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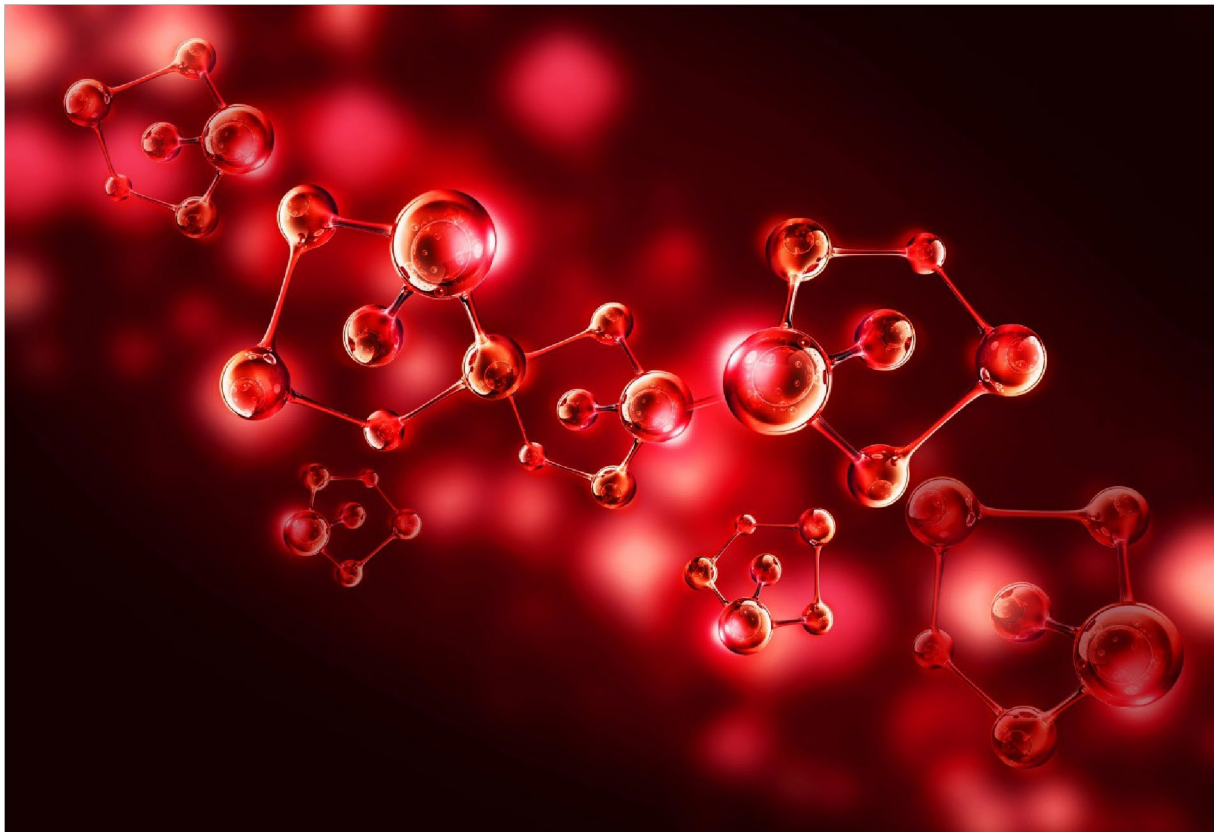

ABSTRACT BOOK 2024

Bachelor's and Master's Theses in Biomedical Laboratory Science

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Verification of LC-MS/MS method for detection of methylphenidate

By Heba Alyousef

Bachelor thesis in Biomedical Laboratory Science performed at Clinical Chemistry, Area 4, Norra Älvsborgs Länssjukhus in Trollhättan, 2024.

Background: Methylphenidate is widely used in the treatment of attention deficit hyperactivity disorder (ADHD). Monitoring of methylphenidate and its main metabolite, ritalinic acid , in urine is important to ensure that abuse does not occur. A sensitive and rapid method exists to measure methylphenidate and ritalinic acid in urine by using liquid chromatography tandem mass spectrometry (LC-MS/MS).

This project aims to verify a new LC-MS/MS instrument (Agilent 6470) called number 199 at The Clinical Chemistry Lab, Norra Älvsborg County Hospital, to analyze methylphenidate and ritalinic acid in urine. Verification will take place in comparison with another similar instrument called number 198, this is to ensure that, to the greatest extent possible, there is an instrument available to analyze methylphenidate and ritalinic acid and thus that test results are not delayed.

Methods: The verification plan included conducting the inter and intra series precision using low and high controls with ten and five repetitions respectively. Also, method comparison was performed by analyzing urine samples from 20 patients on both instrument 199 and 198. In addition, the lower limit of quantification (LLOQ), sample stability over time, carryover between runs were determined. An ion suppression test was also performed to study possible matrix effects.

Results: The inter and intra series precision for methylphenidate and ritalinic acid resulted in a correlation of variance <10%, which was according to set targets. The method comparison showed good correlation, with R2 = 0.99 for both methylphenidate and ritalinic acid. Ritalinic acid on instrument 199 was 0.38% lower than on instrument 198, approximately -11.50 µg/L, while methylphenidate on instrument 199 was 1.9% higher than on instrument 198, approximately 18.51 µg/L. These small differences have no medical significance and are below the set targets. The LLOQ for ritalinic acid was measured to be 25 µg/L, and for methylphenidate to be 25 µg/L. There was no ion suppression observed where the analytes eluted. Carryover between runs was <20%, so the instruments use of the "multi-wash" method reduced contamination to a negligible level. Methylphenidate and ritalinic acid were stable for at least one week after the processing of samples.

Coclusion: From this study it can be concluded that the method on the new instrument (199) works as well as on the old instrument (198). Thus, instrument 199 can be reliably used to analyze both methylphenidate and ritalic acid.

Minimal impact on image quality through intake of glucose and sweeteners during combined positron emission tomography (FDG-PET/CT) - A potential improvement in our clinical work

By Anna-Karin Blomqvist

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, 2024
Supervisors: Caroline Schmidt, Associate Professor, Anna Dudás, Nuclear Medicine Specialist, Emilia Gianello, Biomedical Scientist

Background

An FDG-PET/CT scan is conducted to assess whether a patient has cancer or to investigate its extent. Typically, Fluorine-18 labelled with the tracer 2-[18F] fluoro-2-deoxy-D-glucose (18FDG) is used, utilizing the cell's natural glycolysis process. The issue with this radioactive isotope and tracer is that some patients accidentally ingest glucose through medications, snuff, and chewing gum, among other things, despite existing restrictions prior to the examination. The study aimed to investigate whether minimal amounts of glucose or sweetener intake affect image quality in FDG-PET/CT scans.

Method

The data consisted of a test group (n=67) and a control group (n=13), where images from FDG-PET/CT scans were reviewed for image quality and Standard Uptake Value (SUV) in the liver and muscles. This was carried out at Sahlgrenska University Hospital, Gothenburg, in the Department of Nuclear Medicine.

Results

There was a significant difference ($p < 0.001$) between the test group and the control group, with a difference in image quality of 0.3 quality points in the assessment, where the image quality of the test group was minimally better. Regarding SUV, the test group showed a lower mean and median uptake in both the liver and muscle. The p-value was statistically significant for SUV.

Conclusion

The test group, consisting of patients who had ingested minimal amounts of glucose or sweeteners prior to their FDG-PET/CT scan, experienced minimally impacted image quality. However, this impact is considered negligible.

Individuals that regularly exercise at Low intensity have a lower risk for coronary plaque

By Oskar Carlsson

Bachelor thesis in Biomedical Laboratory Science performed at the Wallenberg laboratory, Shalgrenska Academy, University of Gothenburg, 2024
Supervisor: Caroline Schmidt, Associate Professor

Background

Cardiovascular disease (CVD) is one of the most common causes for death in Sweden and has multiple risk factors. Such as: lifestyle, hypertension, smoking and age. The cause for CVD is quite often atherosclerosis that can in turn rupture and cause complications for the individual. An active lifestyle can mitigate some of the risks for CVD and especially with more intensive physical activity.

Aim

The aim of this study was to investigate the relationship between individuals daily activity measured with an accelerometer, with the coronary artery calcium score (CACS) assessed with Coronary Computed Tomography Angiography (CCTA), in 1770 individuals.

Method

Total of 1894 Swedish people in the area of greater Gothenburg, at an average age of 58 ± 4,5 comprised over 846 men and 1048 women. Individuals were screened for with Impaired glucose tolerance or impaired fasting glucose. They had two more visits and body measures, blood sample, feces test, completing a questionnaire and a CCTA scan. The data was collected between September 2013 and June 2018.

Results

Low intensity physical activity (LIPA) was significantly correlated with CACS, and also the only physical intensity with statistically significant correlation with CACS. Steps/day had no significant correlation with CACS. Age, overweight, higher BMI, increased waist circumference had statistically significant correlation, as well as systolic/diastolic blood pressure and cigarettes/year. All markers from the blood sample were also significantly correlated apart from high sensitivity C-reactive protein (hsCRP) and cholesterol.

Summary

A significant association between LIPA and CACS have been observed in this study, and insignificantly for the other volumes of intensity. These associations differ from other similar studies and could be caused by insufficient amount of time spent exercising at the insignificant intensities.

