Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.186190.2741 Volume 29, Issue 3, May 2023
Manuscript ID ZUMJ-2302-2741 (R1)
DOI 10.21608/zumj.2023.186190.2741

ORIGINAL ARTICLE

Prevalence and Prediction of Subclinical Atrial Tachyarrhythmias Detected by Continuous Holter Monitoring in Cryptogenic Stroke

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Submit Date	2023-02-20 19:54:32
Revise Date	2023-03-01 10:34:12
Accept Date	2023-03-03

ABSTRACT

Background: Cryptogenic stroke (CS) is a symptomatic cerebral infarct with no identifiable cause after adequate diagnostic workup. Subclinical atrial arrhythmias are increasingly recognized as a source of CS. The study aimed to investigate the association between cryptogenic stroke and atrial tachyarrhythmias using 24-hour Holter monitoring.

Methods: This was a case-control study that was conducted on a total of 30 adult patients with CS who were admitted at Mansoura University Hospital during the period From December 2019 to December 2021 as a case study group matched with another 40 normal persons as a control study group using 24-hour Holter monitoring.

Results: There was no statistically significant difference between the studied groups as regards age, sex, and history of the previous stroke. There was a statistically significant higher mean systolic blood pressure (BP) among cases than in the control group (p=0.02). There was no statistically significant difference between the studied groups as regards Holter findings. Among cases, one case showed frequent premature atrial ectopics (PACs), one supraventricular tachycardia (SVT) run, frequent premature ventricular ectopics (PVCs), 2 cases showed runs of non-sustained ventricular tachycardia (VT) and 3 cases (10% of cases) showed low burden atrial fibrillation (AF) runs.

Conclusions: 24-hour Holter monitoring could detect subclinical AF or other tachyarrhythmias in CS and could guide subsequent treatment as regards anticoagulants use. However, it could not be enough, and a longer duration of follow-up is required.

Keywords: Cryptogenic; Stroke; Silent; Atrial fibrillation; Holter

INTRODUCTION

Cryptogenic stroke (CS) is a symptomatic cerebral infarct with no identifiable cause after adequate diagnostic workup [1]. CS is responsible for 10 to 40% of all ischemic strokes and nearly half of all strokes in younger populations [2]. AF can be asymptomatic and thus subclinical. Silent AF is becoming more widely recognized as a cause of CS, particularly in elderly patients [3].

There is mounting evidence that there is a link between biomarkers of atrial cardiopathy and ischemic stroke that is independent of AF. Electrocardiogram (ECG) parameters of left atrial dysfunction have been linked to an increased risk of ischemic stroke [4]. Prolonged outpatient cardiac monitoring detects low-burden AF in 15% of patients whose ischemic strokes are cryptogenic after conventional inpatient evaluation [5]. The frequency of detection of paroxysmal AF in the multicenter CRYSTAL AF trial was 9% at 6 months, 12% at 1 year, and 30% at 3 years [6]. Current guidelines recommend 24 hours or more of ECG monitoring to rule out AF in patients with an ischemic stroke, but the most effective duration of monitoring has yet to be determined. The use of additional ECG monitoring beyond 24 hours after

CS is currently at the discretion of the physician [7].

Our study objective is to examine the relationship between CS and atrial tachyarrhythmias using 24-hour Holter monitoring.

METHODS

This was a case-control study that was carried out on 30 adult patients with CS who were admitted to the Mansoura University Hospital between December 2019 and December 2021 as a case study group and another 40 normal people as a control study group. The research ethics committee of the Faculty of Medicine at Mansoura University approved the study, and all subjects gave their written informed consent. All procedures involving human participants were performed in conformity with the Declaration of Helsinki, a code of ethics established by the World Medical Association. Patients were divided into 2 groups: those with CS (n = 30 'adults over the age of 18') and those without any neurological symptoms (n = 18) to rule out stroke as a possible cause (40 adult patients).

