Human clinical hemorheological investigations in the field of cardiac rehabilitation, renal transplantation and pharmacological innovation

Ph.D. dissertation

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1st Department of Medicine, University of Pecs
Hungary
2014

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List of abbreviations

ACC	American College of Cardiology	**hsCRP**	high-sensitivity C-reactive protein
ADP	adenosine diphosphate	**i.e.**	id est
AHA	American Heart Association	**IL6**	interleukin 6
AI	aggregation index	**KDIGO**	Kidney Disease Improving Global Outcome
ASA	acetylsalicylic acid	**LDH**	lactate dehydrogenase
BAO	basic acid output	**LDL**	low-density lipoprotein
BMI	body mass index	**MCHC**	mean corpuscular hemoglobin concentration
BUN	blood urea nitrogen	**MCV**	mean corpuscular volume
CAD	coronary artery disease	**MET**	metabolic equivalent
CGRP	calcitonin gene-related peptide	**NR**	nonresistant
CMV	cytomegalovirus	**NR-PC**	nonresistant, positive control
COX	cyclooxygenase	**NR-RT**	nonresistant renal transplanted
CR	cardiac rehabilitation	**NSAID**	non-steroidal anti-inflammatory drugs
CV	cardiovascular	**PC**	positive control
e.g.	exempli gratia	**PDE**	phosphodiesterase
EBV	Epstein-Barr virus	**PPP**	platelet pure plasma
ECG	electrocardiography	**PRP**	platelet rich plasma
EI	elongation index	**PV**	plasma viscosity
EI_{max}	maximal elongation index	**R**	resistant
ESC	European Society of Cardiology	**RBC**	red blood cell
FDA	Food and Drug Administration	**R-PC**	resistant, positive control
FIS	fatigue impact scale	**R-RT**	resistant, renal transplanted
GGT	gamma-glutamyl transpeptidase	**RT**	renal transplanted
GMBF	gastric mucosal blood flow	**SCORE**	systemic coronary risk evaluation
GOT	glutamic-oxaloacetic transaminase	**$SS_{1/2}$**	shear stress required for half of EI_{max}
GPT	glutamic-pyruvic transaminase	**TNFα**	tumor necrosis factor α
HBsAg	hepatitis B surface antigen	**TRPV**	transient receptor potential vanilloid
Hct	hematocrit	**TXA2**	thromboxane A2
HCV	hepatitis C virus	**UGIC**	upper gastrointestinal complication
HDL	high-density lipoprotein	**UK-HARP-I**	United Kingdom Heart and Renal Protection
HIV	human immunodeficiency virus	**WBV**	whole blood viscosity

Prologue

From cardiovascular risk stratification to cardiovascular risk management

In the past few decades, mortality of coronary artery disease has decreased substantially in the industrialized countries, but it still remains the leading cause of premature death worldwide. In addition to the optimal pharmacological therapies and modern revascularization procedures, numerous preventive strategies have been created with a view to the further reduction of morbidity and mortality of CAD (89).

Preventive strategies should be classified as primary and secondary prevention. Primary prevention means the avoidance of cardiovascular diseases through lifestyle and environmental changes. Secondary prevention describes the medical treatment of patients after cardiovascular events to avoid furthers. The exact differentiation between primary and secondary prevention among a young or middle-aged population can not be defined easily, because underlying atherosclerosis can be found even in young, healthy people with no symptoms and in patients with definitive cardiovascular diseases.

Therefore, two main preventive strategies were developed by Geoffrey Rose in 1985: the population and the high-risk strategy (91). The population strategy aims to reduce the incidence of CAD among a large population with long-time lifestyle and environment changes e.g. regular physical activity, ban of smoking, reduction of salt and fat intake. The limitation of this approach is that it provides more for the whole population but the individuals benefit less. In the opposite, the high-risk strategy reaches patients with a high cardiovascular risk, and helps to manage the cardiovascular risk factors i.e. medication for hypertension, for elevated lipid or fasting glucose level, antiplatelet therapy, smoking cessation programs, cardiac rehabilitation programs (including not just medical supervision but basic medical education, dietary consultation, psychological guidance and physical training designed by a physiotherapist). Although the population strategy is more cost-effective, the effective pharmacological therapy, the successful smoking cessation and cardiac rehabilitation programs resulted in an increased efficiency of the high-risk strategy. Nevertheless, the best prevention could be achieved by the combination of the two approaches.

The appropriate risk management requires precise risk stratification including consideration of all cardiovascular risk factors. Accurate risk assessment could help to avoid the under-

treatment of patients suffering from a small number but “major” risk factors as well as the inappropriate over-use of invasive or non-invasive therapies in subjects with low cardiovascular risk. To promote the quick but proper risk estimation, it is recommended to use the SCORE system currently (2). The SCORE system evaluates the 10-year risk of the first fatal atherosclerotic event e.g. myocardial infarction, stroke and peripheral arterial disease using age, gender, smoking, systolic blood pressure and total cholesterol level (2). Since the first publication of the results from the SCORE cohort in the late 80’s, the system has been recalibrated several times, because it predicted higher risk for countries where the cardiovascular mortality showed reduction and lower risk for countries where it became higher. Accordingly different SCORE systems were developed for low-risk (e.g. Austria, Belgium, Finland, France, Germany) and high-risk (e.g. Hungary) countries. In countries with very high cardiovascular risk (e.g. Bulgaria, Latvia, Lithuania, Russia, Ukraine) the SCORE system could underestimate the absolute cardiovascular risk. There exists a third SCORE chart for the assessment of the relative cardiovascular risk, to advance the adjudication of the beneficial effect of lifestyle changes in young people with low absolute risk (88).

Factors for risk assessment are age, gender and genetic background, also known as nonmodifiable parameters of a patient. The traditionally called “major” but modifiable (consequently preventable/treatable) risk factors are hypertension, dyslipidemia, diabetes mellitus, smoking, overweight, lack of regular physical activity (88). Other modifiable factors are the psychological factors e.g. low socio-economic status, lack of social support, social isolation, stress at work or in family, depression, anger and type D personality (negative emotional affectivity and avoidance of social contacts). These could inhibit the effectiveness of a treatment; however certain psychological factors could also play a part in the development of cardiovascular diseases. Further important modifiable risk factors are: elevated high-sensitivity C-reactive protein, inflammatory cytokines (e.g. IL-6, TNF-α) and fibrinogen, inflammatory diseases (e.g. influenza, rheumatoid arthritis, SLE), obstructive sleep apnoea, chronic kidney disease, abnormal hemorheological factors.

According to the medical history (co-morbidities, clinical chemistry) and the SCORE value, 4 risk groups could be generated. Very high risk patients are those with previous cardiovascular and/or cerebrovascular event, and/or peripheral arterial diseases, as well as with known diabetes mellitus, chronic kidney disease or a calculated SCORE ≥10%. To the high risk group belong patients suffering from one elevated risk factor (dyslipidemia or

hypertension), diabetes mellitus, moderate kidney disease or a calculated SCORE of ≥5% and <10%. Moderate risk have subjects with SCORE ≥1 and <5%, low risk category could be described by SCORE <1% (88).

After risk stratification an appropriate risk factor management should be started. In generally subjects with low cardiovascular risk (SCORE <1%) should be advised to maintain this status. Patients with an absolute risk of ≥5% SCORE require intensive medical supervision, lifestyle changes and they could benefit from drug therapy. Patients with >10% SCORE require drug treatment as well as additionally lifestyle changes. While there exist a prevention strategy for almost all of the modifiable risk factors, not every risk factor can be treated/prevented by medical therapy (see above: nonmodifiable factors) (88).

Correct risk factor management includes lifestyle changes i.e. changes in behavioral patterns, effective communication, stress management, smoking cessation intervention (a cornerstone in successful cardiovascular prevention) with or without pharmacological therapies, healthy diet (mediterranean diet in first line), moderate alcohol consumption (mainly red wine, containing antioxidants – French paradox), reaching BMI <25 kg/m^2 and >20kg/m^2 and regular physical activity (healthy subjects 2.5-5 hours weekly, cardiovascular patients 3X30 minutes weekly). These changes could be applied in the primary as well as in the secondary prevention strategies (88).

Beneath lifestyle changes several conditions should be medically treated in case of clinical symptoms. Psychosocial problems could be managed by individualized or group psychotherapy and by certain medication against depression and anxiety. Appropriate treatment should be started for hypertension (thiazides, beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor antagonists), diabetes mellitus type 1 and 2, hypercholesterinemia and hypertriglyceridemia (statins, fibrates, bile acid sequestrants, niacin, selective cholesterol absorption inhibitors), and against thromboembolic events antiplatelet therapy (acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor) (88). The above mentioned therapeutical options (applied according to the latest guidelines) are part of the secondary prevention of cardiovascular diseases (88).

Clinical role of hemorheological parameters

Hemorheology is focusing on the flow properties of the blood. In the last few decades several studies have indicated, that abnormal rheological factors should be handled as risk factors of cardiovascular and cerebrovascular diseases (9, 109). Impairment of these factors could be responsible for tissue hypoperfusion and disturbances in the microcirculation (19, 57, 71).

Hematocrit:

Hematocrit is the mostly used hemorheological parameter in the clinical routine describing the percentage of the cellular fraction of the whole blood. The normal value is between 35-45 %, and it affects all the other hemorheological parameters.

Whole blood and plasma viscosity:

Viscosity is the intrinsic friction of the fluids. Literature describes two types of fluids regarding the flow characteristics. Accordingly we can differentiate Newtonian and non-Newtonian fluids regarding the relationship between shear stress and velocity gradient.

Whole blood viscosity (Cassonian fluid - a type of non-Newtonian fluids) is influenced by the hematocrit, plasma viscosity, red blood cell aggregation (at low shear rates) and deformability (at high shear rates). Elevated whole blood viscosity (hyperviscosity) can be induced by exsiccosis and myeloproliferative diseases as well as chronic hypoxia (due to secondary polycythemia).

Plasma viscosity is determined by the quantity of the plasma proteins (fibrinogen and certain globulins) as well as the triglyceride level (60). Although smoking increases plasma viscosity by accelerating the progression of chronic bronchitis, physical activity decreases fibrinogen level leading to decreased plasma viscosity (60).

Red blood cell aggregation:

Red blood cell aggregation is a reversible process and occurs at low shear conditions or at stasis. The process has three different phases: 1) without shear forces rouleaux formation (cells in a row like stack of coins) appears in few minutes then 3 dimensional aggregates appear, 2) the aggregates starts to sink with a permanent velocity, 3) sinking slows down then finally stops. This hemorheological parameter depends on hematocrit, intrinsic cell

characteristics (also known as red blood cell aggregability) and the quantity of plasma proteins and lipids.

In the background of the process two parallel theories can be found. According to the bridging theory red blood cell aggregation is caused by macromolecules promoting the connection of the cells. On the other hand, the depletion layer theory suggests that the decreasing macromolecules concentration creates an osmotic gradient between two erythrocytes leading to cell-cell interactions (14).

