ISSN 2193-3863

Archiv EURO MEDICA

1·2014

EUROPÄISCHE
WISSENSCHAFTLICHE
GESELLSCHAFT

EDITORIAL

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You are holding in your hands the journal *Archiv Euromedica*, which was released by the Editorial Board of European Scientific Society in Hanover. Among authors there are specialists representing various fields of medicine and 3 countries: Germany, Russia, and Belarus.

The purpose of the journal *Archiv Euromedica* is to promote exchange of information between scientists and doctors from different countries, in educating of doctors throughout their professional lives and, thereby, to contribute to improving the health of the public.

Journal *Archiv Euromedica* highlights researches on all aspects of medicine and particularly applied fundamental researches in medicine, latest developments and methods of treatment and prevention as well as new technologies in medical education and postgraduate education of medical professionals.

Modern medicine and medical problems is a fairly complex, interrelated and multidisciplinary science, whose successful development is based on regular communication and cooperation of specialists with different backgrounds. This goal is put forward by the international medical congress EuroMedica-Hannover, which is annually convened in Hanover and the journal *Archiv Euromedica*.

We hope that our forum and the new journal *Archiv Euromedica* will make its best in bringing together specialists from different countries and therefore improving the quality of the medicine.

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ARCHIV EUROMEDICA
ISSN 2193-3863

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Vorstand Dr. G. Tyminski, Vorsitzender
Eingetragen ins Vereinsregister
am Amtsgericht Hannover: VR 7957

Design & layout by
Tří barvy, s.r.o.
Mariánské Lázně,
Česká Republika

Printed by
Tiskárna POLYGRAF, s.r.o.
Turnov, Česká Republika
www.tisk.cz

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DIE NOTFALL- UND INTENSIVMEDIZINISCHE GRUNDVERSORGUNG DES SCHWERBRANDVERLETZTEN

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GRUNDLAGEN

Verbrennungen oder Verätzungen sind durch lokale und systemische Störungen der Hämo-dynamik mit traumatisch-hypovolämischem Schock, beeinträchtigte Thermoregulation und den Verlust der kutanen Schrankenfunktion gekennzeichnet. Ähnliche Reaktionen liegen bei der toxischen epidermalen Nekrolyse (TEN, Lyell-Syndrom) vor.

Ab 10 % VKOF (verbrannter Körperoberfläche) besteht Schockgefahr, bei Kindern bereits ab 5% VKOF. Ab etwa 20% VKOF entwickelt sich beim Erwachsenen ein generalisiertes Verbren-nungsödem - auch außerhalb der direkt betroffenen Areale. Ursache ist ein mediatoreninduzier-tes Kapillarleck im Sinne eines SIRS.

Die Verbrennungstiefe wird wie folgt bewertet:

— Grad I — Rötung. Auf die Epidermis begrenzt; Juckreiz bis Schmerz.
— Grad II a (oberflächlich zweitgradig) — Blasen mit rotem Untergrund; starker Schmerz.
— Grad II b (tief zweitgradig) — Blasen mit hellem Untergrund; starker Schmerz.
— Grad III (und IV) — Gewebe weiß bis verkohlt; kein Schmerz.

Die Ausdehnung wird mit der Neuner-Regel nach Wallace erfasst, wobei erstgradige Läsionen unberücksichtigt bleiben. Beim Erwachsenen entspricht die gesamte Handfläche, beim Kleinkind die Palmarfläche der Hand 1% VKOF.

Verbrennungstiefe und VKOF können präklinisch nicht verlässlich bestimmt werden.

PRÄKLINISCHE VERSORGUNG

Basisuntersuchung und spezielle Anamnese

Eine noch so eindrucksvolle Verbrennung darf nicht dazu verleiten, die gewissenhafte Ba-sisuntersuchung des Patienten zu unterlassen. Je nach Unfallhergang können Begleitverlet-zungen vorliegen, die vorrangig zu behandeln sind.

— Brände oder die Freisetzung ätzender Substanzen in geschlossenen Räumen sind auf ein Inhalationstrauma verdächtig. Hinweise sind Gesichtsverbrennungen oder verätzungen, Versen-gungen oder Verätzungen der Gesichts- und Kopfbehaarung, Rußspuren an Zähnen, Mundhöhle und Gaumen sowie entsprechende Symptome im Bereich des Hypopharynx und des Kehlkopfs. Eine Verpuffung oder Explosion kann ein Barotrauma der Lunge herbeiführen.
— Viele Brandverletzte leiden unter einer psychiatrischen Erkrankung mit Neigung zur Selbstschädigung. Durch Fremdanamnese können wertvolle Hinweise für die weitere Behandlung gewonnen werden. Wichtig sind die Erfassung einer Kontaktperson und deren Erreichbarkeit.

Erste-Hilfe-Maßnahmen

Die wichtigsten Erste-Hilfe-Maßnahmen beim Brandverletzten sind die Verhinderung eines weiteren thermischen Schadens, der Schutz vor Unterkühlung und die Verhinderung einer Wundkontamination.

— Brennende Personen werden mit Wasser abgelöscht. Ist dies nicht möglich, werden die Flammen durch eine Feuerlöschdecke, sonstige schwer entflammbare Decke oder durch Ausrollen der Person auf dem Boden erstickt. Dabei ist auf Eigensicherung zu achten.
— Zur Minimierung des thermischen Schadens werden betroffene Kleidungsstücke und Schmuck entfernt; fest verbackene Kleidungsteile (Synthetik) werden dagegen umschnitten und belassen.
— Nur bei kleinflächigen Brandverletzungen bis etwa 5% VKOF darf eine protrahierte Kühlung mit Leitungswasser zur Analgesie erfolgen. Längerfristige Kühlungen großflächiger Brandverletzungen (etwa mit Löschwasser) zur Verminderung des sog. Nachbrennens oder Nachtiefens sind zu unterlassen. Die Temperatur im betroffenen Areal normalisiert sich nach kurzer Zeit, so dass eine weitere Kühlung lediglich die

Gefahr der Hypothermie erhöht.
— Oberflächliche Verätzungen werden ausgiebig mit Wasser gespült und das auslösende Agens sichergestellt.
— Brandwunden und Verätzungen sind großflächig mit einem sterilen metallbeschichteten Brandwundenverbandtuch abzudecken, das locker fixiert wird.

Atmung

Wegen der drohenden lokalen und systemischen Ödembildung muss die Atemwegssicherung vorausschauend und im Einzelfall prophylaktisch erfolgen.

Indikationen zur prophylaktischen Intubation (Blitzeinleitung) und Beatmung sind:
— Verbrennungen und Verätzungen im Gesichts- und Mundbereich sowie Anzeichen für ein Inhalationstrauma mit erwartbarem lokalem Ödem.
— Großflächige Schädigungen auch anderer Körperregionen mit über 20% VKOF und erwartbarem generalisiertem Ödem.
— Bis zum Ausschluss einer Kohlenmonoxid (CO) — oder Zyanid-Vergiftung sind die Patienten zwingend mit einer FiO_2 von 1,0 zu beatmen.
— Zur Überwachung der $psaO_2$ sind möglichst Pulsoxymeter mit Acht-Wellenlängen-Ab-sorptionstechnologie (simultane Bestimmung von O_2Hb, COHb und MetHb) zu nutzen.

Kreislauf

Zur Abschätzung des Volumenbedarfs sind mehrere Formeln und deren Modifikationen ge-bräuchlich, z. B. die Parkland-Formel nach Baxter (4 ml × kg KG × % VKOF/24 h). In die Be-rechnung der VKOF gehen nur zweit- und drittgradige Schädigungen ein.

Präklinisch ist keine vorauseilende Flüssigkeitstherapie erforderlich — für die kurze Zeitspanne der notärztlichen Versorgung genügt die Orientierung an Blutdruck und Puls.
— Als Faustregel werden bei Erwachsenen 1.000 ml/h und bei Kindern 10 ml/kg KG/h eines (möglichst balancierten) Kristalloids infundiert.
— Schwere Begleitverletzungen — z. B. nach einem Sprung — werden mit Kristalloiden oder auch künstlichen Kolloiden wie bei einem Patienten mit Polytrauma behandelt.

Analgesie

Bei allen Patienten mit Verbrennungen und Verätzungen usw. ist für eine suffiziente Analgesie (patientengerecht mit Metamizol, Morphin, Esketamin usw.) zu sorgen, ohne dass dazu zwingend eine Narkoseeinleitung erforderlich ist.

Organisatorische und logistische Aspekte

Gemäß der Leitlinie der Deutschen Gesellschaft für Verbrennungsmedizin sind folgende Patienten in ein Brandverletztenzentrum zu verlegen:
— Patienten mit Verbrennungen an Gesicht, Hals, Händen, Füßen, Anogenitalregion, Achselhöhlen, Bereichen über großen Gelenken oder sonstiger komplizierter Lokalisation,
— Patienten ab 15% VKOF zweitgradig,
— Patienten ab 10% VKOF drittgradig,
— Patienten mit mechanischen Begleitverletzungen,
— Patienten mit Inhalationstrauma,
— Patienten mit (relevanten) Vorerkrankungen oder einem Alter unter 8 bzw. über 60 Jahren,
— Patienten mit elektrischen Verletzungen.

Der direkte Transport von der Unfallstelle in ein Brandverletztenzentrum ist nur bei geringer Entfernung indiziert. Ansonsten soll die Erstversorgung in einem nahegelegenen Akutkrankenhaus erfolgen; von dort erfolgt der koordinierte Transport in ein Brandverletztenzentrum. Die Organisation erfolgt über die zentrale Bettenvermittlung für Brandverletzte (ZBB) bei der Feuerwehr Hamburg,

Telefon (040) 42851-3998 oder -3999.

INTENSIVMEDIZINISCHE GRUNDVERSORGUNG

Führende Aspekte der intensivmedizinischen Grundversorgung, die weitgehend der bei Sepsis-Syndrom (SIRS, Sepsis, schwere Sepsis, septischer Schock) entspricht, sind:
— Suffiziente Atemwegssicherung; frühe Anlage eines plastischen Tracheostomas bei Patienten mit generalisiertem Ödem.
— Sog. lungenschonende Beatmung, Lagerungstherapie, Infusion von Ambroxol und ggf. von Broncholytika sowie gezielt indizierte Bronchoskopie.
— Sicherung der Kreislauffunktion durch Flüssigkeitsersatz mit balancierten Kristalloiden. Falls notwendig werden zusätzlich Gelatine-Lösung (wegen potentieller renaler Nebenwirkungen kein HES) und letztlich auch Dobutamin oder Noradrenalin (unter erweiterter hämodynamischer Überwachung) eingesetzt. Zielgrößen der Kreislauftherapie sind:
— Kein Anstieg von Hämatokrit oder Hb-Konzentration,
  – MAP > 65 mm Hg, ggf. auch höher,
  – Diurese 0,5 ml/kg KG/h,
  – CVP 10–15 mm Hg, ggf. 20 mm Hg,
  – svO_2 > 70%.
— Analgosedierung bevorzugt mit Esketamin und Midazolam, um die endogene Katechol-amin-Homöostase nicht zu konterkarieren. Darüber hinaus ist diese Kombination katecholaminsparend und broncholytisch.
— Fortgesetzte oder frühe enterale Ernährung.
— Engmaschige Blutzuckerkontrolle, Ziel < 180 mg/dl (10 mmol/l).
— Gezielte Antibiotikatherapie nach mikrobiologischem Befund, keine „Abdeckung".
— Subtile Überwachung bei Transporten und operativen Eingriffen.

MINI VOLUME LOADING TEST (MVLT) FOR THE EVALUATION OF HYDRATION STATUS: INITIAL VALIDATION IN PATIENTS

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ABSTRACT

Introduction — The hydration status of patients is mostly unknown. The aim of this prospective clinical trial was to determine the ability of a mini Volume Loading Test (mVLT) to detect the difference in hydration status between pre-operative and post-operative patients by administration of three relatively small boluses of crystalloids.

Patients and methods — Twelve patients (9 females, 3 males) undergoing elective primary total knee arthroplasty completed the study. The mVLT was performed on two different occasions for each subject — before anaesthesia induction (preoperative session), and after a 24 hour postoperative stay in the PACU (postoperative session). Three boluses (5 ml kg — 1 each) of Ringer´s were given, separated by 5 min periods without infusion (3 mini fluid challenges). Arterial and venous haemoglobin was sampled for dilution calculation purposes. Conventional haemodilution and new derivatives of haemoglobin concentration calculated by the novel mathematical model of Bolus Induced Response of Deviations (BIRD-math) were used for the comparison between the preoperative and postoperative mVLT sessions.

Results — There was no difference in haemodilution, but the new variables — residual dilution efficacy and its inter-step tendency — showed that residual plasma volume expanding efficacy was similar in the first two mini fluid challenges of both sessions, but significantly higher in the third postoperative mini fluid challenge ($P < 0.01$).

Conclusion — The mVLT suggested that patients were better hydrated postoperatively since they required fewer steps to fulfil the criteria for the optimization of hydration status.

KEYWORDS

plasma dilution, mini volume loading test, fluid therapy, hydration status, crystalloids, goal directed fluid therapy

INTRODUCTION

The clinician often struggles with decisions concerning the choice of type, amount and time of fluid infusion during the peri-operative period. Recently, the focus has been on using fixed volume protocols restricting fluids, or individualized goal-directed regimes which more consistently address efficacy of fluid administration [1, 2]. Fixed volume strategies do not, however, observe individual differences such as gender, age and baseline hydration status [3]. Maximization of stroke volume, as in goal-directed fluid therapy, is thought to better reflect individual needs. Although goal-directed protocols have improved outcome for particular groups of patients [4], there is still a risk of imprecise fluid administration.

To assess baseline hydration status for individual subjects, a volume loading test (VLT) was introduced [5]. The VLT is a method to evaluate the body hydration status and its changes from the plasma dilution response to a single fluid load [6]. The interstitial space can be regarded as a two-phase structure while having a dense fibre framework which prevents albumin from entering the matrix. This makes it more resistant to the development of oedema, but the framework can be disturbed by tissue injury, increased lymph flow and increased capillary pressure. The physiologic background of the VLT method is that interstitial space will move from a low-compliance state with small pressure increases with increasing hydration status to a high-compliance state with further infusion. Thus, a plasma dilution efficacy of fluid bolus will decrease because of progressively increasing interstitial fluid accumulation in higher levels of interstitial hydration. The increase of renal elimination with better hydration status will have additive impact. Identifying this point would theoretically imply an optimized hydration status. A series of small boluses would probably more easily detect the change in interstitial fluid compliance than a single bolus. Thus, a mini Volume Loading Test (mVLT) was suggested. It implies evaluation of plasma

dilution response during stepwise infusion.

The aim of this study is to describe whether a mVLT could detect a difference between preoperative and postoperative baseline hydration status of patients by administration of three relatively small (5 ml kg^{-1} each) boluses of crystalloids. The hypothesis is that the patients with a better initial baseline hydration status will require fewer boluses to reach optimized hydration status during stepwise infusion of a crystalloid.

PATIENTS AND METHODS

Ethical approval (Approval N° 158200-9-071-22) was obtained. Fifteen patients (12 females, 3 males) scheduled to undergo elective primary total knee arthroplasty (TKA) surgery were enrolled. They had ASA physical status I-II, Body Mass Index 30.0±3.1, and were 68.2±7.1 years old. All TKA operations were performed by the same senior surgeon.

On arrival at the operating theatre at 07:00, the standard peri-operative monitoring (ECG, pulse oximetry and non-invasive blood pressure measurement) was applied. An intravenous line for fluid infusion was placed in the independent arm. Additionally, cannulation of an antecubital vein solely for venous blood sampling was performed in the other arm. Cannulation of a radial artery in the same arm was performed for arterial blood sampling and for continuous monitoring of arterial blood pressure (DASH 3000®, GE Medical Systems Information Technologies, Inc, Milwaukee, Wisconsin, USA) and stroke volume by the arterial pulse contour analysis technique (LiDCO™Plus, London, UK). This monitoring continued for the duration of the trial.

Induction of spinal anaesthesia with 2.5–3.0 ml of 0.5% bupivacaine solution was performed immediately after the preoperative mVLT. Each patient underwent two consecutive mVLTs during the peri-operative period. A preoperative mVLT session was performed after an overnight fasting period. A postoperative mVLT was administered after a 24 hour stay in the post-anaesthesia care unit. Each mVLT session consisted of three mVLT steps (Fig. 1). Each step consisted of an infusion of 5 ml/kg of acetated Ringer's. The boluses were infused over 5 min followed by a 5 min steady-state period when no fluid was given. The boluses were given to incrementally increase plasma dilution from individual *baseline* at timepoints 0, 10 and 20 min to *peak* values measured at the end of infusions at timepoints 5, 15 and 25 min (Fig. 2). Seven pairs of arterial (aHb) and venous (vHb) blood haemoglobin samples were simultaneously taken during each mVLT: before each bolus (baseline Hb), at the end of bolus (peak Hb) and 5 min later (residual Hb). Prior to taking the blood samples for analyses, three millilitres of blood were drawn and immediately returned via the other arm's cannula. All blood samples were analysed for aHb and vHb using a bedside device (HemoCue®, Ängelholm, Sweden). Additionally, the first and seventh samples in each series were analysed in the laboratory for both Hb and haematocrit (Hct).

All data were collected by the study coordinators and entered into a database sheet. The aHb and vHb records were processed in a mathematical model, Bolus Induced Response of Deviations (BIRD-math), aiming to derive variables that would represent plasma volume expansion (PVE) and plasma volume expanding efficacy (PVEE) of a single mVLT step or the whole session (See ***Appendix*** which describes the BIRD-math model). The specific abbreviations (Table 1), mathematical description and physiological meaning (Table 2) and diagnostic criteria are applied (See Table 3, which describes the diagnostic criteria for the evaluation of hydration status). Intermediate Hb derived variables were therefore calculated as follows (Fig. 3). The *Residual Continuous Dilution* (resC_D) was defined as the dilution at timepoint 10, 20 or 30 min compared to the initial invasive arterial baseline value at timepoint 0 min. *Continuous Residual to Baseline Deviation of Dilution* (C_RBD) is the difference between resC_D of consecutive steps. The resC_D corresponds to the sum of all C_RBDs which is equivalent to a *total* PVE of all previous steps.

The *Residual Shifting Dilution* (resS_D) is a fractional change of continuous dilution (C_D) between timepoints 10 and 0, 20 and 10, 30 and 20 min, respectively. Thus, in contrast to resC_D, which represents the total PVE during mVLT, the resS_D corresponds to the individual residual PVEE of a single mVLT step. *Shifting Residual to Baseline Deviation of Dilution* (S_RBD) is the difference between resS_D of consecutive steps, thus representing the difference in individual residual PVEE of consecutive steps.

The BIRD model will, by using Hb samples for plasma dilution calculations, identify an interstitial "*hydration plateau*". This is a transitory state and will appear when two resC_Ds are equal, and the corresponding resS_D is zero (Fig. 3). When this occurs, interstitial compliance is said to have moved from a low-compliance state to a high-compliance state.

When hydration status is at its optimum, interstitial compliance will be at its maximum [16]. *Continuous and shifting Residual to Baseline Deviations of Dilution* (C_RBD and S_RBD, respectively) were used to investigate the differences in dilution in two separate mVLT sessions.

To achieve normalized fluid balance between mVLTs, normal saline infusion targeted to compensate for urine output plus basal physiological fluid needs

(1.0 ml/kg/hr) was administered. A decrease in arterial blood pressure of more than 30% and/or in stroke volume of more than 10% from the individual baseline was an indication of additional fluid load of 5 ml/kg of normal saline infused over 5 min. Blood or colloids were not administered during the study period. If these interventions did not restore SV and/or blood pressure, a titrated intravenous infusion of epinephrine was administered.

All patients were transferred to the post anaesthesia care unit for a 24-hour postoperative stay. Continuous epidural analgesia with an individually titrated dosage of fentanyl and 0.25% bupivacaine was administered. The treatment was stopped 30 min before the start of the postoperative mVLT. The postoperative mVLT protocol was similar to the preoperative. Statistical analysis was performed using PASW (PASW Statistics 17, SPSS, IBM Corporation, NY). Data are presented as mean ± SEM where appropriate. Mean values were compared by using the Student's *t*-test and Levene's test was used for comparison of variances. $P<0.05$ was considered significant.

RESULTS

Fifteen participants were enrolled in the study. Three female patients were excluded from analysis because of blood transfusion administered between mVLTs. Thus, a total of 24 mVLT procedures were performed in 12 TKA patients in two sessions.

There was a significant difference between the preoperative and postoperative mean Hb after the mVLTs in the two separate sessions. Mean preoperative aHb as well as vHb were significantly higher than the corresponding values in the postoperative session (120 ± 1.3 vs. 95 ± 1.2, $P<0.00$ for aHb and 119 ± 1.29 vs. 93 ± 1.2, $P < 0.00$ for vHb), with no statistical difference in variances (Fig. 2).

The residual continuous dilution (resC_D at time point 30 min) which corresponds to the total PVE for all steps was similar in both preoperative and postoperative mVLT sessions as follows: mean arterial resC_D was similar (0.144 ± 0.015 vs. 0.129 ± 0.017, $P<0.5$) with no statistical difference in variances ($P<0.79$), and mean venous resC_D was also similar (0.141 ± 0,015 vs. 0.127 ± 0.016, $P<0.52$) with no statistical difference in variances (Fig. 3).

In Figure 3, the hydration plateau in the preoperative session appears between step 2 and 3, where resC_D in step 3 is equal to resC_D in step 2. In step 3, resS_D is zero. In the postoperative mVLT session resC_Ds were not equal, nor did resS_D reach zero. However, there was no difference between mean preoperative and postoperative total residual PVE (resC_D in the 3rd step) or individual residual PVEE (resS_D) variables in any step. The significant differences between the preoperative and postoperative mVLT sessions were found by comparing the RBDs (Table 3). The hemodiluting impact of the 3rd step on the total residual PVE (C_RBD) was significantly more pronounced in step 3 of the postoperative mVLT session: the arterial difference of C_RBD means was statistically significant ($P<0.01$), while the difference of variances was not; similarly, the venous difference of C_RBD means was also significant ($P<0.04$), while the difference in variances was not.

Similarly, the difference in individual residual PVEE between the 2nd and 3rd steps (S_RBD) was significantly more pronounced in the postoperative mVLT session: the arterial difference in S_RBD means was statistically significant ($P <0.03$), while the difference in variances was not ($P<0.250$); similarly, the venous difference in C_RBD means was also statistically significant ($P<0.04$), while the difference in variances was not ($P<0.11$) (Table 4). The significance of RBD changes (Fig. 4) during a single mVLT session was evaluated (Table 5).

In the preoperative mVLT session, the decrease in continuous arterial (Fig. 4-A) and venous (Fig. 4-C) RBD was not significant between step 1 and 2, but the decreases in the corresponding shifting arterial (Fig. 4-B) and venous (Fig. 4-D) RBDs were significant.

Meanwhile, the only significant shift in RBD between steps 2 to 3 was the decrease in continuous arterial RBD (Fig. 4-A). The decrease in continuous and shifting, arterial and venous RBDs (Fig. 4 A-D) was significant between steps 1 and 2 in postoperative mVLT.

Meanwhile, only the increase in shifting arterial (Fig. 4-B) and venous (Fig. 4-D) RBDs was significant between steps 2 and 3.

The hydration plateau could only be identified in step 3 of the pre-operative mVLT session where the mean resC_D were equal in steps 2 and 3 and the resS_D and C_RBD were both close to zero and S_RBD was negative. In contrast, using the same criteria, the hydration plateau was not identified in the postoperative session. Nevertheless, the shift in S_RBD from negative to positive in the 3rd postoperative mVLT step suggests that the plateau was reached in step 2 during the postoperative mVLT session.

DISCUSSION

This study focused on the ability of the mVLT to detect differences between preoperative and postoperative hydration levels by administration of relatively small (5 ml kg-1) boluses of crystalloid separated by 5 min steady states with no fluids. Changing levels of haemodilution is a sign of volume loading. Inference

is made to changed interstitial compliance and when pertinent parameters are fulfilled a "hydration plateau" is reached interstitially [7]. This should be an indication that the tissue is well hydrated.

Since our concept of defining the hydration status is based on the acknowledgement that intravascular fluid retention is highly dependent on the hydration of perfused tissues, the mVLT mathematically investigates the dynamics of haemodilution related variables. Aiming for the most appropriate clinical applicability, the method deploys the above described fast relatively small volume infusions and short steady states between them. The induced changes of haemodilution are relatively minor. Thus, more sensitive markers were proposed by the novel mathematical model of Bolus Induced Response of Deviations (BIRD-math; see Appendix for details). It provides calculation of haemoglobin concentration derived variablesthat enable sufficiently sensitive monitoring of changes in haemodilution efficacy of consecutive mVLT steps. Only these new variables — residual dilution efficacy and its inter-step tendency — showed the significant difference between two mVLT sessions, while conventional trends of dilution have failed.

This study aimed to see whether this method could be used to detect such a transitory state and difference between hydration levels in a surgical setting. The impact of a fluid bolus on plasma dilution is not always easy to predict since the response differs depending on the clinical situation [8]. Conventionally, a crystalloid is allocated in the plasma space and should eventually distribute to the interstitium [9]. This flux is prolonged during surgery and bleeding [10]. Kinetically, fluid distribution is a mixture of perfusion and distribution to adjacent tissues [11, 12]. Volume kinetics is a tool to describe this mixture of perfusion to distant parts of the body and the actual translocation of fluids between fluid spaces [13, 14]. Volume kinetic analysis does not require knowledge of the hydration baseline but is hampered by repetitive sampling of haemoglobin samples [12]. However, to use the kinetic models better it would be beneficial to know the actual baseline of hydration in order to plan intravenous fluid therapy. In this study, a key concept is the "hydration plateau", which can be said to be a point where interstitial compliance changes from a low to a high-compliance state. This study aimed to determine the baseline by trying to identify a transitory state, hydration plateau, based on repetitive observations of plasma dilution. The criteria for the detection of that state are defined in Figure 1 and Figure 3 (Table 3). The criteria are fulfilled when two consecutive steps reach the same resC_Ds and the resS_D is zero at the same time.

This occurred in step 3 in the preoperative session, but was not obvious in the postoperative. The BIRD-math was used for the evaluation of differences between the fluid handling in preoperative and postoperative mVLT sessions (Fig. 4). The evaluation provided support for the mVLT method by detecting significant difference in the last of a series of three boluses. The PVEE were similar in the first two mVLT steps, but the 3rd postoperative step showed a significant increase in PVEE, while it was negligible in the 3rd preoperative step. Plausibly, the explanation could be that it is a result of different interstitial fluid compliance. We speculate that, according to the model, the negligible preoperative PVEE is a result of maximal interstitial fluid compliance together with a transcapillary flux of fluid into the interstitium. The activation of urine output and other routes of fluid elimination in states of higher hydration status may have additive effect. We suggest that the postoperative increase of PVEE in step 3 is explained by a steep rise in interstitial hydraulic pressure when interstitial fluid compliance falls after exiting the state of interstitial hydration plateau. It can further be explained by an increase in lymphatic flow. The evacuation of interstitial lymphatics significantly increases the lymphatic flow, which in turn promotes central venous plasma dilution in addition to the prior venular plasma dilution induced by the drop of transcapillary hydraulic pressure as a result of the falling interstitial compliance. That causes a steep increase in central plasma dilution. The physiologic background to this concept lies in the previously established relationships of interstitial volume-pressure and lymphatic flow-interstitial pressure [15, 16]. When the former relationship turns from linear to a plateau of hydraulic pressure (hydration plateau) it significantly reduces intravascular fluid retention in the capillary beds. When the lymphatic flow-interstitial pressure relationship turns into a stable lymphatic influx into circulation, the impact on the changes in venous plasma dilution is negligible. This pattern, which is considered as a marker of hydration plateau, was seen in the 2nd and 3rd steps of the preoperative mVLT (Fig. 2 and 3). It was expected that these criteria would be met in both the preoperative and postoperative mVLTs, with its earlier manifestation in better hydrated subjects. However, this was not the case since the markers of the hydration plateau were missing in the postoperative mVLT. However, in contrast to the preoperative plasma dilution in the last two fluid loading steps, there was a steep rise of plasma dilution in the corresponding postoperative steps 2 and 3. Acknowledging that the hydration plateau is a short-lasting transitory state during a fluid loading interstitially, it can obviously be missed. Thus, aiming to

verify the interstitial hydration states in the range before and after the hydration plateau, and to predict the plasma dilution response and related shift of interstitial hydration in the upcoming mVLT step, also addressing the inherently low sensitivity of changes in Hb and its first-line derivative continuous plasma dilution (C_D), the second and third line derivative variables were calculated by the equations from BIRD-math (Table 1) (See Text, Supplemental Digital Content 1, which describes the Mathematical Model of Bolus Induced response of Deviations or BIRD-math). Despite this complexity, all these derivative variables are required and equally important since none of them is fully sufficient.

This study has several weaknesses. First, it is a small sample size. We assume that patients in the postoperative state are better hydrated although this was not validated. Furthermore, the model is based on a theoretical concept that has not been validated in a controlled model. Several concepts have been defined for model development that may be difficult to grasp and may seem unfamiliar to the non-specialist reader. Furthermore, this is a model that deals with fluid translocation across a semi-permeable membrane that may change significantly due to stress and surgery [17].

The concept of different levels of body hydration that can be identified by simple plasma dilution estimations is, however, very attractive. If such a test can be performed with accuracy before surgery and particularly if it can be based on non-invasive samples, it would be possible to determine the hydration status of patients. This would facilitate planning of intravenous fluid peroperatively and ensure that patients receive more precise amounts of fluid. Our research team's investigations [18–26] are therefore focused on investigating the applicability on noninvasive haemoglobin measures for the mVLT purposes.

CONCLUSION

The findings of the mVLT suggest that TKA patients were better hydrated postoperatively than preoperatively, since preoperatively they required three and postoperatively only two mini fluid challenges during mVLT to reach the same transitory state of interstitial hydration referred to as the dilution plateau.

ACKNOWLEDGEMENT

Preparation of this manuscript is funded by the European Social Fund under the Global Grant measure.

APPENDIX

Mathematical model of Bolus Induced Response of Deviations (BIRD-math)

Dilution

1. Residual continuous dilution (resC_D) – Fractional change of the hemoglobin concentration in respect to arterial obtained just before the start of mVLT:

$$resC\_xD_n = (aHb_0/xHb_n - 1) / (1 - aHct_0) \quad [1]$$

where resC_xDn — Residual continuous dilution at the variable's measuring time n; xHbn — Hemoglobin concentration at the variable's measuring time n; n — Time point 10, 20 or 30 min during mVLT.

2. Residual shifting dilution (resS_D) — Fractional change of continuous dilution (C_D) in a single mVLT step derived by comparing dilution after the 5 min steady state and dilution before the bolus:

$$resS\_xDn = (aHb_0 (xHb_{n-10} \cdot xHb_{n-1} - 1)) \times \times (aHb_0 + aHct_0 xHb_{n-10}) - 1 \quad [2]$$

where resS_xDn — Residual shifting dilution at the variable's measuring time n (min) during mVLT; n — time point 10, 20 or 30 min during mVLT.

