

## Large-vessel stenosis in the patients with ischemic stroke in Iran: Prevalence, pattern, and risk factors

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### Abstract

**Running Title:** Large-vessel stenosis in ischemic stroke. [#of figures: 2, # of tables: 2]

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**Background**—Large artery disease (LAD) is a common cause of stroke, but a little is known regarding its role in Iranian stroke patients. The current study investigates the prevalence and risk factors for cervicocephalic arterial stenosis in the patients with ischemic stroke using digital subtraction angiography (DSA).

**Methods**—This was a prospective cross-sectional study performed in hospitals affiliated to Shiraz University of Medical Sciences from March 2011 to March 2013. Patients with ischemic stroke underwent noninvasive vascular and cardiac investigations to find the etiology of the stroke. Patients suspected of having large artery stenosis underwent DSA. The severity of the stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy (NASCET) and Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial criteria. The presence of cigarette smoking, hyperlipidemia, hypertension, and diabetes mellitus were documented for all subjects.

**Results**—A total of 3703 stroke patients were identified. Of them, 342 patients (62.3%, male) underwent DSA for LAD. The mean age at the time of angiography was 66.7±10.3 years. Extracranial and intracranial arteries were involved in 305 (89.2%) and 162 (47.4%), respectively. And 301 patients (88%) had anterior circulation and 128 patients (37.4%) had posterior circulation involvement. Diabetes mellitus but not age, sex, hypertension, hyperlipidemia, or smoking was significantly associated with intracranial involvement. (P = 0.002)

**Conclusion**—It can be concluded that the distribution of the large arterial atherosclerotic disease in Iran is similar to that seen in North America and Europe. Intracranial stenosis was more prevalent in diabetic patients.

## Keywords

Stroke; Ischemic; Stenosis; Occlusion; Cerebral Angiography; Extracranial; Intracranial

## Introduction

Stroke is among the leading causes of mortality and disability in both developed and developing countries.<sup>1</sup> LAD is an important cause of stroke due to its high prevalence, frequent recurrence, and treatable nature.<sup>2</sup>

Although noninvasive studies, such as color Doppler sonography (CDS), transcranial Doppler sonography (TCD), magnetic resonance angiography (MRA), and computerized tomographic angiography (CTA), have been used to evaluate patients with ischemic strokes, cerebral DSA is the gold standard for identifying and quantifying atherosclerotic stenoses.<sup>3</sup>

Stroke is a crucial health problem in the Middle East. Previous studies have shown a higher prevalence and higher in-hospital mortality compared with western countries.<sup>4</sup> Despite these facts, data regarding the pattern of the different causes of stroke is limited. It has been shown that genetics, diet, and the distribution of atherosclerosis risk factors of the Iranian population are different with both Caucasians and Asians.<sup>4</sup> Accordingly, results from other populations cannot be applied to Iranians. In particular, the distribution of large-vessel involvement in the patients with ischemic stroke in the Middle East has not been thoroughly studied. We performed this study in order to determine the distribution of cervicocephalic arterial stenosis in the patients with ischemic stroke using DSA.

## Methods

Prospectively collected cross-sectional data were collected on patients seen in Kowsar and Alzahra hospitals affiliated to Shiraz University of Medical Sciences from March 2011 to March 2013.

We included consecutive patients who were admitted to the neurology wards of the teaching hospitals of Shiraz University of Medical Sciences fulfilling all inclusion and exclusion criteria. These are high-volume referral centers for stroke in southwestern Iran.

Ischemic stroke was defined according to the Recognition of Stroke in the Emergency Room scale as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients, documented by a brain CT or an MRI indicating the presence of infarction

and the absence of hemorrhage.<sup>5</sup> Patients with acute ischemic infarcts underwent noninvasive vascular and cardiac investigations, including electrocardiography, transthoracic echocardiography (transesophageal echocardiography, if needed), CDS of cervical arteries, TCD, brain and neck CTA and/or brain and neck MRA, and evaluation for vasculitis, to find the etiology of the stroke.

