의학 석사 학위 논문

뇌졸중전문치료실에서의 빈맥이 뇌경색의 기능적 예후에 미치는 영향

Tachycardia Burden in Stroke Unit is Associated with Functional Outcome after Ischemic Stroke

2016년 2월

서울대학교 대학원
의학과 중개의학 전공
정한길

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지도교수 윤병우

이 논문을 의학석사 학위논문으로 제출함.

2015년 10월

서울대학교 대학원

의학과 중개의학 전공

정한길

정한길의 의학석사 학위논문을 인준함.

2016년 12월

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Abstract

Tachycardia Burden in Stroke Unit is Associated with Functional Outcome after Ischemic Stroke

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Background: Stroke unit care is associated with decrease in mortality and improvement in neurological outcome in patients with acute stroke. Heart rate is a commonly monitored variable in the stroke unit. However, little is known about tachycardia burden in the stroke unit and its association with outcome. In this study, we investigate the effects of tachycardia burden in the stroke unit on functional outcome in patients with acute ischemic stroke.

Methods We collected data from 246 patients with acute ischemic stroke admitted to our stroke unit between July 2013 and June 2014. Tachycardia burden was defined as duration of heart rate over 95 per minute divided by the total monitoring time, using the heart rate data sampled every 1 minute. We divided the study population into quartiles of tachycardia burden and analyzed their association with poor 3-month functional outcome (modified Rankin Scale

score of ≥3).

Results: Among included patients (age, 67.4±12.8; male, 53.7%), tachycardia burden was 0.7% (median, interquartile range [0.1%-5.7%]). The patients with higher tachycardia burdens were older, more likely to have higher stroke severity, cardioembolic etiology, atrial fibrillation, fever, pneumonia, higher initial glucose level and higher white blood cell count. As compared with the lowest quartile (<0.1%), the highest quartile of tachycardia burden (≥6.0%) was significantly associated with poor outcome (adjusted odds ratio, 5.10; 95% confidence interval, 1.38-18.90; P=0.01) after adjustment for covariates.

Conclusions: Patients with increased tachycardia burden during stroke unit stay have poor functional outcome. Countermeasures against worsening factors might be utilized for patients with increased tachycardia burden.

Key words: Tachycardia, Heart rate, Stroke units, Acute, Ischemic stroke, Outcome

Student Number: 2014-21160

Contents

Introduction

Stroke unit (SU) care has been shown to render significant benefit to patient with acute stroke by decreasing mortality and morbidity. (1-5) Early detection and timely management of neurological and medical complications may account for beneficial effects of SU care. (6-8) In addition to blood pressure, electrocardiogram (ECG), respiration or oxygen saturation, and heart rate are commonly monitored physiologic variables in the SU. (9-11) However, clinical utility of continuous heart rate monitoring still remains to be elucidated in the setting of acute ischemic stroke. Tachycardia can be triggered by various clinical scenarios including enhanced catecholamine release, fever, volume depletion, sepsis, anemia, hypoxia or anxiety. (12) Increased tachycardia burden is associated with major cardiac event in critically ill, cardiac high risk patients. (13) Moreover, prolonged elevated heart rate is significantly associated with poor functional outcome and major cardiopulmonary events in patients with subarachnoid hemorrhage (SAH). (14) However, it is not clear whether tachycardia is associated with functional outcome in patients with acute ischemic stroke. In this study, we sought to investigate the association of tachycardia burden during stroke unit stay and 3-month functional outcome after ischemic stroke.

Methods

Collection of patients' data

A total of 356 consecutive patients with acute ischemic stroke and transient ischemic attack (TIA) (≤7 days after onset) were admitted to stroke unit between July 2013 and June 2014. Patients with enough data for analysis (SU monitoring time > 12 hours) were included. Therefore, a third of patients (n=105) were excluded. We also excluded 5 patients who had no information of modified Rankin Scale (mRS) score at 3 months after stroke due to loss of follow-up. Finally, a total of 246 patients were included for analysis. The analysis was performed retrospectively using a prospectively collected stroke registry database. This study was approved by the Institutional Review Board at the Seoul National University Hospital [IRB approval No. H-1212-087-450]

