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Histopathological differences between the anterior and posterior brain arteries as a function of aging

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Abstract

Background and Purpose—We tested the hypothesis that posterior brain arteries differ pathologically from anterior brain arteries and that this difference varies with age.

Methods—Brain large arteries from 194 autopsied individuals (mean age 56 ± 17 years, 63% men, 25% non-white, 17% with brain infarcts) were analyzed to obtain the areas of arterial layers and lumen as well as the relative content of elastin, collagen and amyloid. Visual rating was used to determine the prevalence of atheroma, calcification, *vasa vasorum,* pattern of intima thickening and internal elastic lamina gaps. We used multilevel models adjusting for age, sex, ethnicity, vascular risk factors, artery type and location, and multiple comparisons.

Results—Out of 1362 large artery segments, 5% had *vasa vasorum*, 5% had calcifications, 15% had concentric intimal thickening, and 11% had atheromas. Posterior brain arteries had thinner walls, less elastin, and more concentric intima thickening than anterior brain arteries. Compared to anterior brain arteries, the basilar artery had higher arterial area encircled by the internal elastic lamina, while the vertebral arteries had higher prevalence of elastin loss, concentric intima thickening and non-atherosclerotic stenosis. In younger individuals, vertebral artery calcifications were more likely than calcification in anterior brain arteries, but this difference attenuated with age.

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Conclusions—Posterior brain arteries differ pathologically from anterior brain arteries in the degree of wall thickening, elastin loss and concentric intimal thickening.

BACKGROUND

Intracranial large artery atherosclerosis (ILAA) is a well-known cause of stroke and may account for up to 15% of ischemic strokes.[1-3] Although traditional vascular risk factors are associated with ILAA as well as with extracranial atherosclerosis, diabetes and metabolic syndrome seem to be important determinants of ILAA. [1, 4] Furthermore, differential associations with vascular risk factors and stroke mechanisms have been cited between the posterior and anterior intracranial vasculatures[5], and pathological evidence exists that more advanced brain arterial aging is noted in the posterior circulation compared with the anterior circulation[6]. American and Asian studies have shown higher incidence of radiographic ILAA in the internal carotid and middle cerebral arteries (ICA and MCA) than in the basilar and vertebral arteries (BA and VA)[5, 7]. Possible explanations for the pathological differences between the anterior and posterior flow systems include differences in flow dynamics due to geometrical disparities[8], divergent embryological origins[9], or perhaps even differences in arterial wall nourishment as conferred by the relative paucity of *vasa vasorum* reported in posterior circulation arteries[10, 11].

Large prospective cohort data is equivocal, however, regarding differential mechanisms of anterior and posterior circulation stroke[12, 13]. Additionally, focal luminal narrowing of arteries is often used as a radiographic surrogate for ILAA[14-16], a method that underestimates the extent of atherosclerosis and cannot distinguish atheromas from non-atherosclerotic intima thickening seen with aging[6, 16]. Consequently, the study of the differences between anterior and posterior circulation radiographically- and histologically-defined intracranial atherosclerosis is problematic due to the preponderance of lumen-based studies, samples restricted to patients with stroke, and limited sample size[11, 17, 18]. Identifying whether the arterial remodeling responses to aging and vascular risk factors vary in the anterior versus the posterior circulation may allow individualized therapies beyond the recommended aggressive control of vascular risk factors.

In a large sample of autopsied brains with carefully characterized large brain arteries, we aim to test the hypothesis that posterior circulation arteries differ in their histopathological characteristics compared to anterior circulation arteries and that this difference varies with age.

METHODS

Specimens for this study were collected as part of the Brain Arterial Remodeling Study (BARS), a collection of large brain arteries from 336 subjects with and without HIV. We included in this analysis 194 subjects without HIV, whose brains were collected from four brain banks: The New York Psychiatric Institute/ Macedonia Tissue Collection (N=104), the Manhattan HIV Brain Bank (N=52), New York Brain Bank at Columbia University (N=25) and the Brain Endowment Bank at University of Miami (N=13). Demographics and vascular risk factor information were obtained from chart review, self-reported by subjects while alive

or by family proxy report during post-autopsy interview. Each case underwent neuropathological assessment which included the identification of brain ischemic infarcts.