PREANALYTICAL STABILITY OF IONIZED CALCIUM IN SST-TUBES BEFORE CENTRIFUGATION AND SEPARATION

By Jonas Carlsteg

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Chemistry, Halland's Hospital Halmstad, 2024

Supervisor: Per Bengtson (Hospital Chemist, Ph.D.), Jan Miller (M.D Laboratory Medicine)

Background: Calcium is an essential mineral in the human body, critical for many physiological processes such as nerve signaling, blood coagulation, and muscle function. Calcium exists in various forms, but the most relevant one is often Ca^{2+}. Proper pre-analytical handling of blood samples is crucial to ensure reliable results in the analysis of Ca^{2+} concentration. Previous research has shown that storage time before centrifugation can affect the concentration of Ca^{2+} in blood samples, but recommendations vary. This study aims to investigate how storage time affects Ca^{2+} concentrations to confirm the viability of this method change.

Method: Thirty healthy individuals participated in the study, and venous blood samples were taken and stored at room temperature at different time intervals (30, 60, 120, 240 minutes) before centrifugation. The concentrations of uncorrected and pH-corrected Ca^{2+} were analyzed using a blood gas instrument (ABL825 Flex, Radiometer Medical). Linear mixed-effect models were used to evaluate the impact of time on Ca^{2+} concentrations, and Bland-Altman analyses were performed to compare uncorrected and pH-corrected values. Limits for analytical (±1%) and clinical (±6.69%) significance were based on instrument precision and reference change values derived from the biological variability database, respectively.

Results: Uncorrected Ca^{2+} showed a very small decrease over time (-3.35×10^{-5} mmol/L per minute, $p = 0.041$), while pH-corrected Ca^{2+} showed a more significant decrease (-1.58×10^{-4} mmol/L per minute, $p<0.001$). Statistically significant changes were observed after 120 minutes for uncorrected Ca^{2+} ($p = 0.017$) and already after 60 minutes for pH-corrected Ca^{2+} ($p<0.001$). The Bland-Altman analysis showed a statistically significant but relatively small difference between the two methods. No samples exceeded the limits for clinical significance, although many fell outside the analytical limits.

Conclusion: Uncorrected Ca^{2+} remains stable for up to two hours before centrifugation, supporting the method change implemented at the Department of Clinical Chemistry Halmstad. In contrast, pH-corrected Ca^{2+} is significantly more sensitive to storage time and may be less reliable for longer storage periods. It may be appropriate to limit the use of pH-corrected Ca^{2+} and primarily rely on uncorrected Ca^{2+} to ensure stable and reliable results.

Calcified plaques in the coronary arteries measured with CACS after performed CCTA is highly prevalent in a healthy population with plaques in the carotid arteries

By: Susan Chow

Bachelor's thesis in Biomedical Laboratory Science performed at the Wallenberg Laboratory, Sahlgrenska Academy, University of Gothenburg, 2024.

Supervisor: Caroline Schmidt, Associate Professor

BACKGROUND: Cardiovascular diseases affect a big part of the Swedish population. Myocardial infarction can occur in both symptomatic and asymptomatic individuals, with the latter being more difficult to prevent since their heightened risks go unnoticed. The most effective way of lowering the mortality rates of cardiovascular diseases is to screen healthy individuals and prophylactically establish life-style changes.

AIM: The prevalence of coronary artery plaques in a healthy population with plaques in their carotid arteries will be determined to establish if carotid artery plaques is a risk factor for predicting plaques in the former vessels.

METHOD: 1795 healthy individuals born in Sweden and currently living in the area surrounding Gothenburg were included in the study. Their carotid arteries were examined for intima-media thickness (IMT), lumen diameter (LD) and presence of plaque with ultrasound and the coronary arteries with coronary artery calcium score (CACS) from the non-contrast part of a coronary computed tomography angiography (CCTA) imaging.

RESULTS: 813 men and 998 women were among the examined, of which 527 had no detectable plaques in any sites and 536 had plaques in both examined vessels. CACS>0 was found in 56.1% of the group with carotid artery plaques, whereas 37.2% of the coronary artery plaque-group had no plaques in the carotid arteries.

CONCLUSION: Plaques in the coronary arteries is highly prevalent in the group with carotid artery plaques, which as a result can be used as a risk factor to warrant screening of coronary artery plaques in healthy populations.

Comparison Between the AI based Software TruCorr and Manually Reconstructed Images during Myocardial Scintigraphy with D-SPECT

By Lydia Engholm

Bachelor thesis in Biomedical Laboratory Science, performed at the Department of Clinical Physiology, Östra Hospital, Sahlgrenska Academy, University of Gothenburg 2024

Supervisor: Jörgen Elgqvist, Medical Physicist PhD, Associate Professor and Rebecka Larsson, leg. Biomedical Scientist.

Background: Myocardial scintigraphy is a medical examination used to evaluate the coronary artery blood flow to the myocardium. In nuclear medicine, tissue attenuation occurs when the emitted radiation is absorbed or scattered in patient's tissue. To minimize the problem with attenuation as much as possible, attenuation correction is used. At Östra Sjukhuset, Göteborg, myocardial scintigraphy performed in two positions (upright and supine) using a dedicated single photon emission computed tomography (D-SPECT) system, makes it possible to correct for attenuation. If the reduced uptake has different locations in the images from the different positions, likelihood that it is an attenuation artifact increases.

Artificial intelligence (AI) in healthcare is becoming increasingly common. There is ongoing research and evaluation in nuclear medicine regarding the use of AI for attenuation correction. TruCorr, an AI-based software, can recreate information about emitted radiation and be used for attenuation correction in myocardial scintigraphy.

Aim: To evaluate if there is an equivalence between images using manual reconstruction and images for which the AI software TruCorr has been used for attenuation correction.

Material and Methods: A retrospective cohort study was performed, in which patients who underwent myocardial scintigraphy on a D-SPECT system were included. Exercise stress tests and imaging were performed before image reconstruction, using both manual and TruCorr reconstruction. Physicians assessed and scored the degree of similarity between the different reconstruction methods, using a three-point scale (1- Major differences, 2- Small differences, 3- Equal). Means were calculated for both positions (upright and supine), and Cohen's Kappa coefficient was used for an agreement score.

Results: Mean (±standard deviation) for upright 1,64 (±0,43) and supine 1,77 (±0,49), Kappa agreement score, $\kappa = 0,68$. Patient examples show that the attenuation artifacts became smaller when TruCorr was used.

Conclusion: There is an equivalence between the different reconstruction methods. However further studies are needed including larger study populations and more assessors.

EMG findings in inclusion body myositis- a population based study in Västra Götaland 1985-2017

By Josefin Engström

Bachelor's thesis in Biomedical Laboratory Science performed at the department for clinical neurophysiology at Sahlgrenska university hospital, Gothenburg, 2024.

Supervisor: Joakim Strandberg, M.D., Ph.D. and Ulrika Lindgren, M.D., Ph.D.

Introduction

Inclusion body myositis (IBM) is the most frequent idiopathic inflammatory myopathy in patients over 50 and affect approximately 2,5 per 1 million in Västra Götaland, Sweden. It is characterized by slow progressive asymmetric muscle weakness of striated musculature. IBM is hard to diagnose and is often overlooked or misdiagnosed as ALS or normal ageing. The diagnosis is confirmed by histopathologic assessment of muscle biopsy. Electromyography (EMG) is performed as part of the IBM investigation, however, EMG findings for IBM is not yet fully known.

The aim of this study is to review EMG findings in IBM patients to identify which muscles most frequently present with pathological findings as well as how common myopathic findings are.

Method

The study is a retrospective population based review of 89 patients with biopsy confirmed IBM between 1985-2017 in Västra Götaland, Sweden. The findings were categorized as myopathic, suspected myopathic, pronounced myopathic, neurotic, suspected neurotic, normal, pathological, suspect pathological, mixed picture, spontaneous activity, or spontaneous activity with polyphasia. Findings in contralateral muscles as well as findings in different regions of one muscle were combined. For review of the myopathic frequence, findings were classified as myopathic, including suspected and pronounced myopathic, other assessments were classified as non-myopathic.

Results

The study found the most commonly examined muscles to be interosseus dorsalis I (IOD), trapezius (TZ), biceps brachii (BB), tibialis anterior (TA), paravertebralis (PVB), flexor digitorum profundus (FDP), flexor carpi radialis (FCR), extensor digitorum communis (EDC), deltoideus (DD), quadriceps femoris (QF), gastrocnemius and adbuctor pollicis brevis. 11 of the 12 muscles examined showed higher frequency of myopathic findings and 8 of the 12 muscles showed between 3,0-7,7% mixed findings. Muscled with the highest incidence of myopathy were QF (75%), FDP (89,5%) and BB (75,6%).

Conclusion

This study found the most common pathological findings in the examined muscles to be myopathy. The muscles that most frequently expressed myopathic findings were where quadriceps femoris (75%), flexor digitorum profundus (89.5%) and biceps brachii (75.6%).

A Time-Lapse Study of Cryopreserved Human Embryos:

Rate of development in relation to pregnancy and birth

By Emelie Ewards Thulin

Bachelors thesis in Biomedical Laboratory Science performed at Reproduction Medicine, Sahlgrenska University Hospital, University of Gothenburg, 2024.

Supervisors: Julius Hreinsson, PhD, Hannah Park, med. LIC., Kersti Lundin, docent

Background: In IVF treatment, the oocyte is fertilized outside in vitro and then cultured in an incubator until the embryo is transferred to the patient. Culture now often takes place in a time-lapse incubator connected to a computer that shows the embryo in real time and saves film sequences for assessment afterwards. The embryos that are not transferred immediately after cultivation can be cryopreserved, then thawed and transferred at a later occasion. The aim of the project is to identify whether there is an optimal time, day 5 or 6, for cryopreservation of embryos based on their developmental stages and morphology at specific times. Through annotations and assessments using time-lapse technique, it is investigated whether there is a correlation between the embryos' development rate and outcome after transfer.

