SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Clinical examination of the evolution, diagnosis and treatment of the abdominal compartment syndrome

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The Examination takes place at the library of Department of Ophthalmology, Faculty of Medicine, University of Debrecen
September 6, 2017, at 11:00 AM

Head of the **Defense Committee**:	András Berta MD, PhD, DSc
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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
September 6, 2017, at 1 PM

1. INTRODUCTION

Human body is subdivided into smaller or larger units by well-defined compartments. The function of these compartments is to mechanically protect and separate from one another the organs or organ systems situated inside them. Distinctively separated spaces of our bodies are the different fascial compartments, the skull, the spinal canal, the orbit, the pericardium, the thoracic and the abdominal cavities. The elasticity of the tissues of the separating walls (bone, muscle, connective tissue) have a strong determinative effect on the tolerance for volume or pressure changes exerted on the organs which can be found inside these compartments. Compartment syndrome in a wider sense defines those changes which occur in the given compartments due to the increased pressure (which apart from some lesser and/or greater fluctuations is constant under physiological circumstances) and to the decrease in local circulation developing in consequence of this. Detrimental effects of the increased pressure are widely known and precisely described in the medical literature. Herniation syndromes occurring as a consequence of the increased intracranial pressure, the clinical appearance of pneumothorax and haemothorax caused by pathological accumulation of air or fluids inside the thoracic cavity, as well as the concept of pericardial tamponade are known by everybody. Although approaching these from this point of view is not routinish, yet no one questions that all the above cases represent a compartment syndrome occurring as a consequence of the increased pressure having been elevated due to certain specific reasons. Upon mentioning, associations are immediately made to fascial compartments, however, the term compartment syndrome means the clinical picture of the entirety of pathophysiological alterations developing in consequence of the increased pressure occurring within a closed space; and this is irrespective whether the separating compartment itself is formed by the skull, the thorax, the abdominal cavity or a given fascial compartment. A common characteristic of these syndromes is the permanent and irreversible damage that may affect the organs which can be found inside the given compartment if quick intervention cannot be provided. If vital organs are affected these damages can be life-threatening or may even lead to death.

Abdominal compartment syndrome (ACS) was first described in relation to abdominal traumatic injuries, but its occurrence is not a bit scanty in the general

surgical patient material, despite the fact that its etiology is completely different. Kron was the first, who albeit did not use the term itself, yet described compartment syndrome in 1984. It was again Kron who routinely used abdominal pressure measurement through bladder catheterisation, which became widespread by 1989; however, the fundamentals of the method were described 100 years prior by Oderbrecht. Later on several research groups developed the method (Iberti, Sugrue, Malbrain, Balogh). The creation of abdominal compartment syndrome as technical term is associated with the work of Fietsam et al in 1989. The golden age of ACS has been launched by two papers of Schein and Burch published in 1995 and 1996, respectively.

Beforehand it could only be found in the international literature, but in the domestic relation the last ten year can certainly be designated as the decade of abdominal compartment syndrome. In the Hungarian literature the abdominal variety of the compartment syndrome was first reported in the journal review written by Lajos Kollár in the "Orvosi Hetilap" ("Medical Journal") in 2000. The internationally recognised pioneering activity of Zsolt Balogh carried out at the University of Szeged is immensely important to be mentioned, because he founded the Hungarian research on compartment syndrome, which was carried on by working groups in Budapest (Záborszky et al, "Honvéd" Hospital) and in the "Kenézy" Hospital of Debrecen. Accounts were given on the results of the working group operating in Budapest in the medical officer trade paper entitled "Honvédorvos" in 2005, 2007, and 2009. In 2006 our working group, while in 2012 Szentkereszty et al. published a review paper in the journal entitled "Magyar Sebészet" ("Hungarian Surgery"). Our papers dealing with the laboratory and pathophysiological deviations observed in relation to conditions with increased abdominal pressure in a human patient population were published in 2010 and 2011 ("Langenbecks Archives of Surgery"). Our review presenting our experience gained within ten years spent with the research of abdominal compartment syndrome was published in the "Orvosi Hetilap" in 2014.

Pancreatitis, inflammatory processes or haemorrhage of the retroperitoneum, paralytic ileus, ascites, severe visceral oedema caused by extreme fluid replenishment, blunt abdominal trauma, peritonitis, or even massive transfusion can be found among the triggering factors of ACS; i.e. all factors which may and can lead to a sudden increase in the intra-abdominal pressure (IAP, 5-10 mmHg under physiological circumstances), to conditions of intra-abdominal hypertension (IAH, IAP $\geq$ 12 mmHg) associated with organ or multiple organ failure, or without intervention to abdominal

compartment syndrome (IAP ≥ 20 mmHg, which is associated with the failure of vital organs). Despite the modern and quick diagnostics, and the adequate surgical interventions performed in time the mortality of ACS is extremely high (38-71%). It affects practically all vital organ systems: cardiovascular, respiratory, urinary and central nervous systems, as well as the parenchymatous organs.

