Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2014;37:128–133
DOI: 10.1159/000357215

Received: October 4, 2013
Accepted: November 12, 2013
Published online: January 30, 2014

The Prognostic Value of Midregional Proatrial Natriuretic Peptide in Patients with Hemorrhagic Stroke

Marlene Fischer[a] Mira Katan[b] Nils G. Morgenthaler[d] Marleen Seiler[e] Beat Müller[c] Peter Lackner[a] Mario Errath[a] Raimund Helbok[a] Bettina Pfausler[a] Ronny Beer[a] Erich Schmutzhard[a] Gregor Broessner[a]

[a]Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; [b]Department of Neurology, Universitätsspital Zürich, Zürich, and [c]Medical University Department of the University of Basel, Kantonsspital Aarau, Aarau, Switzerland; [d]Institut für Experimentelle Endokrinologie und Endokrinologisches Forschungszentrum, EnForCé, Charité, Campus Virchow, Berlin, and [e]Clinical Diagnostics, Thermo Scientific Biomarkers, Thermo Fisher Scientific, Hennigsdorf, Germany

Key Words
Atrial natriuretic peptide · Subarachnoid hemorrhage · Intracerebral hemorrhage · Outcome

Abstract
Background: Atrial natriuretic peptide (ANP) is a well-known prognostic marker of outcome and mortality in patients with cardiovascular disease. Midregional proatrial natriuretic peptide (MR-proANP) is a stable fragment of the ANP precursor hormone. As a prognostic marker after ischemic stroke, it reliably predicts poststroke mortality and functional outcome. This study aimed to analyze the prognostic value of MR-proANP in patients with hemorrhagic stroke, i.e. subarachnoid (SAH) and intracerebral hemorrhage (ICH). ***Methods:*** MR-proANP was analyzed in patients with spontaneous SAH or spontaneous ICH. All patients were prospectively randomized into two treatment arms: (1) a prophylactic normothermia group with a target core temperature 36.5°C using endovascular cooling, and (2) a control group with conventional stepwise predefined fever management using antipyretic medication and surface cooling. Blood samples were obtained on admission and on days 4 and 7. Measurement of MR-proANP was performed in serum using sandwich immunoassay. The primary endpoint was functional outcome [assessed by the Glasgow Outcome Score (GOS)] and the secondary endpoints were mortality within 180 days after hemorrhagic stroke and influence of temperature on MR-proANP. A favorable outcome was defined as GOS 4–5, and the patients were considered to have a poor outcome with a 180-day GOS score between 1 and 3. ***Results:*** Analysis of MR-proANP was performed in 24 patients with spontaneous SAH and 22 patients with spontaneous ICH. MR-proANP was elevated on days 4 and 7 as compared to baseline levels ($p < 0.05$ and $p < 0.001$, respectively). High MR-proANP levels (>120 pmol/l) were associated with increased mortality and poor outcome (after 180 days; $p < 0.05$, respectively). There was no significant difference regarding MR-proANP serum concentrations between the endovascular and the control groups. ***Conclusions:*** Increased levels of MR-proANP are independently associated with poor functional outcome and increased mortality after 180 days in patients with hemorrhagic stroke. Endovascular temperature control had no significant influence on MR-proANP levels.

KARGER

© 2014 S. Karger AG, Basel
1015–9770/14/0372–0128$39.50/0

E-Mail karger@karger.com
www.karger.com/ced

Gregor Broessner, MD, Assistant Professor of Neurology
Innsbruck Medical University
Department of Neurology, Neurologic Intensive Care Unit
Anichstrasse 35, AT–6020 Innsbruck (Austria)
E-Mail gregor.broessner@i-med.ac.at

Introduction

Hemorrhagic stroke, i.e. subarachnoid (SAH) and intracerebral hemorrhage (ICH), is a devastating neurological disease [1–3]. Prognostic markers may improve risk stratification and allow early prognostication, both for functional outcome and mortality, thus improving individual treatment and allocation of hospital and human resources.

Atrial natriuretic peptide (ANP) is a prognostic marker of cardiovascular-based mortality [4]. Accounting for about 98% of all circulating natriuretic peptides, ANP is released from intracellular granules in atrial myocytes upon atrial dilation, with myocyte stretching through volume and blood pressure challenge being the most potential stimulators [5]. ANP-immunoreactive glial cells have been found in ischemic brain tissue, suggesting regulation of cerebral blood flow through ANP [6]. Moreover, release of ANP from brain tissue has also been reported during cerebral ischemia [6, 7].

