Examination of the cerebral ischaemia-induced inflammatory response after carotid artery stenosis and cardiopulmonary resuscitation

Ph.D. thesis

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Contents

1. Introduction

According to recent statistical analysis, leading causes of mortality in Europe are cardiovascular diseases. 45% of the total mortality has cardiovascular origin. Ischaemic heart disease is the most common form of cardiovascular diseases. Among patients with ischaemic heart disease one of the main cause of mortality is sudden cardiac arrest. The range of incidence of out-of-hospital cardiac arrest is 38-55/100,000/year. Stroke is the second most common cardiovascular disorder in Europe and in other developed regions. A significant proportion of these cases are developed from thromboembolic complications of atherosclerotic lesions of the carotid arteries. The complex diagnostic and therapeutic considerations of extracranial carotid artery stenosis, such as cardiopulmonary resuscitation (CPR) and post-resuscitation care are controlled by international guidelines. Milestones of post-resuscitation care are the optimal target temperature management for favourable mortality and neurogical outcomes and the optimal and reliable prognostication after CPR. One pillar of this later could be the appropriate use of biomarkers.

Matrix metalloproteinases (MMPs) are zinc and calcium dependent endoproteinases with specified structure. In the human tissues 23 different MMP were identified. Main role of these are the breakdown of protein structure of the extracellular matrix. Beside this, MMPs play significant roles in complex physiological and pathological processes such as morphogenesis, angiogenesis, and inflammatory response. Four different tissue inhibitors of matrix metalloproteinases (TIMPs) perform the inhibition of MMP activity in human tissues. TIMPs have identified roles in the activation of pro-MMPs and in the regulation of cellular differentiation, morphological development and apoptosis.

Near intact cerebral endothelial function, the production of MMPs and other proteinases are minimal. During cerebral ischemic-reperfusion damage the expression of MMPs (mainly MPP-9 and MMP-2) increases significantly. As a result of this process, endothelial and blood-brain-barrier dysfunction and cerebral oedema can be developed. In this doctoral thesis, we aimed to investigate the time courses of MMP-TIMP system during partial and global cerebral ischaemic-reperfusion in connection with elective carotid artery stenting and cardiopulmonary resuscitation. Other aims were the research of the mortality rate, the effects of therapeutic hypothermia and function of protein S100B as a prognostic marker after CPR.

2. Aims

Regarding the perioperative period of elective carotid artery stenting (CAS), we aimed to investigate:

1. The time course of MMP-9.
2. The time course of TIMP-1.
3. The time course of MMP-9/TIMP-1 ratio.
4. The effects of comorbidities and medical treatments on the MMP-9 and TIMP-1 levels.
5. The time course of MMP-TIMP system compared to elective carotid endarterectomy (CEA).

After cardiopulmonary resuscitation, we aimed to investigate:

6. The 30-day-mortality rate.
7. The effects of therapeutic hypothermia on the 30-day-mortality and serum lactate levels
8. The use of the protein S100B as a prognostic marker.
9. The time course of MMP-9.
10. The time course of TIMP-1.
11. The time course of MMP-9/TIMP-1 ratio.

3. Methods

Our study protocols fulfilled the ethical guidelines of the Declaration of Helsinki 2008, and written permission was obtained from the Institutional Scientific and Human Research Ethics Committee of the University of Pécs. (Permission numbers: 4330/2011, 4330/2013, 5016/2013, 5016/2014.). Following verbal and written information about the study, all enrolled patients (or closest relative of unconscious patients) provide their written informed consent to participate in our study.

3.1. Patient groups

Investigation of the MMP-TIMP system regarding elective CAS

30 patients were enrolled to our prospective study, by whom elective carotid artery stenting was performed at the Clinical Centre of University of Pécs between 1 October 2013 and 30 November 2015.

The exclusion criteria were:

- age under 18 years
- a diagnosis of malignant diseases
- inflammatory and systemic autoimmune disorders
- psychiatric disorders
- previous debilitating stroke
- previous medication affecting the inflammatory response (steroids, cytostatic treatment)

Five patients were excluded as three met the exclusion criteria and two refused to participate.

Investigations after CPR

For the retrospective examination of the 30-day-mortality rate and the effects of therapeutic hypothermia 57 patients, who were treated at the multidisciplinary intensive care units of the University of Pécs between 1 June 2009 and 28 February 2012 after non-traumatic cardiac arrest and successful CPR, were included. Cause of the cardiac arrest, type of the initial cardiac activity or chronic comorbidity were not declared as exclusion criteria.

The exclusion criteria were:

- age under 18 years

20 patients were included in our prospective analysis of the role of protein S100B as a prognostic marker. The patients were treated at the multidisciplinary intensive care units of the University of Pécs between 15 June 2011 and 28 February 2012 after non-traumatic cardiac arrest and successful CPR. Cause of the cardiac arrest, type of the initial cardiac activity or chronic comorbidity were not declared as exclusion criteria.

