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CHAPTER SIX

Atherosclerosis and Cognitive Functioning

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It is well recognized that the incidence and severity of cognitive impairment and dementia increase with age (Graham et al., 1997; Ritchie & Kildea, 1995). However, aging does not inevitably lead to cognitive decline, although subtle changes in cognitive function may occur with age (Rapp & Amaral, 1992). An expanding literature indicates that both subtle alterations in cognition and more severe deficits may be associated with hypertension, atherosclerosis, and other cardiovascular (CV) diseases or risk factors (Breteler, Claus, Grobbee, & Hofman, 1994; M. F. Elias, Wolf, D'Agostino, Cobb, & White, 1993; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Launer, Feskens, Kalmijn, & Kromhout, 1996; Waldstein, Manuck, Ryan, & Muldoon, 1991). The purpose of this chapter is to review the available evidence linking atherosclerosis and cognitive impairment and decline.

This chapter is divided into five sections. We begin by briefly discussing the pathophysiology of atherosclerosis, including clinical manifestations of the disease and three hypotheses about the initiation of atherogenesis. Then we discuss some epidemiological aspects of atherosclerosis, including current statistics regarding prevalence of atherosclerosis and risk factors for atherosclerosis. Next,

we discuss cross-sectional and longitudinal evidence for an association between atherosclerosis and poorer cognitive functioning. We proceed to a discussion of potential mechanisms underlying the associations between atherosclerosis and cognitive function, which is followed by a discussion of the clinical relevance of these associations. We conclude with an overall summary and suggestions for future research.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is a disease of the arteries in which the lumen of the artery becomes narrowed by fatty deposits and fibrous tissue that accumulate on the intimal layer of the vessel wall. Atherosclerotic lesions originate as fatty streaks, characterized by subendothelial accumulation of large foam cells that are derived from macrophages and consist of intracellular lipids. Fatty streaks typically develop early in life and can be found in the coronary arteries and aorta of most people by age 20. The more advanced atherosclerotic lesions, fibrous plaques, develop from the fatty streaks and often contain a necrotic core of degenerating foam cells, cholesterol crystals, and cellular debris separated from the arterial lumen by a fibrous cap of connective tissue. Fibrous plaques are found, in order of frequency, in the abdominal aorta, coronary arteries, popliteal arteries, descending thoracic aorta, internal carotid arteries, and the circle of Willis (Bhattacharyya & Libby, 1998). It is not uncommon for plaques to occur in multiple locations or at multiple arterial sites. In other words, atherosclerosis tends to co-occur in the coronary, carotid, cerebral, and peripheral arteries. Atherosclerotic plaques typically develop gradually and go unnoticed until clinical symptoms develop.

Clinical manifestations or complications of atherosclerosis may result from fibrous plaques in several ways. For example, fibrous plaques may become calcified, thereby increasing the rigidity of the blood vessel and making the blood vessel more fragile. In addition, fibrous plaques are prone to rupture or ulceration and thus may induce thrombosis that can occlude the vessel and lead to myocardial infarction or stroke. Hemorrhage into the plaque may occur if the fibrous cap or any of the capillaries that vascularize the plaque ruptures. The resulting hematoma may further narrow the lumen of the artery and obstruct blood flow. Emboli may occur at distal sites if atherosclerotic plaques become fragmented. Finally, vessel walls become weakened from plaque formation, thus increasing the likelihood of aneurysm formation and rupture. Complications of atherosclerosis include ischemia, angina pectoris, myocardial infarction, stroke, and claudication (Bhattacharyya & Libby, 1998).

The pathophysiologic characteristics of atherosclerosis have long been known, whereas the mechanisms by which atherosclerosis develops are less completely understood. Three important hypotheses about the core processes or

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mechanisms related to the initiation of atherogenesis have been postulated, and each has supporting evidence. Endothelial denudation, activation, or injury are considered the initiating event(s) in the *response-to-injury* hypothesis, oxidation of lipoproteins is thought to be the primary event in the *lipoprotein oxidation* hypothesis, and subendothelial retention of lipoproteins is considered the initiating event in the *response-to-retention* hypothesis. Regardless of the initiating event, it is recognized that several important steps or components are involved in atherogenesis, including involvement of the smooth-muscle cells and endothelial cells of the vessel wall, accumulation of lipoproteins, circulating platelets and monocytes, and cytokine mediation (Ross, 1993).