Assessment of circulating ANP is challenging since early destruction of this protein by endopeptidases leads to a short half-life of 1–5 min [5]. By contrast, the prohormone proANP has a longer half-life [8]. Midregional proatrial natriuretic peptide (MR-proANP) is a stable fragment of the ANP precursor hormone and is secreted in equimolar amounts to ANP [9].

In patients with acute ischemic stroke, MR-proANP has been shown to reliably predict functional outcome and mortality [4, 10, 11]. This study evaluates the prognostic value of MR-proANP in SAH and ICH patients regarding functional (neurological) outcome, mortality after 6 months and stability of MR-proANP regarding novel targeted temperature measurements.

Methods

Ethics Statement

The study was approved by the institutional review board of Innsbruck Medical University (protocol No. UN1734/AM1734a). According to Austrian law, written informed consent was obtained either before enrollment in competent patients or as soon as the patient regained competence. The informed consent procedures were approved by the institutional review board. All potential participants, who declined to participate or otherwise did not participate, were eligible for treatment and were not disadvantaged in any other way by not participating in the study.

Study Site and Participants

This study was designed as an extension of a prospective randomized controlled trial on endovascular-based normothermia in patients with cerebrovascular disease and was performed at Innsbruck University Hospital, Austria, a 1,500-bed tertiary care hospital with approximately 74,000 admissions per year. The neurologic intensive care unit is a 10-bed neurocritical care unit admitting, on a nonelective basis, about 700 adults per year, with a significant proportion of the patients being diagnosed with SAH or ICH. A detailed description of the study population has been published previously [12]. Patients were randomized into two treatment arms: (1) prophylactic endovascular-based controlled normothermia with a target temperature of 36.5°C (CoolGard 3000 and CoolLine devices; Zoll®), and (2) conventional fever management strictly following a predefined protocol. Temperature control management including calculation of fever burden has been described in detail previously [12].

Sample Collection and Measurement of MR-proANP

Analysis of MR-proANP was performed in the patients' sera, collected at the time of enrollment as well as 4 and 7 days after admission to the neurologic intensive care unit using Sarstedt Monovette serum tubes. Data collection used in the present analysis was done prospectively since the original design of the study included subgroup analysis of inflammatory parameters as an additional endpoint. To minimize bias probably introduced by daytime variation, blood drawing was done immediately after enrollment and at 7 a.m. on the respective days thereafter. Serum was obtained by centrifugation at 1,500 *g* for 15 min after at least 30 min of clotting time and stored at –20°C until use. MR-proANP was detected in serum from all patients with a sandwich immunoassay (Thermo Fisher BRAHMS, Hennigsdorf/Berlin, Germany), as described in detail elsewhere [9].

Endpoints

The primary endpoint was functional outcome at 180 days after the acute event assessed by a dichotomized Glasgow Outcome Score (GOS; favorable outcome = GOS 4–5, poor outcome = GOS 1–3). Secondary endpoints were mortality within 180 days after the acute event and dependency of temperature management. Follow-up telephone interviews 180 days after the event were performed by a blinded trained physician with the patient or next of kin.

Statistical Analyses

Baseline characteristics were compared using a t test (age, APACHE II score, body core temperature, BMI, fever burden), Fisher's exact test (gender, treatment group, diagnosis) and Kruskal-Wallis test (Hunt and Hess grade, Glasgow Coma Scale). To eliminate the risk of a putative selection bias, baseline characteristics were compared using a t test (age, APACHE II score, body core temperature, BMI, fever burden), Fisher's exact test (gender, treatment group, diagnosis) and Kruskal-Wallis test (Hunt and Hess grade, Glasgow Coma Scale).

