

TEHNOMEEDIKUMI

TEADUS- JA ARENDUSTEGEVUSE AASTAARUANNE 2014

1. Struktuur

TTÜ Tehnomeedikum, TTU Technomedicum

Direktor Kalju Meigas

- **Biomeditsiinitehnika instituut, Department of Biomedical Engineering, Ivo Fridolin**
Biomeditsiinitehnika õppetool, Chair of Biomedical Engineering, Kalju Meigas
Meditsiinifüüsika õppetool, Chair of Medical Physics, Ivo Fridolin
- **Kardiovaskulaarse meditsiini instituut, Department of Cardiovascular Medicine**
Kardiovaskulaarse meditsiini õppetool, Chair of C Cardiovascular Medicine
- **Kliinilise meditsiini instituut, Department of Clinical Medicine, Ruth Sepper**
Kliinilise meditsiini õppetool, Chair of Clinical Medicine, Ruth Sepper
Tervishoiutehnoloogia õppetool, Chair of Health Care Technology, Peeter Ross
- **E-mediitsiini laboratoorium, eMedicine Laboratory, Peeter Ross**
- **NMR grupp, NMR group, Ago Samoson**

2. Struktuuriüksuse T&A iseloomustus

2.1. Department of Biomedical Engineering, Professor Ivo Fridolin

Chair of Biomedical Engineering, Professor Kalju Meigas

Chair of Medical Physics, Professor Ivo Fridolin

Instituudi kaks parimat artiklit:

1. Pilt, Kristjan; Meigas, Kalju; Ferenets, Rain; Temitski, Kristina; Viigimaa, Margus.
Photoplethysmographic signal waveform index for detection of increased arterial stiffness.
Physiological Measurement 2014; 35, 2027 - 2036.

Kliinilise taustaga artiklitest tuleb ära märkida:

2. White, HD.; Held, C.; Stewart, R.; Tarka, E.; Viigimaa M et al. Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. New England Journal of Medicine 2014; 370, 1702 - 1711.

2.1.1. Biofluid optics group, Ivo Fridolin

Teadustöö kirjeldus

On-line monitoring of uremic toxins. Today, there is no method available for on-line monitoring of uremic toxins with different molecular size for the end stage renal disease (ESRD) therapy quality assessment. Firstly in the world, the research of prof. Fridolin proposed a solution for the optical on-line HD monitoring [Fri01, Fri02] by BFOS, enabling determination of Kt/V for urea [Uhl03]. The implementation studies during technology transfer [She08, Fri08, Lum09] led to a successful commercial technology - the first integrated HD dose monitor in the world - Option Adimea, (BBraun Avitum AG) [Cas10]. The sensor is manufactured by an Estonian SME (Ldiamon AS), demonstrating the high potential of the optical signals for monitoring and social impact to Estonian economy.

The biofluid optics research within the project is the first in the world presenting concept of a new multicomponent dialysis monitor utilising optical techniques. The multicomponent monitor incorporates on-line removal estimation of all three uremic toxins' groups (small, middle and

protein bound) resulting: (i) Water soluble small molecular weight uremic toxins. Novel algorithms for measuring concentration of water soluble small molecular weight uremic toxins, urea, uric acid and creatinine, in the spent dialysate for estimation of dialysis dose and nutritional status (protein nitrogen appearance and lean body mass) on dialysis patients were developed [Tom14a,b,c]; (ii) Middle and protein bound uremic toxins. Unique method compared to earlier known state of the art for determining middle and protein bound uremic toxins in the spent dialysate utilizing fluorescence spectroscopy was proposed, which was a base for the Estonian and international PCT patent applications. The promising results have been achieved in developing and implementing novel optical technologies to assess the small [Hol2010c] and protein bound and middle uremic toxins [Hol12, Tom12, Tom13, Jer10, pUhl2010a, pUhl2010b, pUhl11, Kal14] – CVD risk and malnutrition–inflammation syndrome markers [Hol11, Enb12, Tom12, Hol13, Jia13, pUhl13, Hol14], among some potential IR markers. A review of the topic related to dialysis dose monitoring assessing uremic toxins by various optical methods [Uhl12] has been published.

Moreover, it was confirmed at first time that the light emitting diode based miniaturised optical monitor is capable to estimate dialysis dose and nutritional status without blood samples and offers a possibility for simplified mapping of the dialysis.

Analysis of uremic toxins- cardiovascular disease markers. No standard laboratory analyses are available for a number of protein bound and small uremic toxins' measurements in the biological fluids so far. Many of the uremic toxins are candidates being cardiovascular disease markers. For this reason an appropriate high performance liquid chromatography (HPLC) method, capable to measure more uremic toxins compared to existing standard laboratory methods, was developed during the project, making it possible to: (1) show that the molecular mass of the main UV chromophores in the uremic fluids do not exceed 3 kDa; (2) identify and quantify 5 uremic toxins in the serum and in the spent dialysate (uric acid, hypoxanthine, indoxyl sulfate, indole-3-acetic acid, and hippuric acid); (3) determine the optical spectra for 16 chromophores in the uremic fluids; (4) investigate the behaviour of water soluble small molecular weight and protein bound uremic toxins, and UV-absorbance in respect to low and high flux dialyzers during hemodialysis [Aru12].

Cooperation: Centre of Nephrology, North-Estonian Medical Centre, Tallinn (Estonia), Linköping University Hospital, Linköping (Sweden).