Several lines of evidence suggest that the primary event in atherogenesis is injury to the arterial endothelium and thus support the *response-to-injury* hypothesis (Ross, 1993; Ross & Glomset, 1976a, 1976b; Ross, Glomset, & Harker, 1977). Large shear stress gradients and fluid mechanical forces can induce morphological and functional changes in the endothelium (DePaola, Gimbrone, Davies, & Dewey, 1992; Dewey, Bussolari, Gimbrone, & Davies, 1981). Areas susceptible to flow turbulence and shear stress—for example, at arterial branch points such as the carotid bifurcation—are where most advanced atherosclerotic lesions occur (Asakura & Karino, 1990; DePaola et al., 1992). In addition, animal studies indicate that atheromatous lesions develop in response to injury to the endothelium (J. R. Kaplan, Pettersson, Manuck, & Olsson, 1991), and several known risk factors for atherosclerosis (e.g., cigarette smoking, high cholesterol, diabetes, and hypertension) are associated with endothelial dysfunction (Ross, 1993; Vogel, 1997). Research also has found a link between infectious agents such as cytomegalovirus, herpesvirus, and chlamydia pneumoniae and atherosclerosis, suggesting that the development of atherosclerotic lesions may be part of an infectious process that damages the endothelium (Nieto, 1998; Nieto et al., 1997). Further support for the role of infection in atherosclerosis comes from the observation that fatty streaks, the earliest type of atherosclerotic lesion seen in children and adolescents, consist only of T lymphocytes and monocyte-derived macrophages (Ross, 1999).

Oxidative modification of low-density lipoprotein (LDL) or other lipoproteins also is involved in the pathogenesis of atherosclerosis and is thought by some to be the primary or initiating event (Salonen et al., 1992; Witztum, 1994; Witztum & Steinberg, 1991). This is called the *lipoprotein oxidation hypothesis* of atherosclerosis. Oxidized LDL is necessary for cellular accumulation of cholesterol and uptake of macrophages (Berliner et al., 1995). Additionally, lipid peroxidation, which occurs primarily in the intimal layer of the arteries, generates a variety of biologically active substances that can have diverse biochemical, hormonal, and immunologic effects that are proatherogenic (Berliner et al., 1995; Witztum, 1994). Lipid peroxidation, mediated by free radicals, may induce endothelial injury or dysfunction, enhance platelet aggregation, and increase uptake of LDL into the arterial walls (Hennig & Chow, 1988).

It also has been argued that subendothelial retention of atherogenic lipoproteins is the primary pathogenic process in atherosclerosis and is both necessary and sufficient for the development of atherosclerotic lesions (Guyton & Klemp, 1996; Simionescu & Simionescu, 1993; Williams & Tabas, 1995). Support for this *response-to-retention* hypothesis derives largely from animal studies, which demonstrate substantial and rapid accumulation and retention of atherogenic lipoproteins within the arterial walls following induction of hypercholesterolemia and in prelesional focal arterial sites susceptible to atheromatous lesions (Nievelstein, Fogelman, Mottino, & Frank, 1991; Schwenke & Carew, 1989a, 1989b). Support also comes from the observation that the core of atherosclerotic plaques, which consists of extracellular lipids that are rich in free cholesterol—including oxidized LDL, proteins, and peptides—can be found in fatty streaks in the human aorta in the very early stages of lesion development and prior to formation of fibrous plaques (Guyton & Klemp, 1996).

EPIDEMIOLOGY OF ATHEROSCLEROSIS

CV diseases, including hypertension, coronary heart disease (CHD), stroke, atherosclerosis, congestive heart failure, rheumatic fever and rheumatic heart disease, congenital heart defects, and arrhythmias, are the leading causes of death for men and women in the United States and most westernized countries. In 1996 more than 959,000 deaths in the United States were attributed to one or more CV diseases, accounting for more than 41% of all deaths; of these, 50% were attributed to CHD and 2% were attributed to atherosclerosis (American Heart Association [AHA], 1998). It is critical to note, however, that atherosclerosis is the underlying disease process for the vast majority of CHD and thus can be considered the leading cause of death in the United States. The prevalence of CHD among American adults over the age of 20 is 7.2% for the general population (AHA, 1998), with an estimated 12 million Americans alive today who have a history of CHD or atherosclerosis.

Several risk factors for atherosclerosis or CHD have been identified. These include biological and disease-related factors, such as diabetes, hypertension, hypercholesterolemia, homocysteine, and Lp(a); demographic factors, such as older age and lower socioeconomic status; and behavioral and psychosocial factors, such as smoking, sedentary lifestyle, diet, obesity, and stress (Marmot & Elliott, 1992). Research shows that many of these risk factors are related to both the prevalence and incidence of atherosclerosis in the population as well as to accelerated progression of the disease over time. Moreover, the prevalence of certain risk factors—for example, physical inactivity and obesity—appears to be increasing and represents a growing threat to the health of populations (AHA, 1998).