Increased red blood cell aggregation could be found in cardiovascular diseases, myeloma multiplex, sepsis, autoimmune disorders and malignant conditions caused by the elevated level of certain plasma proteins (102).

Red blood cell deformability:

Red blood cell deformability is a pivotal ability of the cells to pass the capillary system which is required for sufficient tissue oxygenation. Deformability is determined by the internal viscosity of the cell, the membrane viscoelasticity, the surface-volume ratio and the morphology of erythrocytes.

Routinely measured lab parameters are the MCV and the MCHC referring to the surface-volume ratio and the intrinsic viscosity of red blood cells, respectively. These parameters are mainly modified in hemoglobinopathies (thalassemia, sickle cell disease) caused by pathological hemoglobin formation.

Modifications in the structure of the membrane proteins and the underlying cytoskeleton network can have genetic origin (herediter spherocytosis or elliptocytosis) and can also be changed by oxidative stress or mechanical trauma on the cells (artificial heart valve, extracorporeal circulation).

Platelet aggregation:

Platelet aggregation has a key role in the arterial thrombus formation. The activation of this process is mostly evoked by endothelial injury where free collagen releases ADP, epinephrine, serotonin and TXA2 from platelets. These substrates accelerate and sustain platelet aggregation.

Acetylsalicylic acid is one of the most important antiplatelet agent in primary and secondary prevention of cardio- or cerebrovascular events (95, 5, 37, 46, 92, 99, 115, 122), but routine

control on the efficacy of ASA therapy is now not recommended in patients after percutaneous interventions (6).

Methodology

In our studies the hemorheological measurements were performed within 2 hours after blood sampling.

Hematocrit was measured by a micro-Hct centrifuge (Haemofuge Heraeus Instr., Germany).

Whole blood viscosity and *plasma viscosity* were determined at a shear rate of 90 s^{-1} with a Hevimet 40 capillary viscometer (Hemorex Ltd., Budapest, Hungary). Plasma was prepared by a 10-minute centrifugation of whole blood at 1500 g. Measurements were made at 37 °C. The ratio of Hct/WBV was utilized to characterize the oxygen transport efficiency of the blood (9).

Red blood cell aggregation was measured with both Myrenne (MA-1 Aggregometer, Myrenne GmbH, Roentgen, Germany) (10, 121) and LORCA (Laser-assisted Optical Rotational Cell Analyzer; R&R Mechatronics, Hoorn, The Netherlands) (10) aggregometers using blood samples with native Hct.

Myrenne provides two dimensionless indices at room temperature (M, aggregation at stasis; and M1, aggregation at low shear) using the Schmid-Schönbein principle; both M and M1 are increased with enhanced red blood cell aggregation.

LORCA aggregometer determines RBC aggregation index at 37 °C via syllectometry (i.e. laser backscattering versus time). The RBC disaggregation threshold (γ) describes the minimal shear rate which is needed to prevent RBC aggregation formation. It was was determined using a re-iteration procedure. Measurements were made at 37 °C.

RBC deformability was characterized with a LORCA ektacytometer (32) at 37 °C provided nine values of elongation index in the shear stress range from 0.3 to 30 Pa. The deformability results were analyzed by the Lineweaver-Burke nonlinear equation calculating the maximal EI at infinite shear, and the shear stress value required for half of this maximal elongation.

For deformability measurements, blood samples were suspended in a highly viscous (32.6 mPas) polyvinylpyrrolidone solution.

Platelet aggregation measurements were performed by using a Carat TX4 optical aggregometer. Blood samples were centrifuged first at 150 g for 10 minutes to obtain platelet rich plasma then the centrifugation was repeated at 2500 g to separate platelet pure plasma. Following the separation procedure platelet aggregation was determined with Carat TX4 optical aggregometer (Carat Diagnostics Ltd, Budapest, Hungary) at 37 °C. Firstly, the aggregometer was calibrated with 270 µl PPP (optical density of the sample is 0%) and 270 µl PRP (optical density of the sample is 100%) followed by the platelet aggregation induction with 30 µl epinephrine (final concentration: 10 µM) added to the PRP sample. Based on the Born method, aggregation measurements provide an aggregation index curve describing the light transmission intensity changes of the PRP samples (15, 64). Rate of the platelet aggregation was determined as the maximum point on the aggregation index curve and considered clinically significant and effectively inhibited below 40% in case of efficient Aspirin therapy.

Focus and aim of the studies

1) Effects of moderate aerobic exercise training on hemorheological and laboratory parameters, and on psychological functioning in ischemic heart disease patients:

The recent guidelines of the European Society of Cardiology and the American Heart Association/American College of Cardiology indicate that physical activity has a pivotal role in the primary prevention in healthy subjects, and moreover it reduces all-cause and cardiovascular mortality, too. Moderate aerobic exercise training in patients with CAD improves myocardial perfusion, muscular endurance and psychosocial well-being leading to enhanced flexibility, ameliorated symptoms, better cardiorespiratory fitness and a reduced CV risk. Training from 2.5 to 5 hours a week can result in a 20-30% CV and all-cause mortality risk reduction. In summary, moderate physical activity reduces the CV risk in a dose-dependent manner in both male and female healthy subjects, and even in patients with known CAD (89).

Prior to this study was never an investigation performed to examine hemorheological changes in ischemic heart disease patients during a long-term physical activity. For this reason our first study had the aim of determining the beneficial effects of aerobic physical training on ischemic heart disease patients participating in a long-term (24 weeks) ambulatory cardiac rehabilitation program.

2) Aspirin resistance as cardiovascular risk after kidney transplantation:

Chronic kidney diseases have a pivotal role in cardiovascular risk assessment. Patients with severe, progressive kidney disorders will need temporary or permanent hemodialysis and later eventually renal transplantation.

The controlled legal background of the transplantation procedure and the development of modern surgical techniques and immunosuppressive drugs resulted in a better overall survival and life quality after kidney transplantation (58, 61). Beyond infections, urological complications, malignant disorders and bone diseases the main cause of mortality (35-40 %) after renal transplantation has cardiovascular origin (75).

Based on the high cardiovascular mortality of kidney transplanted patients could be highly recommended, that these patients receive daily low dose ASA. While ASA is a widely used antiplatelet agent in the primary and secondary prevention of cardio- or cerebrovascular

diseases (88, 92, 95), ASA resistance could develop in certain circumstances. The exact rate of ASA resistance among renal transplanted patients and the connection between ASA resistance and high cardiovascular mortality in the mentioned population has not clearly been specified. The aim of our trial was to determine ASA resistance and to describe the eventual role of ASA resistance in the cardiovascular mortality among kidney transplanted patients.

3) Orally given gastroprotective capsaicin does not modify Aspirin-induced platelet aggregation in healthy male volunteers; human phase I. clinical study:

ASA is an important antiplatelet agent in the primary and secondary preventive care of cardio- or cerebrovascular events (95), like stable coronary artery disease, acute coronary syndrome, stroke and peripheral artery disease (5, 37, 46, 92, 99, 115, 122). But ASA has Janus-faced characteristics; on one hand it prevents cardio,- and cerebrovascular diseases, on the other hand causes severe gastrointestinal mucosal damages (bleedings, ulcers), which could limit the cardiovascular efficiency of the drug.

Several investigations were conducted to prevent the gastrointestinal side effects of ASA with low doses of capsaicin. Szolcsányi, Barthó (1981) and Holzer started human research with capsaicin (20, 49. 50, 102), and these studies have shown that low doses of capsaicin can prevent the development of gastric mucosal damage caused by NSAID-s or ethanol (28, 80, 82, 83, 101). The pathomechanism has not yet been described, but several investigations have suggested that capsaicin activates TRPV1, which releases CGRP and substance P in the gastric mucosa which enhance the GMBF via vasodilatation in the gastric mucosa, moreover, capsaicin reduces the BAO.

Aims of our recent study were: 1) to investigate the tolerability of capsaicin alone (in different gastroprotective doses) and in co-administration with 500 mg ASA; 2) to measure the pharmacokinetic parameters of capsaicin alone (administered in two gastroprotective doses) and in combination with ASA, 3) to study the ASA-induced platelet aggregation, 4) to evaluate the capsaicin action on the platelet aggregation and on the ASA-induced platelet aggregation inhibition.

Effects of moderate aerobic exercise training on hemorheological and laboratory parameters, and on psychological functioning in ischemic heart disease patients

Introduction

In the past few decades, mortality due to CAD has decreased substantially in the industrialized countries thanks to the optimal pharmacological therapies, modern revascularization procedures and preventive strategies, but it is still the leading cause of death worldwide (89).

The recent guidelines of the ESC and the AHA/ACC indicate that physical activity has a pivotal role in the primary prevention in healthy subjects, and moreover it reduces the all-cause and CV mortality too. Moderate aerobic exercise training in patients with CAD improves myocardial perfusion, muscular endurance and psychosocial well-being leading to enhanced flexibility, ameliorated symptoms, better cardiorespiratory fitness and a reduced CV risk. Training from 2.5 to 5 hours a week can result in a 20-30% CV and all-cause mortality risk reduction. In summary, moderate physical activity reduces the CV risk in a dose-dependent manner in both male and female healthy subjects, and even in patients with known CAD (89.

Physical activity conducted by physiotherapists and supervised by a cardiologist in a cardiac rehabilitation program is an excellent possibility for secondary prevention, where effective risk factor management can be achieved through long-term life style changes (89.

Impaired hemorheological parameters, including reduced erythrocyte deformability and increased aggregation, may have a deleterious effect on the vascular system leading to the development of various CV, cerebrovascular and peripheral arterial diseases (9, 19, 57, 71, 109). Whereas publications from the last 25 years have clearly revealed a relationship between hemorheological factors and physical training, those studies involved healthy volunteers or a small numbers of CV patients participating in short-term (10-12 weeks) exercise training. Furthermore, the possible connections between hemorheology and long-term, moderate aerobic physical activity have not been investigated in a relatively large population with ischemic heart disease.

Our study had the aim of determining the beneficial effects of aerobic physical training on ischemic heart disease patients participating in a long-term (24 weeks) ambulatory CR program.

Methods

79 non-smoker patients with stable ischemic heart disease (39 males and 40 females, mean age: 65.3 ± 5.68 years) were selected for the study; their co-morbidities are presented in Table 1. The patients received their medication in accordance with current guidelines for the secondary prevention of CAD (76) and with their co-morbidities (Table 2). Modifications in either agent or dose were not made during the trial. Patients with an ejection fraction < 40%, and MET < 5 or a significant ST depression during a treadmill-based exercise tolerance test using the Bruce protocol were excluded from the study (31, 51).

population characteristic		number of patients	%
ischemic heart disease	myocardial infarction	32/79	40.51
	CABG	35/79	44.3
	previous PCI	18/79	22.78
	proven by coronary angiography or coronary CT	18/79	22.78
hypertension		71/79	89.87
diabetes mellitus		24/79	30.38

Table 1 Characteristics of the study population.

medication	number of patients	%
cholesterol lowering drugs	70/79	88.61
antiplatelet drugs	79/79	100
β-blocker	59/79	74.68
RAAS inhibitor	65/79	82.28

Table 2 Medication during the 24 week long physical training.