Tähtsamad teadustulemused:

- A study was undertaken to examine the possibility of post-dialysis urea rebound assessment utilizing UV-absorbance measurements in spent dialysate. Twenty-six patients on chronic three-times-a-week hemodialysis (HD) were studied in two separate studies. Double-beam spectrophotometer was used for the determination of UV-absorbance in the collected spent dialysate samples. Also, on-line UV-absorbance was monitored. The equilibrium concentration (C_{eq}) of urea at the end of the rebound phase was calculated based on urea concentration in blood, in dialysate and UV-absorbance in spent dialysate. Based on C_{eq} , urea rebound was expressed relative to urea concentration at the end of HD ($R1$) and relative to the fall in urea concentration during HD ($R2$). Estimates based on UV-absorbance values in spent dialysate ($R1_a$, $R2_a$) slightly over assess post-dialysis rebound compared to results based on the blood sample drawn 30 min after HD ($R1_30post$, $R2_30post$), but $R1_a$ and $R2_a$ presented greater consistency and accuracy compared to the estimates based on the intradialytic blood sample ($R1_b$, $R2_b$). In summary, the results show that it is possible to assess post-dialysis urea rebound in blood based on UV-absorbance measurements in spent dialysate. [Tom14a]

- Survival rate of dialysis patients is still alarmingly low and various factors may have in it an important role. The purpose of this study was to observe the relationship between the survival of dialysis patients and the serum level of urea, creatinine, and uric acid (UA). Serum urea and creatinine concentrations may express patients nutritional status and muscle mass, and high UA value may refer to higher risk for cardiovascular events. The idea of combining the concentrations and removal of urea and UA into a single model for predicting the patients outcome is introduced. The study included 33 hemodialysis patients from Linköping, Sweden and 10 from Tallinn, Estonia. Kaplan-Meier analysis was used for survival analysis. Logistic and Cox regression analysis was applied to create models for predicting patients three-year survival. It was observed that higher serum UA is significantly related to poor survival in dialysis patients ($p = 0.026$). A reverse effect was observed in case of urea ($p = 0.095$). The level of creatinine was not related to survival ($p = 0.905$). The best logistic regression model for predicting patients outcome included both UA and urea based parameters (Chi Square 21.0, $p = 0.0001$). Survival of dialysis patients seems to be determined by a set of causal factors and combined models may have a predictive relevance. A possibility for automatic online monitoring of small molecule uremic markers is proposed. Since the number of participating patients was small, larger studies including more patients and testing the models in independent validation cohort is the future goal. [Hol14]
- A study investigated the possibility to determine if fluorescence chromatography can be used to measure modified beta-2-microglobulin (B2M) from the spent dialysate. Amyloid B2M is the main pathogenic component of dialysis-related amyloidosis. This component is in our sphere of interest being one of the fluorescent advanced glycation end products (AGE). AGEs are potential uremic toxins that can cause amyloidosis and cardiovascular problems in chronic kidney failure patients. Two haemodialysis patients with high levels of B2M were selected for this study. Their spent dialysate samples were collected 10 minutes after the start of the dialysis process and less hydrophilic compounds were concentrated using solid phase extraction (SPE) column. Sediment from the concentrate and spent dialysate were analysed with electrospray ionisation mass spectrometer (ESI-MS) MicrOTOF-Q II coupled to high pressure liquid chromatography (HPLC) Dionex UltiMate 3000 RS. The sediment was analysed with Poroshell 120 EC-C18 column and spent dialysate with Kinetex C18 100A column. MagTran was used to interpret mass spectra. Brown coloured fluorescent sediment of the concentrate was identified as amyloid B2M on the basis of MS and fluorescence spectra. AGE modified B2M was also found from spent dialysate. However the fluorescence intensity was very low compared to overall fluorescence of spent dialysate. In summary, the study revealed that the fluorescence of AGE modified B2M is possible to detect in spent dialysate. However, the measuring system needs high selectivity and sensitivity for detection due to low contribution of AGE modified B2M to overall fluorescence. [Kal14]
- A study assessed the connection of urea rebound and the difference between $spKt/V$ and eKt/V and also the possibility of utilizing UV-absorbance measurements to assess urea rebound. Ten patients of chronic three-times-a-week hemodialysis (HD) were studied. On-line UV-absorbance of spent dialysate was monitored. Single-pool Kt/V ($spKt/V$), equilibrated Kt/V (eKt/V) and the percentage difference between $spKt/V$ and eKt/V ($\Delta Kt/V$) were calculated. Urea rebound was calculated based on urea concentration in blood (R_b) and UV-absorbance in spent dialysate (R_a). $\Delta Kt/V$ and R_b were not statistically different. Also, R_a and R_b were not statistically different. In summary, the results show that it is possible to assess post-dialysis urea rebound in blood based on

UV-absorbance in spent dialysate, which may offer the opportunity to estimate the true dialysis dose and a more personalized approach to the dialysis treatment. [Tom14b]

