Human clinical hemorheological studies in healthy subjects and in patients with coronary artery disease

PhD thesis

Author:
Andras Toth MD

Interdisciplinary Medical Sciences
Doctoral School
Molecular and cellular biochemistry
Doctoral Program

Doctoral School and Program leader:
Prof. Balazs Sumegi PhD, ScD

Project leaders:
Istvan Battyani MD, PhD
Gabor Kesmarky MD, PhD

University of Pecs, Medical School
Pecs, Hungary

2014

ABBREVIATIONS

AFRW	alcohol free red wine extract
AI	LORCA aggregation index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CHD	coronary heart disease
CT	computed tomography
CV	cardiovascular
EI	elongation index
Hct	hematocrit
HDL	high density lipoprotein
Hgb	hemoglobin
LDL	low density lipoprotein
LORCA	Laser-assisted Optical Rotational Cell Analyzer
M	Myrenne aggregation index (M mode)
M1	Myrenne aggregation index (M1 mode)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
PCI	percutaneous coronary intervention
PV	plasma viscosity
RBC	red blood cell
S.E.M	standard error of mean
t½	LORCA aggregation half time
WBV	whole blood viscosity

INTRODUCTION

The French paradox

Series of prospective epidemiological studies observed a J-shaped relationship between the relative risk of coronary heart disease (CHD) and alcohol intake: consumption of alcohol up to 2 drinks/day in women and 4 drinks/day in men is inversely associated with total and cardiovascular (CV) mortality, while higher doses of alcohol increases it.

Further studies have described that wine is more beneficial than any other forms of alcohol. According to the *Copenhagen City Heart Study*, low-to-moderate intake of wine is associated with lower mortality from cardiovascular and cerebrovascular

diseases, while similar intake of spirits increases and beer drinking does not affect mortality.

The beneficial effect is likely to depend on the type of wine. In spite of the much lower cholesterol levels in Alsace, a white wine drinking region in France, higher mortality rates were observed there, compared to the red wine drinking Mediterranean regions. Studies examining alcohol free red wine extract (AFRW) also support that red wine has additional positive effects beyond alcohol alone.

Mortality from cardiovascular diseases is much lower in France than in other Western European countries, although the consumption of saturated fats and blood cholesterol level – considered as major CV risk factors – are higher in this country. Furthermore, prevalence of other risk factors such as smoking and hypertension are similar in France as in other developed regions of Europe. According to epidemiological studies, this phenomenon, called as “French paradox”, may be caused by the moderate and regular consumption of red wine.

Clinical importance of hemorheological parameters in cardiovascular diseases

The alterations of hemorheological parameters in coronary artery disease (CAD) have been described by several prospective epidemiological studies, moreover elevated hematocrit (Hct), plasma fibrinogen level, plasma viscosity (PV) and whole blood viscosity (WBV) have been identified as primary CV risk factors.

In spite of the systemic nature of CV risk factors, atherosclerotic lesions do not occur randomly in the vascular system. These lesions tend to develop at specific locations, suggesting the importance of hemodynamic and hemorheological factors in their pathogenesis.

The coronary vessel system has the narrowest capillaries in the human vascular system, thus hemorheological alterations might have a more significant impact on myocardial perfusion compared to other organs. At normal circumstances coronary blood flow is mainly determined by hemodynamic factors, but in certain conditions, such as a pre-existing coronary stenosis, alteration of hemorheological parameters may early impair myocardial microcirculation.

AIMS

Hemorheological effects of moderate red wine consumption

Only a limited number of controlled studies have reported the medium term effects of regular red wine intake on hemorheological parameters in healthy volunteers. These experiments gave information about PV, WBV and red blood cell (RBC) deformability, but no literature data have been found about RBC aggregation. Our previous *in vitro* experiments showed that red wine, AFRW and ethanol significantly and dose dependently decrease RBC aggregation.

In our current study we aimed to confirm the *in vitro* findings and examine the effects of moderate red wine consumption on hemorheological parameters, including WBV, RBC aggregation and deformability.

Hemorheological parameters in CT-detected coronary artery disease

Previous clinical studies reported significantly elevated Hct, fibrinogen level, PV, WBV and RBC aggregation in CAD, however only a few were able to detect statistically significant differences between the various stages of CAD.

Our previous study showed significantly increased Hct, fibrinogen level, PV and WBV in CAD compared to healthy controls, moreover significant differences were found between CAD subgroups, suggesting a correlation with the severity of it.

We aimed to conduct a full scale hemorheological study on patients with CAD, including the measurement of RBC aggregation and deformability which was not carried out previously. To the best of our knowledge, all previous studies used invasive coronary X-ray angiography to evaluate for CAD. In our current study, a new and well established method, coronary CT angiography was used for the evaluation of the coronary vessel system.

HEMORHEOLOGICAL EFFECTS OF MODERATE RED WINE CONSUMPTION

Methods

Subjects

Forty healthy, non-smoking male volunteers between the ages of 18-40 were enrolled. No alcohol consumption was allowed in the first 7 days of the study. On the morning of the 8th day the subjects were assigned into 2 groups:

- In the **control group**, volunteers drank mostly water for 3 weeks, coffee and soft drinks were permitted, no alcohol consumption was allowed.
- In the **red wine group**, 2 dl of red wine was consumed each day during dinner for 3 weeks, no other forms of alcoholic beverages were allowed.

Hemorheological measurements

Venous blood samples were obtained in the mornings of the 8th and 29th days.

Hct was determined by microhematocrit centrifuge (12,000 RPM, 3 minutes). In order to completely eliminate the influence of Hct on the dependent hemorheological parameters (WBV and RBC aggregation), Hct was adjusted to 40% with autologous plasma.

PV and WBV were measured by *Hevimet 40* capillary viscometer. Plasma was obtained by centrifugation of blood samples at 2500 g for 10 minutes. Viscosity values interpolated at 90 s^{-1} shear rate were used.

Hct/WBV ratio was calculated to determine rheological oxygen carrying capacity of blood.

