Stroke in the Patients with Ischemic and Nonischemic Dilated Cardiomyopathy

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Abstract: ***Objectives**: Patients with dilated cardiomyopathy (DCM) may have a high incidence of clinically asymptomatic or symptomatic stroke. Prevalence of Stroke and its risk factors may be different between ischemic and nonischemic DCM. The purpose of this study was to evaluate the prevalence and related parameters of silent stroke in patients with ischemic and nonischemic DCM. **Methods**: 72 Patients with ischemic and nonischemic DCM (53 male, 19 females, aged 62 ± 12 years) were included in the study. Etiology of DCM was ischemic in 45 and nonischemic in 27 patients. Fifty-five age- and gender-matched healthy volunteers served as a control group for comparison of stroke prevalence. **Results**: Prevalence of stroke was 38%, 28%, and 3.6% in ischemic, nonischemic DCM, and control group, respectively (ischemic DCM vs control group, p < 0.001, nonischemic DCM vs control group, p = 002). In patients with nonischemic DCM, the mean age of the subjects with SCI was significantly higher than that of subjects without lesions (68 ± 5 years vs 52 ± 13, p < 0.001), whereas in ischemic DCM NHYA Functional Class was statistically higher in patients with SCI than without SCI (p = 0.03). In both groups, patients with SCI had lower systolic functions than patients with normal MRI findings. In multivariable logistic regression analysis, restrictive type of diastolic filling pattern was found as an independent factor for SCI occurrence on the whole patient population (OR: 16.5, 95% CI: 4.4–61.8, p < 0.001). **Conclusion**: Stroke is common in patients with both ischemic and nonischemic DCM. In univariate analysis, both groups have similar systolic and diastolic characteristics for the occurrence of SCI. Restrictive diastolic filling pattern is found to be an independent risk factor in the occurrence of SCI for the whole patient population in logistic regression analysis.*

Keywords: ischemic dilated cardiomyopathy, nonischemic dilated cardiomyopathy, silent cerebral infarction, restrictive diastolic filling, age, functional status

1.Introduction

A silent cerebral infarction (SCI) is classified as a type III cerebrovascular disorder by the National Institute of Neurological Disorders and Stroke (NINDS 1990). Prevalence of SCI varies between 10% and 28% in general population. SCI was identified to be a risk factor for clinical stroke. It may be related to dementia, cognitive deficits, and depression. To prevent SCI, it is important to know its related factors, especially preventable or treatable risk factors.

Both ischemic and nonischemic dilated cardiomyopathies are important reasons for chronic heart failure4 . Dilated cardiomyopathy (DCM) is associated with an increased risk of thromboembolism because of low output state, relative stasis of blood in a dilated chamber, and altered coagulation status. The reported incidence of thromboembolism in the chronic heart failure population varies widely, ranging from 2.7% to 22% (7). In patients with heart failure, the prevalence of silent ischemic stroke was 34%. The prevalence of stroke, related risk factors, and characteristics may differ between patients with ischemic and nonischemic cardiomyopathies. The purpose of this study was to evaluate the prevalence and related parameters of stroke in patients with ischemic and nonischemic dilated cardiomyopathies.

2.Methods

Patient Selection

One hundred five patients with DCM, with New York Heart Association (NYHA) II-IV Functional Classification, diagnosed according to WHO criteria (WHO 1996) were recruited for the study over a period of six months in department of cardiology LLRM Medical College Meerut. Patients with poor acoustic window, heart valve disease with hemodynamic significance, atrial fibrillation, uncontrolled ventricular arrythmias, atrio ventricular block, previous transient ischemic attack or stroke, or neurological deficit secondary to cerebral pathology were excluded from the study (n = 18). The remaining 72 patients (53 males, 19 females; mean age 62 ± 12 years) comprised the study group. Etiology of the DCM was investigated by coronary angiography in all patients. All patients underwent coronary angiography to determine coronary artery disease before magnetic resonance imaging (MRI) studies.

Forty-five of the patients had ischemic dilated cardiomyopathies and 27 had nonischemic dilated cardiomyopathies. In all patients, left ventricular enlargement (end-diastolic diameter ≥56 mm) and systolic dysfunction (ejection fraction ≤45%) were documented by 2-dimensional and M-mode echocardiography.

Fifty-five, age- and gender-matched healthy volunteers (35 males, 20 females; mean age 61 ± 10 years) were accepted as a control group after routine clinical and laboratory evaluation.