Bolus Induced Response of Deviations (BIRD)

BIRD is the dilution difference — continuous or shifting — between the two time-points of a single mVLT step:

1. Continuous residual-to-baseline deviation (C_RBD) — Continuous dilution difference between the residual and baseline time points of a single mVLT step:

$$C\_xRBDn = aHb_0 (xHb_{n-1} - xHb_{n-10} - 1) \times \times (1 - aHct_0) - 1 \quad [3]$$

where C_xRBDn — Continuous residual-to-baseline deviation at the variable's measuring time n; n — Time point 10, 20 or 30 min during mVLT.

2. Shifting residual-to-baseline deviation (S_RBD) — Shifting dilution difference between theresidual and baseline time points of a single mVLT step:

$$S\_xRBD_n = (aHb_0 (xHb_{n-10} \cdot xHb_n^{-1} - 1)) \times \times (aHb_0 + aHct_0 xHb_{n-10})^{-1} - - (aHb_0 (xHb_{n-20} \cdot xHb_{n-10}^{-1} - 1)) \times \times (aHb_0 + aHct_0 xHb_{n-20})^{-1} \quad [4]$$

where S_xRBDn — the shifting residual-to-baseline deviation at the variable's measuring time n; n — Time point 10, 20 or 30 min during mVLT.

In all equations — aHb_0 and $aHct_0$ — the initial baseline value of *arterial* blood samples (time-point 0 min just before the start of mVLT; lab scan results); x — the blood sampling site — arterial or venous.

Table 1. *Definitions, abbreviations and physiological meaning of variables from the mathematical model of Bolus Induced Response of Deviations (BIRD-math)*

Plasma (Hb) dilution 1. Residual continuous dilution (resC_D) — Fractional change of the residual hemoglobin concentration (timepoints 10, 20 or 30 min) in respect to arterial concentration obtained just before the start of mVLT. *Physiological meaning*: **Total residual PVE** represents the total (summarized) residual plasma volume expansion after 5 min following each bolus.
2. Residual shifting dilution (resS_D) — Fractional change of continuous dilution (C_D) in a single mVLT step derived by comparing dilution after the 5 min steady state and dilution before the bolus. *Physiological meaning*: **Individual residual PVEE** represents individual residual plasma volume expansion efficacy of a single mVLT step.
Bolus Induced Response of Deviations (BIRD) is the dilution difference — continuous or shifting — between the two time-points of a single mVLT step: 1. Continuous residual-to-baseline deviation (C_RBD) — Continuous dilution difference between the residual and baseline time points of a single mVLT step (available at timepoints 10, 20 or 30 min). *Physiological meaning*: **Difference of total residual PVE** between two consecutive mVLT steps evaluates the impact of the latest step on the total PVE (was it hemodilution or hemo-concentration).
2. Shifting residual-to-baseline deviation (S_RBD) — Shifting dilution difference between the residual and baseline time points of a single mVLT step (available at timepoints 10, 20 or 30 min). *Physiological meaning*: **Difference of individual residual PVEE** between two consecutive mVLT steps (thus, not applies to the 1st mVLT step) evaluates its tendency — increase or decrease.

Table 2. *Variables calculated by the BIRD-math model*

Generic variable		Derivative variable		Initial	mVLTstep			Equation # in BIRD-math	Mathematical description of derivative variable	Physiological definition / meaning of the derivative
Definitions	Abbreviations	Definition	Abbreviation	baseline	1	2	3			
				Timepoint (min)						
				0	10	20	30			
Arterial and venous hemoglobin concentration	aHb and vHb	Residual continuous dilution	res.C_D	A	A	A	A	1	Fractional change of Hb at timepoints 10, 20 and 30 min in respect to intial baseline (0 min)	**Total residual PVE** represents the total (summarized) residual plasma volume expansion after 5 min following each bolus
Residual continuous dilution		Residual shifting dilution	res.S_D	NA	A	A	A	2	Fractional change of C_D during a single mVLT step considering res.C_D and C_D before the bolus	**Individual residual PVEE** represents individual residual plasma volume expansion efficacy of a single mVLT step
	res.C_D	Continuous residual-to-baseline continuous deviation of dilution	C_RBD	NA	A	A	A	3	Residual continuous dilution difference between two consecutive mVLT steps	**Difference of total residual PVE** between two consecutive mVLT steps evaluates the impact of the latest step on the total PVE (hemodilution vs hemoconcentration)
		Shifting residual-to-baseline deviation of dilution	S_RBD	NA	A	A	A	4	Residual shifting dilution difference between two mVLT steps	**Difference of individual residual PVEE** between two consecutive mVLT steps (thus, not applies to the 1st mVLT step) evaluates its tendency — increase vs decrease.

Generic — Measured parameter or previously calculated derivative used to calculate new derivatives. Derivative — Non-measurable variable that was derived by equations of the BIRD-math model.
mVLT step — Minimal volume loading test step.
Hb — Hemoglobin concentration (aHb-arterial and vHb-venous).
PVEE — Plasma volume expansion efficacy.
PVE — Plasma volume expansion. A — Available variable or criteria met. NA — Not applicable.

Table 3. *Diagnostic criteria for the evaluation of hydration status*

Criteria	Diagnosis	Diagnostic criteria in perioperative mVLT sessions						
		Preop. step #				Postop. step #		
Variables in dynamics	Transitory hydration status	1	2	3		1	2	3
		10	20	30	(min)	10	20	30
≈ equal res.C_D in *two consecutive* mVLT steps	NORMOHYDRATION*: maximal interstitial fluid compliance and *minimal* PVEE of the *last of two* mVLT steps			A				
res.S_D ≈ 0	NORMOHYDRATION*: maximal interstitial fluid compliance and *minimal* PVEE of a *single* mVLT step			A				
C_RBD ≈ 0	NORMOHYDRATION*: maximal interstitial fluid compliance and minimal impact of a single mVLT step on the total residual PVE			A				
S RBD ≤ 0 (not applies to the 1st mVLT step)	DEHYDRATION**: *increasing* interstitial fluid compliance and *decreasing individual residual* PVEE	NA	A	A		NA	A	
S RBD >0 (not applies to the 1st mVLT step)	OVERHYDRATION***: *decreasing* interstitial fluid compliance and *increasing individual residual* PVEE	NA				NA		A

* **Normohydration** is haemodilution associated with optimized interstitial hydration.
Note: These criteria are the specific markers of hydration plateau.

** **Dehydration** is optimized interstitial hydration with maximized interstitial fluid compliance or hydration plateau.
Note: dehydration turns into normohydration when res.S RBD < 0 is associated with at least one of the NORMOHYDRATION (hydration plateau) specific criteria.

*** **Overhydration** is maximized interstitial hydration with minimized interstitial fluid compliance.

Table 4. *The residual to baseline deviation of dilution*

Parameter		Residual to baseline deviation of plasmadilution (RBD)											
		Pre-operative mVLT						Post-operative mVLT					
		Step 1		Step 2		Step 3		Step 1		Step 2		Step 3	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
C_RBD	Arterial	0.084	0.014	0.055	0.024	-0.007	0.015	0.098	0.012	0.017	0.011	0.058	0.019
	Venous	0.083	0.010	0.082	0.030	-0.041	0.029	0.110	0.018	0.021	0.018	0.034	0.020
S_RBD	Arterial	0.083	0.014	-0.031	0.029	-0.056	0.034	0.096	0.012	-0.080	0.019	0.036	0.021
	Venous	0.083	0.010	-0.008	0.029	-0.104	0.046	0.109	0.018	-0.088	0.030	0.010	0.025

SEM — Standard error of the mean.
RBD — Residual to baseline deviation of plasmadilution as marker of plasma volume expansion efficacy.
C_RBD — Continuous residual to baseline deviation of plasmadilution.
S_RBD — Shifting residual to baseline deviation of plasmadilution.

Table 5. *The significance of changes in residual to baseline deviation of dilution*

Diagnostic (matrix- BIRD)	RBD type		Difference of RBD between consecutive mVLT steps											
			Pre-operative mVLT						Post-operative mVLT					
			Between step land 2			Between step 2 and 3			Between step land 2			Between step 2 and 3		
			Significance between		Significant	Significance between		Significant	Significance between		Significant	Significance between		Significant
			means	variances		means	variances		means	variances		means	variances	
			P	*P*		*P*	*P*		*P*	*P*		*P*	*P*	
$RBD_n > RBD_{n+1}$	C_RBD	Arterial	0.314	1.154	–	0.043	0.172	+	0.000	0.565	+			
		Venous	0.967	0.014	–	0.617	0.991	–	0.002	0.836	+			
	S_RBD	Arterial	0.003	0.017	+	0.059	0.889	–	0.000	0.034	+			
		Venous	0.009	0.013	+	0.816	0.718	–	0.000	0.104	+			
$RBD_n < RBD_{n+1}$	C_RBD	Arterial										0.074	0.316	–
		Venous										0.064	0.477	–
	S_RBD	Arterial										0.001	0.938	+
		Venous										0.018	0.359	+

n — Sequence number of the mVLT step. + Statistically significant difference.
RBD — Residual to baseline deviation of plasmadilution.
C_RBD — Continuous residual to baseline deviation of plasmadilution.
S_RBD — Shifting residual to baseline deviation of plasmadilution.

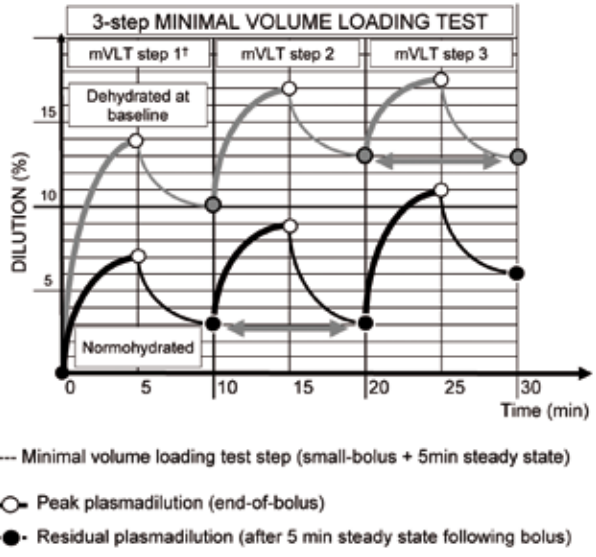

Figure 1. *Dilution trends during a theoretical 3-step minimal volume loading test*

Plasma dilution values (dimensionless, in per cent) during a theoretical three-step minimal volume loading test (mVLT). Three small boluses (5 ml/kg) of acetated Ringer's solution are given. Each step is followed by a 5 min steady state period when no fluid was given. Peak points are at 5, 15 and 25 min. Residual plasmadilution is defined as dilution value at time point 10, 20 and 30 minutes in respect to initial baseline at time point 0 minutes. The figure shows two hypothetical initial baseline states of body hydration — hydrated and dehydrated. A *hydration plateau* is reached when two residual dilution values are equal (values connected by the bidirectional horizontal arrows). Presumably, the better hydrated patients will reach this plateau earlier than less hydrated subjects.

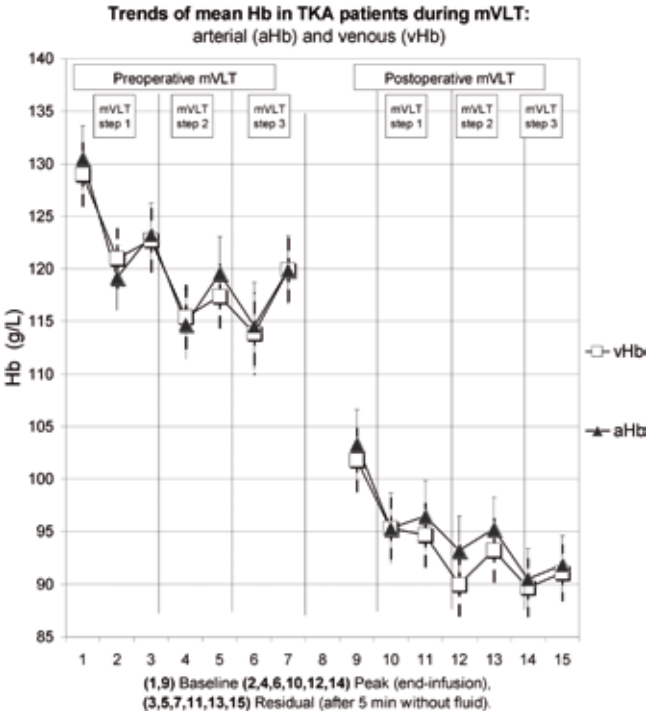

Figure 2. *Trends of arterial and venous henoglobin concentration*

Arterial (aHb) and venous (vHb) haemoglobin concentration at baseline before each infusion, at the end of the bolus (peak) and after 5 min steady state (residual). There was no significant difference between mean aHb and vHb and their variances, but preoperative Hb was significantly higher than postoperative due to perioperative blood loss. Data are expressed as means ± SEM.

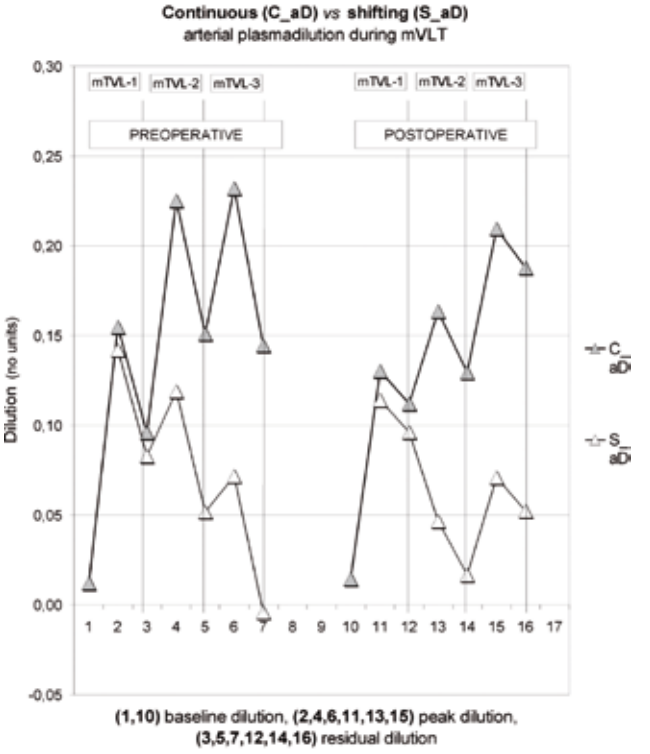

Fig. 3. *Continuous and shifting arterial dilution trends*

The minimal residual individual PVEE of the fluid challenge is seen in the 3rd preoperative and 2nd postoperative mVLT steps. The mean residual shifting arterial dilution (resS_aD) is close to zero at checkpoint 7 preoperatively and 14 postoperatively. The mean residual continuous arterial dilution (resC_aD) at these checkpoints is close to residual dilution of the preceding step. Both patterns are markers of maximized interstitial fluid compliance (hydration plateau).

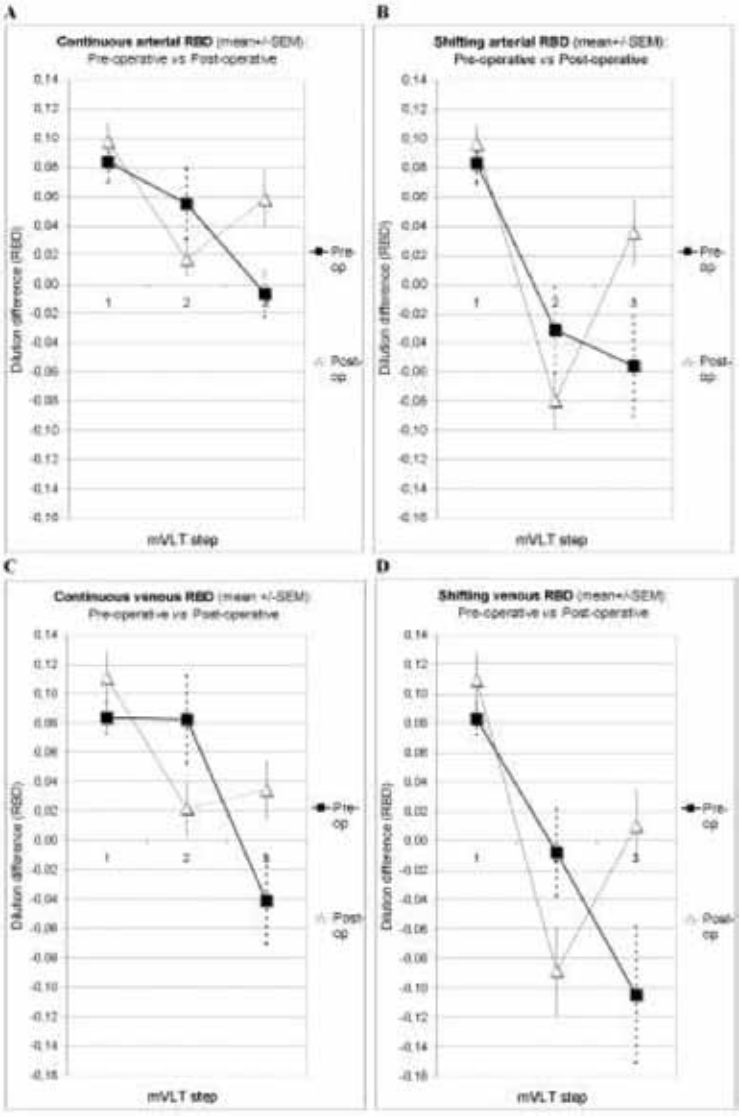

Figure 4. *Continuous and shifting residual to baseline deviation of dilution*

The significant differences between preoperative and postoperative mVLT sessions were found by comparing the residual to baseline deviation of dilution (RBD) of preoperative and postoperative mVLT sessions. The x-axis is a sequence number of the mVLT step, the y-axis is the continuous or shifting residual to baseline deviation of dilution (C_RBD and S_RBD respectively). (A) preoperative and postoperative continuous arterial RBD (C_aRBD), (B) preoperative and postoperative shifting arterial RBD (S_aRBD), (C) preoperative and postoperative continuous venous RBD (C_vRBD), (D) preoperative and postoperative shifting venous RBD (S_vRBD). Data are expressed as means ± SEM.

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CHANGES INTERFERON STATUS IN CORONARY HEART DISEASE

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ABSTRACT — Currently, coronary heart disease (CHD) is the leading cause of death in developed countries (up to 57% of all diseases) [L.A.Bokeriya, 2006]. In the present study analyzed literature data on studying immune spectrum of blood (in particular, interferons IFN-α, IFN-β, IFN-ω, IFN-τ and soluders) for ischemic heart disease. Investigation of violations of the immune status opens new pathogenetic mechanisms of ischemic heart disease, which require a more detailed study.

KEYWORDS — immune status, interferons, coronary heart disease

Currently, coronary heart disease is the leading cause of death in developed countries (up to 57% of all diseases). [1] Ischemia and myocardial damage alters protein structure myocardium, which leads to their antigenic properties and new formation of autoantibodies antikardialnyh [3]. At various periods of myocardial infarction the emergence and growth of circulating immune complexes and fixed protivokardialnyh circulating autoantibodies have been seen, and change of the properties of T and B lymphocytes and their subpopulations. [3] Insufficient production of factors contributes to the progression of immune protection subepicardial and subendocardial ischemia in Q-myocardial infarction [Hanferyan RA, Orange PP, 2009].

At present, the authors of medical publications are more often considered an immunological component in various pathological conditions and diseases, given the inextricable link of the nervous, endocrine and immune systems. There was technically possible on the one hand, and the urgent need on the other hand, for the discovery of new mechanisms of pathology at the cellular and molecular level in order to find new methods and approaches to the treatment of diseases.

Interferons (IFN) are key regulators not only protective, but also of many physiological processes in the body. IFN I type regulates hematopoietic processes, immune response, tumors, responses to infection. IFN produced and acts locally autocrine and paracrine manner. The first type has four subtypes of IFN: IFN-α, IFN-β, IFN-ω, IFN-τ. The receptor consists of two subunits, IFNAR1 and IFNAR2. IFNAR1 is species-specific — human, bovine, sheep, chicken, mouse. A soluble form of human (hu) IFNAR2 was first detected in the urine. This identification led to the cloning of its own DNA and two forms of hu hu IFNAR2b and IFNAR12e . All three forms are associated IFN I type only form IFNAR12e involved in signal path. Functions hu IFNAR2α (extracellular soluble form), and hu IFNAR2b have only a short intracellular dominant. A soluble form can often bind ligands, block or reduce the maximum opportunity to compete with other cytokines, membrane- stabilizing components for general ligand. Another function of the soluble receptor ligand is protection from destruction or separation. Soluble receptors may also be converted into sensitive ligands resistant. Soluble

receptors can act as agonists or as antagonists. The role of inflammation in the soluble receptor agonists or antagonists, concentrated ligand -related proteins, cytokines require active learning. Solyudery are ekstrotsellyulyarnymi dominant transmembrane receptors, attaching molecules in biological fluids. Cellular release of soluble receptors is regulated by two mechanisms: first, production and secretion of only the extracellular dominants (interleukin 4 , epidermal growth factor and IFNAR2): Second, proteolytic specificity to cell surface receptor (IL-1, interleukin-2 , TNF-α).

Currently actively studied due IFN-α and-β receptors, and the importance of their strength. Interferons I (IFNs) determine antiviral, antiproliferative, immunomodulatory response through communications with the receptors which are transmembrane proteins of IFNAR1 and IFNAR2 [9].

Signalling IFN-α and IFN-β implies involvement of the different receptor zones . The authors used reflectometry interference spectroscopy to study the kinetics and chemical properties of the interaction between IFNs and ekstrotsellyulyarnymi receptor, which is dominated by IFNAR1 and IFNAR2. The result revealed that the relationship between IFN-α and IFN-β receptor , which is dominated IFNAR2 stronger, and the relationship to the receptor , which is dominated IFNAR1, less stable . The results showed that IFN first binds to IFNAR2, and then gradually interact with IFNAR1, and this second stage is more significant for IFN-β, than IFN-α, which may explain the different activity IFNs [9]. Obviously, the concentration of these components and a surface receptor depends genetic stabilization.

In the study of the mechanism of action of IFN-α in the treatment of chronic myelogenous leukemia patients with leukemia cell installed immediately in IFNAR2 expression unlike control group. In contrast, the expression of cell surface IFNAR1 was lower than IFNAR2, and correlated with the level before treatment and clinical outcomes [7]. The authors examined Publication interferon receptor comprising IFNAR1 and IFNAR2, IFN I type virus and their antiproliferative activity [2, 3].

Conducted studies have demonstrated that binding of IFN-α2 with IFNAR2 is a N-terminal dominant and increase immobility receptor may play an important role in intracellular signal cascade stage interferon. The study turned knowledge about components IFN I receptor type interaction force with ligands and their role in the transmission of different signals.

Now the question remains little known changes of immune status in coronary heart disease. It is known that in ischemic heart disease, myocardial infarction increased concentration of circulating immune complexes, JgG, and reduced JgM, decreases the level of T-cells, B-cells is increased . Phospholipid syndrome in the study of coronary heart disease little work. The development of these diseases associated with overproduction of an extremely wide range oganospetsificheskih autoantibodies reactive with DNA and other nuclear antigens , cytoplasmic and membrane components [2]. However, patients who died of myocardial infarction in postmortem copper on the intima of the aorta and the coronary vessels were found circulating immune complexes and antibody class IgM and IgG antibodies to their own cardiomyocytes [9, 10, 11]. This suggests the formation of autoimmune mechanism as one of the variants of the anti-phospholipid syndrome [10, 11].

Many authors believe that the cytokine system in ischemic heart disease, myocardial infarction, has been actively involved in the implementation of the immune response in aterosklerotromboticheskih coronary events [1]. In acute myocardial infarction found to have high serum concentrations of interleukin-6.8, correlated with high levels of troponin and creatine kinase [4,9].

Analysis of published data shows that the commonly used serological and biochemical markers for the first time detected in the later stages of the disease. While the study of more subtle mechanisms of autoimmunity opens broad prospects of early diagnosis. Patients with poliendokrinologicheskoy pathology in 100% were recorded antiinterferonovyh high titers of antibodies in the early stages of the disease, which allows to think that these antibodies may be used as a diagnostic marker in patients with metabolic syndrome , diabetes mellitus, coronary heart disease. Antiinterferonovye antibodies pushing for the development of other autoantibodies with various endocrine clinical features. This raises the question of the role of these antibodies in the manifestation of the disease. When poliendokrinologicheskom syndrome observed defects γ-interferon and interleukin-12 [11]. Conducted studies have identified new lines disorders of immune response in patients with poliendokrinologicheskim syndrome. Suggested noted an important role of type 1 interferons as well as its role in the regulation of self-tolerance.

In the literature there are individual information about the early changes in the immune status — serum levels of interferon and antibodies to it in acute Q-myocardial infarction, however, there is a description of the increase in activity only later γ-interferon [6, 9, 10]. Changes in the activity of the earliest violation of interferon status, — α-interferon, myocardial infarction have been conducted.

Thus, the study of immune status opens new pathogenetic mechanisms of ischemic heart disease,

which require a more detailed study. At this stage, the data conducted worldwide research raises more questions than from quick advice. They play a key role in the autoreactive antiinterferonovye antibody response of T and B cells in reducing T-cell attack antibodies in other tissues and organs (such as heart) in these disorders? Whether there was an increase in production of anti IFN antibodies on the progression of coronary heart disease? This encourages further study of the role of type 1 interferons, their receptors IFNAR1 and IFNAR2 and their antibodies in the interferometer new immunity in patients with ischemic heart disease.

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CHOOSING THE 5TH TYPE PHOSPHODIESTERASE INHIBITORS FOR TREATMENT THE PATIENTS WITH ERECTILE DYSFUNCTION AND CHRONIC PROSTATITIS

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ABSTRACT

The study of the genital system' vessels in patients with erectile dysfunction and chronic prostatitis was accomplished using ultrasound Dopplerography and pharmacological testing by phosphodiesterase inhibitors of 5th type (PDEI-5). The positive impact of PDEI-5 (such as Sildenafil, Vardenafil, Udenafil and Tadalafil) on organs' blood supply was revealed. The changes of USDG parameters were found comparable and, at the same time, individual. For patient-specific choosing the medicinal agent it is advisable to perform the pharmacological tests for each patient. The choice of the medicine for treating erectile dysfunction and chronic prostatitis should be made on the basis of the results of ultrasound Dopplerography and pharmacological testing for each selected and tested medicine. For this purpose it is preferably to choose the medicine, which improves the blood flow in penis and, at the same time, in prostate gland and in testes.

KEYWORDS — ultrasound Dopplerography, pharmacological testing, penis, prostate gland, testes, Sildenafil, Vardenafil, Udenafil, Tadalafil, erectile dysfunction, chronic prostatitis, phosphodiesterase inhibitor selection.

INTRODUCTION

Appearance on the market several 5th type phosphodiesterase inhibitors (PDEI-5), such as Sildenafil, Vardenafil, Udenafil and Tadalafil, has raised a point about their preferable choice [1–5]. The clinicians are based on subjective patient's impression of intake one or another medicine (International Index of Erectile Function questionnaire) and try minimizing adverse reaction and adverse events (AE) [6–11]. Objectification of the response to medicine intake with relation to evidential medicine is of current importance and thus was the ***objective*** of our study [12–14]. We proposed the method of pharmacological testing [15, 16], which allows in some measure to clear up this point.

MATERIAL

30 patients aged from 30 to 68 years with chronic prostatitis (CP) of III A, B category associated with erectile dysfunction (ED) were observed. Erectile dysfunction duration constituted from 1 till 5 years. All patients had various concomitant diseases — systemic atherosclerosis, metabolic syndrome, adenoma of prostate gland of I stage. Exclusion criteria were: severe intercurrent background.

METHODS

Ultrasound Dopplerography of male organs vessels, namely deep and dorsal arteries of penis [17], intra-prostatic and paraurethral arteries [18], as well as testicular arteries [19]. The values of peak blood flow velocity (Vmax in cm/sec) in these vessels were measured with calculation of average accumulative values of these parameters in above-noted vessels of male genital system. Then the patient took one of tested medicines, namely: Sildenafil 50 mg, Vardenafil 10 mg, Tadalafil 20 mg, Udenafil 100 mg and was reinvestigated in 1 hour. The pharmacological test was performed using each of medicines at 4–7 days interval. Similar measurements, calculation and comparison of obtained values percentage wise were made.

RESULTS

All obtained parameters, their changes and statistical treatment are shown in Table 1.

Table 1. *Vmax changes in vessels of penis, prostate and testes (cm/sec)*

	sildenafil			vardenafil			tadalafil			udenafil		
n = 30	penis	prostata	testis	penis	prostata	testis	penis	prostata	testis	penis	prostata	testis
M_1	8,38	8,83	9,6	8,71	10,46	9,17	9,42	10,28	8,57	10,04	11,73	9,29
m_1	0,83	1,2	0,63	0,67	0,62	0,26	0,83	0,47	0,87	0,73	0,76	0,49
M_2	12,3	11,78	9,55	14,25	13,01	10,88	14,17	13,51	11	13,73	14,14	11,5
m_2	2,35	0,91	1,04	0,75	0,71	0,46	1,54	0,73	0,69	0,85	0,73	0,52
p=	≤0,02	≤0,05	≥	≤0,001	≤0,02	≤0,002	≤0,02	≤0,001	≤0,05	≤0,002	≤0,03	≤0,005
K	1,61	1,33	0,99	1,64	1,24	1,19	1,5	1,31	1,28	1,37	1,21	1,24

Vmax — peak blood flow velocity
M_1 — arithmetic mean in background (before pharmacological test)
M_2 — arithmetic mean after pharmacological test
m_1 — mean error of arithmetic mean in background (before pharmacological test)
m_2 — mean error of arithmetic mean after pharmacological test
K — aspect ratio M_2/M_1
Statistical treatment with method of comparison arithmetic means using Student's test Significant difference — $p \leq 0.05$

The detailed results are presented below.

TEST WITH SILDENAFIL

Mean Vmax (M±m) in deep arteries of left and right cavernous bodies of penis before testing was 8.4±0.8 cm/sec. In 1 hour after oral administration of Sildenafil 50 mg, Vmax in the same penis vessels was 12.3±2.4 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 61 %. Mean Vmax in three regions of prostate blood supply (left, right lobes, periurethral zone) before testing was 8.8±1.2 cm/sec, and after testing = 11.8±0.9 cm/sec. That is peak blood flow velocity in three regions of prostate had increased on average by 33%. Blood flow velocity did not change reliably in funiculus vessels as a result of Sildenafil intake. The weighted mean of Vmax increase in male genital organs was +31%. Only the tendency to increase the index of resistance (IR) and systolic-diastolic index S/D was noted in penis vessels and the tendency to decrease of peripheral resistance parameters (IR, PI, S/D) was observed in prostate vessels.

TEST WITH VARDENAFIL

Mean Vmax (M±m) in deep arteries of both cavernous bodies of penis before testing was 8.7±0.7 cm/sec. In 1 hour after oral administration of Vardenafil 10 mg, mean Vmax in the same penis vessels was 14.2±0.7 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 64%. Mean Vmax in threecorresponding regions of prostate before testing was 10.5±0.6 cm/sec, and after testing = 13.0±0.7 cm/sec. That is averaged peak blood flow velocity in prostate vessels had increased on average by 24%. Blood flow velocity after Vardenafil intake in funiculus vessels increased from 9.2±0.3 cm/sec to 10.9±0.5 cm/sec that is on average by 19%. The weighted mean of Vmax increase in male genital organs was +36%. Slight tendency to increase of all parameters in penis, prostate and testes (statistically not significant) was noted on the part of peripheral vascular resistance (Fig. 1).