RBC aggregation was measured by *Myrenne* and *LORCA* aggregometers. *Myrenne aggregometer* measures the infrared light intensity passing through the blood sample. 30 µl of blood is injected between the glass cone and plate. The sample is sheared at 600 s^{-1} to disperse all pre-existing RBC aggregates, then shear rate falls to zero (in M mode) or to 3 s^{-1} (in M1 mode). As RBCs aggregate the light intensity gradually increases. The extent of aggregation was characterized by the aggregation indices (M, M1) calculated from the surface area under the light intensity curve in a 10 s period of time.

LORCA aggregometer detects the laser back-scattering generated by the RBCs. 1 ml of oxygenated blood was injected into the gap between the static inner glass cylinder and the rotating outer glass cylinder. RBCs are first disaggregated at 500 s^{-1} shear rate, then shear rate falls to zero. The intensity of back-scattering laser light is drawn in the function of time (syllectogram). Aggregation behavior of blood was characterized by the aggregation index (AI), calculated from the first 10 seconds of the syllectogram after the shape recovery period; and the time that elapses until peak intensity of back-scattering laser light is reduced by half the amplitude (t½).

RBC deformability was measured by LORCA, using the laser diffraction ellipsometry technique. 25 µl of blood was suspended in 5 ml of high viscosity polyvinylpyrrolidone solution dissolved in phosphate buffered saline. 1 ml of this suspension was injected into the gap between the two cylinders. RBCs are deformed by various shear stresses from 30 Pa to 0.3 Pa, generated by the rotation of the outer cylinder, meanwhile a laser diode is projecting through the sample. The elongated RBCs create a laser diffraction pattern, captured by a video camera and analyzed by a computer. RBC deformability was characterized by the elongation index (EI), calculated from the two radiuses of the ellipsoid diffraction pattern as (A-B)/(A+B).

Results

Red wine consumption had no effect on **Hct** and no difference was found between the two groups neither at baseline, nor after 3 weeks.

PV did not change during the 3 weeks in either group compared to baseline, and there was no significant difference between the two groups, neither at baseline, nor after 3 weeks.

Adjusted **WBV** remained constant in the control group, while in the red wine group it decreased, and after 3 weeks WBV in the red wine group became significantly lower compared to the control group ($p<0.05$).

The **Hct/WBV** ratio remained steady in the control group, while in the red wine group the parameter tended to increase: after 3 weeks, significantly higher ($p<0.05$) ratio was calculated in the red wine group compared to the control group.

Both Myrenne (M and M1) and LORCA **aggregation** indices significantly decreased ($p<0.05$) in the red wine group. LORCA t½ also indicates significantly ($p<0.05$) decreased RBC aggregation in the red wine group. Furthermore, after 3 weeks, Myrenne

M1 parameter was also significantly lower ($p<0.05$) in the red wine group compared to the control group. M1 significantly decreased ($p<0.05$) in the control group, but none of the other RBC aggregation parameters (M, AI, t½) showed a significant change.

At the highest, 30 Pa shear stress, RBC **deformability** significantly increased ($p<0.05$) in the red wine group, while it did not change in the control group.

Discussion

Several studies have demonstrated an inverse association between red wine or polyphenol intake and cardiovascular events, but not all sources of this cardioprotective effect are known. Most authors have emphasized the effect of elevated HDL level, decreased platelet aggregation and fibrinogen level, thus these were mostly examined.

Only a few controlled results are known about other important hemorheological parameters – such as PV, WBV, RBC aggregation and RBC deformability – in healthy human subjects consuming red wine. A randomized controlled study reported that moderate red wine consumption, up to 2 weeks, significantly increased HDL level, but it did not change Hct, WBV, RBC deformability and fibrinogen level. Another controlled experiment observed significantly reduced PV and fibrinogen level after 3-week moderate red wine intake. Our prospective, controlled study presents new data about the in vivo hemorheological effects of moderate red wine consumption.

Red wine consumption had no significant effect on **Hct**, confirming the results of Kaul, et al. (2010).

PV did not change significantly after 3-week red wine consumption. Although we did not measure plasma fibrinogen level (the main determinant of PV), Kaul, et al. (2010) reported no significant change after 2 weeks of red wine intake. On the other hand, lower plasma viscosity and fibrinogen level were measured after 3 weeks in a different study.

The observed reduction of **WBV** in the red wine group may result from the reduction of RBC aggregation and the increased RBC deformability. Red wine consumption increased WBV of Hct-standardized samples after 3 hours, but no difference from baseline was observed 13 hours after ingestion. This suggests that the observed reduction of WBV in our study was not due to the short-term effect of the red wine, consumed in the previous evening. Kaul, et al. (2010) found no changes after 2 weeks, but Jensen, at al. (2006) reported decreased WBV after 3 weeks. It is assumed that more time is required until the effect can be detected.

The significantly higher **Hct/WBV** ratio in the red wine group (due to unaffected Hct and lowered WBV) means greater oxygen carrying capacity of the blood.

The reduction of **RBC aggregation** was observed both by Myrenne and LORCA in the red wine group. The decrease of RBC aggregation may be a consequence of the modifications of plasma proteins. It is known that polyphenols, such as resveratrol, are bounded to plasma proteins due to their poor water solubility. The phenol-protein interactions may change the properties of plasma proteins and RBC surface molecules, therefore decreasing RBC aggregation. It has been reported that resveratrol binding to albumin or hemoglobin changes their secondary structures. The reported fibrinogen lowering effect of red wine may also be a reason of the observed decrease in RBC aggregation.

RBC deformability in our earlier in vitro study, no significant changes were observed after direct addition of red wine or AFRW to the blood samples. It was assumed that under no significant oxidative stress, RBC of healthy humans has optimal deformability; therefore no further improvement could be expected. On the other hand, RBC deformability even of healthy volunteers could be improved with moderate red wine consumption. Contrarily, another study reported no significant changes in RBC deformability after 2 weeks of red wine consumption. It is possible again, that more time is required till the changes become significant.

