

Association between Ischemic Stroke and Left Ventricular Systolic Dysfunction

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Abstract:

Background: Globally, Ischemic stroke (IS) is a major cause of morbidity and mortality. Left ventricular systolic dysfunction (LVSD) has been reported as an important clinical predictor of ischemic stroke. LVSD may involve in the pathophysiology of IS through different mechanisms. It has been suggested that LVSD may predispose to in situ thrombosis as well as proximal thrombosis formation, leading to intracranial vascular occlusion after detachment which decreases global cerebral blood flow. In addition, LVSD causes a state of global cerebral hypoperfusion with decreased brain blood flow and cerebrovascular reactivity, which contributes to a higher risk of ischemic insult. It is hypothesized that LVSD assessed using the LVEF may be associated with an unfavorable functional outcome after IS.

Purpose: To determine the left ventricular systolic dysfunction among the ischemic stroke patients.

Materials & method: This case-control study was conducted in Department of Neurology and Cardiology, Bangladesh Medical University (BMU), Dhaka from July 2008 to June 2010. A total 120 subjects were selected and allocated in to two groups; Group-A (case group or patients with ischemic stroke) and Group-B (control group or age-sex matched non-stroke volunteer). LV ejection fraction (LVEF,%) was used for assessing systolic dysfunction, and LVSD was classified as normal (EF $\geq 50\%$), mild dysfunction (EF 41–50%), moderate dysfunction (EF 31–40%), and severe dysfunction (EF $< 30\%$).

Result: Mean age was 57.83 ± 12.09 years and 58.02 ± 12.34 years in case and control respectively. Out of 120 cases, total 86(71.7%) were male and 34(28.3%) were female. Male – female ratio was 2.52:1. Out of all stroke patients, 45(75.0%) had normal LV function and 15(25.0%) had LV systolic dysfunction. Mean $\pm$ SD of LVEF was 57.33 ± 10.26 and 63.62 ± 7.78 in case and control respectively. It was found that mild LV dysfunction was observed in 16.7% cases of stroke patients, whereas it was 1.7% in control group. Moderate LV dysfunction was observed in 8.3% in stroke patients, only 1.7% in control group. The differences were statistically significant ($P < 0.05$), means left ventricular systolic dysfunction is significant predictor of ischemic stroke.

Conclusion: Present data concluded that Left Ventricular Systolic Dysfunction is independently associated with an increased risk of ischemic stroke.

Key words: Ischemic Stroke, Left Ventricular Systolic Dysfunction, Left ventricular ejection fraction (LVEF).

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Introduction:

Stroke is the global burden of disease¹ and second leading cause of death globally and a significant contributor to disability.² It accounted for 6.55 million deaths and 143 million disability-adjusted life- years (DALYs) worldwide.³ The incidence rate of ischemic stroke (IS) was projected to increase across all age groups between 2020 and 2030. The global

age-standardized incidence rate of ischemic stroke was projected to increase to 89.32 per 100 000 populations in 2030 (EAPC=0.89).⁴ Between 1990 and 2019, the global number of IS deaths increased from 2.04 million to 3.29 million and is expected to increase further to 4.90 million by 2030. The downward trend was more pronounced in women, young people, and high sociodemographic index (SDI) regions. At

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the same time, a study of attributable risk factors of IS found that 2 behavioral factors, smoking and diet in high sodium, and 5 metabolic factors, including high systolic blood pressure, high low-density lipoprotein cholesterol, kidney dysfunction, high fasting plasma glucose, and a high BMI, are major contributors to the increased disease burden of IS now and in the future⁵.

Ischemic stroke represents about 85% of all stroke cases⁵. It is accounting for 50.3% of stroke deaths and 17.7% of all cardiovascular disease (CVD)-related deaths, making the prevention of IS particularly important^{6,7}. Rapid economic development, social progress, changes in dietary habits, life style and population aging has resulted in an increased prevalence of behavioral and metabolic risk factors of CVD^{8,9}. Ischemic stroke occurs due to reduced cerebral blood flow, leading to a cascade of events initiated by oxygen and nutrient deprivation, triggering excitotoxicity, oxidative stress, and inflammation and finally culminating in neuronal injury and death^{10,11}. This results in cellular acidosis, energy (ATP) depletion and disruption in ion homeostasis, excess intracellular calcium levels, free radical-mediated toxicity, and finally culminating in neuronal death^{12,13}. Both apoptotic and necrotic pathways are believed to play a crucial role in ischemia-induced neuronal cell death.

