Cardiovascular Damage in Alzheimer Disease: Autopsy Findings From the Bryan ADRC

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Autopsy information on cardiovascular damage was investigated for pathologically confirmed Alzheimer disease (AD) patients (n = 84) and non-AD control patients (n = 60). The 51 relevant items were entered into a grade-of-membership model to describe vascular damage in AD. Five latent groups were identified: “I: early-onset AD,” “II: controls, cancer,” “III: controls, extensive atherosclerosis,” “IV: late-onset AD, male,” and “V: late-onset AD, female.” Expectedly, Groups IV and V had elevated APOE $\epsilon^4$ frequency. Unexpectedly, there was limited atherosclerosis and frequent myocardial valve and ventricular damage. The findings do not indicate a strong relationship between atherosclerosis and AD, although both are associated with $\text{APOE$\epsilon^4}$.

INTRODUCTION

It is well known that Alzheimer’s disease (AD) is the most common form of senile dementia in the US and Europe. Population studies suggest that 47% of persons over age 85 are affected [1, 2, 3]. The established genetic risk factor is the E4 isoform for the lipid transport molecule apolipoprotein E (APOE: gene; ApoE: protein) [4, 5, 6, 7, 8, 9, 10] which is also a risk factor for coronary atherosclerosis [11, 12, 13, 14, 15, 16, 17, 18, 19]. The $\epsilon^4$ allele for APOE has sometimes been implicated in vascular dementia (VaD) and stroke [20, 21, 22], the second most common form of senile dementia.

Previous studies have shown decreased smooth muscle actin in brain blood vessels of AD patients when compared to nondemented controls [23]. Possibly, more extensive amyloid deposition in heart and brain vessels determines the 5-fold worse prognosis (8% compared to 40% mortality) within three months following a diagnosis of heart disease or stroke at ages 85+ for $\epsilon^3/4+$ persons, compared to $\epsilon^2/3+$ [24], and largely accounts for reduced $\epsilon^4$, and elevated $\epsilon^2$, frequencies found among centenarians [25].

The role of cardiovascular damage in the development of AD is consistent with a number of existing reports in the literature, although few deal with pathologically confirmed AD and pathologic cardiovascular findings in age-matched samples. Certainly, cardiovascular damage is common among subjects with neuropathologically confirmed AD [26, 27]. Hypertension has been suggested as a risk factor for subsequent AD, normal or low blood pressure at the end stages of the disease [28, 29, 30, 31, 32].

Skoog et al [31] investigated a population cohort and found an association between elevated blood pressure at age 70 years and the development of dementia 10 to 15 years later. They hypothesized that hypertension causes hyalinization of the vessel walls in the brain and hypoperfusion in the deep white matter.

Atherosclerotic disease and silent myocardial infarcts have been associated with cognitive impairment [26, 27]. In the Rotterdam study [33], the extent of atherosclerosis was assessed by ultrasonography of the carotid arteries and by the ratio of ankle to brachial systolic blood pressure. Subjects were scored from 0 to 3, from no to severe, atherosclerosis. The odds of a clinical AD diagnosis

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increased 2-fold with the extent of atherosclerosis, 3-fold for VaD. Autopsy studies are limited, but suggest that cardiovascular disease contributes to the expression of dementia for patients who exhibit Alzheimer neuropathologic changes. Sparks et al [28] showed that significant coronary artery disease was present in 90% (19 of 21) of AD patients undergoing a complete postmortem examination. Patients with peripheral vascular disease, cerebrovascular accidents, and myocardial infarcts had lower antemortem cognitive scores on the miniminal state exam [27]. Patients with end-stage renal disease have cognitive impairment thought to be due to multifacart dementia [34].

However, Irina et al [35] did not find a correlation of dementia or pathologically confirmed AD with pathologic cardiovascular index (CVI), that is, the extent of atherosclerosis in the brain and periphery combined with evidence of cardiovascular lesions and cardiomegaly. Specifically, the CVI was higher for 103 nondemented subjects compared to 106 demented subjects, 9.2 versus 7.5 out of a possible 15 (P < .05). Mean CVI was 5.2 for subjects meeting CERAD criteria for possible AD, 7.3 for definite AD, increasing to 8.5 for vascular and mixed dementia. Thus atherosclerosis was associated with VaD, not the extent of Alzheimer’s lesions (associated with the ε4 allele for APOE).

