT changes showed the common segment to have a range of 0.84–1.1 mm IMT, with a mean of 0.68 mm, and for the carotid bulb, 0.90–2.1 mm, with a mean of 0.87 mm [14]. The association, among different segments of carotid IMT, and risk factor variables all occurred in the expected direction. Systolic blood pressure, race, age, LDL cholesterol and HDL cholesterol explained 16% of variance in the common carotid IMT; age, systolic blood pressure, HDL cholesterol, LDL cholesterol, race and, importantly, insulin explained 19.4% variance in the carotid bulb IMT. Changes in relationship to the risk factors occurring in the internal carotid IMT were less evident. Of importance is the increase of IMT with increasing number of risk factors (0, 1, 2, 3 or more) as occurs in coronary vessels [7,14,28]. The observations related to multiple risk factors for the common carotid and the carotid bulb segments are shown in Fig. 2. These findings are consistent with pulsatile hemodynamic forces at the carotid bifurcation area, which makes this area more susceptible for atherosclerotic damage than at the common carotid or inter-

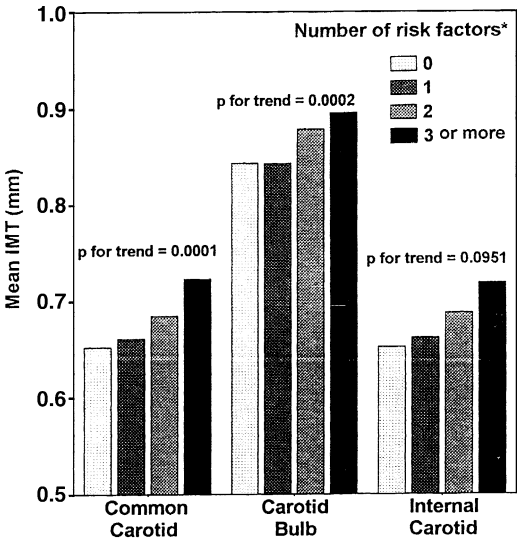

Fig. 2. Mean intima media thickness of three segments of the carotid artery related to the number of risk factors. Multiple risk factors relate to carotid segments in the order of bifurcation area (bulb), common and internal carotid. *Total cholesterol to HDL cholesterol ratio, waist circumference, systolic BP, and insulin (>75th percentile specific for age, race, and gender), and smoking (Urbina, Ref. [24]).

nal segments. Zarins et al. [30] showed the importance of the hemodynamic effects on the arterial wall structure. Such relations led Glagov and his group to the concept of remodeling. The thicker IMT at the bulb segment has a stronger association with multiple risk factors. Of considerable importance is that these changes are similar to that noted in autopsy studies of coronary arteries.

The presence of underlying IMT in the carotid arteries being strongly related to clinical C-V risk factors in young individuals should help identify individuals who are of particular risk for future C-V events. Douglas [10] have considered the carotid IMT in youth as indicative of "vascular aging versus chronological aging. Therefore, understanding risk factors at a young age and defining their underlying effects on the C-V system will help guide approaches to treatment and intervention.

In addition to structural changes in the heart and carotids, vascular elasticity or stiffness of different sites of the arterial system can be studied. In 109 individuals, 10–17 years old, we were able to show an association of increased carotid stiffness, in terms of pressure-strain elastic modulus (Peterson Elastic Modulus, Ep), with elevated levels of serum total cholesterol, systolic blood pressure and a positive parental history of myocardial infarction [23]. More recent studies also show that the carotid Ep is related to increasing numbers of risk factors [29]. Observations of the compliance and distensibility of the arterial systems could conceivably provide evidence of vascular functional changes preceding structural changes. Importantly, documenting structure-function of the C-V system in life can aid in understanding aging.

5. Comments

Observations from the Bogalusa Heart Study beginning in childhood, and continuing through adolescence, young adulthood and now into middle age show that characteristics of C-V risk factors vary by age, race and sex. The presence of multiple risk factors in individuals over an extended period creates a lifetime burden associated with underlying silent C-V disease. The relation of risk factors to C-V change is evident for both atherosclerosis and hypertension. Although individuals in these studies are still too young to manifest clinical C-V events such as myocardial infarction or stroke or heart failure, autopsy studies and non-invasive subclinical C-V studies clearly link a risk factor burden to future C-V risk. In terms of preventive cardiology, the application of clinical risk factor profiling in conjunction with non-invasive studies of the vascular tree in youth can guide prevention management and ultimately promote successful aging.

Acknowledgment

The Bogalusa Heart Study is a joint effort of many individuals whose cooperation is gratefully acknowledged. We are especially grateful for the children who grew up contributing to this research.Supported by grants HL38844 from the National Heart, Lung and Blood Institute, AG16592 from the National Institute on Aging and HD43820 from the National Institute of Child Health and Human Development.

