Perioperative monitoring of neurocognitive functions and vascular parameters in patients with coronary heart disease

PhD thesis

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1. INTRODUCTION

Cardiovascular diseases are the main leading causes of mortality in the developed countries, responsible for 17.1 million lives a year. The history of cardiac surgery runs back over not more than 100 years. The first succesful heart operation was performed by Rehn in 1896: stab wound of the right ventricle was sutured on beating heart. Almost fifty years had to pass from the beginning of cardiac surgery till the first open heart surgery with extracorporal perfusion by the help of technical development and the 20 years long researcher-developer work. As a result of introducing the first cardio-pulmonary bypass machine in the 1950s, coronary bypass surgery, valve replacement and heart transplantation became widely available. The rapidly developing cardiological and surgical techniques resulted series of succesful interventions. The special improvement of cardiac catheterization established a new discipline, the invasive cardiology. The invasive cardiology came more and more into view at the end of the 20th century, beside the above mentioned PTCA there are many opportunities to replace coronary surgery: percutan transluminal atherectomy, stent implantation.
More than one million coronary artery bypass graft (CABG) surgical operations are performed world-wide every year. The aim of our study was to measure the changes of the neurocognitive, vascular and metabolic parameters of patients during the perioperative period of open heart surgery.

2. AIMS OF THE STUDY

1. Brain injury after open heart surgery has been a well-known phenomenon since the first successful application of the cardio-pulmonary bypass machine in 1952, and can be a devastating complication. Due to rapid developments in the fields of general and cardiac surgery and anaesthetics in the second half of the 20th century, morbidity and mortality declined enormously. However, brain damage after heart surgery has shown a growing tendency – based on the experience of the last 20-30 years. It is well known that 60% of neurocognitive dysfunction appears about one week after heart surgery and declines to 25-30% after one year. Our aim was to measure the neurocognitive damages such as attention disorder, deterioration of memory, depression and change of personality by observing the patients after heart operation. We developed a novel, clinically feasible, non-invasive method which provides enough information after open heart surgery about the changes in the neurocognitive system and physiological tremor.
2. The main cause of cardiovascular diseases is atherosclerosis. The atherosclerosis is such a disease which affects the whole arterial system of the body. The most common types of cardiovascular diseases are coronary heart diseases (heart attack, angina pectoris), cerebrovascular diseases (stroke) and high blood pressure. According to the recent studies plasma concentration of nitric-oxide synthase inhibitor asymmetric dimethylarginine (ADMA) is elevated in patients with coronary artery disease (CAD). We aimed to compare arterial stiffness parameters measured by a new oscillometric, occlusive method (Arteriograph) in patients with coronary artery disease. It was also our aim to follow the changes of the plasma concentration of the new biochemical marker (ADMA) in patients having on pump and off pump coronary artery bypass graft.
3. According to recent studies hormones, mediators produced by the epicardial adipose tissue play an important role in the development of inflammatory processes, insulin resistance, endothel dysfunction and coronary atherosclerosis. The aim of our study was to measure plasma concentration of these metabolic hormones (ghrelin, leptin, resistin, adiponectin) in patients undergoing on pump and off pump CABG. We compared also the plasma

concentration of these hormones between these two surgical groups in the coronary sinus and in the peripheral vein also to identify if the epicardial adipose tissue plays an important role in the development of coronary atherosclerosis.

3. MEASUREMENT OF NEUROCOGNITIVE FUNCTION AND PHYSIOLOGICAL TREMOR DURING CABG SURGERY

3.1. Patients and methods

We investigated 110 patients (age: 30-74 year; 76 male, 34 female; 51 coronary artery bypass grafting, 25 valve replacement, 25 combined open heart surgery, 9 off-pump CABG) before surgery and after open-heart surgery on the 3rd to 5th post-operative day. The mean cross-clamp time during the operation was 51.5±2.8 minutes (mean±SEM), and the average time of the cardiopulmonary bypass (CPB) procedure proved to be 60.3±3.1 minutes in the investigated population of patients (not including the off-pump CABG group). Among these patients reaction time was investigated in total of 50 cases.

Table 1. Characteristics of study patients who underwent open heart surgery

Open heart surgery	Men	Women	Σ
Off pump CABG	5 (60.2±3.6)	4 (58.7±2.1)	9 (59.6±2.2)
On pump CABG	39 (58.0±1.1)	12 (55.3±2.1)	51 (57.4±1.0)
Isolated valve replacement	11 (54.3±3.9)	14 (53.7±2.9)	25 (54.0±2.3)
Combined surgery	21 (59.9±1.9)	4 (53.8±5.7)	25 (58.8±1.9)
Σ	76 (58.2±1.0)	34 (54.7±1.6)	110 (57.1±0.8)

Cognitive function evoked by auditory or visual (and other) stimuli is reflected in the brain potentials obtained by signal averaged EEG (event related potentials, ERP). Positive-going potentials are the P200 and P300 at a latency of approximately 200 and 300 ms, and these potentials are linked to simple reaction time (sRT) and choice reaction time (cRT). The special digital instrumentation and the analyzer software were developed at our laboratory which is able to measure and record these two type of reaction times and tremor during the observation. We used a commercial stereo headphone on the patients' ears and a blinker over their eyes to exclude disturbing factors from the environment. The hand-unit with the accelerometer was held in the patients' dominant hand and they were asked to raise and hold their hands at a 45 degree angle for 30 seconds.

sRT (simple reaction time): The patient heard random 1000 Hz sound waves and he or she had to turn them off as quickly as possible by pressing the button on the hand-unit. After 30 seconds the patient was allowed to rest his or her arm on the bed. The number of target signal cycles can be set to 32, 64 or 128.

cRT (choice reaction time**)**: In 250 Hz random sound waves, generated by Odd-ball paradigm, we hide 1000 Hz sound waves randomly. The cRT measurement requires 4-5 times more standard signals of 250 Hz than target signals of 1000 Hz. The patient had to react only to the 1000 Hz signals.