Five-millimeter long cross-sectional cuts were obtained from large arteries of the circle of Willis in formalin-fixed brains, including the intracranial portion of the internal carotid artery (ICA), anterior, middle and posterior cerebral arteries (ACA, MCA, PCA), vertebral and basilar arteries (VA, BA). From each segment, when available, two segments were obtained, one in the most proximal aspects of the artery and one before its bifurcation or coalescence into another arterial segment (for example, as in the VA). Each segment was labeled accordingly and embedded in paraffin. Six-micron-thick cuts were obtained from each arterial block for staining (one section per staining) with hematoxylin & eosin for structural evaluation, elastic Van Gieson (EVG), Masson's trichrome, and Congo red to approximate content of elastin, collagen and amyloid, respectively. Each slide was photographed using Olympus Soft Imaging Solutions software and microscope (Münster, Germany), at 10× magnification and resolution of 0·643 μm/pixel. Each artery was segmented into individual files. Debris artifact was corrected by systematically removing impurities from the background.[16] Folding artifact was addressed by using the outer perimeter of the artery as the referent the potential arterial size.[19] Shrinkage artifact was corrected by multiplying the perimeter by a factor of 1.25.[20, 21]

We collected 8 semi-automated and 4 visually-rated characteristics from each artery. Percentage of luminal stenosis, arterial area encircled by the internal elastic lamina (IEL proportion), and the thickness of the arterial wall and the media were derived from the areas of the lumen, intima, media and adventitia obtained through color segmentation with good to excellent reliability[22]. Elastin, collagen and amyloid approximate content were defined by automated pixel color intensity measurement carried out using Visiopharm Integrator System ® version 4.6.3.857 (Hoersholm, Denmark) as reported elsewhere. The pixel intensity was adjusted by background color intensity in order to be able to more fairly use the samples stained in different batches, which may introduce method-related artifact in color intensity (online figure e1). Additionally, we discarded unevenly stained slides and repeated the staining until the coloration appeared even across arteries. Large artery amyloidosis and high collagen deposition were ascertained if the background-adjusted pixel intensity fell in the upper tertile of the pixel distribution, and elastin loss was defined if the pixel adjusted intensity for EVG fell in the lowest tertile of the pixel distribution. Concentric intimal thickening, IEL gaps, presence of calcifications, and *vasa vasorum* were rated visually as present or not, with good reliability (Figure 1)[23]. The presence of atherosclerosis as well as measurements related to atheroma and fibrous cap were carried out using the revised AHA atherosclerosis classification system[24].

Statistical analysis

As stated above, the outcome for this study was 12 arterial characteristics and the main independent variable of interest was the posterior circulation as a whole, and also the vertebral and basilar arteries separately. We did not carry out a stratified analysis for the PCA due to the small number of available samples. We used multilevel models to adjust for the expected covariance between arteries from within the same individual. Mixed models

were used for continuous variables and generalized linear models for categorical variables. We first analyzed whether the arterial characteristics varied by anterior vs. posterior. We carried out Bonferroni correction for multiple comparisons as stated in each table. To test whether the differences in pathological characteristics vary by age, we tested for interactions with age (continuously), and only if the interaction reached a significance of 0.004 or less (after adjusting for multiple comparisons), we stratified the model by age groups. Also, we were interested in determining the correlation between anterior brain arteries pathological features with posterior brain arteries. In this case, we used the same arterial characteristic noted in the anterior circulation as predictors of the same characteristics in posterior brain arteries. In each model, we adjusted by the arterial size, arterial segment (ACA, MCA, etc), and whether the given segment was proximal or distal within the artery to account for expected differences in dimensions and pathology attributable to size and location. The statistical analysis was carried out with SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

A) Sample description

The sample mean age was 56 ± 17 years; the majority were men (63%), non-Hispanic white (75%) and smokers (52%, Table 1). The prevalence of brain infarcts was 17%, and in only a few of these cases the infarct was related to the cause of death. Of 1362 large artery segments, 5% had *vasa vasorum*, 5% had calcifications, 15% had concentric intimal thickening, and 19% had IEL gaps. Atherosclerosis (defined by the presence of an atheroma) was found in 11% of the arteries.

