UNIVERSITY OF LATVIA
FACULTY OF MEDICINE

MONITORING OF CONTINUOUS FEMORAL NERVE BLOCK USING REMOTE PHOTOPLETHYSMOGRAPHY

DIPLOMA THESIS

Author: **Aurora Lövegren**
Student ID: 14097
Thesis supervisor: Prof. Aleksejs Miščuks, PhD

Edgars Vasiļjevs, MD

RIGA 2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologist
BMI	Body Mass Index
LA	Local Anesthetic
rPPG	Remote photoplethysmography
PPG	Photoplethysmography
VAS	Visual Analogue Scale

ABSTRACT

Title: Monitoring of continuous femoral nerve block using remote photoplethysmography.

Background: Remote photoplethysmography (rPPG) is a non-invasive imaging method of monitoring the microcirculation of the skin. This method can be implemented to monitor regional anesthesia. One of the main issues in regional anesthesia is the late and subjective prediction of block success.

Objective: The objective of the study is to measure the changes in the skin microcirculation of the knee after a femoral nerve block, by using rPPG and to evaluate whether rPPG can differentiate between placebo and LA injection in a peripheral nerve block.

Assignments:
1. To assess whether rPPG of the skin of the knee can differentiate between placebo and LA injection after femoral nerve block.
2. To compare rPPG with other conventional regional anesthesia assessment methods.

Materials and methods: We enrolled four patients to our prospective randomized double-blinded pilot study. Patients received preoperatively a continuous femoral nerve block. For the block a nurse would prepare one syringe containing *Ropivacaine* 0,375% 20mL and another syringe containing *NaCl* 0.9% 20mL placebo. Randomly chosen two patients received LA in the first syringe, while the two other patients received placebo. The rPPG camera was attached to a light source and adjusted to the desired skin area, the medical side of the knee. The imaging started a few minutes before the insertion of the femoral block and continued for 12 minutes after the injection of the first syringe and second syringe. During the imaging we assessed the block by using cold sensation and visual online rPPG mapping.

Results: After blind analysis first syringe injection in all four cases showed statistically significant increases in rPPG signal AC/DC ratio in Kruskall-Wallis ($p_{1-4}<0.001$) and showed positive time correlation ($r_1=0.161$, $r_2=0.380$, $r_3=0.125$, $r_4=0.149$, $p_{1-4}<0.001$), with some statistically significant increase after second syringe injection ($r_1=-0.072$, $r_2=0.038$, $r_3=0.043$, $r_4=0.064$, $p_{1,4}<0.05$ and $p_{2,3}>0.05$).

Conclusion:

1. The rPPG showed time sensitive changes during measurements in all groups, however rPPG couldn't distinguish LA from placebo in our small pilot study.
2. Cold sensation assessment showed 100% sensitivity of syringe content and remains the golden standard for block assessment in clinical practice.

Author: Aurora Lövegren
Supervisor: Prof. Aleksejs Miščuks, Edgars Vasiļjevs M.D.

Key words: Regional anesthesia, peripheral nerve block, remote photoplethysmography (rPPG), microcirculation.

KOPSAVILKUMS

Virsrakst: Attālinātas fotopletizmogrāfijas metode femorāla nerva blokādes monitorēšanai.

Priekšvēsture: Attālināta fotopletizmogrāfija (aFPG) ir neinvazīva ādas mikrocirckulācijas izvērtēšanas metode, ko potenciāli var izmantot reģionālas anestēzijas sekmīguma pārbaudei. Viena no reģionālas anestēzijas problēmām ir vēlīnā un subjektīvā bloka iznākuma prognozēšana.

Mērķis: Izvērtēt ādas mikrocirkulācijas izmaiņas ceļa locītavas ādā pēc prolongētas femorāla nerva blokādes ar aFPG metodi. Izvērtēt aFPG metodes efektivitāti diferencēšanā starp placebo un lokālo anestētiķu injekciju femorāla nerva blokādes laikā.

Uzdevumi:
1. Izvērtēt aFPG spēju identificēt šļirci ar lokālo anestētiķi vai placebo pēc femorāla nerva blokādes.
2. Salīdzināt reģionālas blokādes izvērtēšanas spēju ar aFPG un aukstuma aplikācijas metodi.

Materiāli un metodes: Prospektīvā randomizēti dubultaklā pilot-pētījumā tika iekļauti četri pacienti. Pacientiem pirms operācijas bija veikts prolongēts femorāla nerva bloks, ar iepriekš sagatavotām divām šļircēm: *Ropivacaine* 0,375% 20mL un *NaCl* 0.9% 20mL placebo. Šļirces satura perineirāla ievades kārtība bija randomizēta: divi pacienti pirmā šļircē saņēma LA, pārējie divi pacienti placebo. Fotopletizmogrāfijas kamera ar gaismas avotu bija nopozicionēta virs ceļa locītavas ādas mediālā pusē. Attēlveidošana ar aFPG kameru sākās dažas minūtes pirms femorāla nerva blokādes un turpinājās 12 minūtes pēc katras šļirces ievades. Reģionālas blokādes pārbaudei izmantoja aukstuma aplikācijas un vizuālas aFPG kartes.

Rezultāti: Pēc aklas FPG analīzes visos gadījumos (n=4) pēc pirmās šļirces bija novērojamas statistiski ticamas atšķirības AC/DC koeficentam aFPG signālā: ar *Kruskall-Wallis* testu ($p_{1-4}<0.001$) un pozitīvu korelāciju ($r_1=0.161$, $r_2=0.380$, $r_3=0.125$, $r_4=0.149$, $p_{1-4}<0.001$). Gandrīz visos gadījumos arī otras šļirces injekcija veicināja statistiski ticamas atšķirības ($r_1=-0.072$, $r_2=0.038$,$r_3=0.043$, $r_4=0.064$, $p_{1,4}<0.05$ and $p_{2,3}>0.05$).

Secinājumi:

1. aFPG metode atspoguļoja laika atkarīgas statistiski ticamas izmaiņas mērījumos, visās grupās, tomēr aFPG metode nevarēja statistiski ticami atšķirt LA no placebo.
2. Aukstuma aplikācijas metodei bija 100% sensitivitāte šļirces satura noteikšana, salīdzinot ar FPG, kaut arī tam bija nepieciešama pacienta subjektīva izvērtēšana.

Autors: Aurora Lövegren

Darba vadītājs: Prof. Aleksejs Miščuks, Edgars Vasiļjevs M.D.

Atslēgvārdi: Reģionāla anestēzija, perifēra nerva blokāde, attālināta fotopletizmogrāfija (aFPG), mikrocirkulācija

1. Introduction

Regional anesthesia, especially peripheral nerve blocks have become very popular in the modern days. Several different methods have been developed and there is a constant development in new techniques and equipment. Regional anesthesia has several benefits compared to general anesthesia. Several studies have shown that peripheral nerve blocks decrease post-operative pain and can be customized for each patient and their needs.

The greatest disadvantage of regional anesthesia is the lack of monitoring of the success of the block. Currently the golden standard in clinical practice is to rely on patient's subjective sensation. To ensure proper regional anesthesia it is vital to have good patient compliance. Several methods have been developed and studies have been made in order to develop a monitoring system for regional anesthesia success that would be objective. (Rosenberg et al., 2014)

Thermography is one of the monitoring methods that has been studied the most. Studies have shown that regional anesthesia causes blockade to both somatosensory, motor and sympathetic fibers. As a result of the blockade vasodilation occurs, which leads to increase in the blood flow and temperature of the skin. These temperature changes can easily be detected with by infrared thermography. (Hermanns et al., 2018)

Another fast developing and promising objective monitoring method is photoplethysmography. PPG was first introduced in the 1930's as a non-invasive optical technique that was capable of registration of blood volume changes in the blood vessels. The PPG method is based on light transmitted through or reflected from tissues modulated in time that is synchronized with the heartbeat. From the basic principles of PPG the pulse oximeter was invented in the 1970's. In year 2000 the first remote PPG was developed and since then there has been a rapid growth in the further development of PPG techniques and in its application to clinical practice. (Kamshilin et al., 2017)

U. Rubins (2016) developed an algorithm and a photoplethysmography imaging system that was efficient enough and suitable for continuous remote monitoring of the microcirculation of the skin. They developed a software that was able to process high-resolution microcirculation amplitude maps in real-time. The processing algorithm combined both spatial and temporal processing. For application to clinical practice they enrolled six

patients, who underwent surgery of the upper extremity. The rPPG imaging maps were compared with thermography images to confirm the applicability of the developed technique. The results showed that the developed algorithm showed improved sensitivity, compared to previously used methods.

U. Rubins (2017) continued their study and further developed their rPPG prototype and software. During their study they discovered that the hemoglobin absorbs light mainly in the green spectral range of light. They modified the prototype with a green optical filter to optimize the measurements. They developed a simple and convenient rPPG system for non-contact monitoring of regional anesthesia. They adjusted the prototype so that it could be used together with a surgical lamp as its light source. They enrolled eight patients, who all underwent surgery of the upper extremity. The results demonstrated that the green optical filter gave more precise rPPG maps and the surgical lamp was a sufficient enough light source.

All together the PPG is a cost-efficient and simple technique of non-contact optical monitoring of the skin microcirculation. As regional anesthesia is becoming more popular the demand for objective monitoring of block success is growing. Thermography is the method that has been studied the most, however it has some limitations as the temperature of the environment and the individual body temperature that may cause fluctuations in the measurements.

Remote PPG is a method that has not been studied as much but has showed a lot of promising results. Most studies regarding the monitoring of regional anesthesia have been studies regarding the upper extremity, more specifically the palm. The skin of the palm is glabrous and is characterized by intense vascularization that will cause dramatic vasodilation after injection of local anesthetics that will cause blockade of both somatosensory and sympathetic nerves.

Currently the rPPG has been used for glabrous skin on distal parts of the human body. To further develop the rPPG method and increase its application to clinical practice it would be useful if the rPPG could be applicable on any skin area. This would increase the clinical application to any peripheral nerve blocks and local infiltration.

1.1 Objective

The objective of the study is to measure the changes in the skin microcirculation of the knee after a femoral nerve block, by using rPPG and to evaluate whether rPPG can differentiate between placebo and LA injection in a peripheral nerve block.

1.2 Assignments

1. To assess whether rPPG of the skin of the knee can differentiate between placebo and LA injection after femoral nerve block.

2. To compare rPPG with other conventional regional anesthesia assessment methods.

2. Literature review

2.1 Regional anesthesia

The peripheral nerve blockade techniques have been developed early on in the history of anesthesia. It started with the American surgeons Halsted and Hall, who injected cocaine into peripheral sites for minor surgical procedures in the late 19th century. From there many great physicians have furthered both injection technique and developed new injectable anesthetics and additives, to achieve optimal anesthesia to desired area. Peripheral nerve blocks have grown popular as they decrease the postoperative pain and the need for postoperative analgesia. They also decrease the incidence of nausea and shortens the time in postoperative department. Peripheral nerve blocks can be customized and have several purposes ranging from anesthesia to chronic pain treatment. (Miller et al., 2015)

2.1.1 Anatomy and physiology of peripheral nerves

Neurons consist of a cell body, that contains a nucleus and a cytoplasm, several dendrites that protrude from the cell body and one long axon. The dendrites carry electrical impulses to the cell and the axon carries impulses away from the cell. Each axon is covered by a sheath of connective tissue, called the endoneurium. Perineurium consists of several layers of cells and binds axons into fascicles. Epineurium surrounds the fascicles and binds them into a nerve. (Rosenberg et al., 2014)

Peripheral nerves are classified according to fiber size and physiologic properties. Myelinated nerves have a faster conduction velocity than the non-myelinated. In non-myelinated nerves the action potential travels along the axon, whereas in myelinated nerves the myelin has insulated the axolemma so that the active impulse can only be regenerated in the nodes of Ranvier. The axonal membrane consists of a lipid bilayer with long hydrophobic fatty acyl tails that face each other within the membrane center and polar hydrophilic head groups that project into the cytoplasm or the extracellular fluid. (Miller et al., 2015)

The neural membrane constantly maintains a resting membrane potential of -60 to -90 millivolts. At rest the neural membrane is relatively impermeable to sodium ions but

selectively permeable to potassium ions. The voltage difference is maintained by an energy dependent Na^+/K^+ pump. An action potential begins at the axon hillock as a result of depolarization. An action potential is produced only when the threshold is reached, as action potentials are described to be functioning by "all or nothing" principle. During depolarization the sodium channels open and allow tremendous amounts of positively charged sodium ions to enter. This changes the membrane potential from negative to positive. Shortly after this the sodium channels begin to close, and the potassium channels become more permeable, causing repolarization. Slowly the membrane restores its polarized state. The Na^+/K^+ pump aid in the restoration of the resting membrane potential. (Guyton et al., 2006)

2.1.2 Techniques and procedure

By injecting local anesthetics into the close proximity of a single nerve or plexus, we achieve anesthesia of the area that is innervated by that nerve or plexus. A successful block anesthetizes both sensory and motor nerve fibers. The local anesthetic must penetrate the perineurium, epineurium and endoneurium in order to reach the nerve axon and thereby be able to act as an anesthetic. For regional anesthesia we may use any nerve or block that can be anatomically easily recognized and accessible with an anesthesia needle. For nerve localization there are several devices that can be used. The procedure is done following standard aseptic principles.