We compared sRT and cRT values with Mann-Whitney probe.

We measured physiological tremor as well. The physiological tremor acts as an indicator of oscillomotoric regulation, involving a significant area of the cortex through the motoric control system. Physiological tremor consists of two main oscillations. The first type is the 8-12 Hz neuronal oscillation, which arises from the central nervous system. The central oscillation probably arises from the thalamic nuclei which have a strong connection to the cerebral cortex. The second is peripheral oscillation, which controls the body posture against the Earth's gravity. The assessment of the physiological tremor analysis was performed with our newly developed equipment based on Analog Devices ADXL 320 JPC integrated accelerometer chip. Recordings were stored on a PC and spectral analysis was performed by Fast-Fourier transformation (FFT). We compared power integrals in the 1-4 Hz, 4-8 Hz and 8-12 Hz frequency ranges, after which we calculated the ratio of the low and high frequency ranges:

$LowsRT1 = P_{1\text{-}4\ Hz}/(P_{4\text{-}8\ Hz} + P_{8\text{-}12\ Hz})$ frequency ranges at sRT1 measurement
$LowsRT2 = P_{1\text{-}4\ Hz}/(P_{4\text{-}8\ Hz} + P_{8\text{-}12\ Hz})$ frequency ranges at sRT2 measurement
$LowcRT1 = P_{1\text{-}4\ Hz}/(P_{4\text{-}8\ Hz} + P_{8\text{-}12\ Hz})$ frequency ranges at cRT1 measurement
$LowcRT2 = P_{1\text{-}4\ Hz}/(P_{4\text{-}8\ Hz} + P_{8\text{-}12\ Hz})$ frequency ranges at cRT2 measurement

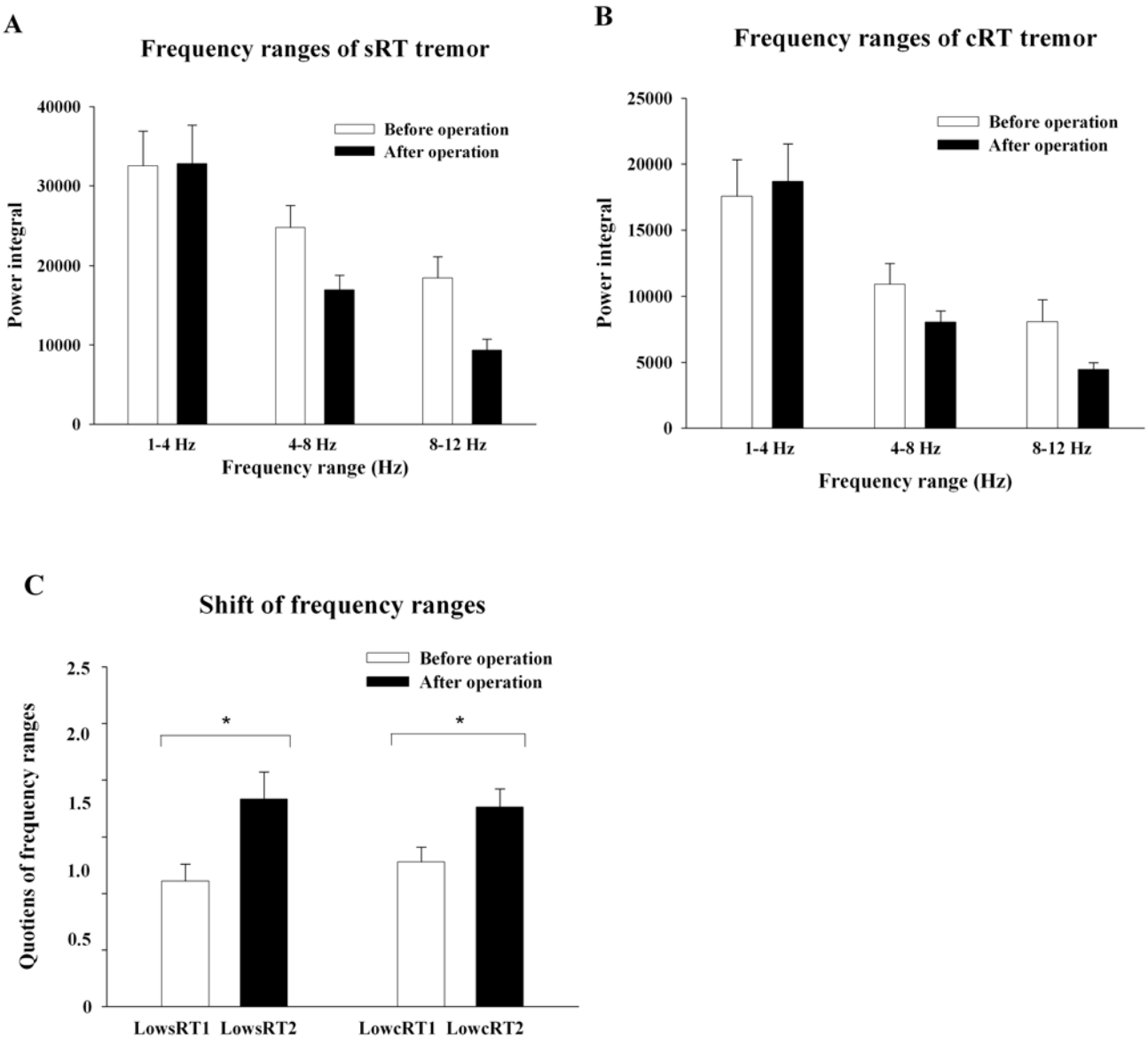
The Wilcoxon rank correlation test – a non-parametric rank test – was used to compare the power integrals.