TEST WITH UDENAFIL

Mean Vmax in deep arteries of penis before testing was 10.0±0.7 cm/sec. In 1 hour after Udenafil intake 100 mg, mean Vmax in the same penis vessels achieved 13.7±0.8 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 37%. Mean Vmax in threeabove mentioned regions of prostate before testing was 11.7±0.8 cm/sec, and after testing constituted 14.1±0.7 cm/sec. That is averaged peak blood flow velocity in prostate vessels had increased on average by 21%. Average blood flow velocity (Vmax) after Udenafil intake in both funiculus vessels (left and right) increased from 9.3±0.5 cm/sec to 11.5±0.5 cm/sec that is on average by 24%. The weighted mean of Vmax increase in male genital organs was +27%. Slight tendency to increase of peripheral vascular resistance parameters in penis and prostate (statistically not significant) was noted. Peripheral vascular resistance parameters in funiculus vessels did not change (or had slight tendency to decrease).

TEST WITH TADALAFIL

Mean Vmax (M±m) in deep arteries of both cavernous bodies of penis before testing was 9.4±0.8 cm/sec. In 1 hour after intake Tadalafil 20 mg, mean Vmax in the same penis vessels was 14.2±1.5 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 50 %. Mean

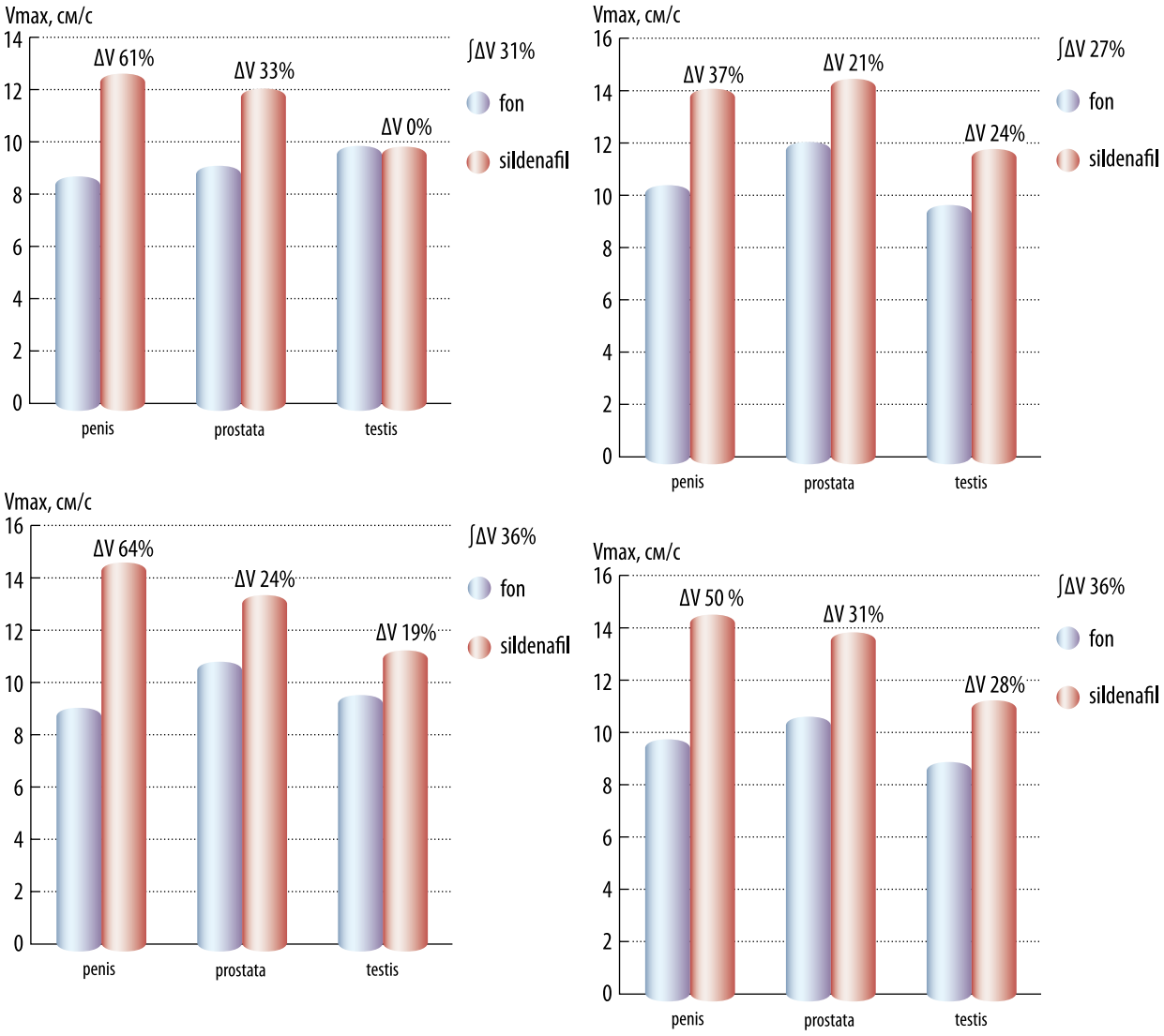
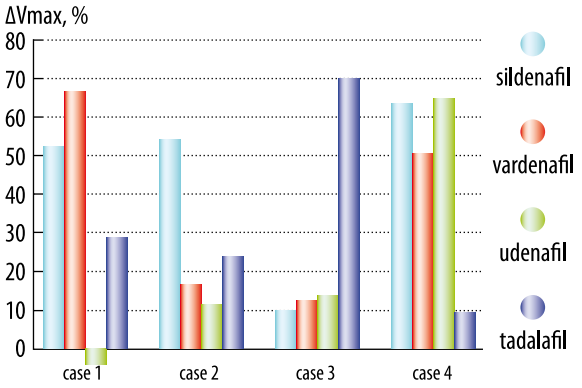


Fig. 1 a–d. *Vmax changes in vessels of penis, prostate and testes in 1 hour after intake Sildenafil (a), Vardenafil (b), Udenafil (c), Tadalafil (d).*
ΔV% — index of blood flow increase in vessels of penis, prostate and testes after pharmacological test in percentage terms
∫ΔV% — index of integral blood flow increase in vessels of male genital organs after pharmacological test in percentage terms

Vmax in threeregions of prostate before testing was 10.3±0.5 cm/sec, and after testing = 13.5±0.7 cm/sec. That is averaged peak blood flow velocity increase in prostate vessels amounted 31%. Averaged peak blood flow velocity after Tadalafil intake in both funiculus vessels increased from 8.6±0.9 cm/sec to 11.0±0.7 cm/sec that is on average by 28%. The weighted mean of Vmax increase in male genital organs was +36%. Parameters of peripheral vascular resistance in penis, prostate and testes after Tadalafil intake had statistically not significant tendency to increase (Fig. 2).

The following is a case example.



Pic. 2. *Indices of integral blood flow changes Vmax (in percentage terms) in vessels of male genital organs after pharmacological test with various PDEI-5 inhibitors in presented cases.*

Case 1. Patient S., 57 years. Diagnosis: erectile dysfunction, chronic prostatitis IIIA. The score according to IIEF-5 questionnaire was equal 19. The

investigation of PDEI-5 choosing was performed. The tested medicines were: Sildenafil 50 mg, Vardenafil 10 mg, Tadalafil 25 mg, Udenafil 100 mg. Intervals between tests were 5 days. The results — see Table 2, Fig. 1a.

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Sildenafil (Viagra) 50 mg (+54.3%). This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire became equal to 24 points.

Case 2. Patient I., 65 years. Diagnosis: erectile dysfunction, chronic prostatopathy, age-related androgens deficiency. The treatment by empirically chosen medicines had no effect. The score according to IIEF-5 questionnaire is equal = 14 points. The investigation of PDEI-5 choosing was performed. The tested medicines and doses were the same. Intervals between tests were 4 days. The results — see Table 3, Fig. 1b. The percent of average blood flow velocity increase in male genital organs vessels after performing the test are shown on axis of the ordinates (Table 3).

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Vardenafil (Levitra) 10 mg. Average blood flow velocity increase in male genital system organs constituted 66.7%. This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire achieved 19 points.

Table 2. *Blood flow velocity parameters in male genital organs of patient S., 57 years*

	Vmax (cm/sec)			Vmax
	penis	prostate	testes	mean
background	9	10	10	9.7
Sildenafil	21	13	10	14.7
Vmax, %	133	30	0	54.3
background	15	9	12	12.0
Vardenafil	17	11	14	14.0
Vmax, %	13	22	16	17.0
background	10.6	9.5	7.7	9.3
Tadalafil	8.9	11.4	10.1	10.1
Vmax, %	-16	20	31	11.7
background	13	10	13	12.0
Udenafil	15	14	15	14.7
Vmax, %	16	40	16	24.0

Table 3. *Blood flow velocity parameters in male genital organs of patient I., 65 years*

	Vmax (cm/sec)			Vmax
	penis	prostate	testes	mean
background	10	11	13	11.3
Sildenafil	9.1	27.5	11.8	16.1
Vmax, %	-9	175	-9	52.3
background	6	14	13	11.0
Vardenafil	18	14	13	15.0
Vmax, %	200	0	0	66.7
background	7	12	13	10.7
Tadalafil	7	12	11	10.0
Vmax, %	0	-15	0	-5.0
background	11	13	7	10.3
Udenafil	16	11	11	12.7
Vmax, %	45	-15	57	29.0

Case 3. Patient K., 59 years. Diagnosis: erectile dysfunction, chronic prostatitis IIIB. The score according to IIEF-5 questionnaire is equal 18 points. The investigation of PDEI-5 choosing was performed. The tested medicines and doses were the same. Intervals between tests were 6 days. The results — see Table 4, Fig. 1c.

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Udenafil (Zydena) 100 mg (+70%). This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire became 24 points.

Table 4. *Blood flow velocity parameters in male genital organs of patient K., 59 years.*

	Vmax(cm/sec)			Vmax
	penis	prostate	testes	mean
background	7	13	9	9.7
Sildenafil	9	16	7	10.7
Vmax, %	29	23	-22	10.0
background	9	21	11	13.7
Vardenafil	13	16	13	14.0
Vmax, %	44	-24	18	12.7
background	4	13	10	9.0
Tadalafil	6	8	13	9.0
Vmax, %	50	-38	30	14.0
background	14	9	8	10.3
Udenafil	24	17	12	17.7
Vmax, %	71	89	50	70

Table 5. *Blood flow velocity parameters in male genital organs of patient O., 42 years*

	Vmax(cm/sec)			Vmax
	penis	prostate	testes	mean
background	8.3	8	6.6	7.6
Sildenafil	24	9.7	5.3	13.0
Vmax, %	189	21	-20	63.3
background	7	7	10	8.0
Vardenafil	12	12	11	11.7
Vmax, %	71	71	10	50.7
background	8	7	6	7.0
Tadalafil	9	15	16	13.3
Vmax, %	13	14	167	64.7
background	9	11.1	8.9	9.7
Udenafil	9.7	11.3	10.7	10.6
Vmax, %	7	2	20	9.7

Case 4. Patient O., 42 years. Diagnosis: erectile dysfunction, chronic prostatitis II. The score according to IIEF-5 questionnaire was equal 20 points. The investigation of PDEI-5 choosing was performed. The tested medicines and doses were the same. Intervals between tests were 7 days. The results — see table 5, Fig. 1d.

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Tadalafil (Cialis) 20 mg (+64.7%). This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire became 24 points.

DISCUSSION

Our study showed that the efficiency of various PDEI-5 and their potential ability to increase blood supply of male genital organs is comparable. Patients' responses are individual, therefore it is necessary to personify the testing.

Blood flow velocity increase along penis vessels is not an erection, but only readiness to erection appearance and maintenance in the presence (appearance) of sexual stimulant — the NO source. This is essential for vasculogenic erectile dysfunction. The response is less marked at not-vasculogenic erectile dysfunction, and sometimes even paradoxical, that may help in differential diagnosis of erectile dysfunction origin [20]. Essential feature of PDEI-5 action is their effect on prostate blood flow [21–25]. Anatomical evidence is that penis and prostate have unified feed from the basin of internal iliac artery branches. Histological evidence is that 5thphosphodiesterase receptors present in prostate gland [26]. Pathogenetic evidence is that vasculogenic form of erectile dysfunction is combined with ischemic prostatopathy, i.e. chronic prostatitis IIIB, at which blood supply of the prostate is decreased by 2 times against norm [27–29]. The effect on blood flow is less marked in funiculus, since testicular artery deviates from aorta and is defined by the condition of central hemodynamics. Blood flow increase in the vessels takes place, usually, with the participation of rising the tone of appropriate vascular walls of responsive nature. These changes are not significant statistically, and generally are evident as a slight tendency. Therefore for clinical purposes one might use only peak blood flow velocity parameters, both averaged and integral.

Our study was of clinical applied nature, thereby we could not examine these patients for several hours in due course. Therefore the issue about blood flow parameters in male genital organs after administration 5thphosphodiesterase inhibitors in further hours remains to some extent open. In this study we also aimed to get information about the efficiency and the presence of known adverse events after intake medicine in test doses using subjective estimation scale IIEF-5.

The possibilities to choose not only specific medicine, but also to accomplish functional diagnostics of male genital organs hemodynamic disorders arise as a result of testing. Thus, for example, disorders' reversibility degree is more at chronic prostatitis IIIA and it is less at chronic prostatitis IIIB of atherosclerotic origin [30, 31].

CONCLUSION

The obtained results show very positive hemodynamic effects of studied PDEI-5 which are comparable and very individual at the same time. Integral increment percent of blood flow velocity when applying phosphodiesterase inhibitors constituted, on average roughly, 30–40% in male genital system organs (40–60% in penis, 25–40% in prostate, 15–30% in testes). So it is advisable to perform first the described pharmacological test with Dopplerography control according to developed algorithm and only after that to choose the medicine and to prescribe it to the patienton an individual basis.

While choosing the medicine for treatment erectile dysfunction and chronic prostatitis we suggest to rely on specific hemodynamic testing results of selected medicinal agents. In addition it is preferably to choose the medicine, which improves blood flow both in prostate and testes that is having the greatest integral percent of blood flow velocity increment in male genital system organs. It is essential also to consider subjective data about tolerance of the medicine and the presence of adverse events as well as patient's compliance to intake of one or another phosphodiesterase inhibitor.

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NEUERE ASPEKTE IN DIAGNOSTIK UND THERAPIE DES DEMENZSYNDROMS

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ZUSAMMENFASSUNG:
Die Krankheitsgruppe der Demenzen wird in den nächsten Jahren zentraler Versorgungspunkt, sowohl der akut-klinischen Medizin als auch der sozialmedizinischen Aufgaben des Gesundheits- und Sozialwesens.
Dies liegt einerseits an der steigenden Lebenserwartung der Bevölkerung, als auch an der Tatsache, dass aufgrund öffentlichkeitswirksamer Aufklärung, die Demenz mit einer höheren diagnostischen Wertigkeit und therapeutisch optional behandelt wird. Die Prävalenz von Demenzen steigt mit dem 70igsten Lebensjahr exponenziell an. Der wesentlichste Grund für die Einweisung von Dementen in Pflegeeinrichtungen sind mit an Sicherheit grenzenden Wahrscheinlichkeit die Verhaltensauffälligkeiten die im Rahmen und im Verlauf der Demenz auftreten. Der größte Anteil aller Demenzpatienten sind Patienten mit Alzheimerdemenz. Bis zu 80% von alzheimerdementen Patienten sind von Verhaltesauffälligkeiten betroffen. Die Verhaltensauffälligkeiten sind die häufigste Ursache für eine Heimeinweisung und sind in vielen Fällen auch mit akuter Krankenhauseinweisung in meist gerontopsychiatrischer stationärer Versorgung verbunden. Auch führen genau diese Verhaltensauffälligkeiten Demenzkranker bei den Bezugspersonen zu einem erhöhten Leidensdruck.

KEYWORDS — Alois Alzheimer, Gedächtnisstörung, Verhaltensstörung, cholinerges Defizit, Amyloid- Precursor- Protein, glutaminassoziierte toxische Prozesse, Cholinesterasehemmer, Antiglutaminergika

Wenn heute auch allgemein anerkannt ist, dass die wesentliche Ursache für die Demenz ein cholinerges Defizit ist, so ist der Startmechanismus und das Bedingungsgefüge für dieses cholinerge Defizit bis heute im Wesentlichen nicht bekannt.

Hier liegen Forschungsschwerpunkte sowohl der neurobiologischen als auch der neurologischen, als auch der internistischen Wissenschaften. In den letzten Jahren kristallisierte sich ein diagnostisches Grundkonzept heraus, welches den Hausarzt, den Facharzt und den Neuropsychologen braucht. Hier geht es vor allen Dingen um Basisuntersuchungen, um neurologisch-psychiatrische Untersuchungen und um differentialdiagnostische Wertungen verschiedenster selektiver psychometrischer Verfahren.

Die am 03. und 04.11.1906 vorgetragene Arbeit "über eine eigenartige Erkrankung der Hirnrinde" von Alois Alzheimer, bezugnehmend auf die Krankengeschichte von Frau Auguste Deter, hat bis heute an Bedeutung gewonnen, ist bis heute hoch aktuell und stellt nach wie vor Forschung und therapeutische Bemühungen vor große notwendige Anstrengungen. Sehr viel ist im Wissen um die Ätiologie der Alzheimererkrankung geschehen, letztendlich sind die ursächlichen Ursachen der Entstehung eines cholinergen Defizites auf mikrozellulärer Ebene auf der Ebene der Pathologie von Neurotransmittern und Stoffwechselvorgängen am Hirn im Detail unbekannt. Insofern ist die Alzheimerdemenz bis heute eine "eigenartige" Erkrankung der Hirnrinde.

Auch neuere diagnostische, bildgebende Verfahren, wie die zerebrale Computertomografie, die zerebrale Magnetresonanztomografie, die Magnetresonanzspektroskopie, die Spect- und die PET- Untersuchungen konnten das Geheimnis um den Startermechanismus nicht ausreichend klären.

So richten sich die primären aktuellen Therapieziele der Demenzerkrankungen auf die Verzögerung der Heimeinweisung, Verringerung der Pflegebedürftigkeit, Stabilisierung und Verbesserung der kognitiven Fähigkeiten, vor allem den Erhalt der Sprachfähigkeit, den Erhalt und der Verbesserung der alltagsrelevanten Fähigkeiten der Selbstversorgung und somit den Erhalt von Lebensqualität.

Die pharmakotherapeutischen Zielrichtungen auf der Basis der neuromolekularpathologischen und pathobiochemischen Kaskade der Alzheimererkrankung sind die Minderung des cholinergen Defizites, die Optimierung mikrozirkulatorische Prozesse zur Verbesserung des mikozellulären Metabolismus und die Reduzierung der zytotoxischen glutaminergen Prozesse.

Nach neueren molekularpathologischen Untersuchungen scheint der wesentliche Auslösemechnismus zur Bildung von Amyloidplaques und Neurofibrillen der pathologische Abbau des Amyloid-Precursor-Proteins (APP) zu sein. In aller Regel wird dieses Protein nonamyloidogen über den Alpha-Sekretasepfad gespalten. Dies geschieht in über 90% der Verstoffwechselung desAPP. In 10% geschieht dieser Abbau über den Beta- Sekretasepfad, wobei in Endeffekt Tau- Protein, senile Plaques und neurofibrilläre Bündel mit dem Effekt des cholinergen Defizites und des subdtanziellen Verlustes in der Summe dieser pathologischen Prozesse entsteht. Dieser Beta- Sekretasepfad der amyloidogenen Spaltung ist bei Demenzpatienten nach neusten Erkenntnissen der wesentliche Auslösemechanismus für die Bildung der pathologischen Substrate intra- und extrazellulär im Gehirn.

Bisher gibt es aber kein pharmakologisch etabliertes Verfahren, diesen "Schlüsselprozess", die Beta-Sekretase getriggerte amyloidogene Spaltung des APP therapeutisch zu beeinflussen. Deshalb konzentrieren sich die pharmakologischen Möglichkeiten im Wesentlichen in der Minderung des cholinergen Defizites durch Einsatz von Cholinesterasehemmern und die Optimierung mikrozirkulatorischer Prozesse zur Verbesserung des mikozellulären Metabolismus, wie z.B. durch Gingobelobaextrakt in hoher Konzentration und Reduzierung der glutaminergen zytotoxischen Prozesse durch z.B. Einsatz von Memantine.

Die medikamentöse Therapie der Alzheimerdemenz zielt im Wesentlichen somit auf zwei Symptomkomplexe ab.

Erstens auf die Behandlung der Kernsymptomatik der Dezemenz (vor allem kognitive Störungen, Beeinträchtigung der persönlichen Aktivitäten des täglichen Lebens und der ADL-Funktionen) und zweitens auf die evtl. erforderliche Behandlung von psychischen- und Verhaltenssymptomen (Depression, Angst, Agitation, psychotische Syndrome und Apathie).

An nicht medikamentösen Verfahren haben die Ergotherapie, die Musiktherapie, die Kunsttherapie, allgemeine Maßnahmen und physikalisch-therapeutische Interventionen Einzug in die klinische Praxis gehalten.

Bei den allgemeinen Maßnahmen ist insbesondere bei der Angehörigenarbeit mit dem Ziel der Patient-Proxy-Beziehung eine gute klinische Praxis datenmäßig erfasst.

Für alle anderen nicht medikamentösen Verfahren ist die Datenlage heterogen.

Zusammenfassend muss festgestellt werden, dass wir in der medikamentösen Therapie der Demenzen immer noch das Ende der pathoplastischen Kaskade therapieren, woraus sich die Forderung ergibt, dass wir therapeutische Intervetionsmöglichkeiten mit früherem Wirkeinsatz brauchen.

Es gibt derzeit in klinischer Prüfung verschiedene innovative Therapieansätze für die Behandlung des Morbus Alzheimers, welche von der aktiven Immunisierung über die passive Immunisierung bis hin zur Immunglobulintherapie, Gammasekretaseinhibition, Proteaseaktivierung und Modulation von Rezeptoren reichen.

Daraus ergibt sich für die klinische Forschung und für die Grundlagenforschung, dass insbesondere Zusammenhänge zwischen Umweltmedizin, toxischen Einflüssen, genetischen Bedingtheiten und konsitutionellen Faktoren dedektiert werden müssen, um letztendlich herauszufinden, warum bei Demenzpatienten der molekular-pathologische Starterweg der Erkrankung, nämlich die Beta- Sekretase getriggerte Verstoffwechselung des Amyloid-Precurso-Proteins gewählt wird.

EPIDEMIOLOGY AND CLINICAL CHARACTERISTIC OF CONGENITAL DEFECT OF SUPPORTING-MOTOR APPARATUS AMONG NEW BORNS IN ASTRAKHAN AND ASTRAKHANIAN REGION

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ABSTRACT — The exploration of gas complex for more than 20 years, which had high content of sulphur combinations, changed to worse the ecological condition in Astrakhan and Astrakhanian region. The statistic analysis for 15 years of congenital skeletal defects was made. It was found out, that the increase of dysplasia, congenital scoliosis and coxofemoral joint multiplied defects.

KEYWORDS — children, congenital defects of supporting-motor apparatus, ecology.

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INTRODUCTION

The main medical and social problem of contemporary Russia is to preserve the health of nation in connection with real effect of depopulation (1), it means the usage of prophylaxis of morbidity among new-borns and the perfection of rehabilitative treatment of children with already formed defects (3, 5).

At present the physical development of children and teenagers from the point of ecosensitivity is taken into consideration as the main index of health level of population and quality of environmental media. The growing organism quickly react to unfavourable factors of environment, its reaction may not be simple. There were described out of level measures and non-proportional growth of long tubular bones during the period of growing impulses and disharmonic physical development of children (6) in the region of ecological unfavourability and defects of mineral metabolism (4). However, the most complex, real and demonstrative thing is the congenital pathology of supporting-motor apparatus (7, 8).

The congenital skeletal deformations take the second place in distribution after pathology of cardio-vascular system and the first in socio-economic significance among all defects of development. The children, having congenital deformations of supporting- motor apparatus, especially of spinal column, during a long period of time or the whole life, should be supplied by expensive operative means, apparatuses, orthesises and other appliances which may help them to study, to move and have an adequate way of live. It's necessary to remember about care, pay for sick-lists, various means, sanatory-resort treatment and so on. The above mentioned things explain the high interest of children surgeons and orthopedists to discovery reasons, characteristics and working-out the modern rehabilitative measures for children with congenital skeletal deformations.

The aim of present work is to define epidemiological parameters and clinical peculiarities of congenital defects of supporting- motor apparatus in ecologically unfavourable region — Astrakhan and its districts.

MATERIAL AND METHODS

There was made the investigation of supporting-motor apparatus condition of new- borns in the period from 1991 to 2011 years in populated places and centers of the Astrakhanian region, in maternity homes of Astrakhan. The investigated group included the children with defects of motor system development (spinal column, extremities, tendon- joint apparatus). There were studied the types of pathology, nosological forms, their distribution, variants of connection and combinations with other kinds of congenital pathology (other organs and systems).

For this purpose there was done the analyses of medical documentation in maternity homes №1 and № 2, Astrakhan. Town's children clinical hospital №1 (neurological department and the department of newborn pathology, Regional children clinical hospital (orthopedic department)). There were chosen and analysed the cases of children with congenital defects of supporting-motor development, with the combined defects of development. There were 968 observations. The data from cases and register admissions, operative registers, analysis of X-rays in dynamics, other special types of observation (nucleo-magnetic resonance, computer tomography) were taken for study. The remote results of treatment using invitations for examination and repeated hospitalization were studied. For statistic analyses and mathematical work-out the received data was taken to the department of statistics of the Astrakhanian region.

The statistic work-out of data was done on the personal computer using specialized program for this purpose "Statistica 6,0" for " Windows-XP.".

The other methods were used as: neuroinformatics, hybrid expert system in specialized program complex " AO-2009" made in scientific- producing unit of laboratory "New technology," Astrakhan.

RESULTS AND DISCUSSION

From the very beginning of existence of orthopedic science as an independent clinical subject the specialists' attention was focused on the congenital defects in the development of supporting-motor apparatus and their complications. Different, hard and combinated deformations of bones and joints often made children become invalids, gave birth to serious social, medical and pedagogical problems of the society. It proved the doctors of various specialities, biologists and workers of health protection service to find ways and methods of early diagnostics, treatment and prophylaxis of this pathology. During the long period of observation there were found out and classified etiologic factors which were united as exogenous and endogenous. The previous researches showed that serious disturbances of metabolism, biosynthesis and waste of components of collagenous and elastic fibers may appear under the influence of changeable factors of surrounding media and may lead to change of structure and function of connective tissue organs (2).

The present investigation showed the growing number of congenital defects especially the defects of skeleton.

The division in years and dynamics of quantitative data are given in the Table 1.

Table 1. *Absolute data of congenital anomalies in Astrakhan and Astrakhanian region*

Years	The whole number of newborns	The number of diseases with congenital anomalies	
		The whole number	With the firstly stated diagnosis
1991	13938		1119
1992	12131		1221
1993	10384		1280
1999	9662	6219	1596
2000	10027	6109	1457
2001	10549	5997	1320
2002	11623	6339	1472
2003	12160	6847	1674
2004	12358	6913	1733
2005	12121	6822	1665
2006	12375	7154	2121
2007	13437	7358	2184
2008	14203	7424	1958
2009	14887	7636	2230

As it is seen from the given data there is the marked increase in number of children with CDD including SMA, the dynamics of it can be seen in Fig. 1.

The analysis of all nosologic forms of such pathology showed the most frequent cases of defects

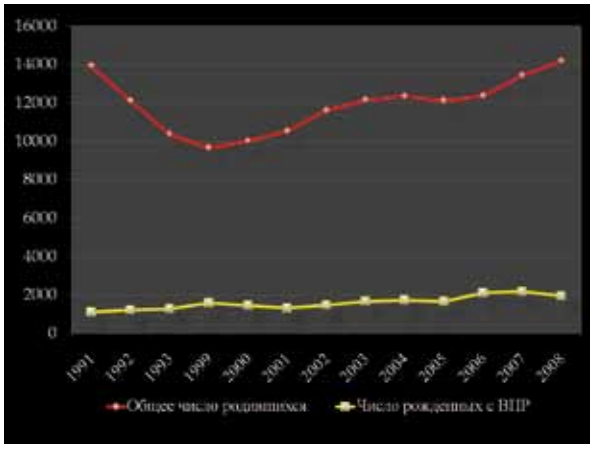

Table 2. *The data of congenital defects development (CDD) in Astrakhan*

The analysed year	General number of new-borns (GNNb)	The number of new-borns with CDD	The number of new-borns with CDD, % from GNNb	The number of new-borns with CDD of supporting-motor apparatus (SMA),n	The number of new-borns with CDD SMA, % from GNNb	The number of new-borns with CDD of SMA, % from CDD
1991	9499	454	4,78	66	0,69	14,54
1992	6971	632	9,07	79	1,13	12,50
1993	7461	591	7,92	81	1,09	13,71
1999	69,21	520	7,51	118	1,71	22,69
2000	7976	610	7,65	123	1,54	20,16
2001	7223	576	7,97	144	1,99	25,00
2004	8723	581	6,66	107	1,23	18,42
2005	8112	516	6,36	116	1,43	22,48
2006	9002	602	6,69	134	1,49	22,26

in supporting-motor apparatus, they were: dysplasia of coxofemoral joint, hand anomalies, torticollis, and deformation of chest. In 1991 the dysplasia of coxofemoral joints was 16,3%, in 1992 — 25,7%, in 1993 — it became 41,6% from the general number of congenital defects (CDD) of supporting motor apparatus (SMA). The diagnosis of torticollis was the same during the long period, its number was on the same level. At the same time the congenital talipes which had 30% in 1991 gradually decreased and to 1993 it had only 19% from the general pathology of motor organs.

In this period there was found out the definite member of rare severe combined skeleton defects such as arthrogryposis, chondrodysplasia, metaphysical chondrodysplasia, multiplied congenital dislocations of extremities. During the last 5 years this tendency preserved but there were some peculiarities. There were decreased numbers of talipes, but increased numbers of congenital scoliosis form, more cases when children were born with multiplied defects in development of supporting-motor apparatus, combined deformations, various syndromes. This group of children is united in the column "others" and may demonstrate stable tendency to growth. The number of children with congenital defects of SMA has 1,48%.

The districts of the Astrakhanian region having different geographical location and remote space from the main source of pollution have various chemical load. According to data of main department of natural resources and protection of environment in Russia in the Astrakhanian region it may be considered to be the most polluted parts such as: the Khasnyi, Ahtubinsk districts and Astrakhan itself. According to data the highest degree of suffering had the districts nearest to sanitary-protective zone.

