Baroreflex sensitivity is associated with post-stroke infections. An open, prospective study

Marek Sykora[a,b,*], Pavel Siarnik[c], Jozef Szabo[c], Peter Turcani[c], Stefan Krebs[a,g], Wilfried Lang[a], Stanislava Jakubicek[d], Marek Czosnyka[e,f], Peter Smielewski[e]

[a] Department of Neurology, St. John's Hospital, Medical Faculty of Sigmund Freud University Vienna, Austria
[b] Department of Neurology, Ruprecht Karls University Heidelberg, Heidelberg, Germany
[c] Department of Neurology, Comenius University Bratislava, Bratislava, Slovakia
[d] Department of Neurology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic
[e] Institute of Electronic Systems, Warsaw University of Technology, Poland
[f] Div. of Neurosurgery, Department of Clinical Neurosciences, Cambridge University, Cambridge, UK
[g] Department of Neurology, St. John's Hospital, Vienna, Austria

ARTICLE INFO

ABSTRACT

Background and purpose: Autonomic nervous system (ANS) seems to play an important role in the post-stroke immunosuppression syndrome with increased susceptibility to infections. The aim of this study was to investigate if ANS activity measured at admission is associated with post-stroke infections.
Methods: We prospectively analyzed patients with acute ischemic stroke. ANS was measured using the cross-correlational baroreflex sensitivity (BRS) at admission. The occurrence and cause of in-hospital infections was assessed based on the clinical and laboratory examination. Demographic and clinical variables including initial stroke severity, dysphagia, procedures as nasogastric tubes, central venous and urinary catheters and mechanical ventilation were included in the analysis.
Results: We included 161 patients with ischemic stroke, of those 49 (30.4%) developed a nosocomial infection during the first 7 days of hospital stay. Patients with infections had significantly lower BRS (median 3 vs 5 ms/mmHg, $p < .001$) higher initial NIHSS (median 15 vs 5, $p < .001$), had more often non-lacunar etiology and underwent more invasive procedures. In the multivariable regression model decreased BRS (adjusted OR 1.21, 95% CI 1.03–1.41, $p = .02$), admission NIHSS (adjusted OR 1.10, 95% CI 1.02–1.19, $p = .02$) and invasive procedures (adjusted OR 1.46, 95% CI 1.03–2.06, $p = .03$) were independently associated with infection after ischemic stroke.
Conclusions: Decreased BRS was independently associated with infections after ischemic stroke. Autonomic shift may play an important role in increased susceptibility to infections after stroke. The possible diagnostic and therapeutic relevance of this finding deserves further research.

1. Introduction

Infections after ischemic stroke are frequent with high rates up to 30% [1,2] Pneumonia followed by urinary track infection are the most common types. Post-stroke pneumonia is associated with age, stroke severity, impaired consciousness, oropharyngeal dysphagia as well as with feeding tube placement, orotracheal intubation and mechanical ventilation [3,4]. Moreover, evidence cumulates that brain-immune interactions become impaired after stroke resulting in a stroke-related immunosupression syndrome [5]. Animal models of stroke and research in humans suggest stroke-induced immunodeficiency to be mediated via hypothalamic pituitary axis and sympathetic nervous system [6]. Catecholamine- and stress mediated impairment of cellular immune responses include lymphocyte apoptosis, decreased lymphocyte activation, cytokine changes, or atrophy of lymphoid organs [7–10]. Accordingly, enhanced sympathetic activity with subsequent suppressed immune function has been associated with the occurrence of post-stroke infections [8,11]. Heart rate variability (HRV), a marker of autonomic impairment, has been recently suggested to be associated with post-stroke infections [12].

