Glycemic Status Underlies Increased Arterial Stiffness and Impaired Endothelial Function in Migrant South Asian Stroke Survivors Compared to European Caucasians

Pathophysiological Insights From the West Birmingham Stroke Project

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Background—The pathophysiology of an increased risk of cerebrovascular disease mortality among South Asians (SA) remains unclear. Indices of arterial stiffness and endothelial dysfunction are independent markers of vascular disease, having both prognostic and diagnostic implications. We hypothesized that there are ethnic variations in indices of arterial stiffness and endothelial dysfunction between SA and European Caucasian (EC) stroke patients, which may underlie a poorer prognosis in the former, and further investigated promoters of vessel wall abnormalities.

Methods—Using a cross-sectional approach, a total of 100 SA stroke survivors were prospectively recruited from the ongoing West Birmingham Stroke Project. Indices of vessel wall characteristics (arterial stiffness and endothelial function [change in reflective index]) were measured noninvasively using the digital volume pulse analysis technique in a temperature-controlled environment, using a direct standardized approach. SA stroke subjects were compared to 60 EC stroke survivors, 60 SA with risk factors, and 73 healthy controls.

Results—Among stroke patients, both ethnic groups were comparable for cardiovascular risk profile, except for more diabetes mellitus in SA (P=0.007) subjects and a higher prevalence of atrial fibrillation in EC (P=0.04) subjects. According to the TOAST and Bamford classifications, SA subjects had more small vessel (P=0.04) and lacunar infarctions (P=0.01). SA subjects had higher measurements of arterial stiffness (P<0.001) and impaired endothelial-dependent vascular function (change in reflective index %; P<0.001). On univariate analysis, endothelial function was negatively correlated with fasting plasma glucose (r=−0.4; P<0.001) and total cholesterol level (r=−0.2; P<0.001). On multivariate analysis, glycemic status was independently associated with impaired endothelial function (P=0.008) and increased arterial stiffness (P<0.001) among SA subjects.

Conclusion—SA stroke survivors had more small vessel disease-related cerebrovascular events compared to EC subjects. Underlying glycemic status in SA subjects had an adverse impact on the vascular system, leading to abnormal vessel wall characteristics. (Stroke. 2009;40:2298-2306.)

Key Words: arterial stiffness ■ endothelial function ■ glycemic status ■ South Asian

Stroke is a continuing yet preventable cause of significant morbidity and mortality in the Western world, and it will rapidly reach epidemic proportions in developing countries such as those across Asia.2-5 South Asians (defined as people originating from the Indian subcontinent) living in the United Kingdom have disproportionately higher rates of mortality from ischemic cerebrovascular disease than do the general population.4,5 According to the few available epidemiological studies, this excess cerebrovascular disease risk is closely allied with established cardiovascular comorbidities, but the precise pathophysiological mechanism underlying this excess risk among migrant South Asians remains poorly understood.

Indices of arterial stiffness and endothelial dysfunction are accepted as independent markers of vascular disease, having both prognostic and diagnostic implications.9,10 Established cerebrovascular disease risk factors such as diabetes and hypercholesterolemia are known to alter the underlying vessel wall characteristics,11 causing impaired endothelial function12 and increased arterial stiffness,12 with a consequent increase in greater cerebrovascular disease risk.13,14 South Asian stroke survivors in the United Kingdom have an increased prevalence of diabetes and hypertension,7 and it is likely that these established risk indices exert an adverse impact on the vessel wall characteristics of these individuals.
The objective of the present study was to test the hypothesis that indices of arterial stiffness and endothelial dysfunction are higher in South Asian stroke survivors compared to European Caucasians, and to investigate whether conventional cerebrovascular disease risk indices are able to explain these vessel wall abnormalities.