Nerve stimulators may be used as localization aid. The stimulator is set on a low current, around 1mA. A specific needle that is attached to the stimulator is then injected according to the anatomical landmarks of the specific nerve. Once the needle is in close proximity of the nerve, we will observe muscle twitching of the muscles that are innervated by that specific nerve. In this way we may ensure that we inject the local anesthetics into the desired area.

Another widely used method is ultrasound-guided injections. Ultrasound allows visualization of the anatomy of the region of interest. This allows more informed guidance of the needle pathway to the target while avoiding structures that could be damaged by the needle. Ultrasound also allows visualization of the delivery of local anesthetic to the desired location. (Rosenberg et al., 2014)

2.1.3 Femoral block

N. femoralis arises from the ventral rami of the spinal nerves L2-L4. It emerges from the lateral border of *m. psoas major* to descend in the groove between *m. psoas major* and *m. iliacus.* From there it enters the thigh by passing beneath *lig. inguinale* laterally to *a. femoralis*. At this point *n. femoralis* divides into multiple terminal branches that can be divided into anterior and posterior groups. *N. femoralis* gives sensory innervation to the anterior thigh from *lig. inguinale* to the knee. The terminal branch *n. saphenous* gives sensory innervation to the medial side of the leg from the knee to the big toe. *N. femoralis* also gives muscular innervation to *m. quadriceps femoris, m. sartorius, m. iliacus* and *m. pectineus*.

For the femoral block, the patient is in supine position. First *a. femoralis* is palpated. *N. femoralis* is located on the lateral side of the artery at a few centimeters' depth. The procedure is performed using standard aseptic principles. The injection site is first anesthetized with local anesthetic, most often *Lidocaine* 1%, to provide adequate analgesia for the patient. By using a neurostimulator the nerve can be localized. Movement of the knee assures the proper localization of the needle. Once the correct location has been found, we may inject the anesthetics. The anesthetics may be given as a single injection, but most often a catheter is introduced. The femoral block is mainly used as post-operative pain management in operations of the knee. (Kokki et al., 2006)

2.1.4 Anesthetics mechanism of action

In regional anesthesia the mechanism of action is based on the blockade of the sodium channels that are located on the cell membrane of the neurons. The normal function of the sodium channel is to open and allow influx of sodium ions into the cell, as the action potential proceeds along the nerve. The sodium channels are formed by macromolecules that extend through the cell membrane and are composed of proteins and carbohydrates. Their external surface is glycosylated. Amino acids form four alpha subunits that determine the function and the ion specificity of each sodium channel. There are several different types of alpha subunits in different types of nerves. This difference could be used in the future to develop anesthetics that would selectively affect only a certain type of sodium channels, and thereby only a certain type of nerves. As the anesthetic molecules come in contact with the sodium channels, they will alter the structure of the channel and make it impermeable. As the channel is

impermeable it will remain polarized. This will inhibit the influx of sodium ions during the action potential and prevent the depolarization. The anesthetic that enters the neuron will remain in its ionized form, water-soluble with a positive charge, and prevents the function of the amino acids that open and close the sodium channels. The unionized form, fat-soluble with no charge, can easily pass through the cell membrane and affect the sodium channels from within the cell membrane, by attaching to specific receptors. (Rosenberg et al., 2014)

2.1.5 Advantages and disadvantages of regional anesthesia

Regional anesthesia may be applied to all limb surgeries and many operations regarding the lower abdomen. When choosing the most suitable form of anesthetics we must encounter a broad spectrum of variables that vary among all individuals. We must take into consideration the patient, both their wishes and their whole general status, which method will be safest for the patient. We must also take into consideration the operating environment as well as the operator.

One of the main advantages of regional anesthesia is that it does not compromise patients' level of consciousness, the breathing is secured and the risk of aspiration is lower. By using regional anesthesia, we may operate on high risk patients who could not undergo general anesthesia. Another great advantage of regional anesthesia is the fact that the patient can be moved from the operating room to the recovery ward as soon as the operation is over, which allows faster mobilization and thereby reduces risk of thrombotic events. Regional anesthesia also provides effective perioperative analgesia and reduces postoperative nausea and vomiting.

The greatest disadvantage of regional anesthesia is the slow development of the block and the success of the block is measured by the patient's subjective sensation. When comparing to general anesthesia the regional anesthesia is slower as the anesthetics are injected into the tissues surrounding the nerves and from there the anesthetic slowly affect the nerve tissues. When evaluating the block success, the golden standard is to evaluate the sensory and motor functions of the anesthetized area. Proper evaluation of the block success requires good patient compliance and communication between the patient and the anesthesiologist. Proper regional anesthesia is also operator dependent and highly dependent on the skills and training of the anesthesiologist. (Rosenberg et al., 2014)

2.2 Monitoring of regional anesthesia

2.2.1 Thermography

The homeostasis of the body is accurately regulated by several complex feedback-driven neuronal mechanisms, which involve several thermoregulatory pathways. One of the most effective regulatory systems of the body is the skin temperature that is regulated by the skin blood flow. The skin blood flow is highly dependent on sympathetic activity. Regarding thermoregulation the skin can be divided into glabrous and non-glabrous skin. The glabrous skin is located in the distal parts of the body. The glabrous skin is characterized by the abundance of arteriovenous anastomoses, an intense vascularization and a large surface-to-volume ratio. Thereby cutaneous vasodilation through these anastomoses can dramatically increase the overall blood flow in the periphery.

Regional anesthesia blocks both somatosensory and motor nerve fibers as well as sympathetic fibers. As cutaneous arterioles are innervated solely by noradrenergic sympathetic vasoconstrictor nerves, the blockade leads to revoked vasoconstrictor activity and vasodilation that leads to increase in skin blood flow and temperature. In non-glabrous areas the skin has double control of blood flow, both noradrenergic vasoconstrictor and cholinergic vasodilator nerves. Therefore, blockade of sympathetic nerves has more pronounced effect in the distal parts of the extremities. (Hermanns et al., 2018)

J. Klaessens (2011) conducted a study combining thermal and oxygenation imaging. The aim of the study was to evaluate if these two methods are quicker and more reliable than currently used methods as cold sensation and pin prick tests. They enrolled 22 patients, who all underwent surgery of the upper extremity and received a supraclavicular block. The results showed that a successful block would give a temperature response within 5 minutes after block placement with a maximum temperature change reached in 12-14 minutes. In an unsuccessful block the temperature response would be smaller and occur after 6-13 minutes. The cold sensation was measured, and the average response was significantly slower. At 15 minutes the sensitivity for cold sensation was 52% and for the thermography was 95%. The oxygen imaging was disturbed by the fluctuations of the ambient light in the room and by movements of the hand, which made the calculated oxygenation images noisy and difficult to interpret.

V. Minville (2009) conducted a study using a simple infrared thermometer to evaluate whether it can reliably predict block success. They enrolled 30 patients, who all underwent upper extremity surgery and received an infraclavicular block. The skin temperature was measured in all four major nerve distribution areas, radial, ulnar, median and mucocutaneus areas. The sensory block onset was evaluated every five minutes for 30 minutes. The results showed that when temperature increases in a specific sensory territory 1°C or more at five and 10 minutes the specific nerve was blocked. Average temperature variations in blocked and non-blocked nerves at the same time were statistically significantly, at five minutes $p < 0.05$ and at 10- and 30-minutes $p < 0.0001$. Temperature increased > 1°C in 60% of successful distribution area at five minutes and 80% at 10 minutes, giving sensitivity 84% and specificity 100%.

S. Asghar (2015) conducted a study combining thermography and objective sensation of temperature change. They included 40 patients, who all underwent surgery of the upper extremity. All received a lateral infraclavicular block. Eight observers were trained to examine the patients in a standardized manner. The examiners would at regular intervals gently squeeze the patients both second phalanges and fifth phalanges. They would then register any sensed skin temperature differences. Simultaneously thermography was used to verify significant temperature changes. The results showed that blinded observers were able to predict block success with high validity and reliability based on sensed differences with sensitivity 92% and specificity 85%. They estimated the Fleiss κ as a combined measure for agreement among all the observers. Fleiss κ was 0.87 for the distal second phalanx and 0,74 for the fifth phalanx, respectively.

K. Lange (2011) conducted a study using thermography imaging to monitor temperature changes in specific nerves of the upper extremity; *n. musculocutaneus, n. radialis, n. ulnaris* and *n. medianus.* They enrolled 42 patients, who all underwent upper extremity surgery, and all received specific nerve blocks. The patients were divided into six groups, radial, musculocutaneous, medial palmar view, medial dorsal view, ulnar palmar view and ulnar dorsal view. The results showed substantial and significant increase in temperature in ulnar nerve, both palmar and dorsal view, groups ($p < 0.001$), with a mean temperature increase of 5.2°C (1.4-10.7) °C from the baseline. Similarly, the specific blocking of the median nerve resulted in significant increase in temperature in both palmar and dorsal groups ($p < 0.001$), with a mean temperature increase 5.1°C (1.7-10.4) °C from the baseline. The median nerve also resulted in significant increase of temperature in the area innervated by the radial nerve

($p < 0.004$). The temperature increase was more pronounced on the palmar side and more in the fingertips than the wrist. In contrast, there was no increase in temperature after performing specific musculocutaneous or specific radial nerve blocks.

S. Asghar (2014) conducted a study were the aim of the study was to investigate thermographic patterns after a lateral infraclavicular brachial plexus block. They enrolled 40 patients, but only 30 blocks were successful. The thermographic imaging was performed simultaneously on both arms, as the non-operated arm served as control. The results revealed four distinct patterns of skin temperature changes with highly significant changes in temperature, depending on the block success. Temperature increase of at least 1°C in the ipsilateral hand from baseline to 30 minutes predicted a successful block, with positive predictive value of 100%. When comparing the successfully blocked hand with the contralateral hand, they discovered that if the temperature change between the both hands was at least 5°C at 30 minutes prediction of a successful block, with positive predictive value of 96%. A partially failed block showed two distinct patterns; either increased skin temperature in the first four digits and the hand, excluding the ulnar side, or increased skin temperature of the fourth and fifth digits including the ulnar side of the hand. A failed block showed no increase in skin temperature in any area.

From these studies we can conclude that the innervation of the arteriovenous shunts of the glabrous skin are responsible for the fast and prominent temperature rise after nerve blockade. These changes can be easily detected using thermography.

2.2.2 Doppler ultrasonography

Doppler ultrasonography is a non-invasive method of imaging that is used to estimate the blood flow through blood vessels by rebound high-frequency sound waves of circulating erythrocytes. With Doppler ultrasonography we can evaluate the morphology of blood flow in different vascular beds. Different vascular beds have their own distinct waveforms, depending on the flow of the blood within the vessels.

J. Li (2012) conducted a study where they included eight patients, who all underwent elective hand surgery. The aim of the study was to evaluate changes in regional hemodynamics after an axillary brachial plexus block. The regional hemodynamic parameters

were measured at the brachial artery of the ipsilateral arm, using pulsed-wave Doppler ultrasonography. They monitored the hemodynamic changes before the block and at regular intervals until 30 minutes after the block. The earliest observational changes were changes in the morphology of the pulsed-wave Doppler spectral wave form from a triphasic to a monophasic wave form and an elevation in the diastolic blood flow velocity ($p < 0.05$). Later changes were increased peak systolic velocity, diameter of artery and decreased pulsatility index.

VK. Erel (2018) conducted a study where they included 30 patients. The aim of the study was to evaluate the relationship between different local anesthetic volumes and hemodynamic changes using a pulsed-wave Doppler ultrasonography. Patients were divided in groups of 10 patients each. The first group received in total 20mL of local anesthetics, the second group received 30mL and the third group received 40mL of local anesthetics. The earliest observational changes in all groups were changes in the spectral waveform from triphasic to monophasic. Additionally, for groups who received 30mL and 40mL, there was an increase in end diastolic volume and peak systolic volume ($p < 0.05$). For the group who received 20mL there was no significant increase in end diastolic volume and peak systolic volume ($p > 0.05$).

From these studies we can conclude that regional anesthesia causes vasodilatation that can be observed with pulsed-wave Doppler ultrasonography. The spectral waveform changes from triphasic to a monophasic waveform, with the disappearance of reversed blood flow during early diastole and an increase in the diastolic flow.

2.2.3 Pulse oximetry and pulse oximeter perfusion index

The adequacy of respiratory function is easily assessed by using oxygen saturation of arterial blood. This can be measured in a non-invasive way using pulse oximetry. The pulse oximetry is based on photoplethysmography pulses in two wavelengths, generally in the red and infrared regions. For the assessment of oxygen saturation various optical techniques have been developed based on the different light-absorption spectra of oxyhemoglobin and deoxyhemoglobin. Hemoglobin is the main source of light absorption in tissue in the red and infrared regions. Assessment of oxygen saturation by using pulse oximetry is based on photoplethysmography as the measurement of light-absorption increases due to the systolic

increase in arterial blood volume. The transmitted light intensity decreases during systole when the peripheral arterial blood volume is increased as blood is ejected from the left ventricle into the circulation. The minimal and maximal values of the photoplethysmography pulse reflect light irradiance transmitted through the tissue when blood volume is minimal or maximal.