Due to the relatively high incidence and prevalence of stroke across the globe, stroke prevention is one of the most heavily investigated areas of interest in order to reduce the burden of stroke on the community. The risk factors can typically be categorized into two separate groups: modifiable and non-modifiable risk factors. Modifiable risk factors are susceptible to various interventions to help reduce the risk of stroke whereas non-modifiable factors cannot be controlled and serve as indicators for high risk of stroke. A recent INTERSTROKE study from 2016 analyzed the potential effects of modifiable risk factors associated with stroke in 32 countries. Among the 13,000 stroke cases, it was shown that modifiable risk factors such as diet, physical inactivity, hypertension, psychosocial

factors, cardiac causes, diabetes, smoking, abdominal obesity, hyperlipidemia, and alcohol consumption accounted for approximately 90% of all strokes¹⁴. Heart failure and acute ischemic stroke (AIS) are frequently associated, due to similar risk factors and intertwined pathophysiologic mechanisms, and both result in a high mortality rate. It was evident that left ventricular systolic dysfunction (LVSD) is associated with acute ischemic stroke (AIS)^{15,16}.

LVSD was observed in 30(21.13%) patients of ischemic stroke. Association of LVSD with clinical severity and extent of the stroke had of positive correlation statistically. Coexisting coronary artery disease and diabetes mellitus had positive correlation with left ventricular systolic dysfunction. Patients with symptomatic heart failure of NYHA class III and IV had a positive correlation with left ventricular systolic dysfunction and clinical morbidity in ischaemic stroke¹⁶. Another study among 270 patients with first ischemic stroke versus 288 age-gender matched community controls revealed that left ventricular dysfunction (LVD) of any degree was more frequent in stroke patients (24.1%) than in controls (4.9%; $P<0.0001$), as was moderate/severe LVD (13.3% versus 2.4%; $P<0.001$). A decreased ejection fraction was associated with ischemic stroke even after adjusting for other stroke risk factors¹⁷. LVSD, even of mild degree, is independently associated with an increased risk of ischemic stroke.

The left ventricular ejection fraction (LVEF) is routinely assessed as a parameter to evaluate left ventricular systolic function in the management of patients with stroke. Studies have reported that 9.6%–28.0 % of patients with acute ischemic stroke (AIS) have an impaired LVEF in the acute phase¹⁸. In another study a total of 1181 patients were included, of which 87 (7.4 %) patients were found to have LVEF of <60 %. In the entire study population, LVEF<60 % was significantly associated with functional disability of ischemic stroke patients¹⁹. Left ventricular systolic dysfunction (LVSD) has been reported as an important clinical predictor of higher morbidity and mortality in ischemic stroke patients²⁰. Therefore, evaluation of the

association between ischemic stroke and Left ventricular systolic dysfunction is pivotal for comprehensive stroke management. Aim of the study was to assess the left ventricular systolic dysfunction among the ischemic stroke patients.

Methodology:

This case-control study was conducted in Department of Neurology and Cardiology, Bangladesh Medical University (BMU), Dhaka from July 2008 to June 2010. A total 120 subjects were selected, 60 cases and 60 control. Case group (Group A) included patients age 21-80 years with clinical features of WHO defined stroke, ischemic in type, within 1 month of attack, and that was confirmed by CT scan or MRI were enrolled for study. The patients in the control group (Group B) were age-sex matched non- stroke subjects. Detailed medical history, clinical examination and thorough investigations were done and the findings were recorded in data collection sheet.

Consent: Informed written consent was taken from all patients after explanation of risk, benefit and procedure of study.