Method: The study included 354 couples who had undergone IVF treatment at Reproductive Medicine, Sahlgrenska University Hospital. A total of 510 cultured blastocysts were obtained, which after five or six days had been cryopreserved and then thawed before transfer. The blastocysts underwent retrospective assessment using time-lapse technology. Annotations of time points for significant developmental stages were documented.

Results: Significant results showed that blastocysts cryopreserved on day 5 and which had an earlier development resulted in both more pregnancies and births than blastocysts cryopreserved on day 6 and which reached their developmental stages later.

Conclusion: The study shows that a later development of the embryo leads to both fewer pregnancies and births. Blastocysts cryopreserved on day 5 result to a greater extent in a positive outcome for the patient compared to blastocysts cryopreserved on day 6.

MAPPING CANNABINOID SIGNALING PATHWAYS IN MALIGNANT EPITHELIAL CELLS

By Vilma Gerdén Särman

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Neuroscience and Physiology, section of Pharmacology
Sahlgrenska Academy, University of Gothenburg, 2024
Supervisor: Michael Winder, PhD, Associate Professor

Background: Cannabinoids are a large group of chemical compounds with origin from the plant *Cannabis Sativa.* Today, cannabinoids are used to treat epileptic conditions and muscle spasms in patients with multiple sclerosis. In some countries, it is also used as pain relief and treatment of chemotherapy side effects, such as nausea and vomiting. In recent decades, cannabinoids and their potential as drugs for many different medical conditions has become relevant. Previous studies have suggested the cannabinoids CBD and its oxidation product cannabidiol hydroxyquinone (CBDHQ/HU-331) as potential candidates for anticancer drugs.
Aim: The aim of this study was to investigate the antiproliferative effect of the cannabinoids CBD and HU-331 on malignant PC-3 cells and to identify the signaling pathways to which these effects are mediated.
Method: PC-3 cells were seeded to 96 well plates and CBD or HU-331 were added in a wide concentration range. For each plate, one antagonist was added in different concentrations to some of the wells with CBD/HU-331 to try and block the effect of CBD and HU-331. The five antagonists that were tested were Rimonabant (CB_1 antagonist), SR144528 (CB_2 antagonist), SB-705498 (TRPV1 antagonist), ML-193 (GPR55 antagonist) and GW9662 (PPARγ antagonist). The plates were incubated for 24h and the cell viability was measured using the MTT method. Negative control with just cell medium and control cells without any substances added were included in each experiment.
Results: Treatment with CBD and HU-331, respectively, generated a significant decrease in proliferation in PC-3 cells. No significant difference in proliferation was observed in the presence of any of the antagonists, as compared to treatment with CBD/HU-331 alone.
Conclusion: The antiproliferative effects of CBD and HU-331 are not mediated through the activation of the receptors CB_1, CB_2, TRPV1, GPR55 or PPARγ. For future studies, it may be relevant to investigate whether CBD and HU-331 exert their antiproliferative effects through induction of apoptosis. Another possible pathway to explore is via topoisomerase II.

Total protein is interchangeable with factorized albumin in cerebrospinal fluid in case of subarachnoid haemorrhage

Method development in bleeding diagnostics

By: Elin Gustafsson

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Chemistry at Östra Hospital, Sahlgrenska University Hospital, Gothenburg, 2024.

Supervisors: Maria Lohmander, PhD, Technical manager, Hospital chemist.
Carina Gustafsson, Technical process manager.
Marcus Clarin, Resident physician.

Background: Analysis of cerebrospinal fluid proteins as biomarkers in central nervous system diseases has an important role in clinical diagnostics, including damage to the blood-brain barrier. Subarachnoid hemorrhage is a type of stroke that can cause barrier dysfunction and is primarily diagnosed with computed tomography and spectrophotometric analysis of cerebrospinal fluid. The light absorbance at wavelengths corresponding to oxyhemoglobin and bilirubin are analyzed to establish a diagnosis. There are no internationally recognized guidelines for interpreting the absorbance curve, and in Sweden, Equalis has drawn up guidelines for bleeding diagnostics to support Swedish laboratories with interpretation routines. In Equalis' latest guidelines, cerebrospinal fluid total protein is included as part of the assessment of the absorbance curve, but the analysis is only performed in a few laboratories in Sweden, where albumin is more commonly analyzed. Thereby, the aim of this study was to create a conversion factor that converts albumin to total protein in cerebrospinal fluid.

Method: The conversion factor was created by analyzing albumin and total protein on 45 samples containing cerebrospinal fluid on three different platforms – Alinity, Atellica and Cobas. The relative bias between albumin and total protein was calculated to constitute the factor after observing the relationship between the two analytes. Furthermore, total protein in cerebrospinal fluid is not a validated analysis at Sahlgrenska University Hospital Östra and therefore a method comparison and precision analysis were performed to ensure reliable results.

Results: Calculation of mean relative bias resulted in three different conversion factors for the separate instruments. The factors obtained showed good correspondence to measured total protein when applied to albumin. A strong linear significant relationship indicated a reliability for the conversion factor for all instruments, though conformity and bias varied for Atellica compared to Alinity and Cobas.

Conclusion: In conclusion, factorized albumin corresponds well to total protein in cerebrospinal fluid for Alinity and Cobas, but the suitability of the Atellica factor can be questioned. A conversion factor is applicable to interpret the absorbance curve to diagnose subarachnoid hemorrhage in laboratories lacking analysis of protein in cerebrospinal fluid.

Echocardiography from two worlds: A similar trend is seen in several echocardiographic parameters between dogs and humans with mitral regurgitation

By: Lovisa Gustafsson

Bachelor thesis in Biomedical Laboratory Science performed at Clinical Physiology – Sahlgrenska University Hospital, Sahlgrenska Academy, University of Gothenburg and AniCura Västra Djursjukhuset, Gothenburg, 2024.

Supervisor: Anita Persson, PhD, Biomedical Scientist and Katarina Bewig, Veterinarian.

Background: In the hearts anatomy there are several similarities, but also differences between humans and dogs, which are similarly affected by mitral regurgitation. Echocardiography is commonly used in human and veterinary medicine to assess the structural and functional aspects of the heart.

Aim: To compare echocardiographic parameters and performance between dogs and humans with different degrees of mitral regurgitation. A secondary aim was to explore Swedish veterinarians opinions concerning biomedical scientist performing echocardiography on dogs and cats.

Method: A retrospective study compared 34 dogs (9 ± 2 kg) with myxomatous mitral valve disease to 34 humans with mitral regurgitation <65 years old. Echocardiographic parameters such as left ventricular inner diameter, mitral doppler (pulsed wave), left atrium and ejection fraction were examined. Parameters were indexed to body surface area. Kruskal- Wallis and independent t-test were used for statistical analysis of each parameter in relation to the regurgitations severity. A questionnaire with seven questions was distributed to Swedish veterinary hospitals and clinics.

Results: Significant differences were observed in left ventricular inner diameter and ejection fraction between dogs and humans. A similar trend in left atrial dimension was observed with increasing severity of regurgitation between the species. For E and A waves, as well as E/A ratio, no significant differences were observed in relation to the severity of mitral regurgitation. Within veterinary practice, 19 out of 37 surveyed veterinarians expressed positivity towards biomedical scientist performing echocardiography on dogs and cats.

Conclusion: Humans and dogs vary in left ventricular size and function, that can been affected by the chosen indexing method. Similarities are observed for the diastolic parameters and left atrium. About half of the veterinarins showed positivity towards echocardiography being performed by biomedical scientist, which could open up the possibility for a bigger work field in the future.

Whole genome sequencing of HIV with NEXT generation sequencing, a comparison in specificity between Sanger and NGS with Illumina

By Tobias Hamlin

Bachelor thesis in Biomedical Laboratory Science performed at molecular microbiology, Sahlgrenska Academy, University of Gothenburg, 2024
Supervisor: Kristina Nyström, docent in clinical microbiology

HIV Drug Resistance testing is an important part in the treatment of patients, to ensure that the correct antiretroviral therapy is applied. In Sweden this is primarily done with Sanger-sequencing in order to chose suitable protease- reverse transcriptase-, and integrase inhibitors. However there are more ARTs that could be used, but Sanger can not sequence the whole genome in order to check if the virus is resistant, something that is possible with NGS.
The purpose of this study is to validate the specificity of applying NGS to HIVDR-testing in comparison with Sanger sequencing, using both Illumina and PrimerID. Samples from monitored HIV positive patients were selected with a variation in viral load, subtype, and mutation pattern. The RNA was extracted and amplified with PCR and nest-PCR before building a library in preparation for NGS with Illumina. The acquired reads were analysed in CLC for coverage and depth as well as low frequency variants before being run through the Stanford database to check mutation patterns.
The results showed that Illumina could give the exact same information concerning mutations on protease, reverse transcriptase, and integrase, as well as subtypes provided by the previous Sanger-sequencing. The specificity showed a remarkable pickup of low frequency variants as low as 1% from sequencing on Illumina.
The presented results lead to the conclusion that NGS is a valid option for replacing Sanger-sequencing as analysis for HIVDR in Västra Götalandsregion, Sahlgrenska.