There was studied the distribution of congenital skeleton deformations in districts of the Astrakhanian region, as it gives the picture about epidemiology of pathological processes. The highest number of defects of supporting-motor apparatus was observed among inhabitants of the town during the whole period of investigation. It was stated that the unfavourable districts of the region were — Narimanov (6,1 to 14,2%), Privolzhskyi (5,4 to 7,5%), Krasnyi Yar (3,7 to 8,2%).

CONCLUSION

The analysis of statistical indexes, retrospective analysis of medical papers and clinical observation may give the possibility to come to the conclusion concerning the increase of CDD, especially dysplasia columna vertebralis anomalies, change of structure to the growth of multiplied deformations. The investigation of CDD in the districts of region discovered unfavourable zones of distribution of children with congenital development defects of supporting-motor apparatus that shows the necessity to find exogenous reasons and etiological factors connected with location, climate, etc.

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MIXED SALIVA TRACE ELEMENT COMPOSITION IN CHILDREN WITH DENTOALVEOLAR ANOMALIES THROUGH APPARATUS-INVOLVED TREATMENT

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ABSTRACT

Lab-diagnostic methods have been employed to study immunoglobulin E and microelements in the non-stimulated oral liquid in children aged 4.5 yrs. – 8 yrs. using removable orthodontic appliances. It has been shown that an appropriate index of correlation connection between the immune system stress and the level of microelements is the growth of the copper/zinc ratio gradient in case of increasing concentration of iron and tungsten in the mixed saliva. It has been proven there is a need for conducting allergen-specific immune-modifying therapy to bring to normal the humoral immunity factors in order to improve the anti-microbial protection of the oral cavity.

KEYWORDS — microelements, correlation analysis, salivodiagnostics, antigenic stress, sensibilization.

TOPICALITY

The current stage in the evolution of medical technologies has witnessed specific significance in laboratory-diagnostic research into the role that macro- and microelement imbalance plays in the health of the child population. Trace element metabolism has been proven to depend significantly on the immune status as well as on climate-geographic, environmental, genetic, bio-social, and chronobiological factors that determine the body resistance at large. The effect of chemical elements is specified by the concentration intervals allowing normal metabolism. The intensity of metabolic reactions depends on the adjustment ability and the macroorganism capacity, which are coded and "approved" in the genotype [1,4,5].

Based on the threshold concentration theory by V.V. Kowalski we can say that functions in an organism can be regulated only under specific limits of the geochemical environment variability. Below the level of the minimum threshold concentration (lack of assimilation or insufficient intake of chemical elements), and above the upper threshold concentration (excessive supply of chemical elements) the homeostatic regulation function will be disturbed due to reduced resistance and joint activity of adjustment mechanisms [2,10].

Childhood has been shown to possess significant features in the immune and trace element status, as well in the tissues responsiveness to various xenogeneic materials. Note to be made that through a lengthy mechanical impact on the abutment teeth periodontium tissues, removable orthodontic appliances cause realignment of the entire dentoalveolar set; this comes along with altered microbiocenosis in the oral cavity, which is an important pathogenic mechanism disturbing the oral cavity homeostatic balance [6,7].

Scientific literature contains serious proof to the fact that the presence of IgE in any biological liquid may be viewed as a sign of an allergic reaction [3,8,9]. Given that it appears reasonable to investigate the correlation links between the presence of the allergic component (IgE) and the level of microelements in the oral cavity in children undergoing treatment for their dentoalveolar issues involving removable orth-

odontic appliances from base materials pertaining to different classes, while following the dynamics of their use. The data obtained from the correlation analysis – taken as an integral index for homeostatic balance through various stages of orthodontic treatment – would allow not only predicting allergy components and hypersensitivity, yet could also help reveal the efficiency of adjustment mechanisms for stabilizing immunological and trace element parameters in the mixed saliva.

Purpose of the research – to study the correlation links between the level of microelements and IgE in the mixed saliva of children undergoing treatment for dentoalveolar anomalies employing removable orthodontic devices of various base materials.

MATERIALS AND METHODS OF RESEARCHING

The modern international classification ISO 1567:1999 (Dentistry – Materials for base prostheses) was used to select three types of base materials used to manufacture removable orthodontic appliances. The 1st type material was polymethylmethacrylate-based (PMMA) cold-cured plastic Meliodent RR (Heraus Kulzer, Germany), which is an acrylic-based copolymer. Powder – fine-dispersed, suspension PMMA, containing the initiator – benzoyl peroxide and the activator – disulfanil; liquid – methacrylic acid methyl ether containing the activator – dimethylparatoluidine. The orthodontic appliances were made through hydropolimerization on gypsum base in the Ivomat IP3 (Ivoclar-Vivadent) polymerizer. The 2nd type material was hot-cured PMMA plastic ProBase Hot (Ivoclar-Vivadent, Lichtenstein), which is an acrylic graft-copolymer. Powder – fine-dispersed, suspension and the graft copolymer of methacrylic acid methyl ether; liquid – methacrylic acid methyl ether containing the cross-linking agent – diphenylpropane. The orthodontic devices were produced through compression pressing in the water polymerizer Acrydig 4 (F. Manfred). The 3rd type material used was the base material Versyo (Heraus Kulzer, Germany), which is a cross-linked composite acrylic plastic with a structure of interpenetrating polymer networks. The monomer system is a mix of multifunctional radicals with a high molecular weight containing no PMMA. The content of the non-organic filler (SiO_2) – 8%, particle size – 0.6–0.8 μm. The orthodontic appliances were made using the gypsum-based photo curable technology with a prior polymerization in the Heralight polymerizer (Heraus Kulzer) and the final polymerization in the Heraflash (Heraus Kulzer). All the materials were polymerized observing the cycle parameters as indicated by the manufacturer.

The investigation of the microelement content and IgE in the non-stimulated oral liquid (NOL) was done in 67 children aged 4.5–8 years with satisfactory and good oral hygiene. The patients were divided into a control a three major groups for out-patient observation. The control group was 18 children with orthognathic occlusion undergoing regular check-up and needing no orthodontic treatment.

Group 1 included 16 patients with abnormal teeth position and no dentition defect who had their 20 orthodontic appliances made of the 1st type material.

Group 2 was 18 patients with abnormal teeth position while their 22 orthodontic devices were made of the 2nd type material.

Group 3 included 15 patients who had abnormal teeth position and who had 19 orthodontic appliances made for them of the 3rd type material.

The tested appliances were permanently used for two months. All the participants were instructed regarding the standard tooth brushing methods in view of their age and the respective device maintenance requirements. The hygiene skills in the children were monitored using the hygiene index (Fedorov-Volodkina, 1972).

To study the level of microelements and that of IgE each of the patients had their NOL samples taken in a clinical setting, on an empty stomach at 8–9 o'clock, four times (prior to the treatment; 14 days after; 30 after; 60 days after the start of the orthodontic treatment). The patients were asked to restrain from any salivation inducing activities – eating; gum chewing; teeth brushing, and mouth rinsing. The patients in all the groups under investigation received a prior professional teeth cleaning. To collect NOL each patient was seated with their head down for some time; swallowing saliva was not allowed. When investigating the microelement content mixed saliva (0.7 ml) was taken straight from the oral cavity; the samples were placed in test-tubes (volume – 10 ml) (method by R.V. Karaseva, 2006) to be further stored under 0 to +4° C. When analyzing the IgE content the patient had to spit the accumulated NOL (5–7 ml) out into a sterile graded chilled glass test-tube. After that the mixed saliva was centrifuged for 15 minutes at 8.000 rev/min. The NOL supernatant fraction was separated in plastic tubes and stored under –30° C. When analyzing the immune and element content of the NOL lab-diagnostic methods were used to check all the patients' level of microelements to be found in the removable orthodontic appliances (Mn, Cu, Co, Mo, Ni, Ti, Fe, Zn, Cr, W), as well as the IgE rate was established in each case.

The study of the microelement content in mixed saliva was done through the methods for Inductively

Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) on the device Optima 2000 DV (Perkin Elmer, USA) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS) on ELAN-9000 (Perkin Elmer, USA) following the methodology as approved by the Ministry of Healthcare, Russian Federation (S.I. Ivanov et al., 2003; L.G. Podunova et al., 2003).

Method: this method is based on the oxidation-acid "wet" mineralization of the biosubstrate samples through the sample preparation and its further analysis for the required chemical elements with atomic emission spectroscopy employing high frequency inductively coupled argon plasma as the source of excitation. The ICP-AES method implies excitation of atom emission spectrum in the inductively coupled argon plasma and automatic registration of the position and intensity for the spectrum lines, which correspond particular elements.

All the biosubstrate samples went through preparation following the Methodological Recommendation approved by the Ministry of Healthcare and Social Development of the Russian Federation (Detection of Chemical Elements in Biological Environments and Preparations Through Inductively Coupled Plasma Atomic Emission Spectroscopy and Inductively Coupled Plasma Mass Spectrometry) (2003). The samples were analyzed following the Organizational Standards for Measuring Methodology 01-2009 (СТО МВИ 01-2009).

The substrate sample (0.7 cm^3) was weighed on analytical scales in fluoro-plastic insulation test-tubes. Each tube was placed in a thermo block heated up to 115 °C, and then steamed dry. After that each tube was filled with 2 cm^3 of high purity nitric acid and then sample volume (chilled down to room temperature) was brought up to 10 cm^3 with distilled deionized water to be further mixed. The test-tube was covered with the self-adhesive protective film Parafilm(R) M, placed in the automatic sampler socket, after which measuring was conducted on the spectrometer Specord-M40 (CARL ZEISS JENA, Germany) under the following parameters: power output – 1300 Watts; cooling stream – 15 l/min; auxiliary stream – 0.2 l/min; bearing stream – 0.85 l/min; sample feed rate – 1.5 l/min. The following element spectrum lines were used for the measures (λ): Mn – 257.610 nm, Cu – 327.393 nm, Co – 267.716 nm, Mo – 202.031 nm, Ni – 221.648 nm, Ti – 334.940 nm, Fe – 238.204 nm, Zn – 206.200 nm, Cr – 267.716 nm, W – 292.464 nm.

The prepared samples were introduced into the spectrometer, just like the sample element atomic emission, was done in the automatic mode according to the operations manual. The emission intensity, once the light penetrated the monochromator grating and the optic scheme, was registered with a photosensitive device where the photocurrent was measured and processed in the spectrometer computer system. The analytical signals from the spectrometer Specord-M40 were processed through the respective software. The measuring result was approved as the arithmetic mean value of two parallel estimates, the divergence between them not exceeding the recurrence limit ($r \geq 14\%$).

The IgE index in the biological material was determined following the A.I. Karpischenko method (1998). Method: monoclonal antibodies (moAb) directed towards two different antigenic areas of IgE molecules (immunoglobulin concentration determined with calibrating graphs). In each couple one of the moAb was used to sensitize the tray surface and provided for coupling at the solid phase of IgE from the analyzed samples. A second moAb, coupled with peroxidase, interacted with another antigenic determinant coupled at the solid phase of the IgE molecule. The non-coupled components of the samples as well as the excess of the labeled moAb were removed from the solid phase by repeated washing with buffer solution containing Twin-20. The peroxidase activity at the solid phase was assessed based on the decomposition of orthophenylenediamine substrate and hydrogen peroxide. The decomposition product turned chromogen molecules into colored derivative substance the amount of which was proportionate to fermentative activity. The reaction was terminated with sulphuric acid. The result was registered on the microtray reader Infinite F 50 (Tecan), using the MagellanTM software for immune-enzyme assay with a vertical path in transmission density units with a wave length of 492 nm.

RESULTS AND DISCUSSION

The trace element analysis in the NOL in the control group showed the presence of the following microelements: Cu, W, Fe, Zn, Cr. The statistically meaningful fluctuations of the microelement content in the NOL were: Cu – from 0.64±0.03 to 0.75±0.04 mg/l; W – from 0.48±0.03 to 0.61±0.03 mg/l; Fe – from 1.23±0.06 to 1.38±0.07 mg/l; Zn – from 0.61±0.03 to 0.72±0.03 mg/l; Cr – from 0.47±0.03 to 0.60±0.03 mg/l. We took the averaged values (Cu – 0.70±0.04 mg/l; W – 0.55±0.03 mg/l; Fe – 1.31±0.07 mg/l; Zn – 0.67±0.03 mg/l; Cr – 0.53±0.03 mg/l for a conditional norm, which offers the best description for the parameters of the mixed saliva microelement status in children.

Table 1 contains the numbers for the microelement content in the NOL of the 1st Group's patients through various parts of the orthodontic treatment.

The microelement content in the NOL of the patients in the 2nd Group through various stages of the

orthodontic treatment is shown in Table 2.

In Table 3 you can see the microelement content detected in the NOL in Group 3 through various stages of the treatment.

The published data on the scientific research miss information on the microelement content in the mixed saliva, as well as potential changes at various stages of orthodontic treatment in children. The results obtained from the investigation of the mineral composition of the NOL before and after the removable appliances were used, showed that the patients demonstrated significant alterations in the chemical elements content. Thus, all the patients showed statistically reliable increase in the concentration of the microelements that are part of the removable orthodontic appliances (Mn, Cu, Co, Mo, Ni, Ti, W, Fe, Zn, Cr), while many of these (Mn, Co, Mo, Ni, Ti) had not been found in the mixed saliva prior to the orthodontic treatment.

The evaluation of the results of the laboratory-diagnostic research makes it safe to say that of all the microelements found in the mixed saliva the most significant growth (if compared to the initial data) was registered in iron (129.3±5.2% – 168.8±6.8%) and tungsten (156.1±6.4% – 224.2±9.2%). It has been proven that in the etiology of gingivitis a significant role is played by microorganisms, in particular staphylococci that are to be found in the dental deposit, the subgingival space, and in the saliva, and which need iron to function. Excess of iron inhibits the bacteriostatic effect of lactoferrin, leukocyte chemotaxis and phagocytosis, macrophage phagocytosis, transformation of lymphocytes, as well as the bactericide role of antibodies and complement. The death of staphylococci under the influence of polymorphonuclear leukocytes is inhibited with free (protein-bound) iron but not hemoglobin or catalase. Besides, mixed saliva also accepts erythrocytes, which, while decomposing, release non-protein iron this increasing its general level in the given environment. The combination of the factors in question facilitates progressive growth of the microflora and the development of allergic (inflammation) processes in the oral cavity.

Zinc is known to play an important role in the cell and humoral immunity. Zinc deficit increases susceptibility to infection, reduces the production of g-interferon and interleukine-2, the lytic activity of natural killers, and their relative content in the T-lymphocyte population. An analysis of the results showed that in all groups the patients going through the initial stage of orthodontic treatment showed a reliable decrease of Zinc concentration in the saliva (8.2±0.4% – 21.1±0.9%) while the level of Copper went up (16.2±0.8% – 27.6±1.1%), if compared to the control group and the data obtained prior to the treatment. In 60 days of orthodontic treatment an increase of Copper due to Zinc deficit in mixed saliva provides for an increased gradient in the ratio Copper/Zinc in all the groups under control: Group 1 – from 1.07 to 1.70; Group 2 – from 1.15 to 1.58; Group 3 – from 1.10 to 1.40. The gradient increase in the Copper/Zinc ratio in NOL promotes the permeability of mucous tunic epithelium for bacterial flora, which stimulates the activity of inflammatory processes in the oral cavity.

The IgE index in the NOL at various stages of orthodontic treatment in the groups can be seen in Table 4.

The control group patients just like those in the groups under out-patient observation, revealed no IgE in their NOL before the start of the orthodontic treatment. A comparative analysis of the IgE content in the NOL of the patients belonging to the groups that were under investigation, done after 2 months of orthodontic treatment, allows concluding that the

Table 1. *Microelements in the NOL through various stages of orthodontic treatment, patients of Group 1 (mg/l) (M±m)*

Element	Maximum concentration limit in water	Term of investigation			
		Prior to treatment	After 14 days	After 30 days	After 60 days
Mn	0.1	Not detected	0.28±0.01	0.34±0.01	0.37±0.02
Cu	1.0	0.76±0.04	0.82±0.04	0.93±0.05	0.97±0.05
Co	0.1	Not detected	0.08±0.01	0.09±0.01	0.11±0.01
Mo	0.25	Not detected	0.10±0.01	0.09±0.01	0.10±0.01
Ni	0.1	Not detected	0.14±0.01	0.16±0.01	0.17±0.01
Ti	0.1	Not detected	0.14±0.01	0.18±0.01	0.19±0.01
W	0.05	0.58±0.03	1.34±0.07	1.53±0.08	1.88±0.09
Fe	0.03	1.38±0.07	2.82±0.14	3.56±0.17	3.71±0.18
Zn	5.0	0.71±0.04	0.68±0.03	0.63±0.03	0.57±0.03
Cr	0.05	0.61±0.03	0.82±0.04	0.76±0.03	0.93±0.05

Table 2. *Microelements in the NOL through various stages of orthodontic treatment, patients of Group 2 (mg/l) (M±m)*

Element	Maximum concentration limit in water	Term of investigation			
		Prior to treatment	After 14 days	After 30 days	After 60 days
Mn	0.1	Not detected	0.18±0.01	0.23±0.01	0.21±0.01
Cu	1.0	0.73±0.03	0.76±0.03	0.81±0.04	0.92±0.04
Co	0.1	Not detected	0.09±0.01	0.08±0.01	0.09±0.01
Mo	0.25	Not detected	0.08±0.01	0.09±0.01	0.09±0.01
Ni	0.1	Not detected	0.12±0.01	0.14±0.01	0.15±0.01
Ti	0.1	Not detected	0.18±0.01	0.16±0.01	0.15±0.01
W	0.05	0.51±0.02	1.12±0.06	0.96±0.05	1.31±0.07
Fe	0.03	1.28±0.07	2.05±0.11	2.34±0.12	2.86±0.14
Zn	5.0	0.63±0.03	0.61±0.03	0.60±0.03	0.58±0.03
Cr	0.05	0.51±0.03	0.73±0.03	0.67±0.03	0.56±0.03

Table 3. *Microelements in the NOL through various stages of orthodontic treatment, patients of Group 3 (mg/l) (M±m)*

Element	Maximum concentration limit in water	Term of investigation			
		Prior to treatment	After 14 days	After 30 days	After 60 days
Mn	0.1	Not detected	0.19±0.01	0.21±0.01	0.24±0.02
Cu	1.0	0.74±0.03	0.74±0.03	0.77±0.03	0.86±0.04
Co	0.1	Not detected	0.09±0.01	0.08±0.01	0.09±0.01
Mo	0.25	Not detected	0.09±0.01	0.09±0.01	0.08±0.01
Ni	0.1	Not detected	0.13±0.01	0.15±0.01	0.16±0.01
Ti	0.1	Not detected	0.15±0.01	0.17±0.01	0.17±0.01
W	0.05	0.54±0.03	0.95±0.05	1.28±0.07	1.41±0.08
Fe	0.03	1.23±0.06	2.27±0.11	2.62±0.13	2.82±0.14
Zn	5.0	0.67±0.04	0.65±0.03	0.63±0.04	0.61±0.03
Cr	0.05	0.56±0.03	0.83±0.04	0.75±0.03	0.73±0.03

Table 4. *IgE in NOL at various stages of orthodontic treatment (IU/l) (M±m)*

Term of investigation	Control group	Group 1	Group 2	Group 3
Prior to treatment	Not detected	Not detected	Not detected	Not detected
After 14 days	Not detected	1.72±0.09	1.65±0.09	1.36±0.06
After 30 days	Not detected	2.68±0.14	2.33±0.12	1.54±0.08
After 60 days	Not detected	3.24±0.16	2.86±0.15	2.07±0.09

highest increase (88.4±3.5%) was in case of using appliances of cold-cured base plastic, while light-cured base plastic materials offered the lowest increase in the values (52.2±2.1%).

The published scientific data provide no complete information on the dynamics of the change in the IgE level in NOL at various stages of orthodontic treatment in children. Detecting IgE in the NOL of the patients who were somatically healthy and in whom this immunoglobulin was not detected at the initial check-up, sends us suggesting that this presence is due to the treatment involving appliances and the orthodontic devices in the oral cavity. We believe that when orthodontic appliances are constantly washed by the oral liquid then there is a continuous bilateral ion exchange between the mixed saliva and the chemical substances that are part of the device. The chemical microelements in the removable appliances (Mn, Cu, Co, Mo, Ni, Ti, Fe, Zn, Cr, W) diffuse into the mixed saliva, while being antigens that cause sensitizing.

The data available in the respective literature nowadays prove that the chemical elements in removable appliances play a significant role in the development of IgE-dependent pathogenic mechanisms. A specific issue in the development of immunological reactions involving the cytophilic IgE is the ability to get fixed on the surface of mast cells and basophiles, which can be accounted for by a large number of receptors to the Fc-fragments of IgE, which are found on these cells. In case of further coupling of the IgE, which is fixed on mast cells or basophiles, with an antigen (microelement), there appears degranulation of these cells with a release of histamine and other vasoactive substances leading to an allergy reaction.

Our view is that the maximum level of IgE in the NOL that is found on Day 60 is related to the saturation of mixed saliva with microelements, and a rise of an allergy component. Proof to it is that at first the removable appliances were kept in the oral cavities for some limited time (1–1.5 hours), this period of time to go up further on (by Day 14 – up to 4–5 hours), and on Day 60 only they started to use the devices for 16–18 hours per day.

The scientific data available as well as the results of our own research projects make it possible to state that in children using removable orthodontic appliances, at the initial stage, the most significant increase in the level of iron (168.8±6.8%), tungsten (224.2±9.2%), the copper/zinc ratio gradient (58.9±2,4%) as well as IgE (88.4±3.5%) was shown in case of cold-cured base plastics. The serious strain that the immune system suffers in case of using cold-cured materials can be explained, as we see it, by high water solubility, the presence of peroxidates in the base material, as well as a significant level of the residual monomer. The lowest increase in iron (129.3±5.2%), tungsten (156.1±6.4%), the copper/zinc ratio gradient (27.3±1.2%), and IgE (52.2±2.1%) was detected in case of light-cured base plastic materials; we believe this could be explained by low water solubility and complete absence of the residue monomer and peroxidates in the base composite plastic.

FINDINGS

1. Comparative evaluation of mixed saliva microelement composition in children through various stages of orthodontic treatment with removable devices manufactured of various base materials is an informative and prognostically meaningful test in determining the intensity of allergic process, which also offers a proper view of the physiological condition at large.
2. Correlation analysis allows the most complete understanding of the dynamics as well as interrelation between the microelement content and E-immunoglobulin in children's mixed saliva; this shows mobilization of adjustment mechanisms aiming at the body's increased functional activity through treatment with orthodontic devices.
3. Using removable orthodontic appliances for children results in a strain to the immune system due to antigen stress, which, in turn, is explained by a statistically proven increase in the mixed saliva of virtually all the chemical microelements that are to be found in the orthodontic appliances.
4. A proper indicator of correlation dependence between the level of microelements and the strain in the immune system is an increased copper/zinc ratio gradient, which is the case in the event of a higher concentration of tungsten and iron in the oral liquid. The level of other microelements that play smaller roles in producing antigens does not change significantly, which is to be taken into account when making a comprehensive assessment of the impact that orthodontic treatment has on the patient's immunological defense mechanisms.
5. The most significant increase in the concentration of iron, tungsten, the copper/zinc ratio gradient, as well as IgE in children at the initial stage of their orthodontic treatment, was seen in case of using cold-cured base plastic appliances.
6. The mixed saliva microelement analysis can be justified if used as a diagnostic test for evaluating the general condition at various stages of the orthodontic treatment. This would allow "tailor-made" scheme for correcting the mineral metabolism in order to increase the efficiency of therapy for dentoalveolar anomalies and deformations in children with allergies in the anamnesis.
7. It has been shown that when orthodontic appliances are used to treat children it is advisable to carry out allergen-specific immune-modifying therapy to improve the humoral immunity factors in order to strengthen the oral cavity antimicrobial protection.
8. The issue of the allergy component (IgE) and disturbed oral liquid homeostasis in case of using removable orthodontic appliances to treat children has not been widely covered and requires further investigation.

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ÄNDERUNGEN DES FUNKTIONSZUSTANDES DER MIKROZIRKULATION DURCH EINE ADJUVANTE BIOKORREKTUR-BEHANDLUNG BEI PATIENTEN MIT DIABETES MELLITUS TYP II

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SCHLÜSSELWÖRTER — spontane arterioläre Vasomotion, physische Konditionierung, Diabetes mellitus Typ II, Mikrozirkulation

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EINLEITUNG

Zur Erhaltung bzw. Wiederherstellung physiologischer Organfunktionen und damit einer möglichst hohen körperlichen und geistigen Leistungsfähigkeit des Organismus sind stoffwechseladäquate Transportvorgänge erforderlich, welche im Gewebe auf den „Transitwegen" des Stoffaustausches zwischen dem Organ Blut und den Gewebezellen erfolgen. Der funktionell wichtigste Teil des Blutkreislaufes ist hierbei der Bereich der Mikrozirkulation (Arteriolen, Kapillaren und Venolen), da vor allem im Bereich der Kapillaren die Gewebenutrition und vorwiegend im Bereich der Venolen die ersten Schritte von Immunreaktionen realisiert werden.

Abgesehen von den makrozirkulatorischen Regelungen der Organdurchblutung über Herzfrequenz, Schlagvolumen des linken Ventrikels, zentralvenöser Rückstrom in den rechten Vorhof und elastomechanische Merkmale der großen Blutgefäße, wodurch im Wesentlichen der Druckgradient zwischen der arteriellen Seite und der venösen Seite des Blutkreislaufes und die systemische Größe des Herz-Minuten-Volumens beeinflußt werden, erfolgt die bedarfsgerechte Regulierung der Organdurchblutung vor allem im Bereich der arteriolären Mikrogefäße. Neben den Diameteränderungen der muskelbewerten Mikrogefäße spielen die biorhythmisch unterschiedlichen Vasomotionen im großkalibrigen Arteriolenabschnitten und den diesen nachgeschalteten kleinkalibrigen Arteriolenabschnitten, welche unmittelbar in die kapillären Netzwerke münden, eine herausragende Rolle. Diese beiden Vasomotionsvorgänge determinieren die Entmischungsphänomene zwischen Blutzellen und Blutplasma im Bereich der Mikrogefäße und damit den Verteilungszustand des Plasma-Blutzell-Gemisches in den kapillären Netzwerken, wobei die Vasomotionen im großkalibrigen Arteriolenabschnitt übergeordnet, d.h. nerval und humoral, geregelt werden, die Vasomotionsschwingungen im kleinkalibrigen Arteriolenabschnitt jedoch spontan, autorhythmisch erfolgen und damit einer lokalen Regulierung im Rahmen der schubspannungsabhängigen endothelvermitteltelen Tonusregulation via Bildung und Freisetzung von Stickstoffmonoxyd dienen (1, 2, 3).

Bedenkt man, daß im Organismus die stoffwechselseitige Energiebereitstellung in Abhängigkeit von der körperlichen Bewegung über die Verbrennung von Kohlehydrtaten (Glucose) und Fetten erfolgt, so kommt einer wirksamen adjuvanten Bewegungstherapie bei Diabetes-Patienten eine besondere Bedeutung zu. Eine erhöhte Glucoseverbrennung als Folge einer gesteigerten körperlichen Bewegung ist eine wirksame Unterstützung der Behandlung von Diabetespatienten. Denkt man bei den zumeist mehr oder weniger adipösen Patienten ferner daran, daß dabei der Anteil der Fettverbrennung an der Energiebereitstellung u.a. von der verfügbaren Sauerstoffmenge für die aktivierten Organe (insbesondere Skelettmuskulatur) abhängt und daß bei der Fettverstoffwechselung mehr Sauerstoff benötigt wird als beim Abbau der Kohlehydrate (4), so erscheint bei Patienten mit Diabetes mellitus Typ II eine definierte Bewegungsbehandlung unter hyperoxischen Raumbedingungen (Raumluft mit 26

Vol.% Sauerstoffanteil) als adjuvante Behandlungsmaßnahme erfolgversprechend. Hierzu haben Schulz et al. eine praxisrelevante Behandlungsmethode unter der Bezeichnung „BioKorrektur“ eingeführt und anhand systemischer laborklinischer Befunde therapierelevante Wirkungen insbesondere auf Parameter des Fettstoffwechsels nachgewiesen (5).

Es stellt sich die Frage, ob die von Schulz et al erhobenen laborklinischen Meßdaten und deren Interpretation im Einklang stehen mit entsprechenden Merkmaländerungen zum Funktionszustand der Mikrozirkulation. Es ist bekannt, daß bei Patienten mit Diabetes mellitus Typ II defizitäre (stoffwechselinadäquate) Durchblutungsregulationen auftreten, die ihre Ursache zumeist in Einschränkungen oder Störungen vor allem der sponatenen, autorhythmischen arteriolären Vasomotion haben. Die Folgen sind Limitationen bei der stoffwechseladäquaten Verteilung des Plasma-Blutzell-Gemisches in den kapillären Netzwerken (Diffusionswege und Diffusionszeiten !) und damit der venolenseitigen Sauerstoffausschöpfung. Trägt das adjuvante Behandlungsverfahren „BioKorrektur“ stoffwechseladäquat zu einer Stimulierung körpereigener Regulationsmechanismen der Organdurchblutung bei Pateinten mit Diabetes mellitus Typ II bei?

AUFGABENSTELLUNG, MATERIAL UND METHODEN

Im Rahmen einer placebokontrollierten Untersuchungsreihe war an einer biometrisch definierten Stichprobe aus ambulanten Patienten mit Diabetes mellitus Typ II durch valide Messungen repräsentativer Merkmale des Funktionszustandes der Mikrozirkulation mit hochauflösenden Untersuchungsmethoden zu prüfen, ob und in welchem Ausmaß durch die Anwendung der adjuvanten Bewegungsbehandlung „BioKorrektur“ eine stoffwechseladäquate Stimulierung mikrozirkulatorischer Durchblutungsregulationen realisiert wird. Von den Ergebnissen dieser Untersuchungen wird eine Aussage darüber erwartet, ob ein therapeutischer Erfolg der „BioKorrektur“ im Einklang mit den von Schulz et al (5) erhobenen systemischen Stoffwechseldaten letztlich auch funktionsdiagnostisch in der Mikrohämodynamik repräsentativer Targetgewebe bestätigt und begründet werden kann.

In die Untersuchungen war eine Stichprobe aus 8 älteren männlichen und weiblichen Patienten mit Diabetes mellitus Typ II einbezogen (ambulante Rehabilitanden mit eingestelltem Diabetes, mäßig adipös, geringe arterielle Hypertonie, GCP-konforme Definition der Ein- und Ausschlusskriterien). Die Tabelle 1 informiert über die Konstitutionsdaten der untersuchten Patienten.

Tabelle 1.

Konstitutionsmerkmale der Patienten (Mittelwerte und Standardabweichungen)			
Alter (Jahre)	Körpermasse (kg)	Körperlänge (cm)	Geschlecht
70,9 ± 2,8	83,8 ± 3,9	171,8 ± 4,1	4♀, 4♂

Alle Patienten absolvierten 2 Behandlungsgänge (Kontrolle und Test) mit je 10 Behandlungen im Abstand von 2 bis 3 Tagen, wobei zwischen den beiden Behandlungsgängen ein Zeitintervall von 3 bis 4 Wochen lag.

Kontrolle (Placebo) n = 8

Bewegungsbehandlung „BioKorrektur“ mit definierter Laufbandbelastung (Zeitdauer 60 min an den Behandlungstagen 1.d bis 10.d) unter normoxischen Raumluftbedingungen (Sauerstoffanteil der Raumluft 20,9 Vol.%).