Conclusions

This *in vivo* study confirmed our previous *in vitro* findings about the beneficial hemorheological effects of red wine on RBC aggregation. Decreased WBV, RBC aggregation, higher calculated oxygen carrying capacity and increased RBC deformability may positively affect microcirculation. These findings may take part in the cardiovascular protection of moderate red wine consumption.

HEMORHEOLOGICAL PARAMETERS IN CT-DETECTED CORONARY ARTERY DISEASE

Methods

Patients

130 patients, admitted to coronary CT angiography at the *Department of Radiology, University of Pecs Medical School*, participated in the study. Patients were classified into four groups based on their coronary vessel state:

Negative	no coronary stenosis or atherosclerotic lesion **and** zero calcium-score
Non-significant	below 40% area stenosis on one or more coronary vessels **and** no PCI or CABG
Single-vessel	1. over 40% area stenosis on <u>one</u> coronary vessel **or** 2. history of PCI or CABG on <u>one</u> coronary vessel
Multi-vessel	1. over 40% area stenosis on <u>multiple</u> coronary vessels **or** 2. over 40% area stenosis on <u>one</u> coronary vessel **and** history of PCI or CABG on <u>one</u> coronary vessel **or** 3. history of PCI or CABG on <u>multiple</u> coronary vessels

Coronary computed tomography angiography

Coronary CT angiography examinations were performed at the *Department of Radiology, University of Pecs Medical School* with a first generation 64-slice, dual source *Siemens Somatom Definition* CT device.

Prior to the examinations no food or caffeine containing fluid consumption was allowed for 4 hours. Sublingual nitrate was given to all patients and depending on the resting heart rate, intravenous beta-blocker was administered. First a native scan was carried out to estimate total coronary calcification. After that a contrast enhanced scan was performed to evaluate coronary system. Coronary calcification was characterized by Agatson-score; lesions were defined as area of stenosis.

Hemorheological measurements

Blood samples were obtained via a peripheral vein, just before the coronary CT examinations. The instruments and measurement protocols used in this study are identical to the ones in the previous work, therefore only the differences will be detailed here:

- RBC aggregation was determined by Myrenne aggregometer. Both native samples and suspensions of RBCs, adjusted to 40% Hct with autologous plasma, were measured.

Central laboratory measurements

Additionally, the following parameters were measured: Hgb concentration, RBC count, MCV, MCH, MCHC, LDL, HDL and fibrinogen level.

Results

Hct increases in a *Negative*<*Non-significant*<*Single-vessel*<*Multi-vessel* manner. In the *Non-significant*, *Single-vessel* and *Multi-vessel* groups Hct is significantly higher compared to the *Negative* group.

No significant difference was found in **PV**. **WBV** shows the following rank order: *Negative*<*Non-significant*<*Single-vessel*<*Multi-vessel*. WBV in the *Multi-vessel* group is significantly higher compared to the *Negative* group.

In native samples, both M and M1 **aggregation** parameters increase in a *Negative*<*Non-significant*<*Single-vessel*<*Multi-vessel* manner. The M parameter is significantly higher in the *Multi-vessel* group compared to the *Negative* group.

In case of adjusted samples, the M and M1 parameters show the similar trend. Both indices are significantly higher in the *Multi-vessel* group compared to the *Negative* group, moreover the M parameter is significantly higher in the *Multi-vessel* group compared to the *Non-significant* group.

RBC **deformability** shows a decreasing trend at all shear stresses. EI at 30 and 16.87 Pa was significantly lower in the *Non-significant* group compared to the *Negative* group.

RBC count, Hbg concentration, MCV, MCH, and MCHC have the same rank order: *Negative*<*Non-significant*<*Single-vessel*<*Multi-vessel*. In the *Multi-vessel* group all parameters are significantly higher compared to the *Negative* group. **LDL** levels are

similar in all groups. **HDL** has a decreasing trend and it is significantly lower in the *Multi-vessel* group compared to all the other ones. **Fibrinogen** level has an increasing tendency in the *CAD* subgroups, although no significant difference was found.

Discussion

Hct was significantly higher in the *CAD* subgroups compared to the patients with no vessel disease which result is similar to the findings of our earlier study. However, we were not able to detect significant differences between *CAD* subgroups, although the increasing tendency is well visible. Elevated Hct has also been reported by Lowe, et al. (1980) and Rainer, et al. (1987). On the other hand Pfafferott, et al. (1999) did not find significant difference between healthy controls, patients with stable/unstable angina and acute myocardial infarct, but the epidemiological studies strongly support our findings.

Our study found similar **PV** levels in all groups, supporting the findings of Lowe, et al. (1980). On the other hand, our earlier study, Rainer, et al. (1987), Pfafferott, et al. (1999) and Lee, et al. (2008) found significantly elevated PV in CAD.

No significant difference was found in **fibrinogen** level, although an increasing trend is evident in the *CAD* subgroups. Lowe, et al. (1980) reported similar plasma fibrinogen levels in CAD compared to healthy controls, while Kesmarky, et al. (1998) and Rainer, et al. (1987) observed a significant increase.

WBV was significantly elevated in the most severe vessel state, confirming our previous result. This result is supported by the findings of Lowe, et al. (1980), Rainer, et al. (1987) and Lee, et al. (2008). Kesmarky, et al. (1998) and Lee, et al. (2008) reported statistically significant differences between *CAD* subgroups, while Vosseler, et al. (2012) found no significant difference between CAD and healthy controls.

RBC aggregation was significantly increased in *CAD* and significant difference was found between the subgroups. Rainer, et al. (1987), Pfafferott, et al. (1999) and Lee, et al. (2008) confirm our results.

RBC deformability has a decreasing trend, being significantly lower in non-significant vessel disease compared to patients with no vessel disease. Pfafferott, et al. (1999) reported no significant difference in RBC filterability.

RBC count, Hgb concentration, MCV, MCH and MCHC were significantly increased in severe CAD. Increase of RBC count and MCV explains the same elevating trend of Hct. Increased Hgb concentration may be a counter mechanism against stenosis-caused low flow rate, in order to maintain oxygen delivery. In case of increased MCV, RBCs may require higher force to enter and to pass through the capillaries. Elevated MCH and MCHC may increase intracellular viscosity, which can decrease RBC deformability.