Baroreflex sensitivity (BRS) is another established and reliable marker of autonomic nervous system and has been clinically proven in

---

* Corresponding author at: Department of Neurology, St. John's Hospital, Johannes von Gott Platz 1, 1020 Wien, Austria.
E-mail address: marek.sykora@med.sfu.ac.at (M. Sykora).

numerous studies [13–15]. Previously, we found decreased BRS to be related to nosocomial infections after intracerebral hemorrhage [16]. Hence, here we aimed to investigate, in a prospective manner, if BRS measured at admission may be associated the occurrence of in-hospital infections after acute ischemic stroke.

2. Methods

2.1. Population

From 2011 to 2018, consecutive acute stroke patients were prospectively enrolled into the study when following criteria has been fulfilled: 1) acute ischemic stroke confirmed by computer tomography (CT) or magnetic resonance imaging (MRI); 2) negative history of previous stroke, atrial fibrillation, myocardial infarction, diabetes mellitus, chronic renal failure, or other medical conditions known to affect autonomic functions; 3) absence of antihypertensive therapy or cardiovascular active treatment for at least 24 h; 4) no clinical or laboratory signs of infection at admission.

2.2. Stroke severity, localization and etiology

Stroke severity at admission was scored using to the National Institute of Heath Stroke Scale (NIHSS). The side and supratentorial/intratentorial localization of stroke lesion on CT/MRI was recorded. Stroke etiology was classified according to TOAST criteria [17] and for the purposes of statistical analysis dichotomized into lacunar and non-lacunar etiology.

2.3. Clinical management

General management included standard stroke unit monitoring and blood pressure management, dysphagia screening using Gugging swallowing test, nasogastric tubes in severe dysphagia and orotracheal intubation and ventilatory support when Glasgow Coma Scale (GCS) < 8. All patients requiring ventilatory support received central venous catheters, urinary catheters and nasogastric tubes. Blood samples were drawn on a daily basis, including leukocyte count and C-reactive protein (CRP) levels. Body temperature was checked at least three times a day. Urine analysis and bacterial analysis of sputum was performed regularly twice a week, even if no clinical infection was suspected. In case of suspect clinical infection, chest X-rays, urine, blood and sputum cultivations were performed.

2.4. Assessment of infection

Patients were monitored up to 7 days after admission for signs and symptoms of infections. Monitored characteristics included the presence of clinical signs of infections, daily CRP values and leukocyte count, temperature measurement at least 3 times a day, urine screening and chest X-rays. Based on the results, patients were classified into 3 groups as described previously [16,18]: The first group included patients with pneumonia: diagnosis was based on clinical criteria including fever, purulent sputum or respiratory deterioration and positive chest X-rays in combination with laboratory findings of leukocytosis and CRP > 50 mg/ml [19,20] The second group comprised patients with urinary tract infection that was diagnosed based on elevated leukocyte count and positive nitrite in the urine screening in combination with leukocytosis and CRP > 50 mg/dl and positive urine culture. The third group included patients without clinical and laboratory signs of infection during the first 7 days of hospital stay. Additionally, dysphagia, nasogastric tube use, central venous and urinary catheters, ICU stay, mechanical ventilation and antibiotic treatment in first 7 days of hospitalization were recorded. Due to the high co-linearity between variables dysphagia/nasogastric tube use, central venous and urinary catheters, intubation and mechanical ventilation, we calculated for the

further analysis "invasiveness" score giving 1 point for each procedure [16].