The exclusion criteria were:

- age under 18 years
- a diagnosis of malignant diseases

For the examination of the MMP-TIMP system 38 patients were included prospectively. All patients were treated at the multidisciplinary intensive care units of the University of Pécs between 15 June 2011 and 28 February 2012 after non-traumatic cardiac arrest and return of spontaneous circulation (ROSC). Cause of the cardiac arrest, type of the initial cardiac activity or chronic comorbidity were not declared as exclusion criteria.

The exclusion criteria were:

- age under 18 years
- a diagnosis of malignant diseases
- previous medication affecting the inflammatory response (steroids, cytostatic treatment)

3.2. Control groups

Investigation of the MMP-TIMP system regarding elective CAS

A randomly selected subgroup of 30 patients from a previously obtained data served as a historical control. The elective CEAs were performed at the Clinical Centre of the University of Pécs between 1 January 2012 and 31 December 2012.

The exclusion criteria of the prior study were:

- age under 18 years
- a diagnosis of malignant diseases
- previous debilitating stroke
- previous medication affecting the inflammatory response (steroids, cytostatic treatment

Investigations after CPR

20 matched patients scheduled for ophthalmological examinations were invited as controls for the analysis of the MMP-TIMP system after CPR. No significant difference was observed regarding age, gender, and coexisting diseases compared to the study group. Presence of acute inflammation was excluded.

3.3.Blood sampling and assays

Blood sampling regarding CAS

Blood samples were collected via arterial cannula. Sampling was performed at three time points (T1-3): T1: at the time of the insertion of the arterial line; T2: 60 min after stent insertion; and T3: the first postoperative morning. The fourth sampling (on the third postoperative morning) was not performed because the patients were discharged from the hospital on the second postoperative day.

The control CEA group samples were collected at the following four time points (T1-4): T1: at the time of the insertion of the arterial line; T2: 60 min after cross-clamp release; T3: the first postoperative morning; and T4: the third postoperative morning.

Blood sampling after CPR

After CPR. to determine the protein S100B, MMP-9 and TIMP-1 levels, blood samples were taken at four time points.T1: within 2 hours after ROSC; T2: 24 hours after ROSC; T3: 72 hours after ROSC; T4: 120 hours after ROSC

In the control group blood sampling was carried out once from each patient.

Protein S100B assay

Arterial native blood samples were centrifuged (1500g, 10min) and stored on –80ºC until analysis. Protein S100B quantitative measurement was performed by sandwich enzyme immunoassay according to manufacturer's instructions (RD192090100R, BioVendor – Laboratornímedicína a.s., Brno, Czech Republic). The concentrations of protein S100B (ng/l) were determined spectrophotometrically (Multiskan Ascent „microplate" photometer Type 354; Thermo Electron Corporation, Waltham, MA, USA) at 450nm absorption wavelength in comparison with standard curve.

MMP-9 and TIMP-1 assay

Plasma was isolated from heparin-anticoagulated arterial blood samples by low speed centrifugation at 4 °C and stored at -80 °C until they were analysed. MMP-9 and TIMP-1 levels were measured with quantitative sandwich enzyme-linked immunosorbent assay (ELISA) techniques according to the manufacturer's instructions (R&D Systems Inc., Minneapolis, MN, USA). Then, spectrophotometric (Multiskan Ascent microplate photometer, Type: 354, Thermo

Electron Corporation, Waltham, MA, USA) reading of the absorbance at 450 nm was compared to standard curves. Plasma concentrations of MMP-9 and TIMP-1 were expressed as ng/ml.

3.4.Statistical analysis

The analyses were conducted by the Statistical Package for the Social Sciences for Windows Statistics software, version 21.0 (SPSS, IBM Corporation, Armonk, NY, USA). Distribution analysis was performed by Kolmogorov-Smirnov test. Non-parametric tests were used (Wilcoxon or Mann-Whitney U test) since the data distribution was found to be not normal. In case of normal distribution, Student's t test was applied. Data of the patient and control groups were compared with the Mann-Whitney U test. Intergroup data analysis was carried out by Wilcoxon signed-rank test. Data were expressed as minimum, maximum, median, and interquartile range (standard 25th-75th percentile).Values of $P < 0.05$ were considered statistically significant.

4. Results
4.1.Results regarding the perioperative period of CAS

There was no significant difference between the CAS group and the control CEA group in the number of patients enrolled, age, gender, medications, comorbidities and major complications. Age, gender, procedure laterality, prior stroke or TIA, presence of contralateral carotid stenosis, prior ipsi- or contralateral surgery, smoking, pre-existing hypertension and diabetes treated with oral antidiabetic medication did not influence the plasma levels of MMP-9 and TIMP-1 at any time points. The plasma levels of MMP-9 among diabetic patients treated with insulin analogues were significantly higher in the T2 samples ($P<0.05$).