LITERATURE REVIEW AND METH

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LITERATURE REVIEW AND METHODOLOGIC CRITIQUE

Several recent studies have examined the impact of atherosclerosis or risk factors for atherosclerosis on cognitive performance and neuropsychological functioning. To date, much of the evidence for such an association comes from cross-sectional studies, although some prospective evidence is now available. The present lack of prospective or cohort studies is partly due to the fact that until relatively recently it was difficult to reliably assess the extent and severity of atherosclerosis without invasive procedures. However, advances in ultrasonography have allowed scientists and clinicians to noninvasively measure atherosclerosis in certain arterial beds and in the carotid arteries in particular. Indeed, much of the evidence reviewed next comes from studies in which atherosclerosis in the carotid arteries was measured noninvasively. It should be noted that research and clinical data have shown that carotid atherosclerosis is a reliable marker of the atherosclerotic process throughout the body, including the coronary arteries (Grobbee & Bots, 1994; Salonen & Salonen, 1991; Wong, Edelstein, Wollman, & Bond, 1993).

Cross-Sectional Findings

G. A. Kaplan, Everson, Koivisto, Salonen, and Salonen (1996) reported that mild to moderate carotid atherosclerosis is significantly related to poorer cognitive performance in a subset of more than 500 participants from the Kuopio Ischemic Heart Disease Risk Factor Study (Salonen, 1988), an ongoing epidemiologic investigation of risk factors for ischemic heart disease and associated morbidity and mortality in a population-based sample of middle-aged men. These men completed a series of five brief neuropsychological tests as part of a follow-up examination, and carotid atherosclerosis was assessed noninvasively using B-mode ultrasonography of the right and left common carotid arteries (CCA). Measures of carotid atherosclerosis included mean intimal–medial thickness (IMT) of the CCA, the mean of approximately 100 measurements in the right and left CCA, considered a measure of the overall atherosclerotic process in the carotid arteries, and maximal IMT, the average of the points of maximum thickness from the right and left CCA and indicative of the depth of intrusion of atherosclerotic thickening into the lumen in this part of the arteries.

Age-adjusted regression models revealed that mean and maximum atherosclerotic thickening were significantly associated with lower scores on the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a measure of overall cognitive abilities; Russell's adaptation of the Visual Reproduction Test–Immediate Recall (Lezak, 1983), a test of nonverbal memory; the Trail Making Test, Form B (Trails B; Reitan, 1958), a measure of cognitive flexibility and frontal lobe functioning; a verbal fluency test on letters (Borkowski,