Materials and Methods
Using a stratified representative sampling approach, all the stroke patients were recruited from patients who initially presented to the acute hospitals of Sandwell and West Birmingham Hospital NHS Trust. The diagnosis of stroke was established on the basis of clinical symptoms supported by a cerebral imaging (CT/MRI scans) in accordance with the WHO criteria for diagnosis of acute stroke. In keeping with local hospital practice, which is based on standard national guidelines, each patient admitted with symptoms and signs of stroke is examined by a stroke physician before routine blood tests and special radiological investigations (CT/MRI) so that the diagnosis of acute stroke and its pathological type can be made within 72 hours. All CT/MRI scans were reported by a neuroradiologist and each patient’s clinical condition, including the functional status (EQ5D), stroke severity (using modified Rankin scale and Scandinavian Neurological Stroke scale), and neurological deficit, and were recorded on a standard clinical research form. Each patient was assessed by at least one ECG recording, with monitored with pressure measurements and carotid duplex scan imaging. Based on this information, ischemic stroke subtypes were classified according to TOAST and Bamford criteria by a qualified stroke physician.

All stroke patients with a history of first-ever ischemic stroke were included in the current study and were assessed >3 months from the initial presentation. Written informed consent was obtained, and the protocol was approved by the West Birmingham Research Ethics Committee.

South Asians were defined by self-reported ethnicity as being Indian, Pakistani, Sri Lankan, Nepalese, and Bangladeshi, and whose grandparents (at least 3) also originated from the Indian subcontinent. Information from the 2001 census revealed that between 20% and 25% of the 300,000 population of Sandwell are from ethnic minority groups (including Bangladeshi [1.21%], Indian [9.14%], and 25% of the 300,000 population of Sandwell are from ethnic minority groups). Using a stratified representative sampling approach, controls were also recruited from the same catchment area as the stroke patients (Sandwell and West Birmingham, West Midlands, United Kingdom). The total cohort (age 30–75 years) comprised people with and without any known established cardiovascular disease risk factors. South Asian risk factor controls were assessed clinically and included the following criteria: evidence of cardiovascular disease (hypertension, diabetes mellitus, hyperlipidemia), but without any established cardiovascular disease (stroke or TIA) or ischemic heart disease (MI, coronary artery bypass graft, or percutaneous coronary intervention). Hence, subjects who were without any of these risk factors and who were not using any regularly prescribed cardiovascular medications at the time of entry into the study were considered as healthy controls.

Systolic and diastolic brachial arterial blood pressure levels were measured with the validated semiautomatic Omron HEM-705CP (Omron Healthcare Europe). Fasting plasma glucose levels and cholesterol levels were measured using an auto analyser (Roche Cobas Integra 800).

Measurements of Arterial Stiffness
Arterial stiffness was measured using the digital volume pulse analysis (DVP) technique. The DVP analysis method is a noninvasive technique of measuring pulse wave reflections to determine the arterial stiffness peripherally. Arterial stiffness using this technique has been proven to be a validated, reproducible technique with minimal intraobserver variation. The stiffness index derived from this method has been demonstrated to have a good correlation to pulse wave velocity, whereas the sensitivity and specificity of this technique are comparable to the pulse wave velocity method in the identification of patients with latent cardiovascular disease.

Figure 1. Derivation of endothelial function by calculating the reflective index from digital volume pulse analysis technique. $X$ = forward wave/systolic peak, $Y$ = reflected wave/diastolic peak, $RI = [b/a] \times 100$; endothelial function $= \frac{RI_{baseline} - RI_{Salbutamol}}{RI_{baseline}} \times 100$.

Measurement of Endothelial Function
The reflective index (RI) is a parameter derived from the analysis of the DVP. Similar to other noninvasive measurements such as flow-mediated dilatation, this is an indirect method of determining endothelial function peripherally. Endothelium-dependent vessel function can be determined by calculating the relative change in reflective index ($\Delta RI$) after the administration of a nitric oxide (NO) releasing $\beta$-receptor stimulant agent such as Salbutamol. For comparison, endothelium-independent vessel function can be similarly calculated by administration of exogenous NO in the form glyceryl trinitrate (GTN).