The Kolmogorov-Smirnov test was used to test for normal distribution of continuous variables. To analyze repeated measurements of serum levels, a Wilcoxon signed-rank test or Friedman test was performed followed by Dunn's test for multiple comparisons. The Mann-Whitney U test was performed for comparison between two groups (favorable vs. poor outcome, survivors vs. nonsurvivors); for more than two comparisons the Kruskal-Wallis test was used. In order to confirm the association between MR-proANP and poor functional outcome/mortality and test for important covariates (age, gender), general estimating equation models with a linear link function were cal-

culated. Days after hemorrhage and GOS score were used as factors. Receiver operating curve analysis was used to evaluate the predictive value of MR-proANP serum levels regarding functional outcome and mortality. GOS values were dichotomized for this approach to receive binary outcome measures. GOS was categorized into values for unfavorable outcome (GOS 1–3, i.e. unable to live independently or worse) and favorable outcome (GOS 4–5, i.e. able to live independently). Data are presented as medians [interquartile range (IQR)] unless otherwise stated. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using the PASW 18.0 package (SPSS Inc., Chicago, Ill., USA) and the GraphPad Prism 5 software (GraphPad Prism Software Inc., San Diego, Calif., USA).

Results

Baseline Characteristics

Excluding patients with ischemic stroke, 92 patients were eligible for this study. After preanalytical screening, workup of MR-proANP was not possible in another 46 patients. A total number of 46 patients were included in the final analysis (demographic and clinical data of the study population are listed in table 1). Of those, 24 patients were diagnosed with spontaneous SAH and 22 patients suffered from spontaneous ICH.

Time Course of MR-proANP Serum Levels

MR-proANP serum levels showed a significant increase throughout day 7 (fig. 1). Baseline serum concentrations were lower (96.0 pmol/l, IQR: 63.8–130.9) compared to days 4 (113.5 pmol/l, IQR: 77.0–167.2; $p < 0.05$) and 7 (140.8 pmol/l, IQR: 87.0–208.5; $p < 0.001$). There was no statistical difference between patients with SAH and ICH regarding MR-proANP serum levels. We did not find an association between MR-proANP concentrations and the presence of hypo- or hypernatremia, cardiac arrhythmia, or pulmonary edema (data not shown).

Functional Outcome

Serum levels of MR-proANP on days 1 and 4 differed significantly between patients with favorable (GOS 4–5) and poor functional outcome (GOS 1–3) after 180 days [day 1: 69.0 pmol/l (IQR: 40.9–112.4) vs. 118.0 pmol/l (IQR: 65.3–138.2); day 4: 83.5 pmol/l (IQR: 61.1–113.5) vs. 154.5 pmol/l (IQR 110.3–216.5); $p < 0.05$]. Accordingly, mean MR-proANP (days 1–7) was significantly higher in patients with an unfavorable outcome [87.3 pmol/l (IQR: 40.7–120.1) vs. 124.6 pmol/l (IQR 97.3–192.6); $p < 0.05$] (fig. 2). Receiver operating characteristics curve analysis revealed AUC values for MR-proANP on day 1 of 0.67 (95% CI: 0.49–0.84) and 0.77 (95% CI: 0.55–0.99) for mean MR-proANP from day 1 to day 7 ($p < 0.05$). A MR-proANP threshold of 120 pmol/l [13] had a sensitivity of 50% and specificity of 21% for day 1, and a sensitivity of 78% and specificity 80% for mean MR-proANP.

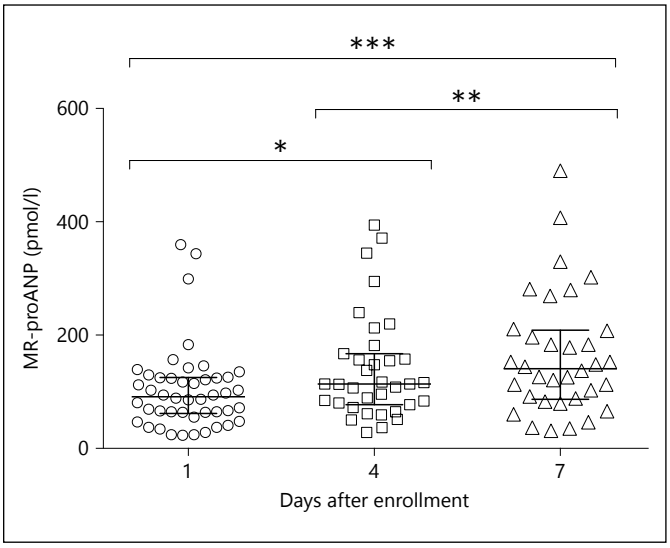

Fig. 1. Temporal development of MR-proANP. Temporal profile of MR-proANP serum levels on days 1, 4 and 7 after enrollment. For comparison between single days, the Wilcoxon signed-rank test was used. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 1. Baseline characteristics of the study population