- A study investigated the possibility of assessing lean body mass (LBM) based on UV-absorbance measurements in spent dialysate. Nine patients on chronic three-times-a-week haemodialysis (HD) were studied. A double-beam spectrophotometer was used for the determination of UV-absorbance in the collected spent dialysate samples. LBM was calculated based on creatinine concentration in blood (LBM_{blood}), creatinine concentration in spent dialysate (LBM_{dialysate}) and UV-absorbance in spent dialysate (LBM_a). Although LBM_a was slightly lower compared to LBM_{blood}, the estimates based on UV-absorbance in spent dialysate were not statistically different from LBM_{blood}. In summary, the results show that it is possible to assess LBM based on UV-absorbance in spent dialysate. [Tom14c]

Uurimisgrupi viis olulisemat publikatsiooni:

1. R. Tomson, F. Uhlin, I. Fridolin. (2014) Urea rebound assessment based on UV-absorbance in spent dialysate. *ASAIO Journal*. 60(4):459-465, July/August 2014.
2. Holmar, J; Fridolin, I; Uhlin, F; Fernström, A; Luman, M. (2014). Estimation of dialysis patients' survival through combined approach of small molecule uremic markers. *Proceedings of the Estonian Academy of Sciences*, 63, 227 - 233.
3. Kalle, S; Kressa, H; Tanner, R; Holmar, J; Fridolin, I. (2014). Fluorescence of Beta-2-microglobulin in the Spent Dialysate. In: 16th Nordic-Baltic Conference on Biomedical Engineering: Nordic-Baltic Conference on Biomedical Engineering and Medical Physics & 10th Medicinteknikdagarna, Göteborg, Sweden, 14-16.October.2014. (Toim.) Mindedal, H., Persson, M.. Springer-Verlag, 2014, (IFMBE Proceedings; 48), 59 - 62.
4. Tomson, R.; Uhlin, F.; Fridolin, I. (2014). Optical Urea Rebound Estimation During Dialysis. In: IFMBE Proceedings: 16th Nordic-Baltic Conference on Biomedical Engineering, October 14-16, 2014, Göteborg, Sweden. Springer, 2014, 109 - 112.
5. Tomson, R.; Fridolin, I.; „Lean Body Mass Assessment Based on UV-absorbance in Spent Dialysate.“ The 14th Biennial Baltic Electronics Conference, October 6-8, 2014, Tallinn, Estonia.

Välisakadeemiate või muude oluliste T&A- ga seotud välisorganisatsioonide liikmed.

Jana Holmar - IEEE EMBS(IEEE Engineering in Medicine and Biology Society) liige

Jürgen Arund - IbioMep liige

Ivo Fridolin - the European Uremic Toxin Working Group of ESAO, endorsed by ERA-EDTA (EUTox) liige

2.1.2. Brain research group, Hiie Hinrikus

Teadustöö kirjeldus

The research activity is continuously aimed to development of algorithms for detection of characteristic changes in the brain electroencephalographic (EEG) signal related to the mental disorders and the effect of external physical stressor. For this purpose:

- the new recordings of EEG signals from healthy persons selected from medical centre Qualitas and patients with mental disorders selected by family doctors were performed;
- sensitivity of various electroencephalogram (EEG) analysis methods as spectral asymmetry index (SASI), Lempel Ziv Complexity, Detrended Fluctuation Analysis and Higuchi's fractal dimension for detection of depression was analyzed;

- SASI was applied for analysis of the effect of microwave radiation as a physical stressor on the human brain;
- optimal EEG frequency bands were selected for detection of depression;
- the mechanism of the effect of microwave radiation as a physical stressor on the brain was explained using the model of hydrogen bonding and diffusion.

Tähtsamad teadustulemused:

SASI as an original spectral asymmetry method for EEG analysis, protected by our US patent from 2012, was shown to have 1) a sensitivity for detection of characteristic features in depression comparable and even better compared to various much more complicated nonlinear EEG analysis methods in a single-channel EEG and 2) ability to detect the effect of physical stressor on human EEG.

Uurimisgrupi viis olulisemat publikatsiooni;

1. Hiie Hinrikus, Jaanus Lass, Denis Karai, Kristjan Pilt, and Maie Bachmann. Microwave effect on diffusion: a possible mechanism for non-thermal effect. *Electromagnetic Biology and Medicine*, Posted online on May 23, 2014. doi:10.3109/15368378.2014.921195
2. Maie Bachmann, Jaanus Lass, Anna Suhhova, and Hiie Hinrikus. Spectral asymmetry index and Higuchi's fractal dimension for detecting microwave radiation effect on electroencephalographic signal. *Proceedings of the Estonian Academy of Sciences*, 2014, 63, 3, 234–239
3. Bachmann, Maie; Kalev, Kaia; Suhhova, Anna; Jaanus, Lass; Hiie, Hinrikus. Lempel Ziv Complexity of EEG in Depression. In: *IFMBE Proceedings vol. 45*, pp. 58 - 61. 6th European Conference of the International Federation for Medical and Biological Engineering, Dubrovnik, 7-11.09.2014.
4. Bachmann, M.; Suhhova, A.; Lass, J.; Adamsoo, K.; Võhma, Ü.; Hinrikus, H. Detrended Fluctuation Analysis of EEG in Depression. *IFMBE Proceedings*, vol. 41, pp. 694 - 697: XIII Mediterranean Conference on Medical and Biological Engineering and Computing, 25-28 September, Sevilla, Spain.
5. K. Kalev, M Bachmann. Selection of EEG Frequency Bands for Detection of Depression. *IFMBE Proceedings*, Vol. 48, pp. 55-58, 16. NBC & 10. MTD 2014 joint conferences. October 14-16, 2014, Gothenburg, Sweden.