B) Posterior brain arteries characteristics

In a model adjusted for arterial location (i.e. proximal and distal), arterial size, arterial segment (i.e., MCA, ICA or ACA), and multiple comparisons, posterior brain arteries had larger IEL proportion, less elastin, and more concentric intimal thickening compared with anterior circulation arteries (table 2). Adjusting further for demographics and vascular risk factors did not change the significance of these associations. In this same fully adjusted model, both the BA and the VA had more elastin loss and concentric intimal thickening than arteries in the anterior circulation (table 2). The BA and the VA differed in other features, however, with respect to arteries in the anterior circulation. While the BA had a higher IEL proportion (indicative of arterial dilatation) than arteries in the anterior circulation (B=1.7 ± 0.5%, P<0.005), the VA had a higher degree of stenosis (B=2.5 ± 0.7 %, P<0.005) and the VA also had higher prevalence of *vasa vasorum* (B=2.2 ± 0.5, P<0.005) than arteries in the anterior circulation or in the basilar.

We found that the differences between anterior and posterior brain arteries collagen deposition and arterial calcification differed by age (p for interaction =<0.05, supplemental table 1). For both the VA and BA, the collagen content was higher than in arteries in the anterior circulation, but in older age categories, there was less collagen deposition in arteries in posterior brain arteries compared with anterior brain arteries. We also found evidence that

vertebral calcification appeared prematurely in younger individuals compared to arteries in the anterior circulation, and this difference attenuated in older age groups.

C) Atherosclerosis and posterior brain arteries

Basilar artery segments had a lower AHA atherosclerosis score (−0.35 ± 0.09, $p<0.005$) than anterior circulation arterial segments; this difference was not seen with VA segments or with posterior brain arteries as a whole (Table 3). More specifically, BA segments had significantly less pathological intimal thickening (B=−1.07 ± 0.49, $p<0.05$) and thin fibrous cap atheroma (M=−1.80 ± 0.51, $p<0.005$) than anterior circulation arteries. Vertebral artery segments had significantly more intimal thickening (0.87 ± 0.30, $p<0.05$) but were otherwise not significantly different than anterior circulation arteries.

D) Association between posterior brain arteries with anterior brain arteries pathology

Posterior brain arteries media thickness (0.12 ± 0.04, $p<0.003$), stenosis (0.13 ± 0.04, $p<0.003$), elastin loss (2.20 ± 0.49, $p<0.003$), and large artery amyloidosis (2.36 ± 0.58, $p<0.003$) were significant predictors of the same features in the anterior circulation. Posterior brain arteries atherosclerosis score (0.11 ± 0.02, $p<0.003$) used continuously, or categorically as thin fibrous cap atheromas (2.19 ± 0.35, $p<0.003$) were associated with the presence of the same features in the anterior circulation, irrespective of whether the BA or VA were analyzed separately.

DISCUSSION

In our study, posterior brain arteries had greater concentric intimal thickening, more elastin loss and increase in IEL proportion, suggesting outward remodeling compared to the anterior circulation arteries. When the BA and VA were analyzed separately, the BA had greater IEL proportion, elastin loss and thinner arterial wall, all of which point towards a predisposition to dilate. This fits well with the previous notion that among all the intracranial arteries, the BA has the highest prevalence of dolichoectasia.[25] The VA had higher prevalence of concentric intimal thickening, stenosis and *vasa vasorum*, but not of markers specific of atherosclerosis. This latter finding suggests a special susceptibility of the VA to non-atherosclerotic aging. This susceptibility is further supported by the premature VA non-atherosclerotic calcification in respect to arteries in the anterior circulation among 20-39 years old individuals. The lack of association between calcification with atherosclerosis in cerebral arteries is not novel,[26] and recent data provides evidence that calcification of intracranial arteries does not predict stroke.[27]

Interestingly, BA proximal or distal segments did demonstrate less atherosclerosis compared to anterior circulation segments. Prior autopsy studies have suggested that the distal BA is among the most commonly affected behind only the ICA bifurcation segments[28]. This discrepancy in findings may be related to patient demographics, as the present study included a high proportion of Hispanic and African-American individuals (Table 1). Prior studies have shown increased incidence of strokes related to intracranial atherosclerosis in these communities[1, 29], though comparisons between posterior and anterior circulation were not performed. Additionally, prior studies in Korean and Japanese communities have shown

relative increase in atherosclerotic changes in the anterior compared to posterior circulation arteries, though these communities were not represented in the present study[5, 7]. Moreover, asymptomatic infarcts are underrepresented in the posterior circulation,[30] which may suggest a lower clinical threshold for brainstem infarcts.

