Vascular Function in Older Adults with Depressive Disorder

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Background: Cerebrovascular disease plays an important role in depressive disorder, especially in older adults. An understanding of vascular function in depression is important etiologically and to develop innovative treatments that may improve prognosis by ameliorating vascular damage.

Methods: This study assessed endothelial function, arterial stiffness, and atherosclerosis in a variety of vessel beds in 25 elderly subjects with depressive disorder compared with 21 nondepressed control subjects. Subjects underwent pulse wave velocity, pulse wave analysis, carotid intima media thickness analysis, and magnetic resonance imaging. A subset (16 patients and 15 control subjects) had assessment of biopsied small artery dilatation to acetylcholine to further assess endothelial function.

Results: The mean sample age was 72.4 years with an average age at onset for depression of 60 years. Mean carotid intima media thickness was significantly higher in depressed subjects ($p < .01$). Pulse wave velocity was 1.6 m/sec higher in depressed subjects (borderline significance). There was a significant reduction in the dilatation response to acetylcholine in preconstricted small arteries ($p = .01$). On magnetic resonance imaging, depressed subjects had significantly more dilated Virchow–Robin spaces in the basal ganglia ($p = .01$). Depressed subjects had greater volume of white matter lesions in all regions, but this did not reach statistical significance. There were no baseline differences in vascular risk.

Conclusions: Depression in the elderly is associated with poorer endothelial function and more atherosclerosis. This is associated with a greater white matter hyperintensities lesion load and basal ganglia microangiopathy. The use of vasoprotective drugs to improve endothelial function or retard atherosclerosis as depression-modifying agents should be explored.

Key Words: Atherosclerosis, depression, endothelial function, geriatric, mood disorders, old age, vascular function

In older patients with depression, cerebrovascular disease may predispose to, precipitate, or perpetuate depression, which is the basis of the vascular depression hypothesis (1). An important component of the hypothesis is a consistent finding of an increased white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) in depressed subjects compared with nondepressed control subjects (2,3). These hyperintensities are taken to indicate white matter damage (4). A range of pathologic changes can lead to WMH, but postmortem studies support ischemia as an important cause (5,6). However, ischemia is an end product of a range of potential vascular mechanisms, including systemic (atheroma, endothelial dysfunction, and inflammation) (7–9), hemodynamic (hypotension) (10,11), and localized (vascular damage to frontostriatal circuitry and subcortical regions) (12,13). Clarifying vascular processes that may underlie visualized WMH is of relevance both to etiology and to potential new treatment approaches aimed at ameliorating brain injury associated with depression (14).

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The literature regarding vascular mechanisms in depressive disorder is small compared with that for WMH but suggests that endothelial dysfunction and atherosclerosis occur. Endothelial dysfunction is the first step in atherogenesis and the pathway to atherosclerosis. In two studies of younger depressed adults (under 60 years), flow-mediated dilatation (FMD), an indirect measure of endothelial function, was impaired (15,16). Old age depression (aged 60 and older) has been shown to be associated with increased pulse wave velocity (PWV), a measure of arterial stiffness (17), and increased intima media thickness (IMT) (7,18), a measure of atherosclerosis. Augmentation index as measured by pulse wave analysis (PWA) is another measure of arterial stiffness and correlates with endothelial function (19).

The aim of this study was to perform measures of vascular function in older patients with depression and concomitantly measure structural brain abnormalities on MRI. Drawing on the literature, the following vascular measures were chosen: PWV and PWA for arterial stiffness and IMT for atherosclerosis. FMD when used in small samples is not considered reliable (20), thus it was decided to use a novel technique successfully applied to small groups of subjects as an assessment of endothelial function. This involves the acquisition of small vessels from gluteal fat biopsy and analysis in vitro (8).

Although other imaging modalities exist to assess white matter integrity (e.g., diffusion tensor imaging) (4), most work exploring links between depression and cerebrovascular disease has been conducted using measures of WMH, either with visual rating scales (3) or automated or semiautomated assessment of volume (12,13,21). Additionally, we have demonstrated abnormally dilated Virchow–Robin spaces (VRS), notably in the basal ganglia, in geriatric depression (22). Basal ganglia lesions are known to be predictive of depression (23). VRS are perivascular spaces that when abnormally dilated are thought to indicate cerebral microangiopathy (24–26).

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As discussed, if WMH is the product of cerebral ischemia, there are several possible mechanisms. Two of these, endothelial dysfunction and atherosclerosis, are explored in this study. The main hypothesis was that in late-life depressive disorder, there is impairment of vascular function (as assessed by endothelial function, arterial stiffness, and atherosclerosis) compared with a nondepressed control group. Secondary hypotheses were first that neuroimaging markers suggestive of ischemia as assessed by WMH and cerebral microangiopathy as measured by VRS occur more commonly in depressed subjects and second that there is a correlation between WMH and peripheral vascular function.

Methods and Materials

Subjects

Following ethics committee approval, patients with depressive disorder were recruited from the case registers of two clinical secondary care sites in Greater Manchester. Approximately 40% of those eligible declined, and 25% had contraindications (discussed subsequently). There were no age or gender differences between those who refused and those who agreed to participate. Control subjects could be spouses or partners of depressed subjects or were recruited via advertisement in day and community centers. All participants gave full informed consent.