Calculation of the Arterial Stiffness and Endothelial Function ($\Delta RI$)
The DVP waveform consists of a systolic peak (a) and a second diastolic peak (b), which is formed by the reflection of the pulse wave from the small arteries in the lower body (Figure 1). The time delay between the systolic and diastolic peaks is related to the transit time of pressure waves from the root of the subclavian artery to the apparent site of reflection and back to the subclavian artery. The degree of pulse wave reflection (arterial stiffness) depends on the impedance of the microvascular bed and the tone of the large and small blood vessels. This path length can be assumed to be proportional to height; therefore, the index of arterial stiffness can be calculated from: arterial stiffness = height/time delay between the systolic and diastolic peaks. The RI is the percentage of systolic pulse wave reflected in each cardiac cycle. Small artery function can be assessed by measuring absolute change in $\Delta RI$ from baseline after salbutamol ($R_{Sal}$) and GTN ($R_{GTN}$) administration. RI can be calculated from: $RI = [b/a] \times 100$ and the endothelial function is determined by: $\Delta RI = (R_{baseline} - R_{Sal/ GTN}) \times 100$.
Arterial Stiffness and Endothelial Measurement Protocol

Measurements of arterial stiffness and endothelial function were performed during the morning after an overnight fast (each subject was instructed to refrain from caffeine-containing beverages, alcohol, and smoking in the previous 12 hours), after which the DVP was recorded in the person’s right index finger. Subjects were laid supine, resting for at least 20 minutes in a temperature-controlled environment (24 ± 1°C) before the measurements were taken. All the volunteers were advised to refrain from talking and sleeping while the measurements were performed. Recorded digital pulse wave forms were used to predict indices of vessel reactivity (RI) and arterial stiffness using a standard validated protocol.32 Each person had at least 3 measurements (recorded for 30 seconds) taken 1 minute apart, and an average was calculated and used for the analysis. Thereafter, subjects were given a predetermined dose of Salbutamol by inhalation (400 micrograms via a spacer device) and sublingual GTN (200 micrograms), each separated by a washout period of 60 minutes. Relative change in RI was calculated as (RI after drug - RI baseline) / RI baseline × 100%. The measurements were performed by the same operator. Intraobserver variation (coefficient of variation) of the repeated measurements of arterial stiffness in the same subject on the same day and 6 weeks later was 5.4% and 7.4%, respectively,25 confirming the findings from recent studies by our group and others that the DVP analysis technique has been shown to have excellent repeatability and reproducibility (mean difference [SD], −0.2 [4.9%]).

Power Calculation and Statistical Analysis

Based on previous work by our group and other pilot data,22 to have 80% power at 0.05 and to observe ½ SD difference in arterial stiffness and RI, at least 60 people were needed in each group. After being tested for normality using the Kolmogorov-Smirnov test, all the indices measured demonstrated a normal distribution. Data are presented as the mean±SD, and Student t test and 1-way ANOVA tests were used to determine differences between groups with continuous variables. The χ2 test was used to compare the categorical variables. In univariate analysis, Pearson correlation was used to test the relationship between arterial stiffness and other cardiovascular risk indices. Linear regression models were used for multivariate analysis. A 2-tailed P<0.05 was considered statistically significant for all comparisons. Data were analyzed using SPSS version v14 (SPSS Inc).

Results

South Asian stroke survivors (70% male; mean age, 62.6 years; SD, 13 years) were initially compared to 60 age- and gender-matched European Caucasian counterparts (Table 1). The majority of the South Asian stroke survivors were of Indian origin (67%). Both ethnic groups were comparable for cardiovascular risk profile, except for the higher prevalence of diabetes mellitus in South Asians (46.5% vs 25.1%; P=0.007) and atrial fibrillation in European Caucasians (13.3% vs 3.8%; P=0.04). Among South Asians there was a lower prevalence of alcohol and tobacco consumption (P=0.01) compared to European Caucasians. The majority were using antidiabetic (South Asians, 64% vs European Caucasian, 26%; P<0.002) lipid-lowering (South Asians, 96% vs European Caucasians, 94.6%), and antihypertensive (South Asians: 80% vs European Caucasians: 86%) medications. The use of warfarin (P=0.04) and dipyridamole (P=0.03) was higher among European Caucasian stroke patients, whereas there was a greater use of sulfonylureas (P<0.001) among South Asian stroke survivors.

Of the total cohort, 9.5% of the stroke patients with clinical symptoms of stroke had normal CT/MRI scan results, without any evidence of ethnic variation. The majority had radiological evidence of fronto-parietal infarctions: 37.1% of the South Asian stroke patients had evidence of anterior circulation infarcts compared to 51.7% of European Caucasians (P<0.05). The majority of the South Asians had normal duplex scan results (76.3% vs 36.7%; P<0.001). Of the patients with abnormal scan findings, 20.1% European Caucasians demonstrated evidence of significant carotid artery stenosis (>50%; Table 1).