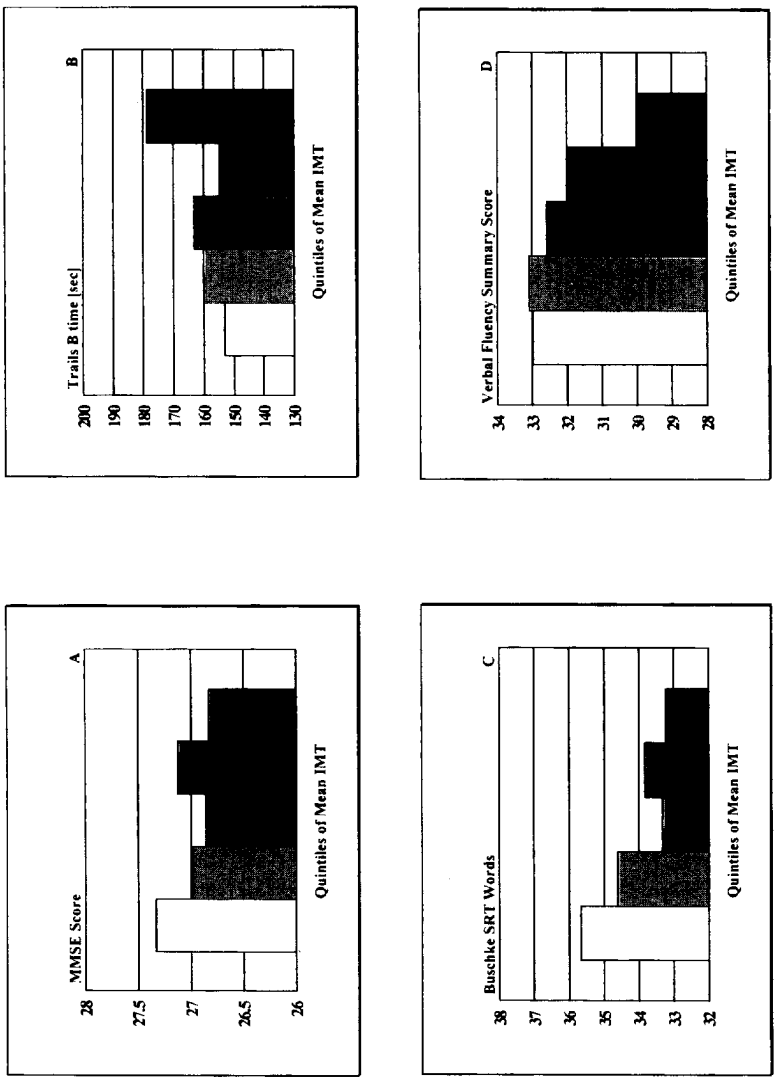

FIG. 6.1. Quintiles of atherosclerosis, assessed as intimal–medial thickness (IMT) of the common carotid arteries, and age-adjusted performance on the Mini-Mental State Exam (MMSE; Panel A); the Trail Making Test, Form B (Trails B; Panel B); the Buschke Selective Reminding Test (SRT; Panel C); and verbal fluency (Panel D) among middle-aged men from the Kuopio Ischemic Heart Disease Risk Factor Study (Salonen, 1988). Men with the least atherosclerotic thickening in the carotid arteries are represented by the white bars, and those with the greatest degree of atherosclerosis are represented by the black bars.

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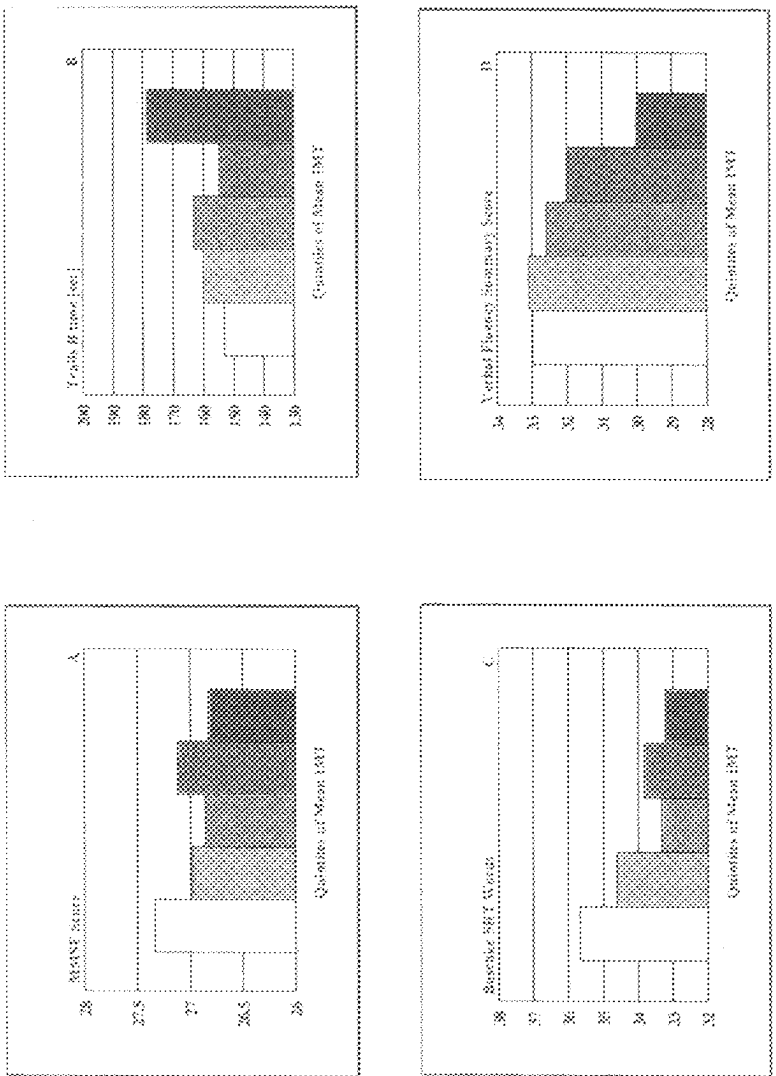

FIG. 6.1. Quintiles of atherosclerosis, assessed as intimal-medial thickness (IMT) of the common carotid arteries, and age adjusted performance on the Mini-Mental State Exam (MMSE; Panel A), the Trail Making Test, Form B (Trails B; Panel B), the Buschke Selective Reminding Test (SRT; Panel C), and verbal fluency (Panel D) among middle-aged men from the Kuopio Ischemic Heart Disease Risk Factor Study (Salonen, 1988). Men with the least atherosclerotic thickening in the carotid arteries are represented by the white bars, and those with the greatest degree of atherosclerosis are represented by the black bars.