According to the results of these investigations, patients with acute ischemic stroke were classified according to causative classification of stroke (CCS) criteria.<sup>6</sup> The CCS system classifies stroke etiology in five major categories: 1) large artery atherosclerosis, 2) cardio aortic embolism, 3) small artery occlusion (lacunar), 4) other uncommon causes, and 5) undetermined causes. The undetermined cause subtypes included (Va) patients with two or more “possible” or “evident” mechanisms for stroke and (Vb) patients for whom definite or possible causes of stroke could not be found with noninvasive tools. Patients with subtypes I and Va were included.

Patients with intracranial hemorrhage, cerebral infarcts with a cardio aortic embolic cause (CCS II), lacunar stroke (CCS III), vasculitis, arterial dissection, or fibromuscular dysplasia, (CCS IV) were excluded. In addition, patients who were comatose or had severe neurologic deficit (NIHSS > 18) were excluded.

Patients who had relative contraindications for angiography, including coagulopathy, previous anaphylactoid reaction to contrast media or hypersensitivity to such agents, acute renal failure or severe chronic non-dialysis-dependent kidney disease, unexplained fever, or untreated active infection, were also excluded.

All patients who had stenosis of more than 50% in non-invasive procedures and needed to be evaluated for carotid endarterectomy, carotid/vertebral angioplasty and stenting, or intracranial stenting underwent DSA. Some patients who had controversial findings in CTA and MRA were also considered for DSA.

DSA was performed utilizing standard procedures. Severity of stenosis was calculated according to the NASCET and WASID Trial criteria.<sup>7,8</sup> The severity of stenosis was dichotomized between patent (0%–49%) and stenotic (50%–100%).

**Table 1. Demographic manifestations and frequency of more than 50% stenosis in cervical and cerebral arteries (for bilateral arteries right and/or left side involvements were considered).**

Involved Artery	All Patients N = 342 [Stenosis (%) / Total Occlusion (%)]	Males N = 213 [Stenosis (%) / Total Occlusion (%)]	Females N = 129 [Stenosis (%) / Total Occlusion (%)]	P-Value [Stenosis (%) / Total Occlusion (%)]
<i>Innominate artery</i>	0(0%)/1(0.3%)	0(0%)/0(0%)	0(0%)/1(0.8%)	_/0.4
<i>Common carotid arteries</i>	41(12%)/4(1.2%)	26(12.2%)/4(1.9%)	15(11.6%)/0(0%)	0.9/0.3
<i>Extracranial internal carotid arteries</i>	203(59.4%)/53(15.5%)	130(61%)/36(16.9%)	73(56.6%)/17(13.2%)	0.4/0.4
<i>Intracranial internal carotid arteries</i>	50(14.6%)/39(11.4%)	32(15%)/27(12.7%)	18(14%)/12(9.3%)	0.8/0.3
<i>Middle cerebral arteries</i>	37(10.8%)/7(2%)	21(9.9%)/2(0.9%)	16(12.4%)/5(3.9%)	0.5/0.1
<i>Anterior cerebral arteries</i>	11(3.2%)/0(0%)	5(2.4%)/0(0%)	6(4.7%)/0(0%)	0.2/_
<i>Subclavian arteries</i>	5(1.4%)/0(0%)	4(1.9%)/0(0%)	1(0.8%)/0(0%)	0.7/_
<i>Extracranial vertebral arteries</i>	85(24.8%)/21(6.1%)	55(25.9%)/16(7.5%)	30(23.3%)/5(3.9%)	0.6/0.2
<i>Intracranial vertebral arteries</i>	7(2%)/0(0%)	4(1.9%)/0(0%)	3(2.3%)/0(0%)	1/_
<i>Basilar artery</i>	14(4.1%)/0(0%)	9(4.2%)/0(0%)	5(3.9%)/0(0%)	0.9/_
<i>Posterior cerebral arteries</i>	20(5.8%)/3(0.9%)	15(7%)/3(1.4%)	5(3.9%)/0(0%)	0.2/0.3

\* Demonstrates the statistical difference of stenosis/occlusion between male and female populations.