Patients with any of the following conditions were excluded from the study: chronic AF or atrial flutter, stroke with known cause e.g.: arteritis, drug misuse, dissection, and vasospasm, diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), smokers, myocardial infarction in the last 4 weeks, intracardiac thrombus, prosthetic cardiac valve, mitral stenosis, infective endocarditis, valve vegetation, left ventricular (LV) EF < 30%, and atrial septal defect (ASD).

The patients were subjected to history taking with special emphasis on age, gender, smoking, HTN, DM, dyslipidemia, CKD, family history(FH) of stroke, cardiovascular diseases including heart failure (HF) and AF, CHA_2DS_2-VASc stroke score calculation, general examination with special emphasis on pulse (rate and rhythm), BP, neck vein assessment, abdomen assessment for liver, spleen and ascites, chest assessment for air entry, breath sounds and added sounds, cardiac examination, auscultation for heart sounds (S1 and S2), added sounds (S3 and S4) and murmurs, Neurological examination with the stress on lateralization, the National Institutes of Health Stroke Scale (NIHSS) (15-item impairment scale to assess stroke severity in emergency departments), laboratory investigations (CBC, lipid profile, serum creatinine, creatinine clearance, HBA1c, random blood sugar (RBS) test, protein S. protein C, factor V Leiden, lupus anticoagulant and anti-cardiolipin antibodies. Brain computed tomography (CT) ±magnetic resonance imaging (MRI), Two-dimensional conventional transthoracic echo assessment for resting left ventricular function, evaluation of all valves and evaluation of presence or absence of septal defects, resting 12 leads surface electrocardiogram, 24-hour Holter monitoring for basic rhythm, average, maximum, and minimum heart rate (HR), ST-T wave changes, ventricular arrhythmias (ventricular ectopics, bigeminy, trigeminy, runs of sustained ventricular tachycardia) and supra ventricular arrhythmias (supra ventricular ectopics (SVE), sustained supra ventricular tachyarrhythmias and episodes of AF or atrial flutter.

Statistical analysis and data interpretation:

SPSS software, version 18 (SPSS Inc., PASW Statistics for Windows version 18), was used to analyze the data. SPSS Inc. is based in Chicago. Numbers and percentages were used to describe qualitative data. The mean and standard deviation were used to describe quantitative data (normally distributed) after using the Kolmogrov-Smirnov test. The significance of the results obtained was determined at the (0.05) level. To compare the qualitative data between groups, Chi-Square, Fischer exact test, and Monte Carlo tests were used as needed. Mann Whitney was used for non-normally distributed data, the U test was used to compare two groups. For non-normally distributed data, the student t-test was used to compare two independent groups. Spearman's rank-order correlation was used to determine the strength and direction of a non-normally distributed linear relationship between two non-normally distributed continuous variables and/or ordinal variables. Binary logistic regression was used to assess the effect of the combination of more than 2 independent variables on the dichotomous outcome using the Stepwise / forward Wald / Enter technique.

RESULTS

The present study was a case-control study that was carried out on 30 CS matched with 40 control groups to investigate the association between CS and atrial tachyarrhythmias using 24-hour Holter monitoring.

There was no statistically significant difference between the studied groups as regards age, sex & history of the previous stroke. The mean ± SD age of the control group was 38.1 ± 7.13 versus 36.33 ± 9.04 among cases. Among cases, 56.7% were males versus 50% among the control group. Among cases, 6.7% had a previous stroke. A statistically significant difference was detected between the studied groups as regards CHA_2DS_2-VASc score with 43.3% of cases having CHA_2DS_2-VASc score 3 and 56.7% of cases having CHA_2DS_2-VASc score 2 as shown in Table (1).

There was a statistically significant higher mean systolic BP among cases than the control group (127.0 ± 11.49 versus 120.5, respectively). No statistically significant difference was detected between studied groups as regards diastolic BP and HR as shown in Table (2).