The photoplethysmographic measurement in each wavelength enables the assessment of the contribution of arterial blood to the total absorption of light, as the photoplethysmography signal reflects the changes in the arterial blood volume. The photoplethysmography signal amplitude (AC) is divided by its baseline (DC) and is related to the maximal blood volume change during systole. In order to measure oxygen saturation using photoplethysmography, curves of two wavelengths are recorded and the oxygen saturation is derived from the ratio of of AC divided by DC for each wavelength. (Nitzan et al., 2014)

A. Abdelnasser (2017) conducted a study with the aim of evaluating the success of nerve blocks by using a special pulse oximeter. Several other objective methods have been developed but the authors considered them to be either time consuming or dependent on sophisticated equipment and thereby they decided to conduct a study using a pulse oximeter. The parameter that they focused on was the perfusion index. The perfusion index is a numerical value for the ratio between pulsatile and non-pulsatile blood flow. They enrolled 77 patients who underwent surgery of the upper extremity and all patients received a supraclavicular block. The perfusion index was recorded at baseline and at 10, 20 and 30 minutes in both blocked and non-blocked limbs. The perfusion index (PI) ratio was calculated as the PI after 10 minutes divided by the PI at the baseline. The results showed that PI was higher in the blocked limb at all time points and this paralleled by a higher PI ratio compared to the unblocked limb. Both PI and the PI ratio showed at 10 minutes 100% sensitivity and specificity for block success. The authors concluded that a PI ratio > 1.4 is a good predictor of block success.

2.2.4 Photoplethysmography

Photoplethysmography was first introduced in the 1930's by Hertzman who described it as a non-invasive optical technique capable of transcutaneous registration of blood volume changes in the blood vessels. The underlying principle of the PPG is the empirical observation that the light transmitted through or reflected from living tissues obtains a modulation in time that is synchronized with the heartbeat frequency. The technique is very simple and cost efficient, as it only requires two components, a light source and a photoreceiver. Due to these discoveries an optical device for measurement of oxygen saturation of arterial blood, pulse oximeter, was invented in 1970's by Takauo Aoyagi. Since then the PPG technology has developed at a rapid pace. Since the year 2000, when the first noncontact imaging photoplethysmography was proposed by Wu et al, there has been a rapid growth on development of PPG techniques and applications to clinical practice. (Kamshilin et al., 2017)

The photoplethysmography waveform consists of two components. The pulsatile or alternating component (AC) is a physiological waveform that is attributed to cardiac synchronous changes in the blood volume with each heartbeat. The non-pulsatile or direct component (DC) is a slowly varying baseline of light absorption of the tissue with various lower frequency components attributed to respiration, sympathetic nervous system activity and thermoregulation. (Allen, 2007)

Today the photoplethysmographic waveform is one of the most commonly displayed clinical waveforms. It is also known as the pulse oximeter waveform. The waveform is an amplified and very filtered measurement of light absorption by the tissue over time. The detailed mechanism of photoplethysmography phenomena is still not well understood. It is the result of a complex interaction between the cardiovascular, respiratory and autonomic systems. The PPG is displayed in the infrared waveform (~940 nm) and has two major filters on it. The first filter is a band-pass filter that eliminates slow gradual changes as well as fast and spiky changes. The band-pass filter makes the wave form smooth. The waveform amplitude is also being constantly adjusted by two different ways, modification of its amplification by electronics and an adjustment of the intensity of the light source. (Alian et al., 2014)

Currently there is no known method for calibration of the PPG. Therefore, we cannot directly compare the absolute values of one person's PPG to another's. Factors that affect the PPG values are such as different thickness of fingers, skin color, amount of fat and muscle in tissues. Despite the fact that the PPG cannot be calibrated one can still measure the light absorption changes over time and the impact of various physiological systems. One can also measure the changes at different wavelengths and thereby measure the ratio between different substances as oxygenated and deoxygenated hemoglobin. The PPG amplitude is also affected by several factors. Factors that decrease the amplitude are pharmacological or physiological vasoconstriction, increased venous tissue congestion and low stroke volume. Factors that increase the amplitude are decreased venous congestion and vasodilation. The vasodilation can be either pharmacological, physiological as warming, sedation and sepsis or vasodilation can also be caused by anesthetics in regional blocks.

All modern pulse oximeters have PPG sensors that extract PPG signals at multiple wavelengths and display them as heart rate and oxygen saturation. Photoplethysmography can also be implemented in monitoring of cardiac arrhythmia when used in conjunction with the electrocardiogram. It is particularly sensitive to any irregularities of the pulse. When combined with the electrocardiogram the PPG can be used to measure the pulse transit time. Decreased pulse transit time has been associated with hypertension, diabetes, arterial sclerosis and aging. PPG can also be used to estimate the systolic blood pressure. The height of the PPG pulse does not correlate with a high arterial pressure. The systolic blood pressure can be determined with PPG by using a manually controlled blood pressure cuff. On the ipsilateral arm the PPG finger probe is attached. The cuff is inflated until all signs of cardiac pulsation are absent from the PPG. The cuff is slowly deflated, and the systolic pressure can be estimated when the pulse is detected on the PPG. This method has been proven useful in noisy environments and in neonates, as it is difficult to auscultate their small vessels. (Alian et al., 2014)

Photoplethysmography is a convenient and low-cost technology that can be applied in various aspects of cardiovascular monitoring. These include blood oxygen saturation, heart rate, blood pressure, cardiac output, arterial aging, endothelial function and microvascular blood flow. As the volume and distention of the arteries can be related to the pressure in the arteries the photoplethysmography signal produces pulse waveforms that are very similar to pressure waveforms generated by tonometry. The advantage with PPG over tonometry is that

PPG monitoring can be continuous using miniature, low-cost and wearable optical electronics. (Elgendi et al., 2019)

U. Rubins (2016) conducted a study using remote photoplethysmography. For this study the authors developed an efficient photoplethysmography imaging system and an advanced algorithm that was suitable for continuous monitoring of skin microcirculation. The system consisted of a compact device and computer with software for visualizing changes in blood volume of the skin. The software processed high-resolution microcirculation amplitude maps in real-time. Six patients were enrolled, who all underwent upper extremity surgery and received axillary brachial plexus block. The hand was placed in a foam rubber hand support to minimize movement of the hand during the measurements. The processing algorithm combined spatial and temporal processing. The spatial processing was done by multi-scale decomposition and the temporal processing was done by band-pass filtering. After the processing the next step was reconstruction of resulting amplitude map from multiple images. The final step included the normalization, thresholding and color-indexing of the resulting map. The rPPG maps were compared with thermography images to confirm the applicability of the developed technique. The results showed that the developed algorithm showed improved sensitivity compared to previously used methods and that the developed prototype was proven to be efficient for monitoring of blood volume changes of the palm.

U. Rubins (2017) conducted a study where the group had further developed the prototype devices and software. They discovered that blood hemoglobin absorbs light mainly in the green spectral range. the measurements would be more accurate if a green light or green optical filter would be used. The aim of the study was to develop a simple and convenient rPPG system for non-contact monitoring of regional anesthesia. For practical clinical application the group chose to use a surgical lamp as a light source, as it is widely available and convenient to use and adjust. The same algorithm was used that had been developed in the previous study of the group. Eight patients were enrolled, who all underwent upper extremity surgery and received axillary brachial plexus block. The results showed that the surgical lamp can function as a sufficient light source for rPPG monitoring. The team developed a simple and easy to use rPPG system that is suitable for clinical settings.

A. Kamshilin (2011) conducted a study using photoplethysmography with the aim of demonstrating that the high spatial resolution imaging is capable to detect minimal irritations of the body. Five volunteers from the members of the research team were enrolled to the

study. The region of interest was the palm. First imaging was performed while the subject kept their hand relaxed. After this the subject was asked to gently scratch their palm with their finger. Second imaging was performed immediately after the scratching. The results showed that small impact caused by gentle scratching resulted in increased amplitude of blood volume pulsations. The increase of blood pulsation after scratching in the scratching area was observed in all subjects. The study showed that the high-resolution imaging they developed could be used for analysis of the blood perfusion process in live tissues.

Photoplethysmography is a simple and non-invasive photometric technique that measures the volume changes in the arterial blood. This method has a broad range of functions and can be implemented in various clinical settings.

3. Materials and methods

3.1 General information

The study was done by using volunteering patients at the Hospital of Traumatology and Orthopedics, Riga. The measurements were done from December 2019 till January 2020. The selected patients had to be undergoing elective surgery of the lower extremity under spinal anesthesia, with an intended peripheral nerve block analgesia. Additionally, the patient would have to be ASA I-III, age 18-75 years of age and have BMI < 35 kg/m^2. Exclusion criteria were contraindication for peripheral nerve block or spinal anesthesia, *Diabetes mellitus*, chronic opioid use (> 6 months), peripheral vascular disease and usage of vasodilating drugs on the day of the surgery. Before the surgery written informed consent was obtained from each patient. The research was approved by a local Ethics Committee in December 2019. In total we enrolled five patients to our prospective randomized double-blinded pilot study. One patient was excluded due to excess movement during the imaging that caused artifacts that made the data impossible to analyze.

3.2 Imaging process and statistics

Before imaging the patients were brought to the pre-operative area outside the operation room. Throughout the imaging we monitored patient heart rate and O_2 saturation. Blood pressure was measured before the insertion of the femoral block.

Before insertion of the femoral block the skin area was cleaned by standard aseptic principles and after infiltrated with *Lidocaine* 1%. The femoral nerve was localized by using Stimuplex® HNS 12 (B. Braun, Melsungen AG, Germany). The stimulator was set on 1,0mA. Once the nerve was identified, the catheter was inserted.

All participants involved in the procedure were blinded to the syringe content. A nurse was asked to randomly pick an envelope prepare the syringes according to the instructions written and to label them as syringe 1 and syringe 2 respectively. One of the syringes contained *Ropivacaine* 0.375% 20mL and the other syringe contained *NaCl* 0.9% 20mL placebo. Two patients (50%) randomly chosen received LA in the first syringe, while the

other two (50%) received randomly chosen placebo in the first syringe. The femoral catheter was be removed on the third post-operative day.

The rPPG system involved a camera, equipped with a handle to be attached to the light source. As a light source we used a mobile surgical examination lamp. The camera was connected via USB-3 cable to a laptop computer, which would also serve as the power supply for the camera. The rPPG camera was attached to a light source and adjusted to the desired skin area, the medial side of the knee.

The imaging started a few minutes before the insertion of the femoral block catheter and continued for 12 minutes after the injection of the first syringe, and for 12 minutes after injection of the second syringe. In addition to the rPPG statistical analysis, we assessed the block using cold sensation, by applying ice, and visual online rPPG mapping.

Preoperatively we collected patient age, weight, height and calculated their BMI. On the first post-operative day we collected data from the patient files regarding usage of the femoral nerve block (time and VAS) and if the patient had received *Morphine* subcutaneously (time and amount).

The statistics are made with Microsoft® Excel 2019 for Mac and IBM® SPSS Statistics standard 25.

4. Results

4.1 General characteristics of the participants

We enrolled four volunteering patients to our study. Three patients were female (75%) and one male (25%). The mean age was 74,25 ± 0.95 years. The mean height was 167 ± 4.2cm and the mean weight was 86 ± 11.2kg. The mean BMI was 30.9 ± 4.4 kg/m^2. All four patients needed additional analgesia, both *Ropivacaine* through the femoral catheter and *Morphine* s.c., during the first post-operative day. All four blocks were successful.

	N	Minimum	Maximum	Mean	Std. Deviation
Age	4	73	75	74,25	,957
Weight	4	77	100	86,00	11,165
Height	4	161	170	167,00	4,243
BMI	4	26,6	34,7	30,875	4,3783
Valid N (listwise)	4				

Table 4.1 General characteristics of the participants.

4.2 Determination of distribution of data

The general characteristics of each patient was analyzed descriptively. The data from the imaging of each patient was analyzed separately. From the imaging we recorded time, pulse, AC, DC and AC/DC values. The DC component is large as it is the component that corresponds to the light diffusion through tissues and non-pulsatile blood layers. The AC component is small as it consists only of the pulsatile part, diffusion of light through the arterial blood. We chose to analyze the AC/DC values, as it is the most precise and clear value to detect and analyze changes in the microcirculation of the skin. The AC/DC can also be called the perfusion index.

To start our analysis of the data we began with determination of distribution. To determine the distribution, we analyzed the distribution of the frequency of the AC/DC values and performed tests of normality.