The investigation was approved by the Regional Ethics Committee (licence number: 4378) of the University of Pecs and written informed consent was signed by all subjects.

Study design:

At baseline, the following measurements were performed: psychological tests, resting ECG, resting echocardiography, treadmill-based exercise tolerance testing using the Bruce

protocol, clinical chemistry (fasting total cholesterol, triglyceride, HDL, LDL, uric acid, hsCRP, fasting glucose, total plasma protein, albumin, blood cell counts, fibrinogen, cytokines (TNF-α and IL-6) and hemorheological measurements (Hct, WBV, the ratio Hct/WBV, PV, red blood cell aggregation and red blood cell deformability).

The patients participated in a 24-weeks physical training program lasting for 1 hour 3 times weekly, designed and conducted by a physiotherapist and supervised by a cardiologist. After 12 weeks, the hemorheological measurements, clinical chemistry (except cytokines) and psychological tests were repeated. At the end of the 24 weeks, the resting ECG measurements, the treadmill tests with the Bruce protocol, the clinical chemistry, the hemorheological measurements and the psychological tests were repeated.

Aerobic exercise training program:

The aerobic exercise training program was preceded and ended with blood pressure and pulse measurements.

The patients began with warm-up exercises (breathing exercises, and stretching of the large joints) for 5-10 minutes.

In the second phase, they participated in moderate-intensity training, which included CV and vascular physiotherapy, supplemented with interval training and intensification of the musculature. The aerobic phase lasted 35-40 minutes. Finally, relaxation exercises were performed (jogging, stretching and breathing exercises) for 10 minutes.

Blood collecting:

Blood samples were obtained from the antecubital vein at baseline, after 12 weeks and after 24 weeks. The blood was collected into two lithium heparin-coated (12 ml), one clot activator-coated and gel-containing (5 ml), one potassium EDTA-coated (3 ml) and one sodium fluoride and potassium oxalate-coated (2 ml) Vacutainer tube with a 21-gauge Eclipse™ Blood Collection butterfly needle set, using a minimal tourniquet.

Hemorheological measurements:

Hemorheological measurements were performed according to the above mentioned methodological description (see page 10-11.).

Cytokine measurements:

Cytokines were determined with an automated chemiluminescence immunoassay system (Immulite 1000, Siemens). For TNF-α, a solid-phase chemiluminescent immunometric assay (cat. no. LKNF1), and for IL-6, a solid-phase chemiluminescent sequential immunometric assay (cat. no. LK6P1) was used. Master calibration and bi-level cytokine controls were applied during the runs.

Psychological surveys:

In order to examine the effects of the 24-week physical training on the patients' subjective experience with fatigue, we applied the Fatigue Impact Scale (35, 38). The FIS consists of 40 items which evaluate the impact of fatigue on three aspects of daily life: physical (10 items), cognitive (10 items) and psychosocial (20 items) functions.

Statistics:

Data are shown as means ± S.E.M. Differences were evaluated by a one-way repeated ANOVA statistical test (Tamhane post-hoc test) after using the Kolmogorov–Smirnov test to check on the normality of the data distribution. Multivariate linear regression and stepwise analyses of the data were performed with regard to differences between the baseline and the 24-week MET values.

The psychological data revealed a significant deviation from the normal distribution, and; the nonparametric Friedman test was therefore applied to analyze potential changes in psychological functioning. The analysis of psychological data was restricted to those patients who gave no indication of moderate or severe depression and had no missing surveys.

Significance level was defined as $p < 0.05$. SPSS statistical software, version 11.0.1. was used to conduct descriptive analyses and to describe the sample.

Results

As concerns the hemorheological results, the Hct displayed a decreasing tendency during the investigated period, while the WBV exhibited a significant reduction ($p<0.05$), resulting in a significantly increased Hct/WBV ratio ($p<0.05$). The PV was significantly decreased after 12 weeks and remained significantly lower relative to the baseline at the end of the program ($p<0.001$) (Table 3).

hemorheological parameters	week	mean ± SEM	p value	significance (p<0.05)
hematocrit (%)	0	44.18 ± 0.51	0.11	NS
	12	42.98 ± 0.67		
	24	42.13 ± 0.86		
whole blood viscosity (mPas)	0	4.35 ± 0.06	0.03	S
	12	4.26 ± 0.07		
	24	4.08 ± 0.08		
plasma viscosity (mPas)	0	1.27 ± 0.02	0.001	S
	12	1.18 ± 0.02		
	24	1.14 ± 0.02		
Hct / WBV (1/Pas)	0	10.2 ± 0.07	0.04	S
	12	10.25 ± 0.13		
	24	10.33 ± 0.19		

Table 3 Changes in certain hemorheological parameters (Hct, WBV, PV and the Hct/WBV ratio) after the 12- and 24-week ambulatory exercise training of ischemic heart disease patients. N = 79; values are means ± SEM. Levels of significance and p values are also shown. NS = not significant.

The red blood cell aggregation parameters of the Myrenne and LORCA aggregometers likewise demonstrated significant reductions. The Myrenne aggregation index M already revealed a significant reduction ($p<0.001$) after 12-weeks, and this continued up to the end of the follow-up. The LORCA parameter (AI) decreased significantly during the 24-week training program ($p<0.05$) (Table 4).

hemorheological para0meters		week	mean ± SEM	p value	significance (p<0.05)
Myrenne	M	0	6.98 ± 0.22	6.36E-27	S
		12	5.92 ± 0.13		
		24	4.02 ± 0.12		
	M1	0	13.18 ± 0.37	6.71E-08	S
		12	12.59 ± 0.24		
		24	10.84 ± 0.21		
LORCA	AI	0	66.67 ± 0.67	0.04	S
		12	61.63 ± 1.90		
		24	62.25 ± 1.73		
	γ (1/s)	0	117.53 ± 4.21	0.06	NS
		12	103.86 ± 4.66		
		24	106.55 ± 4.26		

Table 4 Changes in erythrocyte aggregation measured with Myrenne and LORCA aggregometers after the 12- and 24-week ambulatory exercise training of ischemic heart disease patients. N = 79; values are means ± SEM. Levels of significance and p values are also shown. NS = not significant.

The LORCA EIs of erythrocyte deformability increased significantly at 12 weeks compared to the baseline. The increase relative to the baseline was still significant after 24 weeks ($p<0.001$), but the difference between the 12 week and 24-week data was not significant (Fig. 1).

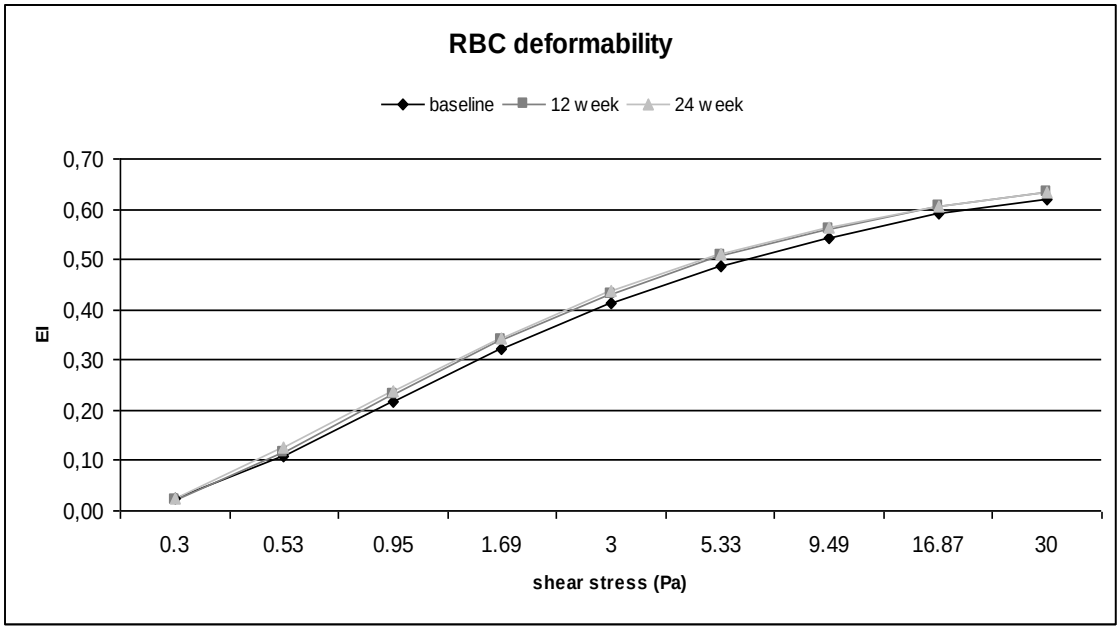

Figure 1 Elongation indices during the 24-week physical training.

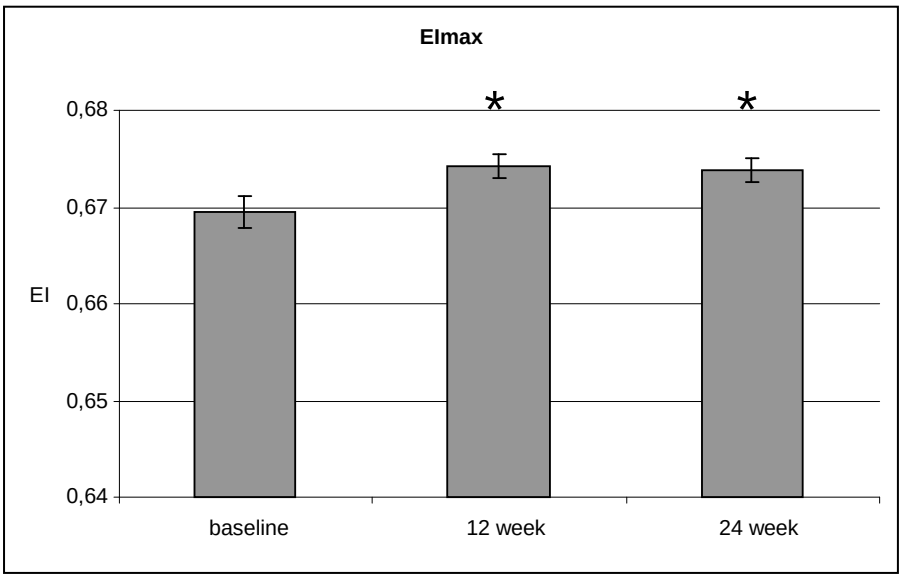

Figure 2 The maximal elongation indicis during the 24-week physical training.

The results of the RBC deformability measurements are also supported by the Lineweaver-Burke nonlinear equation analyses showing a significantly higher EImax and a significantly lower SS1/2 ($p<0.05$) (Fig. 2 and 3).