Large artery stenosis was defined as the presence of stenosis in the innominate artery (IA); common carotid arteries (CCA); internal carotid arteries (ICA); subclavian arteries; vertebral arteries (VA); basilar artery; and anterior, middle, and posterior cerebral arteries (MCA, ACA, and PCA) according to the Reed definition.<sup>9</sup>

The extracranial arteries were considered to be the IA, right and left CCA, cervical ICA, subclavian arteries, and V1, V2, and V3, segments of VA. The intracranial arteries were the anterior, middle, and posterior cerebral arteries (MCA, ACA, and PCA); the petrous, laceral, cavernous, clinoid, and terminal (communicating) segments of ICA; the V4 segment of VA; and the basilar artery.

Major cerebrovascular risk factors were investigated for all subjects. They included current or previous cigarette smoking, hyperlipidemia (positive history fasting total cholesterol level >200 mg/dL, LDL > 130 mg/dL, and/or fasting triglycerides level >180 mg/dL), arterial hypertension (positive history, systolic blood pressure > 140 mmHg, and/or diastolic pressure >90 mmHg out of the acute phase, treated or not), and diabetes mellitus (positive history and/or fasting plasma glucose >126 mg/dL out of the acute phase).

All patients signed informed consent for DSA. The study protocol was approved by the Institutional Review Board of Shiraz University of Medical Sciences. (89-01-01-2614)

Statistical analyses were performed using SPSS statistical analysis software, version 16.0 (SPSS Inc., Chicago, IL, USA). The analysis proceeded in two stages. First, a univariate analysis was performed as follows. Normality of each continuous variable was observed on the Kolmogorov–Smirnov test. Continuous data are presented as means, standard deviations, and 95% confidence inter-

vals (CIs); categorical data are reported as proportions. The Kruskal–Wallis test was performed to test for statistical relationships between age and patterns of vascular involvement. The Pearson chi-square and Fisher's exact tests were used for determination of any statistical relationships between categorical parameters. In the second step, multinomial logistic regression modeling was used for determination of the risk factors effect on the pattern of vascular involvement. The associations were considered significant when the *P*-value was <0.05.

## Results

During study time, 3703 stroke patients were seen. Of them, 2849 patients (76.9%) had ischemic stroke. Among patients with ischemic stroke the subtypes were 324 patients CCS I (11.4%), 338 patients CCS II (11.9%), 704 patients (24.7%) CCS III, 30 patients (1%) CCS IV, and 215 patients (7.5%) CCS Va. A total of 1238 patients (43.5%) had CCS Vb, and 539 patients had large arterial disease as the sole (CCS I) or part of the etiology of the stroke (CCS Va) confirmed by non-invasive studies. One hundred ninety-seven patients were excluded due to presence of at least one exclusion criterion. Three hundred forty-two patients underwent DSA.

Two hundred and thirteen patients (62.3%) were male and 129 patients (37.7%) were female. The mean age ( $\pm$  standard deviation) at the time of angiography was 66.7 years ( $\pm$ 10.3), 95% CI (65.5–67.7). The minimum age at time of referral was 42 years and the maximum age was 88 years.

Patterns of cerebral arteries involvement and their demographic manifestations are summarized in Table 1 and Figures 1 and 2.

Overall, extracranial arteries were involved in 305 (89.2%) patients, whereas intracranial arteries were