2.5. Assessment of spontaneous BRS

Blood pressure for spontaneous BRS assessment was measured noninvasively using the Finometer device (FMS, Finapres Medical Systems BV, Amsterdam, Nederlands). This device employs a volume clamp method to capture beat-to-beat (continuous) values of blood pressure and pulse rate in the finger artery. A cuff of appropriate size was attached to the middle finger of the non-hemiparetic hand of the patient in supine position and the hand was maintained at heart level. Using the Finometer device, continuous blood pressure and pulse rate for BRS assessment were recorded within 24 h after stroke onset, usually upon admission, for a period of 10 min. The ICM + ® software (Cambridge Enterprise Ltd., Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) was used for the analysis of stored Finometer signals. Baroreflex sensitivity (BRS) was calculated using a modification of the sequential cross-correlation method [21]. The modified function uses arterial blood pressure systolic peaks to create RR intervals time series, using an automated detection algorithm. The slope of the linear regression between 10s series of RR intervals and the corresponding 10s series of systolic blood pressure is then calculated. In order to remove the influence of an unknown time delay of the baroreceptors response, cross-correlation function is used to maximize the correlation coefficient. The RR window is shifted against the systolic pressure window in a stepwise manner and the highest correlation is reported, if it fulfills the criteria outlined below. In order to ensure that the correlation calculations are always performed on the same number of data points irrespective of the lag applied to RR series, the actual data buffer is extended with each window shift. Valid BRS value is returned only if the correlation coefficient is significant at $p < .01$, and if no irregular beats (ectopics) are detected by the software. To compensate for the influence of uncorrelated noise the slope returned is adjusted (divided by) the correlation coefficient. The BRS is updated every 10s and expressed as median in ms/mmHg.

2.6. Ethics

The local ethics committee approved the study. All patients or their next of kin gave written informed consent.

2.7. Statistics

Distribution of the data was visualized using histograms and tested using the one-sample Kolmogorov-Smirnov test. For normally distributed data the results are presented as mean, range, and standard deviation, for non-normally distributed data as median, range, and interquartile range. For comparison between the groups Fisher's test, Mann-Whitney test, or Student's unpaired *t*-test was used, as appropriate. When significant in the univariate analysis, variables entered a stepwise logistic regression model to study the relationship between predictive variables and dependent variable as follows: A stepwise regression analysis was employed to select which of the variables should be included in a regression model to predict the dependent variable. The procedure applied the variables one by one using a criterion such that the F-statistic for the variable to be added must exceed the level of 0.05. After a variable was added to the model, the procedure analyzes all included variables and deletes any variable that fails to produce an F-value < 0.1. After necessary deletions are accomplished, a further variable can be added to the model. The procedure terminates when no variable outside the model exceeds the necessary threshold and every variable included is significant. Values of $p < .05$ were considered statistically significant in all tests. All statistics were performed using statistical software SPSS 24.0 for Windows.

Table 1
Demographic and clinical characteristics of the study population.

N	161
Age, years (mean, range, SD)	65 (15–97, 20)
Sex, male, n (%)	84 (52.2)
Etiology	
Small vessel disease, n (%)	41 (25.5)
Large vessel disease, n (%)	76 (47.2)
Cardioembolic, n (%)	26 (16.1)
Other, n (%)	9 (5.6)
Cryptogenic, n (%)	9 (5.6)
History of hypertension, n (%)	113 (70.2)
Previous antihypertensive therapy, n (%)	87 (54)
Beta-blockers, n (%)	50 (31.1)
Angiotensin-converting enzyme inhibitors/Angiotensin-receptor antagonists, n (%)	65 (40.4)
Calcium channel antagonists, n (%)	42 (26.1)
Diuretics, n (%)	26 (16.1)
NIHSS at admission (median, range, IQR)	6 (0–36, 10)
Localization	
Supratentorial, n (%)	140 (87)
Left, n (%)	76 (47.2)
Right, n (%)	64 (39.8)
Infratentorial, n (%)	21 (13)
Dysphagia/Nasogatric tube, n (%)	53 (32.9)
Urinary catheter	68 (42.2)
Central line	22 (13.7)
Intubation and mechanical ventilation, n (%)	18 (11.2)
Decompressive surgery, n (%)	14 (8.7)
Invasivness score (median, range, IQR)	0 (0–5, 2)

NIHSS – National Institute of Health Stroke Scale.