Test n = 8

Bewegungsbehandlung „BioKorrektur“ mit definierter Laufbandbelastung (Zeitdauer 60 min an den Behandlungstagen 1.d bis 10.d) unter hyperoxischen Raumluftbedingungen (Sauerstoffanteil der Raumluft 26 Vol.%).

Zur Laufbandbelastung :

Dauer 60 Minuten am jeweiligen Behandlungstag, Laufbandneigung 5%, mittlere Laufbandgeschwindigkeit 0,8 bis 1,0 m/s (beginnend mit geringer Laufbandgeschwindigkeit, im Verlauf der 60-minütigen Behandlung in Stufen alle 10 min um 0,1 bis 0,2 m/s gesteigert).

Die Meßwerterhebungen erfolgten am jeweiligen Behandlungstag (1.d bis 10.d) unmittelbar vor Beginn der Belasung (Ausgangswerte) und unmittelbar nach dem Ende der 60-minütigen Laufbandbelastung.

Die Erhebung der Meßwerte erfolgte unter konstanten Randbedingungen:

bequemes Sitzen unter konstanten makrozirkulatorischen und temperaturregulatorischen Randbedingungen. Zwei Stunden vor den Untersuchungen kein Alkohol, kein Kaffee, Tee oder Cola-Getränk. Mindestens 6 Stunden Schlaf täglich, keine biotrope Wetterlage im Beobachtungsintervall.

Zur Erfassung von Funktionsmerkmalen der Mikrozirkulation wurden zwei repräsentative Targetgewebe ausgewählt (Meßwerterhebungen jeweils in zwei Eindringtiefen):

- Definierte kutane Geweberegion im epigastrischen Winkel (Subkutis, Fettgewebe). Eindringtiefen 2 mm und 8 mm.
- Definierte Geweberegion am rechten dorsalen Unterscheknkel in der Mitte der Projektionsfläche des Musculus gastrognemius (Subkutis, Skelettmuskulatur). Eindringtiefen 2 mm und 8 mm.

Die Untersuchungen erfolgten nicht-invasiv mit einem hochauflösenden Untersuchungssystem zur kombinierten ***Laser-Doppler-Mikrofluss-Messung und Weißlicht-Spektroskopie*** (LEA, Gießen, Deutschland), welches die Bestimmung spektrometrischer und mikrohämodynamischer Merkmale in Mikrogefäßnetzwerken mit Gefäßdurchmessern 7µm ≤ d ≤ 200 µm in zwei Gewebetiefen erlaubt. Angaben zur Validierung und zu den Meßvorschriften sind der Literatur zu entnehmen (6, 7, 8, 9, 10).

Technische Daten des angewendeten Meßsystems : Lightguide Separation 2000 µm und 8000 µm, Wavelengthrange 500–630 nm (Separation 1 nm) und 650–795 nm (Separation 1 nm), Laser Wavelength 830 nm.

Die Erhebung der Meßdaten erfolgte zu jedem Meßzeitpunkt in der gleichen Geweberegion (exakte Markierung der Meßregion auf der Hautoberfläche und entsprechende Justierung der Meßsonde).

Die Meßwerterhebungen wurden kontinulierlich in einem Gesamtzeitintervall von 80 min am jeweilgen Behandlungstag (10 min Ausgangswerte vor Behandlung, 60 min Behandlung, 10 min nach Behandlung) alle 20 ms vorgenommen. Zur computergestützten Datenauswertung dienten die international anerkannten Datenanalyse-Programme. Im Rahmen der vorliegenden Abhandlung haben die Autoren jene Meßdaten ausgewählt, welche einen Vergleich der Meßdaten vor Behandlungsbeginn und nach erfolgter Behandlung am jeweiligen Behandlungstag gestatten (Angabe jeweils als prozentuale Änderungen).

In beiden Targetgeweben wurden zeitgleich in zwei Endringtiefen (2mm und 8 mm) folgende Merkmale des Funktionszustandes der Mikrozirkulation gemessen:

- Venolenseitige Sauerstoffausschöpfung ΔpO_2 (Differenz der Sauerstoffsättigung des Hämoglobins in den zuführenden Arteriolen und abführenden Venolen des mikrovaskulären Target-Netzwerkes). Angegeben als prozentuale Änderung im Vergleich mit dem jeweiligen Ausgangswert, der gleich Null gesetzt wurde.
- Mittlerer Ströungsfluß der roten Blutzellen im mikrovaskulären Netzwerk, QRBC. Angegeben als prozentuale Änderung im Vergleich mit dem jeweiligen Ausgangswert, der gleich Null gesetzt wurde.
- Mittlere Strömungsgeschwindigkeit der roten Blutzellen im mikrovaskulären Netzwerk, vRBC Angegeben als prozentuale Änderung im Vergleich mit dem jeweiligen Ausgangswert, der gleich Null gesetzt wurde.
- Relative Hb-Sättigung im Bereich des mikrovaskulären Netzwerkes, rHb. Angegeben als prozentuale Änderung im Vergleich mit dem jeweiligen Ausgangswert, der gleich Null gesetzt wurde.

Die statistische Auswertung der erhobenen Messdaten erfolgte mit Hilfe eines parameterfreien Prüfverfahrens für kleine Stichproben. Zur Anwendung gelangte der Wilcoxon-Rangsummentest auf dem Signifikanzniveau α=5%. Die kritischen Werte für T wurden der Literatur entnommen (11).

Im Rahmen der vorliegenden Abhandlung werden die biometrischen Prüfresultate für jeden Meßtag zu jedem Merkmal betreffs Ausgangswerte vor Behandlungsbeginn versus Meßwerte nach Behandlung mitgeteilt. Ferner erfolgt ein Vergleich der Meßdaten Kontrolle versus Test zu gleichen Meßzeitpunkten.

ERGEBNISSE

Die Untersuchungen erbrachten aussagefähige Resultate im Sinn der Aufgaben- und Zielstellung. Die Graphen in den Abbildungen 1 bis 8 veranschaulichen die wesentlichen Meßergebnisse.

Die Abbildungen 1a und 1b zeigen zusammenfassend die Änderungen des Merkmalverhaltens von „Mittlerer Strömungsfluß QRBC „ in den mikrovaskulären Netzwerken der Bauchhaut in Eindringtiefen von 2 mm (Subkutis) und in 8 mm (subkutanes Fettgewebe) vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe.

Ab dem 6. Untersuchungstag bis zum 10. Untersuchungstag unterscheiden sich die Meßdaten von Kontrolle und Testgruppe in beiden Eindringtiefen signifikant voneinander.

In den Abbildungen 2a und 2b sind die Änderungen des Merkmalverhaltens von „Mittlere Strömungsgeschwindigkeit der roten Blutzellen vRBC„ in den mikrovaskulären Netzwerken der Bauchhaut in Eindringtiefen von 2mm (Subkutis) und in 8mm (subkutanes Fettgewebe) vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe zusammenfassend dargestellt.

In beiden Eindringtiefen unterscheiden sich ab dem 6. Untersuchungstag bis zum 10. Untersuchungstag die Meßdaten von Kontrolle und Testgruppe in signifikant voneinander.

Die Änderungen des Merkmalverhaltens von „Relative Hämoglobinsättigung rHb„ in den mikrovaskulären Netzwerken der Bauchhaut in Eindringtiefen von 2 mm (Subkutis) und in 8 mm (subkutanes Fettgewebe) sind vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe zusammenfassend als Abbildungen 3a und 3b dargestellt.

Bei der Eindringtiefe 2 mm wurden vom 8. bis zum 10. Untersuchungstag signifikante Unterschiede beim Merkmalverhalten zwischen Kontrolle und Test-Gruppe ermittelt. Bei der Eindringtiefe 8mm unterscheiden sich die Meßdaten von Kontrolle und Test-Gruppe vom 7. bis zum 10. Untersuchungstag signifikant voneinander.

Das Verhalten des Merkmals „Venolenseitige Sauerstoffausschöpfung ΔpO_2 „ in den mikrovaskulären Netzwerken der Bauchhaut in Eindringtiefen von 2 mm (Subkutis) und in 8 mm (subkutanes Fettgewebe) ist vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe zusammenfassend in den Abbildungen 4a und 4b veranschaulicht.

Sowohl in der Eindringtiefe 2mm als auch in der Eindringtiefe 8mm treten ab dem 6. Untersuchungstag bis zum 10. Untersuchungstag signifikante Merkmalunterschiede zwischen Kontrolle und Testgruppe auf.

Die Graphen in der Abbildung 5 zeigen zusammenfassend die Änderungen des Merkmalverhaltens von „Mittlerer Strömungsfluß QRBC „ in den mikrovaskulären Netzwerken der rechten Wade in der Eindringtiefe von 8 mm (Skelettmuskel) vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe.

Signifikante Merkmalunterschiede zwischen Kontrolle und Test-Gruppe wurden ab dem 6. Untersuchungstag bis zum 10. Untersuchungstag festgestellt.

Als Abbildung 6 sind die Änderungen des Merkmalverhaltens von „Mittlere Strömungsgeschwindigkeit der roten Blutzellen vRBC„ in den mikrovaskulären Netzwerken der rechten Wade in der Eindringtiefe von 8mm (Skelettmuskel) vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe zusammenfassend angegeben.

Signifikante Merkmalunterschiede zwischen Kontrolle und Test-Gruppe traten am 6. Untersuchungstag auf und ab dem 8. Untersuchungstag bis zum 10. Untersuchungstag.

In der Abbildung 7 sind die Änderungen des Merkmalverhaltens von „Relative Hämoglobinsättigung rHb„ in den mikrovaskulären Netzwerken der rechten Wade in der Eindringtiefe von 8 mm (Skelettmuskel) vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe zusammenfassend dargestellt.

Signifikante Merkmalunterschiede zwischen Kontrolle und Test-Gruppe wurden am 6. und 7. Untersuchungstag sowie am 9. und 10. Untersuchungstag ermittelt.

Der Abbildung 8 ist das Verhalten des Merkmals „Venolenseitige Sauerstoffausschöpfung ΔpO_2 „ in den mikrovaskulären Netzwerken der rechten Wade in der Eindringtiefe 8 mm (Skelettmuskulatur) vom 1. bis zum 10. Behandlungs- bzw. Untersuchungstag für die Kontrolle und die Test-Gruppe zu entnehmen.

Die statistische Analyse der erhaltenen Meßdaten ergab vom 6. Untersuchungstag bis zum 10. Untersuchungstag signifikante Merkmalunterschiede zwischen Kontrolle und Testgruppe.

DISKUSSION

Aus der Literatur und aus eigenen Untersuchungen, die in anderem Zusammenhang durchgeführt wurden, ist bekannt, daß bei älteren Diabetikern (nicht nur im dekompensierten Zustand) Regulationsdefizite der Organdurchblutung auftreten. Diese betreffen im Wesentlichen die spontane autorhythmische arterioläre Vasomotion, wobei vor allem bei älteren Diabetikern Reduktionen der Schwingungsamplituden und Verringerungen der Anzahl der Schwingungsweiten pro Zeiteinheit im kleinkalibrigen Arteriolenteil auftreten. Die Folgen sind mehr oder weniger ausgeprägte Restriktionen der Entmischungsphänomene zwischen Blutplasma und Blutzellen in den mikrovaskulären Netzwerken, welche eine stoffwechseladäquate Verteilung des Plasma-Blutzell-Gemisches und damit den Stoffaustausch zwischen Blut und Gewebezellen behindern. Ferner betreffen die Regulationsdefizite Vorgänge der sogenannten diabetischen Mikroangiopathie (Veränderungen der Basalmembran, Permeabilitätsänderungen der Mikrogefäßwände und eine Reihe enzymatischer und metabolischer Veränderungen). Je länger ein manifester Diabetes besteht, umso ausgeprägter sind die vasomotorischen und die mikroangiopathischen Veränderungen (12, 13, 14, 15, 16).

Schulz et al wiesen anhand von spiroergometrischen Meßdaten und laborchemischen Untersuchungsergebnissen (Blutzucker, C-Peptid, HbAIC, Cholesterin, Triglyceride, HDL, LDL, Insulin, antioxydativer Status, HOMA-Index, CgI) einen metabolischen Effekt der Bewegungsbehandlung „BioKorrektur“ nach. Es stellt sich die Frage, ob diese metabolischen Wirkungen durch eine „Überforderung“ defizitärer Regulationsmechanismen der

Organdurchblutung „erkauft“ wurden. In derartigen Fällen würde sich das Risiko hypoxischer Zustände im Gewebe durch die Bewegungsbehandlung verstärken. Dabei ist mit Änderungen der Fließeigenschaften des Blutes (rheologische Merkmale) und Hyperkoagulabilität zu rechnen, die sich letztlich als Mikrozirkulationsstörungen mit den bekannten Folgen auswirken. Man denke auch daran, daß glykosyliertes HbA1c bei Diabetikern ca. 10% des erythrozytären Hb einnimmt und eine größere Affinität zu Sauerstoff besitzt, wodurch die Sauerstoffabgabe ins Gewebe ohnehin schon reduziert wird. Des weiteren ist zu beachten, daß die verstärkte Fettverbrennung Umverteilungsvorgänge in der Mikrozirkulation zwischen den oberflächennahen Netzwerken und den mit diesen kommunizierenden tieferliegenden Netzwerken erfordern.

Die vorliegenden Untersuchungsresultate einer Pilotstudie zum Verhalten aussagefähiger Funktionsmerkmale der Mikrozirkulation nach „BioKorrektur“-Behandlung geben eine eindeutige Antwort auf die oben genannte Frage.

Die Meßdaten, welche bei einer Bewegungsbehandlung unter normoxischen Raumluftbedingungen erhoben wurden (Kontrolle), liefern unter den gegebenen Untersuchungsbedingungen keine eindeutigen Hinweise auf eine Stimulierung vasomotorischer Regulationsmechanismen. Dagegen treten in der Test-Gruppe (Bewegungsbehandlung unter hyperoxischen Raumluftbedingungen) ab dem 6. bis 7. Behandlungstag signifikante Verbesserungen des Funktionszustandes der Mikrozirkulation in den untersuchten Targetgeweben auf. Diese Merkmaländerungen sind ab dem 6. bis 7. Behandlungstag innerhalb der Testgruppe signifikant unterschiedlich zu den Ausgangswerten, die vor Behandlungsbeginn erhoben wurden und gleich Null gesetzt wurden, sowie signifikant unterschiedlich zu den zeitgleich erhobenen Meßdaten bei der Kontrolle.

Nach „BioKorrektur“-Behandlung tritt in der Bauchhaut eine deutliche Zunahme des mikrozirkulatorischen Strömungsflusses auf, beginnend nach ca. 7-tägiger Bewegungsbehandlung. Aus temperaturregulatorischen Gründen sind die Merkmaländerungen im oberflächennahen Mikrogefäß-Netzwerk (Eindringtiefe 2mm) im Vergleich mit den tiefergelegenen Netzwerken des subkutanen Fettgewebes (Eindringtiefe 8mm) etwas stärker ausgeprägt. Die entsprechenden Änderungen der Strömungsgeschwindigkeiten roter Blutzellen weisen auf eine Zunahme überwiegend blutzellperfundierter Kapillaren und damit eine bedarfsgerechtere Verteilung des Plasma-Blutzell-Gemisches in den Netzwerken hin. Das Verhalten des Merkmals „Relative Hb-Sättigung“ ist wie folgt zu interpretieren : die Zunahme der Strömungsgeschwindigkeiten roter Blutzellen bewirkt einen leichter Hämodilutionseffekt, da der lokale Hämatokrit sinkt, was zu einer Verbesserung der Fließeigenschaften des Blutes in der Mikrozirkulation führt. Das Absinken der relativen Hb-Sättigungswerte führt nicht zu einer geringeren Sauerstoffausschöpfung, sondern stellt im Gegenteil unter Beachtung der o.g. Merkmaländerungen eine mikrorheologische Voraussetzung für eine erhöhte, bedarfsgerechtere venolenseitige Sauerstoffausschöpfung dar (17).

Im Muskelgewebe der Wade treten bei allen untersuchten Merkmalen im Vergleich mit den Meßdaten der Bauchhaut gleichgerichtete Merkmaländerungen auf, die jedoch aufgrund der körperlichen Belastung durch die Bewegungsbehandlung stärker ausgeprägt sind.

Die bei den Patienten der Test-Gruppe (Bewegungsbehandlung unter hyperoxischen Raumluftbedingungen, „BioKorrektur“) erhobenen Meßdaten zum Funktionszustand der Mikrozirkulation in den untersuchten Targetgeweben weisen auf eine weitgehend stoffwechseladäquate Stimulierung der körpereigenen vasomotorischen Durchblutungsregulation hin (17). Sie stehen im Einklang mit den von Schulz et al erhobenen metabolischen Daten und bestätigen eine adjuvante therapeutische Wirkung der „BioKorrektur“. Weiterführende Untersuchungen werden empfohlen.

Hinweise auf unerwünschte Wirkungen der adjuvant angewendeten Behandlungsmethode „BioKorrektur“ wurden nicht erhalten.

ZUSAMMENFASSUNG

An einer Stichprobe aus ambulanten älteren Patienten mit Diabetes mellitus Typ II wurde im Rahmen einer Pilotuntersuchung durch valide Messungen repräsentativer Merkmale des Funktionszustandes der Mikrozirkulation mit hochauflösenden Methoden geprüft, ob und in welchem Ausmaß eine Bewegungsbehandlung unter hyperoxischen Raumluftbedingungen („BioKorrektur“) eine stoffwechseladäquate Stimulierung mikrozirkulatorischer Durchblutungsregulationen bewirkt werden kann. Die Ergebnisse der Untersuchungen sprechen dafür, daß durch eine derartige Bewegungsbehandlung eine weitgehende Stimulierung der vasomotorischen Durchblutungsregulation mit ihren therapierelevanten Auswirkungen auf den Verteilungszustand des Blutes in den mikrovasulären Netzwerken und die venolenseitige Sauerstoffausschöpfung erreicht werden kann.

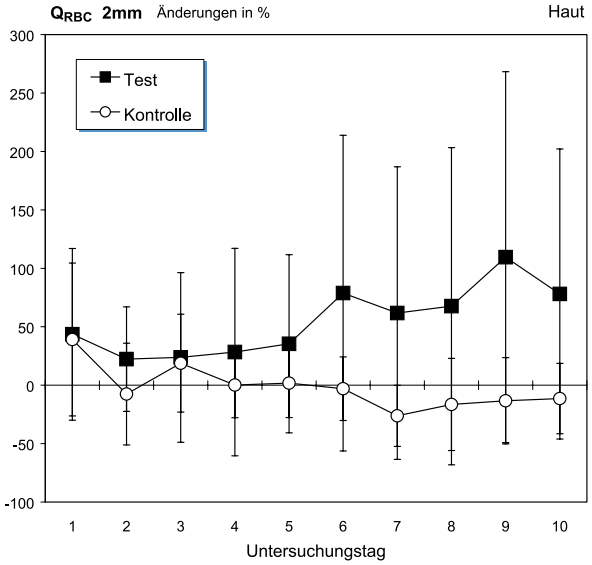

Abbildung 1a.
Meßwerte zum Merkmal „Mittlerer Ströungsfluß der roten Blutzellen im mikrovaskulären Netzwerk, QRBC" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (2mm Eindringtiefe, Subkutis) bei Kontrolle und Test-Gruppe. Ordinate : Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse : Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

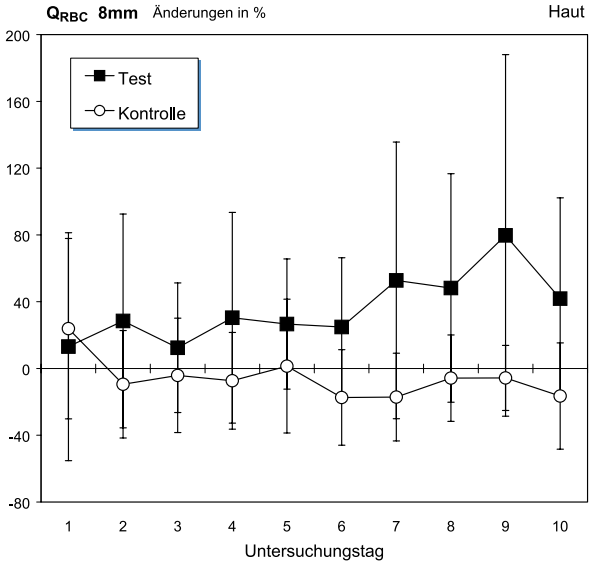

Abbildung 1b.
Meßwerte zum Merkmal „Mittlerer Ströungsfluß der roten Blutzellen im mikrovaskulären Netzwerk, QRBC" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (8mm Eindringtiefe, subkutanes Fettgewebe) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

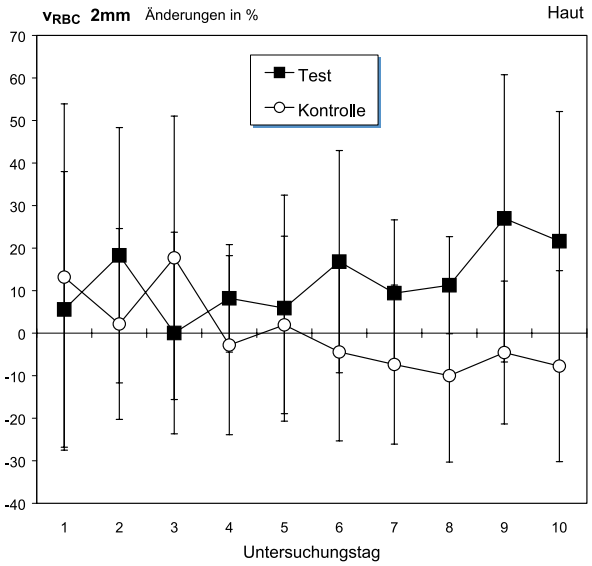

Abbildung 2a.
Meßwerte zum Merkmal „Mittlere Strömungsgeschwindigkeit der roten Blutzellen im mikrovaskulären Netzwerk, vRBC" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (2mm Eindringtiefe, Subkutis) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

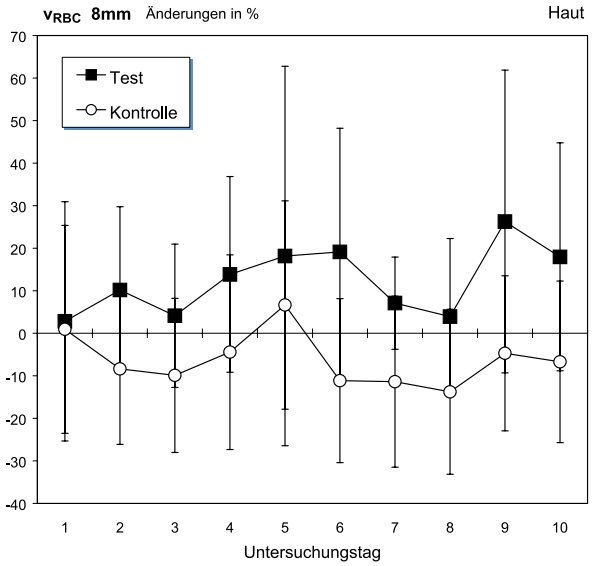

Abbildung 2b.
Meßwerte zum Merkmal „Mittlere Strömungsgeschwindigkeit der roten Blutzellen im mikrovaskulären Netzwerk, vRBC" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (8mm Eindringtiefe, subkutanes Fettgewebe) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

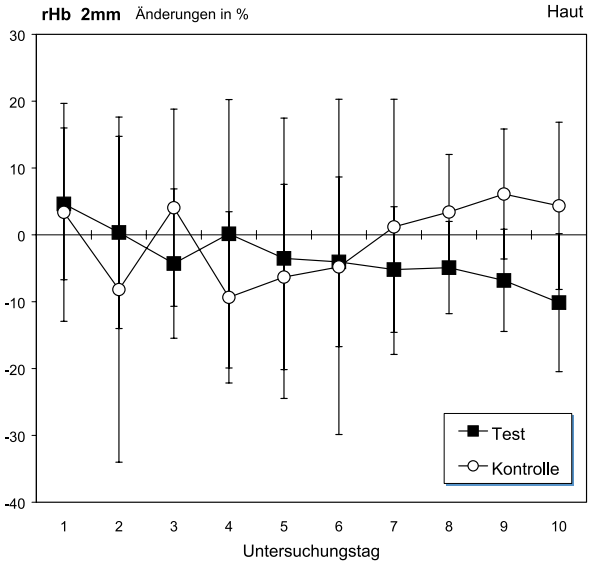

Abbildung 3a.
Meßwerte zum Merkmal „Relative Hb-Sättigung im Bereich des mikrovaskulären Netzwerkes, rHb" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (2mm Eindringtiefe, Subkutis) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

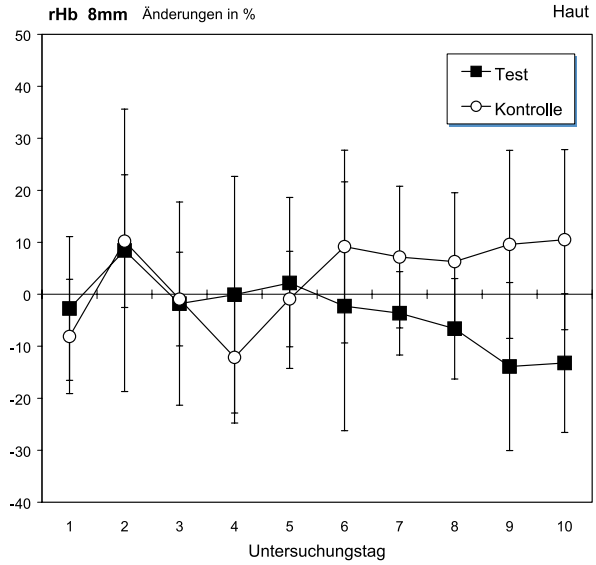

Abbildung 3b.
Meßwerte zum Merkmal „Relative Hb-Sättigung im Bereich des mikrovaskulären Netzwerkes, rHb" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (8mm Eindringtiefe, subkutanes Fettgewebe) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

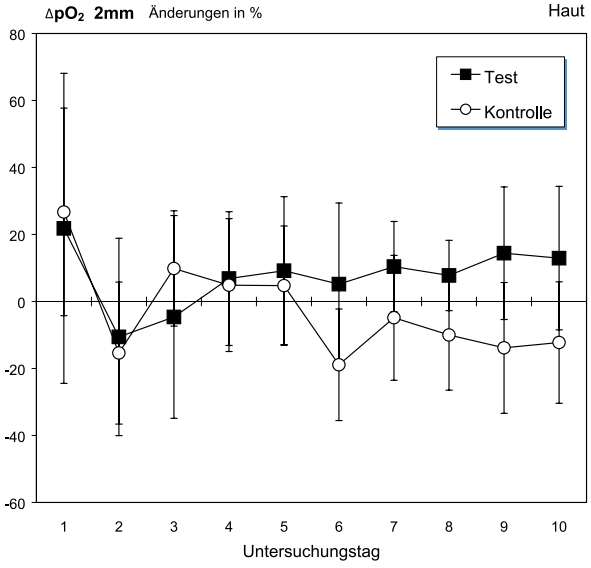

Abbildung 4a.
Meßwerte zum Merkmal „Venolenseitige Sauerstoffausschöpfung ΔpO_2" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (2mm Eindringtiefe, Subkutis) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

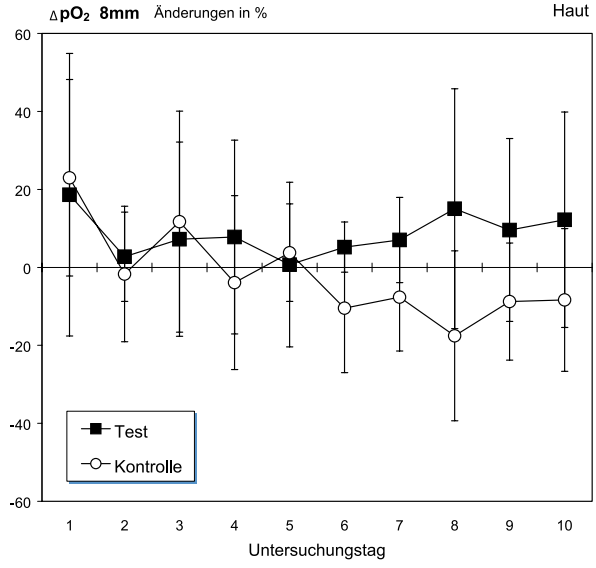

Abbildung 4b.
Meßwerte zum Merkmal „Venolenseitige Sauerstoffausschöpfung ΔpO_2" (Mittelwerte und Standardabweichungen) im Targetgewebe Bauchhaut (8mm Eindringtiefe, subkutanes Fettgewebe) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

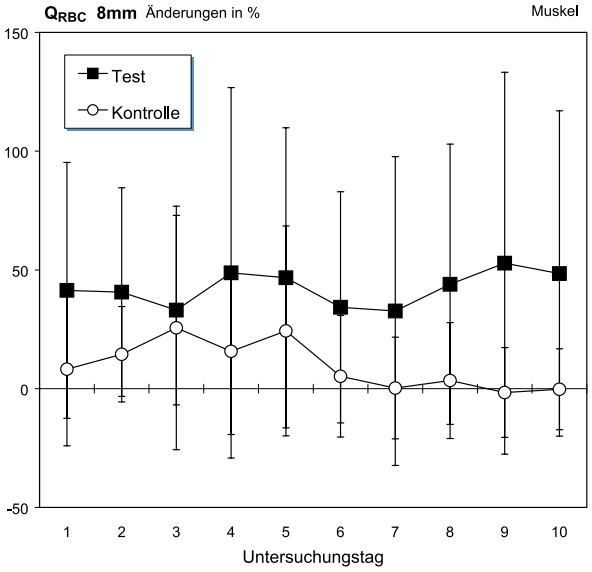

Abbildung 5.
Meßwerte zum Merkmal „Mittlerer Ströungsfluß der roten Blutzellen im mikrovaskulären Netzwerk, QRBC" (Mittelwerte und Standardabweichungen) im Targetgewebe Wadenmuskulatur (8mm Eindringtiefe, Skelettmuskulatur) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

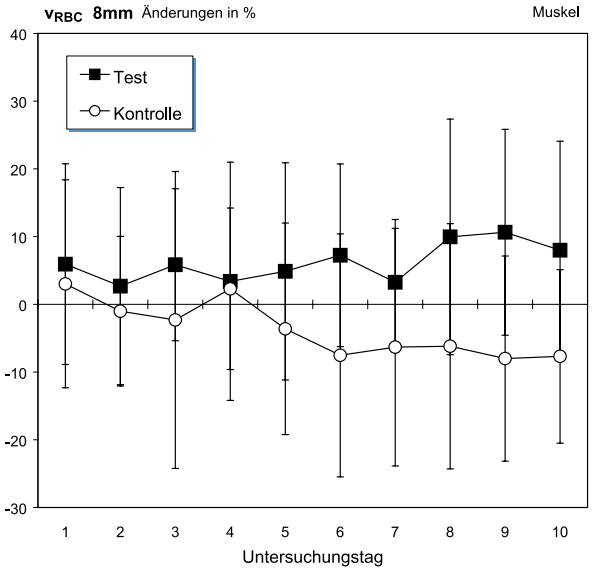

Abbildung 6.
Meßwerte zum Merkmal „Mittlere Ströungsgeschwindigkeit der roten Blutzellen im mikrovaskulären Netzwerk, vRBC" (Mittelwerte und Standardabweichungen) im Targetgewebe Wadenmuskulatur (8mm Eindringtiefe, Skelettmuskulatur) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

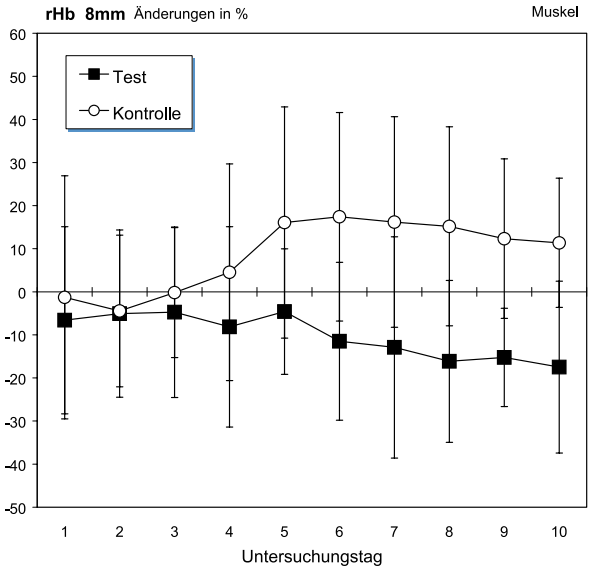

Abbildung 7.
Meßwerte zum Merkmal „Relative Hb-Sättigung rHb" (Mittelwerte und Standardabweichungen) im Targetgewebe Wadenmuskulatur (8mm Eindringtiefe, Skelettmuskulatur) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

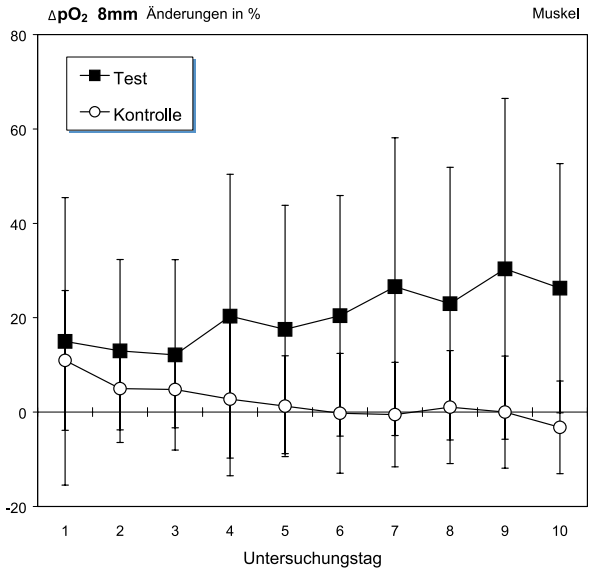

Abbildung 8.
Meßwerte zum Merkmal „Venolenseitige Sauerstoffausschöpfung ΔpO_2" (Mittelwerte und Standardabweichungen) im Targetgewebe Wadenmuskulatur (8mm Eindringtiefe, Skelettmuskulatur) bei Kontrolle und Test-Gruppe. Ordinate: Prozentuale Änderungen im Vergleich mit den Ausgangswerten. Abszisse: Meßzeitpunkte 1. Tag bis 10. Behandlungstag.