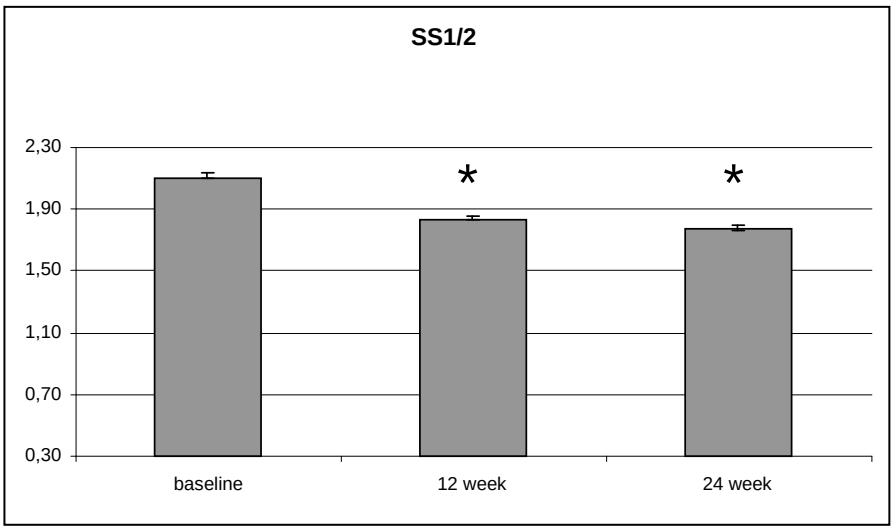

Figure 3 The SS1/2 during the 24-week physical training.

The clinical chemistry parameters relating to uric acid, triglycerides, hsCRP and fibrinogen decreased significantly during the training period (Table 5).

clinical chemistry	week	mean ± SEM	p value	significance (p<0.05)
glucose (mmol/l)	0	5.16 ± 0.32	0.48	NS
	12	5.19 ± 0.19		
	24	4.80 ± 0.23		
uric acid (umol/l)	0	336.39 ± 17.5	0.006	S
	12	327.17 ± 9.3		
	24	312.88 ± 10.7		
total cholesterol (mmol/l)	0	4.99 ± 0.13	0.17	NS
	12	4.87 ± 0.15		
	24	4.61 ± 0.15		
HDL (mmol/l)	0	1.40 ± 0.04	0.53	NS
	12	1.39 ± 0.04		
	24	1.33 ± 0.05		
LDL (mmol/l)	0	2.57 ± 0.08	0.69	NS
	12	2.50 ± 0.09		
	24	2.46 ± 0.1		
triglyceride (mmol/l)	0	1.70 ± 0.09	0.017	S
	12	1.56 ± 0.08		
	24	1.46 ± 0.09		
total protein (g/l)	0	72.33 ± 0.44	0.05	NS
	12	70.80 ± 1.01		
	24	68.84 ± 1.34		
albumin (g/l)	0	46.71 ± 0.22	0.45	NS
	12	45.58 ± 0.62		
	24	46.22 ± 0.88		
hsCRP (mg/l)	0	6.02 ± 1.04	0.0008	S
	12	2.98 ± 0.26		
	24	3.04 ± 0.27		
fibrinogen (g/l)	0	3.28 ± 0.14	0.03	S
	12	3.03 ± 0.06		
	24	3.15 ± 0.09		

IL 6 (pg/ml)	0	3.95 ± 0.71	0.06	NS
	24	1.88 ± 0.88		
TNF α (pg/ml)	0	11.53 ± 0.89	0.11	NS
	24	10.21 ± 0.43		

Table 5 Changes in clinical chemistry after the 12- and 24-week ambulatory exercise training of ischemic heart disease patients. N=79; values are means ± SEM. Levels of significance and p values are also shown. NS = not significant.

The cytokine measurements did not indicate a significant decrease ($p<0.05$), but only a falling trend as compared with the baseline values (Table 5).

As expected, the functional capacity described by the MET significantly improved ($p<0.001$), and the treadmill time also increased significantly, by 17.4% ($p<0.001$), during the training program. Moreover, the patients lost weight, with the BMI undergoing a significant decrease during the trial ($p<0.001$) (Table 6).

treadmill	week	mean ± SEM	p value	significance (p<0.05)
MET	0	7.93 ± 0.27	4.87E-23	S
	24	9.87 ± 1.09		
treadmill time (min)	0	7.68 ± 2.17	0.001	S
	24	9.02 ± 2.18		
BMI (kg/m^2)	0	28.16 ± 0.62	8.06E-79	S
	24	25.45 ± 1.14		

Table 6 Changes in exercise tolerability parameters and BMI after the 24-week ambulatory exercise training of ischemic heart disease patients. N = 79; values are means ± SEM. Levels of significance and p values are also shown. NS = not significant.

For the Δ values between the baseline and 24-week measurements were calculated from every parameter showing a significant difference to the baseline. The Δ parameters, which were in positive or negative correlation to the MET were used for the multivariate linear regression analyses: five independent variables were investigated in association with the difference in MET (ΔMET was regarded as the dependent variable). Regression analysis showed that the predictive model provided a good fit to the data with a significant F value

(F(5), p<0.000), and the five predictors explained 76% of the difference in MET values (R2 = 0.76).

predictor	standardized β	p value (p<0.05)
Δ whole blood viscosity	0.221	0.07
Δ plasma viscosity	-0.017	0.891
Δ LORCA aggregation index	-0.112	0.314
Δ BMI	-0.201	0,06
Δ elongation index (30Pa)	-0.290	0.018

Table 7 Results of the multivariate linear regression analyses after the 24-week ambulatory exercise training of ischemic heart disease patients; N = 79.

The results in Table 7 indicated that the red blood cell deformability value was a significant independent variable of the regression model and the most strongly related to the variation of the MET values (standardized β = 0.29). Furthermore, the analyses revealed a strong independent predictive association between the Δdeformability and the dependent variables (Table 7).

In the course of the psychological study, there was no drop out, and no noteworthy CV event or unplanned hospitalization occurred. Analysis of the FIS data revealed a significant decline in the symptoms of fatigue in the physical (chi2(2) = 6.12, p < 0.05), the psycho-social (chi2(2) = 7.09, p < 0.05) and in the cognitive domain (chi2(2) = 8.85, p < 0.05). More specifically, patients' perception of their physical, cognitive, and social functional limitations caused by fatigue declined significantly over the course of the physical training period.

Discussion

The fundamental problem of CAD patients can not be solved completely via revascularization techniques (percutaneous coronary intervention or a coronary artery bypass graft), effective and long-term lifestyle changes are at least as vital as other therapeutic procedures (39). Recent studies such as EuroAction (117) and GOSPEL (42) have indicated that regular long-term physical activity results in more benefit than short-term

training programs as regards the prognosis of cardiac patients. A physical training program is strongly recommended by the ESC and the AHA/ACC as well (89, 88, 34).

Possible connections between hemorheology and long-term aerobic physical training in a relatively large ischemic heart disease population have not been investigated previously. A systematic literature search in PubMed with the keywords hemorheology, physical activity, physical exercise, cardiovascular diseases and atherosclerosis, identified only 14 nonrandomized controlled studies from the past 25 years in which original data were used to determine changes in hemorheological parameters, mostly in healthy volunteers and athletes (9 publications), but also partially in patients with CV diseases (5 publications), participating in short-term (10-12 weeks) exercise training (25) (Tables 8 and 9).

authors	year of publication	study duration	population	exercise	results
Ernst et al.	1987	3 months	untrained men	regular training	RBC deformability increased, WBV and PV decreased
Neuhaus et al.	1992	before and after exercise	8 healthy athletes	marathon running	no hemorheological changes
Brun et al.	1998	short- and long-term	healthy men	cycling	increased viscosity after short-term training but autohemodilution after long- term exercise
Yalcin et al.	2003	before and after exercise	10 healthy untrained men	heavy anaerobic exercise	RBC deformability and aggregation decreased but normalized 24 hours after exercise
Connes et al.	2004	before and after exercise	20 healthy athletes	progressive exercise test	RBC deformability increased
Connes et. al	2007	before and after exercise	13 healthy sportsmen	progressive and maximal exercise	RBC aggregation did not change
Cakir-Atabek et al.	2009	3 times weekly 6 week long	14 healthy untrained men	resistance exercise training	RBC deformability and RBC decreased after 6 weeks but after training increased immediately
Tripette J. et al.	2011	before and after exercise	9 healthy athletes	10 km running with fluid intake *ad libitum*	no hemorheological changes
Kilic-Toprak et al.	2011	3 times weekly 12 week long	12 healthy untrained men	progressive resistance exercise training	RBC deformability increased, aggregation did not change, WBV and PV decreased

Table 8 Publications relating to hemorheological alterations induced by various exercise training programs in healthy volunteers.

Investigations involving healthy volunteers have proven that short-term physical activity has adverse effects on the hemorheological parameters, including increases in Hct and WBV due to fluid shift, water loss and release of sequestered red blood cells from the spleen (16, 22, 36). In contrast, long-term training causes autohemodilution, resulting in reduction of PV and WBV (16). On the other hand, the findings of red blood cell aggregation and deformability studies are not concordant.

authors	year of publication	study duration	population	exercise	results
Ernst et al.	1987	5 times weekly 8 week long	22 patients with claudication	standardized treadmill exercise	WBV, PV and RBC aggregation decreased, RBC filterability increased
Levine et al.	1995	3 days weekly 10 week long	15 patients with known CAD underwent CR	30-40 minutes moderate-intensity exercise	no hemorheological changes
Reinhart et al.	1998	1 hour daily 8 week long	25 patients with post myocardial infarction and EF<40%	cycling and walking	no difference in WBV, PV
Church et al.	2002	3 days weekly 12 week long	7 female, 16 male patients with CAD underwent CR	30-40 minutes moderate intensity exercise	hematocrit did not change, WBV and PV decreased
Lee et al.	2005	before and after exercise	53 patients with CAD	incremental shuttle walk test	increased PV and fibrinogen

Table 9 Publications relating to hemorheological alterations induced by various exercise training programs in patients with cardiovascular diseases.

Some investigations suggested the deterioration of rheological factors (62, 18, 108), whereas others reached the opposite conclusion (118, 23, 24). This discrepancy might be explained by differences in study designs (21, 23, 27), methods (62, 18, 23, 24), the selected populations (18, 36, 108) and the exercise performed (cycling vs. running) (16, 36). Only a few studies have focused on the effects of exercise on hemorheological factors in CV patients (25). Several investigations have shown that acute training evokes increases in PV and fibrinogen (67). Levine et al. were unable to demonstrate any hemorheological effects after a 10-week CR training (70), but Church et al. reported reductions in WBV and PV after a 12-week CR program (21). In our present study, we investigated whether we could demonstrate any

hemorheological changes in ischemic heart disease patients participating in a 24-week ambulatory CR training program. The results pointed to a slight decrease in Hct, while significant decreases were observed in WBV and PV, resulting in a significantly increased Hct/WBV ratio. The red blood cell aggregation indices and the measured deformability parameters were also significantly enhanced at the end of the training program.