Definition of clinical information

We collected baseline demographic, clinical and laboratory information for all study participants, including age, sex, initial systolic and diastolic blood pressure, history of previous stroke, and cardiovascular risk factors. (15-17) Stroke characteristics included National Institutes of Health Stroke Scale (NIHSS) score at admission, thrombolytic treatment, pneumonia in the first two weeks of admission, and mRS score at 3 months after stroke. TIA was defined as stroke

symptoms lasting less than<24 hours. Stroke subtype was categorized using Trial of ORG 10172 in Acute Stroke Treatment classification. (18)

Monitoring Data Acquisition

A high resolution data acquisition system (BedmasterEX, Excel Medical Electronics) was used to acquire digital data including blood pressure, heart rate and body temperature in the stroke unit via GE Dash 4000 monitor. Physiologic variables were sampled every 1 minute. Heart rate of > 95 beats per minute was defined as an occurrence of tachycardia based on previous study. (13, 14) Tachycardia burden was defined as duration of heart rate over 95/min divided by the total monitoring time. Fever was defined as body temperature elevation over 37.5 °C. (19, 20)

Statistical analyses

Poor functional outcome was defined as 3-month mRS score of 3 to 6. Differences between continuous variables were analyzed using the t test and differences between categorical variables were analyzed using the $\chi 2$ test or Fisher exact test, as appropriate. Logistic regression analysis was used to evaluate the association between tachycardia burden and functional outcome at 3 months. Significance levels were set at a P value of <0.05. Statistical analyses were performed using R statistical software (R, version 3.1.1, R Project).

Results

A total of 246 consecutively admitted patients were included. Excluded patients (n=110) were more likely to be male (66.4% vs. 53.7%, P=0.03) with less hypertension (57.3% vs. 72.8%, P<0.01) compared to the study subjects. All other baseline characteristics were not different between the two groups (Table 1).

Mean age of study patients was 67.4 (standard deviation; 12.8) with higher proportion of male (53.7%). The risk factors included hypertension in 179 (72.8%) patients, diabetes mellitus in 74 (30.1%) patients, hyperlipidemia in 78 (31.7%) patients, habitual smoking in 72 (29.3%) patients, and atrial fibrillation (AF) in 57 (23.2%) of patients. Twenty-five patients (10.2%) had transient ischemia attack. The median NIHSS score at admission was 3 (interquartile range, 1-7) and 8.5% (n=21) of patients received thrombolytic treatment. Sixty-seven (27.2%) patients had fever in the stroke unit and 30 (12.2%) patients had pneumonia in the first two weeks of admission.

Association between tachycardia and functional outcome

Tachycardia burden, the duration of heart rate over 95/min divided by the total monitoring time, was classified into quartiles (median, 0.7%; interquartile range, 0.1%-5.7%) (Table 2). The patients with the highest tachycardia burden (≥6.0%) were older, more likely to have diabetes, AF, cardioembolic etiology with higher

stroke severity at admission, stayed longer in the SU. In addition, they were more likely to have fever in the SU, pneumonia in the first two weeks of admission, and poor functional outcome (mRS 3-6). They were more likely to have higher white blood cell count, initial fasting glucose, HbA1c, but lower hematocrit.

As expected, the patients with the poor functional outcome were older (74.5 years vs. 63.7 years, P<0.01), had higher initial stroke severity (median NIHSS 7 vs. 2, P <0.01), higher initial fasting glucose (112 mg/dL vs. 101 mg/dL, P=0.02), higher proportion of fever (55.4% vs. 12.9%, P<0.01) and pneumonia (31.3% vs. 2.5%, P<0.01), lower hematocrit (36.9% vs. 39.8%, P<0.01), and longer total monitoring time (70.5±43.4 hours vs. 42.7±24.5 hours, P<0.01). (Table 1)

Increased tachycardia burden was associated with an increased odd for poor outcome (mRS 3-6) (odds ratio 1.36, 3.60, and 13.42 in 2nd, 3rd, and 4th quartiles; P for trend, <0.01). As compared with the lowest quartile (<0.1 %), the fourth quartile of tachycardia burden (≥6.0%) was significantly associated with the poor outcome (adjusted odds ratio, 5.10; 95% confidence interval, 1.38-18.90; P=0.01) after adjusting for confounding variables with bivariate P-values <0.05 (age, transient ischemia attack, stroke subtype, initial stroke severity, AF, thrombolytic treatment, fever, pneumonia, initial fasting glucose, hematocrit and total monitoring time). (Table 3; Figure)

Discussion

In this study, we found that increased tachycardia burden during stroke unit stay was associated with overall mortality and disability in patients with acute ischemic stroke. About 68% of the patients in the highest quartile of tachycardia burden (≥6.0%) had poor functional outcome.