3.2. Results

There were no statistically significant changes of mean sRT and cRT values before (sRT: 208±54 s, cRT: 369±59 s) and after (sRT: 229±67 s, cRT: 392±105 s) the surgery assessed in the total group or separately in women and men. Its reason might have been the inhomogeneous patient population, the wide range of CPB time (32-156 s) and the multifactoral etiology of brain injury during surgery. The positive correlation between sRT_2/sRT_1 and cRT_2/cRT_1 was found weak.

The spectrum in the 8-12 Hz range (neuronal oscillation) decreased and a shift was recognised to the lower spectrum.

Figure 1. Panel A and B show each frequency ranges of sRT and cRT tremor before and after heart surgery. Panel C shows the ratio of sRT and cRT tremor before and after open heart surgery.



The spectrum at 8-12 Hz range (neuronal oscillation) decreased during both lowsRT and lowcRT measurements and a shift was recognised to the lower spectrum (low sRT1: 1.11±0.145 vs low sRT2: 1,74±0.22, $p<0.008$; low cRT1: 1.28±0.13 vs low cRT2: 1.76±0.16, $p<0.006$). We did not find significant correlation between the shift and the cross clamp time (lowsRT: $r=0.06$, $p<0.53$; lowcRT: $r=0.10$, $p<0.31$).

3.3. Discussion

Brain injury after open heart surgery has been a well-known phenomenon since the first successful application of the cardio-pulmonary bypass machine in 1952, and can be a devastating complication. The reasons for brain damage associated with CPB are multifactorial: macro- and micro-embolism, hypoperfusion due to extracorporeal circulation and systemic inflammatory response. The measurement of the reaction times and the physiological tremor is fast and simple and can be performed in a hospital ward within 10-15 minutes without exhausting a patient who has undergone open heart surgery. This simple and feasible method can, therefore, be used in routine medical practice. During measurement, we do not need an EEG laboratory background. There were no statistically significant changes of mean sRT and cRT values before and after open heart surgery. Its reason might have been the inhomogeneous patient population and the multifactoral etiology of brain injury during operation. The positive correlation between sRT_2/sRT_1 and cRT_2/cRT_1 was found weak. The spectrum at 8-12 Hz range (neuronal oscillation) decreased during both lowsRT and lowcRT measurements and a shift was recognised to the lower spectrum. It is well known that 60-80% of neurocognitive dysfunction appears about one week after heart surgery and declines to 25-30% after one year. We are planning to undertake large, wide-scale, multicentre clinical research, to analyse the changes in physiological tremor with the help of neuro-psychological tests in order to indicate neurological damages in patients after open heart surgery. In the future, our aim is to develop novel, simple, clinically feasible methods to recognise early cognitive impairment in the central nervous system and to widen neuro-protective rehabilitation which can improve the quality of life.

4. INVESTIGATION OF ARTERIAL STIFFNESS PARAMETERS IN PATIENTS WITH VERIFIED CORONARY ARTERY DISEASE. EFFECTS OF CORONARY REVASCULARIZATION ON PLASMA LEVELS OF ASYMMETRIC DIMETHYLARGININE.

4.1. The measurement of arterial stiffness parameters (PWVao and AIXao) in patients with coronary artery disease

Arterial stiffness – rigidity of the arterial wall - occurs as a risk factor of atherosclerosis. Measurement of the parameters of arterial stiffness can help to diagnose the early stage of endothelial dysfunction and atherosclerosis. Arterial stiffness parameters are pulse wave velocity (PWV) and augmentation index (AIXao). Increased arterial stiffness is associated with an increased risk of atherosclerosis and cardiovascular events.
The measurement is based on the fact that during systole, the blood volume having been ejected into the aorta generates pulse wave (early systolic peak). This pulse wave runs down and reflects from the bifurcation of aorta, creating a second wave (late systolic peak). The return time is the difference between the first and the reflected systolic wave. PWV is related to the stiffness of the aorta. The difference of the amplitudes of the first and second systolic wave (AIX) depends on the tone of the peripheral arteries (endothel function). On the basis of these, aortic pulse wave velocity can be calculated if we measure the distance between the jugulum and the symphysis.
By analysing the amplitudes of the reflected and the first wave, the augmentation index can be calculated, providing information on both the stiffness of the aorta and the peripheral vascular tone. Increased and abnormal arterial stiffness parameters are the early signs and risk factors of arteriosclerosis and cardiovascular events. The measurements of arterial stiffness

parameters were performed with the new oscillometric device (Arteriograph) at Heart Institute, University of Pécs. We compared these parameters (PWV, AIXao) in patients with verified coronary artery disease and healthy controls.