Loetelu töötajate rahvusvahelistest tunnustustest

Kaia Kalevi preemia 16 NBC konverentsil

Loetelu töötajatest, kes on välisakadeemia või muu olulise T&A-ga seotud välisorganisatsiooni liige

Hiie Hinrikus: International Academy for Medical and Biological Engineering – Fellow;
European Alliance for Medical and Biological Engineering and Science –
Founding Fellow

Maie Bachmann: IEEE EMBS

2.1.3. Cardiovascular direction research group, Kalju Meigas

Teadustöö kirjeldus

The focus in preventing and treating cardiovascular diseases (CVD) today is moving from a statistical risk factors approach (age, BP level, cholesterol, diabetes) toward direct assessment of arterial wall impairment (arterial thickness, arterial wall properties). Atherosclerosis is the

main cause for deaths in Europe; unfortunately Estonia belongs to countries with highest mortality levels for CVD in Europe. Therefore availability of inexpensive non-invasive methods for diagnostics of atherosclerosis in very early stage is extremely important. The arterial wall elasticity is a major function of the aorta. Loss of elasticity leads to pulse pressure rise and to increase of pulse wave velocity (PWV). PWV, recognized recently as an independent diagnostic parameter, is widely recognized as a direct marker of arterial stiffness. In early stage the pathogenesis atherosclerotic process can be stopped to prevent serious CVD.

Availability of a range of methods and techniques allow measurement PWV and other variables related to the stiffness of arteries. Currently, measurements using tonometry, pulse wave imaging and arterial compliance using doppler ultrasonography are used to assess arterial parameters. Although some of the techniques and devices are clinically accepted, the methods applied in these devices are complicated. The application of tonometry transducers or ultrasound probes on target arteries can be rather difficult. Therefore, simpler and easier methods are required. Application of PPG for PWV measurement provides a simple method and promising solution of the problem. Modern signal processing creates a novel level of PPG signal application in PWV measurements.

In our previous studies the new second derivative PPG signal waveform analysis algorithm was developed for arterial stiffness estimation and in 2014 we have improved and technically validated the algorithm. The PPG waveform index PPGAI was proposed for the estimation of increased arterial stiffness. In addition the arterial stiffness caused changes in PPG waveform rising front were investigated and the algorithm was developed. The PPG waveform index PPGAI and slope of the rising front were compared with the results of aortic augmentation index measured with SphygmoCor. For this purposes in both studies the signals were recorded from 24 healthy subjects and from 20 type II diabetes patients.

Tähtsamad teadustulemused:

The number of physiological signals and reference parameters (pulse waves from different locations of the body, peripheral pressure pulse wave, electrocardiographic signal, phonocardiography waves, augmentation indices and pulse wave velocity in aorta) has been measured from volunteers and atherosclerotic patients (diabetes mellitus). The novelty is in the concept for the development of the new optical method and its evaluation. The new signal processing methods have been developed and are currently under development.

A strong correlation ($r = 0.85$) between the PPGAI and the aortic augmentation index and a positive correlation of both indices with subject's age were found. Age corrections for the indices PPGAI and augmentation index as regression models from the signals of healthy subjects were constructed. Both indices revealed a significant difference between the groups of diabetes patients and healthy controls. However, the PPGAI provided the best statistical discrimination for the group of subjects with increased arterial stiffness.

Negative correlation relationships ($r = -0.68$ and $r = -0.77$) were found between the age and the slopes of the PPG signal. Significant differences were found between the healthy controls and diabetes patients. The highest difference between the two groups was found using the advanced signal processing algorithm for the slope calculation. The sensitivity, specificity, and accuracy of the method were 85%, 88%, and 86%, respectively.

We conclude that the PPG technology with the advanced signal processing algorithms can be used for the discrimination of subjects with increased arterial ageing and can be considered as a perspective measure of increased arterial stiffness estimation in clinical screenings.

Uurimisgrupi viis olulisemat publikatsiooni:

1. Pilt, Kristjan; Meigas, Kalju; Kõõts, Kristina; Viigimaa, Margus.
Photoplethysmographic signal rising front analysis for the discrimination of subjects

with increased arterial ageing. Proceedings of the Estonian Academy of Sciences 2014; 63(3), 221 - 226.

2. Pilt, Kristjan; Meigas, Kalju; Ferenets, Rain; Temitski, Kristina; Viigimaa, Margus. Photoplethysmographic signal waveform index for detection of increased arterial stiffness. *Physiological Measurement* 2014; 35, 2027 - 2036.
3. White, HD.; Held, C.; Stewart, R.; Tarka, E.; Viigimaa M et al. Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. *New England Journal of Medicine* 2014; 370, 1702 - 1711.
4. Jensen-Urstad, M.; Viigimaa, M.; Sammul, S. et al. Impact of smoking: All-cause and cardiovascular mortality in cohort of 55-year-old Swedes and Estonians. *Scandinavian Journal of Public Health* 2014; 42(8):780 - 785.
5. Lankin, V.; Konovalova, G.; Tikhaze, A.; Shumaev, K.; Kumskova, E.; Viigimaa, M. The initiation of free radical peroxidation of low-density lipoproteins by glucose and its metabolite methylglyoxal: a common molecular mechanism of vascular wall injury in atherosclerosis and diabetes. *Molecular and Cellular Biochemistry* 2014; 395, 241 - 252.