The study was conducted in accordance with the Declaration of Helsinki. Study protocol was approved by the local ethics committee and subjects gave informed consent prior to study entry.

Echocardiography

Transthoracic 2-dimensional and Doppler echocardiographic assessments were performed by a

VIVID E 95 A ultrasound machine using a 3.5 MHz transducer. Measurements of the left atrium, and left and right ventricles were obtained from parasternal long axis view as recommended by the American Society of Echocardiography (Sahn et al 1978). Left ventricular ejection fraction was calculated using the modified Simpson's rule in the apical 2- and 4-chamber views. Spontaneous echo contrast in the left ventricle (LVSEC) was categorized as 'present' or 'absent' by harmonic imaging. Mitral flow pattern was evaluated from the apical 4-chamber view with pulsed-wave Doppler by placing a sample volume at the tips of mitral leaflets during diastole. Early (E) and atrial (A) peak velocities, the E/A ratio, deceleration time of early filling, isovolumic relaxation time, and pulmonary vein flow pattern were measured on three separate beats and averaged. Four types of diastolic filling pattern were considered: normal filling, relaxation abnormality, pseudonormal pattern, and restrictive filling. Left atrial maximum and minimum volumes (LAV_{max} and LAV_{min}) were determined from orthogonal apical views using biplane area-length method. Left atrial total emptying fraction was estimated as follows: $100\times(LAV_{max}-LAVmin)/LAV_{max}$.

Fasting blood samples were drawn from a large antecubital vein of each patient for detecting biochemical and hemostatic parameters before transthoracic echocardiography examination. White blood cells and platelets counts, and hematocrit, lipid, creatin, C-reactive protein levels, and sedimentation rate were measured by standard methods. The plasma fibrinogen was measured by the STA Compact auto analyser using the STA® – Fibrinogen kit.

Neurological examination and brain magnetic resonance imaging

Neurological examination of the study and control groups was performed by a qualified neurologist. Patients and control group were examined with MRI to detect SCI. Cerebral MRI was performed on a 1.5-T MR scanner (Philips Achieva, Eindhoven, Netherlands) using a standard quadrature head coil. After obtaining scout images, routine imaging was performed. Our routine magnetic resonance imaging (MRI) protocol for cerebral disease includes axial dual echo TSE, axial FLAIR, axial T1-weighted TSE, sagittal T2-weighted TSE, and coronal T2-weighted TSE images. All images were acquired with a field of view of 230 × 230 mm, and a section thickness of 5 mm with a 1-mm intersection gap.

Statistical analysis

Statistical analysis was performed with SPSS 13.0 software. Results are expressed as mean ± standard deviation. The frequency of SCI in patients and control groups was compared with results from a chi-square test. Continuous variables of the patients with and without SCI were compared by unpaired Student t-test. If necessary, the Mann Whitney U test was used instead of Student t-test and categorical variables were compared with the chi-square test. Interaction between parameters that could be relevant for the formation of SCI was calculated by multivariate forward stepwise logistic regression analysis, adjusting for age, ejection fraction, restrictive diastolic filling, and coronary artery disease. A p value <0.05 was considered significant.

3.Results

Demographic, clinical, and echocardiographic characteristics of patients with ischemic and nonischemic DCM are shown in Table 1. Prevalence of SCI was 38%, 28%, and 3.6% in ischemic, nonischemic DCM, and the control group, respectively (ischemic DCM vs control group, $p < 0.001$; nonischemic DCM vs control group, p = 002).

Table 1: Demographic, clinical, and echocardiographic characteristics of patients with ischemic and nonischemic DCM

	Ischemic DCM (n = 46)	Nonischemic DCM (n = 26)	P
Prevalence of SCI	18 (39%)	7 (%27)	NS
Gender (male/female)	37/9	16/10	NS
Age (years)	64 ± 10	57 ± 13	0.012
NHYA functional classification	3.0 ± 0.8	3.0 ± 0.8	NS
Previous hypertension	29 (%63)	11 (%42)	NS
Diabetes mellitus	19 (%41)	3 (%1)	0.008
Dyslipidemia	9 (%20)	9 (%35)	NS
Body mass index (kg/m^2)	26 ± 4	26 ± 3	NS
Drug use (%)			NS
Digitalis	19 (%41)	11 (%42)	NS
ACEI/ARB	31 (%67)	17 (%65)	NS
Diuretics	26 (%57)	16 (%62)	NS