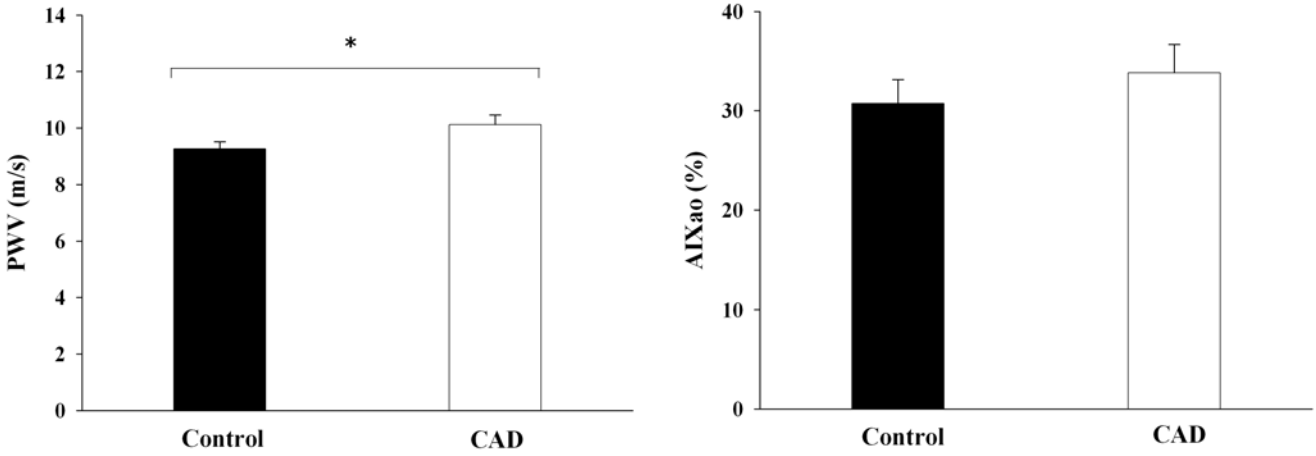
4.1.1. Patients and methods

For the evaluation of arterial stiffness parameters, we investigated 40 patients with coronary artery disease (age: 63.8±12.4 years, male: 15) and 40 age- and gender-matched control patients (age: 63.9±12.4 years, male: 15). The measurements were performed during the first control examinations after the coronary angiography in case of CAD subjects. Control subjects were measured during a routine health examination. The measurements of AIXao, PWV were carried out within 3-4 minutes with the oscillometric, occlusive device (Arteriograph, TensioMed, Budapest; Hungary).

4.1.2. Results

The PWV was significantly higher in the CAD group compared to age- and gender-matched control group (10.11±0.35 m/s vs 9.27±0.25 m/s, $p<0.05$), but no significant differences in AIXao was found between the two groups (33.80±2.87 % vs 30.7±2.43 %, p=0.424).

Figure 2. PWV and AIXao in the control and CAD groups



4.2. Asymmetric dimethylarginine (ADMA)

The concentration of ADMA – an endogenous inhibitor of nitric-oxide synthase (NOS) – is increased in patients with endothelial dysfunction. ADMA is generated by protein arginine methyltransferase type I (PRMT-I), and mainly metabolized by dimethylarginine dimethylaminohydrolase (DDAH). Previous studies have found that ADMA inhibits purified nitric-oxide synthase catalytic activity, the release of NO and NO-mediated vascular responses. An increasing number of prospective clinical trials have shown association between elevated ADMA levels and major cardiovascular events and mortality.

During recent years particular attention was paid to explore the involvement of ADMA in the pathogenesis of coronary heart disease. Prospective studies suggest that high serum level of ADMA may increase the risk of acute coronary syndrome. Our previous observation is that plasma ADMA concentration decreases significantly 1 hour after percutan coronary intervention.
Coronary artery bypass grafting can be performed in extracorporeal perfusion with cardiopulmonary bypass which entails global myocardial ischaemia followed by reperfusion injury after declamping and generates an inflammatory reaction in the whole body leading to increased postoperative morbidity and prolonged hospital stay. In the past 15 years there has been an growing interest in off pump coronary bypass surgery (OPCAB) that has become a well-established alternative to the standard on pump operation. Now we intended to measure and compare serum ADMA levels which were gained from coronary sinus and from peripheral vein in patients who underwent coronary revascularization with or without cardiopulmonary bypass.