EUSTAPF and DKMGN microtiter plates are a good alternative for determining MIC using the broth microdilution method

By Ludwig Härlin

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Microbiology at Sahlgrenska University Hospital, Sahlgrenska Academy, University of Gothenburg, 2024.
Supervisor: Erika Lindberg, PhD

Introduction: Serious bacterial infections often require determination of resistance to decide which antibiotics are best suited as treatment. A method for this purpose is Broth Microdilution (BMD), where several commercial kits have appeared on the market. This method is recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to decide the Minimum Inhibitory Concentration (MIC) for specific antibiotics. The bacteria will then be classified as sensitive (S) intermediate (I) or resistant (R). Due to this the department of Clinical Microbiology at Sahlgrenska University Hospital is seeking to implement this method to decide MIC for various species of staphylococcus and gram negative rod bacteria. The purpose of this project is to verify the use of this method to decide MIC with two commercial microtitre plates, EUSTAPF and DKMGN at the department.
Method: The study is based on reference strains (23 for EUSTAPF and 35 form DKMGN) and clinical isolates (11 for EUSTAPF and 10 for DKMGN) from the routine diagnostics at the department of Clinical Microbiology. The staphylococci was tested against vancomycin, daptomycin, teicoplanin, linezolid, rifampicin and fusidic acid with the EUSTAPF plate while the gram negative bacteria was tested against colistin, meropenem, imipenem, tigecycline, trimethoprim/sulfamethoxazole and piperacillin/tazobactam with the DKMGN plate. The bacterial suspension was added to Müller-Hinton broth which was distributed to each well on the plate. The plates was then incubated for 18-24h at 36℃ before MIC was read and categorized according to SIR. Accuracy and precision for obtained values was calculated statistically through Essential agreement (EA), Categorical agreement (CA), minor error (mE), major error (ME) and very major error (VME). This was based on the total number of tests done for the reference strains and the combined result for each strain where the clinical isolates also were included.
Result: In total, the Essential agreement was measured to 95% for the EUSTAPF plate and 93.6% for the DKMGN plate. Categorical agreement was decided to 98.1% for the EUSTAPF plate and 94.4% for the DKMGN plate. However, a large proportion of VME was received for teicoplanin and piperacillin/tazobactam in particular. The best results were given for antibiotics rifampicin, fusidic acid and linezolid.
Conclusion: The results indicate that the method could be implemented at the department for a majority of the tested antibiotics. However, some of them require further tests before they can be accepted.

Testing of result outcome with new reagent cassette for cholesterol on Alinity c

By Dennis Hedin

Bachelor thesis in Biomedical Laboratory Science Performed at the Department of Clinical Chemistry, Södra Älvsborgs Sjukhus & Mölndals Sjukhus, Sahlgrenska Academy, University of Gothenburg, 2024

Supervisor: Lena Fredriksson, TPA & Maria Lohmander, PhD, TLA

Background: In the event of a suspected lipid disorder in a patient, an analysis of the lipid profile is performed at the clinical chemistry laboratory. The lipid profile includes analysis of total cholesterol in plasma as part of evaluating the risk of cardiovascular disease. An enzymatic analysis method is carried out on the Alinity c instrument with reagent cassettes. Since deviating test values were discovered in 2022, all laboratories in Västra Götaland calibrate when changing the cassette instead of after changing the reagent lot. The purpose of this study was to investigate whether there was still a need to calibrate when changing cassettes or not.

Material and methods: Plasma from patients with a cholesterol concentration close to 3 mmol/L was used which was analyzed on four Alinity c modules located at two different laboratories in Västra Götaland. Plasma was analyzed in 10 replicates using a calibrated reagent cassette. After changing cassettes without calibrating, plasma was analyzed again in 10 replicates, then calibrating and analyzing plasma again in 10 replicates on the same cassette. This was repeated with cassettes from four different lots and performed on all four instruments. In addition to this, an instrument comparison was performed with the same setup but only on one lot.

Results: Analysis with ANOVA showed that 14 of a total of 16 rounds of analysis showed significant differences in cholesterol concentration between calibrated and non-calibrated reagent cassettes ($p<0.05$) and post hoc analysis showed that 31 of 42 comparisons between cassettes had mean values that were significantly different. All mean values showed a spread of CV of 0.2-1.22%. Plasma was pooled to make an instrument comparison, which showed differences at all three cassettes after analysis by ANOVA ($p<0.05$). Post hoc analysis showed that Borås instrument 1 differed from the other instruments for 8 out of 9 comparisons. After changing cassettes between Borås instrument 1 and 2, both showed that the uncalibrated cassette had 7.8% and 5.9% deviation from the average mean value, where the deviating value was due to variation between cassettes within the same lot.

Conclusion: The difference in cholesterol concentration between several of the calibrated and non-calibrated cassettes was significant, but the actual difference was very small and and is likely due to the high precision of the instrument. The results obtained indicate that there is a large cassette-to-cassette variation within the same lot and that calibration per cassette should therefore continue.

The Quality of Blood Components is not impacted by the removal of Compocool cooling plates

By Josefin Hellström

Bachelor thesis in Biomedical Laboratory Science performed at Transfusion Medicine, Södra Älvsborgs Hospital Borås. Sahlgrenska Academy, 2024.

Supervisors: Maria Hermansson, Biomedical Scientist. Mohammad Abedi, specialist doctor.

Background: There are studies that show that the quality of whole blood and its components isn't impacted by the usage of cooling plates. It is important that the quality of blood components is maintained to make sure that the patient receives a safe component. The disadvantage with cooling plates is that they are heavy and add extra work for the personnel handling them. Therefore, the impact on the quality of blood components was investigated before removing the Compocool (Fresenius Kabi) cooling plates.

Aim: The aim of the study was to investigate how whole blood bags and its components are affected by the removal of cooling plates, by comparing component controls taken on whole blood, erythrocyte concentrates, plasma and platelets.

Material and methods: A total of 30 whole blood bags were collected from blood donors who gave consent that the blood was used for research and teaching purposes. Half of the blood bags were on a Compocool cooling plate, and the rest lay without it. The temperature was measured regularly to note when they got down to 22˚C with a cooling plate and 24˚C without a cooling plate. Parameters measured included blood status, glucose, lactate and potassium on whole blood and erythrocyte concentrates. On plasma, among other parameters, factor VIII (FVIII), total protein and erythrocyte particle concentration were measured. Thrombocyte particle concentration, leukocyte particle concentration, glucose and lactate were measured on platelets.

Results: On average it took 3 h and 7 min to reach 22 ˚C and 24 ˚C respectively. No significant differences could be seen between the groups, with the exception of potassium in whole blood and lactate in erythrocyte concentrates, where a weak significance was seen.

Conclusion: Based on the results of the study, it can be stated that the quality of blood components is not adversely affected by the removal of Compocool plates, nor by reaching 24˚C.

Drug Analysis of Syringes Used for Injecting Drugs

By Nooralhuda Hendy

Bachelor thesis performed at the chromatographic special analys, DMK, clinical chemistry.

Sahlgrenska Academy, University of Gothenburg

Supervisor: Moa Andresen Bergström

Background: People who inject drugs have a higher mortality rate compared to the general population, due to overdoses, infections, and the transmission of diseases such as HIV and hepatitis C. It is imponent to reduce the health risks associated with injection drug use. The aim of this thesis is to improve a previously developed method for measuring drugs in syringes used for drug injection.

Materials and Methods: A total of 146 syringes that had been used for drug injection were submitted by 9 different individuals at a needle exchange program in Gothenburg in 2024. Following analysis using liquid chromatography coupled with high-resolution mass spectrometry (LC-HRMS), a dose-adjusted comparison was performed. This comparison was used to distinguish the primary drug from potential contaminants to identify the main drug in each injection. The substances analyzed in the 146 syringes included Amphetamine, Methamphetamine, Methylphenidate, MDMA, Heroin, Buprenorphine, Morphine, Ketamine, Ethylphenidate, and 6-Monoacetylmorphine.

Results: The findings revealed that the majority of the syringes contained only one drug (80 syringes, 55%), with the most common drug being amphetamine (91%), followed by methylphenidate (13%) and methamphetamine (2%). Of the 146 syringes submitted, 99 matched the substances reported by the individuals with the results from the analysis.

Conclusion: Amphetamine is the primary and most common drug among the analyzed injections. The results also demonstrated the presence of contaminants in varying proportions.

Assessing Variability in Treatment-Response in Glioblastoma Cells from Different Patients Using the Cell Division Assay

By Hedvig Hjerpe

Bachelor thesis in Biomedical Laboratory Science performed at Sahlgrenska Clinical Chemistry Unit 12, Sahlgrenska Academy, University of Gothenburg, 2024
Supervisor: Pegah Johansson, Associate Professor

The standard treatment for Glioblastoma multiforme (GBM) is currently maximal surgical resection of cancerous tissue followed by parallel radiotherapy and chemotherapy. Development of tumour resistance to radiation and the primary cytostatic agent, temozolomide (TMZ), contribute to the extremely poor prognosis and recurrence rates experienced by patients. The efficacy of treatments is also influenced by individual predispositions among patients and varying tumour characteristics. Consequently, research is underway to develop new drugs, treatment alternatives, and approaches to improve prognosis and personalize treatment strategies. To facilitate individualised treatment strategies, there is a need for guidelines and methods to assess a patient's tumour-response to current treatments. The cell division assay (CDA) is a flow cytometry-based method used to measure relative responses to treatment by labelling cells able to divide using a thymidine-analogue. In this study the CDA was used to measure the response of patient-derived GBM cell lines to various treatments in vitro. The cells were seeded and then treated with TMZ, radiation and a newly developed radiosensitising drug AZD1390. The data demonstrate varied responses among the five GBM cell lines studied. Results also indicated that AZD1390 had a radiosensitising effect on some, but not all, of the cultures. The study shows the potential of the CDA to evaluate and predict treatment responses for GBM, however, the low number of biological replicates in this study warrants further investigation to establish reproducibility.