The only possible way of establishing the diagnosis is to measure the intra-abdominal pressure, a widespread manner of which is the measurement through the bladder. The fundamental principle of the method is the law which says that if pressure is exerted on the surface of a compartment predominantly containing some kind of fluid, then this pressure imposed upon the practically incompressible fluid will be transmitted unaltered to each and every point of the affected compartment. Consequently the IAP and the intravesical pressure values are strictly identical. If the bladder is filled with 50 mL of physiological saline and the previously inserted catheter is closed, then the pressure predominating the bladder will be transmitted to the catheter and became easily measurable through a sterile needle inserted into the catheter. This procedure was simplified by the working group of Sugrue, who placed a 'T-element' into the catheter, which rendered unnecessary the closure and insertion of it, and also significantly reducing the prevalence of infections associated with this measurement. To surmount points of weakness (laboursome, intermittent) Balogh and his working group developed and validated the method of continuous intra-abdominal pressure monitoring (CIAPM). Owing to their modifications the procedure of vesical filling, catheter closure and needle insertion was smoothed away ("Balogh-Sugrue technique").

Treatment of ACS is nearly always surgical decompression. Within the frame of prevention, or in the case of individual ACS responding well to conservative methods non-surgical solutions may also be possible (evacuation of the intraluminar content, removal of the space occupying process, improvement of the tolerance of the abdominal wall, optimal fluid therapy, optimisation of the systemic and regional circulation). Success is greatly influenced by the aetiology of the given case and by the general condition of the patient. If IAP > 20 mmHg (and/or APP < 50 mmHg, where APP = abdominal perfusion pressure) and new signs of organic dysfunction are occurring, then the ACS is not responding to the conservative method, and the possibility of surgical decompression should be carefully considered.

Surgical treatment for all cases of IAH/ACS is decompression laparotomy with temporary abdominal wall closure or open abdominal treatment. Following

decompression the problem cannot be regarded as solved, and the conservative method should be carried further on (adequate medication, optimal fluid therapy) along with the constant monitoring of IAP. APP above 60 mmHg and IAP under 12 mmHg means the solution of the IAH. If APP > 60 mmHg and IAP > 12 mmHg, then the conservative method is still well-founded, but decompression or the revision of the previous decompression is necessary in case of APP < 60 mmHg.

In the last few decades the consensus definitions were elaborated and following several modifications were published again in 2013, the diagnostic method was brought to perfection, the therapeutic possibilities were revolutionised and developed to a high-tech level, however, the puzzling out of the pathophysiology in its entire depth and as an integer is yet to be achieved. It is known that the basis of the phenomenon is the co-dependent chain reaction of several physiological processes triggered by the increased intra-abdominal pressure, but the exact mechanism still remains in obscurity. Besides the pathophysiological changes in each organ there is also a crucial role of cell abnormalities among which the most important is the hypoxia due to the elevated IAP, leading to a significant increase of serum adenosine level.

Our experiments were planned by knowing all written above with the purpose of making their results and methods incidentally exploited practically and clinically.

2. AIMS

1. In our works we wanted to study whether the method of continuous abdominal pressure measurement is feasible within the everyday practice of diagnosing the conditions having increased intra-abdominal pressure, as well as the ACS at the Ward of General Surgery of the “Kenézy” Hospital of Debrecen. Our aim was not only to introduce this new technique, but to bring it to perfection as well.

2. We wanted to measure whether the values of intra-abdominal pressure show any kind of correlation with the serum levels of adenosine and IL-10.

3. If it turns out to be right that high intra-abdominal pressure is combined with high serum level of adenosine, we planned to study whether the serum levels of adenosine

and IL-10 could be reduced by the administration of theophylline infusion, as well as whether any kind of improvement could be observed concerning the increased intra-abdominal pressure and the ACS.

4. We wanted to study to question of which conclusions can be deduced from our examinations in order to improve the diagnostics and therapy of the compartment syndrome by reason of linking the already available literature data and our new results.

3. PATIENTS AND METHODS

Our studies were carried out on the Wards of General Surgery, Internal Medicine and Intensive Therapy of the "Kenézy" Hospital.

3.1. COMPARATIVE STUDY OF THE TRADITIONAL AND CONTINUOUS INTRA-ABDOMINAL PRESSURE MEASUREMENT TECHNIQUES

3.1.1. Patients of the comparative study of the intra-abdominal pressure measurement techniques

To carry on the comparative study of the intermittent (traditional) and continuous intra-abdominal pressure measurement techniques twenty acute pancreatitis patients were involved. The selection of the patients based on a random nature.

3.1.2. Measurement method

The intra-abdominal pressure was measured on every patients, in every six hours, by the both techniques. To avoid the technical errors all of the measurements were carried out by the same person. Patients were included into the study following the preliminary oral information and signing of the informed consent forms, for which the patients had the right and possibility of withdrawal made at any time without providing any justification.

