REPORT OF THE NHLBI WORKING GROUP ON RESEARCH IN CORONARY HEART DISEASE IN BLACKS: ISSUES AND CHALLENGES

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Despite impressive progress over the past several decades, diseases of the heart remain the leading cause of death for American men and women. The greatest proportion of these deaths are due to coronary heart disease (CHD). Over the last three decades, research on CHD has led to new diagnostic approaches and therapeutic interventions that have contributed to the decline in cardiovascular disease morbidity and mortality in both blacks and whites. However, life expectancy and rates of illness and death from CHD have not improved as much for blacks as for whites. The difference in life expectancy between white males and black males widened from 6.8 years in 1985 to 8.3 years in 1991 and between white females and black females from 5.3 years in 1985 to 5.8 years in 1991. Heart disease mortality in 1991 was almost 40% greater for black men than for white men and was 64% greater for black women than for white women.[1] In 1989-1991, of all racial/ethnic groups, death rates for heart disease in black adults 45 to 64 years of age were 84% higher than corresponding rates for whites. Blacks have not benefited fully from research achievements for a variety of reasons, including insufficient scientific data; lack of research focused on minority populations; and limited access to primary care physicians,[2] health-care resources, and technology. Available data indicate that there is a higher prevalence of smoking, hypertension, diabetes, obesity, and left ventricular hypertrophy (LVH) in blacks.[3] Blacks are also less likely to receive coronary angiography or coronary revascularization.[4-9] Recent technological advances in the basic sciences, as well as in clinical medicine, provide opportunities for innovative research to elucidate the pathogenesis of CHD in blacks, to improve management and treatment, and, ultimately, to develop effective preventive strategies.

In 1994, NHLBI convened a Working Group on Research in Coronary Heart Disease in Blacks[10] to: 1) review the state of knowledge over the past 5 years, 2) explore the pathophysiological mechanisms that underlie CHD in blacks, 3) identify opportunities for developing and assessing new and improved approaches for clinical interventions and preventive and educational measures, and 4) develop a specific plan, including scientific priorities, for NHLBI support of research on CHD in blacks for the next several years. This working group assessed the state of the science and identified research opportunities in four main areas of CHD in blacks: pathogenesis and pathophysiological mechanisms; clinical expression, diagnosis, and treatment; disease patterns and risk factors; and behavioral variables and strategies for education and prevention.

In its deliberations, the working group identified 10 priority research areas, which are listed below in order of research priority:

- treatment,
- epidemiology (data collection and analysis),
- evaluation of chest pain and diagnosis of CHD in blacks,
- prevention and behavior,
- risk factors,

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- genetics,
- vascular biology,
- left ventricular hypertrophy,
- coronary microvasculature, and
- sudden cardiac death.

HIGHLIGHTS OF RECOMMENDATIONS IN PRIORITY AREAS

Treatment

Advances in molecular genetics and vascular biology present unprecedented opportunities to understand the mechanisms of CHD in blacks and to ultimately discover the "secrets" of the prevention of or even a "cure" for ischemic heart disease. However, because blacks have lagged behind whites in the United States in benefiting from progress already made in the treatment of CHD, there is an urgent need to confirm the efficacy of currently utilized therapeutic interventions in blacks and to discover new ways to improve access to more effective and appropriate cardiovascular care. Few data are available on the clinical value, effectiveness, and efficacy of newer therapeutic modalities in blacks. Many of the new therapeutic approaches to the treatment of CHD have been tested primarily in white male populations. Currently established therapeutic algorithms have been refined in majority populations, but other algorithms may be more efficacious in black populations with higher prevalence of hypertension or diabetes, differing clinical presentations, or variations in symptom interpretation and attribution.[11] The high prevalence of hypertension and LVH in blacks makes understanding the role of these risk factors in the development and natural history of CHD in blacks a prerequisite to implementation of new therapeutic interventions. Although understanding of the interactions of LVH, hypertension, and CHD has increased recently, far fewer data exist for blacks. Little is known regarding the impact of LVH on the pathogenesis of CHD or the value of LVH regression on the prognosis of CHD in blacks. There are also limited data on the efficacy of popular antihypertensive, antianginal pharmaceutical agents, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty, atherectomy, or thrombolysis in blacks.[12,13]

Epidemiology (Data Collection and Analysis)