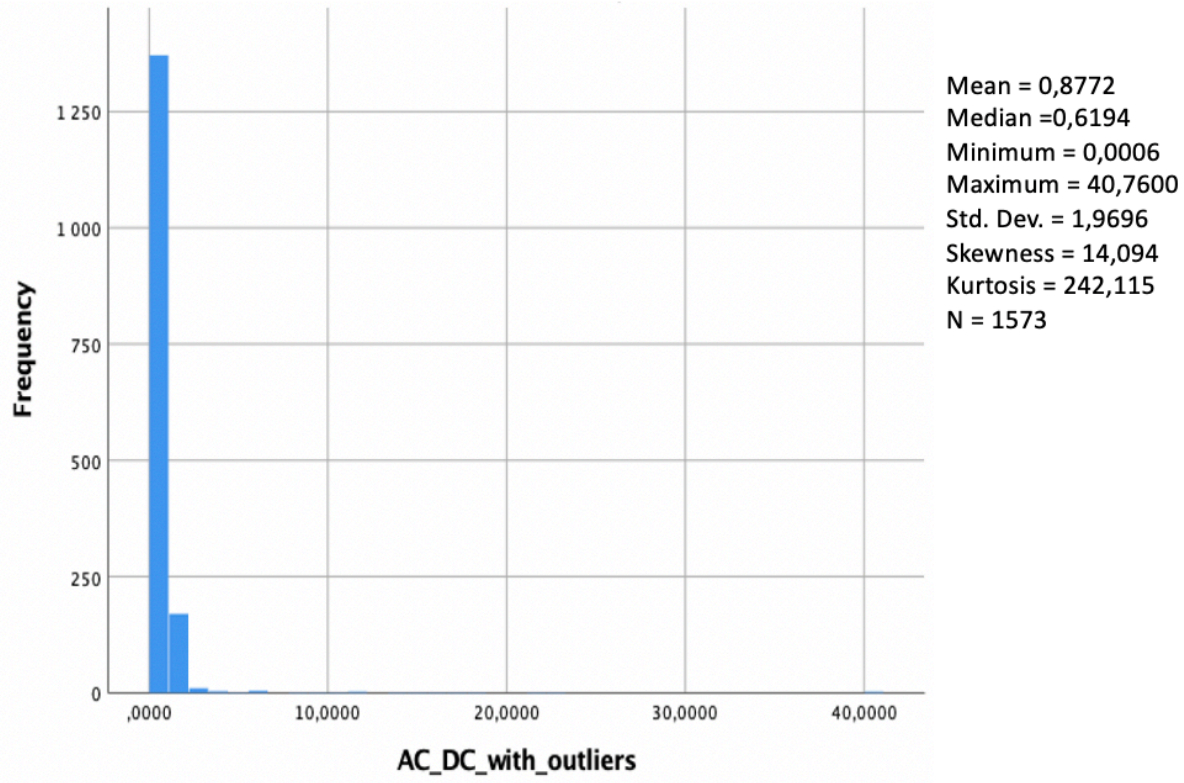

Figure 4.2.1 Patient 1 distribution of data with outliers.

In Figure 4.2.1 we can see that the AC/DC values are not normally distributed. There are some extreme values and the test of normality confirm that the data is not normally distributed, Shapiro-Wilk (Sig. < 0,000). This is also supported by the descriptive data, where skewness is 14,094 and kurtosis is 242,115.

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
AC_DC_with_outliers	,361	1573	,000	,172	1573	,000

a. Lilliefors Significance Correction

Table 4.2.1 Patient 1 Tests of Normality of data with outliers.

For each data set there were some extreme values, so called outliers, in the data due to artifacts. The artifacts are due to patient movements and minor changes of the light at the site of imaging. Before entering the data into the SPSS we used quartile ranges for outlier definition. For the outlier definition we used the extreme outlier formula, IQR times 3 and we determined the upper- and lower bound for each data set. Then we removed those AC/DC coefficient values that were outliers.

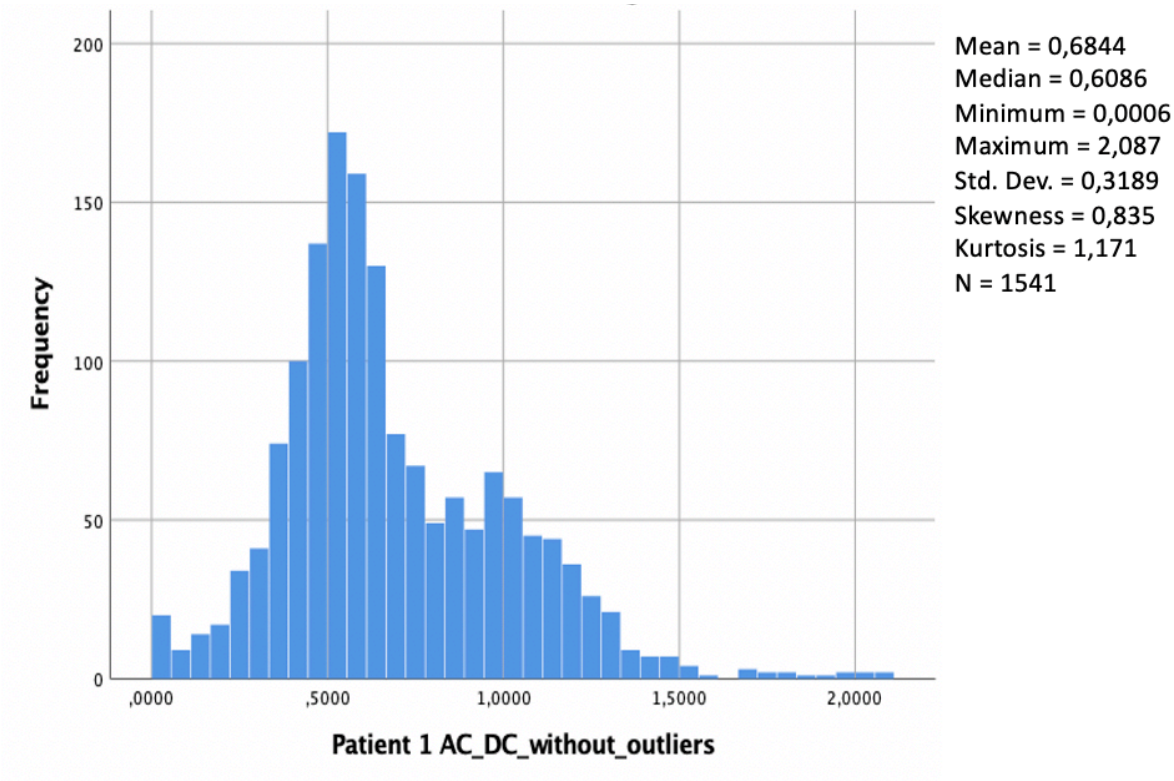

Figure 4.2.2 Patient 1, distribution of data without outliers.

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
AC_DC_without_outliers	,111	1541	,000	,955	1541	,000

a. Lilliefors Significance Correction

Table 4.2.2 Patient 1 Tests of Normality without outliers.

In figure 4.2.2 we can see that after the removal of the outliers the distribution improved. The data is however still not normally distributed, Shapiro-Wilk (Sig. < 0.000).

We performed the analysis for each patient in similar manner as to patient 1. We determined the outliers for each patient data and removed them before further analysis. Frequency of AC/DC without outliers for patient 2; mean = 0.9784, median = 1.0224, minimum = 0.1393, maximum = 1.8610, Std. Dev. = 0.2440, skewness = -0.789, kurtosis = 1.268 and N 2038. The test of normality, Shapiro-Wilk confirmed not normally distributed data (Sig. < 0.000).

Frequency of AC/DC without outliers for patient 3; mean = 0.5236, median = 0.5062, minimum = 0.0001, maximum = 1.4156, Std. Dev. = 0.2428, skewness 0.455, kurtosis = 0.250 and N 2118. The test of normality, Shapiro-Wilk confirmed not normally distributed data (Sig. < 0.000).

Frequency of AC/DC without outliers for patient 4; mean = 0.6922, median = 0.7063, minimum = 0.0025, maximum = 2.1522, Std. Dev. = 0.3292, skewness = 0.154, kurtosis = 0.040 and N 1688. The test of normality, Shapiro-Wilk confirmed not normally distributed data (Sig. < 0.000).

4.3 Grouping of data

Since the imaging was continuous for one patient, we divided the timeline so that we can analyze each part of the measurement; before injection, the time of the first syringe and the time of the second syringe. We divided the timeline into two groups that were further divided into three groups each. Grouping 1 is divided into 1 – before injection, 2 – 1st syringe and 3 – 2nd syringe. Grouping 2 is divided into 1 – before injection, 2 – last 4 minutes of the 1st syringe and 3 – last 4 minutes of the second syringe.

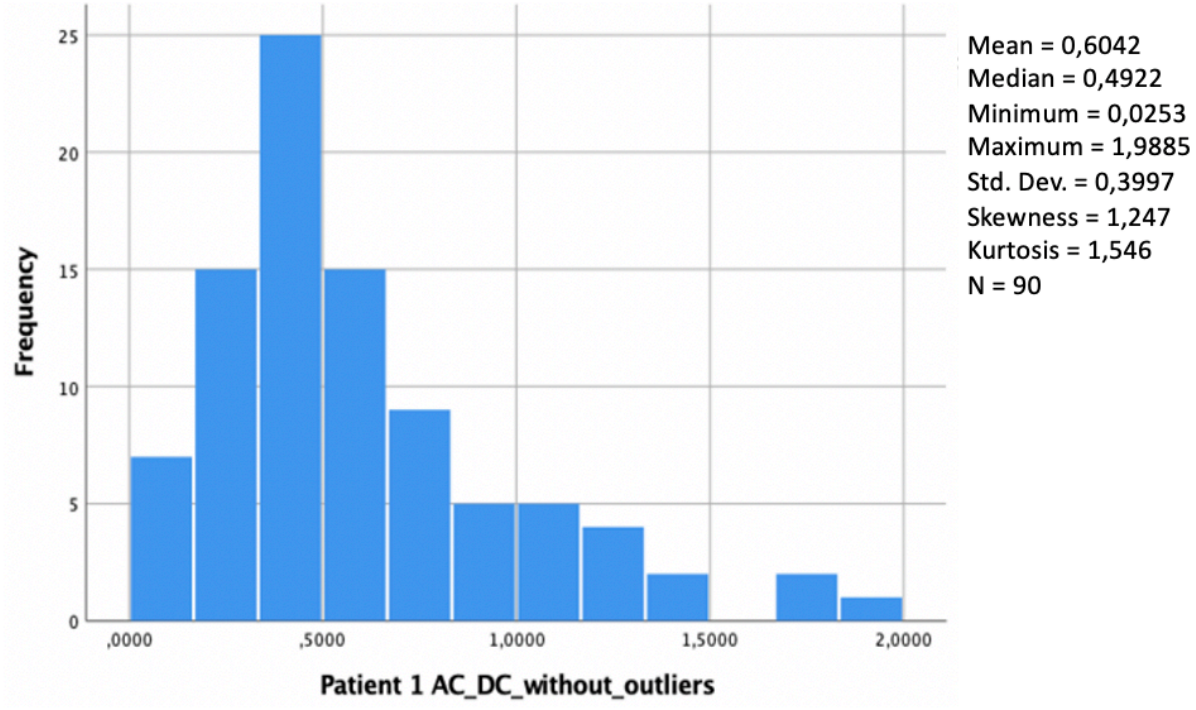

Figure 4.3.1 Patient 1, grouping 2 = 1 before.

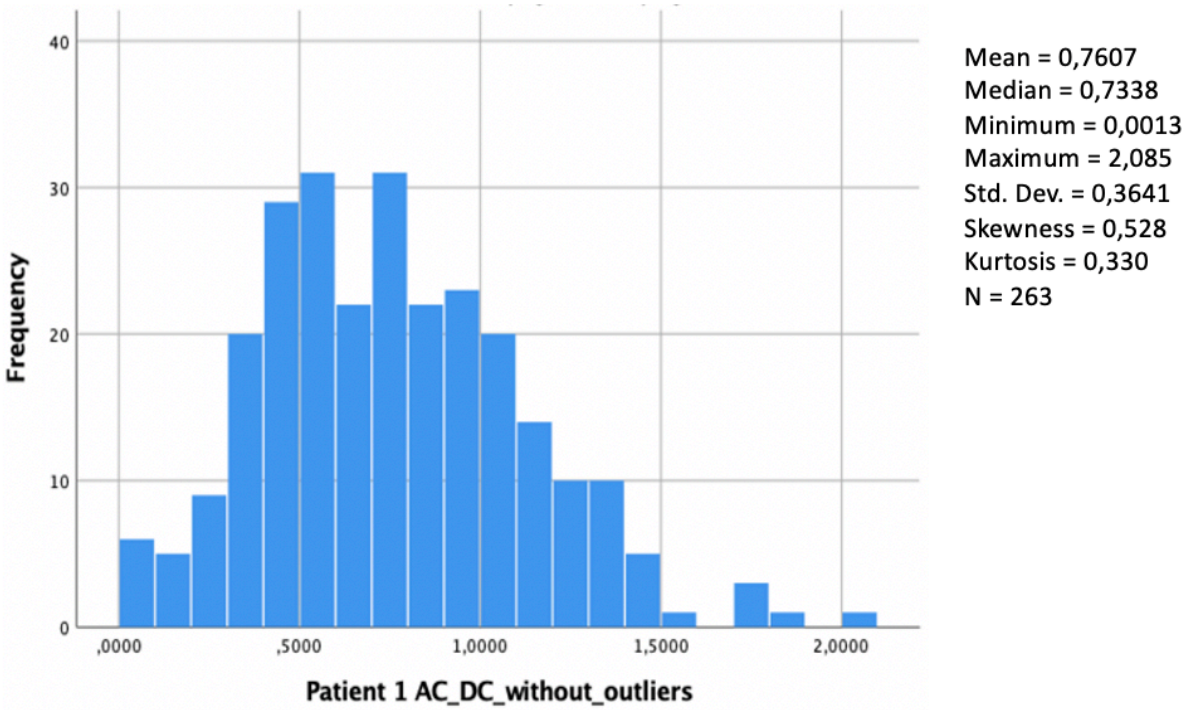

Figure 4.3.2 Patient 1, grouping 2 = 2 – 1st syringe last 4 minutes.