Hemolytic interference in analysis of C-reactive protein, alkaline phosphatase and pancreatic amylase

By Sam Holmberg

Bachelor thesis in Biomedical Laboratory Science performed at Alingsås Lasarett, Sahlgrenska Academy, University of Gothenburg, 2024
Supervisor: Heléne Gustavsson, PhD

One of the most common pre-analytical reasons for rejected blood tests is hemolysis. This will prolong the course of care time for patients and the healthcare need to use more resources. Because of this it is required that the thresholds of hemolytic interference are as high as possible without having a clinically relevant impact on the test results. The current thresholds are based on the reagent deliverer's recommendations, which often do not take clinical relevance into account and instead focus on the analytical qualities. This is why laboratories are recommended to perform internal studies of hemolytic interference.

The aim of this study is to investigate the influence of hemolysis on the analytes alkaline phosphatase (ALP), C-reactive protein (CRP) and pancreatic amylase on the Alinity ci instrument with the goal of optimizing the thresholds for hemolytic interference.

Hemolysate was prepared from EDTA-blood with the freeze-thaw method and diluted to 8 different levels of hemolysis. Lithium-heparinized plasma from patient samples, free from interferents, were collected and pooled separately for each analyte. They were spiked with increasing amounts of hemolysate and analyzed on the Alinity ci. The interference for each analyte was evaluated according to the acceptance criteria the reagent supplier used for establishing their recommended thresholds for hemolytic interference. ALP and pancreatic amylase had an acceptable variation of ±10% while CRP had ±5%.

ALP and pancreatic amylase deviated with -18% and -23% at the hemoglobin levels 237 mg/dL and 111 mg/dL respectively, while CRP deviated -14% at 962 mg/dL hemoglobin. Most of the deviations were found among the lower concentrations of each analyte while the higher concentrations were more stable.

The study proposes new a hemolytic index threshold for ALP at 200 mg/dL while CRP and pancreatic amylase will keep their current thresholds of 800 mg/dL and 200 mg/dL respectively. Pancreatic amylase requires further studies to ensure optimized hemolytic index thresholds.

7 minutes as standard protocol in ^{99m}Tc -MAG_3- Renography for children; potentially faster decision of diuretic administration

By Tova Ihse

Bachelor thesis in Biomedical Laboratory Science performed at Queen Silvia's children's hospital, Clinical physiology, Sahlgrenska Academy, University of Gothenburg, 2024
Supervisor: Anita Persson PhD, Leg BMA, and Tablo Abdolla Leg BMA.

Introduction: Diuretics can distinguish mechanical and functional obstructive uropathies, however, 20 minutes of imaging is required when performing children's ^{99m}Tc -MAG_3- Renography before diuretic decision. A time-saving protocol may be beneficial. Accepted threshold method of 85% residual activity after 7 minutes for diuretic assessment is proposed.

Aim: The aim of the study is to investigate if the standard protocol can be reduced from 20 to 7 minutes while maintaining the result and quality, utilizing the 85% threshold. Furthermore, enable faster estimation of diuretic administration while adhering to guidelines.

Material and method: A retrospective study based on performed renograms (F+20) in the last 6 months was conducted in *Hermes.* A total of 50 patients were randomly selected. Patients were excluded if they only had one kidney, performed Iohexol simultaneously or deviated from standard procedure. Edited renograms of 73 pictures (7 min) was collected with the original imagine. The patients were anonymized. Information regarding age, gender, diuretic administration, late imagines were noted. According to the 85% threshold patients were grouped based on diuretic requirement (YES/NO) after 7 minutes. Patients with ≥85% activity were classified as YES. Descriptive statistic, agreement, diagnostic analysis, and inter-observer variation were performed.

Results: Among the 50 selected patients, 3 were excluded due to Iohexol. Age ranged from 1-18 years, consisting of 29 boys and 22 girls. The methods correspond in 38 of 47 cases regarding diuretic decision, 9 patients received a false positive result with the 7-minute method. Agreement was observed in 37 of 47 cases between a physician´s assessment (7 minutes) and the original imagine (20 minutes). The most suitable threshold resulted in 85%, yielding high sensitivity (1,0) and a relatively high specificity (0,68). McNemars test revealed a statistic significant result (p=0,04), systematic differences were observed between the time points, with 7 minutes showing a higher proportion requiring diuretics.

Conclusion: The 85% threshold after 7 minutes is considered appropriate and facilitates a potentially faster diuretic decision. The conclusion is that the 7 min protocol cannot fully maintain the same quality and result as the original imagine due to false positive results but possesses high sensitivity which can support the purposed method.

Optimization and validation of markers used in immunohistochemical diagnostics, with a focus on pretreatment and visualization systems

By Jonathan Johansson

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Pathology, Sahlgrenska University Hospital, 2024

Supervisor: Ylva Magnusson, PhD

Background: Immunohistochemistry (IHC) is a diagnostic technique used to detect specific proteins in tissue samples using antibodies. This study aims to optimize and validate pre-treatment and visualization methods in IHC, focusing on transitioning from microwave-based antigen retrieval (AR) to the PT Link system and from the Dako EnVision Real to the Dako EnVision Flex visualization system.

Methods: Ten different antibodies were utilized, with six tested for both pre-treatment and visualization methods and four only for visualization. Positive patient samples from Sahlgrenska University Hospital's archives were used to compare microwave AR with the PT Link system and the two visualization systems. The results were evaluated through microscopic grading and statistical analysis using the sign test in SPSS.

Results: The study demonstrated that the PT Link system outperformed microwave AR by providing stronger and more consistent staining, enhancing diagnostic accuracy and reducing the risk of false negatives. No significant difference was observed between the Dako EnVision Real and Dako EnVision Flex visualization systems, although some antibodies performed better with the newer Flex system.

Conclusion: The PT Link system has been adopted as the standard for AR at Sahlgrenska University Hospital for the tested antibodies, improving workflow and patient safety. Both visualization systems are used depending on the specific antibody's performance. This study contributes to ensuring higher quality and reliability in IHC diagnostics.

Left atrial strain – association with other cardiac pathologies

By Ameliné Karlander

Bachelor thesis in Biomedical Laboratory Science performed at Norra Älvsborgs Länssjukhus, Sahlgrenska Academy, University of Gothenburg, 2024

Supervisor: Sofie Ahlin, MD. PhD.

Introduction

During the 1950s ultrasound emerged as a pioneering medical imaging modality, primarily focused on visualizing the human heart. This method is known as echocardiography today. Throughout the development of echocardiography, different measurements of cardiac physiological functions have emerged, including atrial strain. Atrial strain is a technique that measures atrial deformation during contraction and relaxation. In several different heart pathologies, mobility can be compromised for numerous reasons, making atrial strain measurement potentially indicative of different cardiac diseases.

Aim of study

The aim of this study is to investigate the potential association between atrial strain and cardiac pathologies.

Materials and methods

This retrospective study analyzed images and data from 177 patients. Atrial strain was performed on apical views of the heart from both the two-chamber and four-chamber views- Data on atrial strain and information about cardiac diseases were compiled into an Excel spreadsheet. Correlation between atrial strain and cardiac pathologies was analyzed using Pearson's correlation test, point-biseral correlation test and Spearman's correlation test. Gender differences in anthropometry and the presence of cardiac pathologies were analyzed using independent t-tests and chi-square tests.

Results

This study included 177 participants (81 females, 96 males) with a mean age of 69 years. Left atrial strain correlated significantly with age for both genders. Significant correlations were observed between left atrial strain and cardiac rhythm, chamber size, atrial size, indexed atrial volume, valvular abnormalities, insufficiencies, filling pressure and ejection fraction, with some gender specific differences.

Conclusion

This study investigated the correlation between left atrial strain and various cardiac pathologies. The results demonstrate that left atrial strain is associated with anthropometric data, cardiac rhythm, chamber dimensions and valve diseases. Despite some limitations, the study provides valuable insights into the role of atrial strain in assessing heart function and the risk of heart failure, which may have clinical relevance for patient care and treatment.

Sphingosine-1-phosphate's Relation to Retinopathy of Prematurity in Extremely Preterm Infants - Analysis of sphingosine-1-phosphate in serum using LC-MS/MS.

By Mareta Khachatryan

Bachelor thesis in Biomedical Laboratory Science peformed at Natrium, Sahlgrenska Academy, University of Gothenburg, 2024.
Supervisor: Anders Nilsson, Researcher

Premature birth increases the risk of retinopathy of prematurity (ROP), a vascular disease affecting the retina. ROP can result in impaired vision and, in severe cases, blindness. Sphingosine-1-phosphate (S1P) is a lipid with an impact on retinal vascular development and may thus be a relevant biomarker for ROP. This study aimed to investigate potential correlations between S1P levels in serum from extremely preterm infants and their relationship to ROP, as well as to evaluate S1P's potential as a biomarker for this condition. The study included 35 infants born before gestational week 28, with serum samples collected from umbilical cord blood and at various postnatal time points. S1P levels in serum were analyzed using LC-MS/MS. Mann Whitney U-test was used to examine any significance, comparing infants who developed no/mild ROP (stage 0–2) versus those who developed severe ROP (stage 3 and/or treated).
The results from the analysis of 287 serum samples from the 35 infants indicated no significant difference in S1P levels between infants classified with no/mild ROP (stage 0–2) compared to those with severe ROP (stage 3 and/or treated). However, a statistical significance was observed at postnatal week 12, suggesting a potential association that requires further research to understand S1P's role in ROP in preterm infants and its potential clinical significance. Identifying biomarkers like S1P could be crucial for early detection and treatment of ROP in preterm infants, thereby reducing the risk of vision impairment and blindness.