The association between tachycardia and functional outcome in patients with acute stroke is controversial. One study showed elevated heart rate in subacute phase after stroke is a risk indicator for mortality and poor functional outcome. (21) However, it was unknown whether tachycardia is important in stroke patients with acute phase when heart related change is more important in prognosis. (22, 23) A recent study on acute stroke patients showed tachycardia is frequent phenomenon, while its association to poor functional outcome is not significant. (23) However, the study evaluated merely the occurrence of tachycardia within 24 hours as 'yes or no', thus could not assess overall burden of tachycardia during stroke unit stay. However, our study analyzed heart rate data with 1-minute resolution. Therefore, we could evaluate tachycardia burden as the percentage of duration of tachycardia per total monitoring time from continuous ECG monitoring using high resolution data acquisition system. With these strength, we think that our study provides more accurate information on the relationship between tachycardia and clinical outcome.

The factors associated with poor outcome in patients with stroke were old age, initial stroke severity, stroke progression, recurrence, and medical

complications such as pneumonia. (7, 24-26) Likewise, the patients with higher tachycardia burden also were more likely to be old, had higher initial NIHSS score and higher incidence of fever and pneumonia. However, tachycardia burden still showed significant association with poor functional outcome after adjusting for covariates described above.

Well-known causes of tachycardia such as sympathetic hyperactivity, pain, agitation, volume depletion, anemia, heart failure and chronic pulmonary disease are frequent in the acute stroke population. (12) Unfortunately, identifying the main cause of tachycardia which drives the association with poor outcomes is not possible in our study. In addition, it is not clear whether tachycardia itself has a direct negative effect on functional outcome or tachycardia just reflects poor clinical conditions. It is likely that multiple factors may be contributing to this association of tachycardia and poor outcomes. Our finding that tachycardia was strongly associated with poor functional outcome after controlling for potential factors associated poor outcomes suggests that tachycardia is at least a surrogate marker for multiple neurologic and/or medical worsening. One possibility is that pathologic sympathetic activation during the acute phase of stroke is may be a predictor of future cardiovascular and cerebrovascular events. (27) Several studies have shown that elevated heart rate is associated with plaque rupture (28) and recurrent myocardial infarction with coronary artery disease. (29)

There are several limitations in our study. First, our study is a retrospective study which excluded a significant numbers of patients due to lack

of data for analysis, therefore, there is a chance for selection bias. However, excluded patients were not different except for sex and hypertension compared to study population, suggesting that the chances of selection bias are not high. Second, the association of tachycardia and early neurologic deterioration could not be assessed in our study. The lack of information on the specific time point of neurologic worsening and tachycardia occurrence limits the interpretation and further studies are needed to investigate timing of tachycardia and neurologic symptoms. Third, we tried to adjust pneumonia and fever as a possible confounder of fever in analyzing data, however, many unmeasured possible causes of tachycardia may still exist. Volume depletion may be one of the triggering factors of tachycardia in unstable patients. However, our patients were treated aggressively with hydration with normal saline. Therefore, the chances of hypovolemia in our patients are not high. Fourth, there is still a chance that more severe cardioembolic stroke patient had higher tachycardia burden due to frequent AF rapid ventricular response (RVR). In order to solve this issue, we adjusted AF in analyzing the association between tachycardia and functional outcome, and the correlation was still valid even after adjusting covariates.

In conclusion, an increased tachycardia burden during stroke unit stay is associated with poor 3-month functional outcome, which underscores importance of continuous heart rate monitoring in the SU. Moreover, it could be inferred from our results that countermeasures against worsening factors might be utilized for patients with increased tachycardia burden. Future clinical studies

are needed analyzing occurrence of early neurologic deterioration and its association with increased tachycardia burden.