Although the blood flow of the coronary vessel system is primarily determined by hemodynamic factors (i.e. continuous changes in flow, perfusion pressure and shear rate during a cardiac cycle), under certain conditions (e.g. a flow decrease caused by vessel stenosis) the role of rheological parameters becomes important. The observed beneficial changes in the macrorheological parameters (e.g. Hct and viscosity) presumably reduce the CV risk of ischemic heart disease patients (9, 109). Furthermore, the diameter of the narrowest capillaries in the body (3-5 μm), found in the myocardium, is appreciably less than the resting diameter of a normal red blood cell (7-8 μm), which highlights the importance of the microrheological parameters (e.g. erythrocyte aggregation and deformability). Decreased red blood cell aggregation and improved deformability support capillary flow, while the Hct/WBV ratio indicates a better oxygen-carrying capacity leads to a better oxygen supply of the myocardiocytes. Thus, our results may suggest that cardiac patients could achieve a condition of “hemorheological fitness” characterized by improved tissue perfusion, better oxygen delivery and lower vascular resistance (25) by participating in a physical training program for 24 weeks.

The found hemorheological alterations may also contribute to the better exercise tolerability proved by the treadmill test parameter MET and the treadmill time. Moreover, the multivariate linear regression analyses showed that the improvement in red blood cell deformability is an independent predictor of the positive changes in MET. It has been stated in the literature that an increase of 1 in the MET value could reduce the risk of all-cause and CV mortality by 13% and 15%, respectively (2, 63).

Of the clinical chemistry indicators, uric acid, triglyceride, hsCRP and fibrinogen underwent significant decreases during our study. Although we are aware that these biomarkers are considered to display only low specificity in a CV risk assessment and are easily influenced by common inflammatory diseases, our data suggest that regular long-term physical activity might exert a favorable effect on the inflammation status of patients with CAD. Further overproduction of proinflammatory cytokines such as IL-6 or TNF-α could be a marker of

chronic inflammation leading to provoked and accelerated atherosclerosis (72), with a higher risk of CV events and mortality (52). Our data demonstrated an almost significant decreases in IL-6 and TNF-α levels, suggesting that a longer training program might be required to achieve significant reductions in these parameters.

Interestingly, no significant change was observed in the fasting glucose, total cholesterol and LDL cholesterol levels, whereas the triglyceride and uric acid levels decreased significantly by the end of the training program.

It is well known that hypertriglyceridemia is a significant independent CV risk factor (94, 84) and a recently published metaanalysis concluded that an elevated serum uric acid level should be considered a risk factor for CV mortality (119). The significant reductions in triglyceride and uric acid levels in our study may reflect a better metabolic state caused by the regular physical activity.

Beside laboratory parameters, both overweight and obesity are associated with an elevated risk of death in CAD and of all-cause mortality (13, 114, 120). The BMI was significantly decreased by the end of the 24-week exercise training in our study.

The results of the multivariate linear regression model indicated that the positive change in functional capacity is not influenced by the reduction in BMI. Accordingly, the better physical exercise tolerance can not be explained merely by the decreases in BMI and obesity. The beneficial effects of the physical activity generally on all the measured CV risk factors, including the hemorheological factors, must also be involved.

Furthermore, CAD is often accompanied by an increased subjective feeling of fatigue (i.e. a feeling of physical tiredness and a lack of energy) and this might have a serious detrimental impact on a wide variety of everyday functions, including physical, mental and social functioning (44). Our psychological results showed a significant amelioration as concerns the FIS physical, psycho-social, and cognitive aspects, indicating an improvement in the quality of life among our ischemic heart disease patients.

Conclusions

Our study has revealed new data regarding the effects of a long-term ambulatory CR training program on stable CAD patients. Besides the anticipated improvement in functional capacity and the reduction in BMI, the regular, moderate-intensity, long-term physical activity led to favorable hemorheological changes, decreased level of inflammation and improvements in

certain metabolic parameters, such as the triglyceride and uric acid contents, suggesting that these parameters may play important part in the positive effects of regular physical activity in patients with CAD.

Acknowledgement

This study was supported by SROP-4.2.1.B-10/2/KONV-2010-000 (TAMOP 4.2.1.B).

Aspirin resistance as cardiovascular risk after kidney transplantation

Introduction

Since the first kidney transplantation in Hungary performed by Andras Nemeth in 1962 the survival of patients has significantly improved. The controlled legal background of the transplantation procedure and the development of modern surgical techniques and immunosuppressive drugs resulted in a better overall survival and life quality after kidney transplantation (KDIGO) (58, 61). The most common and life threatening post-transplant complications in the first month are the infections (e.g., bacterial infections, HCV, CMV, EBV, Herpes virus, Rhino virus, fungi and other opportunistic agents), responsible for 13% of mortality (113). While urological complications (e.g., lymphocele, ureter stenosis, vesicoureteral reflux and nephrolithiasis) mostly occur during the first couple of months (7), malignant disorders (e.g. skin, lip, lymphoproliferative, kidney, Kaposi-sarcoma, cervix, anogenital and hepatobiliary) (97) and bone diseases (e.g., hyperparathyroidism and osteodystrophy) due to calcium and phosphor imbalance (progressive calcification) (74) appear later and explain 30% of the mortality. Beyond the above mentioned disorders the main cause of mortality (35-40 %) after renal transplantation has cardiovascular origin (75).

Based on the high cardiovascular mortality of kidney transplanted patients, to follow the cardiovascular prevention guidelines of ESC (88) and AHA/ACC (34) could be highly recommended regarding the lifestyle changes and the medications used. Among others, cardiovascular prevention applies three different platelet aggregation inhibitors: a) cyclooxygenase inhibitors (acetylsalicylic acid or aspirin); b) P2Y12 ADP receptor antagonists (clopidogrel, prasugrel and ticagrelor) and c) in Asian countries, phosphodiesterase-3 inhibitor (cilostazol) (27, 30, 43).

While acetylsalicylic acid is a widely used antiplatelet agent in the primary and secondary prevention of cardio- or cerebrovascular diseases (88, 92, 95), ASA resistance could develop in certain circumstances (e.g., smoking, diabetes mellitus, hypertension, coronary artery disease, female gender, high age, low hemoglobin level, COX 1 gene polymorphism, regular non-steroid anti-inflammatory drug treatment, and kidney diseases). The exact rate of ASA resistance has not clearly been specified; between 5 and 65% have been reported previously depending on the compliance of the patients, on the geographical location and on the analyzed population (53, 86).

For examining the origin of the high cardiovascular mortality after kidney transplantation this recent study was aimed to investigate the rate of ASA resistance in a kidney transplanted population and to compare their morbidity and mortality data to a positive control population with high cardio- and cerebrovascular risk.

Methods

Patients:

255 patients of the Department of Surgery, University of Pecs were selected into our study between 03/01/2009 and 31/10/2009 to determine the rate of ASA resistance after kidney transplantation. Results were compared to a positive control group containing 346 age-matched cardio- and cerebrovascular disease patients recruited from the same time interval. The retrospective analysis of the follow-up period was continued for 3 years until 12/31/2012. Patients had taken low-dose ASA (100 mg/day) for at least 6 months prior to their enrollment then until the end of the follow-up period. ASA medication was indicated in the positive control group in accordance with the secondary prevention guidelines of the cardiovascular (ischemic heart disease, myocardial infarction) and cerebrovascular (stroke, transient ischemic attack, vertebrobasilar insufficiency) diseases.

Blood collecting:

After 12 hours fasting, blood samples were obtained from the antecubital vein of the participants into Vacutainer tubes (8.1 ml) containing sodium-citrate using minimal tourniquet and a 21-gauge Eclipse™ Blood Collection butterfly needle set.

Platelet aggregation measurement:

Platelet aggregation measurements were performed 2 hours after blood sampling. The measurements were performed according to the above mentioned methodological description (see page 11.).

Analyzes of the mortality and morbidity data:

In another part of the study morbidity and mortality data of the participants were collected with retrospective data mining using the e-MedSolution program, an integrated information

system of the patient care at the University of Pecs. For the more accurate analyses, both patient groups were divided into an ASA resistant and a non-ASA resistant subgroup.

In the case of morbidity and mortality results, data are shown as percentage and incidence (absolute number compared to total number). Differences were evaluated by using chi-square test analyses. SPSS statistical software, version 11.0.1. was used to describe the sample.

Results

The demographical analyses demonstrated no differences concerning age and gender between the renal transplantation group and the positive control group (Table 10).

	RT	PC	p	level of significance
mean age	49.5 ± 12 years	52.6 ± 11 years	0.86	NS
male	64 %	49.4 %	0.51	NS
female	36 %	50.6 %	0.36	NS

Table 10 Demographical characteristics of the patient.

Our data showed significantly higher rate of ASA resistance in the RT group (36.1%) compared to the PC group (26.9%) ($p<0.001$) (Fig. 4).

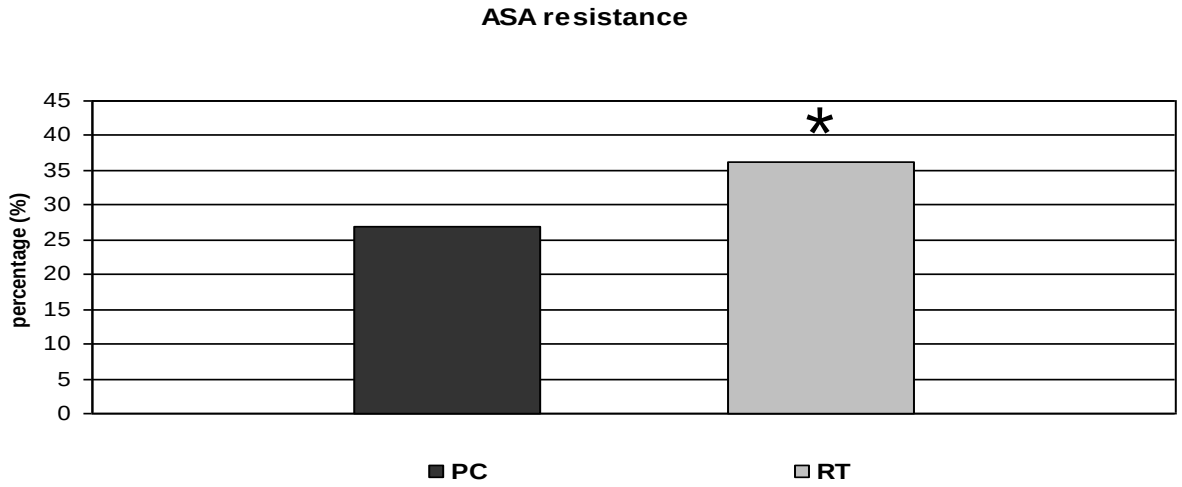

Figure 4 Significantly higher rate of ASA resistance in the RT group compared to the PC group ($p<0.001$).