References

[1] Akerblom HK, Ukari M, Pesonen E, Dahl M, Kaprio EA, Nuutinen EM, et al. Cardiovascular risk in young finns. Ann Med 1991;23:35–9.
[2] Berenson GS, McMahan CA, Voors AW, Webber LS, Srinivasan SR, Frank GC, et al. In: Andrews C, Hester HE, editors. Cardiovascular risk factors in children—the early natural history of atherosclerosis and essential hypertension. New York: Oxford University Press; 1980. p. 450.
[3] Berenson GS, editor. Causation of cardiovascular risk factors in children: perspectives on cardiovascular risk in early life. New York: Raven Press; 1986. p. 408.
[4] Berenson GS, Srinivasan SR, Cresanta JL, Foster TA, Webber LS. Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. Am J Epidemiol 1981;113:157–70.
[5] Berenson GS, Wattigney WA, Tracy RE. Atherosclerosis of aorta and coronary arteries and cardiovascular risk factors in persons aged 6–30 years studied at necropsy: The Bogalusa Heart Study. Am J Cardiol 1992;70:851–8.
[6] Berenson GS, Srinivasan SR, Bao W, Newman III WP, Tracy RE, Wattigney W, for the Bogalusa Heart Study. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Eng J Med 1998;338:1650–6.
[7] Berenson GS, for the Bogalusa Heart Study Research Group. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease: The Bogalusa Heart Study. Am J Cardiol 2002;90:3L–7L.

[8] Boa W, Srinivasan Sr, Wattigney WA, Berenson GS. Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood. Arch Intern Med 1994;154:1842–7.
[9] Burke GL, Arcilla RA, Culpepper WS, Webber LS, Chiang RA, Berenson GS. Blood pressure and echocardiographic measures in children: The Bogalusa Heart Study. Circulation 1987;75:106–14.
[10] Douglas PS. Atherosclerosis: its all in the arteries [editorial]. J Am Soc Echocardiogr 2002;15:25A–6A.
[11] Enos WF, Beyer JC, Holmes RH. Pathogenesis of coronary disease in American soldiers killed in Korea. J Am Med Assoc 1955;158:912–4.
[12] Freedman DS, Newman III WP, Tracy RE, Voors AW, Srinivasan SR, Webber LS, et al. Black/white differences in aortic fatty streaks in adolescence and early childhood: The Bogalusa Heart Study. Circulation 1988;77:856–64.
[13] Gidding SS, Bao W, Srinivasan SR, Berenson GS. Effects of secular trends in obesity on coronary risk factors in children: The Bogalusa Heart Study. J Pediatr 1995;127:868–74.
[14] Krishnan P, Balamurugan A, Urbina E, Srinivasan SR, Bond G, Tang R, et al. Cardiovascular risk profile of asymptomatic healthy young adults with increased carotid artery intima-media thickness: The Bogalusa Heart Study. J La State Med Soc 2003;155:165–9.
[15] Lauer RM, Shekelle RB, editors. Childhood prevention of atherosclerosis and hypertension. New York: Raven Press; 1980. p. 484.
[16] McGarry P, Solberg LA, Guzman MA, Strong JP. Cerebral atherosclerosis in New Orleans. Comparison of lesions by age, sex, and race. Lab Invest 1985;52:533–9.
[17] McGill Jr HC. Persistent problems in the pathogenesis of atherosclerosis. Arteriosclerosis 1984;4:443–51.
[18] McGill Jr HC, McMahan CA, Malcom RT, Oalmann MC, Strong JP. Effect of serum l lipoproteins and smoking on atherosclerosis in young men and women. Arterioscl Thromb Vasc Biol 1997;17:95–106.
[19] McNamara JD, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. J Am Med Assoc 1971;216:1185–7.
[20] Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA, et al. Coronary risk factors measured in childhood and young adult life is associated with coronary artery calcification in young adults: the Muscatine Study. J Am Coll Cardiol 1996;27:277–84.
[21] Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States. J Am Med Assoc 1999;282:1519–22.
[22] Napoli C, Glass CK, Witztum JL, Deutsch R, D'Armiento FP. Influences of maternal hypercholesterolemia during pregnancy on progression of early atherosclerotic lesions in childhood: fate of early lesions in children (FELIC) study. Lancet 1999;354:1234–41.
[23] Riley WA, Freedman DS, Higgs NA, Barnes RW, Zinkgraf SA, Berenson GS. Decreased arterial elasticity associated with cardiovascular disease risk factors in the young: The Bogalusa Heart Study. Arteriosclerosis 1986;6:377–86.
[24] Schoenhagen P, Nissen SE, White RD, Tuzcu EM. Coronary imaging: angiography shows the stenosis, but IVUS, CT, and MRI show the plaque. Cleveland Clinic J Med 2003;8:713–9.
[25] Srinivasan SR, Bao W, Wattigney WA, Berenson GS. Adolescent overweight is associated with adult overweight and related multiple cardiovascular risk factors: The Bogalusa Heart Study. Metabolism 1996;45:235–40.
[26] Srinivasan SR, Myers L, Berenson GS. Temporal association between obesity and hyperinsulinemia in children, adolescents, and young adults: The Bogalusa Heart Study. Metabolism 1999;48:928–34.
[27] Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull Jr W, Richardson M, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Circulation 1992;85:391–405.
[28] Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study). Am J Cardiol 2002;90:953–8.
[29] Urbina EM, Srinivasan SR, Kieltyka RL, Tang R, Bond MG, Chen W, et al. Correlates of arterial stiffness in young adults: the Bogalusa Heart Study. Atherosclerosis 2004;176:157–64.
[30] Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and with shear stress. Circ Res 1983;53:502–11.