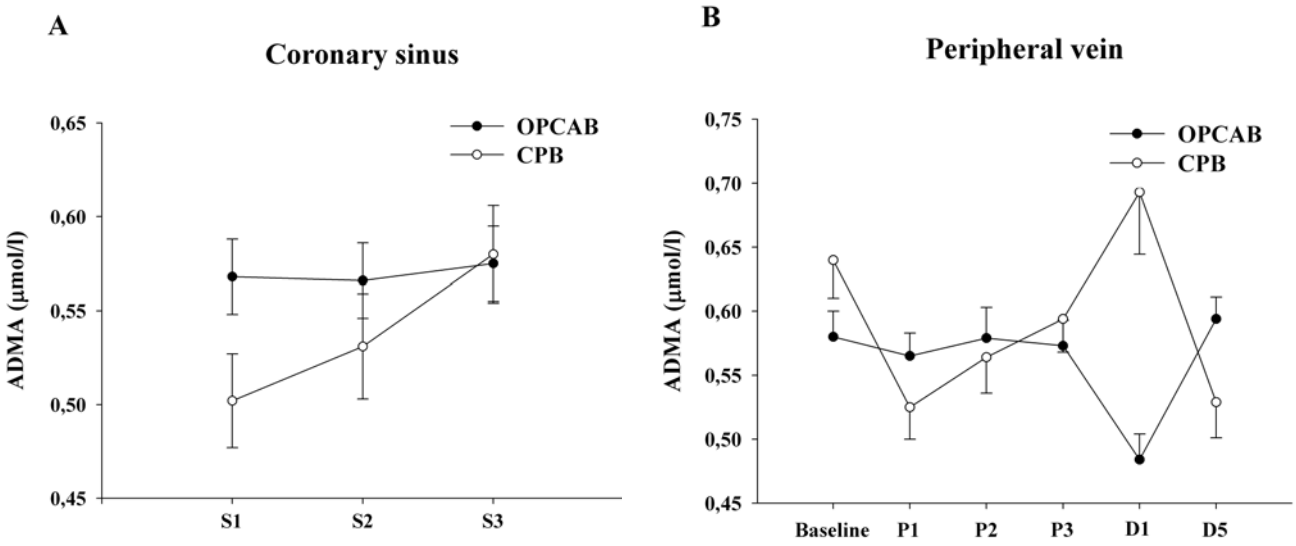
4.2.1. Patients and methods

20 patients with coronary heart disease (CHD) admitted to the Heart Institute, Faculty of Medicine, University of Pécs, Hungary for elective CABG were included in the study and subjected to CPB surgery. 21 patients with CHD hospitalized to the Department of Cardiac Surgery, Zala County Hospital, Hungary and underwent elective CABG served as the OPCAB group for this study. ADMA was measured by liquid chromatography-tandem mass spectrometry (LC-MS-MS). Blood samples were taken for measurement 24 h before, 3 times during the operation, on the 1st and 5th day after surgery. During the operation blood samples were collected from the coronary sinus and from peripheral vein.
Fasting plasma samples were obtained and stored at -70 °C until analysis. The routine biochemical parameters were measured using standard laboratory procedures. T-tests were used to compare coronary risk parameters of CPB group with OPCAB group. A value of $p<0.05$ was considered statistically significant. Repeated measures ANOVA with intrasubject and intersubject factor time was performed for ADMA ratio. Greenhouse-Geisser correction was used when appropriate to account for non-spherocity of the data.

4.2.2. Results

Patients in the OPCAB group preoperatively exhibited increase of creatinine and hsCRP. We found a significant increase both in the time of CABG operation (140.3±5.59 min vs 225.95±12.88 min, $p<0.001$) and in S1-S3 (where S1 = immediately after the insertion of coronary sinus catheter and S3 = immediately after completion of the last proximal anastomosis) time (63.7±3.99 min vs 148.57±12.07 min, $p<0.001$) in OPCAB group compared to CPB group of patients.
ADMA levels remained constant in the OPCAB group both in the coronary sinus samples ($F=0.416$, $p<0.685$) and in the peripheral blood ($F=0.574$, $p<0.562$). However, ADMA concentration increased significantly in patients who underwent on-pump surgery with CPB both in the coronary sinus ($F=14.751$, $p<0.001$) and in the peripheral vein ($F=30.738$, $p<0.001$). Intersubject analysis revealed significant difference in ADMA between the two groups ($F=6.99$, $p<0.002$).

Figure 3. Plasma concentration of ADMA in coronary sinus (A) and in peripheral vein (B)



4.3. Discussion

Extracorporal perfusion with cardiopulmonary bypass is associated with the systemic inflammatory response syndrome (SIRS). Contact of blood components with the arteficial surfaces of the bypass circuit, ischaemic cardiac arrest and reperfusion injury is considered the main causes of this inflammatory response. SIRS significantly contributes to several advers postoperative outcomes such as renal, pulmonary and neurological complications, bleeding and even multiple organ dysfunction. A study by Wan and colleagues of 44 consecutive patients who had on pump or off pump operations found the activation of complements, polymorphonuclear leukocytes and the release of IL-8 and IL-10 was significantly lower in the off pump group. Matata and colleagues showed a significant increase of lipid hydroperoxides, protein carbonyls and nitrotyrosine in the on pump group but not in the off pump group.

In the present study we demontsrated that the plasma level of ADMA is a reliable and feasible marker of an early ischaemia-reperfusion injury which occured in patients underwent CABG surgery. The major findings of our study is that the plasma concentration of ADMA showed significant, intraoperative elevation in the CPB group (both in coronary sinus and in peripheral vein) while in the OPCAB group remained unchanged. The apparent oxidative stress enhances the activity of PRMT-1 and inhibits the activity of DDAH leading to increased ADMA concentration in the CPB group intraoperatively.

We believe that further prospective trials should be carried out to clarify the link of ACE, ATII and PARP enzyme to ADMA and their potential role in endothelial dysfunction during ischaemia-reperfusion injury and oxidative stress.

5. METABOLIC HORMONE LEVELS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

5.1. Metabolic hormones

Framingham study was one of the first which demonstrated a connection between obesity and cardiovascular diseases. The obesity increases the development of further risk factors too: endothelial dysfunction, atherosclerosis, hypertension, diabetes mellitus, dyslipidaemia. Further studies prove that obesity is an important risk factor of cardiovascular events.
The adipose tissue is an important organ with active endocrin and paracrin functions and synthetize different types of hormones, enzymes, cytokines, bioactive mediators. These hormones influence not only the body weight and energy balance, but they play role in the development of inflammatory processes, fibrinolysis, insulin resistance and endothel dysfunction.
We examined the response pattern of metabolic hormones (leptin, resistin, adiponectin and ghrelin) CABG surgery in patients with (on pump) and without (off pump) cardiopulmonary bypass. One of the aim of our study was to compare the plasma concentration of these hormones between the two surgical groups and in the coronary sinus and periphery as well. The ghrelin is produced by the fundus of the stomach and by the pancreas. It plays an important role in the gastrointestinal cell proliferation and in the regulation of the adipose tissue. The leptin stimulates the proliferation of the endothel and skeletal muscle cells, increases the sympathetic tone at the periphery and has an important role in inflammation, vascular dysfunction and impaired fibrinolysis. Recent studies have shown that resistin, a newly discovered adipokine may play a role in the development of insulin resistance. It increases the proliferation of the smooth muscle cells and accesses to the development of restenosis in diabetic patients. Adiponectin is secreted by adipocytes and has been shown to improve insulin sensitivity and to have antiinflammatory and antioxidant properties. Adiponectin levels are reduced in patients with CAD.