The analyses demonstrated a significantly higher incidence of myocardial infarction, hypertension and diabetes mellitus ($p<0.05$) and increasing incidence in tumor appearance and all-cause mortality of the RT group compared to the PC patients at the end of the three year follow-up period (Table 11).

	RT		PC		p	level of significance
	%	cases	%	cases		
all-cause mortality	2.74	7 / 255	1.44	5 / 346	0.26	NS
myocardial infarction	4.31	11 / 255	1.16	4 / 346	0.01	S
stroke	2.74	7 / 255	2.02	7 / 346	0.56	NS
hypertension	80.39	205 / 255	69.36	240 / 346	0.02	S
diabetes mellitus	28.63	73 / 255	20.81	72 / 346	0.02	S
tumor	8.63	22 / 255	5.78	20 / 346	0.17	NS

Table 11 Morbidity and mortality results of the analyzed population

However, the subgroup analyses at finishing of the three-year long follow-up revealed significantly higher incidence of myocardial infarction and stroke in the resistant RT group compared to the RT patients without ASA resistance ($p<0.05$) (Table 12), increasing occurrence was found in connection with myocardial infarction and stroke as well as in diabetes mellitus in the resistant PC group compared to the non-resistant PC patients (Table 13).

	R-RT		NR-RT		p	level of significance
	%	cases	%	cases		
all-cause mortality	3.26	3 / 92	2.45	4 / 163	0.70	NS
myocardial infarction	5.43	5 / 92	3.68	6 / 163	0.03	S
stroke	4.34	4 / 92	1.84	3 / 163	0.02	S
hypertension	77.17	71 / 92	82.21	134 / 163	0.33	NS
diabetes mellitus	33.70	31 / 92	25.77	42 / 163	0.17	NS
tumor	8.70	8 / 92	8.59	14 / 163	0.90	NS

Table 12 Morbidity and mortality results of the renal transplanted patients regarding ASA resistance

	R-PC		NR-PC		p	level of significance
	%	cases	%	cases		
all-cause mortality	2.20	2 / 91	1.18	3 / 255	0.48	NS
myocardial infarction	2.20	2 / 91	0.78	2 / 255	0.27	NS
stroke	3.30	3 / 91	1.56	4 / 255	0.31	NS
hypertension	70.33	64 / 91	69.02	176 / 255	0.81	NS
diabetes mellitus	14.29	13 / 91	23.14	59 / 255	0.17	NS
tumor	5.49	5 / 91	5.88	15 / 255	0.89	NS

Table 13 Morbidity and mortality results of the positive control population regarding ASA resistance

Comparison of the ASA resistant subgroups at the completion of the three years follow-up demonstrated significantly higher incidence of diabetes mellitus ($p<0.05$), besides an increasing incidence was observed regarding myocardial infarction, hypertension and tumor occurrence in the renal transplantation group compared to the positive control patients (Table 14).

	R-RT		R-PC		p	level of significance
	%	cases	%	cases		
all-cause mortality	3.26	3 / 92	2.20	2 / 91	0.65	NS
myocardial infarction	5.43	5 / 92	2.20	2 / 91	0.25	NS
stroke	4.34	4 / 92	3.30	3 / 91	0.71	NS
hypertension	77.17	71 / 92	70.33	64 / 91	0.29	NS
diabetes mellitus	33.70	31 / 92	14.29	13 / 91	0.01	S
tumor	8.70	8 / 92	5.49	5 / 91	0.39	NS

Table 14 Morbidity and mortality results of the ASA resistant patients

On the other hand at the end of the follow-up period the incidence of myocardial infarction and hypertension was significantly higher in the non-resistant RT group than in the group of PC patients without ASA resistance ($p<0.05$) (Table 15).

	NR-RT		NR-PC		p	level of significance
	%	cases	%	cases		
all-cause mortality	2.45	4 / 163	1.18	3 / 255	0.32	NS
myocardial infarction	3.68	6 / 163	0.78	2 / 255	0.03	S
stroke	1.84	3 / 163	1.56	4 / 255	0.83	NS
hypertension	82.21	134 / 163	69.02	176 / 255	0.00	S
diabetes mellitus	25.77	42 / 163	23.14	59 / 255	0.54	NS
tumor	8.59	14 / 163	5.88	15 / 255	0.28	NS

Table 15 Morbidity and mortality results of the ASA non-resistant patients

Discussion

As it was mentioned before the main cause of mortality (35-40%) after kidney transplantation has cardiovascular origin (75) generated by the presence of the conventional cardiovascular risk factors of the patients as male gender, smoking, obesity and co-morbidities (e.g., diabetes, hypertension, hyperlipidemia) (88, 34) as well as the non-traditional risk factors like microalbuminuria, uremia, hyperuricemia, calcium and phosphor imbalance (calcification) and the used immunosuppressive medications (e.g., steroid, ciklosporin, tacrolimus) (58, 96, 110). Unfortunately the renal transplantation can not stop the progression of the cardiovascular status and almost half of the transplanted patients die with a functioning graft.

Recent studies have shown that the incidence of coronary heart disease is more than 15 cases per 1,000 person-years among high cardiovascular risk patients and less than 5 cases per 1,000 person-years among low risk patients (46, 98). The American Heart Association has reported that ASA treatment (i.e., 75-325 mg/day) efficiently decreases the cardio- and cerebrovascular risk around 20% in case of acute coronary syndrome or stroke (57).

However, ASA has an important role in the prevention of cardio- and cerebrovascular events; no large, randomized studies were organized to investigate the beneficial effect of low-dose ASA in kidney transplanted patients. The UK-HARP-I study examined 187 patients after kidney transplantation in connection with the effect of low-dose ASA treatment. This investigation has demonstrated that ASA therapy did not change the risk for major bleeding (8) but the risk for minor bleeding complications became 3 times higher than in the general population due to the uremia-induced platelet and endothelial dysfunction (8). Another

recently published retrospective study has described that low-dose ASA therapy is associated with better graft survival in renal transplanted patients (74). Based on the above mentioned findings the Kidney Disease Improving Global Outcomes guideline has indicated the low-dose ASA therapy after kidney transplantation and the efficiency control of the medication has also been suggested (74).

In our study we examined the cardiovascular morbidity of patients regarding ASA resistance after kidney transplantation and compared to the results of an age-matched cardio- and cerebrovascular control group (Table 10). As expected, the analysis revealed a significantly higher incidence of myocardial infarction in the RT group compared to the group of PC patients (Table 11). This elevated level of cardiovascular events may partly be explained by the significantly higher rate of ASA resistance observed among the RT patients compared to the control group (Figure 4). ASA resistance is a widely investigated phenomenon in the experimental or clinical research (86) and several factors have been revealed to play a role in its development (e.g., genetic factors, female gender, advanced age, low hemoglobin level, renal failure, diabetes mellitus and coronary artery disease) (4, 44, 68, 69, 73, 111). However, laboratory resistance refers to insufficient in vitro inhibition of platelet aggregation, it is not always coherent with clinical resistance but associated with higher risk for cardio- and cerebrovascular events (65).

Our results also demonstrated that the incidences of myocardial infarction and stroke were significantly higher in the RT group compared to the RT patients without ASA resistance. On the other hand these differences between the ASA resistant and the non-resistant subgroups of the control patients were not significant (Table 12). Prior to this study no evidence was found regarding the cardiovascular risk reduction effect of low-dose ASA treatment after kidney transplantation which seems to be more effective than in the population of cardio- and cerebrovascular patients (i.e., the ASA-induced reduction in the incidence of myocardial infarction and stroke is significantly higher in the kidney transplanted group than in the group of control patients).

The analysis revealed higher incidence of diabetes and hypertension among kidney transplanted patients showing the important role of these diseases in the development of chronic kidney failure (Table 11). Moreover, higher incidence of diabetes was observed in the RT group with ASA resistance compared to the ASA resistant control population

suggesting a predictive role of diabetes in ASA resistance after kidney transplantation (Table 14).

Although ASA resistance presumably contributes to the elevated incidence of cardio- and cerebrovascular events after kidney transplantation (Table 12), higher occurrence of myocardial infarction was found in the RT group without ASA resistance than in the non-ASA resistant cardio- and cerebrovascular patient population (Table 15). These results suggest that efficient ASA therapy could reduce the cardiovascular risk after kidney transplantation but the residual risk remains higher than in the cardio- and cerebrovascular patients emphasizing the role of other factors in the development of the high cardiovascular risk.

Conclusion

Our recent study revealed new data about the cardiovascular risk of kidney transplanted patients using low-dose ASA treatment. Authors assume that the control measurements of antiplatelet therapy after kidney transplantation would be clinically useful.

Obviously, further randomized, controlled studies with more patients and longer follow-up period are needed to describe the magnitude of the ASA resistance-induced cardiovascular risk increase, as well as the effectiveness of the available therapeutical possibilities (higher dose of ASA, conversion to clopidogrel or prasugrel in case of ASA resistance).

Orally given gastroprotective capsaicin does not modify Aspirin-induced platelet aggregation in healthy male volunteers; human phase I. clinical study

Introduction

Cardiovascular prevention applies three different platelet aggregation inhibitor agents: a) selective COX inhibitors (acetylsalicylic acid); b) P2Y12 ADP receptor antagonists (clopidogrel, prasugrel, ticagrelor, ticlopidine); c) in Asian countries, PDE-3 inhibitor (cilostazol) (27, 30, 43). ASA is an important antiplatelet agent in the primary and secondary preventive care of cardio- or cerebrovascular events (95), like stable coronary artery disease, acute coronary syndrome, stroke and peripheral artery disease (5, 37, 46, 92, 99, 115, 122).

The absorption of ASA is very fast in the stomach and upper intestine (87). According to this ASA reached the peak plasma level 30-40 minutes after oral administration, though enteric-coated tablets e.g. ASA protect (widely used in Europe) reaches peak plasma concentration in 3-4 hours after oral administration. Enteric-coated tablets have a lower bioavailability as regular ASA, as well as the newest preparations of the drug development technology (sustained-release, microencapsulated, controlled-release preparations and transdermal patch), however they have the same antiplatelet effect as regular ASA because platelets are already acetylated in the presystemic circulation (87).

But ASA has Janus-faced characteristics; on one hand it prevents cardio,- and cerebrovascular diseases, on the other hand causes gastrointestinal mucosal damages (bleedings, ulcers).

The effect of capsaicin (8-methyl-N-vanillyl-6-nonenamide) has been widely studied in the gastrointestinal tract, however the obtained results were absolutely contradictory (from the mucosal protection to the production of mucosal damage) (11, 12, 17, 77, 78, 85, 93, 107).