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HEPATOPROTECTION AGAINST CHEMICAL INFLUENCE: COMPARATIVE EFFECTS 5-HYDROXY-6-METHYLURACIL (OXYMETHYLURACIL), COMPLEX COMPOUND «OXYMETHYLURACIL + SODIUM SUCZINATE» AND SILIMARINE

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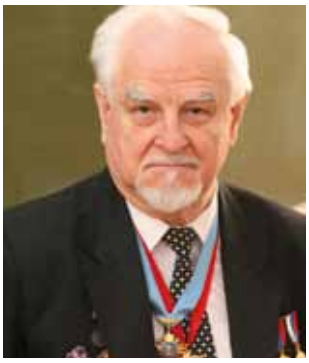
ABSTRACT
Experimental data on comparative hepatoprotective activity of 5-hydroxy-6-methyluracil (oxymethyluracil), complex compound «oxymethyluracil + sodium suczinate» and referent hepatoprotector silimarine have been analyzed and systematized. On the models of liver affection by industrial toxicants – tetrachlormethane, dichlormethane, PCB-containing drug "sovtol-1", 2,4-dichlorphenol, trichlormetafosis and ethanol it was established that oxymethyluracil has a pronounced hepatoprotective influence comparable in its effectiveness with that of silimarine and excels it on the models of liver affection by dichlormethane, trichlormetafosis and ethanol. On the model of liver affection by combination of sovtol and ethanol complex compound «oxymethyluracil + sodium suczinate» proved effective. The data obtained allows to make the conclusion that oxymethyluracil is the drug for which hepatoprotective activity may have an independent clinical significance.

KEYWORDS — hepatotoxicants, hepatoprotectors, toxic hepatopathy, toxic hepatitis, cirrhosis of liver, effectiveness index, oxymethyluracil, silimarine, fermentative markers, functional markers.

1. OXYMETHYLURACIL: ACTIVE MECHANISM AND PHARMACOLOGICAL PROPERTIES

Oxymethyluracil 5-hydroxy-6-methyluracil stimulates the immunity, regenerative processes, has anabolic and anticatabolic effect, activates bioenergetical processes, some ferments of antioxidant protection, suppresses alteration and exudation, regulates the processes of lipids peroxide oxidation, stabilizes cell and organelle membranes, intensifies ATPase activity, performs the function of «radicals trap», protects the biostructures against active forms of oxygen and toxic peroxide compounds. The drug has antioxidant activity, stimulates nonspecific resistance of organism, exerts nootropic, cardio-protective, stress-protective and demethemoglobinising influence (table.1). Previously oxymethyluracil proved to have therapy and preventive effect after bad acute poisoning by chemical substances having neuro-toxic, hemo-toxic and hepato-toxic effect. The drug revealed positive effect being applied as a corrective remedy against side effects of cholinolitic drugs, cholinesterase reactivators, strofantine, digoxine, corasole, etc [4,10].

Prof. V. Myshkin



Prof. D. Enikeev

OXYMETHYLURACIL HAS IMPORTANT PHARMACOLOGY PROPERTIES [4], OXYMETHYLURACIL:

- low-toxic drug without allergic, mutagenic and carcinogenic effect;
- no arrhytmogenic or negative effect at the heart conductive system,
- no general toxic effect;
- when injected in enteral or parenteral way it produces cardiotonic effect, does
- not change the heart rate;
- eliminates depression of heart rate function on the models of experimental myocardial infarction caused by left coronal artery blocking and theophylline-adrenaline myocarditis;
- in therapeutic doses does not change the left ventricle rate phase structure, in two or three times higher doses prolong expulsion phase, shorten

Table 1. *The Action Mechanism and Pharmacology Characteristics of Oxymethyluracil [2–11]*

1. Possible primary action mechanism: Free-radical oxidation inhibition RNA-polymerase activation Right protective influence on membrane Uridinephosphatase blockade **2. Protective and recovery mechanism:** Protection against active forms of oxygen and peroxide compounds Activation of antioxidant ferments (catalyze, SOD) activity Stabilization of cell, subcell membranes Rise of ATPase activity Rise of SDG , NADN-Dg activity Activation of adaptive synthesis of PNA and proteins Alteration and exudation suppression Reparation processes stimulation Demethaemoglobinising effect Rise of cAMPH	**3. Pharmacology effects spectrum:** Antioxidant effect Immunity stimulating effect Antitoxic effect Antiseptic effect Anabolic effect Anti-catabolic effect Rise of the organism non-specific resistance Hepato- and pancreas-protective effect Stress-protective effect Radio-protective effect Membrane-protective effect antispasmodic activity cardioactive effect nootropic activity actoprotective effect

isometric contraction phase with dogs;
- does not change arterial or perfusion pressure under intravenous injection with cats;
- does not influence the bronchus tone or bronchus spasm caused by carbacholine and proserine;
- has some antispasmodic effect on smooth musculature of intestine;
- shortens the latent period of motor-defense conditioned reflex with rats and inhibits its extinction;
- rises motor activity of rats and mice, prolongs the duration of rats' stereotype behavior caused by injection of phenamine;
- rises actoprotective activity of ethimizol, inhibits the extinction of chronic fatigue;
- does not change the coordination of movements;
- does not cause pronounced biochemical changes or changes in blood cell structure;
- compatible with a lot of drugs, used in complex therapy of intoxication (including cholinolitics, cholinesterase reactivators, methylene blue, cystamin, etc.)

Oxymethyluracil and oxymethyluracil sodium suczinate were synthesized by Ch.D. Krivonogov V.P. in Organic Chemistry Institute of Ufa Science Center of Russia Academy of Science.

According to the Order N 302 from July 29, 1996 of Minister of Health and Medical Industry of the Russian Federation the oxymethyluracil drug is allowed for medical practice and industrial output [13].

2. MODELS AND METHODS OF INVESTIGATION

Damage of liver was modeled by injections of hepatotoxicants to white he-rats in the following doses:

tetrachloromethane: 2 ml per 1kg of the body weight every other day within 30 days period;

dichloroethane: 0.01 DL/50 during 3 weeks in 10% olive oil solution;

sovtol-1: 0.25 ml per 100g of the body weight twice a week within 28 days + 10% ethanol solution for drinking (Patent of the Russian Federation № 2197018 from 16.02.2000);

2,4-dichlorphenole: 400 ml per 1kg of the body weight (0.8 DL/50);

ethanol: 7 ml per 1kg of the body weight daily within 30 days period;

trichlormethafos: 47 mg per 1kg (0.2 DL/50) daily within 28 days period.

Complex of biochemical investigation included total protein determination (g/l), cholesterol (in mmole/l), triglyceride (in mmole/l), bilirubin (in mcmole/l), ferments activity: urokaninase (UrN) (in nmole/t.s.), alaninaminotranspherase (AlAt in mmole/t.s.), aminotranspherase aspartat (AsAt in mmole/t.s.) and alkaline phosphatase activity (AP in mmole/t.s.).

Biochemical investigation of blood serum was carried out with biochemical analysator «Encore» (Austria). The estimation of oxymethyluracil and comparative drug (cilimarine) hepatoprotective effect was carried out by defining the index of effectiveness of hepatoprotective effect of investigated drugs – EI (in %) – difference in shares between index of liver damage level in the control group and in the group of animals, which took the drugs under investigation. EI of hepatoprotective effect was determined according to the following formula:

$$EI = (Ic - Ie)/Ic \cdot 100$$

where Ic and Ie — mean values of indices in control and experimental groups correspondingly.

EI was calculated separately according to functional indices data (general bilirubin, total protein, cholesterol and triglycerides) and to liver damage fermentative markers indices (UrN, AlAt, AsAt, AP).

EI positive meaning (plus-effect) points to damage index decrease.

EI negative meaning (minus-effect) points to damage index increase.

The estimation of results was made with the help of Student-Fisher parametrical test.

Oxymethyluracil and cilimarine were injected in equal doses of 50 mg/kg intra-gastric1,5 hours before toxicant.

3. HEPATOPROTECTION WITH THE USE OF OXYMETHYLURACIL, COMPLEX COMPOUND «OXYMETHYLURACIL + SODIUM SUCZINATE» AND SILIMARINE

Since the time of the first pyrimidines introduction into the practical medicine there were attempts to use them as hepatoprotectors. New pyrimidine derivative – oxymethyluracil attacted our attention due to its distinct antioxidant properties, which were revealed in V.A.Myshkin's special investigations [2,7].

It is stated that oxymethyluracil does reveal itself as hepatoprotector on the models of liver affection by industrial toxicants [models 1, 2, 3, 4, 6], as well as ethanol [model 5], (table 2). It reveals itself in real decrease of marked ferments of citolyse and cholestasis level, and also in normalization of bilirubine, cholesterol and triglycerides level. Rise of total protein level in the blood serum indicates the preservation of protein synthesizing liver function under oxymethyluracil. Silimarine proved less effective in this connection on the models of liver affection by tetrachloromethane, sovtol-1 and trichlormethafos, that is confirmed by corresponding EI indices EI (Table 2).

The comparison of oxymethyluracil and silimarine hepatoprotective effect EI drives us to the conclusion that oxymethyluracil does not yield to silimarine in its ability to normalize biochemical indices in rats' blood serum, and consequently the functional and metabolic state of liver when it is damaged by the investigated hepatotoxicants.

The results of previously carried out morphometrical and histachemical investigation of rats' liver correspond to biochemical data and indicate of much less degree of necrotic changes, lipidosis and granular dystrophy with rats which was given oxymethyluracil along with intoxication by 2-dichloroethane, tetrachloromethane sovtol-1, 2,4-dichlorphenole, orthochlorphenole and ethanol [2, 5, 12], beam-like structure of the organ is better preserved and activation of liver regenerative processes is more pronounced.

Specialists in the sphere of toxicology and ecopathology may take interest in the data on oxymethyluracil hepatoprotective effect (OMU) acquired during the experiments on the models of liver affection with PCB-containing drug "sovtol-1" and «sovtol-1 + ethanol» composition (Table 2, 3). Nowadays over 200 000 transformers and condensers containing about 18 000 tons PCB oils [15] are known to be in exploitation and in reserve.

Table 2. *Indices of effectiveness (EI) of oxymethyluracil (I) and silimarine (II) hepatoprotective effect calculated according to fermentative and functional markers of liver damage caused by hepatotoxic substances**

N	Hepatotoxicants	EI (%)			
		Fermentative markers		Functional markers	
		I	II	I	II
1	Tetrachloromethane	+29.9	+36.2	+33.2	+27.6
2	2- dichloroethane	+38.9	-	+41.0	-
3	Sovtol-1	+15.47	+11.7	+24.4	+5.8
4	2,4-dichlorphenole	+16.02	-	+17.8	-
5	Ethanol	+28.5	+15.5	+14.4	+15.7
6	Trichlormethafos	+33.3	+26.2	+35.9	+9.8

Note: ** — Calculated according to data [2, 3, 4, 5, 6, 7, 8, 9, 11]*

Table 3. *Hepatoprotective effectiveness indices (in%) of complex: «oxymethyluracil + sodium suczinate» (I), oxymethyluracil (II) and sodium suczinate (III), calculated according to functional markers of liver affection by PCB-containing drugs «sovtol-1» and «sovtol-1 + ethanol» [8, 14].*

Hepatotoxicants	EI (%)		
	I	II	III
Sovtol-1	+ 33.13	+ 19.9	+ 5.7
Sovtol-1+ethanol	+ 29.3	+ 12.6	+ 3.9

On the models of liver affection with PCB-containing drug "sovtol-1" and «sovtol-1 + ethanol» composition there was investigated the effect of complex drug: «oxymethyluracil + sodium suczinate» which was synthesized in OCI of RAS Ufa Scientific Centre.

Sovtol poisoning of animals causes acute affection of liver, its main symptoms are cytolysis, fibrosis and cirrhosis. In histologic liver drugs the fibrosis fields occupies 3,1% of environment (against 0,5% with healthy rats). Hepatocytes are located mainly in periportal zone, which is in the state of protein and lipid dystrophy. Decomplectation of liver beams and proliferation of connective tissue in portal tract with fibrous bands deep into lobes can be determined. In the field of vi-

sion there are a lot of necrotized hepatocytes, oedema and stroma loosening; in cellular infiltrate there are lymphocyte clusters.

Morphometry of liver drugs revealed lowering of nuclear-cytoplasmic ratio of stroma to parenchyma.

There were revealed pronounced metabolic and functional problems: the rise of concentration of POL-level products of isolated double links, diene conjugates, triene conjugates, and also glycosaminoglycan in liver tissue. Besides the concentration of oxyprolin in acid soluble and acid fast collagen fractions increases. In blood serum there is revealed the rise of activity of marked urokaninase ferments, AlAt, AcAt, acid phosphatase, alkaline phosphatase and lactic dehydrogenase [6, 9].

Under the influence of oxymethyluracil and especially «oxymethyluracil + sodium suczinate» complex the liver architectionics was obviously improved: the lobes beam-like structure and their right radial direction was partially restored. The level of dystrophy became less distinct: clusters of glycogen containing lobes were preserved, lipid dystrophy was less pronounced, though the signs of hepatocytes protein dystrophy remained, they were not so distinct as in control.

Judging to the effect on the value of indices which reflect the functional state of liver (general bilirubine, total protein, cholesterol, triglycerides) the maximum effect was achieved at using «oxymethyluracil + sodium suczinate» complex, when effectiveness index was + 33.13%, less pronounced results were achieved at using oxymethyluracil (+ 19.9%) and especially sodium suczinate (+ 5.7%), On the model of liver affection by «sovtol + ethanol» the maximum hepatoprotective effect was achieved at using the oral «oxymethyluracil + sodium suczinate» complex and was only 29.3%. The effect of oxymethyluracil and suczinate was still lower and made 12,6% and 3,9% accordingly [table 3].

We believe that using of oxymethyluracil together with the known hepatoprotectives aimed at increasing their effectiveness is not deeply investigated but rather perspective as OMU rises the effectiveness of many famous drugs and at the same time lessens their toxic effect, undesirable consequences and rises tolerance [4,10]. In conclusion we present Table 4 in which we tried to systematize our aspect of this problem.

Table 4. *Empirical expediency of oxymethyluracil and hepatoprotectives combination in case of liver toxic affect*

Hepatoprotectives	Oxymethyluracil
Drug of animal origin (hepatosan)	–
Artichoke leaves extract	±
Tykveol	±
Liv 52	±
Essenciale phosphor lipids	+
Lipoic acid	+
Ursofalk	+
Hepa-maerz	+
Lactulose	+
Heptral	+
Metadoxile	±
Hepabens	–

Note: *+ combination is possible*
± expediency of combination is doubtful
– combination is not expedient

CONCLUSIONS

1. Oxymethyluracil shows a pronounced hepatoprotective effect on the models of liver affection with tetrachloromethane, dichlorethane, ethanol, trichlormethafos.
2. Hepatoprotective effect of oxymethyluracil on the models of liver affection with tetrachloromethane, dichlorethane, ethanol, trichlormethafos and also PCB -containing drug «sovtol-1» is revealed in prevention of hyperfermentation, normalization of bilirubin, cholesterol, total protein and triglyceride level.
3. Oxymethyluracil is not inferior to standard hepatoprotective silimarine in its pronounced hepatoprotective effect on the models of liver affection with tetrachloromethane sovtol-1, ethanol and trichlormethafos.
4. Complex compound: «oxymethyluracil + sodium suczinate» has more pronounced hepatoprotective effect than oxymethyluracil and sodium suczinate on the models of liver affection with PCB -containing drug sovtol-1 and its combined affection with «sovtol-1 + ethanol».

PRACTICAL RECOMMENDATIONS

1. The using of oxymethyluracil as hepatoprotective is approved in the cases of subacute intoxications with tetrachloromethane, 2-dichlorethane, sovtol, ethanol, trichlormethafos, and also in the cases of acute intoxication with 2,4-dichlorphenole.
2. Investigations of hepatoprotective effect of oxymethyluracil combinations with suczinate-containing drugs as well as with drugs having presumably detoxical effect like hepa-maerz, glutargine, ademethionine, metadoxile, etc. can be considered reasonable.

3. Investigations on synthesis of new oral and parentheral complex compounds of oxymethyluracil and suczinate can be considered perspective.

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ERFAHRUNGEN MIT INTRATHEKALER BACLOFENTHERAPIE BEI 2 SCHLAGANFALLPATIENTEN

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EINLEITUNG

Physio- und Ergotherapie, serielles Casting sowie Medikamente (orales Baclofen, Tolpersison, Tizanidin und Benzodiazepine) werden bei spastischer Muskeltonuserhöhung nach Schlaganfall, Schädelhirntrauma und cerebraler Hypoxie erfolgreich eingesetzt. Darüber hinaus hat sich die Chemodenervation mit Botulinumtoxin Typ A bewährt, vor allem in Fällen einer fokalen spastischen Muskeltonuserhöhung. Bei Patienten die nach Schlaganfall, traumatischer Hirnverletzung oder cerebraler Hypoxie eine schwere generalisierte spastische Muskeltonuserhöhung erleiden und sich keine ausreichende Minimierung mit den erwähnten Behandlungsmaßnahmen erreichen lässt, einschließlich nicht tolerierbarer Nebenwirkungen der oralen Medikation und der Chemodenervation mit Botulinumtoxin Typ A, kann die intrathekale Baclofentherapie wirksam angewendet werden. Meythaler et al beschrieb als erster die Verwendung der intrathekale Baclofentherapie (ITBTherapie) bei Patienten mit spastischer Muskeltonuserhöhung. Er konnte eine signifikante Reduktion der Spastik in den oberen und unteren Extremitäten zeigen, ohne Beeinträchtigung der Muskelkraft der nicht betroffenen Extremitäten.

Eine weitere Untersuchung konnte zeigen, dass die ITB-Therapie in Kombination mit Physiotherapie, die Gehgeschwindigkeit und die funktionelle Mobilität verbessert (Francisco und Boake). Eine andere Studie mit 94 Patienten konnte eine signifikante Verbesserung der motorischen Fähigkeiten, der Lebensqualtität (Qualtity of Life – QOL) und der Spastik, 3 und 12 Monate nach der Implantation einer Baclofenpumpe beschreiben (Ivanhoe et al). In allen Studien konnte eine sichere Wirksamkeit dieser Behandlungsmöglichkeit dokumentiert werden. Es besteht der medizinische und wissenschaftliche Anspruch bei dieser komplexen Störung und den funktionellen Verbesserungen im Verlauf, geeignete Testverfahren einzusetzen, die ein genaues Abbild der funktionellen Veränderungen widerspiegeln und für einen objektiven Vergleich zwischen verschiedenen Rehabilitationsprogrammen und -kliniken geeignet sind. Hierbei steht die realistische Formulierung von Zielen mit Focus im Bereich Beeinträchtigung (impairment) und Aktivität (activity) gemeinsam mit dem Patienten im Vordergrund und wird in der international angewendeten Form einer Zielerreichungsskala (Goal Attainment Scale – GAS) durchgeführt (Joyce BM et al und Smith A et al).

MATERIAL/METHODE

Das Ziel dieser Anwendungsbeobachtung [positives Ethikvotum der LÄK Brandenburg v. 23.08.2011, S 17(a)2011)] war es, mit geeigneten Tests in Abhängigkeit von der Zielerreichungsskala, passive und aktive Funktionsveränderungen im Bereich der betroffenen oberen und unteren Extremitäten zu beschreiben.

Diese Anwendungsbeobachtung gliedert sich in 3 Visiten, wobei die Visiten T0 und T2 identisch sind. Die Visite T1 dient einer kurzen Dokumentation der spastischen Muskeltonusveränderung und Schmerzbeurteilung unmittelbar nach der Titrationsphase der Implantation einer Baclofenpumpe. Die einfachen und für den Patienten nicht belastenden Untersuchungen wurden in der Neurologischen Rehabilitationsklinik Beelitz-Heilstätten oder der ambulanten Versorgung durchgeführt. Es ist die z.Z. gängige Praxis, um in einer multiprofessionellen Anwendung ein optimales Ergebnis nach Implantation zu erreichen, dass die Patienten nach der Implantation der Baclofenpumpe, einer 2–3 wöchigen stationären Rehabilitation zugeführt werden.

In dieser Anwendungsbeobachtung konnten 2 Patienten aus der stationären und ambulanten Rehabilitation eingeschlossen werden. Sie waren über 18 Jahre und erfüllten verschiedene definierte (siehe unten) Ein- und Aussschlusskriterien. Im Rahmen der notwendiger Visiten sowie einer fakultativen follow-up Beurteilung von Langzeiteffekten, wurden auch ambulante Besuche durchgeführt. Invasive Untersuchungsmethoden werden bei diesen Visiten nicht durchgeführt.

EINSCHLUSSKRITERIEN:

- Der Patient ist über die Studie aufgeklärt worden, ihm wurden alle Fragen beantwortet, er hatte ausreichend Bedenkzeit (24 Stunden) und er hat die Einwilligungserklärung unterschrieben.
- Der Patient ist 18–75 Jahre alt.
- Der Schlaganfall, das SHT oder die cerebrale Hypoxie liegen mehr als 6 Monate zurück.
- Der Wert der modifizierten Ashworth Skala beträgt ≥ 3 in mindestens zwei der betroffenen Gelenke in der unteren Extremität.
- Der Patient ist geeignet für die ITB-Therapie, eine ausreichende Minimierung der Spastik konnte bisher weder durch eine orale antispastische Medikation oder durch eine Botulinumtoxininjektion erreicht werden.
- Stabile Blutdruckwerte
- Weibliche Patienten müssen für die Dauer der Anwendungsbeobachtung entweder postmenopausal oder chirurgisch sterilisiert sein oder medizinisch sichere Verhütungsmittel verwenden.
- Der Patient oder seine Familie sind bereit, das Protokoll der Anwendungsbeobachtung einzuhalten.

AUSSCHLUSSKRITERIEN:

- Der Patient oder seine Familie sind nicht bereit oder in der Lage an der Beobachtungstudie teilzunehmen (Minimental Status Test <23).
- Der Patient reagiert allergisch auf Baclofen.
- Der Patient hat eine systemische Infektion.
- Der Patient hat einen Herzschrittmacher, einen Neurostimulator oder eine Liquordrainage.
- Der Patient hat eine nicht zu kontrollierende refraktäre Epilepsie.
- Der Patient ist schwanger oder stillt ein Baby.
- Der Patient erhielt eine Botulinumtoxininjektion vor weniger als 4 Monaten.

UNTERSUCHUNGSABLAUF

T0:

Enrollment / Baseline Assessment, Untersuchung von Beeinträchtigung (impairment) und Aktivität (activity) nach positiver Testung für eine Baclofenpumpenimplantation.

Folgende Untersuchungen und Tests wurden durchgeführt:

Klinische Untersuchung / Neurologischer Befund NIH-Stroke-Scale

Beeinträchtigung (Impairment)

- mAS (Modified Ashworth Scale)
- PROM (Passive Range of Motion)
- numerische 11-point box scale (BS-11) für die obere Extremität
- Esslinger Transferskala
- FAC (Functional Ambulation Category)

Aktivität (Activity)

- B&BT (Box and Block Test)
- ARAT (Action Research Arm Test)
- NHPT (Nine Hole Peg Test)
- 10-Meter-Gehtest

Lebensqualtität

- EQ5D (EuroQuality of life-5D, Patient)

Gesamtbewertung und Zielerreichung

- GAS (Goal Attainment Scale, Zielerreichung)
- GRS (Global Rating of Response))

T1:

Untersuchung der spastischen Muskeltonusveränderung und Schmerzbeurteilung innerhalb von 4 Wochen nach Implantation und Abschluss der Titrationsphase.

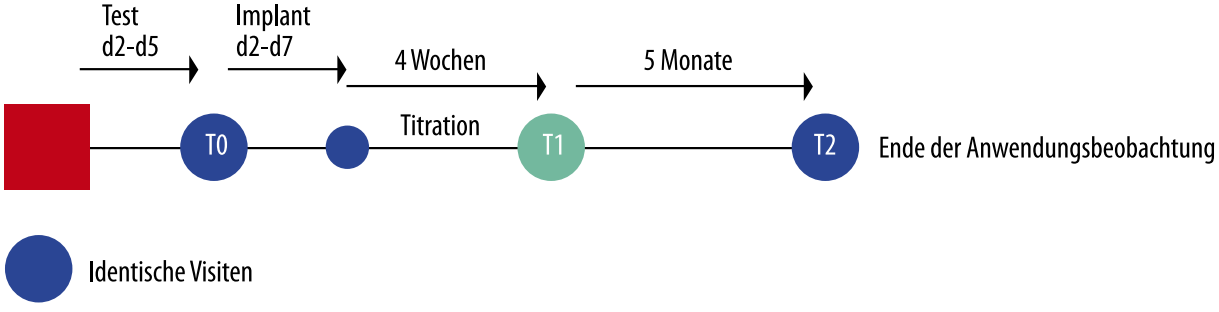
Folgende Tests wurden durchgeführt:

- mAS (Modified Ashworth Scale)
- PROM (Passive Range of Motion)
- numerische 11-point box scale (BS-11)

T2:

5 Monate nach Visite T1, sie beinhaltet die follow up Beurteilung und ist identisch mit der Visite T0.

STUDIENDIAGRAMM:



ERGEBNISSE

Verlaufsprotokoll

Tabelle 1. *Verlaufsbewertung; GAS , GRS, Esslinger Transferskala, FAC, 11-point box scale und MAS*

	T0	T2
GAS Pat. 1	Ziel : 10-Metergehzeit ≤ 17 s Wert vor Implantation: 23 s	Wert am Ende: 21 s
GAS Pat. 2	Stand mit Festhalten	Stand im hohen Gehwagen, schmerzfrei mit 4 m Gehstecke
GRS Pat. 1		leichte Verbesserung
GRS Pat. 2		starke Verbesserung
Esslinger Transferskala Pat. 1	H1, Transfer mit spontaner Laienhilfe	H0, keine Hilfe
Esslinger Transferskala Pat. 2	H0, keine Hilfe	H0, keine Hilfe
FAC Pat. 1	FAC 4	FAC 4
FAC Pat. 2	FAC 0, nicht gehfähig	FAC 1, Abhängigkeitsstufe II
11-point box scale Pat. 1	8	8
11-point box scale Pat. 2	6	5
MAS untere Extremität Pat.1	3	2
MAS untere Extremität Pat.2	4	0

DISKUSSION

Diese Untersuchung zeigt bei Pat. 1 eine leichte Verbesserung und bei Pat. 2 eine gute Verbesserung bei der funktionellen und passiven Beurteilung bei einer schweren generalisierten Spastik nach Schlaganfall mit einem langjährigen Verlauf vor Pumpenimplantation. In weiteren Studien sollte dieser positive Effekt an einer größeren Fallzahl sowie die Nachhaltigkeit dieses Effektes außerhalb der stationären Rehabilitationsbehandlung im ambulanten Langzeitverlauf untersucht werden.

CURRENT INPATIENT TECHNOLOGY IN THE SUCCESSFUL OPERATION OF CHILD OUTPATIENT SURGERY CENTERS, TRAUMA-ORTHOPEDICS

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ABSTRACT

In this paper we present the scientific and organizational concept of the children's outpatient surgery centers operating in the N.F. Filatov Child Clinical Hospital № 13 in Moscow since 1992. The Center includes: Surgical hospital one day (pillar), consultative-diagnostic department, outpatient department of orthopedics department treatment of benign tumors, uroandrologichesky module. In accordance with the directions of the Centre's main divisions flows of patients with the following disorders : Routine surgical pathology, pathology of the musculoskeletal system, benign tumors and scarring of the skin and soft tissue purulent-inflammatory diseases, diseases of the reproductive organs (uroandrologiya). In medical-diagnostic process, we distinguish three phases: pre-hospital, hospital and post-hospital. Bandwidth Branch hospital stay is currently about 2,300 patients a year, performed more than 2,000 surgical procedures performed about 5000 consultations. Formation of patient flows for outpatient or inpatient treatment occurs in the primary treatment of patients. The department advises employees Departments of Pediatric Surgery RNRMU of N.I. Pirogov Hospital and doctors. In the year a total of about 20,000 held consultations. Important section of consultative and diagnostic services, as is the aftercare and follow-up of the operated patients. A multidisciplinary approach reveals not only the main cause of the disorder, but also to develop a reasonable treatment option pathogenesis. The ultimate goal of the treatment program is the social department and functional rehabilitation of the patient. On subsequent follow-up of 18 years. Hospital-complex is a scientific and educational base RNRMU of N.I. Pirogov where trained senior students, interns and residents. Specialized pediatric surgeons, urologists, andrology, orthopedics, traumatology. Total number of students of five hundred people. Past experience has been successfully applied in many areas, including on the basis of departmental medical facilities.