Lipid lowering agents (statins) and aspirin did not influence the plasma levels of MMP-9 and TIMP-1 at any time point.

Baseline (T1) plasma MMP-9 levels of the patients treated with adenosine diphosphate (ADP) receptor antagonists were significantly lower ($P<0.05$). Intraoperative hypo- or hypertension had no effect on plasma MMP-9 or TIMP-1 levels in the present study.

Intraoperative hypo- or hypertension had no effect on plasma MMP-9 or TIMP-1 levels in our study.

In the CEA group, significantly higher plasma MMP-9 levels were measured at T3 compared to baseline (T1) ($P<0.05$). There were no differences in the plasma MMP-9 levels in the CAS

group at any time point. In the T3 samples, plasma MMP-9 levels were significantly higher in the CEA group compared to the CAS group (P<0.05) (Table 1).

Table 1: Plasma MMP-9, TIMP-1 and MMP-9/TIMP-1 levels regarding the perioperative period of CAS and CEA

	Group	T1	T2	T3	T4
MMP-9	*CEA*	290.9±112.1	284.7±247.5	488.6±249.8*	382.9±285.4
(ng/ml)	*CAS*	259.8±244.9	239.1±221.3	180.9±159.7#	
TIMP-1	*CEA*	117.3±43.2	81.7±73.9*	88.5±41.6	117.2±52.3
(ng/ml)	*CAS*	93.5±30.9	61.7±28.8*	70.7±30.2	
MMP-9/	*CEA*	2.73±1.37	4.39±2.69	6.41±3.86*	3.40±2.50
TIMP-1	*CAS*	2.78±1.88	4.33±3.05	2.26±1.79#	

*Data are presented as the mean±standard error of mean. CEA: carotid endarterectomy control group; CAS: carotid angioplasty and stenting group; T1: preoperative values; T2: 60 min after cross-clamp release/stent insertion; T3: postoperative day 1; T4: postoperative day 3; *: P<0.05 compared to T1; and #: P<0.05 compared to CAS.*

Significantly lower plasma TIMP-1 levels were measured in both groups at T2 compared to baseline (P<0.05) (Table 1).

MMP-9/TIMP-1 ratios at T3 were significantly higher than baseline in the CEA group and the CAS group (P<0.05) (Table 1).

4.2. Results regarding CPR

Mortality rate of patients

Among the 57 patients (female: 19, male: 38) the overall mean of age was 62 years, and there was no difference between the two genders (female:64y, male: 61y). The duration of CPRs was between 1 and 50 minutes (mean: 14.5 minutes). After ROSC therapeutic hypothermia was applied on 22 patients. The total 30-day-mortality was 74%. There was no difference in the 30-

day-mortality between the two genders and the age of the patients did not influence the 30-day-mortality. In our study, the therapeutic hypothermia did not reduce the 30-day-mortality (73% vs. 74%). Neither the duration of CPR and nor the initial cardiac electrical activity (ventricular fibrillation, pulseless electrical activity or asystole) influenced the mortality (73% vs 71% vs 78%). SAPSII values were not altered between survivors and non-survivors. Values of Glasgow Coma Scale at ICU admission were significantly related to 30-day-mortality (P<0.05). To differentiate patients GCS: 6 cut-off-point was established. In the GCS<6 group the mortality was significantly higher than in GCS≥6 group.