From the clinical and epidemiological perspectives, the results presented here should raise awareness that intracranial arterial disease in the form of atherosclerosis or aging is rarely restricted to a single artery but it rather diffuse. The best predictor of anterior circulation atherosclerosis, media thickness, stenosis, elastin loss and large artery amyloidosis are the presence of these same findings in the posterior brain arteries. This fact suggests that with aging and exposure to vascular risk factors, intracranial arteries undergo remodeling changes that are not limited to a given branch. When focal stenosis is noted in lumen-based studies, it is likely that atherosclerosis is widespread and at an advanced stage of arterial disease.[16] The finding of focal stenosis fits well with the high risk of stroke recurrence among patients with high-degree stenosis in intracranial arteries,[15, 31] and should alert clinicians to aggressively control vascular risk factors early on before the disease progresses to this late stage. The mechanisms favoring the phenotype of high-degree focal stenosis from a background of widespread non-stenotic atherosclerosis versus longitudinal non-focal high-degree stenosis remain unknown.

Divergent embryological origins of the posterior circulation may account for some of the differences observed in our study. The primitive posterior fossa structures are supplied almost exclusively by the fetal anterior circulation via carotid-vertebrobasilar anastomoses.[9] By the 12 mm stage of growth, however, posterior fossa structures are supplied independently by the nascent BA and VA, and the antero-posterior anastomoses are typically obliterated with the exception of the posterior communicating arteries. The VA throughout its extra- and intracranial course forms from fusion of vascular cells islands, while the BA forms from fusion of the neural arteries. These different origins contrasts to the more typical angiogenesis by sprouting described in the anterior circulation.[32-34] Differential flow dynamics in the posterior circulation, given its unique anatomy, may affect the distribution of blood flow, shear stress, vessel morphology and geometry of intracranial vessels that may explain partially some of the noted discrepancies compared with arteries in the anterior circulation. [35, 36] For example, the obtuse angle of confluence at the vertebrobasilar junction has been proposed as contributing to the susceptibility of the posterior circulation to long-standing stress related to flow dynamics[37].

Strengths and limitations

The strengths of this study include the relatively large sample size; to date this is among the largest reported histopathological surveys of the intracranial vasculature. Additionally, the majority of the measurements of each artery were automated, which increases the reliability of our estimates. Data was also derived from a non-stroke population; hence, the data is more representative of the prevalence of pathological correlates of arterial aging and atherosclerosis in an unselected population. The prevalence of vascular risk factors in the sample population did correspond fairly to broader epidemiological estimates, but categorization of vascular risk may lead to loss of information relating to atherosclerosis.[19]

Hispanics and African-Americans are well-represented in our sample, which is important given the different rates of atherosclerosis in these communities. Our study also has limitations. First, Asian populations were not represented in our data set, limiting generalizability to these populations. The lack of immune-based stainings decreases the specificity of some of the measure reported here, which should be taken into account when interpreting these data. An additional limitation involves sampling of the most proximal and distal portions of the vessels, which omits the central portion of vessels, which limits the sensitivity of identifying structural vascular changes in this part of the vessel.