Clinical value of routine-EEG in the investigation of suspected epilepsy in children

By Adina Landgren

Bachlor thesis in Biomedical Laboratory Science performed at the department of clinical neurofysiology at Sahlgrenska University Hospital, Shalgrenska Academy, University of Gothenburg, 2024
Supervisor: Joakim Strandberg, Associated Professor.

Epilepsy is a condition categorized by random uncontrollable activation of the brain. The prognosis of the disease is usually benign and easily treated with medication. Despite its positive prognosis is there a great deal of misdiagnosis and a reexamination of the disease can take up to 10 years. Routine electroencephalography (REEG) is a common test for epilepsy suspicions. It´s a cheap and non-invasiv test but it displays a variety of flaws, many of which are well known. The aim of this study is to investigate the value of REEG in the diagnostic process of child epilepsy.

The study is a retrospective study which collected information by investigating journals and patient data conducted at the department of clinical neurofysiology at Sahlgrenska University hospital. The patient data was taken from examinations done in the year of 2015 on children (age <17) with a suspicion of an epileptic diagnosis.

The result of this study showed an recurrence rate of a second seizure in 89,5% of patients who showed epileptic activity in the REEG-test. Patients who didn´t show epileptic activity had a prevalence of a second seizure in 68% of the cases. The yield of epileptic activity in REEG was 32,7% and low frequency activity had a yield of 26,5%. REEG showed a specificity of 75% and a sensitivity of 71%.

In conclusion the study showed that REEG gives a somewhat reliable result when displaying negative- and positive results. Though the result needs to be viewed with caution. REEG is an valuable source for further information about the patients condition but preferably should be combined with other examinations to accurately determine an epileptic diagnosis in children.

When is a highly skilled ultrasound specialist necessary in the emergency department?

By: Martin Larsson

Bachelor thesis in Biomedical Laboratory Science performed at Clinical Physiology – Sahlgrenska University Hospital, Sahlgrenska Academy, University of Gothenburg, 2024
Supervisors: Dritan Poci, Associate Professor, Caroline Schmidt, Associate Professor

Introduction

This study investigates non-invasive imaging techniques, focusing on ultrasound and echocardiography, in the diagnosis and treatment of heart diseases at Sahlgrenska University Hospital. By analyzing data from echocardiographic examinations conducted between October and December 2023, the role of echocardiography in the diagnosis and assessment of cardiac function in the Emergency Department is evaluated. Echocardiography is crucial for complementing clinical assessments of heart failure, ischemic heart disease, valvular diseases, and arrhythmias.

Objective

The aim of the study is to map the high-competence echocardiographic interpretation at the Emergency Department of Sahlgrenska University Hospital (SU/S).

Methods and Materials

This retrospective study reviewed data from transthoracic ultrasound examinations of 94 patients. Patient data, including demographics, clinical information, and ultrasound results, were collected from AGFA Healthcare and Melior. The analysis included patients referred for transthoracic ultrasound within 48 hours of arrival at the emergency department.

Results

The study included 94 patients with a mean age of 68 years. The patients were categorized based on their conditions: angina pectoris, heart failure, arrhythmias, infections, and other conditions. Ejection fraction was distributed in four ranges, with 73.9% of the population falling within the 55-65 range. The results showed that the majority of acute referrals yielded normal findings.

Conclusion

In summary, we suggest that clinical assessment should be the cornerstone before ordering specialist examinations.

Connection Between Immunohistochemical expression of p53, Mismatch Repair Protein Deficiency and Clinical Outcomes in Ovarian Clear Cell Carcinoma

By Elina Lövdahl

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Pathology, Sahlgrenska University Hospital, University of Gothenburg, 2024
Supervisor: Claudia Mateoiu, PhD

Epithelial ovarian cancer (EOC) is one of the most lethal gynaecological cancer types. This cancer type is divided into five subgroups of which ovarian clear cell carcinoma (CCC) is one of them. The diagnosis and treatment for CCC is not optimal to this day.
Hence the aim of this study was to determine if connection between p53 alterations, mismatch repair protein (MMR) and the clinical results and characteristics of the CCC-patients exists. If connection exists, it may mean that The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) can be applied to CCC. If this is the case it means that a more effective treatment and diagnostics can be applied for CCC patients and there by less suffering for the patients.

The study was performed by examining the p53 expression of scanned images of Tissue Microarray slides, consisting of 38 CCC cases. In addition, medical history from all 38 cases was collected to identify the characteristics of the individuals and their cancer.

In conclusion connection was found between p53 expression and the clinical outcome of CCC-patients, which implies that ProMisE can be applied to CCC. Among other things, there was correlation between mutated p53 expression and bilateral tumors, relapse of tumors, positive cytology, and tumors in stage III. However, some parts of the result deviates in relation to literature, which may be due to the small sample size in this study. Correlation with MMR could not be assessed in this study because there were not enough patients with aberrant MMR.

ADRENOCORTICOTROPIC HORMONE IS STABLE FOR UP TO TWO HOURS REGARDLESS OF TEMPERATURE

Analysis on CobasPro e801 and Alinity c

By Rozita Mafi

Bachelor thesis on Biomedical Laboratory Science performed at the clinical chemistry laboratory, Sahlgrenska Academy, 2024
Supervisor: Anders Olsson, PhD and Karin Lundberg, MSc

Adrenocorticotropt hormone (ACTH) is a hormone produced in the pituitary gland and secreted in response to stress. Abnormal levels of ACTH in the body can lead to diseases such as Addison's disease, Cushing's syndrome and adrenocortical insufficiency. The purpose of this study was to observe how the stability of ACTH in plasma is affected by factors such as time, temperature and hemolysis. Ten samples in EDTA tubes were collected and handled according to current descriptions for ACTH samples. A custom hemolysate was prepared to achieve the desired hemolysis index. The plasma samples were divided into two parts, a high and a low pool. Each pool was divided into 27 samples, totaling 54 samples. Sodium chloride and two different hemolysis indices were added to each sample along with plasma. The samples were stored for different durations: two hours, 18 hours, and 42 hours. They were stored at different temperatures: 4°C, 20°C, and 37°C. The samples contained different dilution solutions: either sodium chloride, hemolysis index 200, or hemolysis index 800. The samples were analyzed on CobasPro e801 to obtain the ACTH concentration and on Alinity c to obtain the hemolysis index. The results showed that ACTH is stable for up to two hours at room temperature and elevated temperatures as long as hemolysis is not present in the samples. When stored at cold temperatures, ACTH has a longer stability of up to 42 hours as long as hemolysis is not present in the samples. The results were presented in the form of graphs. The conclusion was that ACTH can remain stable for up to two hours at any temperature provided that hemolysis is not present, but the stability is longer at cold temperatures.

Genotyping of risk alleles using real-time PCR in celiac disease

Evaluation of a new method for HLA-genotyping

By: Ruqaya Mohammed

Bachelor thesis in Biomedical Laboratory Science performed at the Tissue Typing Laboratory

Sahlgrenska Academy, University of Gothenburg 2024

Supervisor: Pauline Isakson, PhD

Human leukocyte antigens (HLA) are molecules found on the surface of the majority of the body cells. HLA-genes are known for their variation between individuals, which is called polymorphism. Those antigens play an important role in the immune system of the human body. Celiac disease is an autoimmune disease that is primarily linked to two HLA-genotypes, known as DQ2 and DQ8. An autoimmune disease is a condition in which the body's immune system mistakenly attacks its own tissues, leading to potential inflammation and damage. The disease in question is very common worldwide, thus it is very important to use good, rapid and effective methods to diagnose patients. Quantitative Polymerase Chain Reaction (qPCR) is a sensitive and user-friendly molecular technique suitable for HLA typing. It enables the identification of HLA alleles. Therefore, qPCR appears to be a more suitable option for HLA-typing compared to the currently established method, Eurimmun Microarray. The aim of this study is to compare two methods for HLA genotyping to potentially establish a new qPCR-based method for celiac disease analysis. In this study, the genotyping results of 12 blood samples from microarray were compared with those obtained from qPCR using a new kit, LinkSēq™ HLA – DQ2, DQ8, DQA105 Typing Kit. The results showed that the kit failed in finding the majority of the risk-alleles for celiac. Therefore, it cannot be used. However, additional studies are required to validate the findings of this test using a larger sample number of blood samples.