Effects of therapeutic hypothermia

In our study, the use of therapeutic hypothermia did not reduce the 30-day-mortality (73% vs. 74%). After therapeutic hypothermia serum lactate concentration after ICU admission (0h, P=0.006) and at 12th (P=0.045), 36th (P=0.049) hours after ROSC were significantly higher compared to nomothetic patients. The median of the serum lactate concentrations after reach of therapeutic hypothermia were more than twice that in the normothermic group at the first measurement (6.3 mmol/l vs 2.8 mmol/l). In both groups (normothermic and therapeutic hypothermic) lactate concentrations reached the normal range after 24 hours and stayed within this range in the further samples (Figure 1.).
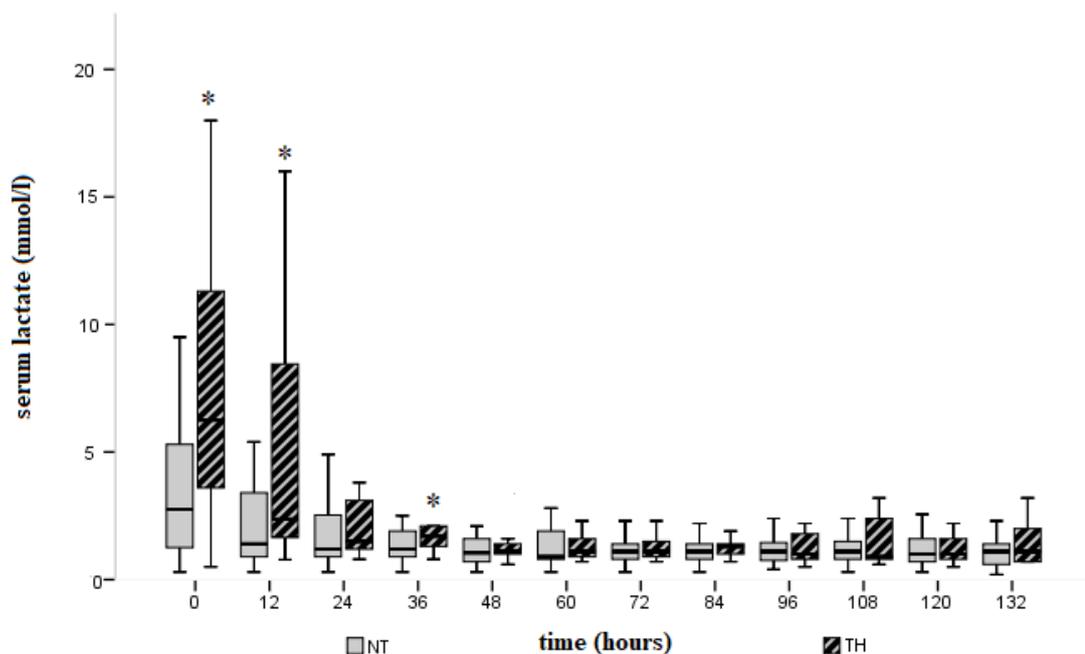

Figure 1.: *Serum lactate concentrations in case of normothermia (NT – grey) and therapeutic hypothermia (TH – striated). Data are expressed as minimum, maximum, median, and inter-*

quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval). *: P<0.05 compared to the NT group.

Protein S100B results

Concentrations of serum protein S100B measured in the 4th samples showed a significant decrease compared to the 1St (p=0.001) and 2nd (p=0.019) samples (Figure 2.)
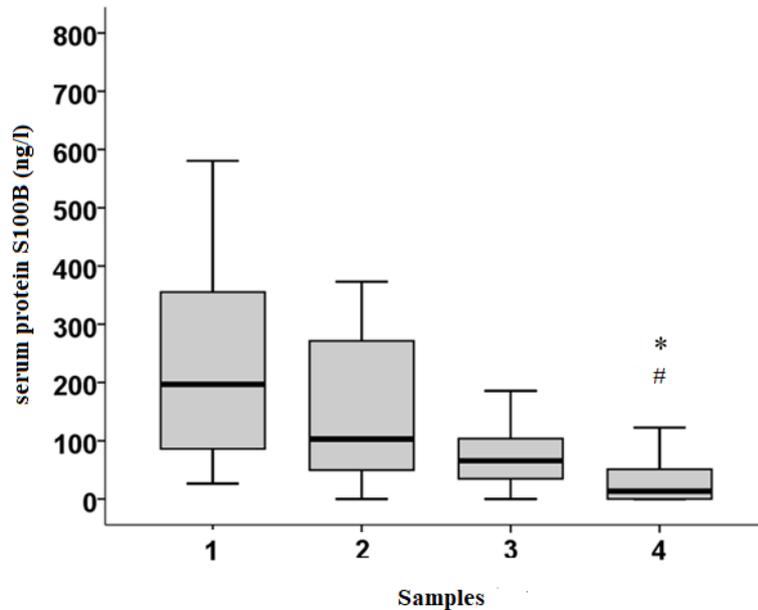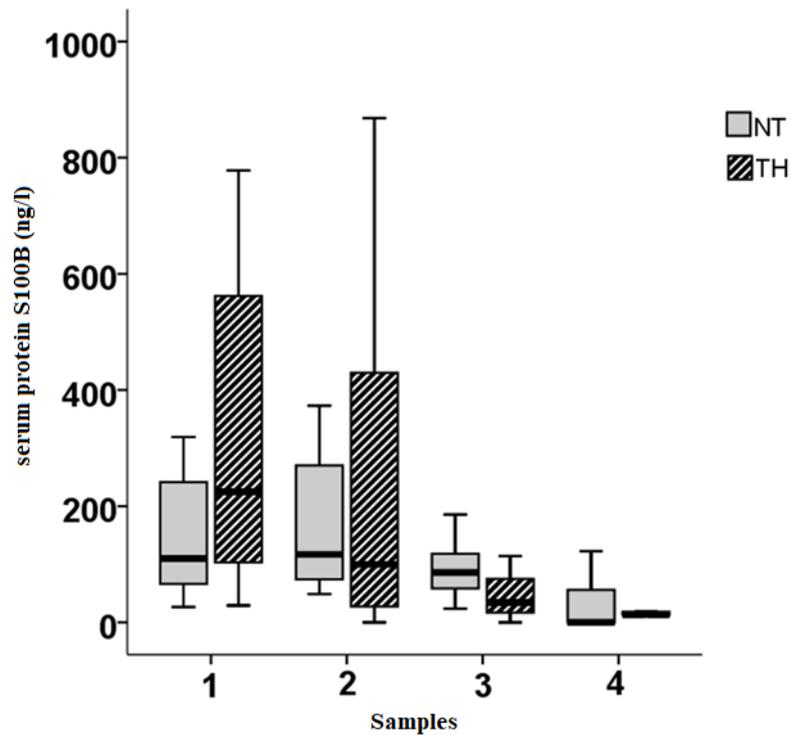