Future directions

We reported that the histological features of the posterior circulation differ from the anterior circulation in the degree of wall thickening, elastin content and concentric intimal thickening. Understanding the drivers of posterior circulation remodeling with immunological staining, hemodynamic measurements and genetic testing may broaden our overall understanding of brain arterial remodeling and open new ways to reduce the burden of related to intracranial arterial disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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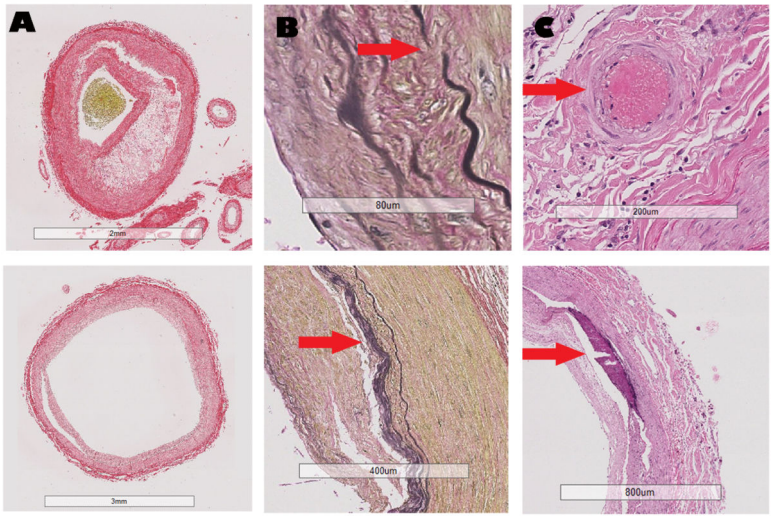

Figure 1. Examples of the arterial characteristics evaluated in this study

Legend: Column A, Red Sirius staining. Top: Evidence of necrotic core separated from the lumen by a thin fibrous cap in the context of eccentric intima thickening. Bottom: Concentric intima hyperplasia without evidence of cholesterol deposition. Column B, Van Gieson staining. Top: Evidence of gap in the internal elastic lamina (arrow). Bottom: Duplication of the internal elastic lamina (arrow). Column C, H&E staining. Top: evidence of *vasa vasorum* (arrow) in the adventitia of an artery. Bottom: Evidence of confluent arterial calcification in absence of cholesterol deposition or atheroma.

Table 1

Characteristics of the sample studied

Age, years (Mean ± SD, range)		56 ± 17, 21-81
Male sex (%)		63
Ethnicity (%)		
	Non-Hispanic white	75
	Black or African American	12
	Hispanic	13
Hypertension (%)		39
Diabetes (%)		17
Dyslipidemia (%)		21
Smoking (%)		52
Prior cardiac disease (%)		39
Evidence of brain infarct at autopsy (%)		17

Abbreviations: SD, standard deviation.

Table 2

Posterior circulation arteries compared with anterior circulation arteries

	Posterior circulation arteries		Basilar Artery	Vertebral arteries
	Model 0	Model 1	Model 1	Model 1
	Estimate ± SE	Estimate ± SE	Estimate ± SE	Estimate ± SE
Continuous variables				
Arterial wall thickness (microns)	−22 ± 9 *	−0.27 ± 9 †	−27 ± 9 †	15 ± 7 *
Media thickness (microns)	−5 ± 3	−5 ± 3	−5 ± 3	−7 ± 3 *
Arterial area encircled by the IEL (%)	1.2 ± 0.4 †	1.0 ± 0.4 *	1.7 ± 0.5 †	0.1 ± 0.5
Lumen stenosis (%)	1.5 ± 0.6 *	1.0 ± 0.6	−1.0 ± 0.8	2.5 ± 0.7 †
Categorical variables				
Elastin loss	0.7 ± 0.2 †	0.6 ± 0.2 †	0.8 ± 0.2 †	0.8 ± 0.2 †
Increased collagen deposition	−0.1 ± 0.2	−0.1 ± 0.2	−0.2 ± 0.2	−0.1 ± 0.2
Large artery amyloidosis	−0.1 ± 0.1	−0.1 ± 0.1	−0.1 ± 0.1	−0.1 ± 0.1
Concentric intima thickening	2.3 ± 0.2 †	2.4 ± 0.3 †	2.6 ± 0.4 †	2.8 ± 0.3 †
IEL gaps	0.2 ± 0.2	0.1 ± 0.2	−0.3 ± 0.2	0.2 ± 0.2
Any calcification	0.7 ± 0.3 *	0.6 ± 0.4	0.1 ± 0.4	1.3 ± 0.8
Vasa vasorum	0.7 ± 0.2	0.6 ± 0.2	−0.9 ± 0.5	2.2 ± 0.5 †

Abbreviations: IEL, internal elastic lamina

Model 0: Adjusted for artery location (proximal versus distal), interadventitial diameter and type (anterior cerebral artery, internal carotid artery, middle cerebral artery, etc.).