LDL levels were similar in each group. Though LDL is a CV risk factor and expected to be elevated in CAD patients, the much higher use of statins in *CAD* groups counteracts. The decreasing **HDL** levels were also expected in CAD.

Study limitations

This is a cross-sectional study; therefore inference on the relationship between the measured variables may be speculative. According to the latest American and European

guidelines, coronary CT is indicated in medium pre-test probability of CAD, while coronary X-ray angiography is performed on high risk patients. In our study, this resulted in a lower number of patients with severe CAD compared to our previous study where 65% of the patient had multi-vessel disease. Due to these guidelines, much fewer multi-vessel CAD cases were expected therefore 40% area stenosis was chosen as a cut-off-point. Another important difference between our studies is the "distance" between control and severely ill groups. We did not have healthy controls, and the most severe cases are likely to be less severe compared to our earlier study. As a consequence, the differences in severity of CAD between the groups are lesser and significant differences are harder to be observed.

Conclusions

Our results indicate that both macro- and microrheological parameters are altered in CAD, therefore myocardial oxygen supply may be reduced at both macro- and microcirculatory levels, and may play a pathophysiological role in the deterioration of this disease.

SUMMARY OF NEW SCIENTIFIC RESULTS

Hemorheological effects of moderate red wine consumption

Our controlled study demonstrated beneficial effects of 3-week moderate red wine consumption on hemorheological parameters in healthy volunteers:

1. Three-week red wine intake decreases whole blood viscosity in healthy subject.
2. As a consequence, red wine consumption elevates hematocrit per whole blood viscosity ratio, suggesting improved oxygen transport efficiency of blood even in healthy volunteers.
3. Moderate drinking of red wine lowers red blood cell aggregation.
4. Moderate consumption of red wine improves red blood cell deformability.

Hemorheological parameters in CT-detected coronary artery disease

Our study revealed that hemorheological parameters are altered in CT-detected coronary artery disease:

1. Hematocrit is higher in patients with coronary artery disease. The increase was already significant in the least severe group.
2. Whole blood viscosity is elevated in patients with severe coronary artery disease.
3. Red blood cell aggregation is increased in severe coronary artery disease.
4. Red blood cell deformability is lower in patients with coronary artery disease.

5. These findings support that in CT-detected coronary artery disease beyond the impaired hemodynamic factors (stenosis), hemorheological parameters are also negatively affected.

ACKNOWLEDGEMENTS

I would like to express my greatest gratitude to my program leader, Professor Balazs Sumegi for his great support throughout my PhD studies. I am grateful for the continuous help and ideas of my project leaders, Dr. Istvan Battyani and Dr. Gabor Kesmarky.

I am thankful to Prof. Dr. Kalman Toth, Dr. Istvan Juricskay, Dr. Laszlo Czopf, Dr. Zsolt Marton and Dr. Peter Kenyeres for assisting my work with useful ideas. I would like to express my special thanks to the present and former Ph.D. students, Dr. Barbara Sandor, Dr. Miklos Rabai and to our technician Kornelia Tapasztone Fazekas for the evening shifts. Moreover, I thank Dr. Judit Papp, Dr. Katalin Biro, Dr. Kinga Totsimon and to the student researchers and the other colleagues for their support and for the friendly lab community.

I am greatly thankful to Dr. Sandor Szukits, Dr. Edit Varady and the assistants and technicians at the Department of Radiology for the friendly atmosphere and for the continuous assistance.

The first study was supported by SROP-4.2.1.B-10/2/KONV-2010-0002 (TAMOP 4.2.1.B).

PUBLICATIONS OF THE AUTHOR

Papers from the topics

1. RÁBAI M., TÓTH A., KENYERES P., MÁRK L., MÁRTON Z., JURICSKAY I., SÜMEGI B., TÓTH K. Vörösbor és alkoholmentes vörösborkivonat kedvező in vitro haemorheologiai hatásai. *Érbetegségek*, 2 (2009), 45-52.
2. RABAI M., TOTH A., KENYERES P., MARK L., MARTON Z., JURICSKAY I., TOTH K., CZOPF L. In vitro hemorheological effects of red wine and alcohol-free red wine extract. *Clin Hemorheol Microcirc*, 44 (2010), 227-236.
3. TOTH A., SANDOR B., PAPP J., RABAI M., BOTOR D., HORVATH Z., KENYERES P., JURICSKAY I., TOTH K., CZOPF L. Moderate red wine consumption improves hemorheological parameters in healthy volunteers. *Clin Hemorheol Microcirc*, 56 (2014), 13-23.
4. TOTH A., PAPP J., RABAI M., KENYERES P., MARTON Z., KESMARKY G., JURICSKAY I., MEISELMAN H.J., TOTH K. The role of hemorheological factors in cardiovascular medicine. *Clin Hemorheol Microcirc*, 56 (2014), 197-204.
5. TOTH A., SZUKITS S., VARADY E., SANDOR B., RABAI M., PAPP J., JURICSKAY I., KESMARKY G., TOTH K., SUMEGI B., BATTYANI I. Hemorheological parameters in coronary artery disease detected by multi-slice CT. *Korea-Aust Rheol J*, 26 (2014), 229-235.