Figure 2.: *Alteration of protein S100B concentrations after CPR. Samples: 1: within 2 hours after ROSC; 2: 24 hours after ROSC; 3: 72 hours after ROSC; 4: 120 hours after ROSC Data are expressed as minimum, maximum, median, and inter-quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval)..*: P<0.05 compared to Sample 1; #: P <0.05 compared to Sample 2.*

Among non-survivors, in the 1st and 2nd samples a tendency to higher serum levels was observed, which disappeared until the 3rd and 4th samples, however the difference was not significant between survivors and non-survivors (Figure 3.).
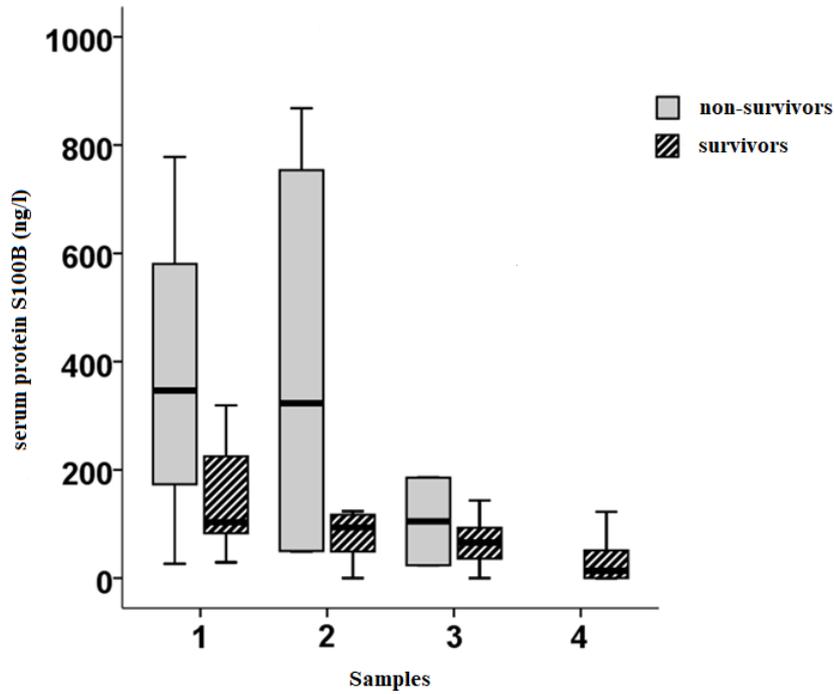
Figure 3.: *Alteration of protein S100B concentrations in non-survivors (grey) and survivors (striated) after CPR. Samples: 1: within 2 hours after ROSC; 2: 24 hours after ROSC; 3: 72 hours after ROSC; 4: 120 hours after ROSC Data are expressed as minimum, maximum, median inter-quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval).*

There was no significant difference in the protein S100B concentrations between the normotermic group and the therapeutic hypothermia group (Figure 4.).

Figure 4.: *Alteration of protein S100B concentrations in normothermic (NT- grey) and therapeutic hypothermia group (TH- striated) after CPR. Samples: 1: within 2 hours after ROSC; 2: 24 hours after ROSC; 3: 72 hours after ROSC; 4: 120 hours after ROSC Data are expressed as minimum, maximum, median inter-quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval).*