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Tables

Table 1. Demographics of study patients

	Included patients (N=246)	Excluded patients (N=110)	P	mRS 0-2 (N=163)	mRS 3-6 (N=83)	P
Male gender	132 (53.7)	73 (66.4)	0.03	94 (57.7)	38 (45.8)	0.10
Age, y	67.4±12.8	64.6±15.5	0.10	63.7±12.5	74.5±10.0	<0.01
Vascular risk factors						
Hypertension	179 (72.8)	63 (57.3)	<0.01	119 (73.0)	60 (72.3)	1.00
Diabetes mellitus	74 (30.1)	29 (26.4)	0.56	45 (27.6)	29 (35.0)	0.30
Hyperlipidemia	78 (31.7)	32 (29.1)	0.71	58 (35.6)	20 (24.1)	0.09
Habitual smoking	72 (29.3)	43 (39.1)	0.09	49 (30.0)	23 (27.7)	0.81
Atrial fibrillation	57 (23.2)	24 (21.8)	0.89	31 (19.0)	26 (31.3)	0.05
Previous stroke history	72 (29.3)	27 (24.5)	0.43	44 (27.0)	28 (33.7)	0.34
Stroke information						
Transient ischemic attack	25 (10.2)	13 (11.8)	0.78	21 (12.9)	4 (4.8)	0.08
Stroke subtype			0.64			0.06
Large artery disease	55 (24.9)	26 (26.8)		37 (26.1)	18 (22.8)	
Small vessel occlusion	43 (19.5)	18 (18.6)		32 (22.5)	11 (13.9)	
Cardioembolism	71 (32.1)	25 (25.8)		46 (32.4)	25 (31.6)	
Other determined etiology	21 (9.5)	14 (14.4)		14 (9.9)	7 (8.9)	
Undetermined etiology	31 (14.0)	14 (14.4)		13 (9.1)	18 (22.8)	
NIHSS score, median [IQR]	3 [1-7]	3 [1-6]	0.78	2 [0-3]	7 [3.5-15]	<0.01
Thrombolytic treatment	21 (8.5)	11 (10.0)	0.81	9 (5.5)	12 (14.5)	0.03
Fever in the SU	67 (27.2)	29 (26.4)	0.97	21 (12.9)	46 (55.4)	<0.01
Pneumonia over 2 week	30 (12.2)	11 (10.0)	0.67	4 (2.5)	26 (31.3)	<0.01
mRS score 3-6 at 3 months	83 (33.7)	36 (32.7)	0.93	-	-	-

Tachycardia burden						<0.01
Quartile 1 (<0.1%)				56 (34.4)	9 (10.8)	
Quartile 2 (0.1%-0.7%)				50 (30.7)	11 (13.3)	
Quartile 3 (0.7%-6.0%)				38 (23.3)	22 (26.5)	
Quartile 4 (≥6.0%)				19 (11.7)	41 (49.4)	
Total monitoring time, h	52.1±34.6	-	-	42.7±24.5	70.5±43.4	<0.01

mRS denotes modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range. mRS scores were missed 7 cases in the excluded patients due to loss of follow up.

Table 2. Characteristics of acute ischemic stroke patients in our stroke unit, according to quartiles of tachycardia burden.

Characteristics	Quartile 1 (<0.1%)	Quartile 2 (0.1%-0.7%)	Quartile 3 (0.7%-6.0%)	Quartile 4 (≥6.0%)	P value for linear trend
Number of patients	65	61	60	60	
Demographic variables					
Male gender	40 (61.5)	29 (47.5)	32 (53.3)	31 (51.7)	0.38
Age, y	66.6±10.7	63.0±13.2	68.1±13.6	71.8±12.2	<0.01
Vascular risk factors					
Hypertension	46 (70.8)	45 (73.8)	45 (75.0)	43 (71.7)	0.87
Diabetes mellitus	15 (23.1)	17 (27.9)	17 (28.3)	25 (41.7)	0.03
Hyperlipidemia	28 (43.1)	17 (27.9)	18 (30.0)	15 (25.0)	0.05
Habitual smoking	26 (40.0)	15 (24.6)	15 (25.0)	16 (26.7)	0.12
Atrial fibrillation	9 (13.8)	3 (4.9)	21 (35.0)	24 (40.0)	<0.01
Previous stroke history	18 (27.7)	15 (24.6)	20 (33.3)	19 (31.7)	0.43
Coronary heart disease	10 (15.4%)	4 (6.6%)	7 (11.7%)	7 (11.7%)	0.71
Congestive heart failure	4 (6.2%)	0 (0.0%)	3 (5.0%)	1 (1.7%)	0.38