To clarify the role of cardiovascular disease in dementia, we investigated 144 subjects prospectively enrolled in the Bryan Alzheimer Disease Research Center Rapid Autopsy Program at Duke University who had had complete body autopsies.

**METHODS**

**The rapid autopsy program**

The Rapid Autopsy Program of the Bryan Alzheimer Disease Research Center has been in continuous existence since 1985 [36]. Recruitment, enrollment, and autopsy procedures have been approved by the Institutional Review Board. After receiving informed consent from the patients and their families, both demented and nondemented control donors are enrolled and followed prospectively until death. While the principal purpose of the program is to retrieve and bank human brain tissue for use in research, many donors have consented to complete diagnostic autopsy. At the time of death, consent for autopsy is again obtained according to Duke University Medical Center regulations. Autopsy is performed in the usual fashion with examination of all body organs and cavities. Autopsies are performed in compliance with Centers for Disease Control precautions against the spread of infectious diseases [37, 38].

**Data abstraction**

APOE genotype (for 46 demented and 38 nondemented subjects) was obtained from existing databases. We abstracted the 144 autopsy records to obtain information on dementia status, cardiovascular disease, medical diagnoses, and organ weights. An Excel spreadsheet was used as the abstract form. Abstraction was done independently by two persons. Inconsistencies were resolved by consensus among the authors. The 51 items are listed in Tables 1–3, respectively.

**The statistical approach**

Detailed clinical profiles were identified using a statistical technique called grade-of-membership analysis or GoM [39, 40]. Use of univariate approaches would necessarily have low power at this sample size, especially if corrected for multiple comparisons (not needed when all variables are jointly examined). An additional advantage is that each variable can be understood in relation to all the other variables allowing a clinical narrative, something like the process of diagnosis, to be achieved for the identified latent model-based groups.

GoM can be described after first identifying four indices. One is the number of subjects $I$ ($i = 1, 2, \ldots, I$). Here $I = 144$ subjects were identified. The second index is the number of variables $J$ ($j = 1, 2, \ldots, J$). There are $J = 50$ variables each representing one of the clinical variables described above. Our third index is $L_j$: the set of response levels for the $j$th variable.

This leads to the definition of the basic GoM model where the probability that the $j$th subject has the $L_j$th level of the $j$th variable is defined by a binary variable (ie, $y_{ijl} = 0,1$). The model with these definitions is

$$
\text{Prob} \left( y_{ijl} = 1.0 \right) = \sum_k g_{ik} \lambda_{kjl},
$$

where the $g_{ik}$ are convexly constrained scores (ie, $0.0 \leq g_{ik} \leq 1.0; \sum_k g_{ik} = 1.0$) for subjects and the $\lambda_{kjl}$ are probabilities that, for the $K$th latent group, the $L_j$th level is present for the $j$th variable. The procedure thus uses this expression to identify $K$ profiles representing the pattern of $J \times L_j$ responses found for $I$ subjects.

The parameters $g_{ik}$ and $\lambda_{kjl}$ are estimated simultaneously using the likelihood function (in its most basic form) [39, 40].

$$
L = \prod_i \prod_j \prod_l \left( \sum_k g_{ik} \cdot \lambda_{kjl} \right)^{y_{ijl}}.
$$

In the likelihood $y_{ijl}$ is 1.0 if the $L_j$th level is present and 0.0 if it is not present. GoM models specifying from $K = 3–5$ groups, that is, clinical profiles, were constructed. The significance of adding the $K + 1$ profile was tested as an independent increment in the fit of the model adjusting for the larger number of degrees of freedom in the larger model. Akaike information criterion [41] was calculated as

$$
\text{AIC} = -2L(\hat{\theta}) + 2P,
$$
Table 1. The clinical variables.