	Ischemic DCM (n = 46)	Nonischemic DCM (n = 26)	P
Spiranolactone	5 (%10)	2 (%1)	NS
Beta-blockers	5 (%10)	7 (%27)	NS
Aspirin	39 (%85)	17 (%65)	0.057
LVDD (mm)	65 ± 7	69 ± 10	0.055
LVSD (mm)	54 ± 7	57 ± 10	NS
Ejection fraction (%)	32 ± 9	31 ± 10	NS
Left atrial diameter (mm)	45 ± 5	44 ± 6	NS
Right ventricular diameter (mm)	28 ± 4	28 ± 7	NS

Abbreviations: SCI, silent cerebral infarction; NYHA, New York Heart Association; ACE-I/ARB, ACE-inhibitors/angiotensin II receptor antagonists; LVDD, Left ventricular end-diastolic diameter; LVSD, Left ventricular end-systolic diameter; NS, Nonsignificant.

Ischemic DCM patients with and without SCI

As demonstrated in Table 2, the NYHA Functional Classification was statistically different in patients with and without SCI ($p = 0.03$). Among ischemic DCM patients, the number of males with SCI was higher than those without SCI, but the difference was not statistically significant ($p = 0.059$). Other variables including age, body mass index, medical treatment, the prevalence of coronary artery disease, hypertension, diabetes, and dyslipidemia were not statistically different in both groups (some data are not shown).

Table 2: Demographic, clinical, hematological, and biochemical parameters of ischemic DCM patients with and without SCI

	SCI (+) (n = 18)	SCI (−) (n = 28)	P
Gender (male/female)	6/12	3/25	0.059
Age (years)	65 ± 12	64 ± 8	NS
NHYA functional classification	3.3 ± 0.8	2.8 ± 0.8	0.03
Body mass index (kg/m^2)	26 ± 5	25 ± 3	NS
Hematocrit (volume fraction)	0.37 ± 0.04	0.40 ± 0.05	0.054
Sedimentation rate (mm/hour)	21 ± 16	23 ± 25	NS
Fasting glucose level (mmol/L)	6.9 ± 2.8	6.6 ± 2.3	NS
Cholesterol (mmol/L)	4.3 ± 1.0	4.2 ± 0.8	NS
HDL-C (mmol/L)	0.9 ± 0.2	0.9 ± 0.3	NS
LDL-C (mmol/L)	2.8 ± 0.8	3.0 ± 0.8	NS
Tryglyceride (mmol/L)	1.2 ± 0.5	1.0 ± 0.4	NS
Creatinine (μmol/L)	122 ± 35	96 ± 27	0.017
Fibrinogen (g/L)	4.58 ± 0.61	4.36 ± 0.98	NS
CRP (mg/L)	9.8 ± 15	13 ± 23	NS

Abbreviations: SCI (+), patients with silent cerebral infarction; SCI (−), patients without silent cerebral infarction; CRP, C-reactive protein; NS, not significant.

Patients with SCI had lower hematocrit levels and higher creatinine levels than those without SCI ($p = 0.054$, $p = 0.017$, respectively). Although fibrinogen level was higher in the SCI group than the other group, the difference was not statistically significant (4.58 ± 0.61 vs 4.36 ± 0.98 g/L) (Table 2).

The echocardiographic findings are summarized in Table 3. End-diastolic and end-systolic left ventricular dimensions, left atrium size, and LV-SEC was similar between two groups. However, the ejection fraction and cardiac index were lower in patients with SCI than without SCI ($p = 0.03$, $p = 0.01$, respectively). The percentage of restrictive diastolic filling pattern was higher in patients with SCI than without SCI in ischemic DCM ($p < 0.001$).

Table 3: Echocardiographic parameters of ischemic DCM patients with and without SCI

	SCI (+) (n = 18)	**SCI (−) (n = 28)**	**P**
LVDD (mm)	60 ± 7	64 ± 6	NS
LVSD (mm)	53 ± 7	55 ± 7	NS
Ejection fraction (%)	32 ± 7	38 ± 9	0.03
Fractional shortening (%)	15 ± 4	16 ± 5	NS
LA (mm)	45 ± 6	46 ± 4	NS
Left atrial total emptying fraction (%)	39 ± 16	42 ± 12	NS
CI (L/min/m^2)	2.4 ± 0.7	2.0 ± 0.4	0.01
LVSEC (n, %)	8 (44%)	8 (29%)	NS
Restrictive filling pattern (n, %)	12 (67%)	3 (11%)	<0.001

The mean age of the patients is higher with SCI than without SCI (67 ± 5 vs 53 ± 13 years, $p < 0.001$). No significant difference was observed between two groups with respect to gender, NYHA Functional Classification, or body mass index.