Model 1: Model 0 plus age, sex, ethnicity, hypertension, diabetes, dyslipidemia, smoking, country of origin.

* P value < 0.05

† P value < 0.005 (Bonferroni correction 0.05/11).

Table 3

Differences in atherosclerosis by anterior versus posterior brain arteries

	All posterior brain arteries	Basilar Artery	Vertebral arteries
	Model 1	Model 1	Model 1
	Estimate ± SE	Estimate ± SE	Estimate ± SE
AHA Athero score	−0.07 ± 0.07	−0.35 ± 0.09†	0.11 ± 0.08
Intima xanthoma	0.22 ± 0.28	0.24 ± 0.45	0.38 ± 0.35
Intima thickening	0.37 ± 0.23	0.12 ± 0.34	0.87 ± 0.30†
Pathological intima thickening	−0.15 ± 0.32	−1.06 ± 0.49*	0.56 ± 0.37
Fibrous cap atheroma	−0.14 ± 0.39	−0.81 ± 0.59	0.32 ± 0.52
Thin fibrous cap atheroma	−0.64 ± 0.45	−1.80 ± 0.51†	0.32 ± 0.54
Fibrocalcific plaque	0.20 ± 1.13	NA	1.78 ± 1.04
Percentage of plaque occupied by necrotic core	−3.1 ± 2.5	−5.3 ± 3.6	−2.9 ± 3.3
Fibrous cap thickness (microns)	13.0 ± 31.0	−11.0 ± 47.0	−20.0 ± 43.0
Area of atheroma (mm^3)	0.1 ± 0.1	0.2 ± 0.2	0.1 ± 0.2

Abbreviations: IEL, internal elastic lamina; NA, not available.

Model 1: artery location (proximal versus distal), arterial size, arterial type (anterior cerebral artery, internal carotid artery, middle cerebral artery, etc.), age, sex, ethnicity, hypertension, diabetes, dyslipidemia, smoking, country of origin.

*P value < 0.05

†P value < 0.005 (Bonferroni correction 0.05/10).

Table 4

Correlation between posterior circulation pathology with anterior circulation pathology

	All posterior brain arteries	Basilar Artery	Vertebral arteries
	Model 1	Model 1	Model 1
	Estimate ± SE	Estimate ± SE	Estimate ± SE
Continuous variables			
Arterial wall thickness (in microns)	0.09 ± 0.03 *	0.09 ± 0.03 *	0.10 ± 0.03 †
Media thickness (in microns)	0.12 ± 0.04 †	0.12 ± 0.04 †	0.13 ± 0.04 *
Arterial area encircled by the IEL	0.04 ± 0.03	0.05 ± 0.03	0.06 ± 0.04
Lumen stenosis (%)	0.13 ± 0.04 †	0.10 ± 0.05 *	0.14 ± 0.04 †
Categorical variables			
Concentric intima thickening	0.74 ± 0.50	1.06 ± 0.66	0.54 ± 0.51
Elastin loss	2.20 ± 0.49 †	2.47 ± 0.57 †	1.91 ± 0.55 †
Increased collagen deposition	0.68 ± 0.29 *	0.52 ± 0.41	0.78 ± 0.29 *
Large artery amyloidosis	2.36 ± 0.58 †	2.96 ± 0.51 †	1.92 ± 0.64 *
IEL gaps	0.51 ± 0.29	0.51 ± 0.36	0.51 ± 0.31
Any calcification	0.48 ± 0.55	0.71 ± 0.73	0.56 ± 0.78
Vasa vasorum	0.37 ± 0.64	−20.06	0.51
AHA atherosclerosis score	0.11 ± 0.02 †	0.08 ± 0.03 †	0.12 ± 0.02 †
Thin fibrous cap atheroma	2.19 ± 0.35 †	2.14 ± 0.46 †	2.22 ± 0.43 †

Abbreviations: IEL, internal elastic lamina;

Model 1: Adjusted for artery location (proximal versus distal), arterial size, arterial type (aca, ica, mca etc), age, sex, ethnicity, hypertension, diabetes, dyslipidemia, smoking, country of origin.

* P value < 0.05

† P value < 0.003 (Bonferroni correction 0.05/13).