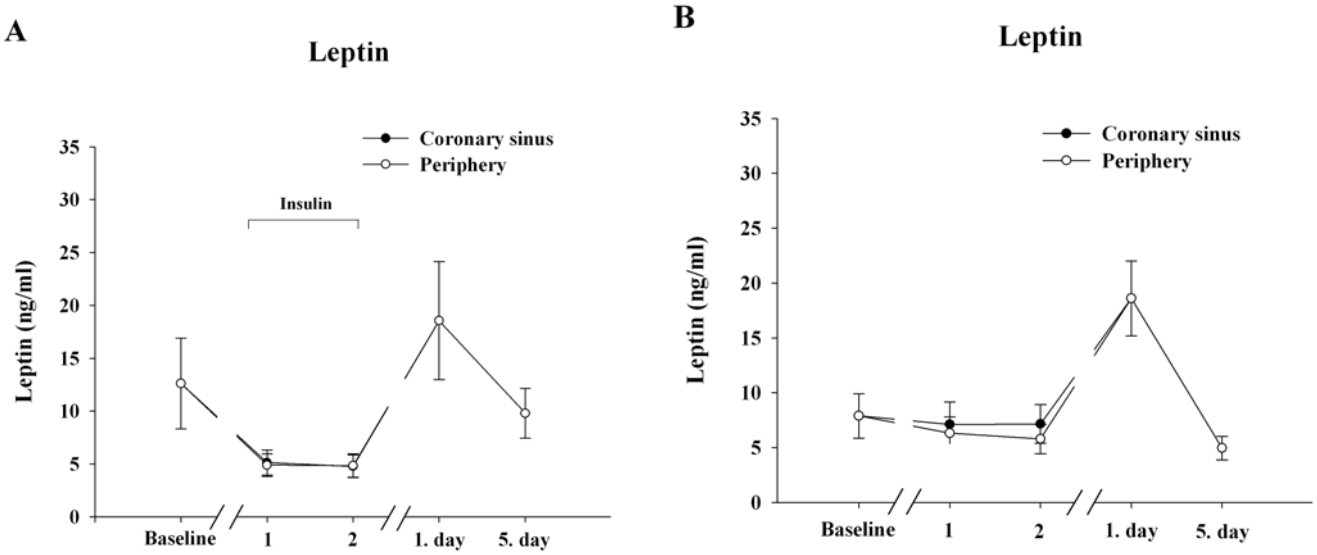
5.2. Patients and methods

16 patients admitted to the Heart Institute, Faculty of Medicine, University of Pécs for elective CABG were included in the study and subjected to CPB surgery. 19 patients hospitalized to the Department of Cardiac Surgery, Zala County Hospital underwent elective CABG served as the OPCAB group for this study. The patients with CPB received glucose-insulin-potassium infusion (GIK) at a rate of 5.2 g/hour glucose, 9.4 U/hour regular insulin and 3 mEq/hour potassium. Blood samples were drawn for hormone measurements from peripheral vein before and twice during surgery, and on postoperative days 1 and 5. Simultaneously with samplings from peripheral vein, blood was obtained intraoperatively from the coronary sinus prior to placement of the first graft and after completing the last graft. Fasting plasma samples were obtained and stored at -70 °C until analysis. Routine biochemical parameters were measured by standard laboratory methods. Plasma insulin, leptin, adiponectin and resistin concentrations were measured with ELISA, while ghrelin was analyzed with RIA using commercially available kits (Mediagnost, Reutlingen, Germany). All statistical analyses were performed with SPSS, version 11.5. Changes in hormone levels during the perioperative period were analyzed using repeated-measures ANOVA or paired t-test as appropriate.

5.3. Results

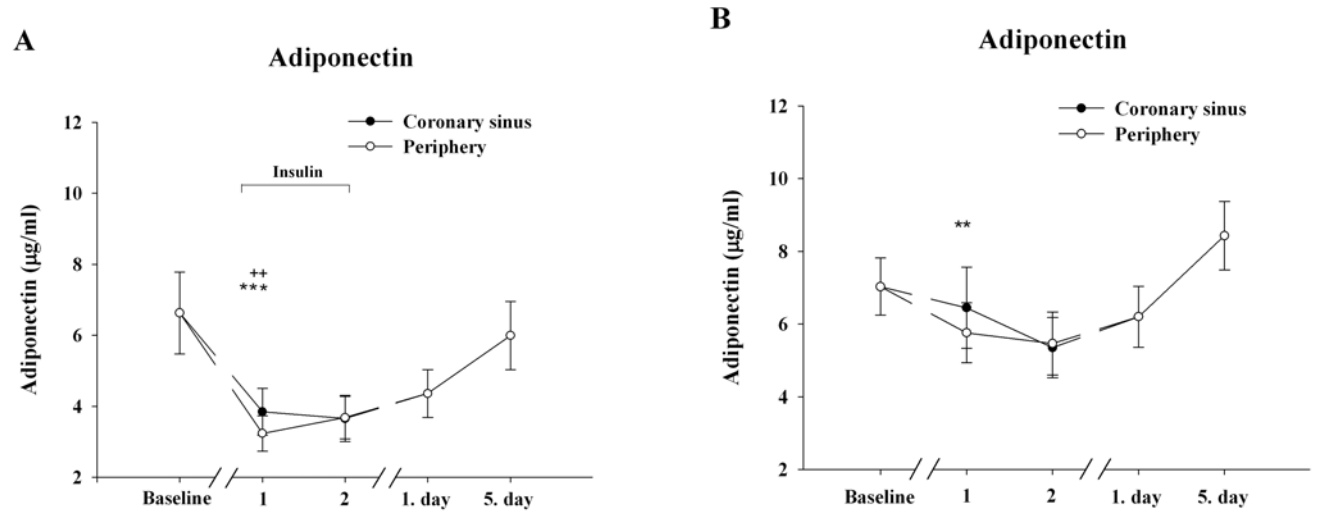
In patients operated on pump on the postoperative day 1 leptin levels increased significantly both in coronary sinus ($p<0.023$) and in peripheral vein ($p<0.012$) then returned to the baseline by the end of the study. It is of note that no discernible difference could be detected in plasma leptin levels between periphery and coronary sinus. In patients operated off pump plasma leptin followed a similar pattern, but at the time of second sampling during surgery its value in the coronary sinus was higher than in the periphery ($p<0.031$).