Other papers

6. VEKASI J., KOLTAI K., GAAL V., TOTH A., JURICSKAY I., KESMARKY G. The effect of aspirin on hemorheological parameters of patients with diabetic retinopathy. *Clin Hemorheol Microcirc*, 39 (2008), 385-389.
7. KENYERES P., RABAI M., TOTH A., KESMARKY G., MARTON Z., TOTH K. Reviewing data reduction methods for ektacytometry. *Clin Hemorheol Microcirc*, 47 (2011), 143-150.
8. PAPP J., TOTH A., SANDOR B., KISS R., RABAI M., KENYERES P., JURICSKAY I., KESMARKY G., SZABADOS S., TOTH K. The influence of on-pump and off-pump coronary artery bypass grafting on hemorheological parameters. *Clin Hemorheol Microcirc*, 49 (2011), 331–346.
9. PAPP J., BÓTOR D., SÁNDOR B., TÓTH A., BIRÓ K., CSERNUS Z., TÓTH K., KÉSMÁRKY G. A Raynaud-jelenség hemoreológiai vonatkozásai. *Érbetegségek*, 20 (2013), 33-39.
10. PAPP J., SANDOR B., VAMOS Z., BOTOR D., TOTH A., RABAI M., KENYERES P., CSEPLO P., JURICSKAY I., MEZOSI E., KOLLER A., TOTH K. Antiplatelet effect of acetylsalicylic acid, metamizole and their combination - in vitro and in vivo comparisons. *Clin Hemorheol Microcirc*, 65 (2014), 1-12.

11. BIRO K., SANDOR B., TOTH A., KOLTAI K., PAPP J., RABAI M., TOTH K., KESMARKY G. In vitro hemorheological effects of parenteral agents used in peripheral arterial diseases. *Korea-Aust Rheol J*, 26 (2014), 243-247.

12. SANDOR B., VARGA A., RABAI M., TOTH A., PAPP J., TOTH K., SZAKALY P. Aspirin resistance as cardiovascular risk after kidney transplantation. *Korea-Aust Rheol J*, 26 (2014), 237-241.

Published abstracts

1. RÁBAI M., KENYERES P., TÓTH A., KÉSMÁRKY G., MÁRTON Z., TÓTH K. Lehetőségek ektacitometriás eredmények egyszerűsítésére, korrekciójára és összehasonlítására. *A Magyar Haemorheologiai Társaság XVII., a Magyar Mikrocirkulációs és Vaszkuláris Biológiai Társaság, illetve a Magyar Szabadgyökkutató Társaság I. Közös Kongresszusa*, 2008. március 18-19., Balatonkenese. *Érbetegségek*, 15 (2008), 21.

2. RÁBAI M., TÓTH A. Lehetőségek ektacitometriás eredmények egyszerűsítésére, korrekciójára és összehasonlítására. *PTE ÁOK Tudományos Diákköri Konferencia 2008*, 2008. április 3-5., Pécs. *Absztraktok*, 155.

3. KENYERES P., RABAI M., TOTH A., KESMARKY G., MARTON Z., TOTH K. Methods to simplify, correct and compare ektacytometric results. *13th International Congress of Biorheology and 6th International Conference on Clinical Hemorheology*, 9-13 July 2008, State College, USA. *Biorheol*, 45 (2008), 138.

4. RABAI M., TOTH A., KENYERES P., MARTON Z., KESMARKY G., TOTH K. Rheological benefit of red wine and its alcohol free extract. *13th International Congress of Biorheology and 6th International Conference on Clinical Hemorheology*, 9-13 July 2008, State College, USA. *Biorheol*, 45 (2008), 147.

5. TOTH K., KESMARKY G., MARTON Z., JURICSKAY I., TOTH A., ALEXY T., MEISELMAN H.J. Hemorheological parameters in acute and stable forms of coronary heart disease. *13th International Congress of Biorheology and 6th International Conference on Clinical Hemorheology*, 9-13 July 2008, State College, USA. *Biorheol*, 45 (2008), 47.

6. KENYERES P., RABAI M., TOTH A., KESMARKY G., TOTH K. The impact of in vitro aging on erythrocyte aggregation. *25th Conference of the European Society for Microcirculation*, 26-29 August 2008, Budapest, Hungary. *J Vasc Res*, 45 (2008), 105.

7. KENYERES P., RÁBAI M., TÓTH A., KÉSMÁRKY G., BOGÁR L., TÓTH K. Egy új megközelítés az optimális hematokrit értelmezésében akut koronária szindrómás betegek adatai alapján. *A Magyar Kardiológusok Társasága 2009. évi Tudományos Kongresszusa*, 2009. május 6-9., Balatonfüred. *Card Hung,* 39 Suppl. A (2009), A66.

8. RÁBAI M., PÁLFI A., BARTHA É., KENYERES P., TÓTH A., MAGYAR K., SÜMEGI B., TÓTH K. Vörösbor és alkoholmentes vörösborkivonat protektív hatásai állatkísérletes és in vitro hemoreológiai modellekben. *A Magyar Kardiológusok Társasága 2009. évi Tudományos Kongresszusa*, 2009. május 6-9., Balatonfüred. *Card Hung,* 39 Suppl. A (2009), A74.

9. KENYERES P., RÁBAI M., TÓTH A., TÓTH K. Új módszer a hematokrit - vérviszkozitás arány, és a virtuális optimális hematokrit meghatározására. *6. Magyar Mikrokeringés Kongresszus*, 2009. május 22-23, Balatonkenese. *Érbetegségek*, 2 (2009), 59.

10. KENYERES P., RABAI M., TOTH A., TOTH K. New method to determine hematocrit to blood viscosity ratio and virtual optimal hematocrit. *15th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 28 June - 1 July 2009, Pontresina/St. Moritz, Switzerland. *Clin Hemorheol Microcirc*, 42 (2009), 191.

11. RABAI M., KENYERES P., TOTH A., PALFI A., BARTHA E., MAGYAR K., SUMEGI B., TOTH K. In vitro hemorheological and cardioprotective effects of red wine and alcohol free red wine extract. *15th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 28 June - 1 July 2009, Pontresina/St. Moritz, Switzerland. *Clin Hemorheol Microcirc*, 42 (2009), 191-192.

12. SÁNDOR B., TÓTH A. A hiperhomociszteinémia hatása a vér reológiai paramétereire. *XVII. Tudományos Diákköri Konferencia*, 2010. március 18-21., Marosvásárhely. *Orvosi és Gyógyszerészeti Szemle*, 56 Suppl. 1 (2010), 12.

13. SÁNDOR B., TÓTH A. Hemoreológiai vizsgálatok hiperhomociszteinémiás patkány modellen. *PTE ÁOK Tudományos Diákköri Konferencia 2010*, 2010. április 15-17., Pécs. *Absztraktok*, 166.