Attempts to explain disparities between blacks and whites in CHD morbidity and mortality, as well as differences in the use of clinical, diagnostic, and therapeutic resources, have been limited by the scarcity of comprehensive data on CHD in blacks. National surveys and clinical trial data provide valuable information but have not been thoroughly analyzed for clinical comparisons of subpopulations. Racial and ethnic identifiers are often variable or absent in existing large data sets. Ongoing observational studies (eg, Atherosclerosis Risk in Communities Study [ARIC] and Coronary Artery Risk Development in Young Adults [CARDIA]) may be informative in the future. Relationships between risk factors and CHD have been clarified in recent years and appear to be universally applicable, but data have been limited to certain regions of the United States and may not necessarily be generalizable to all blacks, particularly in rural compared to urban environments. There is a need for comprehensive assessment of existing CHD data sources, as well as the implementation of clinical surveillance programs of CHD in blacks, especially in urban settings. For more than 30 years, death rates from CHD were higher in white men than black men, but in 1989 death rates for CHD in black men over 60 years of age exceeded that in comparable white men. Epidemiological studies of CHD in blacks have also been hindered by the relative lack of culturally validated, specific, and reliable dietary assessment instruments. This may be especially important in assessing racial, gender, and genetic differences in lipids and lipoproteins and other risk factors that may be influenced by diet, such as salt sensitivity and glucose intolerance.

Evaluation of Chest Pain and Diagnosis of CHD in Blacks

Practical experience has confirmed the need for excellent clinical acumen in the diagnosis of chest pain syndromes in blacks, especially black women. Clinical studies suggest that the sensitivity and specificity of tests established in the white male population may differ for blacks.[14] Diagnostic accuracy and reliability of commonly used tests may need to be validated in blacks because of differences in the prevalence of LVH, hypertension, diabetes, or the lipid profile. Most of the currently used diagnostic tests have been validated in majority populations and their value in risk assessment, prediction of therapeutic responses, and determination of prognosis may need to be reassessed in blacks. Limited available data show higher rates of normal coronary angiograms in blacks with angina-like chest pain compared to whites, raising the possibility of abnormalities in the coronary microcirculation. However, existing angiographic data on blacks may not be representative because blacks are known to have

reduced access to cardiac diagnostic procedures, such as cardiac catheterization and CABG. In addition, the value of newer imaging techniques, such as perfusion scintigraphy, intravascular ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET), have not been adequately studied in blacks. While the use of these more expensive techniques may not be appropriate in white populations, increased difficulty in accurately diagnosing CHD in blacks may justify their use in special populations.

Prevention and Behavior

It is unclear whether disparities in health outcomes and decreased use of cardiac diagnostic and therapeutic procedures are due to cultural or ethnic differences in health-care–seeking behavior,[15] decision-making regarding diagnostic procedures, patient preferences, or elements of the patient-physician interaction. Prevention of CHD necessarily involves behavior change and the decision to change one's lifestyle. For blacks in the United States, the ability to change one's lifestyle is in part a function of socioeconomic status, sense of control of life condition, and social supports. Although behavior change is fundamental to the prevention of CHD by reducing risk factors, differences in health-care–seeking behavior between blacks and whites may also contribute to racial differences in CHD mortality and morbidity. Studies suggest that less tangible social supports may be associated with stroke mortality and hypertension.[16] The role of diminished social supports in CHD in blacks has not been thoroughly studied. Since it is likely that stress related to racial prejudice, economic disadvantage, and social disintegration is more common in blacks, understanding the relationship of these factors to CHD in blacks is likely to be helpful in elucidating strategies for lowering CHD morbidity and mortality rates. Studies also suggest that there may be differences between blacks and whites in symptom perception and symptom attribution.[17] These factors may affect adherence to prevention and treatment recommendations and may also play a role in the use of cardiac procedures and ultimate health outcomes. As the genetic factors that influence the development or manifestations of CHD are discovered, the institution of CHD prevention strategies will be critically important.

Until the relative impact of factors such as diminished access to care, limited medical knowledge, mistaken health beliefs, and inadequate coping styles can be weighed against biological variables, such as cardiovascular reactivity, lipid metabolism, and endothelial function, understanding racial differences in CHD will be difficult. Culturally and ethnically appropriate techniques for individual and community behavior modification and lifestyle change, which would affect primary and secondary prevention of CHD, have not been developed.