Diagnostic Evaluation: Data were collected through face-to-face interview of cases and controls, review of medical records, physical and neurological examination. Control subjects were interviewed in person and evaluated in the same manner as the stroke patients. Routine laboratory tests included complete blood counts, coagulation studies, serum electrolytes, liver function tests, glucose and lipid profile determination. The risk factors taken into account were: arterial hypertension, dyslipidemia, diabetes mellitus, chronic alcohol consumption, obesity, and smoking. Coronary artery disease included history of myocardial

infarction or typical angina or the patient's reporting of a positive diagnostic test (stress test, coronary angiography) or drug treatment. Clinical CHF was diagnosed by history, clinical examination or medical treatment. The neurological work-up in stroke patients included brain CT or MRI. All patients underwent transthoracic echocardiography for assessment of left ventricular systolic dysfunction (LVSD).

Echocardiographic evaluation: All IS patients underwent transthoracic two-dimensional echocardiography. LV ejection fraction (LVEF, %) was determined by biplane Simpson's method. LVEF was then categorized as normal (>50%), mild dysfunction (41% to 50%), moderately (31% to 40%) or severely (<30%) decreased. All the information collected in data sheet. Data was processed and analysed with the help of computer program SPSS and Microsoft excel. Quantitative data expressed as mean and standard deviation and qualitative data as frequency and percentage. Result was presented by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagrams, histogram & charts etc.

Statistical analysis: Data was processed and analysed with the help of computer program SPSS and Microsoft excel. Quantitative data expressed as mean and standard deviation and qualitative data as frequency and percentage. Hypothetical test was done by chi-square test and t-test. Result was presented by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagrams, histogram & charts etc

Result & Observation:

Total of 120 patients fulfilling inclusion/exclusion criteria were studied. Results and observations are given below:

Table I
Demographic profile of the study subjects (n=120)

Variables	Group A (Case)	Group B (Control)	p-value
Mean age (years)	57.83±12.09	58.02±12.34	0.935
Gender			
Male	43(71.7%)	43(71.7%)	>0.99
Female	17(28.3%)	17(28.3%)	
Occupation			
Service	17(28.3%)	19(31.7%)	0.508
Business	20(33.3%)	14(23.3%)	0.277
Housewife	10(16.7%)	15(25.0%)	0.289
Others	13(21.7%)	12(20.0%)	0.854

Table I shows demographic profile of patients. Mean age was 57.83 ± 12.09 years and 58.02 ± 12.34 years in case and control respectively. Out of 120 cases, total 86(71.7%) were male and 34(28.3%) were female. Male – female ratio was 2.52:1. Occupation status revealed that, service holder and businessman were predominant respondents in the study. No significant differences were found in respect of demographic characteristics in between groups.

Table II shows risk factors of the study population. Regarding history of smoking 33(55.0%) of case group and 18(30.0%) had H/O smoking. Diabetes mellitus shows that 27(44.1%) of case and 3(5.0%) of control

subjects had DM. HTN was found in 32(53.3%) of case group and 5(8.3%) of control subjects. Dyslipidemia was found in 17(28.3%) of case group and 3(5.0%) of control subjects. The differences were statistically significant ($P < 0.05$) in between groups.

Table III shows left ventricular ejection fraction. Out of all stroke patients, 45(75.0%) had normal LV function and 15(25.0%) had LV systolic dysfunction. Mean $\pm$ SD of LVEF was 57.33 ± 10.26 and 63.62 ± 7.78 in case and control respectively. The differences were statistically significant ($P < 0.05$), means left ventricular systolic dysfunction is significant predictor of ischemic stroke.

Table II

Distribution of study subjects according to risk factors (n=120)

Risk factors	Group A (Case)*	Group B (Control)*	p-value**
Smoking	33(55.0%)	18(30.0%)	0.016
Diabetes mellitus	27(44.1%)	3(5.0%)	0.001
Hypertension	32(53.3%)	5(8.3%)	0.001
Dyslipidemia	17(28.3%)	3(5.0%)	0.001
Ischemic heart disease	9(15.0%)	2(3.3%)	0.027
Family H/O stroke	10(16.7%)	7(11.7%)	0.432

*Multiple respondents.