Figure 4. Plasma concentration of leptin during on pump (A) and off pump (B) CABG surgery



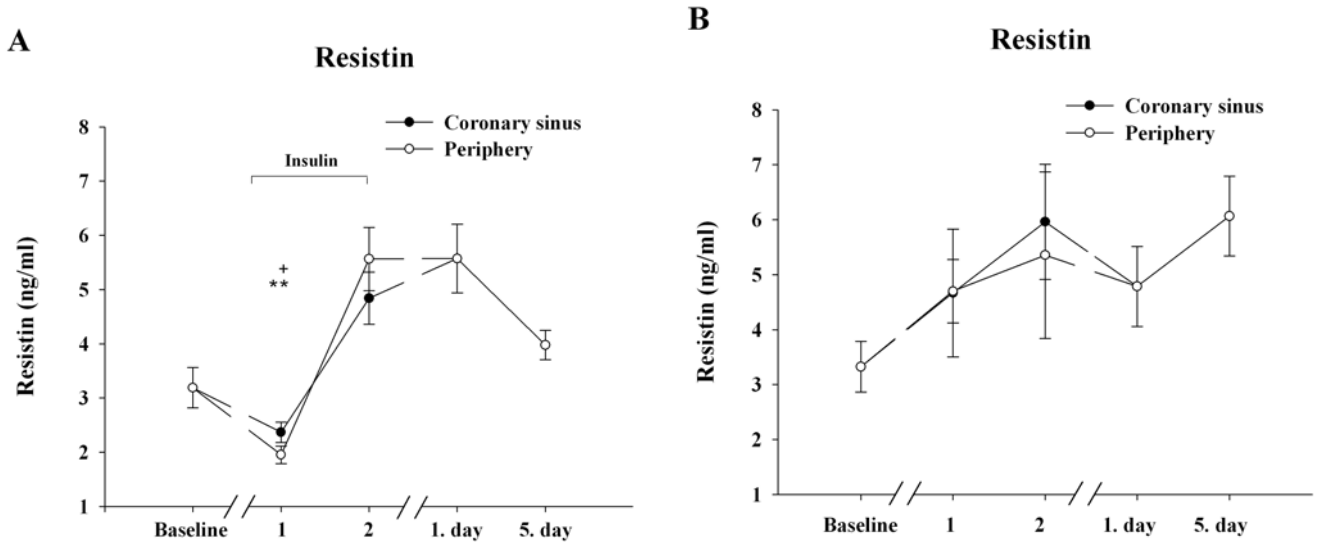
The intervention resulted in an early reduction of plasma adiponectin in both the periphery ($p<0.001$) and coronary sinus ($p<0.001$); the reduction proved to be more pronounced in the peripheral vein than in coronary sinus. During the procedure coronary sinus adiponectin remained unchanged ($p=0.602$), whereas it increased significantly in the periphery ($p<0.01$). Later on, plasma adiponectin increased steadily to approach the initial values on postoperative day 5.

Figure 5. Plasma concentration of adiponectin during on pump (A) and off pump (B) CABG surgery



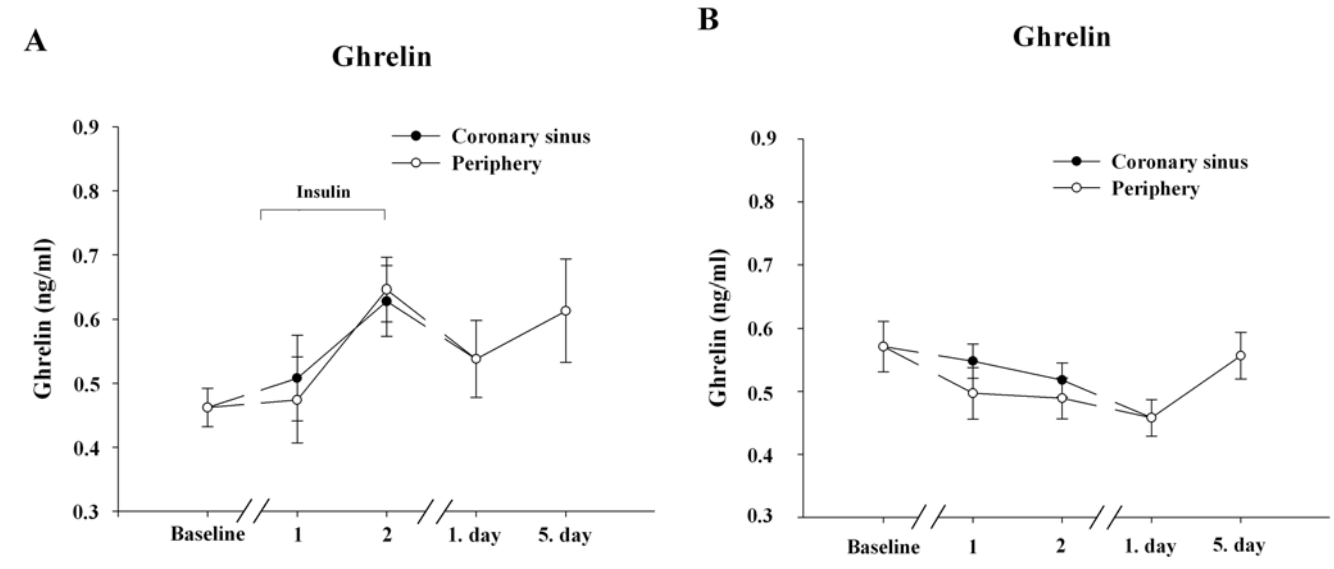
In patients operated on pump there was an initial fall in plasma resistin levels in the periphery ($p<0.002$) and in coronary sinus ($p<0.02$) followed by a marked increase to reach their peak values on postoperative day 1 ($p<0.001$). It is of note that at the end of the surgical procedure resistin levels were significantly higher in the periphery than in coronary sinus ($p<0.009$). Off pump operation did not cause any increase in plasma resistin but rather it was stabilized at higher level when compared with the baseline.