Inclusion and Exclusion Criteria

Patients were aged 60 and older at the time of assessment and fulfilled criteria for past or present history of a depressive episode, moderate or severe, psychotic or nonpsychotic (27), and were on stable medication. Patients with a history of stroke, space-occupying lesion, neurodegenerative disorders (including Parkinson's disease), dementia (27), previous head injury with loss of consciousness, or a history of another psychiatric disorder besides depression were excluded, as were those with severe valvular heart disease or who were taking warfarin (because of contraindications to scan or biopsy) or undergoing atrial fibrillation (because of difficulty in interpreting pulse wave measures). Control participants had no previous history of psychiatric disturbance and had stable medical health. All studies were performed during a visit to the Manchester Wellcome Trust Clinical Research Facility.

General Study Measures

Age, gender, smoking status, medical history, and current medication were recorded for each subject along with waist circumference, weight, height, and fasting blood for blood sugar and lipids. Psychiatric measures included World Health Organization ICD-10 symptom checklist for Depressive Episode, Montgomery–Åsberg Depression Rating Scale (MADRS) for severity (28), and the Mini-Mental Status Examination (29). Physical health was measured by the Cumulative Illness Rating Scale—Geriatrics (30) and the metabolic syndrome by operational criteria (31).

Vascular Measures

Pulse Wave Analysis. The SphygmoCor (PWV Medical, Sydney, Australia) system was used to acquire peripheral artery pressure waveforms noninvasively from the right radial artery. The corresponding central arterial waveform was then generated using a validated transfer function (32) from which Augmentation index (AIx) normalized to a heart rate of 75, a measure of systemic arterial stiffness was calculated.

Pulse Wave Velocity. Aortic PWV was measured from Doppler flow signals obtained sequentially from the right carotid and right femoral arteries using a noninvasive device (Micro Medical, Rochester, Kent, United Kingdom). A minimum of 10 beats were averaged for each site using the R wave of the electrocardiogram for synchronization. Using the distance traveled by the pulse wave over the surface of the body with a tape measure (from the sternal notch to the femoral artery and carotid artery to the sternal notch), PWV was calculated as the distance:transit time ratio and is expressed as m/sec (meters/second).

Intima Media Thickness. The carotid arteries were evaluated with high-resolution B-mode ultrasonography using a Philips/ATL HDI 5000 (Philips, Bothell, Washington) ultrasound system. IMT was measured by two-dimensional ultrasound at three sites (far wall) on both sides: 1) common carotid artery (CCA) 1 cm proximal to the beginning of the carotid bulb, 2) within the carotid bulb, and 3) internal carotid artery (ICA) .5 cm distal to the flow divider. The measurements were repeated three times at each site, and the average was calculated (33). An overall measure of IMT was calculated as the average of the CCA IMT, bifurcation IMT, and ICA IMT of both sides.

Gluteal Fat Biopsy of Resistance Vessels. A single subcutaneous gluteal fat biopsy was obtained using 3 to 5 mL of 2% lignocaine, allowing tissue (2 × 1.5 × 1.5 cm) to be harvested. Small arteries 200 to 250 μm in diameter were dissected from the tissue, and isolated vessels were then transferred to an arteriographic bath chamber and cannulated. Lumen diameter was recorded using a Video Dimension Analyzer (Living Systems Instrumentations, Burlington, Vermont). After viability assessment with potassium-enriched physiologic saline, small arteries were preconstricted with 10^{-5} norepinephrine. Endothelial function in the small arteries was then studied by constructing a cumulative dose response to acetylcholine. The maximal vasodilation in response to a concentration of 10^{-5} mol/L of acetylcholine was taken as a surrogate marker for endothelial function.

PWV and PWA were measured by the same investigator, who was not blind to group status, after appropriate training. Carotid ultrasound scans were conducted by an experienced vascular technologist blinded to clinical data. Gluteal fat biopsy was performed by an investigator who was unaware of the subject's group status.

Neuroimaging Evaluation

Protocol. Magnetic resonance imaging of the brain was carried out at 1.5 T on a Philips Intera Achieva (Philips Medical Systems, Best, The Netherlands) using a SENSE (Sensitivity Encoding) head coil. Fluid-attenuated inversion recovery (FLAIR) and T1-weighted inversion recovery (T1-IR) images were acquired as part of the imaging protocol. For both scans, 45 transverse slices, 3.0 mm thick with no slice gap, were obtained using a field-of-view of 230 × 230 mm, providing full coverage of the brain. Images were reconstructed using a matrix size of 256 × 256, yielding pixels of .9 × .9 mm. Imaging parameters specific to the FLAIR sequence were repetition time/echo time/inversion time (TR/TE/TI) = 11,000/140/2800 msec, echo train length = 53; parameters specific to the T1-IR were TR/TE/TI = 3198/15/400 msec, echo train length = 5.

Visual Ratings (WMH and VRS). All the ratings were conducted by an experienced neuroradiologist (A.J.) who was blind to patient group. The assessment of white matter lesion load was performed on matched T1-weighted inversion recovery and T2-weighted FLAIR images using a modified Scheltens scale, which has four subscales: cortical deep white matter (DWMH)