3.1.2.1. Traditional (intermittent) technique of intra-abdominal pressure measurement

Prior to our study intra-abdominal pressure measurements were never performed at our hospital. Sporadic pressure determinations were performed in one or two clinical centres in Hungary; however, routine measurements defined in protocols could nowhere be mentioned. In order to carry out the initial pressure measurements we performed intermittent measurements following the Sugrue technique. The patients wore a simple bladder catheter (Foley balloon catheter, 16Fr-20Fr, latex or silicone). During the measurement the urine collection bag was removed and the bladder was filled with 50 mL of physiological saline through the lumen of the catheter. In the next step the lumen of the catheter was connected to a set designed and used for the measurement of the central venous pressure (B. BRAUN Medifix® pressure measurement scale) with or without the insertion of a T-tap. The zero point of the scaled measurement tube was designated in the medioaxillary line corresponding to the anterior superior iliac crest. After waiting 1-2 minutes, at the end of exhalation the value of IAP could be read off the scale in unites of cmH_2O. The values read off should be converted to mmHg (1 mmHg = 1.36 cmH_2O). When the measurement was completed the system and the bladder catheter were disconnected and the latter was connected to a urine collection bag.

3.1.2.2. Continuous intra-abdominal pressure measurement

The technique of continuous intra-abdominal pressure measurement was known from the international literature. With the aid of personal consultations with the Australian working group which elaborated the procedure (Prof. Zsolt Balogh, M.D.) we perfected and further developed it, and subsequent to the elaboration of the ward protocol and of further training lectures held for the specialist healthcare workers we – being the only such institution to do so – introduced it to the everyday routine practice. Taking into consideration the nature of the intra-abdominal pressure being oscillatory even on a daily basis we considered the use of the continuous intra-abdominal pressure measurement technique to be essential for the everyday routine, as well as during the design of the studies. For the measurements we used 18 Fr standard three-way bladder catheters (LubriSilTM All-Silicone Foley catheter, C.R. Bard, Inc., Covington, GA, U.S.A.). The catheter and the urine collecting bag remained connected for all the time. In order to perform the pressure measurement the so called flushing port of the catheter

was connected with the insertion of a transducer to a 24-hour bedside monitor. The connection of the flushing port and the transducer was effectuated with a triple tap. The collapse of the bladder was prevented with physiological saline continuously perfused with the speed of 4 mL/h. The zero point for the fixation of the transducer was established in the plane determined by the axillary median line and the anterior superior iliac crest. After the system was set to zero the measured data were continuously recorded, which data could be easily read off from the bedside monitor. The actual IAP value appeared directly in mmHg and required no further conversion. Pressure values were read off in every hour. The IAP mean value determined on a daily basis was calculated as the average of pressure values recorded in 24 hours.

3.2. ELEVATED SERUM LEVELS OF ADENOSINE AND INTERLEUKIN-10 AS NOVEL LABORATORY MARKERS OF INCREASEMENT OF THE INTRA-ABDOMINAL PRESSURE

3.2.1. Patients of determination of the serum level of adenosine and interleukin-10

To investigate the correlation between the intra-abdominal pressure and the changes of the serum levels of adenosine two groups were determined: a.) a low pressure (IAP < 12 mmHg, n=25), and b.) a high pressure (IAP ≥ 12 mmHg, n=45) group. Patients were included into the study following the preliminary oral information and signing of the informed consent forms, for which the patients had the right and possibility of withdrawal made at any time without providing any justification. To separate these two groups only the values of the IAP were taken into account.

The diagnosis justifying the admission to the ward could be varying from patient to patient, but during the planning phase of the study the homogeneous patient group formation was a constant priority. According to the international consensus to characterise the general condition of the patients the APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sequential Organ Failure Assessment) scores were recorded. The average value of the APACHE II score was 26.22±2.4 in the low pressure group and 29.8±3.1 in the high pressure group. The average value of the SOFA score was 11.65±3.2 in the low pressure group and 12.4±2.8 in the high pressure group.

3.2.2. Measurement methods

3.2.2.1. Intra-abdominal pressure measurement

Determination of the intra-abdominal pressure was carried out according to the method described in the 3.1.2.2. chapter.

3.2.2.2. Determination of the serum level of adenosine

Determination of the serum adenosine concentration was carried out according to the method introduced by Capogrossi et al. by using an HPLC (High Performance Liquid Chromatography) (Merck-Hitachi, Germany) method, and by performing the measurements under 254 nm (UV-VIS, L-4250 detector). Following deproteinization the samples were separated on a LiChrospher 100RP-18 column (particle size: 5 μm, 5 mm i.d., length: 125 mm) in isocratic mode. 20 mM KH_2PO_4 was used as solvent in a 10:90 ratio mixture of methanol and water having a pH value of 4.5 and a flow rate of 1.0 mL/min. For the determination of adenosine well-known internal and external standards were used. Data were processed with the D-6000 HPLC-Manager software (Merck, Germany) program. EDTA (2.7 mM) and dipyridamole were used as inhibitors of adenosine deaminase and cAMP phoshodiesterase. Measurements were carried out in the Regional Immunological Laboratory (RIMM) of the Department of Internal Medicine of the University of Debrecen Faculty of Medicine (DE ÁOK by its Hungarian acronym).