Alterations of the MMP-TIMP system

Significantly higher plasma MMP-9 concentration was measured at T1 compared to the control group (P=0,001). MMP-9 levels remained significantly elevated (P=0.001-0.015) during the whole investigation period. We noted a significant decrease (P=0.009) of MMP-9 levels at T2 compared to T1 then values increased gradually to the baseline level (Figure 5.).
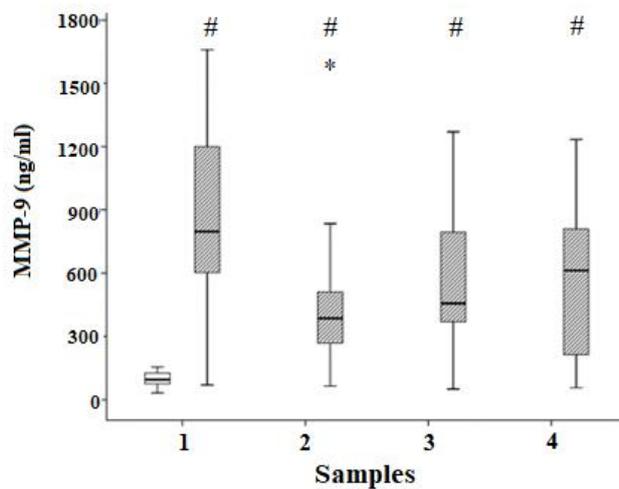
Figure 5.: *Alterations of plasma MMP-9 concentrations after CPR (grey) compared to control group (white). Samples: 1: within 2 hours after ROSC; 2: 24 hours after ROSC; 3: 72 hours after ROSC; 4: 120 hours after ROSC Data are expressed as minimum, maximum, median inter-quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval *: P<0.05 compared to Sample 1; #: P<0,05 compared to control group.*

After CPR there was no difference regarding plasma concentrations of TIMP-1 compared to controls during the study period (P=0.1 – 0.678). Compared to the admission values (T1), 24 hours after ROSC (T2) we experienced increased (P=0.041) TIMP-1 levels. After that, TIMP-1 returned to the initial level (T3), then remained at this level until the end of the observation period (T4) (Figure 6.).
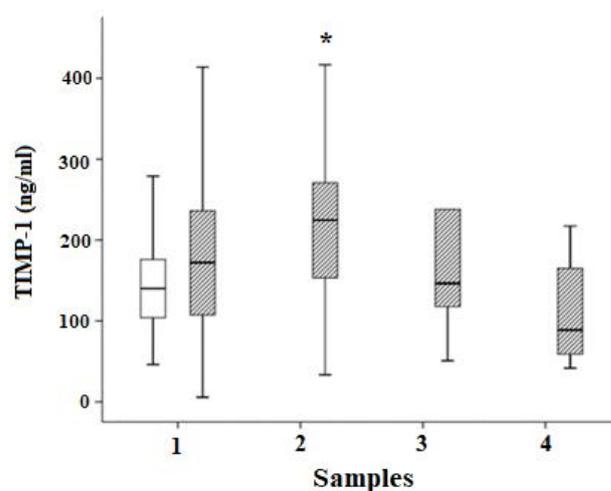
Figure 6.: *Alterations of plasma TIMP-1 concentrations after CPR (grey) compared to control group (white). Samples: 1: within 2 hours after ROSC; 2: 24 hours after ROSC; 3: 72 hours after ROSC; 4: 120 hours after ROSC Data are expressed as minimum, maximum, median inter-*

quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval *: P<0.05 compared to Sample 1.

After CPR MMP-9/TIMP-1 ratios were significantly increased (P=0.001-0.015) in all time points compared to controls. 24 hours after CPR (T2) the ratio of MMP-9/TIMP-1 decreased significantly (P<0.001) compared to the initial level (T1). Thereafter, the ratios were increased gradually to approximate baseline levels by T4 (Figure 7.).

Figure 7.: *Alterations of plasma MMP-9/TIMP-1 ratios after CPR (grey) compared to control group (white). Samples: 1: within 2 hours after ROSC; 2: 24 hours after ROSC; 3: 72 hours after ROSC; 4: 120 hours after ROSC Data are expressed as minimum, maximum, median inter-quartile range (IQR; standard 25th-75th percentile and 5th and 95th confidence interval *: P<0.05 compared to Sample 1; #: P<0,05 compared to control group.*
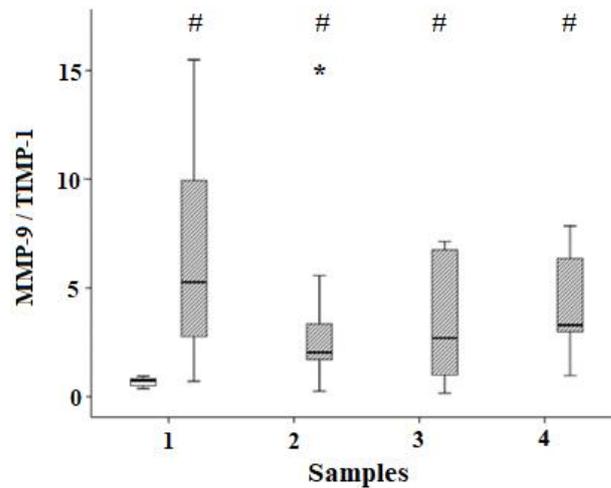
5. Summary