According to the findings of the mentioned studies capsaicin, dihydrocapsaicin, nordihydrocapsaicin and other capsaicinoids specifically modify the function of capsaicin sensitive afferent nerves (20, 54, 55, 56, 90). Szolcsányi and Barthó (1981) clearly described the beneficial and harmful effects of capsaicin in peptic ulcer disease of rats depending on the applied doses of capsaicin (104). Furthermore, Szolcsányi defined four different stages of capsaicin action depending on the dose and duration of the exposure: a) excitation (stage 1); b) sensory blocking effect (stage 2); c) long-term selective neurotoxin impairment (stage 3)

and d) irreversible cell destruction (stage 4) (105, 106). Stages 1 and 2 are reversible; meanwhile stages 3 and 4 are irreversible compound-induced actions on the capsaicin sensitive afferent nerves. These stages of capsaicin actions can be detected in the gastrointestinal tract (79) using animal experiments. After that Szolcsányi, Barthó (1981) and Holzer started a very extensive human research with capsaicin in the field of gastroenterology (20, 49. 50, 102). On the other hand studies of the past decade have shown that low doses of capsaicin can prevent the development of gastric mucosal damage caused by various NSAID-s (indomethacin) and the ethanol-induced gastric mucosal lesions resulting in microbleeding (28, 80, 82, 83, 101). The pathomechanism has not yet been described exactly, but several investigations have suggested that capsaicin activates TRPV1, which releases CGRP and substance P in the gastric mucosa. These neuropeptides enhance the GMBF via vasodilatation in the gastric mucosa leading to a more effective prevention of the gastric mucosal lesions. Moreover, capsaicin reduces the BAO. These study results promoted further human studies to find out whether capsaicin can prevent gastric mucosal lesions in humans as well.

Aims of the recent study were: a) to investigate the tolerability of capsaicin alone (in different low doses) and in co-administration with 500 mg ASA; b) to measure the pharmacokinetic parameters of capsaicin alone (administered in two low doses) and in combination with ASA (the measured kinetic parameters were capsaicin, acetylsalicylic acid and salicylic acid, as a metabolite of ASA); c) to study the ASA-induced platelet aggregation in view of ASA absorption and its metabolic rate; d) to evaluate the capsaicin action on the platelet aggregation and on the ASA-induced platelet aggregation inhibition.

The study protocol was approved by the Hungarian Institute of Pharmacy (Budapest, Hungary) and by the National Clinical Pharmacological and Ethical Committee (Budapest, Hungary) (Protocol number: 1.4.1; EudraCT: 20008-0070048-32). Before the enrollment each volunteers gave their signed informed consent.

The present scientific paper focuses on the platelet aggregation results after administration of capsaicin alone and in co-administration with ASA in healthy human subjects (under classical human phase I. circumstances) and mentions the results of the pharmacokinetic

measurements just as briefly as it is necessary for understanding the platelet aggregation results.

Methods

The administered capsaicin (Asian Herbex Ltd, Andhra Pradesh, India) was approved for oral drug administration by the Food and Drug Administration (FDA: "17856 A II 26.10.2004 Asian Herbex Ltd: Capsicum USP as manufactured in Andhra Pradesh, India). Acetylsalicylic acid (DC -90 Aspirin) was synthesized in Shandong Xinhua Pharmaceutical Co. Ltd., China. Preparation of the administered drug and the capsaicin-ASA combination was performed by PannonPharma Co. Ltd. Pécsvárad, Hungary.

Pharmacokinetic measurements of capsaicin, dihydrocapsaicin, acetylsalicylic acid and salicylic acids were carried out in PannonPharma Co. Ltd. Pécsvárad, Hungary using High Pressure Liquid Chromatographic methods.

The trial was conducted in a randomized single-blind manner in accordance with the Declaration of Helsinki (29, 81). Two weeks before the beginning of the trial, healthy male volunteers participated in a prescreening procedure (according to the accepted protocol by the Hungarian Institute of Pharmacy in Budapest, Hungary) including the registration of demographic data (age and race), body weight, height, BMI, medical history, physical examination (measurement of blood pressure, pulse and ECG), laboratory blood tests (hematology, se-Na+, se-K+, BUN, se-creatinine, se-bilirubin, blood glucose, se-cholesterol, triglycerides, ALP, GOT, GPT, GGT and LDH), urine test (protein, glucose, ubg, ketones and sediment), urine drug test and viral serology (HBsAg, Anti HCV and HIV). Exclusion criteria were any positive findings in the mentioned examinations above. According to the findings 15 healthy male volunteers were selected for the trial. Subjects were 18-55 years old and had a BMI of 18-29.9 kg/m2.

After 10 hours of fasting, an intravenous cannula was inserted into the antecubital vein of the participants, then blood was drawn for pre-dose sample and pharmacokinetic measurements, then subjects received one of the five different therapies (Table 16). Volunteers took the tablets in upright position with 150 ml of water. They had to stay in this upright position for 30 minutes and fast for 4 hours (drinking water was allowed only). All of

the participants received all of the therapies in a randomized order. Between treatments, subjects had a 6-day wash-out period.

Treatment	Number of tablets			
	400µg capsaicin	500mg ASA	ASA placebo	capsaicin placebo
400 µg capsaicin	1		1	1
800 µg capsaicin	2		1	
500 mg ASA		1		2
500 mg ASA + 400 µg capsaicin	1	1		1
500 mg ASA + 800 µg capsaicin	2	1		

Table 16 Treatment protocol.

Following the drug administration, 8.1 ml of blood was collected for platelet aggregation measurements in the 1st, 2nd, 6th and 24th hour into Vacutainer tubes containing sodium citrate.

Platelet aggregation measurement:

Platelet aggregation measurements were performed 2 hours after blood sampling. The measurements were performed according to the above mentioned methodological description (see page 11.).

Statistics:

Mean values of the ASA monotherapy in the 1st, 2nd, 6th and 24th hour samples were evaluated by paired Student's t-test after using the Kolmogorov–Smirnov test to check the normality of the data distribution. Differences of the mean values in every therapy were calculated by one-way ANOVA test, using Dunnett's post-hoc test. Test results were considered as significant at $p<0.05$. Data are shown as means±SD. SPSS statistical software, version 11.0.1. was used to conduct descriptive analyses and to describe the sample.

Results

Main findings of the platelet aggregation measurements:

Based on the results of the one-way ANOVA analysis, 400 and 800 µg of capsaicin monotherapy caused no significant differences on platelet aggregation (Fig. 5).

As expected, ASA treatment resulted in a significant and clinically effective (under 40% aggregation index) platelet aggregation inhibition compared to the ASA baseline sample ($p \leq 0.001$) (Fig. 5).

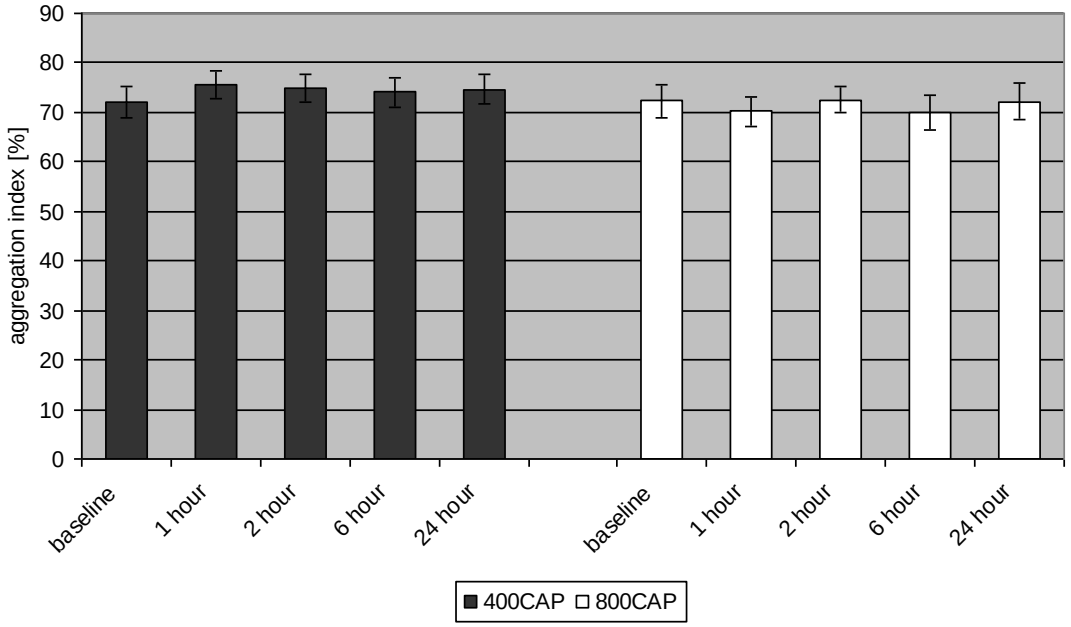

Figure 5 400 and 800 µg of capsaicin monotherapy caused no significant differences on platelet aggregation

The two different doses, 400 and 800 µg of capsaicin in combination with ASA reached an ASA monotherapy-equivalent level on platelet aggregation. No differences were observed between the ASA monotherapy and the combination treatment samples (Fig. 6).

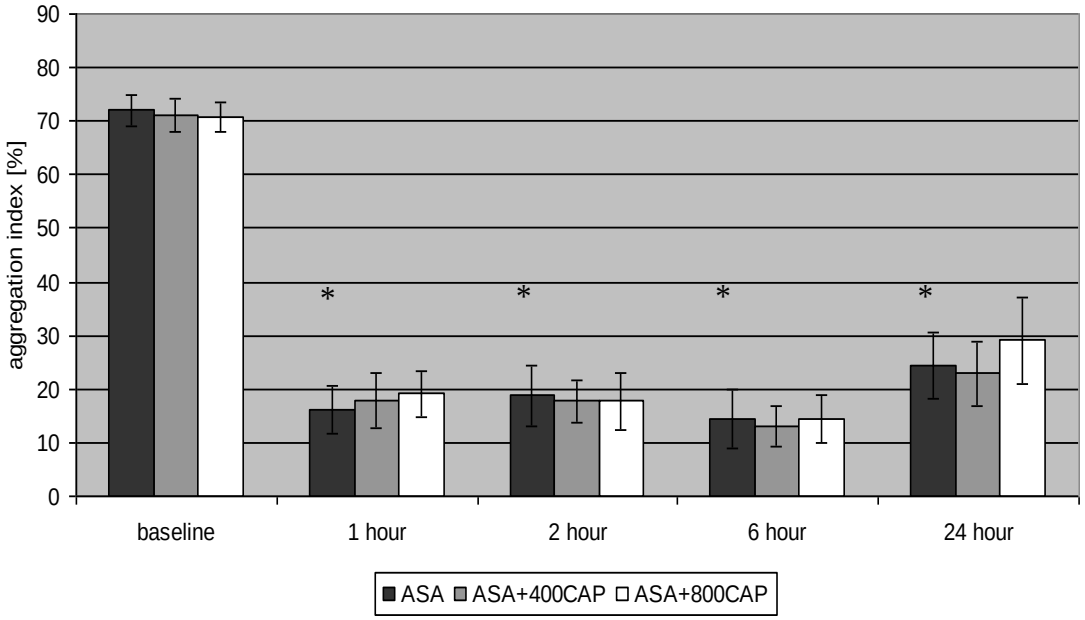

Figure 6 No differences were observed between the ASA monotherapy and the combination treatment samples

Brief summary of the pharmacokinetic measurements:

Neither capsaicin nor dihydrocapsaicin were detected in the sera at any time after administration of capsaicin alone or in combination with ASA. These observations were expected since low doses of capsaicin were chosen for administration according to the previous animal studies describing the gastroprotective dosage of capsaicin. In this study, blood samples were measured by a Liquid Chromatography – Mass Spectrometry (LC-MC) which detection limit for capsaicin is 26 femtogram/mL and for dihydrocapsaicin is 20 femtogram/mL.