| No | Variable                     | Description                                      |
|----|------------------------------|--------------------------------------------------|
| 1  | Dementia                     | 0 = no, 1 = yes (ie, age at onset listed)         |
| 2  | Dementia status              | 0 = normal, 1 = dementia, 2 = normal cognition,   |
|    |                              | 3 = disease control, 4 = early dementia,         |
|    |                              | 6 = Parkinson’s disease (PD)                     |
| 3  | Final diagnosis              | 0 = normal, 1 = AD, 2 = PD, 3 = possible AD, 4 = not listed |
| 4  | Age at onset                 | 0 = not demented, 1 ≤ 60 years of age, 2 = 60–70, 3 = 70–80, 4 = 80+ |
| 5  | Duration of dementia         | 0 = normal, 1 ≤ 5 years, 2 = 5–10, 3 = 10–15, 4 = 15+ |
| 6  | Age at death                 | 1 ≤ 60 years, 2 = 60–70, 3 = 70–80, 4 = 80+     |
| 7  | Sex                          | 0 = male, 1 = female                             |
| 8  | Race                         | 0 = white, 1 = black                             |
| 9  | Body mass index              | 0 = 8–17.9, 1 = 17.9–21.2, 2 = 21.2–25.0, 3 = 25+, 9 = missing |
| 10 | Cancer diagnosis             | 0 = no, 1 = yes                                  |
| 11 | Respiratory system infection | 0 = no, 1 = yes                                  |
| 12 | Urinary system infection     | 0 = no, 1 = yes                                  |
| 13 | Digestive system infection   | 0 = no, 1 = yes                                  |
| 14 | APOE genotype                | 0 = ε22, 1 = ε23, 2 = ε33, 3 = ε24, 4 = ε34, 5 = ε44 |

where \( l \) is the likelihood value and \( P \) is the number of estimated parameters. However, for parameters on the boundary, that is, value = 0, only one is penalized. The rationale for subtracting only one for parameters on the boundary is that the distribution for those parameters is \((1/2)X^2\) (central). The lowest value of the AIC designates the best model, that is, the model with the best fit and least bias. GoM models specifying either 3, 4, 5, or 6 clinical profiles, that is, \( K = 3–6 \), had AIC = −1503, −1647, −1703, and −1678, respectively. The 5-group model is reported.

Information on APOE genotype was not used to construct the groups used to clinically characterize the subjects. One option in the likelihood is to separate calculations for “internal” (here, clinical) and “external” (here, APOE genotype) variables. For internal variables, MLE of \( g_{ik} \) and \( \lambda_{kjl} \) are generated and the information in internal variables is used to define the \( K \) groups. For external variables the likelihood is evaluated (and MLE of \( \lambda_{kjl} \) generated) but the information is not used to redefine the \( K \) groups, that is, the likelihood calculations for likelihood equations involving the \( g_{ik} \) are disabled for external variables so that the \( g_{ik} \), and the definition of the \( K \) groups, is not changed.

RESULTS

Overview

Five model-based groups best represented the autopsy information on diagnoses, cardiovascular disease, and organ weights. They are labeled I, II, III, IV, and V ordered according to increasing age at the time of death. Each group is defined by the probabilities of response for the many variables, akin to the frequencies found in the sample as a whole. Tables 4–6 describe the profiles in terms of diagnoses, cardiovascular damage, and organ weights, respectively. Not all the variables described in Tables 1–3 are shown in the tables of results.

The size of the groups was similar (Table 4). The sizes are the summed memberships of individuals in the respective groups either partial, that is, fractional, or complete, that is, contributing size one to the sum, depending on the extent of resemblance of the individual to the group. Group I was the largest group (\( n = 36.4 \)) and Group II was the smallest (\( n = 21.3 \)). The prevalence of demented and nondemented subjects, that is, sum of memberships, in each model-based group is shown in Table 7, as well as the distribution of APOE frequencies across the model-based groups.

Dementia diagnoses

Next observe that the groups were either demented or not demented (Table 4): Groups I, IV, and V had 100% probability of dementia while Groups II and III were not demented. There was high probability that dementia was specifically due to AD: 81% for Group I, 73% for Group IV, and 72% for Group V. Otherwise, no explanatory diagnosis was given for the dementia for these groups. Groups II and III had no chance of an AD diagnosis. However, possible AD was sometimes found in the nondemented groups, 9% for Group II and 43% for Group III (5–10 years younger than Groups IV and V). Group II had a 22% chance of being a so-called “disease control” and Group III had a 10% chance of having Parkinson’s disease. The dementia status and final diagnoses variables are described in Table 2.

Onset age, sex, and dementia duration

As the age at the onset of dementia for Group I was usually before age 65, Group I represents early-onset AD. Groups IV (male) and V (female) represent late-
onset AD: the mean age at onset was around 70 years of age for both groups, marginally earlier for female Group V compared to male Group IV. Nonetheless Group V had longer disease duration and an older age at the time of death. The 2% of the sample that was black was concentrated in the control Groups II and III (not shown).