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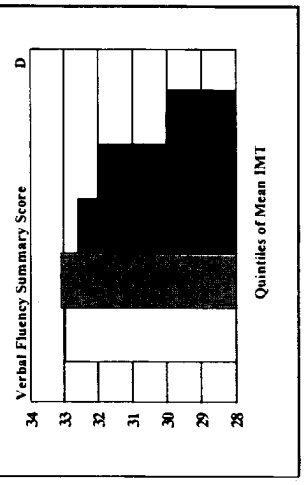
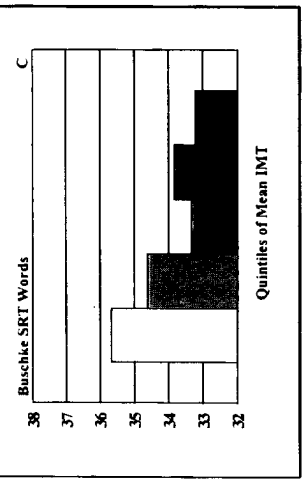
Benton, & Spreen, 1967); and the Buschke Selective Reminding Test (SRT; Buschke & Fuld, 1974), a measure of short- and long-term verbal memory. Results for the MMSE, Trails B, Buschke SRT, and verbal fluency test are shown in Fig. 6.1 (Panels A–D). Data are graphed by quintiles of mean IMT, and there is a clear pattern of worsening performance from individuals with the least disease (represented by the white bars) to those with the most atherosclerosis (represented by the black bars) across the four neuropsychological tests. The pattern of observed findings suggests an involvement of atherosclerotic processes in cognitive functioning, even at a relatively young age (the mean age of the participants in this study was 56.9 years).

Several other studies also provide cross-sectional evidence for an association between poorer cognitive function and atherosclerosis. Auperin et al. (1996) reported modest inverse associations between carotid atherosclerosis and poorer cognitive performance in a community sample of approximately 500 French men, ages 59 to 71. After adjusting for vascular risk factors, the prevalence of atherosclerotic plaques in the carotid arteries, assessed ultrasonographically, was inversely related to performance on the MMSE (Folstein et al., 1975) and the Digit Symbol Substitution test from the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler, 1981), a measure of visual–motor speed and attention and concentration. In men with evidence of carotid plaques, poorer cognitive performance was modestly related to greater atherosclerotic thickening in the carotid arteries. However, no associations between atherosclerosis and cognitive performance were noted among the more than 700 female participants in this study. Auperin et al. reported that this study cohort was better educated and had higher cognitive scores than the general age-matched French population, and thus participation was probably selective. Nonetheless, the pattern of findings indicates consistent mild decrements in cognitive function in men with more numerous atherosclerotic plaques.

Similarly, a recent report from the Atherosclerosis Risk in Communities (ARIC) study found that the WAIS–R Digit Symbol Substitution test (Wechsler, 1981) was inversely related to ultrasonographically assessed IMT of the carotid arteries in a sample of nearly 14,000 middle-aged men and women without a history of stroke or transient ischemic attacks (Cerhan et al., 1998). Performance on the Digit Symbol test also was negatively related to fibrinogen level, smoking, and depressive symptoms in both sexes. In women, IMT also was related to performance on the Delayed Word Recall Test (Knopman & Ryberg, 1989), a measure of long-term memory, but the association became nonsignificant in the multivariate model. In this study the differences in performance on the tests of cognitive function between participants with the least carotid wall thickness (bottom quintile of the distribution) and those with the greatest carotid wall thickness (top quintile) were quite small (on average, between 0.1 and 0.2 *SD*) and thus, as the authors noted, may not necessarily lead to clinically meaningful deficits with age.





Panel C); and verbal fluency (Panel D) among middle-aged men from the Kuopio Ischemic Heart Disease Risk Factor Study (Salonen, 1988). Men with the least atherosclerotic thickening in the carotid arteries are represented by the white bars, and those with the greatest degree of atherosclerosis are represented by the black bars.