Figure 6. Plasma concentration of resistin during on pump (A) and off pump (B) CABG surgery



No consistent changes could be observed in plasma ghrelin levels before and after surgery. During surgery, however the GIK supported CPB induced a significant increase in the peripheral ghrelin levels ($p<0.034$). As a consequence, ghrelin levels in the two venous systems proved to be similar. Ghrelin level remained mostly unaffected by off pump surgery.

Figure 7. Plasma concentration of ghrelin during on pump (A) and off pump (B) CABG surgery



5.4. Discussion

The present study described the dynamic changes in metabolic hormone profiles (insulin, leptin, adiponectin, resistin, ghrelin) in CABG patients with or without CPB. Clinical studies have revealed an apparent association of leptin with established vascular risk factors and with markers of inflammation and vascular dysfunction. In experimental models leptin has been shown to increase oxidative stress in endothelial cells. The changes in leptin levels in CABG patients receiving CPB and GIK solution can be attributed to the enhanced cellular glucose uptake and improved energy metabolism. Ghrelin, a stomach-derived peptide hormone has profound orexigenic and adipogenic properties and has been documented to act as an antiinflammatory factor, that protects functional integrity of endothelial cells, so it may prevent cardiovascular complications. CABG with CPB resulted significant elevation of ghrelin concentration. One can assume, therefore, that this increase in ghrelin is an adaptive mechanism to counterbalance the adverse vascular effects of CABG-related inflammation. Adiponectin is exclusively secreted by adipocytes and has been shown to improve insulin sensitivity, to ameliorate endothelial dysfunction, and to have antiinflammatory and antioxidant properties. Accordingly, hypoadiponectinemia is associated with impaired endothelium-dependent vasodilatation and adiponectin levels are reduced in patients with CAD. In our study the depression of plasma adiponectin proved to be more pronounced when CABG was performed on pump. Later on, plasma adiponectin increased steadily to approach the initial values on postoperative day 5. It is to be stressed, however, that we failed to detect any differences in plasma adiponectin between the peripheral vein and coronary sinus suggesting that the injured coronary vasculature could not take up, accumulate and utilize this protective hormone. A further important issue addressed in this study was to explore the possible insulin-resistin interaction. It was clearly shown that peripheral plasma insulin levels were significantly higher than those in coronary sinus while exogenous insulin was given. This observation appears to suggest that insulin is taken up by the coronary vasculature and it may have a role to protect/improve endothelial function. Recent studies have demonstrated that resistin, a newly discovered adipokine/cytokin, which is secreted by many different cell types including adipocytes and monocytes/macrophages may also play a role in the development of insulin resistance. In patients operated on pump there was an initial fall in plasma resistin levels in the peripheryand in coronary sinus followed by a marked increase to reach their peak values at the end of the study.

In conclusion, the present study described the evolution of plasma levels of insulin, leptin, adiponectin, resistin and ghrelin in patients undergoing CABG surgery with or without CPB and GIK. Furthermore, it provided convincing evidence that epicardial/periadventitial adipose tissue are unlikely to have major contribution to the development of CAD as adipocyte-derived adipokines/cytokines were not elevated in coronary sinus independent of the mode of surgical intervention.

6. SUMMARY OF NOVEL FINDINGS

In our study we have examined the neurocognitive, vascular and metabolic parameters of patients underwent on pump and off pump CABG surgery. Our main findings are:

1. A new equipment, special digital instrumentation and the analyzer software were developed at our laboratory. The measurement of the reaction times and the physiological tremor is fast, simple and can be performed in a hospital ward within 10-15 minutes without exhausting a patient who has undergone open heart surgery.

2. There were no statistically significant changes of mean sRT and cRT values before and after open heart surgery. The positive correlation between sRT_2/sRT_1 and cRT_2/cRT_1 was found weak. The correlation was more pronounced among women.

3. The spectrum at 8-12 Hz range (neuronal oscillation) decreased during both lowsRT and lowcRT measurements and a shift was recognised to the lower spectrum. The magnitude of the shift was not significantly higher for females than for males. We found no significant difference between the shift and the cross-clamp and perfusion time respectively.

4. Comparing the arterial stiffness parameters measured by Arteriograph the PWV was significantly higher in the CAD group compared to the age- and gender-matched control group, but we found no significant differences in AIXao between the two groups

5. We demonstrated that the plasma level of ADMA, is a reliable and feasible marker of an early ischemia-reperfusion injury and endothelial dysfunction which occured in patients undergoing CABG surgery. We confirmed that during CPB operation the plasma concentration of ADMA increased significantly and remained elevated until the first postoperative day. We proved the harmful effect of CPB and demonstrated the potential role of ADMA in endothelial dysfunction during ischemia-reperfusion injury and oxidative stress.

6. We measured the evolution of plasma levels of insulin, leptin, adiponectin, resistin and ghrelin in patients undergoing CABG surgery. It provided convincing evidence that epicardial adipose tissue are unlikely to have major contribution to the development of CAD as adipocyte-derived adipokines were not elevated in coronary sinus independent of the mode of surgical intervention.

7. PUBLICATIONS

Full papers related to the thesis

1. Á. Németh, L. Hejjel, Z. Ajtay, L. Kellényi, A. Solymos, I. Bártfai, N. Kovács, Z. Lenkey, A. Cziráki, S. Szabados. The assessment of neural injury following open heart surgery by physiological tremor analysis. **Archives of Medical Science** (Accepted) ***IF: 1.199***

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