3.2.2.3. Determination of serum levels of cytokines

Serum cytokines (IL-1β, IL-2, IL-4, IL-10, TNFα, IFNγ) was determined with the ELISA (Enzyme Linked Immunosorbent Assay) method. Measurements were carried out in the Regional Immunological Laboratory (RIMM) of the Department of Internal Medicine of the DE ÁOK.

3.2.2.4. Determination of the level of CRP

The level of the C-reactive protein was measured by using nephelometry (Dade-Behring, USA). Measurements were carried out in the Regional Immunological Laboratory (RIMM) of the Department of Internal Medicine of the DE ÁOK.

3.3. BENEFICIAL EFFECTS OF THEOPHYLLINE IN PATIENTS HAVING INCREASED INTRA-ABDOMINAL PRESSURE

3.3.1. Patients of the theophylline effect study

To the third study 78 patients having increased intra-abdominal pressure (IAP≥12 mmHg) were included. The patients were included in the study if during the clinical examination abdominal distension was revealed and the intra-abdominal pressure reached or surpassed 12 mmHg on the day of the admission. Subjects were followed on until their discharge from the hospital, or for a maximum of 30 days. To prevent threatening compartment syndrome surgical decompression was performed if the value of IAP reached 20 mmHg.

The diagnosis justifying the admission to the ward could be varying from patient to patient, but during the planning phase of the study the homogeneous patient group formation was a constant priority. According to the international consensus to characterise the general condition of the patients the APACHE II and SOFA scores were recorded. There were no significant differences between the control and theophylline treated study groups in relation to the average values of the APACHE II (27.42±6.0; n=38 vs. 28.8±8.1; n=40) and SOFA (12.95±4.0; n=38 vs. 13.4±4.8; n=40) scores.

Patients were included into the study following the preliminary oral information and signing of the informed consent forms, for which the patients had the right and possibility of withdrawal made at any time without providing any justification.

3.3.2. Method of patient group formation

Originally we designed and started our study to be a randomised, controlled, prospective clinical study. Our patients were classified into two groups: a.) the group receiving only conservative therapy (ST = standard therapy, n=38) regarding to the nonoperative management protocol of the WSACS, and b.) the group receiving theophylline treatment on top of the conservative therapy (T = theophylline, n=40). The main goal of the theophylline treatment was to take advantage of the supportive effect of theophylline on the cardiovascular, respiratory and diuretic functions.

During the preliminary analysis of the results we got the outcome that no patient treated with theophylline was lost, however the mortality was 50% in the ST group. At this stage (after previous consultation with statistician) a very difficult ethical and technical

decision was taken. The study was continued as a non-randomised interventional cohort study. During the decision made process several important reasons were balanced: a.) There were no articles found in the literature regarding to the medication used in IAH/ACS treatment. Our work was the first in this field. b.) There were no studies regarding to the application of theophylline as andenosine antagonist agent in the treatment of IAH/ACS. c.) Being conscious of the high mortality of ACS, the withdrawal of the chance of the survival due to the lack of theophylline treatment was declared unethical. A well known data from the literature that despite the correct therapy the average mortality of ACS is 40-70%, which was demonstrated in the ST group. Considering all this, at this stage the study designed was changed and all the patients were treated with theophylline (T group). A group of 38 patients –from an earlier study- treated only by the protocol of non-operative management (without theophylline) was appointed as control group (ST group). The study was continued as a non-randomised, interventional cohort (the effect of theophylline was investigated) with historical controls (the result of the present study was compared with the results of a previous one).

3.3.3. Treatment protocols

3.3.3.1. Conservative treatment of intra-abdominal hypertension

The so called standard therapy was identical with the non-surgical treatment protocol of WSACS (World Society of Abdominal Compartment Syndrome) on the treatment and care of IAH/ACS. When care was provided for the ST group the principles of this protocol were followed.

There is a high risk for further progression of IAH, when the IAP in presence of one or more risk factors reaches or surpasses 12 mmHg. At every moment, the IAH/ACS management we should be strictly “proactive”, when the main goal is to prevent the development of IAH and/or ACS. The aim of the useage of nasogastric tube, diuretics, muscle relaxants, etc. is the same, to avoid the IAH/ACS. The mentioned tools form part of the non-operative management protocol. All patients involved in our study were treated by this protocol.

In cases of both the ST and T groups, there were patients (n_{ST}=4, n_T=5) who reached the pressure value of 20 mmHg, for whom upon the decision of the surgical team being at

the time on duty a decompression laparotomy was performed with the implantation of a Bogota bag. The data of these patients were excluded from the study.