Table 2. The cardiovascular variables.

| No | Variable                          | Description          |
|----|-----------------------------------|----------------------|
| 15 | Pericardial cavity fluid          | 0 ≤ 10 mL, 1 = 11–50, 2 = 51–100, 3 ≥ 100, 9 = missing |
| 16 | Right pleural cavity fluid        | 0 ≤ 10 mL, 1 = 11–50, 2 = 51–100, 3 ≥ 100, 9 = missing |
| 17 | Left pleural cavity fluid         | 0 ≤ 50 mL, 1 = 51–200, 2 = 201–500, 3 ≥ 500, 9 = missing |
| 18 | Peritoneal fluid                  | 0 ≤ 50 mL, 1 = 51–200, 2 = 201–500, 3 ≥ 500, 9 = missing |
| 19 | Aorta atherosclerosis             | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 20 | Right coronary artery atherosclerosis | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 21 | Right coronary artery narrowing   | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 22 | Right coronary artery calcification | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 23 | Left main coronary artery atherosclerosis | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 24 | Left main coronary artery narrowing | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 25 | Left main coronary artery calcification | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 26 | Circumflex branch atherosclerosis | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 27 | Circumflex branch narrowing       | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 28 | Circumflex branch calcification   | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 29 | Anterior descending branch atherosclerosis | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 30 | Anterior descending branch narrowing | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 31 | Anterior descending branch calcification | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 32 | Right atrial cavity dilation      | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 33 | Right atrial wall thickness       | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 34 | Right ventricular cavity dilation | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 35 | Right ventricular wall thickness  | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 36 | Left atrial cavity dilation       | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 37 | Left atrial wall thickness        | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 38 | Right ventricular cavity dilation | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 39 | Right ventricular wall thickness  | 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 9 = missing |
| 40 | Aortic valve                      | 0 = normal, 1 = abnormal, 9 = missing |
| 41 | Tricuspid valve                   | 0 = normal, 1 = abnormal, 9 = missing |
| 42 | Pulmonic valve                    | 0 = normal, 1 = abnormal, 9 = missing |
| 43 | Mitral valve                      | 0 = normal, 1 = abnormal, 9 = missing |
| 44 | Ventricular myocardium            | 0 = normal, 1 = abnormal, 9 = missing |

Table 3. The quartiles for organ weights.

| No  | Variable       | Description               |
|-----|----------------|---------------------------|
| 45  | Heart          | 0 ≤ 295 gm, 1 = 295–351, 2 = 351–412, 3 = 412+, 9 = missing |
| 46  | Lungs (mean)   | 0 ≤ 316 gm, 1 = 316–443, 2 = 443–585, 3 = 585+, 9 = missing |
| 47  | Liver          | 0 ≤ 880 gm, 1 = 880–1100, 2 = 1100–1140, 3 = 1140+, 9 = missing |
| 48  | Kidneys (mean) | 0 ≤ 99 gm, 1 = 99–125, 2 = 125–153, 3 = 153+, 9 = missing |
| 49  | Spleen         | 0 ≤ 75 gm, 1 = 75–113, 2 = 113–170, 3 = 170+, 9 = missing |
| 50  | Adrenals (mean) | 0 ≤ 6.95 gm, 1 = 6.95–8.1, 2 = 8.1–10.2, 3 = 10.2+, 9 = missing |
| 51  | Thyroid        | 0 ≤ 9.25 gm, 1 = 9.25–14, 2 = 14–20, 3 = 20+, 9 = missing |

**BMI and nonneurologic diagnoses**

Early-onset dementia (I) was associated with extremely low body mass index (BMI). Women with late-onset dementia and long dementia duration (V) also had very BMI. Cancer was a common diagnosis for Group II, absent for Group III. Men with late onset dementia also frequently had cancer (IV), absent for female Group V.
Table 4. Clinical variable frequencies for each group. Each model-based group is defined by the probabilities of being demented & probabilities of response for the other variables, that is, the model $\lambda$ parameters.