Stroke information					
Transient ischemic attack	8 (12.3)	10 (16.4)	3 (5.0)	4 (6.7)	0.10
Stroke subtype					0.05
Large artery disease	18 (31.6)	14 (27.5)	16 (28.1)	7 (12.5)	
Small vessel occlusion	11 (19.3)	15 (29.4)	9 (15.8)	8 (14.3)	
Cardioembolism	15 (26.3)	10 (19.6)	23 (40.4)	23 (41.1)	
Other determined etiology	5 (8.8)	6 (11.8)	4 (7.0)	6 (10.7)	
Undetermined etiology	8 (14.0)	6 (11.8)	5 (8.8)	12 (21.4)	
NIHSS score, median [IQR]	2 [0-4]	2 [0-4]	3 [1-8]	7 [2-14]	<0.01
Thrombolytic treatment	5 (7.7)	3 (4.9)	7 (11.7)	6 (10.0)	0.40
Fever	6 (9.2)	4 (6.6)	22 (36.7)	35 (58.3)	<0.01
Pneumonia	1 (1.5)	1 (1.6)	8 (13.3)	20 (33.3)	<0.01
mRS score 3-6 at 3 months	9 (13.8)	11 (18.0)	22 (36.7)	41 (68.3)	<0.01
Laboratory information					
Systolic blood pressure, mmHg	153±29	157±31	160.6±30.2	152.6±31.1	0.82
Diastolic blood pressure, mmHg	80±14	87±16	87.7±15.1	85.2±15.5	0.05
Initial fasting glucose, mg/dL	99±32	102±27	105±32	114±40	0.01

HbA1c, %	6.0±0.7	6.1±0.8	6.2±1.1	6.4±0.9	0.01
Total cholesterol, mg/dL	167±40	172±43	172±45	164±39	0.66
White blood cell count, /μL	7926±3331	7871±3085	7725±2786	9177±3237	0.05
Hematocrit, %	39.4±4.9	41.0±4.0	37.6±4.9	37.1±5.7	<0.01
Ejection fraction, %†	61.2±7.0	61.9±6.2	59.9±5.7	59.9±7.2	0.13
Medications to control heart rate					
Diltiazem	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (18.3%)	<0.01
Digoxin	1 (1.5%)	0 (0.0%)	2 (3.3%)	3 (5.0%)	0.12
Beta blockers	8 (12.3%)	0 (0.0%)	9 (15.0%)	4 (6.7%)	0.87
Tachycardia burden, %	0.0±0.0	0.3±0.2	2.3±1.4	34.2±26.8	<0.01
Total monitoring time, h	42.1±24.8	47.3±27.7	49.1±28.5	70.8±47.1	<0.01

mRS denotes modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range.

†Transthoracic echocardiography was performed in 93% of the patients (n=228 of 246) during admission period.

Table 3. Associations between tachycardia burden and poor 3-month functional outcome

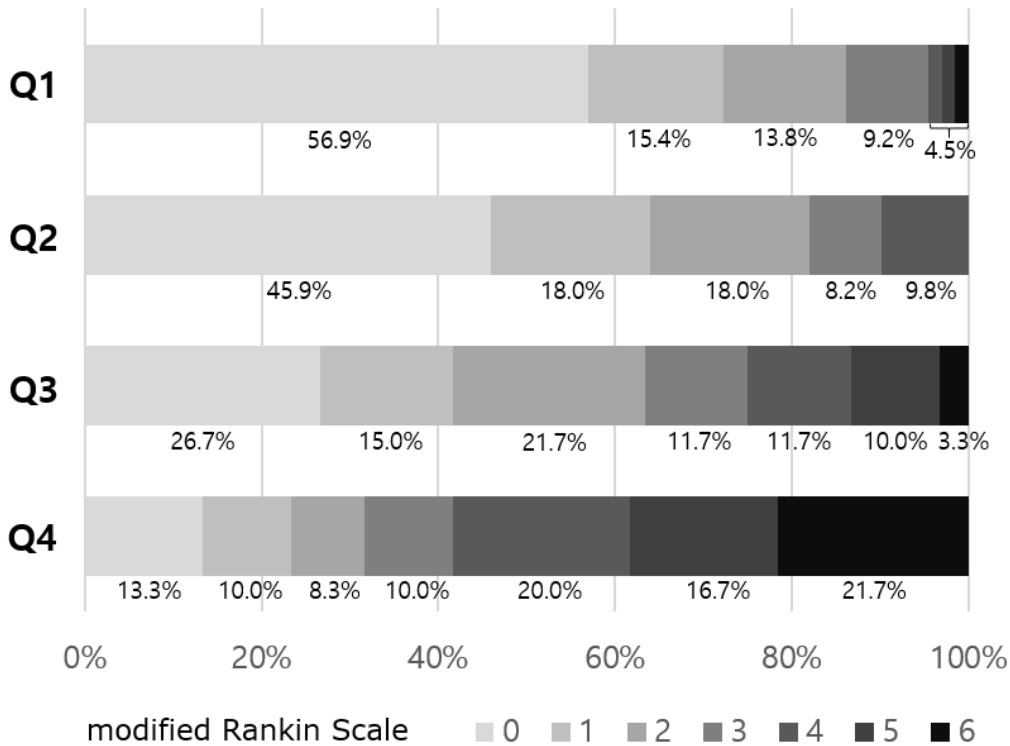
Tachycardia Burden	Univariate models		Multivariable models*	
	Crude OR [95% CI]	P value	Adjusted OR [95% CI]	P value
Quartile 1 (<0.1%)	(Reference)		(Reference)	
Quartile 2 (0.1%-0.7%)	1.36 [0.52-3.57]	0.52	2.13 [0.64-7.09]	0.22
Quartile 3 (0.7%-6.0%)	3.60 [1.50-8.67]	<0.01	3.07 [0.92-10.22]	0.07
Quartile 4 (≥6.0%)	13.42 [5.51-32.68]	<0.01	5.10 [1.38-18.90]	0.01
P for trend	< 0.01		0.01	