2.1.4. Sudden death research group, Jüri Kaik

Unemeditsiini uurimisgrupp /Sleep medicine research group, Jüri Kaik

Teadustöö kirjeldus

Evaluation of new generation event recorders and telemetric data transmission, including ambulatory sleep apnea monitors. Evaluation of novel heart rate and cuff-less blood circulation Holter devices (European Space Agency project: Development of the Heart Rate and Cuff-less Blood Circulation Holter Device for Non-invasive, Simultaneous and Continuous Monitoring of Cardiovascular Parameters on the Earth and in Space, stage 3).

Tähtsamad teadustulemused:

Evaluation of the dependence of various physiological parameters (ventricular repolarization reflecting parameters, pulse arrival time, etc.) on different sleep stages and on the severity of sleep apnea.

Uurimisgrupi olulisim publikatsioon aruandeaastal:

Kaik, Jüri; Pindmaa, Mae; Viigimäe, Moonika; Karai, Deniss; Pilt, Kristjan. (2014). Comparison of Different QT-interval Variability Assessment Models in Patients with Various Degree of Sleep Apnea. *In: 12th International Dead Sea Symposium (IDSS) on Innovations in Cardiac Arrhythmias and Devices Therapy. March 3-5, 2014, Tel-Aviv. p.98 . (1):24-27*

2.2 Department of Cardiovascular Medicine

Teadustöö kirjeldus:

Atherosclerosis is the main cause for deaths worldwide. Therefore availability of inexpensive non-invasive methods for diagnostics of atherosclerosis in very early stage is extremely important. Our studies in 2014 were focused on direct assessment of arterial wall impairment (arterial thickness, arterial wall properties), studies of free radical peroxidation of low-density lipoproteins and vascular wall injury in atherosclerosis and assessment of novel antiatherosclerotic drugs.

In arterial stiffness studies we have investigated the possibilities to use photoplethysmographic (PPG) signal waveform analysis for the arterial stiffness and ageing estimation. PPG is optical, non-invasive, relatively inexpensive method in order to register the pulse wave. The PPG signals are registered from left and right hand index finger of healthy controls and diabetes patients. In addition other physiological signals (ECG, phonocardiographic, piezoelectric signals) are registered as reference for the analysis of PPG waveform. Furthermore, reference devices (SphygmoCor, Arteriograph) are used for estimation of aortic pulse wave velocity and augmentation index, which are intrinsically associated with arterial stiffness.

In our previous studies the new second derivative PPG signal waveform analysis algorithm was developed for arterial stiffness estimation and in 2014 we have improved and technically validated the algorithm. The PPG waveform index PPGAI was proposed for the estimation of increased arterial stiffness. In addition the arterial stiffness caused changes in PPG waveform rising front were investigated and the algorithm was developed. The PPG waveform index PPGAI and slope of the rising front were compared with the results of aortic augmentation index measured with SphygmoCor. For this purposes in both studies the signals were recorded from 24 healthy subjects and from 20 type II diabetes patients.

In oxidative stress studies venous blood samples from healthy donors (in the case of model experiments) or patients with type 2 diabetes mellitus were taken after fast (before meal) and the plasma was used for LDL isolation. Determination of lipoperoxidation products in LDL and blood plasma was performed. The content of lipohydroperoxides in LDL particles was determined spectrophotometrically at 560 nm using a Hitachi 557 spectrophotometer (Japan). Elevated lipoprotein-associated phospholipase A2 activity promotes the development of vulnerable atherosclerotic plaques, and elevated plasma levels of this enzyme are associated with an increased risk of coronary events. Darapladib is a selective oral inhibitor of lipoprotein-associated phospholipase A2. In a double-blind trial, we randomly assigned patients with stable coronary heart disease to receive either once-daily darapladib (at a dose of 160 mg) or placebo.

Tähtsamad teadustulemused:

A strong correlation ($r = 0.85$) between the PPGAI and the aortic augmentation index and a positive correlation of both indices with subject's age were found. Age corrections for the indices PPGAI and augmentation index as regression models from the signals of healthy subjects were constructed. Both indices revealed a significant difference between the groups of diabetes patients and healthy controls. However, the PPGAI provided the best statistical discrimination for the group of subjects with increased arterial stiffness.

Negative correlation relationships ($r = -0.68$ and $r = -0.77$) were found between the age and the slopes of the PPG signal. Significant differences were found between the healthy controls and diabetes patients. The highest difference between the two groups was found using the advanced signal processing algorithm for the slope calculation. The sensitivity, specificity, and accuracy of the method were 85%, 88%, and 86%, respectively.

We conclude that the PPG technology with the advanced signal processing algorithms can be used for the discrimination of subjects with increased arterial ageing and can be considered as a perspective measure of increased arterial stiffness estimation in clinical screenings.

We have found that glucose in the range of concentrations 12.5-100 mM stimulated Cu²⁺-mediated free radical peroxidation of low-density lipoproteins (LDL) from human blood plasma. In accordance with the foregoing the administration of sugar-lowering drug metformin, which binds and utilizes methylglyoxal, caused a stronger inhibition of LDL peroxidation in the blood of patients with diabetes mellitus, probably due to decrease in methylglyoxal-dependent generation of superoxide anion-radicals. Based on the results we set out the hypothesis about autocatalytic mechanism of free radical reactions involving natural dicarbonyls and suppose the common molecular mechanism of vascular wall injury in atherosclerosis and diabetes.