Surgical and invasive radiology interventions on the extracranial internal carotid artery are relatively common vascular procedures worldwide. The gold standard intervention is still CEA; however, according to the recent international guidelines, CAS can be equally effective and less invasive in selected cases. Appropriate preoperative assessment and management are essential to identify the patients who could benefit from the less invasive nature of an endovascular operation compared to an open surgery. Prior studies on the MMP-TIMP system in CEA and CAS have assessed changes at only a single time point. During cerebral ischaemia-reperfusion injury, the role of the MMP-TIMP system has been propounded. After TIA and ischaemic stroke, the elevation of the MMP and concurrent decrease of TIMP levels can developed in the early phase of ischaemic cerebral damage, or later in the subacute phase during the remodelling of the central nervous system. Summarizing our results of the examinations of the MMP-TIMP system regarding the perioperative period of CAS and CEA, we can conclude, that there were no significant differences in the incidence of neurological complications between the two procedures during the perioperative period. However, the endovascular intervention triggers smaller changes in the MMP-9-TIMP-1 system, which may suggest a lower incidence of subclinical central nervous system injury. Primarily, this finding may originate from a lower incidence or smaller degree of blood-brain-barrier dysfunction and/or microembolisation and a shorter carotid flow restriction time.

After respiratory- and cardiac arrest a global anoxia and ischaemia occurs, which affects the whole body. As the result of this, the degree of the developing cell injury is basically influenced by the duration of the ischaemic period, the individual sensitivity of the cell and the actual state of the extracellular environment. At the time of our examinations, the ERC guideline published in 2010 recommended the use of mild therapeutic hypothermia (32-34⁰C core temperature for 12-24 hours) in comatose patients during the post-resuscitation care after CPR to prevent further neuronal damage and improve neurological outcome. According our study results, therapeutic hypothermia could not alter the 30-day-mortality. However, after therapeutic hypothermia significantly higher serum lactate levels after the reach of the hypothermia, 12 and 36 hours after ROSC was observed compared to normotermic patients. Based on recent literature data, elevated serum lactate concentrations after ROSC may correlate with mortality and neurological outcome.

The protein S100B is a small acidic protein, a member of the calcium-binding protein family. Under physiological conditions this protein regulates cellular proliferation and differentiation and calcium-homeostasis. Serum concentration in healthy inviduals is negligible small ($<0,05$ µg/l). As it cannot cross the intact blood-brain-barrier, it may be use as a marker of the integrity of the blood-brain-barrier. In the our study there was no significant alteration in protein S100B between the survivor and non-survivors groups, if 30-day-mortality was determined, however a tendency to higher serum levels was observed among non-survivors after ICU admission and on 1st day after ROSC. Therapeutic hypothermia could not alter the protein S100B levels compared to normotermic care. The actual ERC guideline (published 2015 after our study) propounds protein S100B as possible biomarker of ischaemic cerebral injury, however in the absence of well-defined cut-off value, the use as a prognostic marker is not recommended.

Multiple prior publications revealed the role of MMP-TIMP system and MMP-9 in the focal cerebral ischaemic injury, but the findings focused on the global cerebral ischaemia-reperfusion injury remain poor. Our aim was to examine the time course of MMP-9 and TIMP-1 levels after CPR in patients. According to our result, we can conclude that the concentration of MMP-9 increases after ROSC, and aside from a temporary decrease, stay increased at least after the 5th day. The level of TIMP-1 is normal after ROSC, but temporarily increases on the 1st day after CPR, than returns to the baseline. The MMP-9/TIMP-1 ration remains high during the whole study period. This indicates that after global ischaemia-reperfusion injury the increase of the MMP-9 concentrations in not accompanied by remarkable rise of the TIMP-1 levels. The MMP-9 as a proteinase, in high concentrations without appropriate levels of its main tissue inhibitor, can enhance the inflammatory response. This may contribute to the commonly observed serious cerebral functional loss after global ischaemia.

6. Conclusion and novel findings

We have found the followings regarding the investigation of MMP-TIMP system in perioperative period of elective CAS:

1. Regarding the interventions of internal carotid artery age, gender, procedure laterality, prior stroke or TIA, presence of contralateral carotid stenosis, prior ipsi- or contralateral surgery, smoking, pre-existing hypertension and diabetes treated with oral antidiabetic medication did not influence the plasma levels of MMP-9 and TIMP-1.

2. Regarding the interventions of internal carotid artery, the plasma levels of MMP-9 among diabetic patients treated with insulin analogues were significantly higher 1 hour after the procedure. The reason for this is clearly unknown.

3. Near the treatment with ADP receptor antagonists – which drugs, based on prior publications, can decrease the level of MMP-9 after ischaemic stroke – a significantly lower MMP-9 level was measured before the procedure. This could positively influence the stability of the atherosclerotic plaque. This effect cannot observed in the postoperative period.

4. There was no remarkable alteration in MMP-9 levels during the perioperative period of CAS. MMP-9 increases on the first postoperative day after CEA. 24 hours after the reperfusion MMP-9 levels were significantly lower in the CAS group compared to the CEA group.