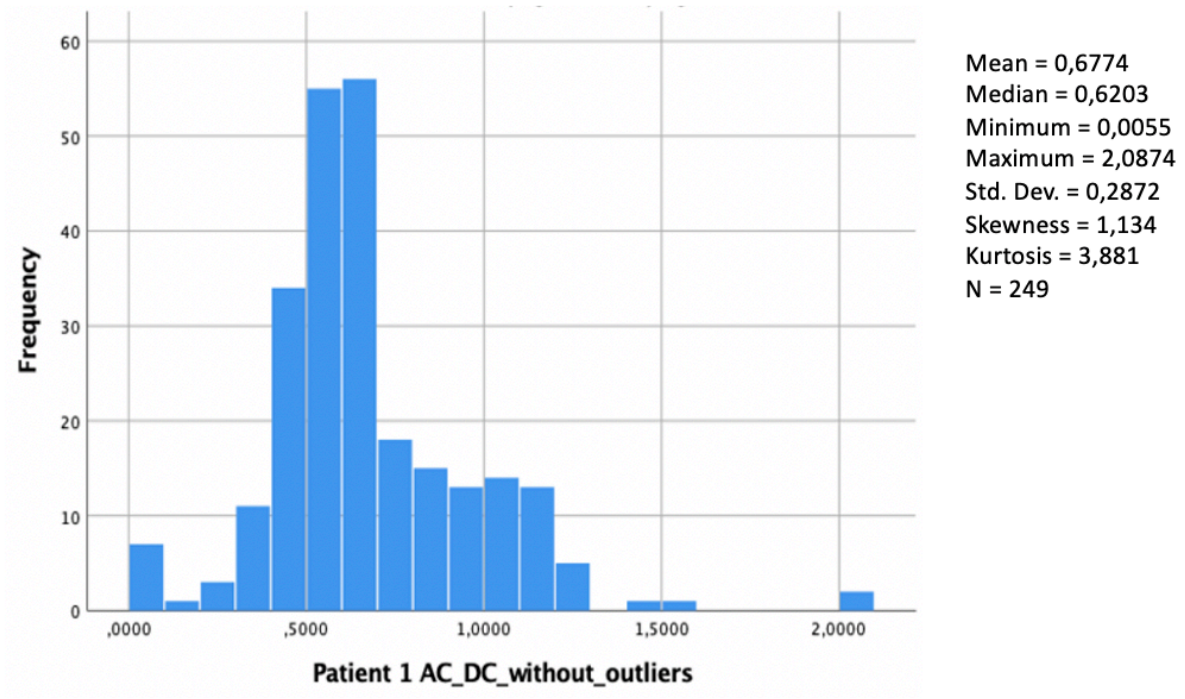

Figure 4.3.3 Patient 1, grouping 2 = 3 – 2nd syringe last 4 minutes.

	Grouping2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
AC_DC_without_outliers	1	,152	90	,000	,902	90	,000
	2	,059	263	,029	,981	263	,001
	3	,154	250	,000	,861	250	,000

a. Lilliefors Significance Correction

Table 4.3.1 Patient 1, grouping 2 without outliers Tests of Normality.

We performed the analysis for each patient in similar manner as to patient 1. For patient 2 the distribution of the grouping 2 was following; before; mean = 0.442, median = 0.416, minimum = 0.139, maximum = 1.621, Std. Dev. = 0.204, skewness = 2.72, kurtosis = 10.39 and N = 134. For 1st syringe last 4 min; mean = 1.015, median = 1.012, minimum = 0.260, maximum = 1.649, Std. Dev. = 0.163, skewness = -0.124, kurtosis = 3.57 and N = 318. For 2nd syringe last 4 min; mean = 1.074, median = 1.067, minimum = 0.589, maximum = 1.486, Std. Dev. 0.119, skewness 0.119, kurtosis 1.274 and N = 328.

	Grouping2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
AC_DC_without_outliers	before	,225	134	,000	,744	134	,000
	1st syringe last 4min	,084	318	,000	,943	318	,000
	2nd syringe last 4min	,056	328	,015	,984	328	,001

a. Lilliefors Significance Correction

Table 4.3.2 Patient 2, grouping 2 without outliers Test of Normality.

For patient 3 the distribution of the grouping 2 was following; before; mean = 0.397, median = 0.402, minimum = 0.0001, maximum = 1.109, Std. Dev. = 0.188, skewness = 0.404, kurtosis 0.426 and N = 360. For 1st syringe last 4 min; mean = 0.582, median = 0.573, minimum = 0.084, maximum = 1.199, Std. Dev. = 0.226, skewness = 0.36, kurtosis = -0.121 and N = 331. For 2nd syringe last 4 min; mean = 0.580, median = 0.571, minimum = 0.015, maximum = 1.389, Std. Dev. = 0.278, skewness = 0.402, kurtosis = -0.071 and N = 303.

	Grouping2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
AC_DC_without_outliers	before	,064	360	,001	,987	360	,002
	1st syringe last 4min	,055	331	,017	,987	331	,004
	2nd syringe last 4min	,051	303	,051	,985	303	,003

a. Lilliefors Significance Correction

Table 4.3.3 Patient 3, grouping 2 without outliers Test of Normality.

For patient 4 the distribution of grouping 2 was following; before; mean = 0.502, median = 0.515, minimum = 0.053, maximum = 1.112, Std. Dev. = 0.235, skewness = 0.135, kurtosis = -0.276 and N = 111. For 1st syringe last 4 min; mean = 0.739, median = 0.756, minimum = 0.003, maximum = 2.152, Std. Dev. = 0.300, skewness = 0.325, kurtosis = 3.545 and N = 259. For 2nd syringe last 4 min; mean = 0,767, median = 0.807, minimum = 0.006, maximum = 1.713, Std. Dev. = 0.366, skewness = -0.199, kurtosis = -0.459 and N = 268.

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Grouping2	Statistic	df	Sig.	Statistic	df	Sig.
AC_DC_without_outliers	before	,073	111	,187	,984	111	,212
	1st syringe last 4min	,105	259	,000	,930	259	,000
	2nd syringe last 4min	,054	268	,053	,981	268	,001

a. Lilliefors Significance Correction

Table 4.3.4 Patient 4, grouping 2 without outliers Test of normality.

The distribution between the grouping 2 of the patients was confirmed by test of normality, Sharipo-Wilk, to be not normally distributed. One exception was for patient 4, grouping 2, before, with Sharipo-Wilk (Sig. 0,212). As this is only a minor part of all the data that is normally distributed, for further analysis we assume that all the data is not normally distributed. To further analyze the difference of the AC/DC values, we used non-parametric tests.

4.4 Nonparametric tests

To continue the analysis of the data the next step was to determine if there were changes in the AC/DC values. For these tests we used the grouping 2 of our data. Grouping 2 is divided into 1 – before injection, 2 – 1st syringe last 4 minutes and 3 – 2nd syringe last 4 minutes. We chose to analyze the grouping 2 data as we assumed that the last four minutes of 1st syringe and 2nd syringe would show the maximum response. Kruskal-Wallis test shows the difference of AC/DC values within the grouping 2. As for Mann-Whitney test, we performed the test for each group with each other within the grouping 2 to analyze if there would be changes between the groups of grouping 2.

Ranks

	Grouping2	N	Mean Rank
AC_DC_without_outliers	before	90	232,61
	2-1st syringe last 4min	263	330,25
	3-2nd syringe last 4min	249	296,03
	Total	602	

Test Statistics[a,b]

	AC_DC_without_outliers
Kruskal-Wallis H	21,554
df	2
Asymp. Sig.	,000

a. Kruskal Wallis Test

b. Grouping Variable: Grouping2

Table 4.4.1 Patient 1 Kruskal-Wallis test

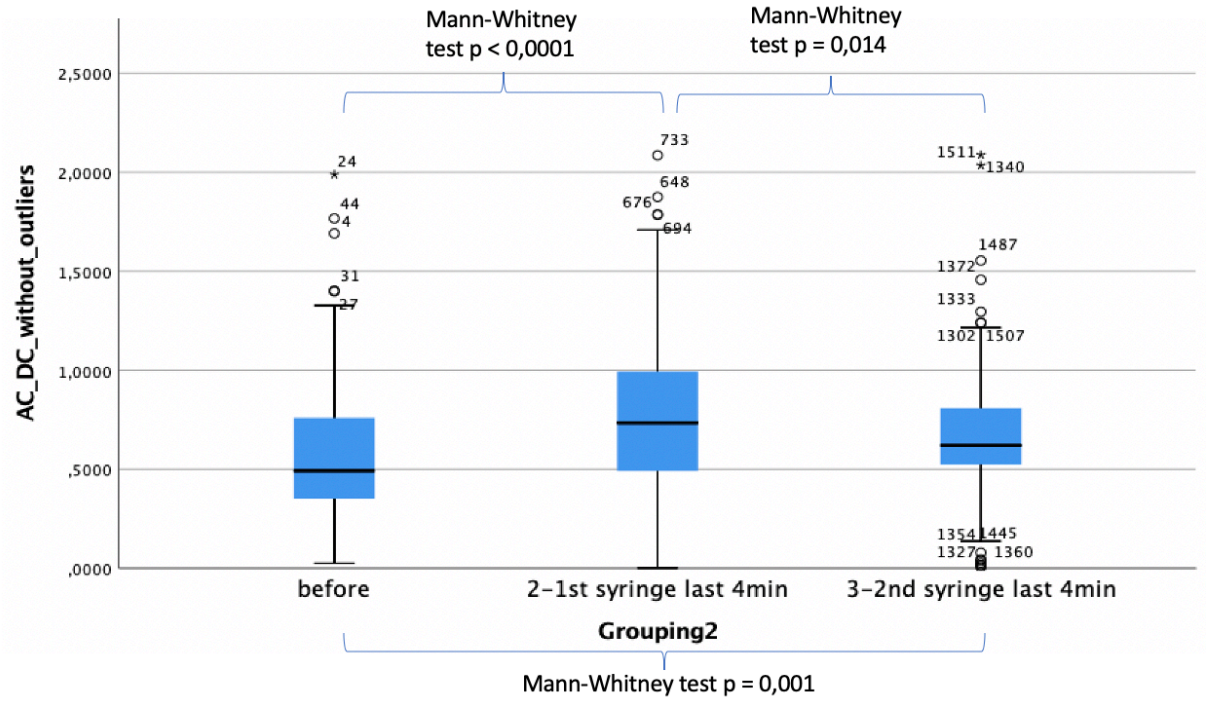

Figure 4.4.1 Patient 1

For patient 1 we can see in Table 4.4.1 that there is a statistically significant (Asymp. Sig. <0.000) difference in the AC/DC values of grouping 2. If we look closer on the differences between the groups within grouping 2 in Figure 4.4.1, we can observe that the difference among the groups were all statistically significant; before – 1st syringe last 4 min ($p < 0.0001$), 1st syringe last 4 min – 2nd syringe last 4 min ($p = 0.014$) and before – 2nd syringe last 4 min ($p = 0.001$).