3. Results

One hundred sixty one patients with ischemic stroke met the inclusion criteria. The demographic and clinical characteristics of the population are shown in Table 1. The mean age was 65 years, 52.2% were male and the median NIHSS score at admission was 6 points. 87% of strokes were localized supratentorially. 51 (31.7%) of patients underwent intravenous thrombolysis and 9 (5.6%) underwent thrombectomy. 49 (30.4%) patients developed an infection within first 7 days after admission. Of those, 29 (18%) had a pneumonia and 20 (12.4%) had urinary infection. Subjects with infection had lower BRS (median BRS 3.00 versus 5.00 ms/mmHg, $p < .001$), more non-lacunar etiology of stroke (47 (96%) versus 2 (4%), $p < .001$), higher NIHSS at admission (median 15 versus 5, $p < .001$), more often underwent thrombolysis (23 (48.9%) versus 28 (25.5%), $p = .005$) and thrombectomy (7 (14.3%) versus 2 (1.8%)). Patients with infections experienced more dysphagia (28 (57.1%) versus 25 (22.3%), $p < .001$) and underwent also more invasive procedures, for details see Table 2. The invasiveness score was median 2 versus 0 points ($p < .001$), respectively.

In the multivariable regression model decreased BRS (per 1 ms/mmHg decrease, adjusted OR 1.21, 95% CI 1.03–1.41, $p = .02$), admission NIHSS (adjusted OR 1.10, 95% CI 1.02–1.19, $p = .02$) and invasiveness score (adjusted OR 1.46, 95% CI 1.03–2.06, $p = .03$) were independently associated with an infection after ischemic stroke, see Table 3. Decreased BRS (per 1 ms/mmHg decrease, adjusted OR 1.34, CI 1.05–1.69, $p = .02$), admission NIHSS (adjusted OR 1.09, CI 1.01–1.17, $p = .03$), invasiveness score (adjusted OR 1.65, CI 1.14–2.40, $p = .008$) and non-lacunar etiology (adjusted OR 1.59, CI 1.00–2.56, $p = .05$) were associated with pneumonia after stroke, see Table 4.

4. Discussion

Changes in the activity of the autonomic nervous system as mirrored by the decreased baroreflex sensitivity seem to be involved in the pathophysiology of post-stroke infections. Our findings underscore

Table 2
Univariate analysis of variables associated with infections after ischemic stroke.

N	No infection, n = 112	Infection, n = 49	p
BRS, ms/mmHg, (median, range, IQR)	5.0 (1.1–34.9, 4.7)	3.0 (1.1–8.6, 2.8)	< 0.001
Age, years (mean, range, SD)	64.64 (32–97, 21)	65.49 (15–89, 19)	0.8[c]
Sex, male, n (%)	59 (52.7)	25 (51)	0.9[a]
Etiology			0.001[a]
Small vessel disease, n (%)	38 (33.9)	2 (4.1)	
Large vessel disease, n (%)	50 (44.6)	26 (53.1)	
Cardioembolic, n (%)	15 (13.4)	11 (22.4)	
Other, n (%)	4 (3.6)	6 (12.2)	
Cryptogenic, n (%)	5 (4.5)	4 (8.2)	
History of hypertension, n (%)	82 (73.2)	31 (63.3)	0.3[a]
Previous antihypertensive therapy, n (%)	57 (50.9)	20 (40.8)	0.3[a]
Beta-blockers, n (%)	39 (34.8)	11 (22.4)	0.1[a]
Angiotensin-converting enzyme inhibitors/Angiotensin-receptor antagonists, n (%)	40 (35.7)	12 (24.5)	0.2[a]
Calcium channel antagonists, n (%)	32 (28.8)	10 (20.4)	0.3[a]
Diuretics, n (%)	16 (14.3)	10 (20.4)	0.4[a]
NIHSS at admission (median, range, IQR)	5 (0–25, 5)	15 (2–36, 12)	< 0.001[b]
Localization			
Supratentorial, n (%)	99 (88.4)	41 (83.7)	0.5[a]
Left, n (%)	52 (52.5)	24 (58.5)	0.6[a]
Right, n (%)	47 (47.5)	17 (41.5)	
Infratentorial, n (%)	13 (11.6)	8 (16.3)	0.5[a]
Intravenous thrombolysis, n (%)	28 (25.5)	23 (48.9)	0.005[a]
Thrombectomy, n (%)	2 (1.8)	7 (14.3)	0.004[a]
Dysphagia/Nasogatric tube, n (%)	25 (22.3)	28 (57.1)	< 0.001[a]
Urinary catheter	33 (29.7)	35 (71.4)	< 0.001[a]
Central line	4 (3.6)	18 (36.7)	< 0.001[a]
Intubation and mechanical ventilation, n (%)	2 (1.8)	16 (32.7)	< 0.001[a]
Decompressive surgery, n (%)	1 (0.9)	13 (26.5)	< 0.001[a]
Invasivness score (median, range, IQR)	0 (0–5, 1)	2 (0–5, 5)	< 0.001[a]