Additional, albeit indirect, evidence for the role of atherosclerosis in cognitive function comes from studies of peripheral vascular disease (PVD; for a review, see chap. 7). For example, Breteler and colleagues (1994) reported that participants in the Rotterdam Study with an ankle–brachial index of less than 0.90, an accepted clinical indicator of PVD, or those with ultrasonographically measured plaque in the internal carotid arteries, had worse cognitive performance, as assessed by the MMSE and after adjustment for age and education, than their counterparts without significant PVD. Breteler et al. importantly noted that although absolute differences in MMSE scores between groups were small and of unknown clinical significance, they reflected an overall shift in the population toward lower levels of cognitive functioning and thus resulted in a higher proportion of participants who met the criteria for dementia. In other words, these data demonstrate that atherosclerosis may account for a considerable proportion of cognitive impairment at the population level.

Another study of elderly patients with PVD but without a history of stroke or clinically evident cerebrovascular disease identified neuropsychological deficits consistent with mild vascular-related brain dysfunction (Phillips & Mate-Kole, 1997). This study compared 29 PVD patients with 29 age- and education-matched patients with documented atherothrombotic cerebral infarcts and 13 healthy elderly control participants, also matched on age and education. PVD patients performed significantly worse than controls on tests of executive function, learning and memory, attention and concentration, and visuospatial and constructional ability. Performance was worse with increasing severity of peripheral atherosclerosis and prevalent ischemic heart disease, suggesting that multiple manifestations of atherosclerosis contribute to greater risk of cognitive dysfunction. Despite a small sample size, this study importantly shows that PVD patients without evidence of prior stroke or neurological deficits, a group that clinically is generally assumed to have normal cognitive function, have a pattern of neuropsychological deficits that is similar to that seen in people with cerebrovascular disease.

Not all data support the hypothesis that atherosclerosis is related to poorer cognitive function, however. No associations between cognitive impairment, assessed by the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), and coronary artery disease or other vascular disease, determined by medical records review, were noted in a sample of nearly 4,000 noninstitutionalized primary-care patients aged 60 and older (Callahan, Hendrie, & Tierney, 1995). Similarly, Ahto et al. (1999) found no differences in cognitive impairment, assessed by the MMSE, between CHD cases and controls in a community sample of noninstitutionalized men and women aged 64 or older. CHD cases were defined as having a medically confirmed history of myocardial infarction or chest pain on effort or ischemia during an electrocardiogram. Ahto et al. noted that several of the cross-sectional studies that have found positive associations between CHD and cognitive impairment have included more severely ill cardiac patients, and they

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UNDERLYING MECHANISMS

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neral vascular disease (PVD; for a re-
d colleagues (1994) reported that par-
nkle–brachial index of less than 0.90,
hose with ultrasonographically mea-
s, had worse cognitive performance,
ent for age and education, than their
teler et al. importantly noted that al-
es between groups were small and of
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PVD but without a history of stroke
e identified neuropsychological defi-
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Questionnaire (Pfeiffer, 1975), and
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4,000 noninstitutionalized primary-
Hendrie, & Tierney, 1995). Similarly,
gnitive impairment, assessed by the
a community sample of noninstitu-
. CHD cases were defined as having
infarction or chest pain on effort or
to et al. noted that several of the
tive associations between CHD and
severely ill cardiac patients, and they

suggested that more complicated forms of CHD, such as cardiac failure, may be related to cognitive dysfunction.

In sum, available cross-sectional data are suggestive, though not entirely consistent. More definitive tests of the hypothesis would come from longitudinal studies of the role of atherosclerosis in cognitive impairment. Although limited in scope, currently available longitudinal data are reviewed next.

Longitudinal Findings

A recent report from the Cardiovascular Health Study (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999) found that baseline assessments of carotid artery atherosclerosis, systolic blood pressure (BP), ankle–arm BP, and prevalent diabetes were significantly related to 7-year declines in cognitive functioning, as measured by the modified MMSE (Teng & Chui, 1987) and the WAIS–R Digit Symbol Substitution test (Wechsler, 1981). Moreover, among participants in that study who had carotid atherosclerosis, diabetes, or PVD, those with at least one apolipoprotein E (ApoE; a plasma protein involved in cholesterol metabolism and transport) ε4 allele showed dramatically greater rates of cognitive decline than those without the ε4 allele.

Similarly, Slooter et al. (1998) found that among 838 Rotterdam Study participants who were nondemented at baseline, those who were ApoE ε4 carriers and who had at least two indicators of atherosclerosis at baseline (i.e., history of myocardial infarction, history of stroke, ultrasonographically assessed carotid artery atherosclerosis, or an ankle–arm index < 90), indicative of more severe disease, had a significantly lower MMSE score at follow-up nearly 3 years later compared to non-ApoE ε4 carriers without atherosclerosis. These effects were not confounded by age, education, sex, or family history of dementia. It is interesting that the main effects of ApoE ε4 and atherosclerosis on cognitive decline were small and nonsignificant, suggesting that the gene–environment interaction is critical in determining cognitive decline in the elderly.