Ranks

	Grouping2	N	Mean Rank
AC_DC_without_outliers	before	134	89,09
	1st syringe last 4min	318	407,49
	2nd syringe last 4min	328	497,16
	Total	780	

Test Statistics[a,b]

	AC_DC_without_outliers
Kruskal-Wallis H	315,130
df	2
Asymp. Sig.	,000

a. Kruskal Wallis Test

b. Grouping Variable: Grouping2

Table 4.4.2 Patient 2 Kruskal-Wallis test

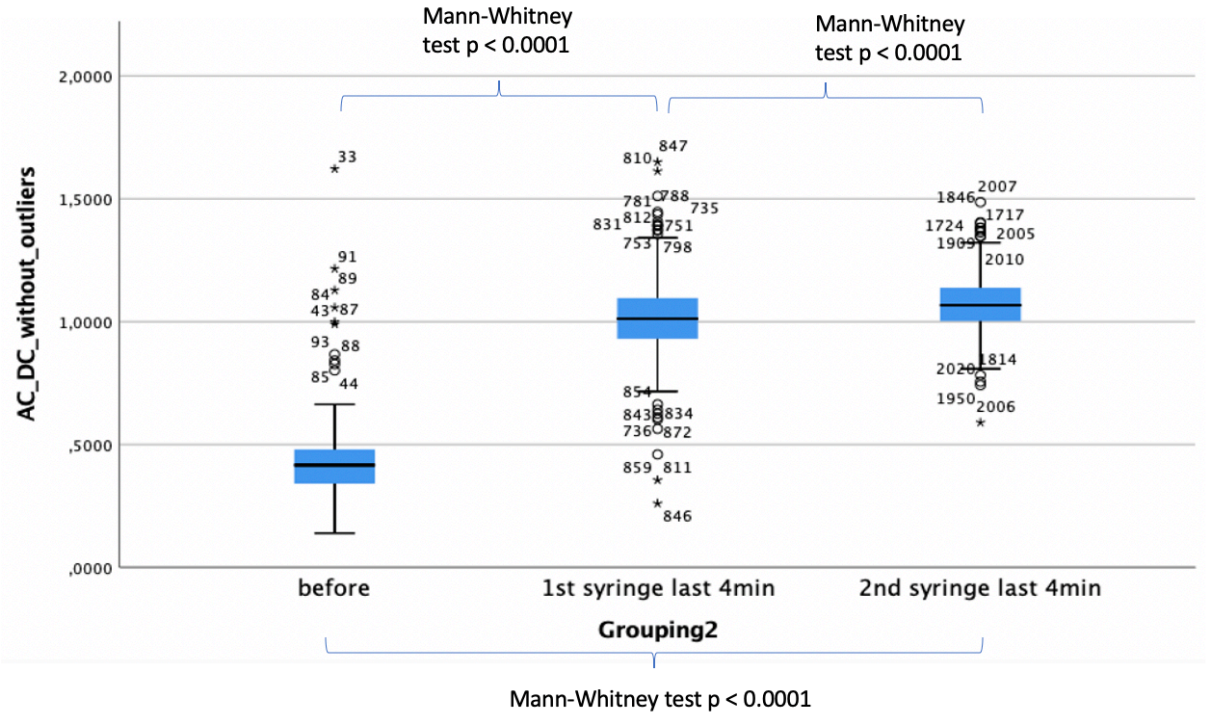

Figure 4.4.2 Patient 2

For patient 2 we can see in Table 4.4.2 that there is a statistically significant (Asymp. Sig. <0.000) difference in the AC/DC values of grouping 2. If we look closer on the differences between the groups within grouping 2 in Figure 4.4.2, we can observe that the differences among the groups were all statistically significant; before – 1st syringe last 4 min ($p < 0.0001$), 1st syringe last 4 min – 2nd syringe last 4 min ($p < 0.0001$) and before – 2nd syringe last 4 min ($p < 0.0001$).

Ranks

	Grouping2	N	Mean Rank
AC_DC_without_outliers	before	360	357,79
	1st syringe last 4min	331	585,69
	2nd syringe last 4min	303	567,14
	Total	994	

Test Statistics[a,b]

	AC_DC_without_outliers
Kruskal-Wallis H	134,320
df	2
Asymp. Sig.	,000

a. Kruskal Wallis Test

b. Grouping Variable: Grouping2

Table 4.4.3 Patient 3 Kruskal-Wallis test

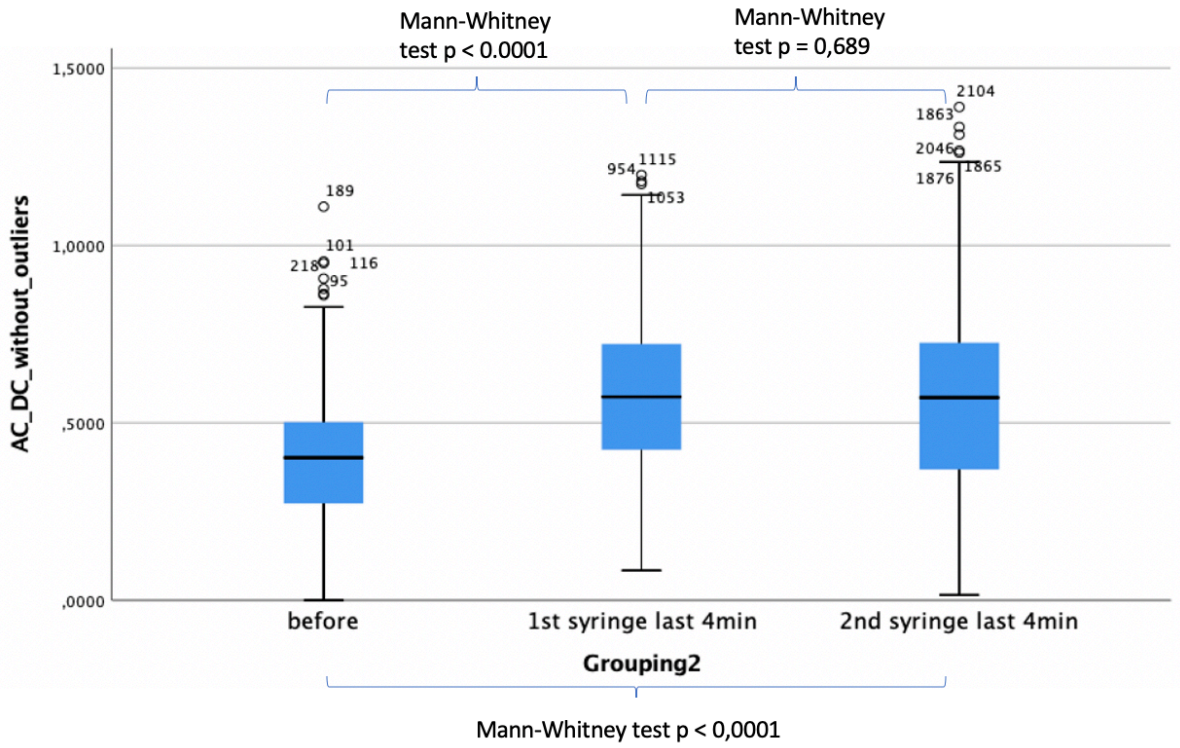

Figure 4.4.3 Patient 3

For patient 3 we can see in Table 4.4.3 that there is a statistically significant (Asymp. Sig. <0.0001) difference in the AC/DC values of grouping 2. If we look closer on the differences between the groups within the grouping 2 in Figure 4.4.3, we can observe that the differences among some of the groups were statistically significant; before – 1st syringe last 4 min ($p < 0.0001$) and before – 2nd syringe last 4 min ($p < 0.0001$). Changes between 1st syringe last 4 min – 2nd syringe last 4 min ($p = 0.689$) was not statistically significant.

Ranks

	Grouping2	N	Mean Rank
AC_DC_without_outliers	before	111	190,22
	1st syringe last 4min	259	337,02
	2nd syringe last 4min	268	356,12
	Total	638	

Test Statistics[a,b]

	AC_DC_without_outliers
Kruskal-Wallis H	67,526
df	2
Asymp. Sig.	,000

a. Kruskal Wallis Test

b. Grouping Variable: Grouping2

Table 4.4.4 Patient 4 Kruskal-Wallis test

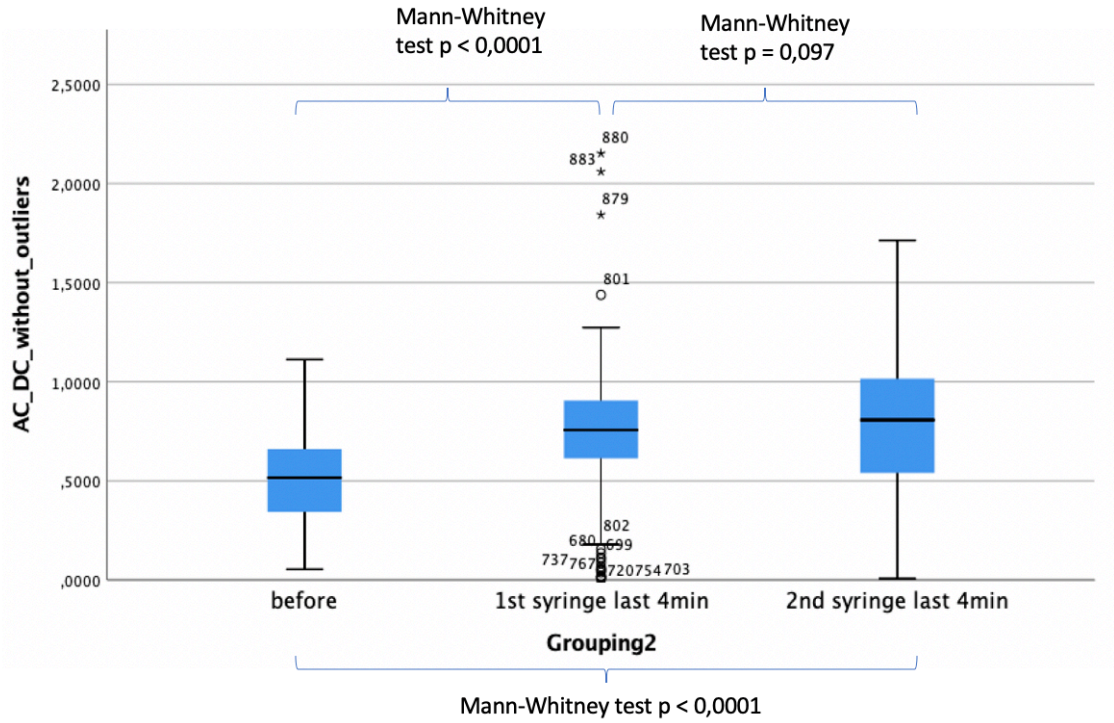

Figure 4.4.4 Patient 4

For patient 4 we can see in Table 4.4.4 that there is a statistically significant (Asymp. Sig. <0.0001) difference in the AC/DC values of grouping 2. If we look closer on the differences between the groups within the grouping 2 in Figure 4.4.4, we can observe that the differences among some of the groups were statistically significant; before – 1st syringe last 4 min ($p < 0.0001$) and before – 2nd syringe last 4 min ($p < 0.0001$). Changes between 1st syringe last 4 min and 2nd syringe last 4 min ($p = 0.097$) was not statistically significant.

As we can see from the Kruskal-Wallis tests there are statistically significant changes in all the patients (Asymp. Sig. <0.0001). The Mann-Whitney test showed the differences between the groups within grouping 2. Despite several of the values being statistically significant, we cannot tell which syringe contained *Ropivacaine* and which syringe contained placebo based on the non-parametric tests.

4.5 Correlation of syringe content

The non-parametric tests showed changes within the grouping 2 in all four patients. In order to analyze this further we look at the correlation between time and the AC/DC changes. We assume that the group with the higher correlation coefficient would be the one that contains *Ropivacaine*, as the local anesthetic blocks the sympathetic nerve fibers that cause vasodilation in the skin microcirculation.

For this measurement we look at the whole time of imaging of each patient with filter grouping. The grouping 1 is used with group 1 – before injection, 2 – 1st syringe time, 3 – 2nd syringe time. For the correlation we use Pearson correlation coefficient (R) and Kendall's tau.

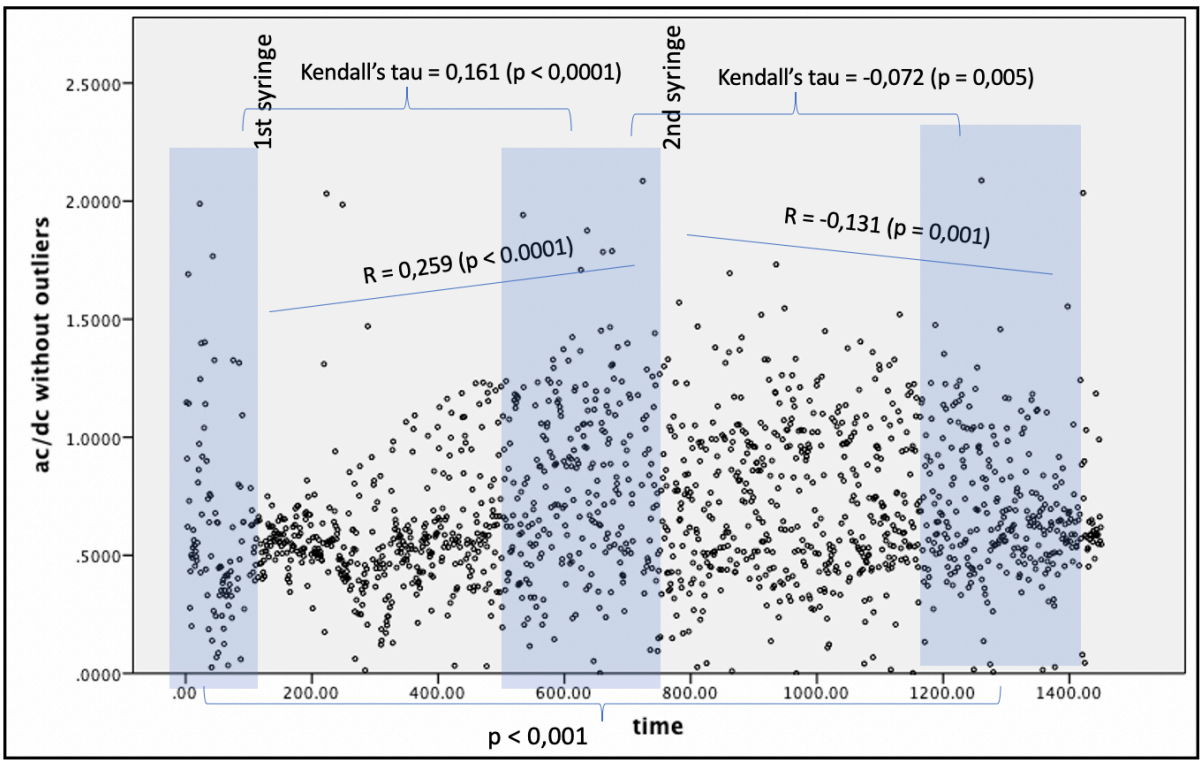

Figure 4.5.1 Patient 1 grouping 1.