[a] Fisher's exact-test.
[b] Mann-Whitney-*U* test.
[c] Student-T-test, NIHSS – National Institute of Health Stroke Scale, BRS – baroreflex sensitivity.

Table 3
Final stepwise multivariable logistic regression model showing associations with infections after ischemic stroke.

	aOR	95% CI	p
BRS (per decrease of 1 ms/mmHg)	1.21	1.03–1.41	0.02
Admission NIHSS (per point)	1.10	1.02–1.19	0.02
Invasiveness score (per point)	1.46	1.03–2.06	0.03

aOR – adjusted odd ratio, CI- confidence intervals, BRS – baroreflex sensitivity, NIHSS – National Institute of Health Stroke Scale.

Table 4
Final stepwise multivariable logistic regression model showing associations with pneumonia after ischemic stroke.

	aOR	95% CI	p
BRS (per decrease of 1 ms/mmHg)	1.34	1.05–1.69	0.02
Admission NIHSS (per point)	1.09	1.01–1.17	0.03
Invasiveness score (per point)	1.65	1.14–2.40	0.008
Non-lacunar etiology	1.59	1.00–2.65	0.05

aOR – adjusted odd ratio, CI- confidence intervals, BRS – baroreflex sensitivity, NIHSS – National Institute of Health Stroke Scale.

previous preliminary observations on associations between increased sympathetic drive, HRV and BRS indices, and the development of post-stroke infection. A small study be Günther et al. suggests HRV indices obtained within 48 h following ischemic stroke were associated with the development of a sub-acute infection before significant clinical and paraclinical signs of infection [22]. A study by Brämer et al. stresses the role of very low frequency band of HRV in the prediction of infectious complications in the immediate post-stroke period [12]. In line, HRV and BRS indices have been suggested to be associated with infections in subarachnoid or intracerebral hemorrhage [16,23].

Our observation may have two important implications. First, in the context of the recent trials on preventive antibiotic treatment in acute stroke, the precise identification of high-risk candidates for infections gains importance and may represent a promising future approach in the preventive antibiotic strategy. Measuring autonomic parameters may increase the accuracy of the predicting scores and models. Second, with increasing evidence that autonomic nervous system plays a role in the immunodepression associated with acute stroke, the question of therapeutic targeting arises. Experimental data on adrenergic blockade possible ameliorating the consequences of pathological sympathetic activation after stroke is promising. In animals, the occurrence of bacterial infections after stroke can be prevented by administration of beta-blockers [7]. Interestingly, in large dataset, stroke patients with beta-blocker treatment less often developed post-stroke pneumonia [24]. Thus, hypothetically, the modulation of autonomic nervous system function, alone or in combination with prophylactic antibiotic treatment, may represent an attractive therapeutic option in preventing infective complications after stroke.