Stroke Severity, Functional Status, and Stroke Subtypes

At baseline and according to the Scandinavian Neurological Stroke scale and modified Rankin scale scores, both ethnic groups had similar stroke severity and functional status (P>0.05). At follow-up, both groups had improvement of their Scandinavian Neurological Stroke scale and modified Rankin scale scores (South Asians, 46.5; SD, 7.8 vs European Caucasian, 43.8; SD, 9.6; P<0.01). Compared to the baseline scores, South Asians had greater improvement of the Scandinavian Neurological Stroke scale score (13.2 vs 5.4; P=0.001) compared to European Caucasians. EQ5D assessment was comparable between both ethnic groups. According to the Bamford and TOAST criteria, South Asians had higher small-vessel and lacunar infarctions, (29.6 vs 15.5; P=0.04) and (32.6 vs 13.3; P=0.01), respectively, compared to European Caucasians. In European Caucasians, 26.7% of the strokes were attributable to cerebral large-vessel disease compared with 16.7% among South Asians (P=0.03; Table 1).

Stroke Subjects Compared to Risk Factor and Healthy Controls

South Asian stroke survivors had significantly elevated serum cholesterol and plasma glucose levels, as well as body mass index compared to European Caucasians (P<0.05). Blood pressure parameters were comparable. As expected, compared to controls, stroke survivors had significantly higher risk indices (P<0.05), but similar waist-to-hip ratio measurements (Table 2).

Measurements of Arterial Stiffness and Endothelial Function

Indices of arterial structure and function were available for 277 (South Asian, 217; European Caucasian, 60) individuals. Of the total cohort, arterial stiffness measurements were significantly higher in South Asian stroke patients compared to European Caucasians (P<0.001; Figure 2). Compared to healthy controls, all other groups had significantly higher arterial stiffness (P<0.001; Table 2). In a separate analysis, comparing South Asian stroke patients vs South Asian risk factor controls, arterial stiffness remained significantly higher among South Asian stroke patients (P=0.002). In a subgroup analysis among South Asians, arterial stiffness was significantly higher in diabetic subjects compared to nondiabetic subjects (P<0.05), whereas RI was
<table>
<thead>
<tr>
<th></th>
<th>South Asian Stroke (N=100) %</th>
<th>European Caucasian Stroke (N=60) %</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
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<td>65.1</td>
<td>0.49</td>
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<tr>
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<tr>
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<td>10.1</td>
<td>15</td>
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<td>32.6</td>
<td>13.3</td>
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<tr>
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<td>Monoparesis</td>
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<td>Aphaslic</td>
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<td>0.89</td>
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<tr>
<td>Expressive</td>
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<td>0.04</td>
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<td>0.187</td>
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<td>6.7</td>
<td>0.35</td>
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<td>0.23</td>
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<tr>
<td>Fronto parietal</td>
<td>42.9</td>
<td>43.3</td>
<td>0.67</td>
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<tr>
<td>Temporal</td>
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<td>0.56</td>
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<tr>
<td>Internal capsule</td>
<td>8.7</td>
<td>6.9</td>
<td>0.78</td>
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<tr>
<td>Cerebellar</td>
<td>6.5</td>
<td>6.9</td>
<td>0.88</td>
</tr>
<tr>
<td>Basal ganglion</td>
<td>30.4</td>
<td>19.0</td>
<td>0.08</td>
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<td>Unspecified</td>
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<td>3.4</td>
<td>0.15</td>
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<td>Duplex scan</td>
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<td>Normal</td>
<td>76.3</td>
<td>36.7</td>
<td>&lt;0.001</td>
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<tr>
<td>&gt;50% stenosis</td>
<td>2</td>
<td>20.1</td>
<td>&lt;0.001</td>
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<tr>
<td>&lt;50% stenosis</td>
<td>11.8</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>9.9</td>
<td>16.0.5</td>
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</tr>
</tbody>
</table>