For patient 1 we can see in Figure 4.5.1 the distribution of AC/DC values over the whole time of measurements. We can observe that there was a weak positive correlation for syringe 1 (R = 0,259 (p < 0.0001) and Kendall's tau = 0.161 (p < 0.0001)). For the second syringe we can observe a weak negative correlation (R = -0.131 (p = 0.001) and Kendall's tau = -0.072 (p = 0.005). The changes for both syringes are statistically significant. The first syringe has a stronger correlation than the second syringe.

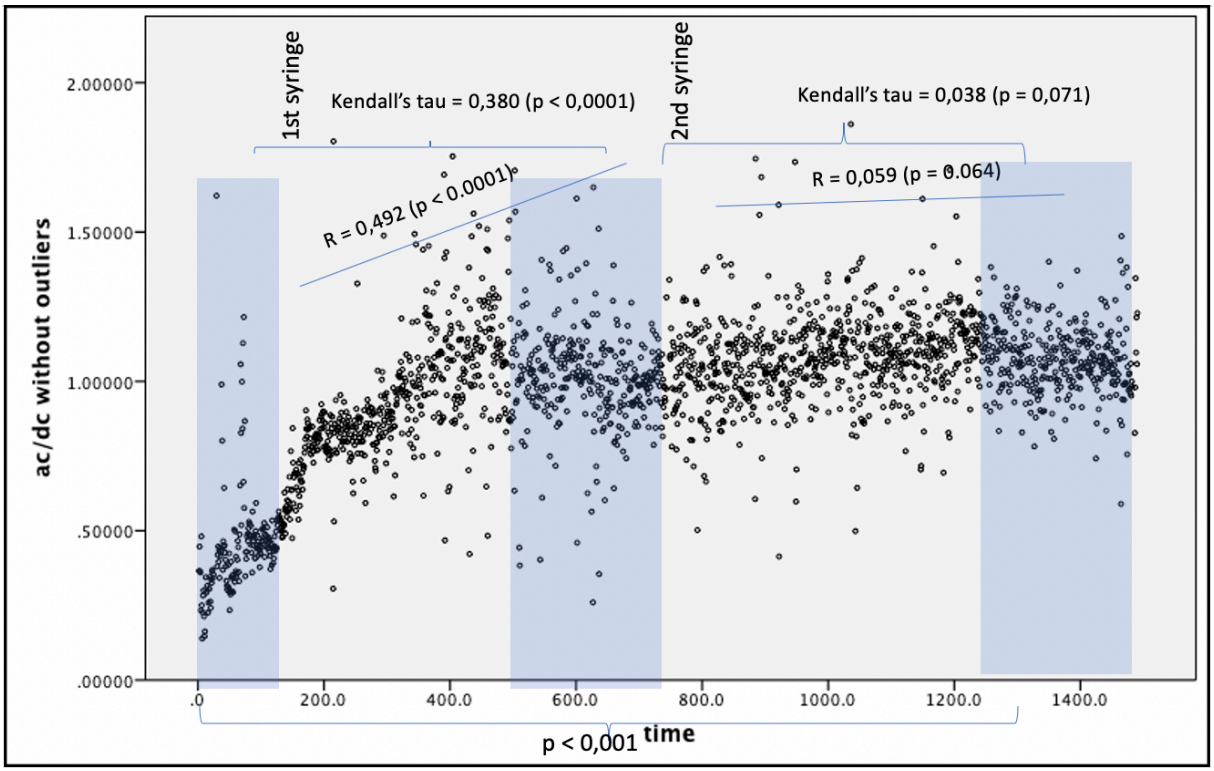

Figure 4.5.2 Patient 2 grouping 1.

For patient 2 we can see in Figure 4.5.2 the distribution of AC/DC values over the whole time of measurements. We can observe that there was a moderate positive correlation for syringe 1 (R = 0.492 (p < 0.001) and Kendall's tau = 0.380 (p < 0.001)). For the second syringe we can observe a weak positive correlation (R = 0.059 (p = 0.064) and Kendall's tau = 0.038 (p = 0.071)). The changes for the first syringe was statistically significant whereas the changes for the second syringe were not statistically significant.

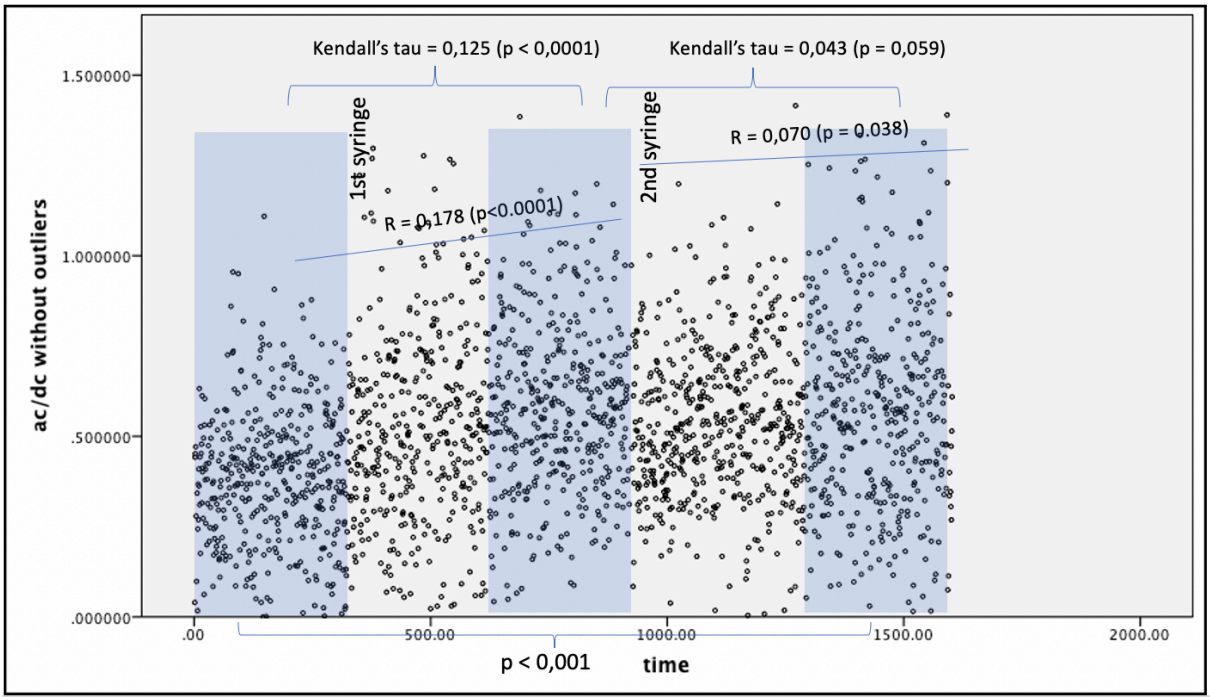

Figure 4.5.3 Patient 3 grouping 1.

For patient 3 we can see in Figure 4.5.3 the distribution of AC/DC values over the whole time of measurements. We can observe that there is a weak positive correlation for syringe 1 ($R = 0.178$ ($p < 0.0001$) and Kendall's tau = 0.125 ($p < 0.0001$)). For the second syringe we can observe a weak positive correlation ($R = 0.070$ ($p = 0.038$) and Kendall's tau = 0.043 ($p = 0.059$). The first syringe has a stronger correlation than the second syringe.

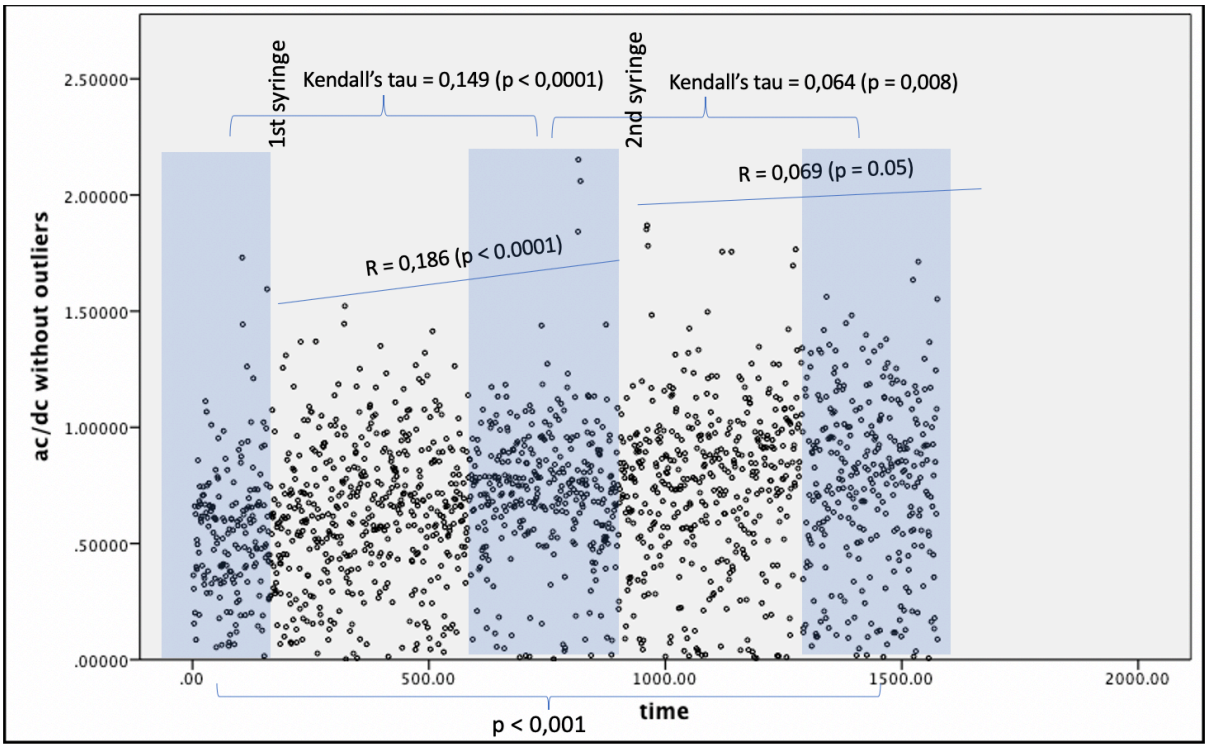

Figure 4.5.4 Patient 4 grouping 1.

For patient 4 we can see in. Figure 4.5.4 the distribution of AC/DC values over the whole time of measurements. We can observe that there was a weak positive correlation for syringe 1 (R = 0.186 (p < 0.0001) and Kendall's tau = 0.149 (p < 0.0001)). For the second syringe we can observe a weak positive correlation (R = 0.069 (p = 0.05) and Kendall's tau = 0.064 (p = 0.008). The changes for both syringes are statistically significant. The first syringe has a stronger correlation than the second syringe.

Once all the measurements and analysis of data were performed, we opened the envelopes that the nurses had randomly chosen and prepared the syringes accordingly. Patient 1 received placebo (*NaCl* 0.9%) in the first syringe and *Ropivacaine* in the second syringe. Patient 2 received *Ropivacaine* in the first syringe and placebo (*NaCl* 0.9%) in the second syringe. Patient 3 received placebo (*NaCl* 0.9%) in the first syringe and *Ropivacaine* in the second syringe. Patient 4 received *Ropivacaine* in the first syringe and placebo (*NaCl* 0.9%) in the second syringe.

For patient 1 we can observe in Figure 4.5.1 that the first syringe contained placebo (*NaCl* 0.9%) and we can observe a weak positive correlation (R = 0.259 and Kendall's tau = 0.161), both values being statistically significant ($p < 0.05$). For the second syringe that contained *Ropivacaine* we can observe a weak negative correlation (R = -0.131 and Kendall's tau = -0.072), both values being statistically significant ($p < 0.05$).