| Variable               | Response | N = 36.4 | N = 21.3 | N = 27.2 | N = 27.5 | N = 31.5 |
|------------------------|----------|----------|----------|----------|----------|----------|
|                        |          | I        | II       | III      | IV       | V        |
| Demented               | Yes (%)  | 100      | 0        | 0        | 100      | 100      |
| Age at onset           | < 60 years | 81       | —        | —        | 7        | 0        |
|                        | 60–70    | 15       | —        | —        | 35       | 53       |
|                        | 70–80    | 4        | —        | —        | 46       | 34       |
|                        | 80+      | 0        | —        | —        | 12       | 13       |
| Duration of dementia   | < 5 years | 12       | —        | —        | 5        | 0        |
|                        | 5–10     | 38       | —        | —        | 62       | 0        |
|                        | 10–15    | 43       | —        | —        | 33       | 37       |
|                        | 15+      | 7        | —        | —        | 0        | 63       |
| Age at death           | < 60     | 20       | 20       | 0        | 0        | 0        |
|                        | 60–70    | 73       | 0        | 12       | 0        | 0        |
|                        | 70–80    | 7        | 73       | 68       | 31       | 12       |
|                        | 80+      | 0        | 7        | 20       | 69       | 88       |
| Sex                    | Female   | 66       | 20       | 35       | 0        | 100      |
| BMI (kg/m²)            | 8–17.9   | 67       | 0        | 0        | 4        | 23       |
|                        | 17.9–21.2 | 11      | 0        | 0        | 37       | 54       |
|                        | 21.2–25.0 | 13     | 41       | 17       | 51       | 14       |
|                        | 25+      | 10       | 59       | 83       | 9        | 9        |
| Cancer diagnosis       | Yes      | 24       | 84       | 0        | 60       | 0        |
| Respiratory infection  | Yes      | 69       | 70       | 82       | 57       | 100      |
| Urinary tract infection| Yes      | 16       | 16       | 27       | 29       | 44       |
| Digestive tract infection | Yes    | 20       | 0        | 22       | 30       | 54       |

Respiratory and urinary infections were common for each group especially for demented women (V). Digestive tract infections were not found for Group II (cancer).

**Cardiovascular disease**

There was little evidence of cardiovascular disease for the early-onset relatively young Group I. Control Group II with cancer uniquely often had pulmonary effusions, ascites, and a moderately dilated right ventricle. Groups II–V had minimal amounts of pericardial cavity fluid, absent for Group I (not shown).

Control Group III without cancer had severe atherosclerosis with narrowing and calcification in the aorta and each of the major coronary vessels—right coronary artery, left main coronary artery, circumflex branch, and anterior descending branch. The extent of atherosclerosis was usually similar for each vessel. Table 5 represents the average over all the coronary vessels. Group III with extensive atherosclerosis often also had moderate atrial dilation and moderately thickened ventricular myocardium (not shown).

Atherosclerosis was unexpectedly less extensive for demented Groups IV and V, limited for Group II, and absent for Group I.

Aortic and mitral valve damage and evidence of ischemic damage to the left ventricular myocardium were common for male late-onset dementia Group IV, and also female Group V. Both of the late-onset dementia groups and Group III had a moderately dilated right atrium.

**Organ weights**

Generally speaking, the organ weights shown in Table 6 paralleled the BMI results shown in Table 4. Nonetheless there were some interesting departures: organ weights were preserved for Group I having the lowest BMI. The low heart weight for this relatively young group is consistent with limited heart damage, as indicated by Table 4. Lung weight was highest for Group II, which often had pulmonary edema and pleural effusions. Group III, most affected by atherosclerosis, had the highest heart weight. Compared to Group III, organ weights and BMI were lower for Group IV. Very low BMI and weight for most organs was found for late-onset dementia Group V, females with long dementia duration. Notably, both late-onset dementia groups had low thyroid weight compared to the early-onset and control groups.
Table 5. Cardiovascular damage for each group. The model-based groups are defined by the probabilities response for the variables sometimes represented on a semiquantitative scale: "++ +" denotes severe, while "++ +", "++ +", and "−− −" denote moderate, mild, and the absence of lesions; "++ −/−" denotes mixture of moderate and absent; "++ −/−" denotes mixture of mild and absent; "++ +/−" denotes a mixture of moderate and mild; "++ +/−" denotes a mixture of severe and absent. * means the average of right coronary artery, left main coronary artery, circumflex branch, and anterior descending branch.