** Chi square test done for level of significance

Table III

Distribution of study subjects by left ventricular ejection fraction (LVEF, %) (n=120)

LVEF (%)	Group A (Case)	Group B (Control)	p-value**
Normal (LVEF >50%)	45(75.0%)	58(96.7%)	0.001*
Abnormal (LVEF <50%)	15(25.0%)	2(3.3%)	
Total	60(100.0%)	60(100.0%)	0.002**
mean $\pm$ SD	57.33 ± 10.26	63.62 ± 7.78	

* Chi square test was done for level of significance.

** Unpaired t- test done for level of significance

Left Ventricular Systolic Dysfunction (LVSD)

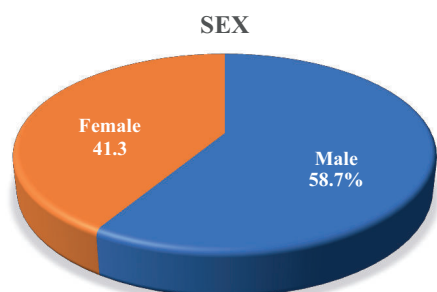


Fig.-1: Frequency of left ventricular systolic dysfunction among the ischemic stroke patients (n=60)

Figure 1 shows the frequency of left ventricular systolic dysfunction among the ischemic stroke patients. In this study amongst IS patients, 25.0% were found to have left ventricular systolic dysfunction.

It was found that mild LV dysfunction was observed in 16.7% cases of stroke patients, whereas it was 1.7% in control group. Moderate LV dysfunction was observed in 8.3% in stroke patients, only 1.7% in control group. The result was statistically significant ($P < 0.05$), means ischemic stroke is commonly associated with left ventricular systolic dysfunction.

Multiple logistic regression model revealed that adjusted odd ration 2.8 for smoking, 5.1 for DM, 2.4 for HTN, 9.6 for IHD and 3.3 for dyslipidaemia. A significant risk was found in patients with LV systolic dysfunction after regressing potential risk factors ($p < 0.001$).

Severity of left ventricular systolic dysfunction

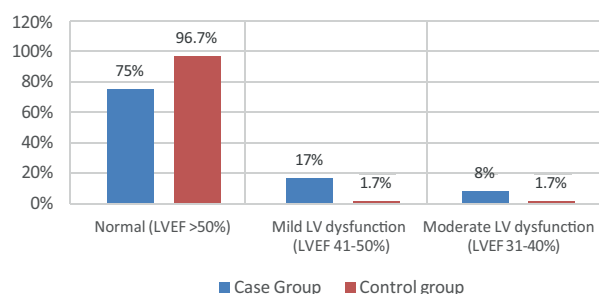


Fig.-2: Severity of left ventricular systolic dysfunction among the ischemic stroke patients (n=120)

Discussion:

In this study mean age was 57.83 ± 12.09 years and 58.02 ± 12.34 years in case and control respectively. Male – female ratio was 2.52:1. Common risk factors were smoking, diabetes mellitus, HTN and dyslipidemia. The demographic features were statistically non-significant ($P < 0.05$) in between groups

Similar study reported that mean age was 67.2 years in both groups. There were no significant differences between the two groups.¹⁵ Diabetes, hypertension, smoking tobacco, obesity and high cholesterol levels have all been shown to be significant risk factors in the development of stroke in Bangladeshi populations.^{21,22} A case-control study conducted in Dhaka, Bangladesh has found that certain risk factors for stroke differ between males and females, highlighting the significant impact of gender on

Table IV

Risk factors analysis for ischemic stroke (multiple logistic regression model)