Among studied cases, 100% of cases showed right side weakness, and 20% disturbed consciousness level. For the NIHSS score, 83.3% were mild, 10% moderate, and 6.7% severe as shown in Table (3), and Figure (s1).

There was 28% mild mitral regurge (MR) among the studied cases. Mean ejection fraction (EF) showed a non-statistically significant difference between studied groups with a mean EF was 64.45 versus 65.1 for control & cases as shown in Table (4).

There was no statistically significant difference between the studied groups as regards Holter findings. Median average HR was 76.0 versus 80.0, minimum HR was 53.0 & 53.0, and maximum HR was 126 versus 131, for control and cases, respectively. Among cases, one case showed frequent PACs, SVT run, and frequent PVCS, 2 cases with runs of non-sustained VT, and 3 cases with episodes of AF as shown in Table (5), and Figure (s2).

Systolic BP was the only statistically significant predictor of CS with 60% of stroke was predicted by systolic BP as shown in Table (6).

There was a statistically significant relation between NIHSS and frequent PVCS (p=0.04) and between frequent PVCS and NIHSS scale (p=0.01). Similarly, a statistically significant association was detected between the NIHS scale and AF episodes with 50% of cases with severe NIHSS having AF, 33.3% with moderate NIHSS, and 4% with mild NIHSS. There was a statistically significant difference between cases with mild and moderate NIHSS with higher CHA_2DS_2-VASc scores among cases with moderate than mild NIHSS as shown in Table (7).

There was no statistically significant relation between mitral valve, mitral regurgitation, and other findings with NIHSS score as shown in Table (s1).

There was no statistically significant relation between NIHSS and EF among studied cases as shown in Table (s2).

Table 1: Comparison of demographic characteristics between the studied groups.

	Control n=40	**Cases n=30**	**test of significance**
Age/years Mean ± SD	38.10±7.13	36.33±9.04	t=0.914 p=0.364
Sex Males Females	 20(50%) 20(50%)	 17(56.7%) 13(43.3%)	 χ^2=0.306 p=0.580
CHA_2DS_2-VASc Score 0 1 2 3	 20(50%) 20(50%) 0 0	 0 0 17(56.7%) 13(43.3%)	 χ^{2MC}=70 p<0.001*
Previous stroke TIA	0	2(6.7%)	FET=2.75 P=0.180
Vascular disease	0	0	

t: Student t-test, χ^2:Chi-Square test, FET: Fischer exact test, MC: Monte Carlo test

Parameters were described as mean ± SD or as numbers & percentages.

*Statistically significant

CHA_2DS_2-VASc Score (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category 'female')

TIA (transient ischemic attack)

Table 2: Comparison of examination results between the studied groups.

Examination	**Control n=40**	**Cases n=30**	**test of significance**
Systolic blood pressure(mm/Hg)	120.50±5.03	127.0±11.49	t=3.19 p=0.002*
Diastolic blood pressure(mm/Hg)	78.50±3.62	80.67±5.83	t=1.91 p=0.06

Examination	Control n=40	Cases n=30	test of significance
HR beat/minute	75.80±8.98	80.28±10.42	t=1.92 p=0.06
Pulse (regular)	40(100%)	30(100%)	…..
Chest (normal)	40(100%)	30(100%)	…..
LL (no edema)	40(100%)	30(100%)	…..
Syncope, Presyncope	0	0	
Palpitation	0	0	
Chest pain	0	0	
Dyspnea	0	0	

t: Student t-test, Parameters were described as mean ± SD or as numbers & percentages.
*Statistically significant

Table 3: Comparison of neurological examination results between the studied groups.