(Continued)
Table 1. Continued

|                        | South Asian Stroke (N=100) % | European Caucasian Stroke (N=60) % | P  
|------------------------|------------------------------|-----------------------------------|------
| Stroke severity        |                              |                                   |      
| SSNS score baseline    | 33.3 (9.5)                   | 38.4 (8.3)                        | 0.15 |
| SSNS score follow-up   | 46.5 (7.8)                   | 43.8 (9.6)                        | 0.01 |
| Follow-up duration     | 18.8 (1.3)                   | 20.45 (1.2)                       | 0.71 |
| MRS score baseline     | 2.0 (0.7)                    | 3.3 (0.1)                         | 0.08 |
| MRS score follow-up    | 8.83 (1.1)                   | 8.17 (2.1)                        | 0.38 |
| EQSD follow-up         | 17.4 (1.01)                  | 1.74 (0.1)                        | 0.34 |
| MRS score improvement  | 1.7                          | 1.6                               | 0.8  |
| SSNS score improvement | 13.2                         | 5.4                               | 0.001|

P comparing South Asians vs European Caucasians significance at P<0.05.

ACEI indicates angiotensin-converting enzyme inhibitor; CVD, cardiovascular disease; EQSD, measure of health outcome; LACI, lacunar infarct; MRS, modified Rankin scale; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; SSNS, Scandinavian Neurological Stroke scale; TACI, total anterior circulation infarct.

The endothelium-dependent vascular function of each individual was calculated by determining the relative change in RI (ΔRI %) after salbutamol inhalation. South Asian stroke patients had significantly poorer endothelial function when compared to European Caucasians (P<0.001; Figure 2B). As expected, South Asian healthy controls had significantly better endothelial function compared to groups with risk factors (P=0.001). In subgroup analysis, patients with diabetes were demonstrated to have significantly poorer endothelial function in both ethnic groups (P<0.01). However, this difference was most notably present among South Asian individuals with stroke. Furthermore, endothelial function was significantly poorer among South Asian stroke patients with lacunar and large-vessel disease strokes compared to European Caucasians (P<0.01), as shown in Table 4.

Analysis of the South Asian stroke patients according to arterial stiffness and ΔRI % tertiles revealed that the majority of South Asian stroke survivors with diabetes had the highest arterial stiffness and poorest endothelial function (Figure 3).

Correlations and Multivariate Regression

On univariate analysis, there was a significant negative association (R) between arterial stiffness and ΔRI (R=-0.28; P<0.001) and arterial stiffness and age (R=0.27; P<0.001) for the total population. Arterial stiffness was significantly associated with fasting plasma glucose (R=0.45; P<0.001), total cholesterol (R=0.24; P<0.001), waist–hip ratio (R=0.3; P<0.001), and mean arterial pressure (R=0.2; P=0.002) among South Asians, and with a total cholesterol level (R=0.3; P=0.01) among European Caucasians. There was a negative association between endothelial function and fasting glucose (R=-0.4; P<0.001), total cholesterol (R=-0.18; P<0.001), and age (R=0.28; P<0.001) among South Asians, and with a total cholesterol level (R=0.3; P<0.001) among European Caucasians. The effect of race and diabetes on arterial stiffness and endothelial function was explored using multivariate regression analysis. The results are shown in Table 5.

Table 2. South Asians vs European Caucasians With Established Cardiovascular Risk Indices