KEYWORDS — Outpatient Surgery Center, inpatient technology, pediatric surgery, outpatient orthopedics.

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One of the urgent problems of modern pediatric surgery is the organization of high quality care for children in an outpatient setting. Our more than 25 years of experience in the development of ambulatory surgery Filatov's hospital showed that the most appropriate structure swarm providing outpatient surgical intensification by power is an outpatient surgery center (OSC) with day surgery hospital, where you can perform many types of surgical benefits including the operation of medium difficulty. The main tasks of OSC, you can specify following: early detection and treatment of patients with surgical diseases and orthopedic pathology, development and introduction of new methods of treatment of, and studying the immediate and long-term results. Thus, OSC should be

considered as therapeutic and preventive unit consisting of a multidisciplinary treatment facility designed to assist surgical patients in an outpatient setting.

Nosological framework defining priority for ambulatory surgical pathology, it should be noted two possible treatment options: a full and complete partial landmark. The first option is a radical surgical treatment within the outpatient management of the patient, including all the necessary manipulations which result in the recovery of the patient and its removal from the dispensary. The second option involves landmark outpatient aftercare as stationary after surgery, and between hospitalizations with prolonged multistage embodiment, correction of pathological states. This group brings together patients with hospital surgical clinic outpatient surgery center and orthopedics hospital-based modern technology. For both groups of patients is an important step in defining the scope of treatment, and if the first group can be guided by a clear sequence of actions, in the second group have to make decisions on the actual condition of the patient at the time of inspection.

In this paper we present the scientific and organizational concept of the children's outpatient surgery centers operating in the Children's City Clinical Hospital № 13. NF Filatov Moscow since 1992. The Center includes :

– Surgical hospital one day (pillar)
– Consultation and diagnostic department
– Branch outpatient orthopedics
– Separate treatment of benign tumors
– Uroandrological module

In accordance with the directions of the Centre's main divisions flows of patients with the following disorders :

1. Routine surgical pathology
2. Pathology of the musculoskeletal system
3. Benign tumors and scarring of the skin and soft tissues
4. Purulent-inflammatory diseases
5. Diseases of the reproductive organs (uroandrologiya)

All surgical procedures are performed in the hospital one day, which was organized in our hospital in January 1985 and was the first such institution in the USSR children. The Department of hospitalized children with the following diseases : the anterior abdominal wall hernia, hydrocele and cysts egg shells and spermatic cord, phimosis, cryptorchidism, orthopedic pathology: hip dysplasia of varying severity, congenital clubfoot-syndromic concomitant orthopedic pathology, as well as soft tissue benign small sizes. The main stream (59%) were patients with pathology of the vaginal process of the peritoneum.

In medical-diagnostic process, we distinguish three phases: pre-hospital, hospital and post-hospital.

A crucial point in the prehospital phase is the careful selection of patients, which is carried out at a consultative reception. Developed a special algorithm for selection of patients for surgical treatment at the Children's Hospital Surgical night stay. The algorithm provides for the evaluation of psycho-emotional status of parents and physical condition of the patient. Based on the correct selection of about 95% of the children of the number who applied, were successfully operated on an outpatient basis. The rest was recommended treatment in an elective surgery hospital.

Bandwidth department is currently about 2,300 patients a year, performed more than 2,000 surgical procedures performed about 5000 consultations.

Child's stay in the hospital one day does not exceed 3.5 hours, during which time he gets the entire spectrum of diagnostic and treatment facilities, including hospitalization, inspection, operation, inspection and postoperative discharge. Further observation of the patient is carried out on post-hospital stage. Parents are given the necessary recommendations for care. On the 1st postoperative day children are invited to re-examine, in which parents receive recommendations for the future. In the last 15 years, we have completely abandoned the removal of sutures, as use intradermal cosmetic suture absorbable material (polyglycolide 4/0). If the patient needs further observation, we spend it yourself. Thus, a child undergoing treatment at a surgical hospital one day, gets the whole range of therapeutic and diagnostic activities, from establishing a correct diagnosis until complete recovery, including surgery.

Also, in an outpatient surgery center treats children with congenital fistulas pararectal. The basis of treatment is sclerotherapy technique. Sclerotherapy produce 1 times a day, every day, regardless of the period of existence of the fistula and the presence of purulent discharge. The process of sticking walls fistula is sufficiently fast and ends substantially between 8 - 15 administration (87% of patients). In 13 % of patients to eliminate fistula requires from 16 to 22 daily injections of 10 % alcohol solution of iodine.

Formation of patient flows for outpatient or inpatient treatment occurs in the primary treatment of patients. The department advises employees Departments of Pediatric Surgery RNRMU of N.I. Pirogov Hospital and doctors. Consultations are held on the following areas:

1. Urology-Andrology
2. Proctology
3. Plastic and Vascular Surgery
4. Thoracic Surgery

5. Neonatal surgery
6. Traumatology

Held every year around 20,000 consultations. Important section of consultative and diagnostic services, as is the aftercare and follow-up of the operated patients.

The department treatment of benign tumors of about 10,000 calls a year falls on patients with hemangiomas, papillomas, pigmented nevi, angiofibroma and other benign tumors. In -patient treatment of this group of patients is widely used modern cryosurgical, radiosurgery modes coagulation and destruction, as well as depending on the speed of blood flow (less than 30 cm/s) in the hemangioma, which can be visualized by ultrasound with dopplerography sclerotherapy performed with the introduction of formations sclerosants interstitially in benign tumor (alcohol-novocaine mixture 700, Fibro-Vein 3%). We can not say about the introduction of our practice of modern surgical lasers, which have been shown excellent cosmetic results in the shortest time.

Application of modern technology opens up new possibilities of diagnosis and treatment of complex patients, including young children. Using ultrasound with color Doppler mapping can determine the velocity of blood flow in the vessels of the hemangioma, allowing you to choose the tactics of treatment from various kinds of conservative to operative. Especially impressive results in our clinic has been achieved in the treatment of hemangiomas complex anatomical localization. Method of treatment is the combined use of embolization of the vessels feeding angioma and microwave destruction in the last 2 years in the correction of this pathology is widely used laser vaporization. Such patients undergo inpatient treatment in microsurgery department of our hospital. Staged outpatient aftercare is carried out on the basis of an outpatient surgery center, or interhospital being the final stage of complex treatment process. In this case, we are talking not about inpatient and about impationt technologies.

Outpatient stage treatment of keloid scars, based on microwave destruction, has been used successfully by us and is an alternative to surgical treatment. Currently we are using a new generation of equipment that allows a greater volume to destroy abnormal tissue in a shorter period of time.

Quite successfully applied in our clinic, the method of tissue expansion (balloon dermotension) with expanders for treating such types of diseases, as alopecia, deformations or defects of the abdominal wall and the front limbs, with an elongation of the facial nerve, as well as the formation of the expanded bladder ureter. Expander — a device for the temporary implantation under the skin, which gradually increases in size due to its filling with liquid, and thus, stretches the tissue located above it. After obtaining sufficient material expander is removed, and the resulting supply of fabrics used for plastics. Actually dermotension can be performed entirely in an outpatient surgery center.

Orthopedics outpatient department is important, integral link of our Center. Uptake of the year is more than 10,000 children. Patients receiving treatment with a wide range of orthopedic pathology, plaster work carried out varying degrees of complexity, minimally invasive surgery. Developed a set of differential diagnostic criteria of congenital and acquired diseases of the hip joints in young children. Much attention is paid to the study of the development of the joint after the treatment with the use of modern diagnostic techniques. With the involvement of specialists from other industries have developed assessment clinic blood in articulation structures schemes physiotherapy, medication support.

With years of experience in the treatment of congenital clubfoot, recently preferred method Ignacio Ponseti, which includes gypsum, minimally invasive achillotomy wearing the brace. This method allowed us to achieve good functional and cosmetic results in less time compared to traditional methods previously applied.

Separate, constantly evolving activity of the orthopedic department is the diagnosis and treatment of dysplastic and acquired pathology of the child's foot. Developed evaluation criteria used plantography digital podoskopphy. In individual orthotics technology is used " Sursil-Ortho," which allows the physician to make an orthopedic brace yourself strictly individually, taking into account the anatomical and physiological and static-dynamic features of the child's foot and, in the future, using the ability of the material to the remodeling, once made correction brace. Also, the department developed a modification of proofreaders "Sursil-Ortho" for the treatment of valgus flat-mentioned stop that also successfully used for the treatment of clubfoot after operative and conservative treatment with elimination bring forefoot valgus and component. This creates an opportunity for the maturation and coordination of the muscles of the foot arches, which is especially important in children and toddlers.

In the outpatient department of orthopedics, also, is the treatment of children with a cyst Becker, lies in its puncture, followed by washing and oral administration of cyclophosphamide in it.

In the second half of 2008 as part of hospital complex started uroandrological module, which includes the department of pathology of the pelvic floor and

pediatric andrology. Relevance due to a significant number of unsolved problems in the disorder of the pelvic organs, clinically manifested incontinence and defecation disorders. Genesis of these disorders and a range of different reasons is extremely broad. The functional — to the damage vegetative maintenance pelvic to severe organic defects.

A multidisciplinary approach reveals not only the main causes of disorders of the pelvic organs, but also to develop a reasonable treatment option pathogenesis. The ultimate goal of the treatment program is the social department and functional rehabilitation of the patient.

In the framework of the State program, aimed at improving reproductive health, and given the high frequency of diseases and malformations of the urogenital system was isolated specialty - pediatric urology - andrology. In this regard, as part of an outpatient surgery center created Pediatric Andrology, whose main task is to identify the most common causes of reproductive disorders in children.

Priority in the work of the department are andrologic following areas :

1. Develop objective criteria for assessing the state children reproduction health and adolescents.
2. Conducting research on the prevalence of diseases causing reproductive failure.
3. Development of scientific methods for the prevention of reproductive disorders.
4. Development of new methods for the diagnosis, treatment and rehabilitation.
5. Development of scientific methods to assess reproductive prognosis in patients in the postoperative period.

An important aspect of an outpatient surgery center is effective analgesia patients. Modern principles of pain management actively introduced into the work of all departments of hospital complex. Modified and adapted versions applicative and wires regional anesthesia proposed scheme preoperative patients. All invasive procedures and surgical interventions provided an experienced anesthetist.

Hospital-complex is a scientific and educational base RNRMU of. N.I.Pirogov where trained senior students, interns and residents. Specialized pediatric surgeons, urologists, andrology, orthopedics, traumatology. Total number of students of five hundred people. Past experience has been successfully applied in many areas, including on the basis of departmental medical facilities.

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STRUCTURE OF SYMPTOMATIC HEART RHYTHM DISORDERS AND CONDUCTIONABNORMALITIES IN PREGNANT WOMEN

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Cardiovascular diseases are among most widespread extragenital diseases in pregnant women [7, 13, 17]. Heart rhythm and conduction disorders play significant role in cardiovascular pathologies during pregnancy period.

Spectrum of arrhythmias observable in pregnant women is quite wide (from isolated extrasystoles and up to complicated and serious rhythm disorders). In essence, from nosologic point of view, there is no difference between the spectrum of rhythm and conduction disorders in non-pregnant patients and pregnant ones. However pregnancy causes a number of physiologic alterations, resulting in development of prerequisites for arrhythmias manifestation and progression. [9,15,16,19, 23]

Frequency of appearance of heart rhythm and conduction disorders in pregnant women varies from 7 to 59% [15, 16]. Out of them, 20 to 44% of arrhythmias have functional genesis [6, 15] and often do not require pharmacotherapy. [5, 8].

Nonetheless, a number of authors consider that pregnancy complications (malignant gestoses, miscarriage, hypotrophies of fetus) appear much more frequently in women with heart rhythm and conduction disorders, even with functional genesis. [19]

Type and character of heart rhythm and conduction disorders, as well as frequency of their appearance during pregnancy materially depend on general physiological background. Frequency is substantially higher in women with structural heart diseases, some concomitant pathologies, as well as genetic conditions. [1,2, 4,10, 19].In case of absence of anatomic substance or geneticdisorder and "electric" abnormality of myocardium, rhythm disorders appear less frequently and usually are less severe. [12]

In case of absence of structural and genetic pathology,in women, who suffered heart rhythm and conduction disorders before pregnancy, development and aggravation of symptoms is quite frequently observed [15].

In particular, authors detected aggravation of symptoms of supraventricular tachycardia in 50% of cases, of atrial fibrillation in 52% of cases and of ventricular tachyarrhythmia in 27% of cases. [18,20,21].

Different authors provide quite different information about a structure of rhythm disorders during pregnancy, however the

majority of researchers agree that most frequently appearing rhythm disorders during pregnancy are monomorphic ventricular and supraventricular premature beats. Premature contractions and instable atrial tachycardia are detected in 50% of pregnant women according to data from D.Lefroi, D. Adamson(2007), while other authors suggest that from 8 to 40% pregnant women suffer from either premature contractions or instable tachycardia. Atrial fibrillation is detected in 2-3 women with uncomplicated anamnesis per 1000, while bradyarrhythmias are more seldom, 1 per 20000, and most frequently are interconnected with sinoatrial blockades, according to the same authors' data. CCCY, as well as AVblockadesare rarely detected in pregnant women. Life threatening heart rhythm disorders are registered even more seldom (VT, FV).

According to published data, severe heart rhythm disorders during pregnancy most frequently appear in structural heart pathology cases, electric instability of myocardium (often genetic), or extracardiac pathology leading to changes in excitability of myocardium. Many authors outline that in a large number of cases heart rhythm disorders during pregnancy pass asymptomatically and appear to be an accidental discovery.

Our study included women, who complained of a feeling of quickened pulse, intermissions and discomfort in heart area. Such selection may be the reason for certain differences between data extracted by the study and the one published earlier.

We examined 128 pregnant women with complains of a feeling of quickened pulse, or intermissions in heart functioning. The age ranged from 19 to 41 (average 30.5, st.dev. 4.69). Patients with structural lesions of heart, cardiomyopathies, systemic connective tissue disease anddiabetes were not included into the target group.

All women underwent complex examination, including but not limited to analysis of complaints, anamnesis, potential risk factors, ECG, 24-hour Holter monitoring, Echo-CG, blood tests (clinical test, biochemical analysis, coagulogramm, levels of free T3, T4, TTG, detection of anticardial antibodies and viral markers.

EXAMINATION RESULTS:

Out of 128 patients, who initiated a consultation with cardiologist due to quickened heart rate and intermissions in heart functioning, isolated sinus tachycardia of more than 100 heartbeats per minute was detected in 38%, sinus bradicardia in 12%, ventricular premature contraction in 45%, unstable ventricular tachycardia in 6%, isolated monomorphic UVES in 18%, atrial fibrillation in 3% of cases; 1 patent was detected an AV blockade of 3rd degree (with average integral levels of HR at 37–42 beats per minute); 4 patients were detected transient AV blockade of 1st and 2nd degree.

The majority of patients (n=80, average age 30.7, st.dev. 4.65) were detected heart rhythm disorders before pregnancy. They were included into the first group. Others were included into the second group. (n=48, average age 30.3, st.dev. 4.83)

There was no statistically significant age difference between the groups, as well as statistically significant differences in such factors as consumption of coffee, smoking habit, existence of chronic anxiety. The second group included statistically significantly more women with pregnancy caused by an extracorporeal fertilization (1 group n=1, (1%), second group n=11, (23%))

Diagnostically significant levels of antimiocardiac antibodies (IgG) were detected statistically significantly more frequently in the 1st group (n=34), comparing to the 2nd group (n=11). Despite it cannot serve a diagnostic criteria for diagnosing of postmiokarditichseky kardiosklerosis, and we had no possibility for verification of fibrosis areas because of particular features of these groups of patients, based on anamnesis, we may suppose the existence of postmiokarditichseky kardiosklerosisin majority of patients with diagnostically significant levels of antimiocardiac antibodies (n=21 (26%) out of the 1st group, n=5 (10%) out of the 2nd one).

Decreases in levels of TTG observed in 2 patients from group 2, at the same time their levels of T3 free and T4 free remained in the referential range. Others women from both groups showed TTG levels within referential range, however TTG levels in the first group were statistically insignificantly higher then in the second group. In each group patients with ventricular rhythm disorders (n=45) show higher levels of TTG (on average 1.28mUn\l, st. dev –0.34) then those with sinus tachycardia (n=38) (on average 0.9 mUn\l, st dev - 0.28), provided that both these levels do not fall out of referential range.

With regards to the structure of rhythm disorders in the examined groups, lighter forms of arrhythmias were detected in the second group, where sinus tachycardia prevailed (n=22, 46%).

Ventricular extrasystolia in the second group was of lower levels according to Lown scale (monomorphic ventricular extrasystolia with average daily number of ventricular extrasystolas (average daily number of ventricular extrasystolas 8967, st.dev - 4434), according to 24-hour Holter monitoring data, was detected in 12 women (25%) and only 4 women

(8%) were detected ventricular rhythm disorders of 4–5th levels according to Lown scale.

In the first group the most widespread type of arrhythmia was ventricular extrasystolia (n=41, 51%). Ventricular rhythm disorders of 4–5th level (Lown scale) were detected in 21% (n=17) of women. (average daily number of ventricular extrasystolas 20383, st.dev – 7764)

Bradiasystulic arrythmias were detected statistically significantly more frequently in the 1st group of patients: sinus bradicardia in 5 of patients in the 1nd group comparing to just 1 woman in the 2nd group. Atrioventricular blockades was detected in the 1st group only (AV blockII degree(Mobits2) in 4 women and AV block III degree in 1 women), as well as atrial fibrillation(was detected in 3 women from1st group).

Supraventricular extrasystolia was detected somewhat more frequently in women from the 2nd group (9 women (19%) compared to 10 woman (13%)).

Subjective evaluation of severity of clinical symptoms in both groups did not correlate with severity of rhythm disorders and conduction, but was attributable rather to some of the concomitant conditions.

Independently from objective severity of rhythm disorders and conduction, patients with concomitant arterial hypertension (8 women, 6%) and obesity (4 women, 3%) evaluated their conditions as more severe.

Patients with concomitant neurotic symptoms (anxiety, sleep disorders, nervous tension – 11 patients, 9%) had more complaints about intermittences in heart functioning and quickened heart rhythm. No statistically significant difference in subjective evaluation of condition between patients with rhythm disorders first detected before pregnancy and others was found.

As for discussion of the results of tool examination of patients, it is important to outline that ECG detected rhythm disorders in the 1st group in 8 women (17%) only, and in the 2nd group in 22 women (28%). Only 24-hour Holter monitoring allowed to detectrhythm and conduction disorders in majority of patients, including those who required a therapy.

Thus most frequent rhythm and conduction disorders among pregnant patients, complaining about quickened heartbeat, intermissions in heart functioning and explicit discomfort in heart area, are ventricular extrasystolia and sinus tachycardia. All pregnant women with such complaints are recommended to undergo a 24-hour Holter monitoring, regardless of ECG results.

More severe rhythm and conduction disorders are detected in the group of women with rhythm and conduction disorders detected before the pregnancy.

Changes in TTG level potentially affect appearance and severity of ventricular rhythm disorders, even in cases when the level does not fall out of the reference range, however this data requires further research and adjustment.

Given a high ratio of patients with ECF in the group of women with rhythm disorders discovered during pregnancy period (23% comparing to 1% in the other group), we consider interesting to continue the research of a role of different factors associated with ECF in development of rhythm and conduction disorders in pregnant patients.

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MIKTIONSSTÖRUNGEN BEI M. PARKINSON DISTURBANCES OF BLADDER EMPTYING IN PARKINSON'S DISEASE

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ABSTRACT

Bladder dysfunction in Parkinson's patients are described in the literature with an incidence 37–93%. Nocturia and urinary urgency usually are perceived as particularly disturbing. A classification of bladder dysfunction based on anamnesis is usually not sufficient because the symptoms can be caused by the neurological disease, age-related changes in the urinary bladder, concomitant diseases, medications, and urologic and urogynecologic pathological changes. There is a need in treatment-resistant cases, especially prior to the implementation of urologic and urogynecologic surgery a differentiated diagnostic investigation of complaints.

KEYWORDS — Parkinson`s disease, bladder dysfunction

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EINFÜHRUNG

Die in vielen Publikationen beschriebene Diagnose einer zerebral enthemmten Harnblase bei Parkinson-Patienten mit den Symptomen Pollakisurie, Nykturie, imperativem Harndrang und Dranginkontinenz, bedarf einer Basisdiagnostik. Die Basisdiagnostik, im optimalen Falle bestehend aus Miktionsprotokoll, Restharnprüfung und Harnstrahlmessung (Uroflow), läßt eine erste Differenzierung zwischen einer Harnblasenentleerungsstörung (z.B. Restharnbildung) und einer Harnspeicherstörung (z.B. Dranginkontinenz) in nahezu allen Fällen zu. Die Therapie einer Harnblasenentleerungsstörung unterscheidet sich von der einer Dranginkontinenz, die empirische Gabe einer anticholinergen Medikation führt hier zu einer Verschlechterung der Harnblasenentleerung, bei der Dranginkontinenz eventuell zu einer Verlängerung der Miktionsintervalle.

In einem zweiten Schritt bedarf es der Ursachensuche. Eine Harnblasenfunktionsstörung kann neurologische, urologische, urogynäkologische, medikamentöse und organisatorische Ursachen haben.

Das Gebiet der Neuro-Urologie bedarf einer engen Zusammenarbeit mit der Neurologie, anderseits können neurologische Primärziele, wie z. B. Verbesserung der Lebensqualität durch Verbesserung der Motorik und Reduktion von Schlafstörungen, nur dann erreicht werden, wenn urologische Beschwerden reduziert werden können. Bei einer Nykturie von 4–6 mal wird das Schlafdefizit ohne urologische Zusatzbehandlung nicht zu beheben sein, nicht zu vergessen ist die hohe nächtliche Sturzgefahr. Eine stündliche Pollakisurie zwingt die Betroffenen und deren Angehörige nicht selten zum Verzicht auf soziale Teilhabe.

Der Schwerpunkt dieses Artikels liegt nicht in der Darstellung der therapeutischen Möglichkeiten, sondern in der diagnostischen Differenzierung, da die Therapie meistens in urologischen Praxen und Kliniken erfolgt. In nicht wenigen Fällen bedarf die differenzierte Abklärung der Miktions-beschwerden einer erweiterten Ausstattung, welche nicht immer in urologischen Praxen vorrätig sein dürfte.

Dem/r neurologischen Facharzt/-ärztin soll jedoch die Komplexität der urologischen Beschwerden und der Diagnostik vorgestellt werden. Im optimalen Falle arbeiten niedergelassene neurologische Ärzte/Ärztinnen, oder neurologische Kliniken eng mit neurourologisch kompetenten, urologischen Ärzten/-innen oder Kliniken zusammen. Meistens läßt sich hierdurch eine urologische Unter- oder Überversorgung der Parkinson-Patienten vermeiden.

Die normale Harnblasenfunktion:

Sofern keine urologische, neurogene oder altersbedingte Störung der Harnblasenfunktion vorliegt gilt eine Frequenz von bis zu acht Miktionen in 24 Stunden als normal. Die anatomische und die funktionelle Blasenkapazität betragen ca. 400 bis 500 ml. Eine Nykturie zwischen 0 und 2 mal pro Nacht kann als regelrecht bezeichnet werden. Die Harnblasenentleerung erfolgt nahezu restharnfrei und mit einem einphasigen Harnstrahl. Ein Nachpressen nach Beendigung der Miktion hat keinen Krankheitswert.

Das nachfolgende Miktionsprotokoll über 24 Stunden (50-jähriger Patient) verdeutlicht eine normale Harnblasenfunktion.

Miktionsmengen und Uhrzeit		Trinkmengen und Uhrzeit	
Uhrzeit	Volumen	Uhrzeit	Volumen
6.00	450 ml	6.10	200 ml
11.10	360 ml	9.00	200 ml
15.05	350 ml	12.00	300 ml
18.10	390 ml	14.30	250 ml
22.05	300 ml	18.00	350 ml
		20.20	250 ml
6.05	500 ml	6.30	200 ml
Gesamtmenge	2350 ml	Gesamtmenge	1750 ml

Abbildung 1.

Das Miktionsprotokoll (Abb.1) zeigt, dass eine regelrechte Miktionsfrequenz, regelrechte Miktionsvolumina, keine Nykturie und regelrechte Trinkmengen vorliegen. Das Miktionsprotokoll (z.B. über 2 Tage durchgeführt) stellt eines der wichtigsten, kostengünstigsten, zeitsparenden und beliebig oft reproduzierbaren diagnostischen Screeningverfahren dar. Auch kann z.B. eine Nykturie aufgrund einer deutlich überhöhten nächtlichen Urinproduktion Hinweise auf eine internistisch zu behandelnde Herzinsuffizienz geben.

Altersbedingte Veränderungen der Harnblasenfunktion:

Mit zunehmendem Alter (oft ab dem 60. Lebensjahr) kommt es altersbedingt zu anatomischen und funktionellen Veränderungen der Harnblase und ihrer Funktion. Die Kontraktilität des Harnblasenmuskels nimmt ab, eine gewisse Restharnbildung ist tolerabel und der Harnstrahl wird etwas schwächer. Die Blasenkapazität kann sich auf 300 bis 400 ml reduzieren. Durch hormonelle Veränderungen (z. B. veränderte Ausschüttung des Antidiuretischen Hormons) kommt es zu vermehrter nächtlicher Urinproduktion, so daß eine Nykturie von zweimal als normwertig angesehen werden kann. Zusätzliche Erkrankungen wie z. B. Herzinsuffizienz, venöse Erkrankungen und Diabetes mellitus verändern ebenfalls Verhältnis von Diurie und Nykturie.

Urologische und urogynäkologische Ursachen von Beschwerden:

Ab dem fünfzigsten bis sechzigsten Lebensjahr ist bei nahezu 50 Prozent aller Männer eine mehr oder weniger deutliche Prostatavergrößerung nachweisbar. Eine symptomatische benigne Prostatavergrößerung geht häufig, aber nicht immer mit deutlicher Restharnbildung oder einem schwachem Harnstrahl einher. Es können auch ausschließlich Symptome wie Pollakisurie, Nykturie und imperativer Harndrang vorliegen. Eine Restharnbildung kann auch medikamentöse oder neurologische Ursachen haben. Die Basisdiagnostik reicht für eine Differenzierung nicht aus. Die erweiterte diagnostische Abklärung erfordert eine urodynamische (Blasendruckmessung), radiologische (Miktionszysturethrogramm, bzw. Videourodynamik) und im Einzelfalle endoskopische (Urethrozystoskopie) Abklärung. Eine der schwierigsten Aufgaben des Urologischen Facharztes ist die Abklärung einer subvesikalen Obstruktion bei einem männlichen Parkinson-Patienten. Es gilt eine Differenzierung zu treffen zwischen einer symptomatischen Prostatavergrößerung, einer so genannten Detrusor-Sphinkter-Dyssynergie (unkoordinierte Harnblasenmuskel- und Schließmuskelfunktion, z.B. bei einer Multisystematrophie) und einer passageren, medikamentös ausgelösten Harnblasenmuskelschwäche (Detrusorhypokontraktilität).

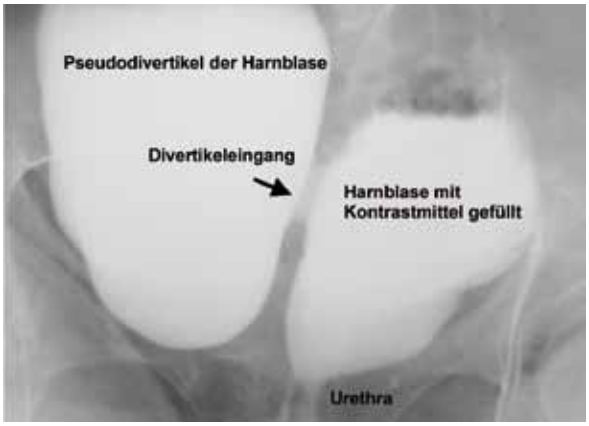

Abbildung 2. *Miktionszysturethrogramm mit großem Pseudodivertikel der Harnblase eines 70jährigen Mannes mit therapieresistenter Pollakisurie und ohne sonographisch nachweisbarer Prostatavergrößerung. Trotz regelrechten Miktionsvolumina (400 ml) waren jeweils Restharnwerte von bis zu 600 ml nachweisbar, welche auch mittels Einmalkatheterismus nicht entleert werden konnten. Therapie: Prostataresektion und Divertikelabtragung.*

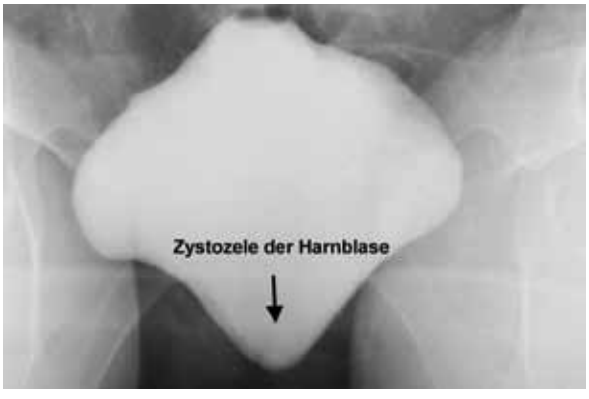

Abbildung 3. *Miktionszysturethrogramm einer Parkinson-Patientin mit deutlicher Senkung (Zystozele) der Harnblase. Neben einer Belastungsinkontinenz traten die Symptome einer Pollakisurie, Nykturie und eines nicht unterdrückbaren Harndranges beim Laufen.*

Bei jeder zweiten Frau finden sich im fortgeschrittenen Alter mehr oder weniger Symptome einer Belastungsinkontinenz mit Urinverlust beim Husten, Niesen und Lachen, insbesondere nach einer Hysterektomie. Eine weitere Gruppe von Patientinnen leidet an einer kombinierten Drang- und Belastungsinkontinenz. Hierbei tritt der imperative Harndrang beim Lagewechsel vom Liegen zum Stehen, bzw. Sitzen auf, nachts bestehen kaum Beschwerden. Auch hier bedarf es einer umfangreichen Diagnostik. Eine der am schwierigsten zu stellenden Diagnose stellt hier eine Harnblasenhals-insuffizienz dar. Mittels Anamnese und Basisdiagnostik kann selten eine Unterscheidung zur zerebral enthemmten Harnblase getroffen werden. Wurde eine neurogene Harnblasenfunktionsstörung ausgeschlossen und eine urogynäkologische Ursache dokumentiert, bedarf es einer weiteren urogynäkologischen Differenzierung um das geeignete konservative oder operative Vorgehen festzulegen.