3.3.3.2. Theophylline treatment in patients with intra-abdominal hypertension

All patients receiving theophylline therapy were given 200 mg of intravenous theophylline (Novartis), twice daily. Theophylline was administered as slow intravenous infusion lasting for 20 minutes during the morning and evening medication administrations. Based on our previous observations independent of this study an uninterrupted treatment of minimum five days was necessary to achieve the desired therapeutic effect. Blood levels of theophylline were controlled in every 24 hours. Normal range was oscillated between 10 and 20 μg/ml.

To develop the length of the effective theophylline treatment is a very difficult question. Before deciding the five days treatment period, the relevant literature was studied. We wanted to put across the well known cardiac, respiratory and diuretic protective effects of theophylline in the treatment provided to the T group, counteracting the harmful effects of the elevated intra-abdominal pressure. Of course we were aware that the theophylline has an adenosine receptor antagonist effect too. We did not find any literature regarding to the application of adenosine receptor antagonists in the management of IAH and/or ACS, this is why the articles published regarding the use of adenosine antagonism in other clinical pictures were taken into account. Regarding to our study based on the main role of the kidney injury, the most valuable articles were published (in very small number) with the topic of protective role of theophylline on the kidney function. However we should take them into consideration under protest due to their uncertainty nature. For example there is not a standard agreement regarding the effective blood level of theophylline used for protection of the kidney function. This effect would be probably alter depending on the timing of the application, before of injury (protective) or after it. The five days treatment period was decided after the analysis and evaluation of the relevant literature and our previous theophylline related independent from the present study experience. It was found, that the five days treatment period in all the cases was enough to reach the useful effects of theophylline presented in details in the present work.

3.3.4. Monitoring of cardiac, respiratory and diuretic functions

Mean arterial pressure (MAP) was chosen as haemodynamic characteristic, while oxygen saturation (SaO2) was chosen to follow the respiratory function, and the actual values of blood urea nitrogen (BUN), creatinine (Crea), daily urine volume (DUV) and fluid balance (FB) were recorded for the monitoring of the renal function. To calculate the value of fluid balance the sum of the values of the daily urine volume and of the 'insensible loss' was subtracted from the quantity of daily fluid intake. Calculation of the 'insensible loss' was carried out by using the Dubois formula.

3.3.5. Intra-abdominal pressure measurement

Determination of the intra-abdominal pressure was carried out according to the method described in the 3.1.2.2. chapter.

3.3.6. Determination of the serum level of adenosine

Determination of the serum adenosine concentration was carried out according to the method described in the 3.2.2.2. chapter.

3.3.7. Determination of the serum level of interleukin-10

Determination of the serum interleukin-10 concentration was carried out according to the method described in the 3.2.2.3. chapter.

3.4. Statistical methods

Data of normal distribution were characterised by providing their means and standard deviations (SD). Mortality data were analysed with the chi-square test. Besides this a multiple linear regression model was fitted in cases of all studied outcome factors, in which models the age, sex and number of treatment days were the explanatory variables. The normality of the outcome variables and the age distribution was investigated and transformation was applied in case of need. Observations made repeatedly in case of the same patient were not considered to be independent from one another. During the modelling the standard error of the coefficients was determined with the so called robust calculation method. The fitting of the models was verified by representing the residual values as a function of the fitted values, by the pointedness-skewness probe of the residues (normality test), as well as by the model specification test. The estimated difference was considered to be statistically significant in all cases of

comparison relations showing *p* values smaller than 0.05. When comparing the two patient groups the mean and standard deviation of the investigated variable were calculated, and the statistical assessment of the difference was carried out by using the two-sample *t*-test. For the estimation of the statistical correlation the value of the Spearman's *r*-coefficient was calculated. Statistical differences were considered to be significant in the case of $p < 0.05$. To compare two measurements techniques the 95% limits of agreement of Bland-Altman method and the Lin's concordance correlation coefficient were calculated.

3.5. Collaboration between departments

Investigation of the pathophysiology of the IAH/ACS was based on the excellent relations long-existing between our Institution and the Division of Clinical Immunology of the Department of Internal Medicine of the DE ÁOK; in which the surgical clinical approach and the research and diagnostics background of the Laboratory were both prevailed.

The idea to study the role of adenosine potentially played in conditions of increased intra-abdominal pressure and during the compartment syndrome was provided by two previous works of the researchers of the RIMM.