Darapladib, as compared with placebo, reduced the rate of major coronary events (9.3% vs. 10.3%; hazard ratio, 0.90) and total coronary events (14.6% vs. 16.1%; hazard ratio, 0.91). In patients with stable coronary heart disease, darapladib did not significantly reduce the risk of cardiovascular death, myocardial infarction, or stroke. Our direct comparison of Estonian and Swedish population (SWESTONIA study) has demonstrated that smoking remains the most important cause of CVD and non-CVD mortality. The study results confirm the need for continued anti-smoking efforts to prevent premature mortality.

Instituudi viis olulisemat publikatsiooni:

1. Pilt, Kristjan; Meigas, Kalju; Kõõts, Kristina; Viigimaa, Margus. Photoplethysmographic signal rising front analysis for the discrimination of subjects with increased arterial ageing. Proceedings of the Estonian Academy of Sciences 2014; 63(3), 221 - 226.
2. Pilt, Kristjan; Meigas, Kalju; Ferenets, Rain; Temitski, Kristina; Viigimaa, Margus. Photoplethysmographic signal waveform index for detection of increased arterial stiffness. Physiological Measurement 2014; 35, 2027 - 2036.
3. White, HD.; Held, C.; Stewart, R.; Tarka, E.; Viigimaa M et al. Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. New England Journal of Medicine 2014; 370, 1702 - 1711.
4. Jensen-Urstad, M.; Viigimaa, M.; Sammul, S. et al. Impact of smoking: All-cause and cardiovascular mortality in cohort of 55-year-old Swedes and Estonians. Scandinavian Journal of Public Health 2014; 42(8):780 - 785.
5. Lankin, V.; Konovalova, G.; Tikhaze, A.; Shumaev, K.; Kumskova, E.; Viigimaa, M. The initiation of free radical peroxidation of low-density lipoproteins by glucose and its metabolite methylglyoxal: a common molecular mechanism of vascular wall injury in atherosclerosis and diabetes. Molecular and Cellular Biochemistry 2014; 395, 241 - 252.

Välisakadeemiate või muude oluliste T&A- ga seotud välisorganisatsioonide liikmed

Margus Viigimaa - Rootsi Hüpertensiooni Ühingu auliige

Margus Viigimaa - Bulgaaria Hüpertensiooni Liiga auliige

Margus Viigimaa - Kasahstani Kardioloogide Assotsiatsiooni auliige

Margus Viigimaa - Ukraina Arstiteaduste Akadeemia Kuldmale laureaat

Margus Viigimaa - Ungari Hüpertensiooni Ühingu auliige.

2.3 Department of Clinical Medicine, Ruth Sepper

Kliinilise meditsiini instituudi teadus- ja arendustegevuse valdkonnad on:

- Astma ja kroonilise obstruktiivse kopsuhaiguse tekke, arengu ja varase diagnostika uurimise põhjused (*Investigations on causes and development and early diagnostics of asthma and chronic obstructive lung disease*). Teadussuuna juht prof. Ruth Sepper, kaastöötajad vanem- teadur Kaiu Prikk, doktorandid Berit Pilden ja Sirje Marran.
- E-tervise teadussuund (*E-health*), mida juhib rahvusvaheline teadlaskond, kuhu kuuluvad Tallinna ja Helsingi Tehnikaülikooli dotsent Hanna Pohjonen, dotsent ja vanemteadur Peeter Ross, PhD

Teadustöö kirjeldus:

- Investigations on causes and development and early diagnostics of asthma and chronic obstructive lung disease - Prof. Ruth Sepper (leader of research group), senior researcher Kaiu Prikk, post-graduates Sirje Marran, Berit Pilden;
- Project „CHROMED“ - Clinical Trials for Elderly patients with Multiple Disease. CHROMED is an European project aimed at evaluating the impact of adopting a health and lifestyle status management system to support elderly patients with a combination of chronic diseases involving respiratory and cardiovascular systems. The CHROMED project focuses its investigation on the applicability of an integrated solution for a pathological condition which: a) is very prevalent in ageing patients and b) severely impairs quality of life: COPD with other typical comorbidities such as congestive heart failure and sleep disordered breathing – Ruth Sepper, Kaiu Prikk, Mariliis Sepper;
- Clinical investigation 117106 for Mepolizumab vs. placebo in case of increasing COPD – Kaiu Prikk;
- E-health R&D projects: eMedic – Developing New Practices for Teleconsultation and Diabetes – project manager Ruth Sepper, senior researcher Peeter Ross, project coordinators Veronika Palmiste-Kallion, Mall Maasik;
- PrimCare IT - Counteracting brain drain and professional isolation of health professionals in remote primary health care through tele-consultation and telementoring to strengthen social conditions in remote BSR - project manager Madis Tiik, senior researcher Peeter Ross.

Tähtsamad teadustulemused:

We demonstrated that lung function deviation and lung structural changes are present in chronic smokers before the clinical signs of airway obstruction reveal and these changes are associated with early onset of chronic obstructive pulmonary disease (COPD). Further investigations have performed to find early COPD biomarkers by use of data mining and bio-informatic approach.