<table>
<thead>
<tr>
<th></th>
<th>SA Stroke (n=100)</th>
<th>EC Stroke (n=60)</th>
<th>SA Risk (n=60)</th>
<th>SA Healthy (n=73)</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.6 (13)</td>
<td>64 (8)</td>
<td>65.2 (9)</td>
<td>50 (15)</td>
<td>0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>6.2 (1.3)</td>
<td>5.4 (0.9)</td>
<td>3.1 (1.7)</td>
<td>2.6 (1.4)</td>
<td>0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L, diabetic subjects</td>
<td>7.2 (0.9)</td>
<td>5.6 (1.2)</td>
<td>3.8 (1)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Fasting plasma glucose, mmol/L, nondiabetic subjects</td>
<td>5.3 (1)</td>
<td>3.6 (0.6)</td>
<td>3.4 (0.8)</td>
<td>3.3 (0.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>33.2 (4.6)</td>
<td>30.1 (5.8)</td>
<td>27.4 (3.8)</td>
<td>25.9 (3.2)</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.95 (0.1)</td>
<td>0.94 (0.1)</td>
<td>0.93 (0.1)</td>
<td>0.91 (0.1)</td>
<td>0.23</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>100.7 (12)</td>
<td>110.5 (13)</td>
<td>107 (11)</td>
<td>100.5 (13)</td>
<td>0.9</td>
<td>0.21</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.4 (0.5)</td>
<td>2.7 (0.7)</td>
<td>4.4 (0.7)</td>
<td>4.1 (0.8)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>1.7 (0.7)</td>
<td>1.8 (0.7)</td>
<td>2.7 (0.9)</td>
<td>2.5 (0.9)</td>
<td>0.75</td>
<td>&lt;0.001</td>
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<td>HDL, mmol/L</td>
<td>0.92 (0.3)</td>
<td>0.98 (0.2)</td>
<td>1.0 (0.3)</td>
<td>0.99 (0.3)</td>
<td>0.74</td>
<td>0.02</td>
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<tr>
<td>Mean systolic pressure, mm Hg</td>
<td>141.5 (21)</td>
<td>135.79 (20)</td>
<td>147.5 (15)</td>
<td>130 (16)</td>
<td>0.9</td>
<td>0.02</td>
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<tr>
<td>Mean diastolic pressure, mm Hg</td>
<td>79.7 (11)</td>
<td>78.7 (12)</td>
<td>84.4 (11)</td>
<td>82.3 (12)</td>
<td>0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate per min</td>
<td>69.2 (15)</td>
<td>68.4 (11)</td>
<td>70.4 (10)</td>
<td>69.5 (9)</td>
<td>0.83</td>
<td>1</td>
</tr>
<tr>
<td>Arterial stiffness (SI) m/sec</td>
<td>11.3 (2)</td>
<td>9.7 (2)</td>
<td>10.1 (2)</td>
<td>9.3 (2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endothelial function after Salbutamol, (ΔRI) %</td>
<td>4.3 (0.3)</td>
<td>7.9 (0.6)</td>
<td>7.1 (0.3)</td>
<td>10.2 (0.5)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After GTN RI</td>
<td>52.5 (13)</td>
<td>54.8 (11)</td>
<td>55.6 (13)</td>
<td>48 (11)</td>
<td>0.9</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*P=comparing South Asian (SA) vs European Caucasian (EC) stroke survivors; significance at P<0.05 level using unpaired t test.
†P=comparing across all groups; significance at P<0.05 levels using 1-way ANOVA.

SI indicates stiffness index.
In a multivariate regression analysis, South Asian ethnicity was independently associated with both arterial stiffness and endothelial function in a stepwise model that included age, gender, diabetes, hypertension, hypercholesteremia, heart rate, waist-to-hip ratio, smoking, and alcohol consumption status (Table 5). In a separate model, South Asian ethnicity was independently associated with diabetic status ($\beta = -0.21; \text{CI}, -0.3--0.06; P=0.007$), whereas glycemic status was independently associated with both arterial stiffness and endothelial function among South Asians. In these models, only 24% of the endothelial function abnormalities and 15% of the arterial stiffness aberrancies were explained by the presence of traditional risk factors among South Asians (Table 5).

**Discussion**

The aim of this study was to investigate the structural and functional properties of the arterial wall in a large migrant South Asian stroke population. In keeping with our original hypothesis, South Asian stroke survivors had significantly impaired endothelial function and increased arterial stiffness compared to an age- and gender-matched European Caucasian population. More importantly, of all the conventional risk factors, glycemic status was independently associated with both structural and functional vascular abnormalities. Given that we previously reported the higher prevalence of diabetes among South Asian stroke survivors compared to European Caucasians,7 and impact of diabetes on South Asian stroke mortality,6 in which people with diabetes had poor 5-year poststroke survival rates, the present study provides a pathophysiological insight for these findings.

According to the current analysis, South Asian ethnicity per se was a significant risk factor, suggesting an underlying aberrant genetic susceptibility. However, 15% to 24% of the abnormalities were explained by prevalence of traditional risk factors, including glycemic status. Hence, not only is diabetes more common among South Asians compared to other ethnic groups,33 but also it is likely that this is a hereditable risk factor in this population.34 In the current study, >40% of the South Asian stroke survivors had evidence of diabetes, and

**Figure 2.** A, Measurements of endothelial function ($\Delta R_I$) among South Asian (SA) vs European Caucasian (EC) stroke patients. B, Measurements of arterial stiffness (SI) among SA vs EC stroke patients. DM indicates diabetes mellitus. $P$ value using 1-way ANOVA comparing vascular risk indices across all groups.