| Outcome       | Location                  | I         | II        | III        | IV         | V         |
|---------------|---------------------------|-----------|-----------|------------|------------|-----------|
| Fluid         | Peritoneal cavity          | −         | ++ +/−    | +/−        | −          | −         |
|               | Pleural cavity             | −         | ++ +      | +/−        | −          | −         |
| Coronary artery* | Atherosclerosis         | −         | +/−       | ++ +      | ++         | +         |
|               | Narrowing                 | −         | +/−       | ++ +      | ++         | +         |
|               | Calcification              | −         | +/−       | ++ +      | ++         | +         |
| Aorta         | Atherosclerosis           | +/-       | ++        | ++ +      | ++         | + +/+     |
| Dilation      | Right atrium              | −         | +/−       | ++ +/−    | ++         | +         |
|               | Right ventricle            | +/-       | ++ +/−    | +/−       | +          |         |
|               | Left atrium               | −         | +/−       | +/−       | +/-        | +/-       |
|               | Left ventricle            | +/-       | +         | −          | −          | +/+       |
| Damage        | Aortic valve              | −         | 20        | −          | 100        | 33        |
|               | Mitral valve              | 14        | 32        | −          | 100        | 45        |
|               | Pulmonic valve            | −         | −         | −          | 37         | 14        |
|               | Tricuspid valve           | −         | 19        | 3          | 64         | 17        |
|               | Ventricular myocardium    | −         | −         | −          | 49         | 46        |

**APOE genotype**

*APOE* genotype data was available on a subset of 84 subjects, 46 with dementia and 38 controls. Although this information was not used to predict the groups, individuals carrying the ε4 allele were more common in the dementia groups. The summed memberships of individuals of each genotype are shown in Table 7. As individuals, the study subjects who exactly resembled a single profile contributed one to the size of the relevant profile and zero to the other profiles. Otherwise, the subject contributed a total of one to the sizes of the relevant profiles depending on the extent of resemblance. In contrast to results, Tables 4–6 that predict frequencies for persons exactly like the group, Table 7 demonstrates that as individuals there was overlap of demented and nondemented subjects in the groups, not surprisingly given the many variables used to construct the groups, frequent comorbidity at advanced ages, and differences from individual to individual.

**DISCUSSION**

We investigated cardiovascular damage found for 84 demented and 60 nondemented subjects enrolled in the Bryan ADRC Rapid Autopsy Program. The subjects could be represented by five distinct latent groups based on detailed pathologic information. The late-onset AD groups, both male (IV) and female (V), had frequent heart valve damage, evidence of ischemic damage to the left ventricular myocardium, low BMI, and low organ weights notably including the thyroid gland. They did not have extensive atherosclerosis compared to control subjects without cancer (III), many of whom had possible AD. In particular, the female group (V) having long AD duration had little atherosclerosis. Control subjects with cancer (II) had little atherosclerosis or valve damage. Instead, pulmonary edema and ascites were common. The early-onset AD group (I) had little cardiovascular damage, with normal organ weights despite low body weight.

The finding of mitral and aortic valve damage, and evidence of ischemic damage to the left ventricular myocardium for the AD groups, especially among men, is interesting. It is consistent with the hypothesis that brain hypoperfusion and microthrombi may contribute to the evolution of AD pathology or to the expression of dementia at an earlier stage in AD pathogenesis [40]. However, the AD groups (IV and V) were the oldest groups. Thus valve and myocardial damage might simply be age related and less rapidly fatal than extensive coronary atherosclerosis. Alternatively, the oldest cohorts in the sample may have valve damage resulting from rheumatic fever not treated with antibiotics. Assuming that mitral valve damage is related to rheumatic fever in the oldest subjects does not, however, rule out the possibility that it contributes to the expression of dementia by decreasing brain perfusion and, possibly, contributing to brain pathology.

In addition, the lack of an age-matched control group requires comment. Since aging is itself a risk factor for valvular disease, an age-matched control group would be
Table 6. Organ weights for each group. The model-based groups are defined by the probabilities response for the variables, here represented on a semiquantitative scale: “+++” denotes the highest quartile of weight, while “++,” “+,” and “+” denote the respectively lower quartiles.

| Organ   | Group | I    | II   | III  | IV   | V    |
|---------|-------|------|------|------|------|------|
| Heart   |       | +    | +++  | ++++ | ++++ | ++++ |
| Lungs   |       | ++   | ++++ | ++++ | ++++ | ++++ |
| Liver   |       | ++++ | ++++ | ++++ | ++++ | ++++ |
| Kidneys |       | ++++ | ++++ | ++++ | ++++ | ++++ |
| Spleen  |       | ++   | ++++ | ++++ | ++++ | ++++ |
| Adrenals|       | ++++ | ++++ | ++++ | ++++ | ++++ |
| Thyroid |       | ++++ | ++++ | ++++ | ++++ | ++++ |