	ICH	SAH
Subjects, n	22	24
Females, n (%)	13 (59)	7 (29)
Age, years	59.3±12.0	55.8±15.1
BMI, kg/m^2	26.6±3.6	25.8±3.0
GOS		
1	3	8
2	1	1
3	6	1
4	8	2
5	1	9
Antipyretic medication		
NSAIDs	16	15
No NSAIDs	6	9

Values represent n (%) or means ± SD. NSAIDs = Nonsteroidal anti-inflammatory drugs.

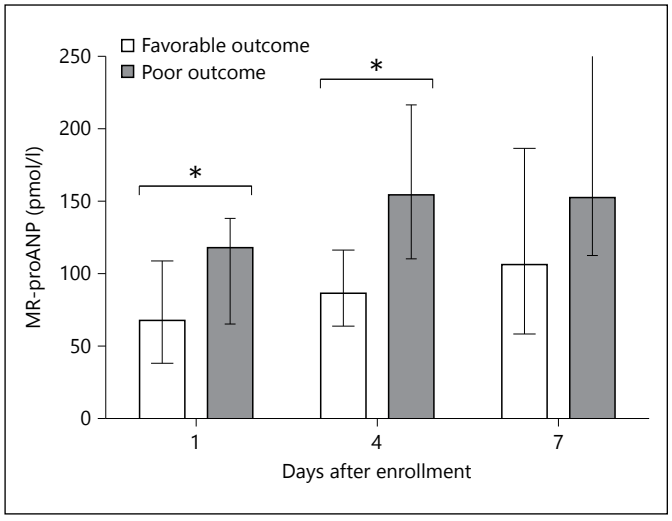

Fig. 2. MR-proANP and functional outcome. MR-proANP serum concentrations in patients with favorable (GOS 4–5) and poor (GOS 1–3) functional outcome, compared using the Mann-Whitney U test. * $p < 0.05$.

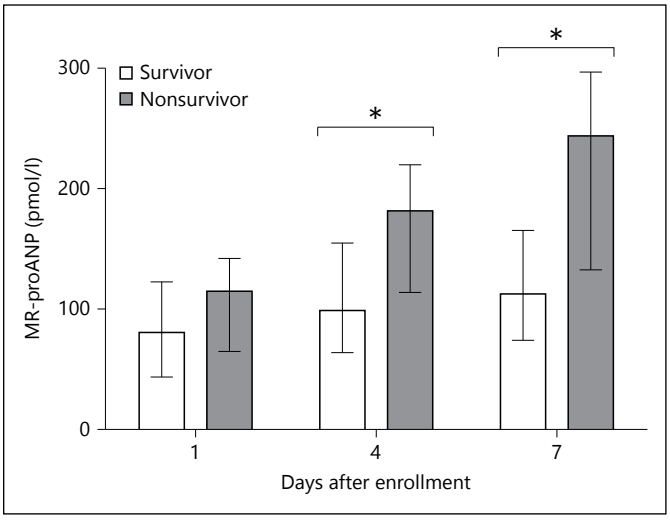

Fig. 3. MR-proANP in survivors vs. nonsurvivors. MR-proANP serum levels are significantly elevated in nonsurvivors on days 4 and 7 ($p < 0.05$). A Mann-Whitney-U test was used for comparison between groups. * $p < 0.05$.

Mortality

A comparison of survivors (n = 29) and nonsurvivors (n = 11) showed elevated MR-proANP levels on days 4 and 7 in nonsurvivors [day 4: 181.7 pmol/l (IQR: 113.8–220.0) vs. 98.9 pmol/l (IQR: 63.8–154.9); day 7: 243.8 pmol/l (IQR: 132.6–296.9) vs. 112.5 pmol/l (IQR 74.2–165.5); $p < 0.05$; fig. 3]. The general estimating equation model for the association between mortality and serum concentrations of natriuretic peptide underlined this finding ($p < 0.001$). When using the receiver operating characteristics curve analysis for prediction of mortality, area under the curve values were 0.62 (95% CI: 0.42–0.82) and 0.92 (95% CI: 0.77–1.0) for baseline MR-proANP and mean MR-proANP (from day 1 to day 7), respectively ($p < 0.05$). A MR-proANP threshold of 120 pmol/l had a sensitivity of 64% and specificity of 59% for day 1, and a sensitivity of 100% and specificity of 67% for mean MR-proANP.