Neurological examination	Control n=40(%)	Cases n=30(%)
Lateralization RT Side weakness	0	30(100)
Disturbed conscious level	0	6(20)
NIHSS Score Mild Moderate Moderate to severe Severe	Control	25(83.3) 3(10) 0 2(6.7)

Table 4: Comparison of ECG & Echo findings between the studied groups

	Control n=40	Cases n=30	test of significance
ECG (sinus rhythm)	40(100%)	30(100%)	……
Echo Finding			
normal size left atrium	N=40 40(100%)	N=25 25(100%)	……
Cardiac Septa(intact)	N=40 40(100%)	N=25 25(100%)	……
Normal Systolic Function	N=40 40(100%)	N=25 25(100%)	……
Aortic Atheroma	0	0	
Mitral Valve Normal Thickened anterior mitral valve leaflet Mild degree prolapse of anterior mitral valve Leaflet	N=40 40(100%) 0 0	N=30 19(76%) 5(20%) 1(4%)	MC=5.54 P=0.063
Mitral Regurge No Mild	40(100%) 0	18(72%) 7(28%)	FET=7.78 P=0.02*
Intracardiac Vegetation mass or thrombi	0	0	
Other Finding Normal TR	40(100%) 0	23(76.7%) 6(20%)	MC=5.43 P=0.07

	Control n=40	Cases n=30	test of significance
Rheumatic heart disease	0	1(3.3%)	
Ejection fraction	64.45±5.94	65.10±5.49	t=0.468 p=0.642

MC: Monte Carlo test,
Parameters were described as numbers & percentages.
*Statistically significant
TR (tricuspid regurge)

Table 5: Comparison of Holter finding between the studied groups.

Holter Finding	Control n=40	Cases n=30	test of significance
Basal Rhythm	40(100)	30(100)	
Average HR	76(59-92)	80(60-108)	z=1.52 p=0.128
Minimum HR	53(36-67)	53(20-86)	z=0.166 p=0.868
Maximum HR	126(89-162)	131(114-157)	z=1.69 p=0.092
Frequent PACs	0(0.0)	1(3.3%)	FET=0.680 P=1.0
SVT Run	0(0.0)	1(3.3%)	FET=0.680 P=1.0
Frequent PVCS	0(0.0)	1(3.3%)	FET=0.680 P=1.0
Runs of non-sustained VT	2(5.0%)	2(6.7%)	FET=0.06 P=1.0
AF	0	3(10%)	FET=2.13 P=0.265

FET: Fischer exact test, MC: Monte Carlo test, Z: Mann Whitney
Parameters were described as median(range), or as number & percentage.
*Statistically significant.
HR (heart rate), PACS (premature atrial ectopics), SVT (supraventricular tachycardia), PVCs (premature ventricular ectopics), VT (ventricular tachycardia), AF (atrial fibrillation).

Table 6: Binary logistic regression for prediction of Cryptogenic stroke among studied cases

	β	p-value	Odds ratio (95% CI)
CHADS VASCS Score	1.05	0.999	undefined
Systolic blood pressure	0.128	0.043*	1.14(1.00-1.29)
Mitral Regurge No Mild	 21.37	 0.999	 1 Undefined
overall % predicted =60%			

β: regression coefficient

Table 7: Relation between NIHSS and Holter findings, CHA_2DS_2-VASc among studied cases.

Holter Finding	NIHSS			test of significance
	Mild	Moderate	Severe	
Average HR	77(60-108)	82(68-98)	88(86-89)	KW=0.605 P=0.553
Minimum HR	52(39-77)	47(20-60)	70(54-86)	KW=3.26 P=0.054

Holter Finding	NIHSS			test of significance
	Mild	Moderate	Severe	
Maximum HR	131(114-457)	135(128-274)	131(130-132)	KW=0.432 P=0.654
Frequent PACs	1(4%)	0	0	MC=0.207 P=0.902
SVT run	1(4%)	0	0	MC=0.207 P=0.902
Frequent PVCs	0	1(33.3%)	0	MC=9.31 P=0.01*
Runs of non-sustained VT	1(4%)	1(33.3%)	0	MC=3.86 P=0.145
AF	1(4)	1(33.3%)	1(50) %	MC=6.37 P=0.041*
CHA_2DS_2-VASc score	2.36±0.49[A]	3.0±0.0[A]	2.50±0.71	F=2.39 P=0.111

KW: Kruskal Wallis test, F: One Way ANOVA test
*Statistically significant, MC: Monte Carlo test
HR (heart rate), PACS (premature atrial ectopics), SVT (supraventricular tachycardia), PVCS (premature ventricular ectopics), VT (ventricular tachycardia), AF (atrial fibrillation).