14. TÓTH A. A vörösbor és alkoholmentes vörösbor kivonat hatásának vizsgálata in vitro hemoreológiai modellen. *PTE ÁOK Tudományos Diákköri Konferencia 2010*, 2010. április 15-17., Pécs. *Absztraktok*, 194.

15. SÁNDOR B., TÓTH A. A hemoreológia és a hyperhomociszteinémia összefüggéseinek vizsgálata. *XV. Korányi Frigyes Tudományos Fórum*, 2010. április 29-30., Budapest. *Absztraktok*, 118.

16. PAPP J., SANDOR B., TOTH A., RABAI M., VAMOS Z., KENYERES P., KOLLER A., TOTH K. Effects of Hyperhomocysteinemia on Various Hemorheological Parameters. *2nd International Symposium on Hypertension*, 18-21 November 2010, Osijek, Croatia. *Kidney Blood Press Res*, 35 (2010), 428.

17. PAPP J., TÓTH A., SÁNDOR B., KISS R., RÁBAI M., KENYERES P., SZABADOS S., TÓTH K. On-pump és off-pump technikával végzett koszorúér bypass műtétek (CABG) hemoreológiai összehasonlítása. *A Magyar Kardiológusok Társasága 2010. évi Tudományos Kongresszusa*, 2010. május 5-8., Balatonfüred. *Card Hung*, 40 Suppl. G (2010), G89.

18. SÁNDOR B., PAPP J., TÓTH A., RÁBAI M., KENYERES P., KOLLER Á., TÓTH K. Hiperhomociszteinémia hatása a vér reológiai paramétereire. A Magyar Kardiológusok Társasága 2010. évi Tudományos Kongresszusa, 2010. május 5-8., Balatonfüred. *Card Hung*, 40 Suppl. G (2010), G69.

19. PAPP J., TÓTH A., SÁNDOR B., KISS R., RÁBAI M., KENYERES P., SZABADOS S., TÓTH K. Különböző technikákkal végzett koszorúér bypass műtétek (CABG) hemoreológiai összehasonlítása. *XVII. Magyar Klinikai Hemoreológiai Kongresszus, a Magyar Haemorheologiai Társaság, a Magyar Mikorcirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság II. közös kongresszusa*, 2010. június 25-26. Pécs. *Absztraktok*, 25.

20. SÁNDOR B., PAPP J., TÓTH A., RÁBAI M., KENYERES P., KOLLER Á., TÓTH K. Hemoreológiai vizsgálatok hiperhomociszteinémiás patkány modellen. *XVII. Magyar Klinikai Hemoreológiai Kongresszus, a Magyar Haemorheologiai Társaság, a Magyar Mikorcirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság II. közös kongresszusa*, 2010. június 25-26. Pécs. *Absztraktok,* 18.

21. PAPP J., TOTH A., SANDOR B., KISS R., RABAI M., KENYERES P., SZABADOS S., TOTH K. The influence of on-pump and off-pump coronary artery bypass grafting (CABG) on hemorheological parameters. *18th International Meeting of the Alpe-Adria Association of Cardiology*, 16-18 September 2010, Vienna, Austria. *J Kardiol*, 17 Suppl. A (2010), 19-20.

22. TÓTH A., SÁNDOR B. On-pump és off-pump technikákkal végzett koszorúér bypass műtétek (CABG) hatása a hemoreológiai paraméterekre. *PTE ÁOK Tudományos Diákköri Konferencia 2011*, 2011. február 17-18., Pécs. *Absztraktok*, 144.

23. KENYERES P., PAPP J., TÓTH A., RÁBAI M., FEHÉR G., KOLTAI K., KÉSMÁRKY G., TÓTH K. Szinergizmus és kereszthatás az acetilszalicilsavval és tienopiridin származékokkal elérhető thrombocyta aggregáció gátlás esetében. *7. Magyar Mikrokeringés Kongresszus*, 2011. április 1-2., Dobogókő. *Érbetegségek*, 18 Suppl. 1 (2011), 13.

24. PAPP J., TÓTH A., SÁNDOR B., RÁBAI M., KENYERES P., KISS R., SZABADOS S., TÓTH K. On-pump és off-pump technikával végzett koszorúér bypass műtétek (CABG) hatása a hemoreológiai és vérzési-transzfúziós paraméterekre. *7. Magyar Mikrokeringés Kongresszus*, 2011. április 1-2., Dobogókő. *Érbetegségek*, 18 Suppl. 1 (2011), 20-21.

25. KENYERES P., TÓTH A., KOLTAI K., FEHÉR G., PAPP J., RÁBAI M., TÓTH K. Acetilszalicilsav és tienopiridinek trombocitaaggregáció gátlásának szinergizmusa. *A Magyar Kardiológusok Társasága 2011. évi Tudományos Kongresszusa*, 2011. május 1-14., Balatonfüred. *Card Hung*, 41 Suppl. F (2011), F33.

26. PAPP J., TÓTH A., KISS R., SÁNDOR B., RÁBAI M., KENYERES P., SZABADOS S., TÓTH K. Különböző technikákkal végzett koszorúér bypass műtétek (CABG) hatása a hemoreológiai és vérzési-transzfúziós paraméterekre. *A Magyar Kardiológusok Társasága 2011. évi Tudományos Kongresszusa*, 2011. május 1-14., Balatonfüred. *Card Hung*, 41 Suppl. F (2011), F47-F48.

27. PAPP J., VÁMOS Z., SÁNDOR B., TÓTH A., RÁBAI M., KENYERES P., CSÉPLŐ P., KOLLER Á., TÓTH K. Acetilszalicilsav és metamizol trombocita aggregáció gátló hatásának in vitro összehasonlítása egészséges önkéntesek vérmintáin. *FAMÉ*, 2011. június 8-11., Pécs. *Acta Phys,* 202 Suppl. 684 (2011), 91-92.