Certain limitations of our study have to be mentioned. As the study started earlier, the used criteria for stroke-associated pneumonia differ from the standardized consensus criteria published by Smith in 2015 [25]. This may eventually explain the higher pneumonia rate (18%) in our study despite including rather mild strokes (median NIHSS 6). Due to the criteria for nonbiased BRS estimation, we excluded patients with previous stroke, myocardial infarction, atrial fibrillation, diabetes mellitus or other conditions known to affect autonomic functions as well as patients with actual antihypertensive treatment, producing thus a selection bias. This bias may limit the translation of our results into the general stroke population. Further, it has been shown previously that age, hypertension, and antihypertensive therapy may influence autonomic activity [26,27]. Therefore, effort has been made to minimize these effects by including patients without previous antihypertensive treatment (50%) or after the drug had been withdrawn at least 24 h and by testing for possible confounding effects in the analysis. In our cohort we found no association between autonomic functions and age, hypertension, or previous antihypertensive treatment (data no shown). Moreover, the possible confounders as age, hypertension, and antihypertensive therapy were distributed equally between the sub-groups with and without infection implicating that significant bias should not be involved. Despite, the results have to be interpreted with caution and regard to the above mentioned limitations. The strength of our study include prospective design, established methodology of BRS measurements and vigorously collected data.

5. Conclusion

Decreased baroreflex sensitivity was independently associated with infections after stroke. Autonomic changes may play an important role in increased susceptibility to infections after ischemic stroke. Thus, measuring and modulating of autonomic functions including BRS may have future diagnostic and therapeutic relevance in acute stroke.

Funding

Declaration of Competing Interest

All authors declare no conflicts of interest.

Acknowledgements

References

[1] H.C. Emsley, S.J. Hopkins, Acute ischaemic stroke and infection: recent and emerging concepts, Lancet Neurol. 7 (2008) 341–353.

[2] W.F. Westendorp, P.J. Nederkoorn, J.D. Vermeij, M.G. Dijkgraaf, D. van de Beek, Post-stroke infection: a systematic review and meta-analysis, BMC Neurol. 11 (2011) 110.

[3] C.C. Ionita, A.H. Siddiqui, E.I. Levy, L.N. Hopkins, K.V. Snyder, K.J. Gibbons, Acute ischemic stroke and infections, J. Stroke Cerebrovasc. Dis. 20 (1) (2011) 1–9.

[4] J.D. Vermeij, W.F. Westendorp, D. van de Beek, P.J. Nederkoorn, Post-stroke infections and preventive antibiotics in stroke: update of clinical evidence, Int. J. Stroke 13 (2018) 913–920.

[5] U. Dirnagl, J. Klehmet, J.S. Braun, H. Harms, C. Meisel, T. Ziemssen, et al., Stroke-induced immunodepression: experimental evidence and clinical relevance, Stroke. 38 (2007) 770–773.

[6] C. Meisel, J.M. Schwab, K. Prass, A. Meisel, U. Dirnagl, Central nervous system injury-induced immune deficiency syndrome, Nat. Rev. Neurosci. 6 (2005) 775–786.

[7] K. Prass, C. Meisel, C. Hoflich, J. Braun, E. Halle, T. Wolf, et al., Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke t helper cell type 1-like immunostimulation, J. Exp. Med. 198 (2003) 725–736.

[8] J. Klehmet, H. Harms, M. Richter, K. Prass, H.D. Volk, U. Dirnagl, et al., Stroke-induced immunodepression and post-stroke infections: lessons from the preventive antibacterial therapy in stroke trial, Neuroscience. 158 (2009) 1184–1193.

[9] X. Urra, A. Cervera, V. Obach, N. Climent, A.M. Planas, A. Chamorro, Monocytes are major players in the prognosis and risk of infection after acute stroke, Stroke. 40 (2009) 1262–1268.

[10] X. Urra, C. Laredo, Y. Zhao, S. Amaro, S. Rudilosso, A. Renu, et al., Neuroanatomical correlates of stroke-associated infection and stroke-induced immunodepression, Brain Behav. Immun. 60 (2017) 142–150.

[11] A. Chamorro, S. Amaro, M. Vargas, V. Obach, A. Cervera, M. Gomez-Choco, et al., Catecholamines, infection, and death in acute ischemic stroke, J. Neurol. Sci. 252 (2007) 29–35.