Keywords: HLA Typing/ Celiac disease/ HLA DQ2/ HLA DQ8/ qPCR/ Microarray

Characterization of alkaline phosphatase isoenzymes in breast milk using Western Blot

By: Tina Nayeri

Bachelor thesis in Biomedical Laboratory Science, Sahlgrenska Academy, University of Gothenburg 2024.
Performed at the Department of Neuroscience and Physiology Academy, University of Gothenburg.
Supervisor: Ulrika Sjöbom Msc
Co-supervisor: Anders Nilsson PhD

Background: In Sweden, 8% of extremely premature infants suffer from necrotizing enterocolitis (NEC) which is a potentially deadly intestinal disease. It has previously been reported that isoenzymes of alkaline phosphatase (ALP) could have a preventive effect against NEC. ALP has four protein encoding genes that are present in humans: non-specific (TNAP), intestinal (iALP), placental (pALP), and germ cell (gcALP). Studies have also shown that iALP has a positive effect on intestinal integrity. How much ALP in breast milk contributes to increased ALP levels and reduced intestinal permeability is unknown. The composition of ALP isoenzymes in breast milk has also not been reported. This project aims to optimize a Western Blot to determine which isoenzyme(s) are present in breast milk.

Materials and methods: Western Blot of human breast milk samples, recombinant proteins (iALP, pALP, gcALP), plasma (TNAP), and purified ALP from *Escherichia coli* (as negative control) was performed. A polyvinylidene fluoride membrane was used and immunodetection was done with primary antibodies against TNAP, iALP, pALP, and gcALP—detected with an HRP-conjugated secondary antibody and CCD-camera, for visualizing the bands. With Dot Blot technique, the detection limit against recombinant iALP was optimized by utilizing various concentrations of primary and secondary antibodies.

Results: The electrophoresis and protein transfer was successful, but immunodetection was poor, and cross-reaction occurred by the primary antibodies against recombinant proteins iALP, pALP, and gcALP. In this project, the isoenzymes of ALP could not be detected in breast milk or plasma; hence, it was not possible to determine which isoenzyme(s) were present in breast milk. Through Dot Blot, the optimal dilution of the primary antibody against recombinant iALP was 1:1000 and the secondary HRP-conjugated antibody 1:5000. The detection limit was 1 ng for recombinant iALP.

Conclusions: The poor sensitivity of the method was assumed to be why ALP in breast milk or plasma was never detected. Throughout this study, the concentration of ALP was never found, which makes it appropriate to determine with commercial ELISA kits before performing further studies aiming at investigating if it is possible to identify the isoenzyme(s) with Western Blot. The enzymatic activity of ALP is well-known. Further research is needed to characterize the composition of ALP in breast milk and its effects on extremely premature infants. This study provides a starting point for a method to use if one wants to identify which isoenzyme(s) are present in breast milk with Western Blot.

Can heart dysfunction from oncological treatment be detected by NT-proBNP?

By Carl Nilsson Melin

Bachelor thesis in Biomedical Laboratory Science performed at Sahlgrenska Academy, University of Gothenburg, 2024
Supervisors: Caroline Schmidt, Leg, BMA, Docent; Lovisa Doracic, Leg. BMA

Introduction: Breast cancer is the second most leading cause of death among women in Sweden. Breast cancer is functionally divided into different types of tumors, of which 15% is HER2-positive. Cytostatic treatment with trastuzumab has increased the survival rates and prognosis of patients affected by HER2-positive breast cancer, but the treatment comes with the risk of developing trastuzumab induced cardiotoxicity (TIC). Heart monitoring is primarily performed with echocardiography, but several studies have investigated the possibility of using diagnostic biomarkers such as NT-proBNP as alternatives.

Purpose: The purpose of this study is to investigate the ability of NT-proBNP to predict subclinical cardiotoxicity in patients treated for HER2-positive breast cancer with trastuzumab, by comparing the test values to LVEF and GLS taken with echocardiography.

Method and materials: This is a quantitative study with data collected from cancer patients being treated with trastuzumab at Sahlgrenska University Hospital. Examinations screening for LVEF, GLS and NT-proBNP were aggregated and organised in order before, during and after the treatment period in order to compare these values over time. Control examinations performed at the start of treatment were designated as baseline values.

Results: Data from a total of 20 patients were used in this study. The majority of patients did not have enough measurements for LVEF, GLS and/or NT-proBNP, which made any further statistical analysis unfeasible.

Conclusion: The question posed by the study could not be answered due to a lack of relevant data and a small sample size. More research is required on the topic with attention to larger population groups and better data collecting methods.

Significance: NT-proBNP has the potential to offer an easier and significantly cheaper alternative to echocardiography for monitoring cardiotoxicity in patients being treated for trastuzumab.The study can be seen as a foundation for further research within the field.

Establishment of an Immunohistochemical Triple Staining Method for the Diagnosis of Ductal Breast Carcinoma

By Johanna Osbeck

Bachelor thesis in Biomedical Laboratory Science performed at the Sahlgrenska hospital, pathology
Sahlgrenska Academy, University of Gothenburg, 2024
Supervisor: Ylva Magnusson, Chief biology

Breast cancer is the most common cancer among women and one of the leading causes of cancer-related deaths. Early and accurate diagnosis of ductal carcinoma in situ (DCIS) and invasive breast cancer is crucial for determining appropriate treatment. Immunohistochemical (IHC) staining is an essential method for differentiating between these cancer types.

The aim of this study is to investigate the possibility of establishing an IHC triple staining method using the two platforms, Dako Omnis and Dako Autostainer to enhance the efficiency of the pathology laboratory and enable the diagnosis of DCIS and invasive breast cancer using the markers CK7, p63, and calponin. These markers are crucial for distinguishing between epithelial and myoepithelial cells.

Eighteen formalin-fixed and paraffin-embedded breast tissue samples were analyzed, including malignant core biopsies, postoperative malignant tumors, and postoperative benign tumors. Triple staining was performed using monoclonal antibodies targeting calponin (stained with DAB), p63 (stained with magenta), and CK7 (stained with Vina Green). Single staining was also performed using monoclonal antibodies targeting CK7, stained with DAB, to compare with the triple staining in identifying CK7 in breast tissue. The stainings were carried out using the Dako Autostainer and Dako Omnis instruments. The samples were graded in collaboration with the responsible pathologist on a scale from 0 to 3, based on differences in expression between the benign and malignant groups, as well as the staining quality and specificity.

The Kruskal-Wallis test showed no statistically significant differences in grading between CK7 stained with DAB and CK7 stained with Vina Green in any of the examined groups ($p>0.05$), indicating that both methods are comparable in identifying CK7 in breast tissue. Additionally, the grading assessments of CK7 stained with DAB were compared with CK7 in the triple staining for each group using the Mann-Whitney U test. No statistically significant differences were found between CK7 stained with DAB and CK7 in the triple staining within any of the three groups.

The developed triple staining method proved to be useful for distinguishing between DCIS and invasive breast cancer and has the potential to be implemented in the pathology laboratory. Future steps includes validation of the method and integration into digital pathology.

Semi-quantitative screening method towards toxic metals using the ICP-MS instrument

By Sadaf Paktiani

Bachelor thesis in Biomedical Laboratory Science performed at the Department Of Clinical Chemestry, Unit Of Enzyme- and Metalanalysis, Sahlgrenska Academy, University Of Gothenburg, 2024

Supervisor: Niklas Forsgard, Senior Chemist
Secondary Supervisor: Rikard Ylmén, Chemist

Metals represent around 25% of the weight of the earth's crust and exposure of heavy metals has increased because they are used more in various products and industries. Some metals in very low concentrations maintain various biochemical and physiological functions in living organisms, but in higher concentrations can they become harmful. In some cases, metal poisoning has been caused by an unusual metal, and there is currently a lack of good methods to quickly identify the cause of the poisoning when the source of exposure is unknown.

The aim of the study is to investigate whether it is possible to analyze patient samples and identify what they are poisoned by. To do this, semi-quantitative inductively coupled plasma mass spectrometry was used to identify unknown metal poisonings in both blood and urine.

Various tests were done to optimize the collision cell, internal standard, calibrator and various parameters in semi-quantitative inductively coupled plasma mass spectrometry. Accuracy was tested with various control samples. Normal samples spiked with toxic metals were compared to normal samples to test whether the method could distinguish patients with metal poisoning, as well as identify which metal they were exposed to.

After optimization, the method showed good accuracy. The majority of the analyzed substances in the analyzed reference materials were within +/-30% of the stated concentrations. However, there were some outliers with lower accuracy. The test with the spiked sample showed that the spiked patient sample deviated from the reference samples and the method was able to identify which substances deviated from the normal pool.

Semi-quantitative inductively coupled plasma mass spectrometry has proven to be a promising method that can quickly identify many elements in unknown patient samples, as well as give a good estimate of their concentration. But more tests are needed to optimize the method and make it better.

Sustainability and stability of fasting insulin in blood and plasma

A sustainability study performed on Alinity *i*

By Sofia Strömhäll

Bachelor thesis in Biomedical Laboratory Science performed at the department of Clinical Chemistry at the Sahlgrenska University Hospital in Gothenburg, 2024

Supervisors: Mats Ohlson, Clinical Biochemist, Ph.D. and Esmira Becirevic, Biomedical Laboratory Scientist

Background

Insulin is a peptide hormone secreted from the pancreas in response to increased blood glucose levels. The release of insulin leads to stimulation of cells to take up the glucose circulating in the blood after food intake. When production and function of insulin are not working properly in the body, it can lead to various diseases. Hypoglycemia can be observed in endocrine disorders such as insulinoma, which leads to increased insulin production and hypoglycemia. In cases of suspected insulinoma, a fasting insulin test can be performed to measure insulin concentration in the body. Despite the clinical relevance of analyzing insulin concentration, there are difficulties with storage and transportation of insulin samples. The aim of the study was to investigate the sustainability and stability of insulin in uncentrifuged lithium-heparin tubes stored at room temperature for up to 24 h, as well as in centrifuged lithium-heparin plasma stored at 4°C for up to 72 h.