28. PAPP J., TOTH A., SANDOR B., RABAI M., KISS R., TOTH K. The influence of various coronary artery bypass grafting (CABG) methods on hemorheological parameters. *16th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 18-21 June 2011, Munich, Germany. *Abstract book*, 96.

29. TOTH A., RABAI M., KENYERES P., MEISELMAN H.J., TOTH K. In vitro hemorheological effects of red wine, alcohol free red wine extract and alcohol. *16th World Congress on Heart Disease*, 23-26 July 2011, Vancouver, BC, Canada. *J Heart Dis*, 8 (2011), 10.

30. KENYERES P., PAPP J., TOTH A., RABAI M., FEHER G., KOLTAI K., TOTH K. Synergic antiplatelet effect of acetylsalicylic acid and thienopyridines. *19th International Meeting of the Alpe-Adria Association of Cardiology*, 15-17 September 2011, Budapest, Hungary. *Interventional Medicine & Applied Science*s, 3 (2011), 148.

31. TÓTH A. Vörösbor, alkohol és alkoholmentes vörösbor kivonat in vitro hemoreológiai hatásának vizsgálata. *PTE ÁOK TDK Miniszimpózium*, 2011 november 24., Pécs. *Absztraktok*, 7.

32. TÓTH A., BÓTOR D., HORVÁTH Z. A vörösbor fogyasztás hatása a hemoreológiai paraméterekre egészséges önkénteseken. *PTE ÁOK Tudományos Diákköri Konferencia 2012*, 2012. április 17-18., Pécs. *Absztraktok*, 118.

33. BÓTOR D., PAPP J., HORVÁTH Z., TÓTH A, SÁNDOR B, RÁBAI M, CSERNUS Z, SZABÓ Z, TÓTH K, KÉRMÁRKY G. Raynaud-kór: Az életet megkeserítő betegség hemoreológia vonatkozásai. *A Magyar Haemorheologiai Társaság, a Magyar Mikorcirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság III. közös kongresszusa*, 2012. április 27-28., Balatonkenese. *Programfüzet*, 29.

34. PAPP J., SANDOR B., TOTH A., HORVATH Z., BOTOR D., RABAI M., KENYERES P., JURICSKAY I., VAMOS Z., CSEPLO P., KOLLER A., TOTH K. In vitro and vivo comparison of platelet aggregation inhibitory effect of acetylsalicic acid, metamizole and their combination. *A Magyar Haemorheologiai Társaság, a Magyar Mikorcirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság III. közös kongresszusa*, 2012. április 27-28., Balatonkenese. *Programfüzet*, 19.

35. TOTH A., SANDOR B., PAPP J., BOTOR D., HORVATH Z., RABAI M., KENYERES P., JURICSKAY I., TOTH K. Red wine and hemorheology: complex results of in vivo and in vitro studies in healthy volunteers. *A Magyar Haemorheologiai Társaság, a Magyar Mikorcirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság III. közös kongresszusa*, 2012. április 27-28., Balatonkenese. *Programfüzet*, 22.

36. PAPP J., KOLTAI K., TÓTH A., BÓTOR D., SÁNDOR B., RÁBAI M., CSERNUS Z., TÓTH K., KÉSMÁRKY G. Hemoreológiai tényezők szerepe perifériás vazospasztikus kórképekben. *A Magyar Kardiológusok Társasága 2012. évi Tudományos Kongresszusa*, 2012. május 9-12., Balatonfüred. *Card Hung*, 42 Suppl. A (2012), A2.

37. TOTH A., SANDOR B., PAPP J., BOTOR D., HORVATH Z., RABAI M., KENYERES P., JURICSKAY I., TOTH K. Red wine and hemorheology: complex results of in vitro and in vivo studies in healthy volunteers. *14th International Congress of Biorheology and 7th International Conference of Clinical Hemorheology*, 4-7 July 2012, Koc University, Istanbul, Turkey. *Biorheol*, 49 (2012), 109.

38. PAPP J., SANDOR B., TOTH A., HORVATH Z., BOTOR D., RABAI M., KENYERES P., JURICSKAY I., VAMOS Z., CSEPLO P., KOLLER A., TOTH K. In vitro and in vivo comparison of platelet aggregation inhibitory effect of acetylsalicylic acid, metamizole and their combination. *14th International Congress of Biorheology and 7th International Conference of Clinical Hemorheology*, 4-7 July 2012, Koc University, Istanbul, Turkey. *Biorheol*, 49 (2012), 110.

39. KESMARKY G., PAPP J., KOLTAI K., TOTH A., BOTOR D., SANDOR B., RABAI M., CSERNUS Z., TOTH K. Raynaud's disease: haemorheological characteristics. *14th International Congress of Biorheology and 7th International Conference of Clinical Hemorheology*, 4-7 July 2012, Koc University, Istanbul, Turkey. *Biorheol*, 49 (2012), 131.

40. KÉRMÁRKY G., BÍRÓ K., SÁNDOR B., PAPP J., TÓTH A., KOLTAI K. A perifériás ütőérbetegség ellátása a bizonyítékok fényében. *A Magyar Haemorheologiai Társaság 20. Kongresszusa*. 2013. július 8., Pécs. *Érbetegségek*, 20 (2013), 31-32.

41. TÓTH A., SANDOR B., PAPP J., BÓTOR D., RÁBAI M., KENYERES P., JURICSKAY I., TÓTH K. A vörösbor fogyasztás hatása a hemoreológiai paraméterekre egészséges önkénteseken. *A Magyar Kardiológusok Társasága 2013. évi Tudományos Kongresszusa*, 2013. május 8-11., Balatonfüred. *Card Hung*, 43 Suppl. B (2012), B46.

42. PAPP J., SÁNDOR B., TÓTH A., BÓTOR D., RÁBAI M., KENYERES P., VÁMOS Z., KOLLER Á., TÓTH K. Trombocitaaggregáció-gátlás metamizollal, acetilszalicilsavval és kombinációjukkal: in vitro és in vivo összehasonlítás. *A Magyar Kardiológusok Társasága 2013. évi Tudományos Kongresszusa*, 2013. május 8-11., Balatonfüred. *Card Hung*, 43 Suppl. B (2012), B115.