The echocardiographic parameters that were observed in two groups are shown in Table 4. Left ventricular systolic function-related parameters such as ejection fraction and systolic shortening were lower in patients with SCI, whereas cardiac chambers dimensions, as well as presence of LV-SEC, were not different between the groups. Percentage of restrictive diastolic filling pattern was higher in patients with SCI than without SCI in nonischemic DCM ($p = 0.017$). Although nonischemic DCM patients with SCI had higher fibrinogen levels than the other group, the difference was not statistically significant (4.60 ± 1.10 vs 4.24 ± 1.26 g/L).

Table 4: Echocardiographic parameters of nonischemic DCM patients with and without SCI

	SCI (+) (n = 7)	**SCI (−) (n = 19)**	**P**
LVDD (mm)	68 ± 11	64± 10	NS
LVSD (mm)	56 ± 12	52 ± 10	NS
Ejection fraction (%)	26 ± 8	35 ± 10	0.05
Fractional shortening (%)	12 ± 4	17 ± 5	0.02
LA (mm)	42 ± 7	44 ± 6	NS
Left atrial total emptying fraction (%)	36 ± 4	41 ± 12	NS
CI (L/min/m^2)	2.2 ± 0.9	2.5 ± 0.8	NS
LVSEC (n, %)	4 (57%)	7 (37%)	NS
Restrictive filling pattern (n, %)	5 (71%)	4 (21%)	0.017

Abbreviations: SCI (+), patients with silent cerebral infarction; SCI (−), patients without silent cerebral infarction; LVDD, left ventricular end-diastolic diameter; LVSD, left ventricular systolic diameter; LA, left atrium diameter; EF, ejection fraction; CI, cardiac index; LVSEC, left ventricular spontaneous echo contrast; NS, not significant.

Multiple logistic regression analysis

In multivariable logistic regression analysis, restrictive type of diastolic filling pattern was found as an independent factor for SCI occurrence for the whole patient population (OR: 16.5, 95% CI: 4.4–61.8, $p < 0.001$).

4.Discussion

SCI was observed in 38% of patients with ischemic DCM. Higher NHYA Functional Classification, lower ejection fraction and cardiac index, decreased hematocrit level, and increased creatinine level were determinants for SCI in this patient group.

A heart failure group was investigated by Siachos and colleagues (2005) for SCI. The prevalence of silent stroke was 34% in this patient group. The group comprised nonischemic and ischemic cardiomyopathy patients. Traditional risk factors such as age, gender, history of hypertension, and diabetes mellitus were not predictive for silent stroke in heart failure patients. Their findings were similar to our data. Among all our patients, the prevalence of SCI was 35% (Kozdag et al 2006).

It is known that both coronary artery disease and cerebrovascular disease frequently coexist and have many common risk factors. A patient with ischemic stroke usually has coronary artery disease and its manifestations (Sandercock et al 1989). In the general population, prevalence of SCI varies between 10% and 28%, whereas in patients with stroke it is as high as 38% (Kase et al 1989; Ricci et al 1993; Price et al 1997; Howard et al 1998; Vermeer et al 2002). Our patient group had higher prevalence of SCI than the general population but had a similar prevalence for SCI as patients with stroke. This finding is very interesting for this patient group. Patients those who have a history of coronary artery disease events show a tendency to have higher cerebrovascular events than those without a history of coronary artery disease events (Reicher-Reiss et al 1998). Advanced SCI also may relate to common coronary artery disease (Hoshide et al 2001). Our study agree with the above-mentioned data for cerebrovascular disease in patients with ischemic cardiomyopathy who have coronary artery disease and high prevalence of SCI. It can be speculated for this patient group that unknown hemodynamic variations, low output states, silent atrial arrhythmias, cardiac catheterization, and advanced atherosclerosis may either decrease cranial blood flow or increase embolic events in patients with ischemic DCM.