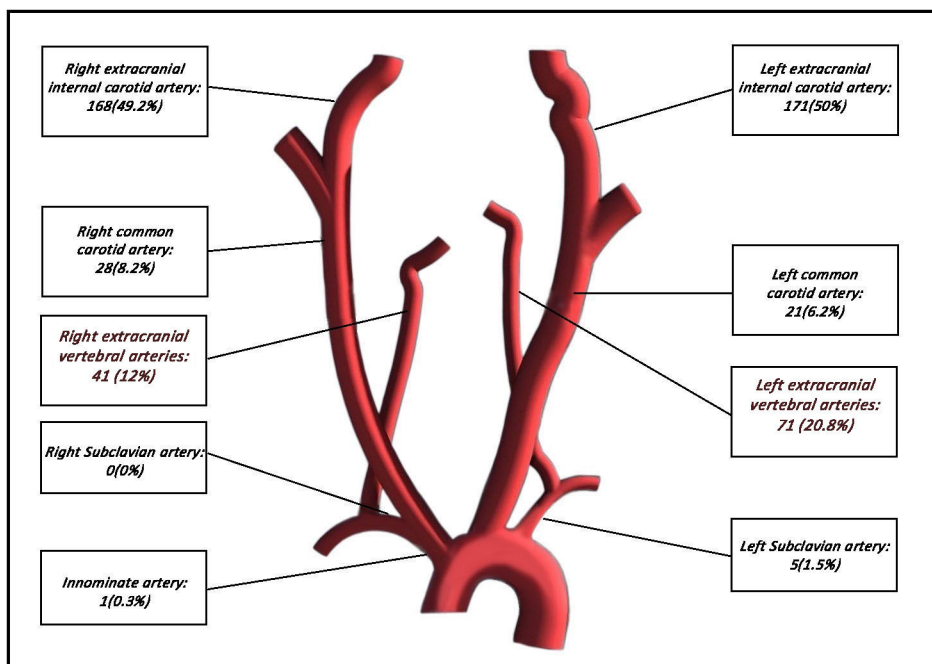


Figure 1. The frequency of stenosis and/or total occlusion in right and left extracranial cervicocerebral arteries. (Numbers in parentheses are percentage in 342 recruited patients)

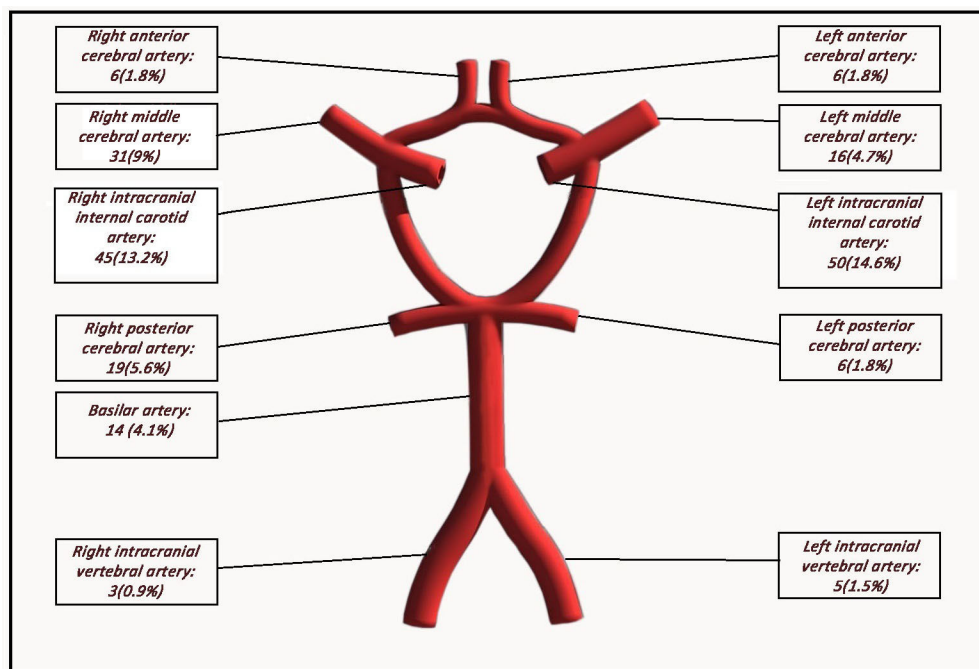


Figure 2. The frequency of stenosis and/or total occlusion in right and left intracranial cervicocerebral arteries. (Numbers in parentheses are percentage in 342 recruited patients)

**Table 2. The frequency of atherosclerosis risk factors among patients with stenosis and/or total occlusion in cervicocerebral arteries**

Risk Factors	Only Intracranial Involvement N = 37	Only Extracranial Involvement N = 180	Both Intracranial and Extracranial Involvements N = 125	P-Value
Mean age (95% Confidence interval)	65.9(62.6-69.2)	66.2(64.6-67.7)	67.7(65.9-69.5)	0.4
Male gender (%)	20(54)	112(62.2)	81(64.8)	0.5
Diabetes mellitus (%)	23(62.2)	71(39.5)	72(57.6)	<b>0.002</b>
Hypertension (%)	29(78.3)	154(85.6)	102(81.6)	0.4
Hyperlipidemia (%)	16(43.3)	106(58.9)	76(60.8)	0.1
Smoking (%)	10(27)	48(26.7)	45(36)	0.2