	Unstandardized coefficients		Standardized coefficients	t	Sig.	OR	95% Confidence interval (CI)	
	B	Std.Error					Lower bound	Upper bound
Smoking	-0.039	0.055	-0.060	-0.702	0.484	2.8	-0.148	0.071
DM	-0.051	0.073	-0.063	-0.695	0.489	5.1	-0.196	0.094
HTN	-0.148	0.065	-0.197	-2.293	0.024	2.4	-0.277	-0.020
IHD	-0.558	0.096	-0.462	-5.794	0.001	9.6	-0.749	-0.367
Dyslipidaemia	0.007	0.083	0.007	0.086	0.932	3.3	-0.157	0.172
LVSD	-0.059	0.094	-0.113	-0.585	0.017	8.1	-0.146	0.086

the distribution of stroke risk factors. For males, the significant predictors of stroke include ever smoking (current and former smokers), which is associated with a higher risk, along with diabetes mellitus, hypertension and elevated total cholesterol levels. In females, the significant predictors include diabetes mellitus, hypertension, elevated serum low-density lipoprotein (LDL) and higher serum triglyceride (TG) levels. These findings suggest that the prevention of stroke may need to be tailored differently for men and women based on these risk factors²³. As one of the South Asian nations considered to be a developing country, Bangladesh is experiencing a dramatic increase in non-communicable diseases of old age, such as coronary artery disease and stroke, due to changes in socio-economic conditions, urbanisation, changes in diet and an increased life expectancy.^{21, 22}

Interstroke study reported that diet, physical inactivity, hypertension, psychosocial factors, cardiac causes, diabetes, smoking, abdominal obesity, hyperlipidemia, and alcohol consumption accounted for approximately 90% of all strokes.¹⁴ Heart failure and acute ischemic stroke (AIS) are frequently associated, due to similar risk factors and intertwined pathophysiologic mechanisms. Recent study found that left ventricular systolic dysfunction (LVSD) is associated with acute ischemic stroke (AIS).^{15,16}

Present study shows that amongst IS patients, 25.0% were found to have left ventricular systolic dysfunction. The present study suggests that decreased LV function is associated with an increased risk of stroke in the community after adjusting for established stroke risk factors. More importantly, the association with increased stroke risk was observed across a wide range of LVD severity, and was as strong for dysfunction of mild degree as for dysfunction of moderate or severe degree.

The association between decreased LVEF and risk of ischemic stroke has been studied in different study. Previous study reported that LVD of any degree was more frequent in stroke patients (24.1%) than in controls (4.9%; $P < 0.0001$), as was moderate/severe LVD (13.3%

versus 2.4%; $P < 0.001$). A decreased ejection fraction was associated with ischemic stroke even after adjusting for other stroke risk factors¹⁷. Kelly et al published a case-control study that examined 522 patients presenting with first-ever noncardiac vascular events defined as stroke, transient ischemic attack or peripheral vascular disease.²⁴ LVD (defined as LVEF $< 40\%$) was 5 times more prevalent among patients with noncardiac vascular events than in age- and gender-matched controls. However, few stroke patients were included, and the study population was predominantly white and male.

LVSD was observed in 30(21.13%) patients of ischemic stroke in another study.¹⁶ LVSD, even of mild degree, is independently associated with an increased risk of ischemic stroke. Studies have reported that 9.6%–28.0 % of patients with acute ischemic stroke (AIS) have an impaired LVEF in the acute phase.¹⁸ Left ventricular systolic dysfunction (LVSD) has been reported as an important clinical predictor of higher morbidity and mortality in ischemic stroke patients.²⁰ The mechanism underlying the association between LVSD and stroke is multifactorial. One possibility is that LVSD promotes increased blood stasis in both the LV and left atrium, increasing the chance of thrombus formation and the risk of stroke. Proper evaluation and early detection with comprehensive manage reduced the burden of stroke.

Limitation of Study:

This was a single center study. Only patients admitted in tertiary care hospital were taken for the study. So, this will not reflect the overall picture of the country. A large-scale study needs to be conducted to reach to a definitive conclusion.

Conclusions:

Present study concluded that left ventricular systolic dysfunction (LVSD) is significantly associated with risk of ischemic stroke. In this study amongst IS patients, 25.0% were found to have left ventricular systolic dysfunction. Present study findings highlight the clinical importance of identifying and optimizing LVSD management among stroke patients to improve outcomes in this population.

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