To our knowledge, no other longitudinal studies directly measuring atherosclerosis and cognitive impairment have been published. Clearly, additional prospective investigations are needed to explicate the causal pathways linking atherosclerosis to decrements in cognitive functioning. Moreover, longitudinal findings will help establish or clarify the clinical significance of the generally mild cognitive impairments associated with atherosclerosis that have been identified to date and will provide important information regarding both treatment and prevention strategies.

UNDERLYING MECHANISMS

Atherosclerosis may adversely affect cognitive performance directly or indirectly, through a variety of mechanisms. As noted above, atherosclerotic plaques may

induce clinical CV or cerebrovascular symptoms through calcification, rupture or ulceration, hemorrhage, fragmentation, weakening of the vessel wall and aneurysm, or some combination of these. Plaques that occur in the carotid or cerebral arteries thus could decrease or obstruct blood flow to the brain, thereby increasing the likelihood of cognitive dysfunction and impairments.

Alternatively, atherosclerotic lesions, cerebrovascular disease, and cognitive performance difficulties may result from or be influenced by a common genetic factor or by metabolic factors. For example, several studies have found that ApoE, and particularly the ε4 allele, is associated with declining cognitive function and increased risk of cognitive impairment (Feskens et al., 1994; see also chap. 3 of this book, for a review). Moreover, ApoE is related to greater prevalence of atherosclerosis and higher levels of total serum cholesterol and LDL cholesterol (Cattin et al., 1997; Kaprio, Ferrell, Kottke, Kamboh, & Sing, 1991).

Metabolic abnormalities that may influence cognitive function, atherosclerotic processes, and cerebrovascular disease included impaired insulin metabolism or insulin abnormalities, such as those seen in diabetes mellitus or hyperinsulinemia, and high levels of homocysteine, an amino acid that is a metabolic byproduct of methionine, an essential amino acid. High levels of homocysteine in the blood are related to poorer cognitive performance and increased risk of vascular dementias and Alzheimer's disease (Clarke et al., 1998; McCaddon, Davies, Hudson, Tandy, & Cattell, 1998) as well as atherosclerosis, thrombosis, and other CV and cerebrovascular diseases (den Heijer, Rosendaal, Blom, Gerrits, & Bos, 1998; Voutilainen, Alfthan, Nyyssonen, Salonen, & Salonen, 1998), although not all data are supportive (Evans, Shaten, Hempel, Cutler, & Kuller, 1997). Insulin abnormalities are related to increased risk of atherosclerosis, hypertension, and stroke (Folsom et al., 1997; Lukovits, Mazzone, & Gorelick, 1999; Salonen et al., 1998) and poorer cognitive functioning, including memory impairments, visuospatial dysfunction, and abstract-reasoning deficits (Helkala, Niskanen, Viinamäki, Partanen, & Uusitupa, 1995; Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; see also chap. 4 of this book). It is interesting that a recent report from the Framingham Study showed that individuals with non-insulin–dependent diabetes *and* hypertension had the poorest cognitive performance (P. K. Elias et al., 1997), demonstrating an important interaction between CV disease and impaired insulin metabolism in relation to cognition.

Taken together, the available literature suggests several metabolic, genetic, and hemodynamic mechanisms by which atherosclerosis may be linked to impaired cognitive performance. These mechanisms may have direct or indirect effects, and the effects may be additive or interactive, thereby markedly increasing the risk for atherosclerosis and cognitive impairments in susceptible individuals. For example, as noted above, high BP and insulin abnormalities appear to interact and lead to greater cognitive deficits than either disorder alone (P. K. Elias et al., 1997). Moreover, as discussed earlier in this chapter, two recent studies

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CLINICAL RELEVANCE

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(Haan et al., 1999; Slooter et al., 1998) reported greater cognitive deficits or declines in people with atherosclerosis who had at least one ApoE ε4 allele compared to people without the ε4 allele or to those with neither risk factor. Additional work is needed to further examine potential interactions among genetic, hemodynamic, and metabolic factors that may underlie the association between atherosclerosis and cognitive impairments.