3.6. Research authorisations

Studies serving as the basis of this thesis were conducted upon the below listed authorisations:

Institutional Ethics Committee of the "Kenézy" Hospital:
KFK 18/142006

Scientific and Research Ethics Committee of the Medical Research Council (ETT TUKEB by its Hungarian acronym):
ad. 311/KO/2006.
ad. 230-117/2006-1018EKU
ETT TUKEB: ad. 310/KO/2006.
ad. 230-116/2006-1018EKU

Authorisations granted by the ward head senior physicians of the "Kenézy" Hospital:
Ward of General Surgery, 13/09/2005
Ward of Internal Medicine, 18/10/2005
Ward of Intensive Therapy, 18/10/2005

4. RESULTS

4.1. Comparative study of the traditional and continuous intra-abdominal pressure measurement techniques

In order to determine the objectivity of the continuous intra-abdominal pressure measurement we carried out measurements in patients with normal and elevated intra-abdominal pressures. Significant difference could not be observed between the results of the intermittent measurements and of the new technique. According to the statistical analysis the concordance correlation coefficient was higher than 0.97 in all cases, which shows a strongly significant agreement between the two different techniques. The 95% limits of agreement of the Bland-Altman method were between the non-significant ±2 mmHg range. According to our results we can summarize that the continuous intra-abdominal pressure monitoring technique is a modern, safe and accurate method for the IAP monitoring, which provides results immediately, in mmHg without need of conversion.

4.2. Elevated serum levels of adenosine and interleukin-10 as novel laboratory markers of increasement of the intra-abdominal pressure

The correlation between IAP, serum levels of adenosine and serum levels of IL-10 was analysed in a study group formed from seventy patients.

We found that there is a linear correlation between the change in the intra-abdominal pressure value (9.42±1.24 mmHg in the low pressure group, and 19.76±4.01 mmHg in the high pressure group; $p<0.001$) and the serum level of adenosine (0.06±0.02 μM in the low pressure group; 1.61±1.52 μM in the high pressure group; $p<0.01$). The same type of correlation was observed between the intra-abdominal pressure value and the serum levels of IL-10 (27.27±5.43 pg/mL in the low pressure group; 63.23±58.41

pg/mL in the high pressure group; $p<0.01$). The normal value of adenosine is < 0.05μM, and the normal value of IL-10 is < 18.7 pg/mL.

We statistically proved that these correlations have strong significance ($p< 0.001$) in conditions having intra-abdominal pressure higher than the value of 12 mmHg. The value of the correlation coefficient (r) for the correlation between the IAP and adenosine is 0.766, for the correlation between the IAP and the IL-10 it is 0.792. We found a significant correlation between the serum level of adenosine and the serum level of IL-10 ($r=0.52$, $p=0.0077$ in the low pressure group; $r=0.888$, $p<0.001$ in the high pressure group).

Significant changes in the concentrations of the other cytokines and inflammatory proteins (IL-1β, IL-2, IL-4, TNFα, IFNγ, CRP) could not be observed.

4.3. Beneficial effects of theophylline in patients having increased intra-abdominal pressure

The correlation identified between the serum levels of adenosine and the changes of the IAP provided the grounds for our hypothesis saying that treatment with the A1 and A2 adenosine receptor antagonist theophylline may reduce the morbidity and mortality of IAH/ACS.

In the case of a homogeneous group consisting of 78 patients we investigated the effect of theophylline on the IAP, serum adenosine levels and serum IL-10 levels. Mortality of the group receiving standard therapy (containing no theophylline) was 55%, while in the group treated with theophylline no patient was lost ($p < 0.0001$). During the five days of the treatment the value of the IAP (1st day 18.2 (3.7) mmHg vs. 5th day 9.5 (3.5) mmHg; $p<0.001$), the serum levels of adenosine (1st day 1.1 (1.7) μM vs. 5th day 0.04 (0.15) μM; $p<0.0001$), and of IL-10 (1st day 48.7 (54.6) pg/mL vs. 5th 4.9 (8.8) pg/mL; $p<0.0001$) were significantly reduced.

Besides the beneficial changes attributable to the effect of theophylline and observed in the cases of IAP, adenosine and IL-10 we analysed the changes which occurred in the characteristics of the respiratory and circulatory systems. Physiological parameters were continuously monitored during the five days of the treatment. The renal function has progressively improved during the five days of the treatment: the serum levels of urea (12.3 (10.33) mM vs. 5.42 (3.39) mM; $p<0.0001$) and creatinine (107.83 (115.78) mM vs. 51.95 (12.74) mM; $p<0.0001$) were significantly reduced, while the amount of urine

voided in 24 hours has significantly increased (1.544 (0.570) litre/day vs. 2.271 (0.359) litre/day; $p<0.001$). By the fifth day the fluid volume intake could be significantly reduced (2.862 (0.725) litre/day vs. 1.862 (0.751) litre/day; $p<0.05$) in the group receiving theophylline therapy. The likewise positive changes observed in the circulatory and respiratory parameters, i.e. the haemodynamic and cardiovascular stabilisation was demonstrated by the increasement of the values of the arterial mean pressure (92.7 (17.5) mmHg vs. 103.9 (15.1) mmHg; $p<0.05$) and of the oxygen saturation (95.1 (3.4) % vs. 97.5 (1.4) %; $p<0.02$). During the five-day treatment period no significant side effect attributable to theophylline was observed.