When ASA therapy was administered alone, T1/2 and Tmax values (hr) were 0.559 ± 0.280 and 0.644 ± 0.294 for ASA and 2.545 ± 0.600 and 1.811 ± 0.963 for salicylic acid (mean±SD), respectively. These values did not change significantly after the ASA-capsaicin combination treatment. Cmax value (ng/mL) was 5219.20 ± 1723 for ASA and 21974 ± 3309 for salicylic acid (mean±SD) after ASA administration alone, and these values did not show significant alteration after co-administration of ASA and 400 and 800 μg capsaicin. No significant changes were observed in other pharmacokinetic parameters when ASA was given alone or in co-administration with capsaicin.

Discussion

Over the past few decades, various capsaicin-investigations have been performed in Hungary. These studies have exposed that capsaicin has a dose-dependent effect on the TRPV1 receptor. Other gastroenterological investigations with low doses ("gastroprotective") of capsaicin (ng/kg to μg/kg) in animals have resulted in reduced BAO and microbleeding caused by different NSAID-s. Elevated level of GMBF via CGRP and substance P was also observed.

Several investigations were conducted to describe the absorption and metabolism of capsaicin in the gastrointestinal tract after per os administration. Kawada et. al. in 1984 published data based on in vivo and in vitro investigations in rats and suggested that capsaicin was absorbed in the small intestine 3 hours after oral administration. After adsorption capsaicin was hydrolyzed by the epithelial cells of the jejunum (first pass effect), then transported to the mesenterial blood and finally excreted in the urine (59). Donnerer in 1990 verified previous findings and concluded form in vivo animal experiments (in rats) a rapid hepatic metabolization therefore a limited the systematic effect of enterally adsorbed capsaicin (33).

Acetylsalicylic acid has a pivotal role in the prevention of cardiovascular events due to its antiplatelet effect. On the other hand, ASA belongs to the NSAIDs and has various side effects including intracranial bleeding, other non-GI bleeding, tinnitus, dizziness, headache, impaired hearing, hypersensitivity reactions and upper gastrointestinal tract complications such as peptic ulcers, which can later become the origin of a GI bleeding or perforation (116).

High percentages (10-20%) of the ASA users observe dyspepsia, which can be caused by the ASA-reduced mucosal prostaglandin level and its acidic characteristic initiating several upper gastrointestinal tract complications (i.e. peptic ulcer, bleeding and perforation) due to the gastric mucosal injury (40, 98). UGIC can be found in the general population as only 1 case per 1000 person-years; however the fatal endpoints are 5-10% of these events (47). On the other hand UGIC can be observed among ASA-user patients as 2-3 cases per 1000 patients per year, thus the relative risk for UGIC is 3 to 5 times increased as in the ASA non-user population (40, 41). Furthermore, the risk for UGIC increases by 85% among patients who are on dual antiplatelet therapy (66).

For the prevention of UGIC several gastroprotective agents were developed and used in clinical care: a) misoprostol, which can increase the prostaglandin level in the gastric mucosa; b) proton pump inhibitors; c) histamine-2 receptor antagonists. Furthermore Szabo et al. in one recently published trial with more than 100 healthy volunteers showed the BAO decreasing effect of small doses, orally administered capsaicin (200 – 400 – 800 μg, Asian Herbex Ldt, Asdhra Pradesh, India) (101). Traditionally, Hungarian red pepper contains ca. 1500-2500 Scoville Hot Unit or more accurate 220-380 American Spice Trade Association unit pungent ingredients (capsaicinoids), which could mean 140 μg capsaicin in 1 g red pepper. According to this the used two low doses capsaicin could be detected; 400 μg in ca. 3 g and 800 μg in ca. 6 g red pepper (3).

Regarding the still limited numbers of human studies with orally given capsaicin the aim of this study was to investigate whether the pharmacokinetic and antiplatelet effect of acetylsalicylic acid could be influenced by two, low, gastroprotective doses of capsaicin. Our hypothesis was that low doses of capsaicin have no systemic but only local gastroprotective effect therefore has no influence on the pharmacokinetic and pharmacodynamic properties of ASA (absorption, concentration, antiplatelet effect, etc.).

Our study showed several important results: a) low doses of capsaicin, 400 and 800 μg had no significant effect on platelet aggregation; b) ASA reached the clinically effective inhibition of platelet aggregation (i.e., the epinephrine-induced aggregation was under 40%) within one hour (despite the rapid clearance of ASA from the circulation, the platelet-inhibitory effect lasts for the life span of the platelet because ASA irreversibly inactivates platelet COX-1 (87)); c) the combined therapies did not result in any unfavorable influences on the ASA-induced inhibition in platelet aggregation; d) the pharmacokinetic properties of ASA and ASA metabolites were not influenced by the administration of capsaicin; e) concentrations of capsaicin and the metabolites were under the detection limit in sera.

Our findings are in contrast with other recent studies describing the antiplatelet effect of capsaicin using human blood or non-human species (48, 112). Further studies have reported that capsaicin decreased the ADP-induced platelet aggregation in a dose-dependent manner via the TRPV1 receptors of platelets (1, 20, 45, 100). The observed discrepancy between these previous studies and our recent trial could be explained by the different study designs. Previously, all studies were performed in non-human species or in vitro manner, and only

one ex vivo study was performed to investigate the capsaicin-induced alterations in platelet aggregation.

Our trial aimed to use a small but still effective dose of capsaicin which could not influence the epinephrine-induced platelet aggregation but could prevent the development of gastric mucosal lesions. In our ex vivo study, the pharmacokinetic results suggest that capsaicin could not be detected in the systemic circulation. Based on these results, we suppose that low, gastroprotective doses of capsaicin do not have any systemic effect and do not influence the antiplatelet effect of ASA. According to the pharmacokinetic findings, capsaicin does not influence the absorption or any other pharmacokinetic characteristics of ASA as well. Furthermore, capsaicin could have only a local influence on the gastric mucosa and therefore could prevent the ASA induced mucosal lesions directly.

Conclusion

Since we found no significant interaction and side effects, our trial could be the first step in a new pharmaceutical development process to investigate whether capsaicin could be used together with acetylsalicylic acid in a fix combination to provide an antiplatelet drug with less GI side effects.

Acknowledgement

This study was granted in part by SROP-4.2.2.B-10/1/KONV-2010-029 (TAMOP 4.2.2./B) and by RET-08/ 2005 and by REG_DD_KFI_09 CAPSATAB.

Number of the accepted protocol is 1.4.1, EudraCT: 2008-007048-32.

Summary of the new scientific results

1) Effects of moderate aerobic exercise training on hemorheological and laboratory parameters, and on psychological functioning in ischemic heart disease patients:

1. Long-term (24 week) moderate exercise training improves hemorheological factors in patients with ischemic heart disease. Our results may suggest that cardiac patients could achieve a condition of "hemorheological fitness" characterized by improved tissue perfusion, better oxygen delivery and lower vascular resistance by participating in a physical training program for 24 weeks.

2. The multivariate linear regression analyses showed that the improvement in red blood cell deformability is an independent predictor of the positive changes in MET.

2) Aspirin resistance as cardiovascular risk after kidney transplantation:

1. The analysis revealed a significantly higher incidence of myocardial infarction in the RT group compared to the group of PC patients. This elevated level of cardiovascular events may partly be explained by the significantly higher rate of ASA resistance observed among the RT patients compared to the control group.

2. Our results also demonstrated that the incidences of myocardial infarction and stroke were significantly higher in the RT group compared to the RT patients without ASA resistance. On the other hand these differences between ASA resistant and non-resistant subgroups of the control patients were not significant. Prior to this study no evidence was found regarding the cardiovascular risk reduction effect of low-dose ASA treatment after kidney transplantation which seems to be more effective than in the population of cardio- and cerebrovascular patients.

3. Higher incidence of diabetes was observed in the RT group with ASA resistance compared to the ASA resistant control population suggesting a predictive role of diabetes in ASA resistance after kidney transplantation.

4. Our results suggest that efficient ASA therapy could reduce the cardiovascular risk after renal transplantation but the residual risk remains higher than in the cardio- and cerebrovascular patients.

3) Orally given gastroprotective capsaicin does not modify Aspirin-induced platelet aggregation in healthy male volunteers; human phase I. clinical study:

1. Low, gastroprotective doses of capsaicin monotherapy caused no significant differences on platelet aggregation in healthy male volunteers. Prior to our study no results were published about the antiplatelet effect of gastroprotective doses of capsaicin in humans.

2. Low, gastroprotective doses of capsaicin in combination with 500 mg ASA reached an ASA monotherapy-equivalent level on platelet aggregation. No differences were observed between the ASA monotherapy and the combination treatment samples. To confirm these findings, the pharmacokinetic tests showed that the pharmacokinetic properties of ASA and ASA metabolites were not influenced by the administration of capsaicin.

3. The pharmacokinetic investigations revealed that the concentrations of capsaicin and the metabolites were under the detection limit in sera. Accordingly we supposed that low, gastroprotective doses of capsaicin do not have any systemic effect and so could not influence the antiplatelet effect of ASA, the absorption or any other pharmacokinetic characteristics of ASA as well. Furthermore, capsaicin could have only a local influence on the gastric mucosa and therefore could prevent the ASA induced mucosal lesions directly.

Acknowledgement

These studies were performed at the 1st Department of Medicine, University of Pecs, School of Medicine, Pecs, Hungary.

I am grateful for the help of my program leaders, Professor Kalman Toth, Dr. Eszter Szabados and Dr. Tamas Habon for the provided support throughout my work. I am also thankful to Dr. Istvan Juricskay for his scientific and statistical information.

I am thankful to Professor Gyula Mozsik, Dr. Gabor Kesmarky, Dr. Bela Mezey, Dr. Peter Szakaly, Arpad Csatho and to Dr. Laszlo Czopf for assisting my work. I would like to express my special thank to the former and present Ph.D. students, Dr. Judit Papp, Dr. Miklos Rabai, Dr. Andras Toth, Dr. Adam Varga, Alexandra Nagy, Dr. Katalin Biro and Dr. Kinga Totsimon and to the research students, Andrea Kiss and Dora Praksch for their support.

At last but not at least, I am thankful to all the nurses and technicians for their kind help throughout the measurements, especially to Tapasztone Kornelia Fazekas, Kovacsne Szilvia Levang, Ildiko Papp and Erika Nagy.

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