DISCUSSION

Patients with CS and TIA of unknown cause can be discovered to have AF, indicating that better efforts are needed to detect AF in this subgroup [8].

The most effective ways to look for potential AF in patients with CS are hotly contested. Patients with CS or TIA who had an ICM implanted had a 30% increase in AF detection within 3 years, according to the CRYSTAL AF study [9].

In this study, we aimed to evaluate the relationship between CS and the incidence of atrial tachyarrhythmias using a 24-hour Holter ECG. To achieve this aim, we conducted this study on 30 CS patients and 40 healthy controls. Holter ECG was performed for all participants and the incidence of arrhythmia was recorded. There was no statistically significant difference between both groups regarding sex distribution or patient's age with a mean age of 36.33 ± 9.04 years for the case group and 38.10 ± 7.13 years for the control group. This could be referred to as the selection criteria of the control group (to be age and sex-matched). These results came in hand with the findings in NAVIGATE trial which included 189 patients distributed in semi-equal 2 groups [10].

In terms of CHA2DS2-VASc score, the control group had 0 or 1 score, whereas the majority of the CS group had 3 (56.7%) or 4 (43.3%), with a statistically significant distinction between the two groups In line with the current findings, Sajeev et al discovered that the stroke group had a higher CHA2DS2-VASc score than the healthy control group [11]. Both groups were comparable in terms of previous incidence of stroke/TIAs, and neither group had any vascular diseases. Along with this finding, both groups had comparable histories of stroke or TIAs [10].

However, Sajeev et al found that stroke patients had a significantly higher rate of positive FH than healthy controls [11]. There were no vascular diseases in either group of patients. This contradicts the findings of Rabinstein et al, who discovered a statistically significant increase in the prevalence of vascular diseases in the non-CS group [12]. Sajeev et al included patients with vascular diseases who had an increased risk of stroke. The difference could be attributed to the older age of the patients in his study [11].

The CS group had higher systolic blood pressure, with a statistically significant difference. However, diastolic blood pressure and heart rate were comparable in both groups, and all cases had normal rhythm pulses in both groups. All of the patients in the case group had a right-sided weakness, and 6 of them had a disturbed consciousness level. The majority of patients (83.3%) had a mild NIHSS score, 10% had a moderate score, and 7.7% had a severe score. The ECG showed normal rhythm in all patients in both groups, with no statistically significant difference. Echo findings were comparable across groups, with the exception that mitral regurgitation cases were higher among CS, with a statistically significant difference. In line with the current study, Rabenstien et al did not report statistically significant differences between CS and stroke of known cause groups based on resting ECG and echo findings [12]. On contrary, Chiang et al. reported the presence of paroxysmal SVT at a higher frequency in the stroke group [13].

All cases had a 24-hour Holter, and there was no statistically significant difference in Holter. In the CS group, there was one case of PACs, one case of SVE, and one case of frequent PVCs. AF episodes were reported in three cases (10%), but there were no statistically significant differences when compared to the healthy control group. In a study by Thijs et al, among 221 patients randomized to ICM, AF episodes were detected in 29 cases within 12 months and 42 cases at 36 months [9].

Furthermore, the NAVIGATE ESUS and RE-SPECT ESUS trials discovered silent AF in about 10% of stroke patients [10, 14].