Patients with a high Acute Physiology and Chronic Health Evaluation (APACHE) II score (>19) were compared with those showing lower APACHE II scores (≤19) on admission. This analysis revealed significantly elevated MR-proANP serum levels in patients with APACHE II scores >19 ($p < 0.05$).

Temperature Management

When comparing endovascular temperature control regimen patients and the control group, no statistical difference in MR-proANP concentrations was found, although fever burden was significantly lower in the patients undergoing endovascular temperature control ($p < 0.0001$).

Discussion

In this study, MR-proANP levels were analyzed in 46 patients with severe spontaneous SAH or ICH requiring intensive care treatment. The main findings were: (1) MR-proANP significantly increases over time in SAH and ICH patients compared to baseline levels, and (2) increased serum levels of MR-proANP are associated with poor functional outcome and mortality after 180 days (GOS 1–3).

ANP has been recognized as a predictor of functional outcome and mortality in patients with cardiovascular disease [14–16]. Recently, results of a prospective study in patients with ischemic stroke showed MR-proANP to be a strong predictor of functional outcome and post-stroke mortality [10]. Patients with poor functional outcome as assessed by the modified Rankin scale revealed significantly higher MR-proANP serum levels compared with patients with favorable functional outcome [10].

To the best of our knowledge, there are no reports about MR-proANP levels in patients with hemorrhagic stroke. We found a significant association of MR-proANP serum concentrations with poor outcome and mortality in SAH and ICH patients. Natriuretic peptides have been

shown to be elevated in patients with SAH and have been found to be associated with a decreased level of consciousness [17, 18]. Data from experimental studies suggest that cerebral ischemia induces ANP release [6, 7]. In patients with ICH, higher levels of brain natriuretic peptide, another member of the natriuretic peptide family, have been reported to be associated with functional neurological outcome [19].

Natriuretic peptides are involved in hemodynamic regulation, fluid and volume homeostasis increasing diuresis and natriuresis [20]. ANP release is triggered by volume challenge of the cardiac atrium [20]. Alterations of ANP levels in hemorrhagic stroke patients seem to be multifactorial: cardiac abnormalities are common in patients with (severe) SAH and ICH [21–24].

Clinical symptoms and electrocardiographic changes may mimic (ischemic) myocardial injury [25]. However, this effect is rather attributable to increased catecholamine release due to cerebral injury than coronary stenosis [22, 25]. Natriuretic peptides reduced circulating levels of catecholamines in animal studies [26]. Upon sympathoadrenal stimulation they act as counterregulators in response to myocardial injury [5]. Thus, increased sympathetic activation, which has been observed in patients with spontaneous SAH and poor outcome, may directly influence ANP release [27]. In addition to neurohumoral effects, ANP increase may be triggered by therapeutic regulation of fluid balance and systemic vascular resistance [5].

Increased sympathetic activation, which has been observed in patients with spontaneous SAH and poor outcome, may directly influence ANP release [27]. In addition to neurohumoral effects, ANP increase may be triggered by therapeutic regulation of fluid balance and systemic vascular resistance [5].

Temperature modulation in this study was performed using endovascular temperature control and administration of antipyretic medication plus surface cooling. Strict temperature control and adherence to a predefined target temperature were achieved in the endovascular group using a catheter-based heat exchange system. Despite significant differences regarding fever burden in the two treatment arms, there was no difference in MR-proANP serum levels [12]. This indicates that MR-proANP remains a stable biomarker even under novel temperature modulations. These results suggest that MR-proANP is a reliable marker of poor outcome, including mortality, even in patients under targeted temperature control. This is of utmost importance since the reliability of biomarkers under targeted temperature modulation has been discussed controversially recently [28–30].