Loetelu töötajatest, kes on välisakadeemia või muu olulise T&A-ga seotud välisorganisatsiooni liige

Ruth Sepper - FP7 Programm Tervis programmikomitee, ekspert
Marie Curie Individual fellowships, Panel Life, FP7, ekspert
American Thoracic Society, liige
Gruusia Teadusfond, ekspert
Eur. Respir. J, Clinical Chem. Acta, retsensent
J Proteomics, retsensent

- PloS ONE, retsensent
- Kaiu Prikk - European Respiratory Society, liige
American Thoracic Society, liige
- Peeter Ross - European Society of Radiology, liige
Finnish Society of Telemedicine and eHealth, liige
- Ave Minajeva - Federation of the Societies of Biochemistry and Molecular Biology, liige
- Katrin Gross-Paju - Euroopa Neuroloogia Ühingute Föderatsiooni Neurorehabilitatsiooni
paneeli liige
Advisory Board – Multiple Sclerosis – Central East Europe, liige

2.4 eMedicine Laboratory, Peeter Ross, MD, PhD

E-mediitsiini laboratoorium kuulus 2014.a. Tehnomeedikumi koosseisu. Alates 2015.a. on eMed Lab Tehnomeedikumi Kardiovaskulaarse Meditsiini Instituudi koosseisus.

E-mediitsiini laboratooriumi uurimisgrupi moodustavad lisaks Peeter Ross'ile Madis Tiik (MD, PhD) ning magistri- ja doktoriüliõpilased Liisa Parv, Aleksandr Kormiltsõn, Evelin Vanker, Kelli Podošvilev. Laboris ei olnud 2014.a. ühtegi täiskohaga töötajat.

Research group of eHealth applications and services E-tervise rakenduste ja teenuste uurimisgrup.

Teadustöö kirjeldus:

Scientific work is concentrating on the effect of the use of e-health services on diagnostic and treatment processes in public health and healthcare. The research topics include investigation of the actors and processes influencing the implementation of shared workflow, the use of digital medical databases in development of early diagnostic algorithms and decision support systems, and research of a medical text as a sublanguage of medicine.

Research area also includes health and medical data exploitation in developing new e-health services for citizen and healthcare professionals, data sharing among healthcare and with the citizen, process reengineering in healthcare, telemedicine services for the patients and personal health record services and patient motivation.

Laboratooriumi neli tähtsamat publikatsiooni:

- Valdre, E.; Ross, P.; Tsepelina, K.; Veskis, K.; Vaino, T.; Kaalep, H.-J. (2014). Corpus-based analysis of abbreviations and abbreviating in Estonian radiology reports (In Estonian – Radioloogiauuringute vastuste lühendite ja lühendamise korpuslingvistiline analüüs). *Eesti Arst*, 93(9), 502 - 512.
- Parv L, Kruus P, Mõtte K, Ross P. An evaluation of e-prescribing at a national level. *Inform Health Soc Care*, Early Online: 1–18, 2014. Informa UK Ltd. ISSN: 1753-8157 print / 1753-8165 online DOI: 10.3109/17538157.2014.948170
- Ristolainen A, Ross P, Gavšin J, Semjonov E, Kruusmaa M. Economically affordable anatomical kidney phantom with calyces for puncture and drainage training in interventional urology and radiology *Acta Radiologica Short Reports June 2014 3: 2047981614534231, first published on June 13, 2014 doi:10.1177/2047981614534231*
- Ranschaert E, Bosmans J, Ross P, Dugar N, Schillebeeckx J, Mildenerger P, Ratib O. ESR white paper on teleradiology: an update from the teleradiology subgroup. *Insights into Imaging* 01/2014; DOI:10.1007/s13244-013-0307-z

Loetelu töötajatest, kes on välisakadeemia või muu olulise T&A-ga seotud välisorganisatsiooni liige

Peeter Ross - Euroopa Radioloogia Ühingu (European Society of Radiology) kolme alamkomitee liige
- Ethical Compliance Subcommittee
- Audit and Standards Subcommittee
- eHealth and Informatics Subcommittee

Aruandeaastal saadud T&A-ga seotud tunnustused:

Alates 2014.a. septembrist kuni 2015.aprillini viibib dr. Madis Tiik USA poolt finantseeritud stipendiaadina Scripps Instituudis San Diegos, Californias.

Esinemised rahvusvahelistel seminaridel ja konverentsidel:

- Sharing of healthcare data with citizen in mobile platform – Estonian experience. Peeter Ross, MD, PhD. Exploratory seminar on eHealth benefits & cooperation in the Southern Mediterranean countries and the EU. December 04, 2014, Rabat, Morocco.
- Estonian nation-wide health information system. Peeter Ross, MD, PhD. Aalto University Alumni Weekend 2014. 25.10.2014. Finland.
- Radiology marketplace. Peeter Ross, MD, PhD. Baltic Congress of Radiology 2014. 10.10.2014, Pärnu, Estonia.
- Estonian Nation-wide Health Information System (HIS). Peeter Ross, MD, PhD. Real World Evidence. 17.09.2014. Brussels, Belgium.
- Five year experience of the use of nation-wide health information system in Estonia. Peeter Ross. 03.06.2014. Swedish Society of Medicine – Svenska Läkaresällskapet – Stockholm, Sweden.
- Five year experience of the use of nation-wide eHealth platform and strategy for the future – Estonian case. Peeter Ross, MD, PhD. 25.04.2014. E-Health Innovations in Europe. Warsaw, Poland.
- New approach to medical data – patient centric care. Peeter Ross, MD, PhD. Towards Effective eHealth. Tallinn, April 23rd-24th, 2014
- Integration of Home-monitoring Data and PHR, EMR. Peeter Ross, MD, PhD. Towards Effective eHealth. Tallinn, April 23rd-24th, 2014
- The strategic opportunities of Tele-consultation and Tele-mentoring for remote primary care. Peeter Ross. Connecting Health Care Professionals via ICT. 14. February 2014, Tallinn, Estonia.
- What happens when the citizen gets access to own information? Peeter Ross, MD, PhD. 05.02.2014. Arctic Light eHealth Conference, Kiruna, Sweden.