Risk Factors

The decline in CHD mortality and morbidity that began several decades ago and continues to the present has been coincident with widespread acceptance of the effectiveness of risk factor reduction in preventing CHD. Because prevalence rates of modifiable CHD risk factors such as hypertension, cigarette smoking, physical inactivity, and obesity have been documented to be greater in blacks than in whites, the opportunities for prevention may be greater for blacks. Lipid and lipoprotein abnormalities are no more common in blacks than whites. There is a need for more information regarding the determinants of smoking topography (kinds of cigarettes, cost of cigarettes).[18] Smoking rates in persons 18 years of age and older have declined in the general population but remain higher in blacks. What are the social, cultural, and environmental prerequisites for smoking cessation? Studies of leisure-time physical activity suggest that blacks are more sedentary and less fit than whites, independent of income and education.[19,20] Obesity, which is associated with hypertension, hyperlipidemia, hyperinsulinemia, and glucose intolerance, is more common in blacks. The prevalence of obesity is higher in black women than in white women or black men, but racial differences are less apparent between black and white men. Dietary patterns may differ slightly between blacks and whites, but foods selected by blacks and whites do not differ substantially in nutritional composition. Valid and culturally appropriate instruments for the assessment of nutrition, physical activity, and social supports are needed. Information on other risk factors is also limited. Data in blacks are conflicting about the relationship of CHD risk to elevated levels of lipoprotein (a) [Lp(a)], a genetically determined lipoprotein associated with CHD. Increased left ventricular (LV) wall thickness is more common in blacks, even in the absence of hypertension.[21] The contribution of LVH to risk of sudden death and out-of-hospital death in blacks is not clear.

Genetics

The recognition that variations in DNA sequence, genetic polymorphisms, could be used to trace inheritance of human disease pedigrees has led to the genetic

mapping of a wide array of human diseases having simple Mendelian inheritance. Further advances in human genetics has led to studies of more "complex" traits, such as heart disease, hypertension, and diabetes, which do not follow simple Mendelian recessive or dominant monogenetic inheritance. The observation of differences between blacks and whites in some heritable risk factors for CHD has led to speculation that racial differences in CHD may be explained on a genetic basis. Lp(a) levels have been suggested as a major CHD risk factor and are largely genetically determined, but levels are significantly higher in blacks. High HDL levels have an inverse correlation with CHD in whites and show genetic heritability.[22] Blacks have higher levels of HDL and a higher familial correlation in blacks than whites.[23] Studies of the differential gene frequencies between blacks and whites and their association with risk factors and disease are needed. Studies of the relationships between genotypes and phenotypes and the interaction of environment are also necessary because of incomplete gene penetrance or heterogeneity and the high likelihood that complex traits are the result of polygenetic inheritance and environmental factors. The genetic dissection of complex traits, like CHD in blacks, will require genetic linkage analysis, allele-sharing analyses of sibships and families, association studies of populations, and the application of the findings of genetic analyses of crosses in animal models.[24,25]

Vascular Biology

Basic research has enhanced understanding of the mechanisms of atherosclerotic vascular disease. The delineation of the events leading to the development of fatty streaks, plaque formation, plaque rupture, and clinical cardiac events are keys to our understanding of the pathogenesis of ischemic heart disease. These phenomena have not been delineated along racial or ethnic lines. The recognition that abnormalities in the functional properties of the endothelium may be influenced by genetic factors that contribute to the development, progression, clinical manifestations, and complications of atherosclerotic vascular disease[26,27] has prompted interest in cell-cell interaction, signal transduction, receptors, and vasoactive substances, to name just a few areas of investigation. Multiple studies have demonstrated the important role of endothelium-derived relaxing factor (EDRF)[28] (probably nitric oxide or a closely related substance)[29] in the control of vascular tone.[30] Studies of potential racial differences in the biochemical, mechanical, hemodynamic, and inflammatory modulators of endothelial function may also provide important insights into the mechanisms of CHD in blacks. With the growth of atherectomy and cardiac transplant, as well as increased numbers of blacks receiving coronary bypass surgery, opportunities to obtain tissue for histopathologic comparisons of atheromas in black and white patients with coronary disease will be possible. Elucidation of the relationship of known risk factors, such as hypertension, hyperlipidemia, and diabetes, to endothelial dysfunction is also needed. Studies of the genetic regulatory elements responsible for the expression of endothelially localized gene products important in the pathogenesis of coronary disease are especially relevant to CHD in blacks.

Left Ventricular Hypertrophy

The increased prevalence of left ventricular hypertrophy in blacks makes knowledge of its role in the pathogenesis and expression of CHD particularly important. Studies have shown that both LVH and hypertension are more common in blacks and both are important risk factors for CHD.[31] The relative role of LVH and hypertension in the pathogenesis of CHD in blacks is unclear, however. Since LVH is more common in blacks, even in the absence of hypertension, it has been postulated that the stimuli for myocardial hypertrophy may differ from those that control peripheral resistance and blood pressure.[32] The relative influence of the substances that control myocardial cell hypertrophy and also play a major role in determining vascular reactivity in blacks remains an area for potential study. It is unclear whether there are racial differences in the effects of biochemical, hemodynamic, and environmental factors in the development of myocardial hypertrophy. LVH predisposes to ventricular arrhythmias and may be a factor in sudden death in blacks. The reliability of current criteria (using electrocardiogram and echocardiography) for the diagnosis of LVH should be validated in blacks. This is particularly important in the assessment of the value of pharmaceutical regression of LVH and the impact or regression on the clinical manifestations and natural history of CHD in blacks. Whether racial differences in myocardial hypertrophy, interstitial hyperplasia, or collagen metabolism play a role in variations in the pathogenesis, diagnosis, and clinical manifestations of CHD (such as ventricular tachyarrhythmias) in blacks is an area for future basic research.