Previous research has found lower rates of subclinical AF in 24-hour Holter ECG. Using 24-hour Holter monitoring, Jabaudon et al identified newly detected AF in 5.0% of patients [15]. Bansil et al discovered AF in 4 % of patients using 48-h Holter [17].

In contrast to the current study, Sajeev et al reported a higher percentage of PACs (up to 25.6%) in the stroke group, with a statistically significant difference when compared to the healthy control group [11]. Previous studies by Todo et al and Acharya et al suggested a higher burden of PACs in CS patients [18,19].

Chiang et al. also discovered a significant increase in the frequency of paroxysmal SVT in the stroke group when compared to the healthy group [20]. Furthermore, Kamel et al discovered higher SVT runs in Holter ECGs in CS cases and proposed SVT as a significant risk factor for CS [21].

Rabenstien et al found paroxysmal AF in 22% of patients under the age of 60, compared to 3% of stroke patients with known causes whereas in patients 65 and older, detection rates were comparable (27% in CS versus 25% in a stroke of known cause; P =.9) [12]. Longer examination duration was associated with a higher rate of AF detection in his study (over 3 months). In general, earlier and longer monitoring after the stroke increased monitoring yield [22].

It is possible that 21 days of monitoring will not be enough to detect AF after a stroke. The median time from the first AF episode to detection in the ASSERT study was 35 days. AF was discovered in the TRENDS study after 1.7 months [17].

Two previous studies used 21-day and 30-day external event monitors to find out how often silent AF happens in people with CS. In 20% of patients, AF was found for the first time even though inpatient telemetry and electrocardiography didn't find it [23]. In the Ziegler et al study, 60% of newly detected AF patients were identified after the first 30 days [16].

Over 2.8 years of follow-up in the ASSERT study, atrial high-rate episodes (> 190 beats per minute for 6 minutes or longer) occurred in 36% of patients and were associated with a 2.5-fold increase in the risk of stroke or systemic embolism [24].

The burden of AF was found to be directly related to the risk of stroke in the TRENDS study [25].

While routine cardiac testing (ECG, 24- to 48-hour Holter) can detect AF in patients with CS, the detection rate increases to approximately 25% when a 28-day cardiac monitor is used [26, 27]. Outpatient cardiac monitoring appears to be cost-effective for detecting silent AF, though the optimal monitoring method and duration are unknown [21].

In the multivariate analysis, the only significant predictor of CS was found to be systolic blood pressure. This agreed with the results found by Sajeev et al., who found that BP has a substantial effect on the prevalence of CS (OR: 1.67; p 0.05) [11].

We compared the different degrees of stroke according to NIHSS regarding Holter findings and we did not notice no statistically significant differences regarding the frequency of tachyarrhythmias as a low number of patients had moderate (3 patients) or severe (1 patient) NIHSS degree which affected the results of the analysis and significant differences could appear in larger sample size.

There were no statistically significant differences in mitral valve echo findings between NIHSS classes. Only one case of mitral valve prolapse (MVP) was reported. Other studies have linked myxomatous degeneration (thickened or redundant leaflets) and supraventricular arrhythmias to an increased risk of stroke [28]. MR was found in 28.6% of the mild NIHSS group and 33% of the moderate NIHSS group. Aoki et al. found that approximately 20% of stroke patients had MR, which is consistent with the current study [29].

In terms of EF, there were no statistically significant differences between the groups studied. Rahmayani et al, on the other hand, found statistically significant differences in stroke severity in terms of EF, with lower values in the severe group. He hypothesized that patients with declining EF had high left ventricular filling pressure, which resulted in a decrease in stroke volume [30].

The study had the advantages of being conducted on the adult population only which was rarely studied before. Also, this is one of the very limited studies which enrolled a healthy control group in the study. We also tried to find the difference

between NIHSS classes regarding echo findings which is not studied well before.

The study had some limitations as a lack of randomization as we did not enroll any interventions in the study. Also, a limited number of cases was present in each NIHSS classification which affected the results.