$P<0.03$, body mass index ($R=-0.2; P=0.007$), and WHR ($R=-0.17; P=0.02$) among South Asians, but no significant association was apparent among European Caucasian stroke survivors.

**Table 3.** South Asians vs European Caucasians With Established Cardiovascular Risk Indices According to Glycemic Status

<table>
<thead>
<tr>
<th></th>
<th>South Asians</th>
<th></th>
<th>P</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Diabetes (N=55)</td>
<td>Without Diabetes (N=105)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.3 (10)</td>
<td>60 (14)</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>100 (14)</td>
<td>101.4 (13)</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>143 (19)</td>
<td>139 (22)</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg</td>
<td>77.6 (11)</td>
<td>83.1 (11)</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.09 (0.8)</td>
<td>3.07 (0.7)</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>0.96 (0.3)</td>
<td>1 (0.3)</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>1.8 (0.9)</td>
<td>2.4 (0.9)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>6.8 (0.8)</td>
<td>3.4 (0.8)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.2 (3.9)</td>
<td>27 (3.4)</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94 (0.1)</td>
<td>0.93 (0.1)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SI, m/sec</td>
<td>11.7 (1.6)</td>
<td>9.9 (1.7)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial function ($\Delta R_I$), %</td>
<td>4.1 (0.3)</td>
<td>8.9 (0.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$P$ comparing South Asians vs European Caucasians stroke survivors; significance at $P<0.05$ levels using unpaired $t$ test.
diabetes status was independently associated with South Asian ethnicity. More importantly, patients with diabetes had the greatest vessel wall abnormalities. It is likely that shown independent interactions between diabetic status and South Asian ethnicity may further explain the demonstrated vascular abnormalities. However, endothelial dysfunction independently predicted increased arterial stiffness among South Asians, which in turn was associated with the highest indices of arterial stiffness. Thus, part of the remodeling processes that have occurred in the vessel wall could be attributed by a primary defect in the endothelium. Glycemic status has an impact on the endothelium-derived NO production, causing a blunted smooth muscle relaxation response in the small to medium vessel walls, with a consequent increase in vessel tone, contributing to increased arterial stiffness.

This hypothesis is further supported by our findings of the current analysis, after the administration of GTN, both groups had similar reflective indices compared to those produced after Salbutamol administration, indicating similar dilation of the vessels wall in both ethnic groups in the presence of adequate NO availability. NO availability is increased using GTN rather than Salbutamol, because the former is an external NO donor drug, whereas the latter acts on the beta adrenoreceptors of the endothelium to release endogenous NO, where the response is based merely on the functional integrity of the endothelium.

In addition, the simultaneous presence of other metabolic, inflammatory, and oxidative stress-related abnormalities that are known to manifest among South Asians may cause a synchronized (adverse) impact on the vascular system. Adverse diet and lifestyle differences observed in migrant South Asians may further augment this unfavorable risk profile despite a lower prevalence of smoking. The present study also demonstrates the clear differences in the distribution of stroke subtypes, whereby South Asian stroke patients had more small-vessel disease (lacunar infarctions) compared to more prevalent large-vessel strokes among European Caucasians. This is consistent with other published studies, particularly among a stroke population with higher prevalence of diabetes. However, De Silva et al recently demonstrated higher rates of intracranial large vessel disease, even among patients with lacunar infarctions, using intracranial Doppler imaging. More studies using more sophisticated imaging methods are needed to determine exactly the type of intracranial vascular pathology among South Asian stroke patients.

This is the first study to our knowledge to report indices of stroke severity among South Asian stroke survivors compared to European Caucasians. In the current study, the severity of the stroke was assessed using 2 validated and commonly used scales. The Modified Rankin scale provides a score based predominantly on the patient’s mobility and motor function as a whole, whereas the Scandinavian Neuropsychiatric Stroke scale is more comprehensive in enabling the user to consistently rate all other parameters such as vision, speech, and continence. At presentation, both ethnic groups had similar stroke severity according to both scales.