[12] D. Bramer, A. Gunther, S. Rupprecht, S. Nowack, J. Adam, F. Meyer, et al., Very low frequency heart rate variability predicts the development of post-stroke infections, Transl. Stroke Res. (2019), https://doi.org/10.1007/s12975-018-0684-1.

[13] T.G. Robinson, S.L. Dawson, P.J. Eames, R.B. Panerai, J.F. Potter, Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischemic stroke, Stroke. 34 (2003) 705–712.

[14] M.T. La Rovere, J.T. Bigger Jr., F.I. Marcus, A. Mortara, P.J. Schwartz, Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Atrami (autonomic tone and reflexes after myocardial infarction) investigators, Lancet. 351 (1998) 478–484.

[15] M.T. La Rovere, G.D. Pinna, S.H. Hohnloser, F.I. Marcus, A. Mortara, R. Nohara, et al., Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials, Circulation. 103 (2001) 2072–2077.

[16] M. Sykora, J. Diedler, S. Poli, T. Rizos, P. Turcani, R. Veltkamp, et al., Autonomic shift and increased susceptibility to infections after acute intracerebral hemorrhage, Stroke. 42 (2012) 1218–1223.

[17] H.P. Adams Jr., B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, et al., Classification of subtype of acute ischemic stroke. Definitions for use in a multi-center clinical trial. Toast. Trial of org 10172 in acute stroke treatment, Stroke. 24 (1993) 35–41.

[18] J. Diedler, M. Sykora, P. Hahn, A. Rupp, A. Rocco, C. Herweh, et al., C-reactive-protein levels associated with infection predict short- and long-term outcome after supratentorial intracerebral hemorrhage, Cerebrovasc. Dis. 27 (2009) 272–279.

[19] T. Calandra, J. Cohen, The international sepsis forum consensus conference on definitions of infection in the intensive care unit, Crit. Care Med. 33 (2005) 1538–1548.

[20] T.C. Horan, M. Andrus, M.A. Dudeck, Cdc/nhsn surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting, Am. J. Infect. Control 36 (2008) 309–332.

[21] B.E. Westerhof, J. Gisolf, W.J. Stok, K.H. Wesseling, J.M. Karemaker, Time-domain cross-correlation baroreflex sensitivity: performance on the eurobavar data set, J. Hypertens. 22 (2004) 1371–1380.

[22] A. Gunther, I. Salzmann, S. Nowack, M. Schwab, R. Surber, H. Hoyer, et al., Heart rate variability - a potential early marker of sub-acute post-stroke infections, Acta Neurol. Scand. 126 (2012) 189–196.

[23] J.M. Schmidt, D. Sow, M. Crimmins, D. Albers, S. Agarwal, J. Claassen, et al., Heart rate variability for preclinical detection of secondary complications after subarachnoid hemorrhage, Neurocrit. Care. 20 (2014) 382–389.

[24] M. Sykora, P. Siarnik, J. Diedler, V.A. Collaborators, Beta-blockers, pneumonia, and outcome after ischemic stroke: evidence from virtual international stroke trials

archive, Stroke. 46 (2015) 1269–1274.

[25] C.J. Smith, A.K. Kishore, A. Vail, A. Chamorro, J. Garau, S.J. Hopkins, et al., Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group, Stroke. 46 (2015) 2335–2340.

[26] C.C. Huang, P. Sandroni, D.M. Sletten, S.D. Weigand, P.A. Low, Effect of age on adrenergic and vagal baroreflex sensitivity in normal subjects, Muscle Nerve 36 (2007) 637–642.

[27] G. Grassi, F.Q. Trevano, G. Seravalle, F. Scopelliti, G. Mancia, Baroreflex function in hypertension: consequences for antihypertensive therapy, Prog. Cardiovasc. Dis. 48 (2006) 407–415.