OR denotes odds ratio; CI, confidence interval

* Multivariable models were adjusted for age, transient ischemic attack, stroke subtype, atrial fibrillation, initial stroke severity, thrombolytic treatment, fever, pneumonia, initial fasting glucose, hematocrit and total monitoring time.

Figures and Figure legends

Figure. Distribution of modified Rankin Scale score according to the quartile of tachycardia burden



초 록

배경: 뇌졸중전문치료실은 급성 뇌졸중 환자의 사망률을 감소시키고 신경학적 예후를 좋게 만든다. 심박수는 뇌졸중전문치료실에서 흔히 감시되는 지표이다. 하지만, 뇌졸중전문치료실 입원 중 발생하는 빈맥의 정도와 예후의 연관성에 대해서는 알려진 바가 없다. 우리는 이 연구에서 뇌졸중 집중치료실에서 빈맥의 정도가 뇌경색 환자들의 기능적 예후에 미치는 영향을 평가하고자 하였다.

방법: 우리는 2013 년 7 월부터 2014 년 6 월까지 뇌졸중전문치료실에 입원한 246 명의 환자로부터 데이터를 수집하였다. 빈맥은 분당 심박수 95 회 이상으로 정의하였다. 빈맥의 정도는 1 분마다 수집된 심박수 데이터를 사용하여 빈맥이 발생한 시간을 총 감시시간으로 나누어 정의하였다. 우리는 대상 환자들을 빈맥의 정도에 따른 사분위수로 나누었고 이를 modified Rankin Scale ≥3 으로 정의한 불량한 3 개월 예후와의 연관성을 분석하였다.

결과: 대상 환자들 중에서 (나이, 67.4±12.8; 남성, 53.7%), 빈맥의 정도는 평균 0.7% 이었고 사분위수 범위는 0.1%-5.7% 이었다. 빈맥의 정도가 높은 환자들은 나이가 더 많고, 초기 신경학적 결손이 심했고, 심장색전, 심방세동, 발열, 폐렴이 많았고, 초기 혈당과 혈청 백혈구 수치가 높은 경향을

보였다. 빈맥의 정도가 제 1 사분위수(<0.1%)에 속한 환자와 비교하였을때, 가장 높은 빈맥의 정도를 가진 환자들은 (≥6.0%) 공변량을 보정한 후에도 나쁜 예후와 통계적으로 유의한 연관성을 보였다 (보정된 오즈비, 5.10; 95% 신뢰구간, 1.38-18.90; P=0.01).

결론: 뇌졸중전문치료실 입원 중에 빈맥의 정도가 높았던 환자들은 나쁜 기능적 예후를 가진다. 빈맥의 정도가 높았던 환자들에게는 여러가지 악화 인자들에 대한 대응책이 필요할 수 있다.

주요어: 빈맥, 심박수, 뇌졸중전문치료실, 급성, 뇌경색, 예후

학번: 2014-21160