Table 7. Distribution of subjects across the groups, subdivided according to dementia status and APOE genotype; $\epsilon_2/2$ and $\epsilon_2/3$ were grouped with $\epsilon_3/3$; $\epsilon_2/4$ and $\epsilon_4/4$ were grouped with $\epsilon_3/4$. The sizes are the sums of the model $g_{ik}$ parameters, that is, the memberships of individuals in the groups, whole or partial.

| Subjects  | Group | I    | II   | III  | IV   | V    | All |
|-----------|-------|------|------|------|------|------|-----|
| Demented  |       | 30.9 | 2.3  | 8.5  | 19.7 | 22.6 | 84  |
| Not demented |     | 5.5  | 19.0 | 18.7 | 7.8  | 9.0  | 60  |
| $\epsilon_3/3+$ | Demented | 4.0  | 0    | 2.0  | 3.9  | 5.0  | 15  |
|         | Normal | 2.4  | 9.1  | 8.6  | 2.2  | 3.6  | 26  |
| $\epsilon_4/4$ | Demented | 12.3 | 1.0  | 3.2  | 8.2  | 6.2  | 31  |
|         | Normal | 1.6  | 3.5  | 3.8  | 1.5  | 1.5  | 11  |
| Total    |       | 36.4 | 21.3 | 27.2 | 27.5 | 31.5 | 144 |

required to fully examine the hypothesis that hypoperfusion contributes to dementia. Unfortunately, this was not possible in this small-human-population-based study. Rigorous analysis must await examination of a larger cohort.

Despite the caveats, the results on valve and myocardial damage are striking and the given frequent finding of the $\epsilon_4$ allele for APOE in the AD groups raises the possibility that ApoE directly damages these structures as it has been demonstrated to damage blood vessels [42, 43]. Muscle actin in the arterioles is replaced by amyloid for $\epsilon_4/4$ subjects to a much greater extent than for $\epsilon_3/3+$ subjects. Meyer et al [44] ($n = 36$) found hypertrophy of the left ventricle (uncommon in the Bryan ADRC sample) in 9 of 19 (47%) $\epsilon_3/4+$ AD patients and only 1 of 11 (9%) $\epsilon_3/3+$ patients ($\chi^2 = 3.8, df = 1, P = 0.05$). There were no statistically significant differences in the presence of stenotic changes or calcification in aortic or mitral valvulae in this small sample. The study results tend to suggest that the 5-fold worse prognosis following a diagnosis of heart disease or stroke at ages 85+ for $\epsilon_4+$ persons may be due to impaired cerebrovascular function due to amyloid deposition [25]. Data presented here would also suggest that cardiovascular malfunction may be a contributing factor.

The study does not support the notion that extensive atherosclerosis is a risk factor for definite AD. Instead, subjects with extensive atherosclerosis died before a diagnosis of probable or definite AD could be made. The relatively low $\epsilon_4$ frequency for control subjects with extensive atherosclerosis was unexpected since the allele carries a modestly increased risk of coronary atherosclerosis [13, 14, 15, 16, 17, 44]. There is also a small ecologic association between $\epsilon_4$ frequency and population rates of myocardial infarction in middle age [45, 46]. Nevertheless the findings from this study are consistent with the lack of risk for heart disease and stroke for $\epsilon_4$ found in the Kungsholmen Project for cohort age of 75 and older [25].

Atherosclerosis may possibly at least partially reverse itself during the clinical progression of AD as weight is lost and food intake diminished. This explanation is supported to some extent by the fact that possible AD was common in the nondemented group with high heart weight and extensive atherosclerosis. So that atherosclerosis might be a common concomitant of early or preclinical AD but may not be found at the time of death many years later.

A strong feature of the study is that comparisons were made based on pathologic features and pathologically confirmed diagnoses. The data analytic approach was helpful in resolving the many items of information into a tractable number of distinct groups consistent with clinical experience, despite the relatively small sample
size. For example, heart weight was highest for the group also having the most extensive atherosclerosis and lung weight was highest for the group also having pulmonary effusions and ascites.

In summary, extensive coronary atherosclerosis at autopsy was associated with death at earlier ages and limited AD pathology. Pathologically confirmed AD was not associated with extensive coronary atherosclerosis. Surprisingly, it was associated with mitral and aortic valve damage and damage to the ventricular myocardium.

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