**Table 4. Indices of Arterial Stiffness and Endothelial Function According to Stroke Subtypes Comparing South Asians vs European Caucasians**

<table>
<thead>
<tr>
<th>Arterial Stiffness (SI, ms⁻¹)</th>
<th>Endothelial Function (ΔRI%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>EC</td>
</tr>
<tr>
<td>Bamford classification</td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>11.5 (1)</td>
</tr>
<tr>
<td>PACI</td>
<td>10.9 (1)</td>
</tr>
<tr>
<td>Lacunar infarctions</td>
<td>10.6 (2)</td>
</tr>
<tr>
<td>POCI</td>
<td>10.6 (2)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>12.5 (10)</td>
</tr>
<tr>
<td>TOAST classification</td>
<td></td>
</tr>
<tr>
<td>Large-vessel disease</td>
<td>11.6 (1)</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>11.7 (1)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>10.1 (2)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>11.6 (2)</td>
</tr>
</tbody>
</table>

*p using independent t test comparing South Asians (SA) vs European Caucasians (EC); significance at <0.05 level.

**Endothelial Dysfunction**

**Arterial Stiffness**

*Figure 3. Distribution of endothelial dysfunction and arterial stiffness among South Asian stroke survivors according to diabetic status in tertiles. Endothelial function tertiles (ΔRI%) %: E1: >8.8; E2: 5.3–8.8; E3: <5.2; arterial stiffness tertiles (ms⁻¹): S1: <9.1; S2: 9.2–11.1; S3: >11.2.*
However, South Asian stroke survivors were found to have significant overall improvement assessed by the Scandinavian Neurological Stroke scale score after a similar period of follow-up. Ethnicity has been previously reported as an independent predictor of stroke severity, and the possible reasons for this difference merit further investigation.

Conclusions
A potential limitation of this study is that this is not a true population-based study, because majority of the patients were recruited from hospitals. As previously reported, the majority of the South Asians are known to seek hospital admission early, and no differences have been observed in hospital admission rates among South Asians when compared to other ethnic groups. The stable population structure observed among ethnic groups in the hospital catchment area over the studied period also legitimizes the comparison. However, assignment of ethnicity is not always reliable and the multiple methods used to identify South Asian ethnicity (self-reported ethnicity, identification of South Asian names) minimizes this potential source of bias. Socioeconomic differences among 2 ethnic groups may have confounded the analysis, but we attempted to minimize this effect by recruiting all the patients from areas with a similar deprivation index and from a same geographical region. Another potential limitation of this study was stroke subtyping was performed by a stroke physician based on the available information on the stroke registry at the time of the presentation. However, this was minimized by rechecking the score against a standard questionnaire and reviewing the case notes accordingly by a second physician. In addition, stroke subtyping was based only on CT/MRI imaging, in which scans of the smaller percentage of the patients who had lacunar infarctions could have been reported as “normal.” Use of more novel invasive imaging techniques, such as subtraction or perfusion imaging techniques, would have minimized these stroke subtyping errors. Moreover, this study may not have the power to observe the differences in vascular measurements in stroke subtypes between the 2 ethnic groups. Other limitations of the current study include the cross-sectional nature of the design and use of single indirect indices to measure endothelial function and arterial stiffness, but these methods have been validated against other invasive and noninvasive methods and have been used in many other clinical studies. The diagnosis of diabetes mellitus was also made on the basis of fasting blood glucose measurements and available documented evidence. None of the volunteers had an oral glucose tolerance test performed for specific disease exclusion.

In conclusion, South Asian stroke survivors had more small-vessel disease-related cerebrovascular events compared to European Caucasians. Underlying glycemic status in South Asians had an adverse impact on the vascular system, leading to abnormal vessel wall characteristics.

References


20. Deleted in proof.


Glycemic Status Underlies Increased Arterial Stiffness and Impaired Endothelial Function in Migrant South Asian Stroke Survivors Compared to European Caucasians.

Pathophysiological Insights From the West Birmingham Stroke Project

Ashan Gunarathe, Jeetesh V. Patel, Shahid Kausar, Brian Gammon, Elizabeth A. Hughes and Gregory Y.H. Lip

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