5. DISCUSSION

Measurement of the intra-abdominal pressure is essential in the differentiated diagnostics of acute abdominal pathologies, in the following of surgery patients being in critical condition, in the prevention of the IAH/ACS, as well as in the monitoring of the already developed syndrome. The IAP (being within the normal range or increased) is never a constant value, but has an oscillatory nature even under 24 hours. This nature was the main demand to develop a continuous control providing measurement method. The continuous intra-abdominal pressure monitoring technique was firstly published by Balogh and his working team in 2004. In order to determine the objectivity of the continuous technique we carried out measurements in twenty patients and we verified that the intermittent and continuous measurements are trusty methods of intra-abdominal pressure monitoring without significant differences between them. Following its first construction the system of CIAPM can be operated without interruption until the next replacement of the bladder catheter (about 7 to 10 days), thereby eliminating the risk of infection originating from the catheter replacements in the intermittent measurements, as well as the need for extra work and tools.

Summing it up the continuous intra-abdominal pressure measurement is the “gold standard” of the intra-abdominal pressure monitoring.

Besides the pathophysiological changes in each organ there is also a crucial role of cell abnormalities among which the most important is the hypoxia due to the elevated IAP, leading to a significant increase of serum adenosine level. During the last few years it was confirmed by numberless studies that hypoxia, trauma and inflammation

are trigger factors of adenosine produce. Above all, the idea to study the role of adenosine potentially played in conditions of increased intra-abdominal pressure was provided by previous adenosine-related experience of the researchers of our working group.

In case of seventy surgical patients having increased or normal intra-abdominal pressure values we studied the correlation between serum adenosine level, CRP, several cytokines (IL-1β, IL-2, IL-4, IL-10), TNFα, IFNγ and the IAP. As an entirely new observation we verified a strongly significant relation between the serum level of adenosine and the changes of the IAP. The same significant correlation was detected between the serum level of IL-10 and the values of the IAP. From all these we deduced that the serum levels of adenosine and IL-10 are very sensitive indicators of the oscillation of the intra-abdominal pressure.

In the development of ACS we assumed the central role of adenosine produced by the hypoxic tissues as effect of elevated intra-abdominal pressure. Adenosine is a very potent vasodilator, however, in a unique manner it exerts a vasoconstricting effect on the renal artery. Because of the vasoconstriction of the renal artery and of the direct renal effects of adenosine (inhibition of renin secretion, Na+ and fluid retention, decreasing GFR) acute renal failure and drop in the blood pressure occur. The drop in the blood pressure and the decrease in the flow of the portal vein activates the HABR (Hepatic Arterial Buffer Response = the system responsible for maintaining the balance in the portal and hepatic veins, and the regulation of the hepatic circulation, being independent of external innervation), which provides that the hepatic vein should be able to modify its circulation depending on the flow changes occurring in the portal vein. This compensating mechanism can work only to a certain limit. It cannot compensate the drastic decrease of the mesenteric circulation. Because of the fact that in response to a minimal increase of the IAP the mesenteric perfusion significantly decreases further adenosine accumulation occurs in the liver due to the insufficiency of the HABR. Proportionately to the progression of hepatic insufficiency the renal dysfunction is also increased, which manifests itself in further sodium and water retention, severely reduced glomerular filtration and threatening circulatory collapse (hepatorenal syndrome).

The gastrointestinal system is also expressly sensitive to the changes of the IAP. Because of the damaged perfusion oedema of the intestinal mucosa, and later of the intestinal wall, due to the local acidosis, ischaemia and permeation intensification, as

well as barrier damage and bacterial translocation occur. The oedema is further deteriorating the already existing hypoperfusion and activates an intensified inflammatory response, which under the above severe conditions leads to a generalised capillary permeation. The acute intestinal distress syndrome is the damage of the gastrointestinal tract, which occurs when it reacts in a so called non-specific way to insults of different origin, in our case to the increasement of the IAP. The development of an intensified local immune response should also be mentioned. The intestines start to produce large amounts of mediators which reach all parts of the body through the lymphatic circulation and activate the processes responsible for the development of the Capillary Hyperpermeability Syndrome (CHS), mitochondrial damage, apoptosis and cellular death. All these mediators together with the activated polymorphonuclear leukocytes leave the intestines through the lymphatic circulation and by reaching the mucosa-rich organs (lungs, liver, kidney) enhance capillary permeability. By evoking an endothelial damage they induce the multiple organ dysfunction syndrome, being the last phase of the ACS. By operating as a vicious circle the process fortifies itself through positive feedbacks and induces the condition known as hyperdynamic circulation. At this point the regulatory mechanisms are unable to control the process and without external intervention the multi organ failure (MOF) and death occur.