2.5. NMR group, Ago Samoson

Teadustöö kirjeldus

Two papers were published on structure of Li-ion battery materials and ion conductivity. Heavy NMR line-broadenings due to presence of the unpaired electron shells are characteristic to these materials. Interaction of the magnetic moment and the external field makes sample spinning even more complicated. We were able to get reasonable spectra due to small sample amounts and low fields. To best of our knowledge, it is the first time that a direct comparison of ESR and NMR spectra was made on the identical structures.

We tested several EMI seals for a reliable contact between probe scaffold and external shield for spectroscopy of biological samples at high magnetic fields.

Uue rotatsioonitehnika rakendamisega õnnestus määrata valgu struktuur "de novo" ning iseloomustada antikehade ja valgu kompleksi. Mõlemad tööd on publitseeritud, viimase kohta pidas Ameerika Keemiaühing kohaseks avaldada ka oma kommentaari.

The first time a prototype for *in situ* MAS-NMR measurements was developed.

Cutting edge results on nano-materials for a new kind of hydrogen storage and improved ion conductor for fluoride ion batteries were published as well presented at a conference.

Grupi kuus olulisemat publikatsiooni:

1. Strobridge, F.C.; Middlemiss, D.S.; Pell, A.J.; Leskes, M.; Clément, R.J.; Pourpoint, F.; Lu, Z.; Hanna, J.V.; Pintacuda, G.; Emsley, L.; Samoson, A.; Grey, C.P. (2014). Characterising local environments in high energy density Li-ion battery cathodes: a combined NMR and first principles study of $\text{LiFe}_x\text{Co}_{1-x}\text{PO}_4$. *Journal of Materials Chemistry A*, 2, 11948 - 11957.
2. Stoyanova, R.; Ivanova, S.; Zhecheva, E.; Samoson, A.; Simova, S.; Tzvetkovac, P.; Barrad, A-L. (2014). Correlations between lithium local structure and electrochemistry of layered $\text{LiCo}_{1-2x}\text{Ni}_x\text{Mn}_x\text{O}_2$ oxides: ^7Li MAS NMR and EPR studies. *Physical Chemistry Chemical Physics*, 16, 2499 - 2507.
3. Lamley, J.M.; Iuga, D.; Öster, C.; Sass, H.-J.; Rogowski, M.; Oss, A.; Past, J.; Reinhold, A.; Grzesiek, S.; Samoson, A.; Lewandowski, J. R.. Solid-State NMR of a Protein in a Precipitated Complex with a Full-Length Antibody. *Journal of the American Chemical Society*, 2014.
4. Agarwal, V.; Penzel, S.; Szekely, K.; Cadalbert, R.; Testori, E.; Oss, A.; Past, J.; Samoson, A.; Ernst, M.; Böckmann, A.; Meier, B.H. (2014). De Novo 3D Structure Determination from Sub-milligram Protein Samples by Solid-State 100 kHz MAS NMR Spectroscopy. *Angewandte Chemie International Edition*, 53(45), 12253 - 12256.
5. Hu, Jianjiang; Witter, Raiker; Shao, Huaiyu; Felderhoff, Michael; Fichtner, Maximilian (2014). Beneficial effects of stoichiometry and nanostructure for a $\text{LiBH}_4\text{-MgH}_2$ hydrogen storage system. *Journal of Materials Chemistry A*, 2, 66 - 72.
6. Rongeat, Carine; Reddy, M. Anji; Witter, Raiker; Fichtner, Maximilian (2014). Solid Electrolytes for Fluoride Ion Batteries: Ionic Conductivity in Polycrystalline Tysonite-Type Fluorides. *ACS Applied Materials and Interfaces*, 6(3), 2103 - 2110.

Rahvusvahelised tunnustused

Invited presentation: Witter, R.; Irshad, M.; Molaiyan, P.; Oss, A.; Anupöld, T.; Rongeat, C.; Reddy, M.A.; Fichtner, M.; Samoson, A. (2014). Developments and Investigations on Battery Materials. 56TH ROCKY MOUNTAIN CONFERENCE ON MAGNETIC RESONANCE. USA., 2014, (Copper Conference Center, Copper Mountain, Colorado,).

T&A-ga seotud tunnustused, ülevaade teaduskorralduslikust tegevusest, teadlasmobiilsusest ning hinnang oma teadustulemustele.

ENMR group continued with complementing functionality the laboratory, it features now medium scale, pumping station, and semi-automation for herb cultivation.

Results are *on par* with funding and team intelligence.