43. SÁNDOR B., TÓTH A., PAPP J., RÁBAI M., JURICSKAY I., MEZEY B., TÓTH K., SZABADOS E. Fizikai tréning hatása a hemoreológia paraméterekre ambuláns kardiológiai rehabilitációban résztvevő iszkémiás szívbetegeknél. *A Magyar Kardiológusok Társasága 2013. évi Tudományos Kongresszusa*, 2013. május 8-11., Balatonfüred. *Card Hung*, 43 Suppl. B (2012), B52.

44. SÁNDOR B., TÓTH A., MEZEY B., PAPP J., RÁBAI M., JURICSKAY I., TÓTH K., SZABADOS E. Fizikai tréning hatása az ambuláns kardiológiai rehabilitációban résztvevő iszkémiás szívbetegekben. *A Magyar Élettani, Farmakológiai és Mikrocirkulációs Társaságok 2013. évi közös Tudományos Kongresszusa*. 2013. június 5-6., Budapest, *Absztraktok*, A-0013.

45. TOTH A., TOTSIMON K., SZUKITS S., VARADY E., SANDOR B., BOTOR D., VRYZAS N., PAPP J., RABAI M., KENYERES P., JURICSKAY I., KESMARKY G., BATTYANI I., SUMEGI B., TOTH K. Hemorheological parameters in ischemic heart disease. *17th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 6-9 July 2013, Pecs, Hungary. *Clin Hemorheol Microcirc*, 52 (2013), 178.

46. SANDOR B., TOTH A., MEZEY B., RABAI M., PAPP J., JURICSKAY I., TOTH K., SZABADOS E. Effect of physical activity in ischemic heart disease patients participating in a cardiological ambulatory rehabilitation program. *17th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 6-9 July 2013, Pecs, Hungary. *Clin Hemorheol Microcirc*, 52 (2013), 178-179.

47. SANDOR B., BIRO K., TOTH A., JURICSKAY I., VARGA A., RABAI M., PAPP J., TOTH K., SZAKAY P. Aspirin resistance after kidney transplantation. *17th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 6-9 July 2013, Pecs, Hungary. *Clin Hemorheol Microcirc*, 52 (2013), 139.

48. KESMARKY G., SANDOR B., TOTH A., BIRO K., KOLTAI K., PAPP J., RABAI M., TOTH K. Peripheral vascular diseases: Role of hemorheological factors. *17th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 6-9 July 2013, Pecs, Hungary. *Clin Hemorheol Microcirc*, 52 (2013), 180.

49. KENYERES P., MIKO A., TOTH A., SANDOR B., CSALODI R., TOTH O., KOSZTOLANYI S., SZOMOR A., NAGY A. Hemorheological disturbances in patients with chronic myeloid neoplasms. *17th Conference of the European Society for Clinical Hemorheology and Microcirculation*, 6-9 July 2013, Pecs, Hungary. *Clin Hemorheol Microcirc*, 52 (2013), 187.

50. TOTH A., BIRO K., SANDOR B., PAPP J., BOTOR D., RABAI M., KENYERES P., JURICSKAY I., TOTH K. The effects of red vine on hemorheological parameters in healthy volunteers. *Conference of Hungarian Medical Association of America 2013*. 16-17 August 2013, Balatonfüred, Hungary. *Archives of the Hungarian Medical Association of America*, 21 (2013), 34.

51. RÁBAI M., TÓTH A., SÁNDOR B., PAPP J., TÓTSIMON K., KENYERES P., JURICSKAY I., MEISELMAN H.J., TÓTH K. Vörösbor, alkoholmentes vörösborkivonat és etanol hemoreológiai hatásai. Magyar Belgyógyász Társaság Dunántúli Szekciójának LVII. Vándorgyűlése és a Hámori Artur Belgyógyászati Napok VI. 2013. június 6-8., Pécs *Magyar Belorvosi Archivum*, 66 Suppl. 1 (2013), 42.

52. SÁNDOR B., TÓTH A., RÁBAI M., PAPP J., MEZEY B., TÓTH K., SZABADOS E. Iszkémiás szívbetegek által végzett hosszú távú anaerob fizikai tréning hemoreológiai és laboratóriumi hatásai. *A Magyar Haemorheologiai Társaság, a Magyar Mikrocirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság IV. közös kongresszusa*, 2014. április 4-5., Balatonkenese. *Érbetegségek*, 21 (2014), 43-44.

53. TÓTH A., SZUKITS S., VÁRADY E., SÁNDOR B., PAPP J., RÁBAI M., JURICSKAY .I, TÓTH K., BATTYÁNI I., KÉSMÁRKY G. Haemorheológiai paraméterek szív CT-vel igazolt coronaria-betegségben. *A Magyar Haemorheologiai Társaság, a Magyar Mikrocirkulációs és Vaszkuláris Biológiai Társaság és a Magyar Szabadgyökkutató Társaság IV. közös kongresszusa*, 2014. április 4-5., Balatonkenese. *Érbetegségek*, 21 (2014), 45.

54. SÁNDOR B., TÓTH A., RÁBAI M., PAPP J., MEZEY B., TÓTH K., SZABADOS E. Hosszú távú fizikai tréning hatásai ambuláns kardiológiai rehabilitációban résztvevő iszkémiás szívbetegekben. *A Magyar Kardiológus Társaság 2014. évi Tudományos Kongresszusa*, 2014. május 14-17., Balatonfüred. *Card Hun*, 44 Suppl. E (2014), E5.

55. TÓTH A., SZUKITS S., VÁRADY E., SÁNDOR B., RÁBAI M., JURICSKAY I., KÉSMÁRKY G., TÓTH K. Hemoreológiai paraméterek CT-vel igazolt koszorúér-betegségben. *A Magyar Kardiológus Társaság 2014. évi Tudományos Kongresszusa*, 2014. május 14-17., Balatonfüred. *Card Hun*, 44 Suppl. E (2014), E89-E90.