5. The perioperative time course of TIMP-1 is similar regarding both procedure. The alteration of TIMP-1 might be the sign of increased ECM turnover.

6. The MMP-9/TIMP-1 ratio did not alter after CAS, however after CEA a higher MMP-9/TIMP-1 ratio was measured on the first postoperative day. The higher MMP-9/TIMP-1 ratio on the first postoperative day in the CEA group originated from the higher plasma MMP-9 levels but seems to have been not significantly influenced by the TIMP-1 levels.

7. The most likely causes of the alterations in the MMP-TIMP system regarding the perioperative phase of CAS and CEA, in parallel with the literature, are the different grade of blood-brain-barrier dysfunction and/or the microembolisation and a shorter carotid flow restriction time.

8. We could not prove significant differences in the incidence of neurological complications between the two procedures during the perioperative period. However the altered kinetics of MMP-/TIMP system, may suggest a difference in the incidence of subclinical central nervous system injury. The long term consequences of this are unclear.

We have found the followings regarding the investigations of cardiopulmonary resuscitation:

1. After CPR, the use of therapeutic hypothermia did not influence the 30-day-mortality.

2. After CPR, as a result of therapeutic hypothermia significantly higher serum lactate levels could be measured 12 and 36 hours following ROSC. Based on the literature, in the early phase after ROSC high serum lactate level may predicts poor neurological outcome.

3. In consideration of 30-day-mortality, the protein S100B did not altered significantly between survivors and non-survivors.

4. There was no difference in the protein S100B levels after therapeutic hypothermia compared to normothermia. This finding is in parallel with the 30-day-mortality rates.

5. After CPR, a permanently (at least 5 days long) elevation of MMP-9 levels can be observed with a transient decrease on the 1st day after ROSC.

6. TIMP-1 increased on the 1st day after ROSC. Based on literature data, this might be consequence of extracellular matrix turnover after the reperfusion.

7. After CPR, the MMP-9/TIMP-1 ration remained permanently high, with a transient decrease on the 1st day after ROSC.

8. The time course of MMP-9 and TIMP-1 suggest that the MMP-9, in high concentrations without appropriate levels of its main tissue inhibitor, can enhance the inflammatory response. This may contribute to the commonly observed serious cerebral functional loss after global ischaemia.

7. Publications of the author

List of publications related to the Thesis:

1. **Merei, A** ; Nagy, B ; Woth, G ; Lantos, J ; Kover, F ; Bogar, L ; Muhl, D: Comparison of the perioperative time courses of matrix metalloproteinase-9 (MMP-9) and its inhibitor (TIMP-1) during carotid artery stenting (CAS) and carotid endarterectomy (CEA). BMC Neurology 18 : 1 p. 128 Paper: 128 , 7 p. (2018) *IF (2017): **2,170***

2. **Mérei, Ákos**; Nagy, Bálint ; Woth, Gábor ; Nóra, Zsidó ; Lantos, János ; Mühl, Diána: Effects of therapeutic hypothermia and kinetics of serum protein S100B after cardiopulmonary resuscitation Signa Vitae 10 : 2 pp. 109-130. (2015) *IF: **0,154***

3. Nagy, B ; Woth, G ; **Mérei, Á** ; Nagy, L ; Lantos, J ; Menyhei, G ; Bogár, L ; Mühl, D: Perioperative time course of matrix metalloproteinase-9 (MMP-9), its tissue inhibitor TIMP-1 & S100B protein in carotid surgery Indian Journal Of Medical Research 143 : 2 pp. 220-226. , 7 p. (2016) *IF: **1,532***

Abstracts:

1. **Mérei Á**, Nagy B, Woth G, Zsidó N, Lantos J, Mühl D: Terápiás hypothermia effektusa és protein S100B kinetika reanimációt követően. Aneszteziológia és Intenzív Terápia. 2014;44(S1):15.

2. Nagy B, Woth G, **Mérei Á**, Lantos J, Bogár L, Mühl D: Dynamics of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) after cardiopulmonary resuscitation. Resuscitation. 2015;96S:137. *IF:**5,414***

3. Nagy B, Woth G, **Mérei Á**, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: Mátrix metalloproteinázok és endogén inhibítoraik vizsgálata carotis endartherectomián átesett betegeken. Érbetegségek. 2013;20(4):96-97.

4. Nagy B, Woth G, **Mérei Á**, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: When should we measure matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 regarding postoperative cognitive dysfunction after carotid surgery? European Surgical Research. 2014;52S:134. *IF: **2,474***

5. Nagy B, Woth G, **Mérei Á**, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: A mátrix metalloproteináz-9 (MMP-9) – endogén szöveti inhibítor-1 (TIMP-1) rendszer perioperatív vizsgálata carotis endartherectomián átesett betegeken. Aneszteziológia és Intenzív Terápia. 2014;44(S1):4.

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