For patient 2 we can observe in Figure 4.5.2 that the first syringe contained *Ropivacaine* and we can observe a moderate positive correlation (R = 0.492 and Kendall's tau = 0.380), both values being statistically significant ($p < 0.05$). For the second syringe that contained placebo (*NaCl* 0.9%) we can observe a weak positive correlation (R = 0.059 and Kendall's tau = 0.038), neither of the values being statistically significant ($p > 0.05$).

For patient 3 we can observe in Figure 4.5.3 that the first syringe contained placebo (*NaCl* 0.9%) and we can observe a weak positive correlation (R = 0.178 and Kendall's tau = 0.125), both values being statistically significant ($p < 0.05$). For the second syringe that contained *Ropivacaine* we can observe a weak positive correlation (R = 0.070 and Kendall's tau = 0.043), neither of the values being statistically significant ($p > 0.05$).

For patient 4 we can observe in Figure 4.5.4 that the first syringe contained *Ropivacaine* and we can observe a weak positive correlation (R = 0.186 and Kendall's tau = 0.149), both values being statistically significant ($p < 0.05$). For the second syringe that contained placebo (*NaCl* 0.9%) we can observe a weak positive correlation (R 0 0.069 and Kendall's tau = 0.064), both values being statistically significant ($p < 0.05$).

5. Discussion

In this small double-blind study, the rPPG showed that it is sensitive enough to detect changes in the tissue microcirculation and temperature that were induced by injection of substances into the peripheral nerve catheter. As the study was a pilot study, we only enrolled four patients. Due to the small number of participants the results are not comprehensive enough to draw exact conclusions regarding the changes detected by the rPPG. For a broader understanding of the changes in the rPPG a larger study group would be beneficial in future studies.

The strengths of this study were that all the measurements were conducted in the exact same manner. The peripheral nerve blocks were performed by one and same person for all the patients. All the setting up of the equipment and the measuring was done by one person. This ensured a standardized study procedure.

For rPPG measurements it is vital that the light source has a constant and high enough light intensity. In our study we used the same camera and software as in the study conducted by U. Rubins (2017). In their study they used a surgical lamp as a light source. As surgical lamps have high illumination, consistent light distribution and light intensity control. For our study we were not able to use surgical lamps, instead we used a mobile surgical examination lamp. The light intensity of the surgical examination lamp was enough, but the lamp had a lower spot diameter and was lacking the intensity control. This caused some variation in the measurements. In case of further studies, a surgical lamp with intensity control would be a preferable choice.

In previous studies regarding monitoring of regional anesthesia the site of monitoring has been the upper extremity and more specific the hand. U. Rubins (2017) conducted a study where they monitored the skin changes of the hand with rPPG. For this study they had a custom-made foam rubber hand support, to ensure that the hand doesn’t move during the measurement and thereby cause artifacts. In our study we asked the patients not to move their leg, but it is impossible to stay completely still. Therefore, there are some artifacts in our study. In further studies it would be beneficial to create a support system that would immobilize the body part that is being measured.

H. Hermanns (2018) concluded that the skin of the human body can be divided into glabrous and non-glabrous skin. Both types of skin have their unique innervation and vascularization. The glabrous skin doesn't contain hair follicles and is localized at the distal part of the body. It is characterized by the rich number of arteriovenous anastomoses that give an intense vascularization and a large surface-to-volume ratio. Sympathetic blockade in glabrous skin area causes vasodilation through the arteriovenous anastomoses, leading to a prominent increase in the peripheral blood flow.

The skin of the knee is non-glabrous, which means that its vascularization is under dual control of both noradrenergic vasoconstrictor and cholinergic vasodilator nerves. It also has very few, if any, arteriovenous anastomoses. Therefore, the blockage of sympathetic nerve fibers doesn't have an effect as pronounced as the effect at the distal part of the extremities, where glabrous skin is rich with arteriovenous anastomoses. Also, the vascular coverage of the anterior knee, angiosomes, may not represent the dermatome concept.

In this small double-blind study, the rPPG showed that it is sensitive enough to detect changes in the tissue microcirculation and temperature that were induced by injection of substances into the peripheral nerve catheter. However, it couldn't distinguish local anesthetics from placebo, compared to the 100% sensitivity of cold sensation assessment. Although in *post hoc* analysis time series 1st syringe local anesthetics group showed more positive correlation coefficients ($R_2=0.492$, $r_2=0.380$, $R_4=186$, $r_4=0.149$). After blind analysis first syringe injection in all four cases showed statistically significant increases in rPPG signal AC/DC ratio in Kruskall-Wallis ($p_{1\text{-}4}<0.001$) and showed positive time correlation ($r_1=0.161$, $r_2=0.380$, $r_3=0.125$, $r_4=0.149$, $p_{1\text{-}4}<0.001$), with some statistically significant increase after second syringe injection ($r_1=-0.072$, $r_2=0.038$, $r_3=0.043$, $r_4=0.064$, $p_{1,4}<0.05$ and $p_{2,3}>0.05$).

Our results show that rPPG detects changes in the tissue but cannot distinguish whether it is placebo or local anesthetics. Subjective methods as cold sensation remains the gold standard in clinical practice. As cold sensation requires good patient compliance and communication the rPPG would be optimal for pediatric patient and patients with dementia, as it wouldn't require the patient's subjective sensation.

For further research of the rPPG methods it would be beneficial to increase the size of the patient group. Additionally, for more precise measurements and less artifacts it would be beneficial to create a custom-made stabilizer that would prevent the area of measurements from moving. As for the equipment a surgical lamp is advised as it has a constant and high enough light intensity. For the conducting of the measurements it is advisable that the blocks would be performed by one person and that the measurements would be conducted by one person. This will ensure a standardized study procedure.

6. Conclusions

1. The rPPG showed time sensitive changes during measurements in all groups, however rPPG couldn't distinguish LA from placebo in our small pilot study. With a larger study sample, we could probably see a more accurate trend of the AC/DC values and thereby receive more precise data regarding the sensitivity of the rPPG.

2. Cold sensation assessment showed 100% sensitivity of syringe content and remains the golden standard for block assessment in clinical practice.

7. Acknowledgement

I would like to express my gratitude to my family for the opportunity to study medicine and for the never-ending support to achieve my dreams. In addition, a special thank you to my partner Yrjö for the constant support and understanding throughout my University studies.

I would like to thank my thesis supervisors Prof. Aleksejs Miščuks and Edgars Vasiļjevs M.D. for guidance and working alongside with me throughout the whole Diploma work. A special thank you to Uldis Rubins for allowing us to use his equipment for our measurements. Finally, I would like to thank the staff at Hospital of Traumatology and Orthopedics for assistance during measurements.

Aurora Lövegren

8. Bibliography

Rubins U, Miščuks A, Lange M; Simple and convenient remote photoplethysmography system for monitoring regional anesthesia effectiveness. EMBEC 2017, NBC 2017. IFMBE Proceedings 2017; 65: 378-381.

Rubins U, Spigulis J, Miščuks A; Photoplethysmography imaging algorithm for continuous monitoring of regional anesthesia. ESTIMedia'16 Proc. of 14th ACM/IEEE Symposium on Embedded Systems for Real-Time Multimedia 2016; 67-71.

Abdelnasser A, Abdelhamid B, Elsonbaty A, Hasanin A, Rady A; Predicting successful supraclavicular brachial plexus block using pulse oximeter perfusion index. British Journal of Anaesthesia 2017; 119: 276-80

Alian A, Shelley K; Photoplethysmography. Best Practice & Research Clinical Anesthesiology 2014; 28: 395-406

Allen J; Photoplethysmography and its application in clinical physiological measurement. Physiological Measurements 2007; 28: https://doi.org/10.1088/0967-3334/28/3/R01

Asghar S, Lange KHW, Lundstrøm LH; Blinded observer evaluation of distal skin temperature for predicting lateral infraclavicular block success. Anesthesia & Analgesia 2015; 120: 246-51.

Asghar S, Lundstrøm LH, Bjerregaard LS, Lange KH; Ultrasound-guided lateral infraclavicular block evaluated by infrared thermography and distal skin temperature. Acta Anesthesiologica Scandinavica 2014; 58: 867-874.

Colombo R, Raimondi F, Corona A, Marchi A, Borghi B, Pellegrin S, Bergomi P, Fossali T, Guzzetti S, Porta A; Pulse photoplethysmographic amplitude and heart rate variability during laparoscopic cholecystectomy. European Journal of Anesthesiology 2017; 34: 526-533.

Elgendi M, Fletcher R, Liang Y, Howard N, Lovell N, Abbott D, Lim K, Ward R; The use of photoplethysmography for assessing hypertension. npj Digital Medicine 2019; 60; https://doi.org/10.1038/s41746-019-0136-7

Erel VK, Eker PD; Pulse wave doppler changes after axillary block using different local anesthetic volumes. Journal of Clinical and Analytical Medicine 2018; 9(5); 458-62

Guyton A, Hall J. Chapter 5 – Membrane Potentials and Action Potentials. Textbook of Medical Physiology, 11th edition, Elsevier, Philadelphia, Saunders, 2006, 61-66, ISBN 0-7216-0240-1

Hermanns H, Werdehausen R, Hollmann MW, Stevens MF; Assessment of skin temperature during regional anesthesia – What the anesthesiologist should know. Acta Anesthesiologica Scandinavica 2018; 62: 1280-1289.

Kamshilin A, Margaryants N; Origin of photoplethysmographic waveform at green light. Physics Procedia 2017; 86: 72-80.

Kamshilin A, Miridonov S, Teplov V, Saarenheimo R, Nippolainen E; Photopletysmographic imaging of high spatial resolution. Biomedical optics express 2011; 4: 996-1006.

Klaessens JHGM, Landman M, de Roode R, Noordmans HJ, Verdaasdonk RM; Objective methods for achieving an early prediction of the effectiveness of regional block anesthesia using thermography and hyper-spectral imaging. Proc. SPIE 7895, Optical Biopsy IX, 78950Q 2011; https://doi.org/10.1117/12.875074

Kokki H, Pitkänen M. Alaraajojen johtopuudutukset, Puudutusopas, 4th edition, Vammalan Kirjapaino Oy, Vammala, 2006, 71-73, ISBN 952-5417-06-9

Lange KHW, Jansen T, Asghar S, Kristensen PL, Skjønnemand M, Nørgaard P; Skin temperature measured by infrared thermography after specific ultrasound-guided blocking of the musculocutaneous, radial, ulnar and median nerves in the upper extremity. British Journal of Anaesthesia 2011; 106: 887-95

Li J, Karmakar MK, Li X, Kwok WH, Ngan KWD; Regional hemodynamic changes after an axillary brachial plexus block: a pulse-wave Doppler ultrasound study. Regional Anesthesia & Pain Medicine 2012; 37: 111-118

Miller R, Cohen N, Eriksson L, Fleisher L, Wiener-Kronish J, Young W. Chapter 36 Local anesthetics. Miller's Anesthesia, 8th edition, Elsevier, Philadelphia, Saunders 2015,1032-1034; 1721-1722, ISBN 978-0-7020-5283-5

Minville V, Gendre A, Hirsch J, Silva S, Bourdet B, Barbero C, Fourcade O, Samii K, Bouaziz H; The efficacy of skin temperature for block assessment after infraclavicular brachial plexus block. Anesthesia & Analgesia 2009; 108: 1034-6

Nitzan M, Romem A, Koppel R; Pulse oximetry: fundamentals and technology update. Medical Devices 2014; 7: 231-239

Rosenberg P, Alahuhta S, Lindgren L, Olkkola K, Ruokonen E. Anestesiamenetelmät, anestesiologinen fysiologia. Anestesia ja tehohoito, 3rd edition, Kustannus Oy Duodecim, Helsinki, Otavan Kirjapaino Oy, 2014, 376-370; 398-402, ISBN 978-951-656-404-6

DOCUMENTATION PAGE

This Diploma Thesis

„ Monitoring of continuous femoral nerve block using remote photoplethysmography”

was developed at the Faculty of Medicine of the University of Latvia.

With my signature, I attest, that this research has been carried out without aid or assistance. Used information was obtained only from indicated sources and the electronically submitted copy of this diploma work complies with printout.

Author: Aurora Lövegren _____

(name, surname) *(signature)*

I recommend the work for presentation.

Supervisor: Prof. Aleksejs Miščuks, PhD. _____ 04.05.2020

(position, name, surname, degree) *(signature)* *(date)*

Supervisor: Edgars Vasiljevs, MD _____ May 4, 2020

(position, name, surname, degree) *(signature)* *(date)*

Reviewer: _____ _____ _____

(position, name, surname, degree) *(signature)* *(date)*

The diploma thesis was submitted to the Faculty of Medicine on: _____

(date)

International students' coordinator, _____

(signature)

The diploma thesis is presented at the meeting of the State Examination Commission of Higher Professional Study Program „Medicine”_____2020.

Protocol No. _____

Secretary of Commission: _____ _____

(position, name, surname, degree) *(signature)*