CLINICAL RELEVANCE

Many deficits in cognitive abilities observed in relation to atherosclerosis are relatively small, and the clinical significance of minor cognitive decrements has yet to be determined. However, a recent study found that a 1-*SD* difference in performance on the WAIS–R Digit Symbol Substitution test (Wechsler, 1981) was associated with a significant 44% excess risk of mortality over 5 years in a sample of community-dwelling older men, after taking into account the effects of age, education, smoking, BP, total serum cholesterol, prevalent ischemic heart disease or history of myocardial infarction or stroke, or self-reported history of cancer (Swan, Carmelli, & LaRue, 1995). It is interesting that, in Swan et al.'s (1995) study, among men without a history of cancer those with the poorest survival rate were the ones who scored 30 or lower on the Digit Symbol test—a score that is still considered in the normal range. In other words, subclinical cognitive deficits were associated with greater mortality risk, suggesting that some of the mild decrements in cognitive performance seen with atherosclerosis may have important health effects. Alternatively, these deficits may be a marker of poorer overall health.

The clinical relevance of the data reviewed here is highlighted by the observation that declining cognitive function and atherosclerotic diseases show similar patterns of increasing frequency with increasing age. Work by Breteler and Hofman and their colleagues (Breteler et al., 1994; Hofman et al., 1997) suggests an overall downward shift in the elderly population toward lower levels of cognitive functioning with increasing age and greater atherosclerosis, indicating that a considerable proportion of cognitive decline in the elderly population may be vascular in origin. Research also suggests that subclinical vascular disease is a risk factor for poorer cognitive function. Taken together, these lines of evidence imply that interventions to delay or reduce atherosclerosis may delay onset of cognitive decline in elderly people.

Finally, both atherosclerosis and cognitive decline are associated with greater morbidity, including greater functional limitations. Several cross-sectional studies have demonstrated that cognitive impairment and atherosclerosis are associated with limitations in activities of daily living (ADL) in men and women age 65 and older (Bassett & Folstein, 1991; Boult, Kane, Louis, Boult, & McCaffrey, 1994; Institute of Medicine, 1991), and a recent longitudinal study found that

lower levels of cognitive functioning predicted 3-year onset of new ADL limitations after controlling for history of chronic diseases and incident health problems (Moritz, Kasl, & Berkman, 1995). Decreases in cognitive abilities also significantly predicted dementia in the elderly (van Duijn, 1996).

SUMMARY AND FUTURE DIRECTIONS

The evidence reviewed in this chapter shows fairly consistent support for the hypothesis that atherosclerosis contributes to mild yet consistent deficits in cognitive performance in middle-aged and elderly men and women. However, to date most of this evidence comes from cross-sectional studies, with very few longitudinal studies of cognitive performance and atherosclerosis reported in the literature. As noted previously, prospective data are needed to assess the causal pathways and the underlying mechanisms by which atherosclerosis may contribute to cognitive declines, to determine the clinical significance of the generally mild decrements in cognitive abilities related to atherosclerotic vascular disease that have been reported and to inform treatment and prevention strategies.

Studies to date have used a variety of measures of cognitive function, some of which are useful as dementia screening tools (e.g., the MMSE) but may be less sensitive to mild decrements or changes in cognitive function thought to result from CHD or atherosclerosis. Future research could benefit from a standardized approach to assessing cognitive functioning, which would allow more reliable comparisons across studies or populations. Moreover, prior studies have varied in terms of the health status of the populations or samples studied. Some cross-sectional studies have found that more severely ill cardiac patients show cognitive deficits, whereas less sick patients do not. It also is plausible that more severe CHD or atherosclerosis contributes to cognitive declines over time, although data supporting this hypothesis are limited at present. Thus, to fully characterize the role that atherosclerosis plays in cognitive dysfunction it will be important to systematically examine the impact of atherosclerotic disease on cognitive abilities, independent of other diseases and risk factors, particularly those associated with aging. Research also is needed to determine if the effect of atherosclerosis on cognitive functioning is confounded or modified by other risk factors for atherosclerosis; for example, male sex, older age, or lower socioeconomic position.

Clearly, atherosclerosis and cognitive impairment can lead to significant loss of quality of life for middle-aged and elderly adults. The elderly are a growing proportion of the population, with an estimated 15% to 18% of the population expected to be age 65 or older by the year 2030 (U.S. Bureau of the Census, 1986). Therefore, atherosclerotic diseases, cognitive impairment, and their consequent effects on health and well-being are a major public health concern that will be increasing in the coming years.

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CHAPTER SEVEN

Thinking On You
A Neuropsychol
of Peripheral Vas

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Concordia University and
Sir Mortimer B. Davis–Jewish Gen

This chapter concerns neurops
atherosclerotic occlusive disease
referred to more generally as *pe*
review risk factors, pathophysio
PVD. The association between a
vascular disease (CVD) is discu
impairment in patients with PV
issues are highlighted. Finally, di

ATHEROSCLEROSIS

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