involved in 162 (47.4%) of those undergoing DSA. Of them, 180 (52.6%) patients had only extracranial vascular involvements, 37 (10.8%) had only intracranial vascular involvements, and 125 (36.5%) had both intracranial and extracranial vascular involvements. 301 patients (88%) and 128 patients (37.4%) had anterior circulation and posterior circulation involvement, respectively. Of them, 214 (62.6%) had pure anterior circulation involvements, while 41 (12%) and 87 (25.4%) had pure posterior circulation involvements and both anterior and posterior circulation involvements, respectively.

Table 2 revealed the frequency of major risk factors for LAD among the patients with only intracranial involvement, only extracranial involvement, and both intracranial and extracranial involvement. Only diabetes mellitus ( $P = 0.002$ ) but not age, sex, hypertension, hyperlipidemia, or smoking was significantly different between these groups.

## Discussion

To the best of our knowledge, the current study is the first study from Iran to investigate the intracranial versus extracranial distribution of large artery atherosclerotic disease. It showed that LAD is the cause of stroke more commonly in men. Extracranial and anterior circulation involvements were more frequent. The ICA (particularly the carotid bulbs) was the most common site of involvement. Diabetes mellitus but not age, sex, hypertension, hyperlipidemia or smoking was significantly associated with intracranial involvement.

Iran includes different ethnic groups. Mitochondrial DNA lineage analysis shows the main mtDNA lineage to be West Eurasian, but East Eurasian, South Asian, and African lineages were also seen.<sup>10</sup>

Ethnicity is one of the most important factors determining the site of involvement in LAD. Previous studies have revealed that African American, Chinese, and Japanese patients tend to have more intracranial stenosis, whereas Caucasians tend to have more extracranial lesions.<sup>11</sup> The current study shows the pattern of predilection of cervicocephalic stenoses in Iranians is similar

to Caucasians rather than Asians. In addition, carotid stenosis was more prevalent than carotid occlusion in our patients similar to North American patients.<sup>12</sup>

Age and sex are the most important non-modifiable risk factors while diabetes mellitus, hypertension, hyperlipidemia, and smoking are the most studied risk factors for atherosclerotic vascular disease.

In other studies, comparing extracranial and intracranial involvement with angiography in stroke/TIA patients, younger age,<sup>13</sup> older age,<sup>14</sup> black race,<sup>15</sup> male sex,<sup>15-17</sup> female sex,<sup>14</sup> smoking,<sup>16</sup> diastolic hypertension,<sup>14,16</sup> DM,<sup>14,18</sup> and alcohol abuse<sup>18</sup> were associated with intracranial stenosis. In studies with recruitment of stroke-free patients, age,<sup>19</sup> black race,<sup>20</sup> hypertension,<sup>21</sup> and DM,<sup>21,22</sup> were associated with intracranial stenosis. These divergent results could not only be due to ethnic and geographic differences but also due to different inclusion and exclusion criteria, algorithms of noninvasive studies before angiography, different definitions of significant stenosis, and/or different definitions of extracranial vs. intracranial involvement.<sup>23</sup>

This study had some shortcomings. First, since two thirds of the patients underwent angiography, it is likely that patients are greater risk for large-vessel disease were selected. The actual prevalence of large-vessel disease may have been lower if all patients underwent angiography. The symptomatic versus asymptomatic nature of the large artery lesions had not been investigated. In other words, degree of large artery stenosis was not studied according to causative relation with symptoms of acute ischemic stroke. Minor risk factors were also not investigated.

The point of strength of this study was the use of DSA as a gold standard for quantification of extra cranial/intracranial stenosis. Prior studies have utilized duplex ultrasound, TCD, CTA, and/or MRA for this purpose that have lower accuracy in comparison with DSA.<sup>16</sup>

## Conclusion

It can be concluded that the distribution of the large arterial atherosclerotic disease in Iran is similar to Caucasi-

ans. Extracranial large arterial diseases are more frequent than intracranial ones. Carotid bulb and VA origin are the most common sites of stenosis in Iranian patients. Intracranial stenosis is more common in diabetic patients.

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