CONCLUSIONS

24-hour Holter ECG could detect the presence of runs of subclinical AF or other tachyarrhythmias in CS. However, it could not be enough, and a longer duration of follow-up is required. Elevated systolic BP is a main predictor for the incidence of CS.

Conflict of Interest: None.

Financial Disclosures: None.

Supplementary Files: Tables S1, S2, Figures S1, and S2.

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To cite:
Othman, S., Egila, H., Sakr, S., Elrayes, M. Prevalence and Prediction of Subclinical Atrial Tachyarrhythmias Detected by Continuous Holter Monitoring in Cryptogenic Stroke.. *Zagazig University Medical Journal*, 2023; (814-823): -. doi: 10.21608/zumj.2023.186190.2741

SUPPLEMENTARY FILES

Table s1: Relation between NIHSS and echo findings among studied cases.

	NIHSS			test of significance
	Mild	Moderate	Severe	
Mitral Valve Normal Thickened anterior mitral valve leaflet Mild degree prolapse of anterior mitral valve Leaflet	 26(76.2) 4(19.0) 1(4.8)	 2(66.7) 1(33.3) 0	 1(100) 0 0	 MC=0.777 P=0.942
Mitral Regurge No Mild	 15(71.4) 6(28.6)	 2(66.7) 1(33.3)	 1(100) 0	 MC=0.435 P=0.805
Other Finding NORMAL TR Rheumatic Heart disease	 18(72) 6(24) 1(4)	 3(100) 0 0	 2(100) 0 0	 MC=1.83 P=0.768

*Statistically significant, MC: Monte Carlo test

Table s2: Relation between NIHSS and ejection fraction among studied cases.

	NIHSS			test of significance
	Mild	Moderate	Severe	
Ejection fraction	65.52 ± 5.75	61.33 ± 4.04	65.50 ± 0.71	F=0.772 P=0.472

F: One Way ANOVA test

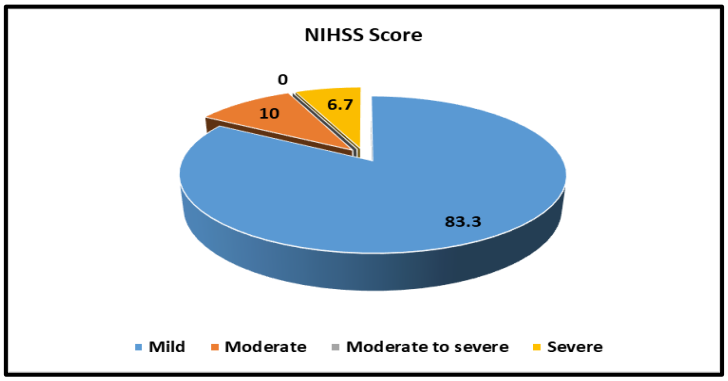

Figure s1: Pie chart showing NIHSS score distribution among studied cases.

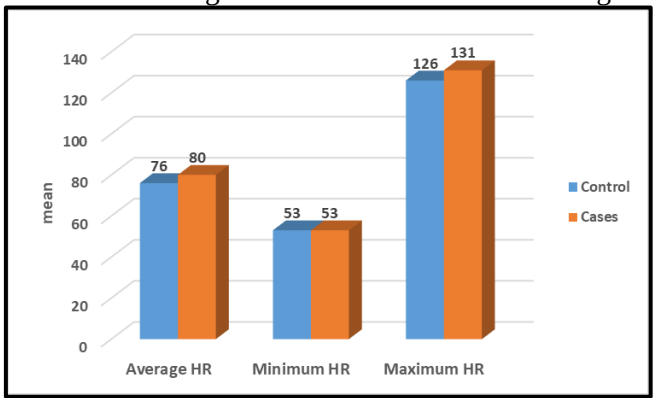

Figure s2: Mean heart rate among studied groups