The present study showed that higher NHYA Functional Classification was related to SCI only in ischemic DCM. As expected, patients with poor functional status who have SCI also have decreased cardiac index, lower ejection fraction, impaired renal function, and low hematocrit level. Decreased ejection fraction in females was shown as a risk factor for overt strokes in large heart failure trials (Dries et al 1997). The Survival and Ventricular Enlargement (SAVE) trial (Pfeffer et al 1992) reported the incidence of stroke as 1.5/100 patient-years in patients who had left ventricular dysfunction after acute myocardial infarction. Patients with ejection fractions of ≤28% after myocardial infarction had a relative risk of stroke of 1.86 compared with patients with ejection fractions >35%, and an 18% increase in the risk of stroke was documented for every 5% decrease in ejection fraction (Loh et al 1997). Decreased ejection fraction seems an important determinant for overt stroke and SCI in patients with coronary artery disease.

SCI was determined in 27% of patients with nonischemic DCM. Older age and impaired systolic function were found as the determinants for SCI in this group. According to previous studies, the occurrence of SCI increases with age (Longstreth et al 2002; Vermeer et al 2002). In the Atherosclerosis Risk in Communities (ARIC) study, the prevalence of SCI was 7.9% in patients between 55 and 59 years of age and 22.9% in those between 65 and 72 years of age (Bryan et al 1999). Kotani and colleagues (2004) studied an elderly population whose mean age was 77.5 ± 8.7 years. They observed SCI in 48% of their elderly population (Kotani et al 2004). Schmidt and colleagues (1991) observed cerebral infarcts in 20% of 20 neurologically asymptomatic patients with idiopathic DCM. Their patients were younger than our patients and Kotani's patients. In the present study, older patients with nonischemic DCM had more SCI lesions than younger patients. The prevalence of SCI increased with age in the previous studies in agreement with our finding. It seems that increased age is important for occurrence of SCI. As expected, the older patients had greater risk than younger patients for occurrence of SCI in the present study.

Patients with nonischemic DCM had similar characteristics as those with ischemic DCM, such as an enlarged cardiac chamber, systolic impairment, stagnant blood, and silent atrial arrhythmias for SCI. Impaired systolic function parameters such as decreased left ventricular ejection fraction and systolic shortening were observed in this patient group. All these parameters may cause silent embolic events to brain in this patient group, as does ischemic cardiomyopathy.

Multivariable analysis showed that restrictive filling pattern was an independent risk factor for occurrence of SCI. Restrictive filling pattern in mitral flow is a marker for markedly impaired left ventricular filling and may show atrial systolic failure (Vanoverschelde et al 1990). Either left atrial systolic failure or stagnant milieu in the left atrium may cause embolic events. Enlarged and dysfunctional left atrium may cause silent arrythymias such as atrial fibrillation in patients with ischemic and nonischemic DCM.

Implications

The present study showed that both groups have similar characteristics for the occurrence of SCI such as impaired systolic function and restrictive filling pattern. Ischemic DCM patients with SCI had advanced disease stage characteristics such as increased creatinine level and decreased hematocrite level compared with patients without SCI. Nonischemic DCM patients with SCI were older than those without SCI. It was shown that left ventricular diastolic filling characteristics were correlated with NYHA Functional Class (NINDS 1990). Ischemic DCM patients with SCI had higher NYHA Functional Class than patients without SCI and restrictive filling pattern in the present study. Advanced disease stage characteristics may be important for the occurrence of SCI. It may be important to prevent or immediately treat decompensation of heart failure, renal failure, and anemia in this patient group. Freudenberger suggested that left ventricular dysfunction needs more aggressive treatment and the physician has to be alert for silent atrial fibrillation episodes for a patient with chronic heart failure (Freudenberger and Massie 2005). Patients who have dilated cardiomyopathy usually undergo cardiac catheterization for the etiology of the disease. This procedure may increase the occurrence of SCI in patients with DCM when compared to patients who do not have the procedure. This patient population requires extra careful attention their treatment to prevent occurrence of overt stroke. Patients with advanced-stage disease characteristics may take anticoagulation therapy to prevent overt stroke in ischemic DCM. Older patients who have decreased ejection fraction, fractional shortening, and restrictive filling pattern

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may be given anticoagulation therapy to protect them from stroke in nonischemic DCM. It was determined that 3-year mortality rate was increased by symptomatic and silent infarcts in elderly people (Liebetrau et al 2004). Patients with SCI may have a higher mortality rate than those without SCI in DCM. Follow-up studies are necessary to determine the relation between mortality and SCI in patients with DCM.

Study Limitations

Because MRI is an expensive tool for investigation, a small patient numbers were included in the present study. Our data will support other research which should include more patients than did our research.

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