Based on the key role of adenosine played in the process the therapeutic blockage of the pathophysiological process through the inhibition of adenosine seemed obvious. We designed our study by reason of the evidence according to which the clinically available, widely known and any time easily obtainable theophylline (dimethyl-xanthine) having a methylxanthine structure is the competitive antagonist of the A1 and A2 adenosine receptors, thus it is a repeatedly proven and effective inhibitor of the effects induced by adenosine. By knowing all these facts we started the five-day long theophylline treatments in the cases of patients admitted to our ward due to a condition of increased intra-abdominal pressure. When we compared the results obtained from 40 patients treated with theophylline with the data of 38 patients who were not treated with this substance we got the outcome that no patient treated with theophylline was lost, nor theophylline related side effect was detected with therapeutic serum level of 10-20 μg/ml. Besides the beneficial changes attributable to the effect of theophylline and observed in the cases of IAP, adenosine and IL-10, we analysed the changes which occurred in the characteristics of the respiratory and circulatory systems.

Physiological parameters were continuously monitored during the five days of the treatment.

In IAH the cardiac function became damaged, the arterial mean pressure decreases, and the abdominal perfusion pressure may approach a critical value. We assume that theophylline infusions started earlier facilitate the normalization of the circulation and the renal function by linking to the adenosine receptors, blocking the vasoconstrictor effect the circulating adenosine exerted on the renal artery, promoting the normalization of the renin secretion, as well as through direct cardiac effects. In other words the MAP increase observed by us may be the consequence of the adenosine receptor blockage developed in response to the effect of theophylline, which at first stabilises the circulation at the level of the individual organs, and this later on manifests itself in a generalized manner as the normalization of the arterial mean pressure leading to the general decrease of hypoxia.

According to our studies it may be presumed that the adenosine production generated by hypoxic condition occurring in consequence of the increased IAP, as well as the pathophysiological processes induced by adenosine through renal vasoconstriction are leading to ACS, multiple organ failure, and later on to death. However, blockage of the adenosine receptors may result in the survival of the patients concerned by subduing this process. Based on all the above we believe in that the adenosine receptor inhibitor theophylline has to get its place in the non-surgical therapeutic protocol of the IAH/ACS, but which may only be taken into consideration in the IAP range of 12 to 20 mmHg. In case of pressure values surpassing this range, i.e. in case of defined ACS the decompression laparotomy being the drastic and immediate reduction of the intra-abdominal pressure is still the only option.

Further studies are required for the demonstration of the effects of theophylline or other adenosine receptor blocking agents exerted on the splanchnic circulation, and of their protective function exerted on these organs. Verification of our observations, as well as the deduction of a final conclusion being generalized from our results requires future multicentre clinical studies having large patient numbers.

The "ARIADNE" (**A**denosine **R**eceptor antagonism in the management of **I**ntra-**A**bdominal hypertension and ab**D**ominal compartme**N**t syndrom**E**) study is a multicenter, prospective, randomized, double-blind controlled trial, supported by the WSACS (World Society of Abdominal Compartment Syndrome) and the CTWG

(Clinical Trial Working Group). The involvement of the study centers and the ethical authorisation are in process.

6. SUMMARY OF NOVEL CONCLUSIONS

1. Pressure measurement through vesical catheters for the monitoring of the IAP, especially its continuous variant is an excellently applicable method. Introduction into the daily clinical routine is recommended.

2. The strongly significant correlation between the IAP and the serum level of adenosine provides new data not just for the resolution of the pathophysiology of the ACS, but indicates a novel therapeutic possibility, as well.

3. Therapeutic use of theophylline as competitive adenosine antagonist in conditions of increased intra-abdominal pressure is pronouncedly recommended due to its proven adenosine level and IAP reducing effects, as well as its positive effects exerted on the physiological parameters (circulation, respiration, diuresis).

4. Theophylline infusions started in the case of IAP > 12 mmHg and administered for a five-day period express a significant protective effect, therefore the administration of these is pronouncedly recommended in the case of an IAH condition. Introduction of theophylline into the non-surgical treatment protocol of IAH is well founded and recommended.

5. If in spite of the theophylline therapy the IAP reaches the value of 20 mmHg or if administration of theophylline infusions is not possible, surgical decompression due to threatening ACS is required in the case if IAP = 20 mmHg.

7. PUBLICATIONS

7.1. List of publications related to the dissertation

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Candidate: Zsolt Bodnár
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Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Bodnár, Z.**, Szentkereszty, Z., Hajdú, Z., Boissonneault, G.A., Sipka, S.: Beneficial effects of theophylline infusions in surgical patients with intra-abdominal hypertension.
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7.2. List of congress abstracts related to the topic of the dissertation

[1] **Bodnár, Zs.**, Ary, F., Bulyovszky, I., et al.: Continuous intra-abdominal pressure measurement technique (CIAP). Eur J Anaesth, 2006, 23, Suppl. 37, 197.

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[2] **Bodnár Zs**., Bulyovszky I., Hajdu Z.: Hasüregi nyomás (IAP) mérésére szolgáló módszerek összehasonlító vizsgálata. MST Kísérletes Sebészeti Szekció XX. Jubileumi Kongresszusa, Hajdúszoboszló, 2005. szeptember 8-10.

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