Several limitations need to be considered when interpreting our results. As the sample size was small, adjustment for multiple potential confounders was not possible. Only a subgroup of patients was included in this final analysis. However, a putative selection bias is unlikely as comparison of baseline parameters of the respective groups did not reveal significant differences, with the exception of sex. This is a hypothesis-generating study showing for the first time that an elevation of MR-proANP serum levels is significantly associated with poor outcome in hemorrhagic stroke patients and might serve even early after SAH onset as a reliable predictor of functional outcome in this patient population.

Conclusions

Timely prognostication and prediction of long-term outcome is especially important in patients with hemorrhagic stroke as it allows for optimization of acute care and risk stratification. Elevation of MR-proANP in patients with hemorrhagic stroke might allow early diagnosis of patients at risk for hemodynamic instability and multiorgan dysfunction, finally leading to unfavorable outcome.

Disclosure Statement

Measurement of MR-proANP was performed by BRAHMS AG. BRAHMS AG was neither involved in the study design, collection, analysis, and interpretation of data nor writing of the reports. BRAHMS AG did not suppress any data or outcome analysis carried out as predefined in the study protocol.

Marleen Seiler is an employee of Thermo Fisher Scientific. Thermo Scientific BRAHMS, Hennigsdorf, Germany provided all MR-proANP assays. This did not alter the authors' adherence to all the *Cerebrovascular Diseases* policies on sharing data and materials.

References

1 Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. N Engl J Med 2001; 344:1450–1460.

2 Suarez JI, Tarr RW, Selman WR: Aneurysmal subarachnoid hemorrhage. N Engl J Med 2006;354:387–396.

3 Broessner G, Helbok R, Lackner P, Mitterberger M, Beer R, Engelhardt K, Brenneis C, Pfausler B, Schmutzhard E: Survival and long-term functional outcome in 1,155 consecutive neurocritical care patients. Crit Care Med 2007;35:2025–2030.