Coronary Microvasculature

Blacks with angina-like chest pain demonstrate

higher rates of angiographically normal epicardial coronary arteries than whites.[33] This disparity has led investigators to speculate that abnormalities of the coronary microvasculature may account for the ischemic type of chest pain and abnormal ECG-monitored exercise test results in these patients.[34] The endothelium is an immense "organ" located in all of the vessels in the heart. Because of the small size of the vessels that compose the microvasculature, gross examination has been limited and many of the histological studies have been restricted to microscopic examination of autopsy material. Clinical diagnosis of abnormal microcirculation has been based largely on the demonstration of reduced coronary reserve.[35] Abnormal coronary reserve is suggested when coronary blood flow does not increase after coronary resistance is lowered, usually in response to the administration of a potent coronary vasodilator, such as dipyridamole or papaverine, or to exercise. Numerous reports note the frequent occurrence of the syndrome in hypertensive patients, with and without LVH, or with hypercholesterolemia.[36] The coronary microvasculature may respond differently to pharmacological agents than the epicardial coronary arteries (the macrovasculature). Epicardial coronary flow responses to acetylcholine are selectively reduced in patients with coronary atherosclerosis and in patients with hypercholesterolemia.[37] In black patients, left ventricular hypertrophy has been shown to be an important determinant of abnormal endothelium-independent coronary flow reserve.[38] Endothelium-mediated microvascular dysfunction has been demonstrated in patients with angiographically normal coronary arteries,[39] atherosclerosis, diabetes, left ventricular hypertrophy, and hypercholesterolemia,[40] but there have been few studies in blacks. Newer cardiac biopsy techniques have made examination of tissue in patients feasible.

Sudden Cardiac Death

Death certificates and autopsy data indicate that more blacks than whites die out of the hospital or experience out-of-hospital cardiac arrest.[41-43] Studies have not confirmed a relationship between race and access to emergency cardiac care or outcome of cardiac resuscitation. Out-of-hospital deaths may also be related to delay in the prehospital phase of acute myocardial infarction care.[44] LVH may be associated with increased atrial and ventricular arrhythmogenesis and potentially with sudden death. It is not clear whether there are racial differences in the electrophysiological substrate in blacks related to the increased prevalence of LVH and hypertension. Diminished coronary reserve may also be more common in blacks and predispose to life-threatening arrhythmias. The value of newer electrophysiological monitoring techniques in predicting risk of sudden death is also not clear, and the value of signal-averaged ECG in predicting arrhythmias has not been well studied in blacks. Studies of diurnal variation in sudden death and other cardiac events are needed to identify the endocrine, paracrine, or autocrine factors that are most important in the pathogenesis of these events. Criteria for identifying individuals at high risk of arrhythmias and sudden death should be validated in blacks. Investigations are also needed on the relationship of traditional risk factors (eg, LVH, hypertension, hyperlipidemia) and behavioral and environmental factors to the risk of sudden death and life-threatening ventricular arrhythmias.

CONCLUSION

It is evident that there are important differences in the biological, environmental, social, and economic context in which CHD develops in blacks. It is a challenge to determine whether differences in phenotypic characteristics common in blacks, such as high blood pressure and LVH, play a primary role in the pathogenesis of CHD in blacks or are merely markers for more fundamental differences in the mechanisms of disease. Establishment of multidisciplinary research efforts focusing on the many unresolved questions regarding coronary heart disease in blacks is necessary. It is also unclear whether differences in the biology of CHD, the clinical expression of common pathogenetic processes, or differences in diagnosis and treatment account for reported racial differences in outcomes. Differences in access to cardiovascular care, the impact of behavioral risk factors, or variations in clinical health-care delivery may be as responsible for the well-documented disparities in health outcomes and resource utilization as any genetic or biological mechanisms. Understanding the reasons for racial differences in the pathogenesis, pathophysiology, epidemiology, and clinical expression of CHD will provide increased understanding of CHD in all populations.

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