Method

Four uncentrifuged lithium-heparin tubes were aliquoted and stored at 0 h, 3 h, 6 h and 24 h at room temperature before centrifugation and separation of plasma were performed in cryovials stored at -80°C prior to analysis. Eleven centrifuged lithium-heparin tubes received and analyzed in the laboratory were analyzed after storage at 4°C for 24 h, 48 h and 72 h. All samples were analyzed regarding insulin concentration on Alinity *i*. Changes in insulin concentrations >10% of the original insulin concentration after different storage conditions were considered clinically significant.

Results

Results for the 4 uncentrifuged samples stored at room temperature showed that none of the samples were sustainable after 24 h. For the 11 centrifuged samples stored at 4°C, 7 of the samples were sustainable for up to 72 h.

Conclusion

Insulin was not stable when stored in uncentrifuged lithium-heparin tubes for 24 h at room temperature, whereas storage in centrifuged lithium-heparin tubes at 4°C showed better sustainability and stability for insulin.

Effect of different fixatives on PD-L1 immunostaining

Evaluation of PD-L1 expression in different cytoblock preparations from malignant pleura fluids with lung adenocarcinoma

By Mahar Taleb

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Pathology and Cytology, Halland Hospital, Halmstad, 2024
Supervisor: Mohammed I. S. Mansour, CT, PhD

Introduction: Programmed cell death ligand 1 (PD-L1) is a transmembrane protein expressed on the surface of immune cells and some tumor cells. Non-small cell lung cancer NSCLC whose tumor cells express PD-L1 can be treated with immunotherapy called Immune Checkpoint Inhibitors (ICI). Cytological samples in the form of pleural fluids can be fixed and prepared in the same way as histological samples if they are cell-rich to form cell blocks. In this way, one can evaluate the expression of immunocytochemical markers such as PD-L1 in such sample types. Cytological samples can be fixed with several different fixatives and therefore there can be a large influence of the fixatives on the immunochemical expression of PD-L1. ***Material and method:*** The immunocytochemical expression of PD-L1 in pleural fluid was analyzed in 10 patient cases with established NSCLC. Each sample was split into two parts, one fixed in formalin and the other fixed in PreservCyt®. PD-L1 reactivity was evaluated in PD-L1 clone 28–8 and PD-L1 clone 22C3. PD-L1 positivity was studied at cutoff ≤ 1 % and ≤ 50 % and only the membranous staining was considered positive for PD-L1. ***Results:*** There is a significant difference in the intensity of PD-L1 depending on which fixative has been used. PreservCyt® appears to reduce intensity compared to formaldehyde. Prevalence in expression of PD-L1 clone 28–8 at the two cutoffs in both fixatives varied between 50 %-70 %. Corresponding to PD-L1 clone 22C3, the expression varied between 30 %-70 %. The percentage agreement in expression of PD-L1 clone 28–8 between the two fixatives was 90% (Cohen's κ=0.78) at cutoff 1 % and 80 % (Cohen's κ=0.6) at cutoff 50 %. Correspondingly for PD-L1 clone 22C3, the agreement was 100 % (Cohen's κ=1.0) resp. 70 % (Cohen's κ=0.44). ***Conclusion:*** Different fixatives seem to tend to affect the immunocytochemical expression of PD-L1 on tumor cells. Consequently, there is a risk of false negative PD-L1 reactivity when fixing in some fixatives. PreservCyt® attenuates the intensity of PD-L1 expression compared to formaldehyde.

Keywords cytology, immunocytochemistry, lung cancer, NSCLC, PD-L1, pleural fluid, predictive marker.

Association between HLA alleles and COVID-19 susceptibility

By Eskil Temnéus

Bachelor thesis in Biomedical Laboratory Science performed at the tissue Typing Laboratory, Sahlgrenska Academy, University of Gothenburg 2024

Supervisor: Pauline Isaksson, PhD

Society still feels the effects from the COVID-19 pandemic that broke out in 2020, its large effect is mainly attributed to its fast spread and a potential for severe infection. The RNA-virus has currently been estimated to be responsible for circa 7 million deaths globally. Its virology has been studied thoroughly and several genetic risk factors have been identified so far, among these are certain alleles of the human leukocyte antigen (HLA) identified as both lacking and protective for the risk of infection and its severity. HLA is a genecomplex made up of several highly polymorphic genes that play a vital role in the adaptive immune system. The carrying of certain alleles and its importance for certain diseases has for this reason been studied and a number of associations has been identified. Studies has so far identified several alleles that pose higher and lower risk for negative clinical outcomes, examples being HLA*A:02 and HLA*C:04. Findings like these can have a big role in treatment development and a higher understanding of the disease, something that even today is lacking. This study investigated HLA-alleles meaning for COVID-19 susceptibility with this study including HLA A, B, C, DRB1, DRB3/4/5, DQB1, DPB1, DQA1 and DPA1. Next Generation Sequencing was used to type a total number of 132 HLA-alleles in a sample size of 71 individuals whereas 12 where COVID-19-positive. This study could not conclude that the carrying of any of these alleles poses a higher or lower risk of susceptibility. However, several other studies have identified certain alleles as significant for susceptibility, but results seem to vary between regions. Further studies are needed that focus on this association from a genetic and molecular biological perspective to reach a deeper insight in the issue.

Keywords:
COVID-19, SARS-CoV-2, Human leukocyte antigen (HLA), HLA alleles, HLA-typing, Next generation sequencing/NGS, HLA-association, HLA-C*04:02, HLA-B*35:08, susceptibility

Performance study of the Point-of-Care instrument NEO analyzer through quantification of total bilirubin

By Lisa R. Toll

Bachelor thesis in Biomedical Laboratory Science performed at the Department of Clinical Chemistry Hallands Hospital Varberg, 2024
Supervisor: Marie Larsson

Background: Hyperbilirubinemia affects many newborn babies worldwide. Within certain concentration ranges of total bilirubin (TB) repeated sampling is required throughout the day. Sample volumes can quickly become large relative to the infant's total blood volume. This highlights the need for Point-of-Care (POC) analysis that requires low sample volumes, generates rapid analysis results, and enables quicker treatment for hyperbilirubinemia in newborns. Quantification differences exist within and between different manufacturers. Therefore, this study aims to investigate, describe, and evaluate the performance of the point-of-care instrument NEO analyzer for quantitative measurement of total bilirubin, through comparison with the laboratory method Cobas c501.

Method: This performance study was conducted at a Swedish accredited central laboratory. Fresh excess whole blood and plasma, with a bilirubin level within the concentration range of 150-500 µmol/L, were collected from de-identified individuals and stored in light-protected conditions. Two instruments were used for analysis: Roche Diagnostics Cobas module c501 for plasma and Calmark's NEO-analyzer for whole blood. Results were evaluated using statistical methods including Bland-Altman and Passing-Bablok to compare agreement between the instruments. An accepted limit of variation was set at ± 10%.

Results: The POC analysis instrument NEO-analyzer shows a statistically significant positive bias of 5% when compared to Cobas c50. Individual result differences reach a maximum of 25%. Observations of a negative bias at concentrations >350 µmol/L have been noted as NEO-analyzer does not exhibit the same linearity as at lower TB concentrations. Compared to Cobas c501, NEO-analyzer has nearly five times higher imprecision in TB analysis.

Conclusion: The advantages of a POC instrument such as NEO-analyzer include low sample volumes, faster analysis results, enabling quicker treatment for neonatal hyperbilirubinemia. However, the NEO analyzer exhibits high imprecision relative to medical needs. It is also previously known that significant level differences exist between instrument platforms in general. The NEO-analyzer is not standardized against any reference material and shows a statistically significant positive bias when compared to Cobas C501. This study was limited in scope and requires further evaluation.

Spirometry in different body positions

Sitting, supine and standing body position and their effect on lung volumes measured with spirometry

By Hanna Åslund

Bachelor thesis in Biomedical laboratory science performed at Department of Clinical Physiology, Sahlgrenska Acadamy, University of Gothenburg, 2024.

Supervisor: Anita Persson (PhD), Josefine Björck

Introduction: Spirometry is a commonly used method that provides a lot of information regarding the lung capacity of an individual. The lung capacity is very individual and can be effected by factors such as sex and body structure. Previous studies have shown that different body positions give varying lung volumes, and which position that gives the largest volume can depend on lung disease or overweight as an example.

Aim: The aim with this study is to see if a change in body position makes a significant difference in lung volumes measured with spirometry.

Method: 22 voluntary participants, both male and female, who had healthy lungs or mild asthma performed the spirometry in sitting, supine and standing position. VC, FEV1 and FVC were measured in all three positions. Smokers and ex-smokers where included. The lung volumes from the different body positions where then compared in a statistical analysis.

Result: The study showed that the lung volumes in supine position were significantly lower for VC, FEV1 and FVC. The result also showed that there was no significant difference between the sitting and standing position. Furthermore, the descriptive statistic showed that for different variables, VC, FEV1 or FVC, the largest volume measured could be either sitting or standing, depending on the variable in question. It was also shown that age and BMI had no effect on the result.

Conclusion: Performing a spirometry in supine position gives falsely low lung volumes whereas there makes no difference if the exam is done sitting or standing in regard to the lung volume. However, there are many factors that could have an effect on this exam, hence further studies are needed.