4 Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–663.
5 Suttner SW, Boldt J: Natriuretic peptide system: physiology and clinical utility. Curr Opin Crit Care 2004;10:336–341.
6 Nogami M, Shiga J, Takatsu A, Endo N, Ishiyama I: Immunohistochemistry of atrial natriuretic peptide in brain infarction. Histochem J 2001;33:87–90.
7 Giuffrida R, Bellomo M, Polizzi G, Malatino LS: Ischemia-induced changes in the immunoreactivity for endothelin and other vasoactive peptides in the brain of the Mongolian gerbil. J Cardiovasc Pharmacol 1992;20(Suppl 12): S41–S44.
8 Davidson NC, Coutie WJ, Struthers AD: N-terminal proatrial natriuretic peptide and brain natriuretic peptide are stable for up to 6 hours in whole blood in vitro. Circulation 1995;91:1276–1277.
9 Morgenthaler NG, Struck J, Thomas B, Bergmann A: Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma. Clin Chem 2004;50:234–236.
10 Katan M, Fluri F, Schuetz P, Morgenthaler NG, Zweifel C, Bingisser R, Kappos L, Steck A, Engelter ST, Müller B, Christ-Crain M: Midregional pro-atrial natriuretic peptide and outcome in patients with acute ischemic stroke. J Am Coll Cardiol 2010;56:1045–1053.
11 Makikallio AM, Makikallio TH, Korpelainen JT, Vuolteenaho O, Tapanainen JM, Ylitalo K, Sotaniemi KA, Huikuri HV, Myllyla VV: Natriuretic peptides and mortality after stroke. Stroke 2005;36:1016–1020.
12 Broessner G, Beer R, Lackner P, Helbok R, Fischer M, Pfausler B, Rhorer J, Küppers-Tiedt L, Schneider D, Schmutzhard E: Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: bicenter prospective, randomized trial. Stroke 2009;40:e657–e665.
13 Daniels LB, Clopton P, Potocki M, Mueller C, McCord J, Richards M, Hartmann O, Anand IS, Wu AH, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Filippatos GS, Di Somma S, Ng L, Neath SX, Christenson R, Morgenthaler NG, Anker SD, Maisel AS: Influence of age, race, sex, and body mass index on interpretation of midregional pro atrial natriuretic peptide for the diagnosis of acute heart failure: results from the BACH multinational study. Eur J Heart Fail 2012;14:22–31.
14 Schnabel RB, Schulz A, Messow CM, Lubos E, Wild PS, Zeller T, Sinning CR, Rupprecht HJ, Bickel C, Peetz D, Cambien F, Kempf T, Wollert KC, Benjamin EJ, Lackner KJ, Munzel TF, Tiret L, Vasan RS, Blankenberg S: Multiple marker approach to risk stratification in patients with stable coronary artery disease. Eur Heart J 2010;31:3024–3031.
15 Kruger S, Papassotiriou J, Marre R, Richter K, Schumann C, von Baum H, Morgenthaler NG, Suttorp N, Welte T: Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia: results from the German competence network CAPNETZ. Intensive Care Med 2007;33:2069–2078.
16 von Haehling S, Jankowska EA, Morgenthaler NG, Vassanelli C, Zanolla L, Rozentryt P, Filippatos GS, Doehner W, Koehler F, Papassotiriou J, Kremastinos DT, Banasiak W, Struck J, Ponikowski P, Bergmann A, Anker SD: Comparison of midregional pro-atrial natriuretic peptide with N-terminal pro-B-type natriuretic peptide in predicting survival in patients with chronic heart failure. J Am Coll Cardiol 2007;50:1973–1980.
17 Wijdicks EF, Schievink WI, Burnett JC Jr: Natriuretic peptide system and endothelin in aneurysmal subarachnoid hemorrhage. J Neurosurg 1997;87:275–280.
18 Nakamura T, Okuchi K, Matsuyama T, Fukushima H, Seki T, Konobu T, Nishio K: Clinical significance of elevated natriuretic peptide levels and cardiopulmonary parameters after subarachnoid hemorrhage. Neurol Med Chir (Tokyo) 2009;49:185–191, discussion 191–192.
19 James ML, Blessing R, Phillips-Bute BG, Bennett E, Laskowitz DT: S100B and brain natriuretic peptide predict functional neurological outcome after intracerebral haemorrhage. Biomarkers 2009;14:388–394.
20 Levin ER, Gardner DG, Samson WK: Natriuretic peptides. N Engl J Med 1998;339:321–328.
21 Hasegawa K, Fix ML, Wendell L, Schwab K, Ay H, Smith EE, Greenberg SM, Rosand J, Goldstein JN, Brown DF: Ischemic-appearing electrocardiographic changes predict myocardial injury in patients with intracerebral hemorrhage. Am J Emerg Med 2012;30:545–552.
22 Lee VH, Oh JK, Mulvagh SL, Wijdicks EF: Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2006;5:243–249.
23 Temes RE, Tessitore E, Schmidt JM, Naidech AM, Fernandez A, Ostapkovich ND, Frontera JA, Wartenberg KE, Di Tullio MR, Badjatia N, Connolly ES, Mayer SA, Parra A: Left ventricular dysfunction and cerebral infarction from vasospasm after subarachnoid hemorrhage. Neurocrit Care 2010;13:359–365.
24 van Bree MD, Roos YB, van der Bilt IA, Wilde AA, Sprengers ME, de Gans K, Vergouwen MD: Prevalence and characterization of ECG abnormalities after intracerebral hemorrhage. Neurocrit Care 2010;12:50–55.
25 Jespersen CM, Fischer Hansen J: Myocardial stress in patients with acute cerebrovascular events. Cardiology 2008;110:123–128.
26 Tota B, Cerra MC, Gattuso A: Catecholamines, cardiac natriuretic peptides and chromogranin A: evolution and physiopathology of a 'whip-brake' system of the endocrine heart. J Exp Biol 2010;213:3081–3103.
27 Moussouttas M, Huynh TT, Khoury J, Lai EW, Dombrowski K, Pello S, Pacak K: Cerebrospinal fluid catecholamine levels as predictors of outcome in subarachnoid hemorrhage. Cerebrovasc Dis 2012;33:173–181.
28 Oddo M: Prognostication after cardiac arrest: time to change our approach. Resuscitation 2012;83:149–150.
29 Rossetti AO, Oddo M, Logroscino G, Kaplan PW: Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67:301–307.
30 Storm C, Nee J, Jorres A, Leithner C, Hasper D, Ploner CJ: Serial measurement of neuron specific enolase improves prognostication in cardiac arrest patients treated with hypothermia: a prospective study. Scand J Trauma Resusc Emerg Med 2012;20:6.