Pathophysiologie der zerebral enthemmten Harnblase bei Parkinson-Syndromen

Die in der Literatur am häufigsten angeführte neurogene Harnblasenfunktionsstörung ist die zerebral enthemmte Harnblase. Die Symptome sind imperativer Harndrang, Pollakisurie und Nykturie, gegebenenfalls mit einer Dranginkontinenz. Die Harnblasenkontrolle erfolgt durch die Zusammenarbeit des pontinen und des sacralen Miktionszentrums. Das pontine Miktionszentrum befindet sich im Bereich des Nucleus coeruleus des Tegmentums im Mesencephalon. Neben den vesicolumbalen Reflexbögen und der Steuerungsfunktion der mesopontinen Strukturen ist auch das Großhirn an der Koordination der Miktion beteiligt. Mit Befall der diencephalen Kerne und dem Auftreten von Störungen des limbischen Systems entfällt die zentrale Hemmung der mesopontinen Regulationszentren. Das Auftreten urologischer Beschwerden ist beim M. Parkinson u. a. auf die Degeneration nigrostriataler Neurone zurückzuführen, der entsprechende Schweregrad der urologischen Beschwerden wird durch die Degeneration des Nucleus caudatus bestimmt. Die Basalganglien haben einen koordinierenden und hemmenden Einfluß auf das pontine Miktionszentrum und somit auf die Funktion des Harnblasenmuskels. Entfällt dieser hemmende Einfluß können sich die Symptome einer zerebral enthemmten Harnblase mit plötzlichem, imperativem Harndrang, Pollakisurie und Nykturie entwickeln, die Betroffenen können die Harnblase allerdings noch restharnfrei entleeren. Als Folge tritt eine Detrusorhyperreflxie ohne Detrusor-Sphincter-Dyssynergie auf. Zusätzlich kann eine Hypersensibilität der Harnblase bei geringen Blasenfüllungsvolumina auftreten. Werden im fortgeschrittenen Erkrankungsstadium zusätzlich die Neurone der Zona intermedia des sacralen Rückenmarks, bzw. der sacrale Nucleus intermediolateralis befallen und tritt somit eine verminderte Innervation der sympathischen Efferenzen der Nn. Pelvici auf, kann eine zusätzliche Blasenboden- und Sphincterschwäche (innerer Sphincter /Blasenausgang) auftreten.

Miktionsmengen und Uhrzeit		Trinkmengen und Uhrzeit	
Uhrzeit	Volumen	Uhrzeit	Volumen
7.00	200 ml	7.10	200 ml
8.15	110 ml	9.00	200 ml
10.05	90 ml	12.00	300 ml
12.20	120 ml		
14.05	90 ml	14.30	250 ml
16.10	95 ml		
18.20	70 ml	18.00	150 ml
19.30	100 ml	19.30	200 ml
22.00	140 ml	21.00	150 ml
1.00	50 ml		
2.40	120 ml		
3.30	100 ml		
6.05	280 ml		
Gesamtmenge	1555 ml	Gesamtmenge	1450 ml

Abbildung 4

Das Miktionsprotokoll (Abb. 4) zeigt, dass eine deutliche Pollakisurie und eine Nykturie mit kleinen Harnmengen vorliegen, die Trinkmenge und die Gesamtausscheidung liegen im Normbereich. Weiterhin ist erkennbar, dass keine übermäßige nächtliche Harnproduktion vorliegt, welche z. B. auf eine andere Erkrankung wie z. B. Herzinsuffizienz, oder die nächtliche Ausscheidung von tagsüber auftretenden Beinödemen auftritt. Im Mittel liegen die Harnmengen bei ca. 130 ml (normal: 300 – 500 ml), die sogenannte maximale (funktionale) Blasenkapazität beträgt im Beispiel 280 ml (normal: 400 – 500 ml). Das Beispiel weist auf eine überaktive Harnblase hin. Sofern der Patient zusätzlich ein oder mehrere Inkontinenzepisoden notierte, bestünde der Verdacht auf eine Dranginkontinenz.

Harnblasenfunktionsstörungen bei einer Multisystematrophie

Urologische Beschwerden treten bei einer Multisystematrophie (MSA) noch weitaus häufiger als bei der idiopathischen Parkinson-Erkrankung und mit besonderen Charakteristika auf. Im Vordergrund stehen die dauerhafte, nicht situative Harninkontinenz und die unvollständige Blasenentleerung. Ein weiteres Symptom kann der Verlust des Blasenfüllungs- und entleerungsgefühls sein. Das Auftreten von Blut-

druckschwankungen während einer Blasenentleerung ist ein weiteres, mögliches Symptom. Die Evaluation der Beckenbodenmuskulatur zeigt häufig eine Schwäche derselben und gelegentlich eine Schwäche des Analsphinkters an. Häufiger als beim IPS und bei der progressiven supranukleären Parese (PSP) kann eine Detrusor-Sphinkter-Dyssynergie, eine fehlende Koordination von Harnblasenmuskels (Detrusor vesicae) und des Harnblasenschließmuskels (Sphinkter vesicae) nachgewiesen werden. Urodynamisch ergibt sich häufig der Befund einer Hypo- oder Akontraktilität des Harnblasenmuskels (schlaffe Harnblasenlähmung). Entsprechend können bei den Betroffenen hohe Restharnwerte bis zur chronischen Überlaufblase auftreten. Bei anderen Betroffenen kann keine Restharnbildung nachgewiesen werden, hier kann es jedoch zu unkontrollierbarem, kontinuierlichem Harnverlust ohne vorherigen Harndrang kommen. Im weiteren Verlauf einer MSA muss von einer Häufigkeit urologischer Symptome in nahezu 100 Prozent der Fälle ausgegangen werden.

Parkinson-Medikation und Harnblasenfunktionsstörungen

Die Interaktionen von urologischen Medikamenten und den häufig verordneten Medikamenten zur Behandlung von Parkinson-Patienten sind bisher nicht umfassend untersucht. Die häufige Kombination mehrerer Parkinsonmedikamente erschwert die Eruierung deren Einzelwirkungen auf die Harnblase. Einerseits kann eine vom Urologen verordnete anticholinerge Medikation die medikamentöse Parkinson-Therapie beeinflußen, im Gegenzug kann die vom Neurologen eingesetzte Parkinson-Medikation, z.B. Anticholinergika die urologische Behandlung beeinflussen. Wenn Patienten über einen zeitlichen Zusammenhang zwischen dem Auftreten ihrer urologischen Beschwerden und einer Veränderung ihrer Parkinson-Medikation berichten, sollte die Möglichkeit einer Anpassung der Parkinsonmedikation geprüft werden.

Tiefe Hirnstimulation und Harnblasenfunktion

Nach Implantation eines Stimulators zur Hirnstimulation (THS) kann eine Änderung der Blasenspeicher- oder –entleerungssituation eintreten. Auch hier gilt, daß eine abschließende Bewertung aller Wirkungen noch nicht umfassend möglich ist. Wichtig zu wissen ist jedoch, daß nach der Implantation alle urologischen Anwendungen kontraindiziert sind, bei denen elektrische Energie auf den Stimulator übertragen werden kann. Dazu zählen Mikro- und Kurzwelle, therapeutischer Ultraschall, Rotlicht und Elektrostimulation. Bei Nicht-Beachtung ist mit schweren Nebenwirkungen, eventuell mit zerebralen Schäden zu rechnen. Da auch zu den elektrisch gestützten Resektionsverfahren und Laserablationen bei BPH keine generellen Angaben der Hersteller vorliegen, wird vom Hersteller der Stimulatoren im Einzelfall eine Kontaktaufnahme mit diesem und eine gemeinsame Einzelfallentscheidung empfohlen.

Komplexität der Ursachen

In der neuro-urologischen Betreuung von Parkinson-Patienten finden sich überwiegend Patienten, welche keine isolierte neurogene Harnblasenfunktionsstörung haben. Im männlichen Klientel findet sich häufig eine Kombination von zerebral enthemmter Harnblase und einer Prostatahyperplasie. Im weiblichen Klientel eine Kombination von Drang- und Belastungsinkontinenz. Ein besonders Problem stellt die intermittierend auftretende Restharnbildung. Insbesondere ältere Patienten reagieren bei Auftreten einer Harnwegsinfektion nicht mit typischen zystitischen Beschwerden, sondern mit einer vorübergehenden Harnblasenentleerungsstörung. Häufig kann auf die Einlage einer dauerhaften Harnableitung weitgehend verzichtet werden, da die Kombination von intermittierendem Selbst- oder Fremdkatheterismus über mehrere Tage mit einer antibiotischen Therapie zu deutlich rückläufigen und tolerablen Restharnwerten führen kann. Auch eine im Rahmen einer medikamentösen Neueinstellung auftretende Harnverhaltung sollte zunächst durch intermittierenden Katheterismus behandelt werden. Nicht selten ist auch von einer situativ aufgetretenen myogenen Überdehnung der Harnblase auszugehen, welche sich unter dieser Therapie binnen kurzer Zeit bessern kann. Die frühzeitige Einlage einer dauerhaften, transurethralen Harnableitung sollte die Ausnahme sein, bei einem Infektionsrisiko von 3–10% pro Tag wird die weitere Diagnostik sowie die Behandlung nur erschwert. Die Komplexität der Ursachen steigt mit der Anzahl der Nebendiagnosen (z.B. Diabetes mellitus, Herzinsuffizienz) und der Art der Medikation.

Weiterführende Diagnostik beim Facharzt für Urologie:

Einem neuro-urologischen Zentrum oder einer Ambulanz stehen der Uroflow (Harnstrahlmessung), die Urodynamik (Harnblasenfunktionsmessung), die Videourodynamik (kombinierte Röntgen- und Harnblasenfunktionsprüfung), die Urethrozystoskopie (Blasenspiegelung) und die isolierte Röntgenuntersuchung der Harnblase (Miktionszysturethrogramm) zur Verfügung. Insbesondere bei Vorliegen oder bei Verdacht auf eine Multisystematrophie mit oder ohne Restharnbildung sollte auf eine urodynamische Untersuchung nicht verzichtet werden. Eine Röntgenuntersuchung der Harnblase kann bei MSA-Patienten einen offenen, oder sich nicht öffenden Blasenhals/

Sphinkter nachweisen, in der Regel aber nicht beim idiopathischen Parkinsonsyndrom. Aufgrund des relativ hohen Risikos einer postoperativen Inkontinenz wird allgemein eine urodynamische Untersuchung vor urologischen Wahleingriffen (z.B. benigne Prostatahyperplasie) empfohlen. Bei einfachen Symptomen einer überaktiven Harnblase ohne wesentliche Restharnbildung, oder einer Dranginkontinenz, sind unkomplizierte Therapieversuche (s. u.) durch den Facharzt für Neurologie durchführbar.

Abbildung 5. *Normales Miktionszysturethrogramm: keine Druckbelastungszeichen (Divertikel, Trabekulierung), regelrechte Öffnung der Harnblase bei der Miktion, keine Obstruktion im Bereich der Urethra*

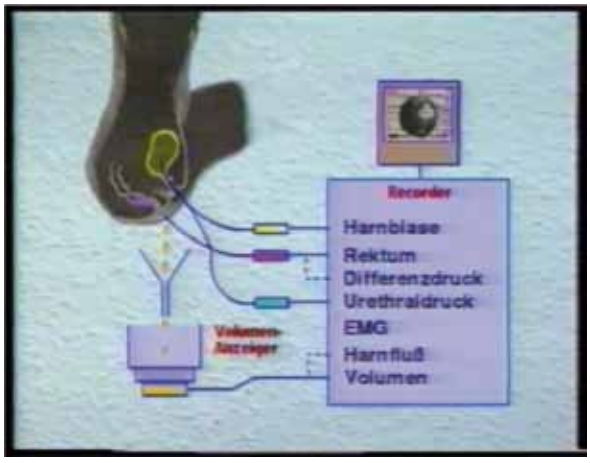

Abbildung 6. *Schema einer urodynamischen Untersuchung: durch Messung des intravesikalen und abdominellen Druckes und eines Beckenboden-EMG wird der Detrusordruck errechnet und der Verlauf der Harnblasenfüllung und –entleerung graphisch dargestellt*

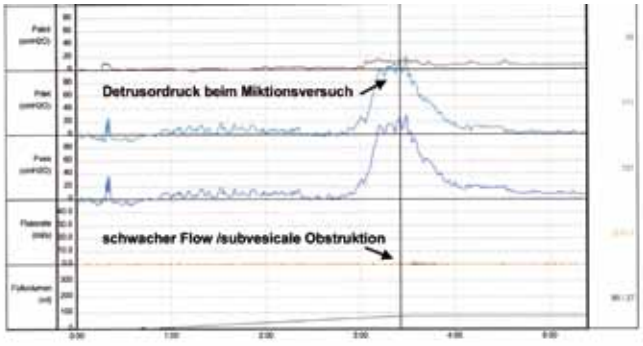

Abbildung 7. *Urodynamik-Kurve eines Patienten mit den Symptomen einer überaktiven Harnblase, Pollakisurie und Nykurie. Ergebnis der weiterführenden Diagnostik: subvesikale Obstruktion durch eine Prostatavergrößerung mit Restharnbildung. OP-Indikation zur Prostataresektion*

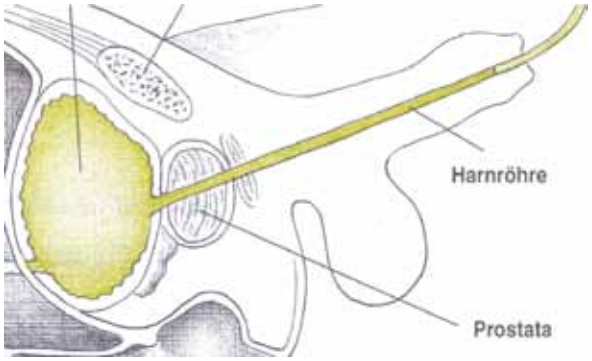

Abbildung 8. *Zystogramm /Miktionszysturethrogramm: die Harnblase wird retrograd mittels Kontrastmittel gefüllt. Anatomische und funktionelle Störungen der Harnblase und der Urethra können während der sich anschließenden Miktion radiologisch dargestellt und dokumentiert werden. Bei der Videourodynamik wird die radiologische und urodynamische Untersuchung simultan durchgeführt*

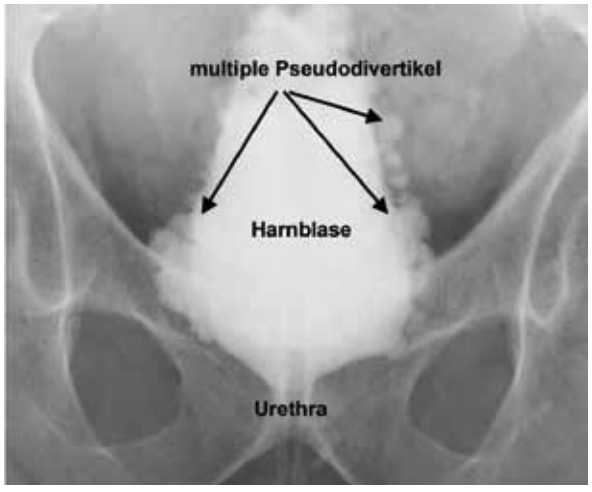

Abbildung 9. *Miktionszysturethrogramm mit massiver Pseudodivertikelbildung bei zerebral enthemmter Harnblase, ohne nachweisbare Prostatahyperplasie und ohne Restharnbildung*

Therapeutische Möglichkeiten:

Die therapeutischen Möglichkeiten müssen sich immer an den motorischen und kognitiven Voraussetzungen des Patienten und seinem sozialen Umfeld sowie der häuslichen Betreuungsmöglichkeiten orientieren. Liegt der Schwerpunkt auf einer urologischen oder urogynäkologischen Diagnose, so muß individuell und interdisziplinär geklärt werden, ob eine Operation möglich und sinnvoll ist.

Orale anticholinerge Medikation

Hierdurch können der imperative Harndrang, die Nykturie und die Pollakisurie deutlich reduziert werden. Als Beispiele können Trospiumchlorid, Tolderodin, Oxybutinin und Propiverin genannt werden. Bei Einschränkung der kognitiven Leistungen, oder bei Halluzinationen sollten selektiv an peripheren M3-Acetylcholin-Rezeptoren ansetzende Wirkstoffe wie Darifenacin und Solifenacin bevorzugt werden. Bei diesen Medikamenten besteht empirisch ein reduziertes Risiko einer symptomatischen Interaktion mit der bestehenden Parkinson-medikation. Auf typische Nebenwirkungen wie Mundtrockenheit, Obstipation und Sehstörungen sollte hingewiesen werden. In nicht wenigen Fällen lassen sich durch eine Kombination von Prostatamedikamenten und anticholinergen Substanzen gute Erfolge erzielen.

Liegt eine medikamentös nicht zu beherrschende Blasenentleerungsstörung vor, so sollte dem intermittierenden Einmalkatheterismus (Fremd- oder Selbstkatheterismus) so oft es geht der Vorzug gegeben werden. Über einen Einmalkatheter oder eine Dauerableitung kann Oxybutinin (als Fertigspritze) lokal in die zuvor entleerte Harnblase appliziert werden.

Intravesikale Botulinumtoxin-Injektion

Bei Kontraindikation oder Unwirksamkeit einer oralen anticholinergen Medikation kann endoskopisch Botulinumtoxin in den Detrusor vesicae injiziert werden. In Abhängigkeit von der Dosierung kann hierdurch eine Reduktion der Detrusorkontraktilität, oder eine Detrusorakontraktilität bewirkt werden. Die Fähigkeit zum Selbstkatheterismus, bzw. die Gewährleistung des Fremdkatheterismus sollte zuvor geprüft werden. Die Injektion erfolgt transurethral-endoskopisch in Allgemeinanästhesie, kann bei manchen Patienten auch in Lokalanästhesie erfolgen. Die Wirkung hält im Mittel 6 bis 9 Monate an. Derzeit liegt nur eine Zulassung zum Einsatz von Botulinumtoxin bei Querschnittlähmung und Multipler Sklerose vor, die Anwendung erfolgt bei Parkinson-Patienten im off label use. Als nachteilig wird von manchen Patienten die Häufigkeit der erforderlichen Eingriffe insbesondere in Allgemeinanästhesie empfunden.

E.M.D.A (Electro Motive Drug administration)

Hierbei wird eine Kombination von Medikamenten über einen besonderen Katheter in die Harnblase eingebracht und durch Gleichstrom die Struktur der Medikamente derart verändert, daß diese in ionisiertem Zustand nicht nur in die Harnblasenschleimhaut, sondern auch in die Harnblasen-Muskulatur gelangen. So kann zum Beispiel auch Oxybutinin mit dieser Methode eingesetzt werden. Das Verfahren dauert jeweils ca. 30 Minuten und wird an drei aufeinander folgenden Terminen in der Regel stationär durchgeführt. Der Effekt kann mehrere Monate anhalten und eine zusätzliche Medikamenteneinnahme überflüssig machen. Das Verfahren ist nicht ohne Risiken und ist nicht für alle Patienten geeignet.

Intermittierender Fremd- oder Selbstkatheterismus

Hierdurch können mittel- und langfristig rezidivierende Harnwegsinfekte und morphologische Schäden der Harnblase vermieden werden. Bei erhaltener, aber relativ ineffektiver Harnblasenentleerung (hoher Restharn) kann der Einmalkatheterismus zur Restharnentfernung nach vorheriger Spontanmiktion (ohne Bauchpresse) und somit zur Reduktion der Pollakisurie und Nykturie eingesetzt werden. Bei Unfähigkeit zur Spontanmiktion und eingeschränktem Blasenfüllungsgefühl (z. B. bei MSA) erfolgt der Einmalkatheterismus ohne vorherige Blasenentleerung in regelmäßigen zeitlichen Abständen (ca. alle 4 Stunden) insgesamt vier bis fünf mal pro Tag. Bei erhaltenem Blasenfüllungsgefühl erfolgt der Katheterismus bei Auftreten von Harndrang.

Miktions- und Harnblasentraining

Als Miktionstraining wird die Anpassung des Lebensrhythmus an den Blasenrhythmus auf der Grundlage eines Miktionsprotokolls („Blasenentleerung nach der Uhr“) bezeichnet. Aufgrund des Wissens um die eigene Blasenkapazität (z. B. 200 ml) versucht der Betroffene unweigerlich auftretenden Inkontinenz- und Drangepisoden zu entgehen, in dem er vorzeitig, noch vor Auftreten von Harndrang die Harnblase entleert. Unter einem Harnblasentraining versteht man die stufenweise Vermeidung von Miktion, bzw. die verzögerte Durchführung einer Blasenentleerung. Bei kurzen Miktionsintervallen wird der Patient angeleitet den ersten Harndrang zu unterdrücken.

Veränderung des Trinkverhaltens

Wurde mittels Miktionsprotokoll eine deutliche Einschränkung der funktionellen Harnblasenkapazität

nachgewiesen (z. B. 150 bis 200 ml), so führt die Anordnung zu hohen Trinkmengen (z. B. 3 Liter/die) zu einer verstärkten Pollakisurie mit bis zu zwanzig Miktionen pro Tag. Andererseits reagieren manche Patienten mit einer erheblichen, bewußten Einschränkung ihrer Trinkmenge mit weniger als 1 Liter/Tag um eine Pollakisurie oder Inkontinenzepisoden zu vermeiden.

Es empfiehlt sich die Vorgabe einer Trinkmenge von 1,5 bis 2,0 Litern pro Tag. Nur in Einzelfällen sollten höhere Trinkmengen bei Vorliegen einer Pollakisurie empfohlen werden. Um eine übermässige Nykturie zu vermeiden kann die abendliche Trinkmenge reduziert werden.

Double voiding bei hohem Restharn

Es handelt sich um ein Verhaltenstraining für Patienten mit Blasenentleerungsstörungen zur Restharnreduktion ohne den Einsatz von Medikamenten. Hierbei entleeren die Patienten ca. 15 bis 30 Minuten nach der letzten Miktion erneut (ohne vorliegenden Harndrang) die Harnblase.

Beckenbodentraining

Die Durchführung und Anlernung von individuell zu gestaltendem Beckenbodentraining zur Muskelkräftigung oder Muskelentspannung nach vorheriger, professioneller Beckenboden-evaluation unterstützt in Kombination mit anderen Therapiemaßnahmen die Möglichkeiten der Betroffenen zur Kontrolle der Blasenentleerung und zur Reduktion von Harninkontinenz.

Transcutane Elektrostimulation der Harnblase (nicht-invasive Neuromodulation)

Die transkutane, intermittierende Elektrostimulation wird zur Behandlung von Harndrang-, Harnbelastungs- und Stuhlinkontinenz eingesetzt. Unter Berücksichtigung möglicher Kontra-indikationen ist die täglich (20 Minuten), von manchen Patienten auch selbstständig und zu Hause durchführbare Therapie frei von Nebenwirkungen. In Einzelfällen kann sie zur Reduktion oder zum Verzicht von Medikamenten eingesetzt werden.

Weitere und operative Therapien

Bei therapieresistenter Nykturie oder nächtlicher Polyurie (Nachweis: Miktionsprotokoll) kann der Einsatz von Desmopressin (z. B. Nasenspray) indiziert sein. Hierdurch wird die nächtliche Urinproduktion reduziert. Die Anwendung bedarf engmaschiger ärztlicher Kontrollen des Elektrolythaushaltes und dem strikten Ausschluß von Kontraindikationen.

Als invasive, neuromodulatorisch wirksame OP-Methode kann die chronische Stimulation der Sakralwurzel S2/S3 genannt werden. Durch einen gering invasiven vorherigen, peripheren Nervenevaluations-Test (PNE- Test) kann die Effektivität der Methode überprüft werden. Andere operative Maßnahmen werden selten eingesetzt, die Indikationsstellung und Durchführung sollte in neuro-urologisch versierten Zentren erfolgen.

Fazit für die Praxis

Die neuro-urologische Diagnostik von urologischen Beschwerden von Parkinson-Patienten erfordert aufgrund der komplexen Ursachen eine entsprechende instrumentelle Ausstattung und eine gewisse Erfahrung in der Behandlung, insbesondere wenn sich die Indikation für einen operativen Eingriff ergibt. Neurologische Kliniken und Praxen sollten die Zusammenarbeit mit entsprechenden neuro-urologischen Zentren und Praxen suchen, da ca. jeder dritte Parkinson-Erkrankte unter urologischen Beschwerden, z.T. mit erheblichem Leidensdruck leidet. Soll nicht nur die Motorik, sondern die Lebensqualität und die soziale Teilhabe verbessert werden und Risiken, wie zum Beispiel die nächtliche Sturzgefahr durch eine erhöhte Nykturie, reduziert werden, so ergibt sich die Erfordernis einer engen Zusammenarbeit zwischen Neurologie und Urologie, bzw. Neuro-Urologie.

Klinikum Braunschweig

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- Leisten- und Narbenbrüche
- Gallensteine
- Blinddarmentzündung
- Divertikelerkrankung des Dickdarms
- Bösartige Erkrankungen des Darms
- Chronisch entzündliche Darmerkrankungen
- Refluxerkrankung
- Kleine Magentumoren
- Speiseröhrenkrebs
- Leberkrebs

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Prof. Dr. Guido Schumacher, Chefarzt

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TREATMENT OF STEROID-RESISTANT NEPHROTIC SYNDROME IN CHILDREN

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Steroid-resistant nephrotic syndrome (SRNS) is one of the leading types of nephropathy with progressive course, often leads to the development of chronic renal failure.

OBJECTIVE

to evaluate the effectiveness of steroid-resistant nephrotic syndrome therapy in children using immunosuppressants and without using once.

MATERIAL AND METHODS

SRNS patients were divided into 3 groups. The first group included 34 patients on immunosuppressive therapy (IST) (chlorambucil, cyclophosphamide, cyclosporin A and mycophenolate mofetil), the second group - 22 patients on immunosuppressive therapy in combination with inhibitors of angiotensin -converting enzyme (ACE), third group included 21 patients treated with ACE inhibitors and symptomatic therapy.

RESULTS AND DISCUSSION

We traced catamnesis on maintenance of renal function in patients (by determination of GFR) during 4 years (Fig. 1). Remaining of renal function in patients receiving immunosuppressive therapy was higher than in patients being treated with ACE inhibitors and symptomatic therapy.

Thus, the use of immunosuppressive therapy in patients with steroid-resistant nephrotic syndrome led to a significant improvement in clinical and laboratory parameters, which is important for the further prognosis of disease. The combination of ACE inhibitors and immunosuppressants is more favorable option for preservation of renal function and prognosis in general.

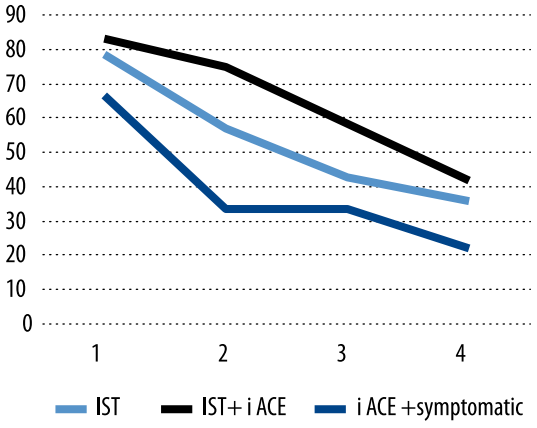

Fig. 1. *Survival of renal function in patients with SRNS on IST background and without it*

CLASSIFICATION OF HYPERTENSION IN THE PULMONARY CIRCULATION

Prof. ***J.S. Brusilovski***

Developing classification of pulmonary hypertension, taken into account, above all, the fact that the latter is not a separate ontological unit, and the syndrome occurs when a number of illnesses of lungs, heart and blood vessels. Therefore, as it seems to us expedient was to highlight the main etiological factors, resulting in increased pressure in the bloodstream of a small circle, pathogenic forms of pulmonary hypertension, clinical variants and their types. Furthermore, as classification should reflect the stage of the disease in several of clinical manifestation in each stage.

Set that this syndrome is manifested in two main causal factors leading to the increase in pressure in the small circle.

A – Factor – Organic (anatomic)

B – Factor – Functional

Each of these factors includes pathogenic form, and recent clinical types. To organic factor include the following pathogenic form.

1. Pre-capillary blood, which is manifested in two clinical variants:

Intravascular and outside the vascular intravascular variant occurs either due to disease, covering the lumen

of the arteries, violation the arterial patency (primary intravascular block), such as thrombosis and embolism pulmonary artery and its branches, thromboarteritis, obliterating arthritis, idiopathic the obliteration of the pulmonary artery disease extravascular clinical variant is associated with diseases, localized outside vessels and compress them as such, the outcome of which is not polysegmental share, or a total pulmonary cirrhosis. Under this option, in addition to the above internal mentioned a chance and extrapulmonary types, as, for example, in connection with compression of the lungs due to the high standing of the diapulmonary (syndrome Pickwick), chest injuries with fractures of lungs.

2. To organic factor includes also the alveolar capillary (diffusion) pathogenetics form. Diffusion of gases, oxygen carbon dioxide are:

Through the membrane, which is the only partition (shell) between the alveoli and capillary types of sensors. In violation of the permeability of the membrane (diffusion blocks) diffusion slows down or stops, and them, due to hypoxia and hypercapnia, reflex limited to the inflow of arterial blood by spasm of the arteries) to the alveolar capillaries. This happens with inflammatory processes in the alveoli, capillary arterioles, venules (alveolitis, exciting significant part of the respiratory surface), as, for example, when dangers and chronic pneumonia syndrome Hamman-rich alveolar.

ALVEOLAR PROTEINOSE: THESE PATHOGENIC FORMS TO FUNCTIONAL FACTORS

3. Pre-capillary pathogenetic form, arising again on the ground of primary organic or functional partial unit (gateway) in the air sacs ways of determining ventilation (external tons of breath deficiency alveolar hypoxia and reflex spasm of the arteries of the small circle (reflex citaev) (3). Thus, a second pre-capillary causes ventilation (alveolar – hypoxi) pathogenic form hypertension pulmonary (4). This form impacts at different stages of the diseases such as diffuse pneumosclerosis and other diseases like emphysema and atelectasis, bronchial asthma (4) and other diseases, "immured" pre-capillary arterioles.
4. Post capillaries pathogenetic form. This form is linked with the localization of the block in venous channel small circle: secondary arterial bloc. Of course, at a certain stage of the development process, joint the block and arterial the tideway of the small circle: secondary arterial block this pathogenetic form of clinically manifested in two versions: mild venous – pulmonary and heart. In the basis of the first clinical variant is increases of venous pressure due to "exhaustion" reserve capacity venous bed of a small circle associated with the "wall" pulmonary veins chronic inflammatory – sclerotic process. As a consequence – increase of pressure in the blood stream. The mild venous – pulmonary option include two clinical types: inside the vascular and out – vascular. The first is related to the primary pulmonary unit as a result of thrombosis. The second – most frequently in chronic poly – segmental pneumonia in the conditions of mild emphysema.

In the basis of cardiac pathogenetic variant lies outside pulmonary process leading to primary pulmonary venous hypertension. Most often, this type develops with mitral stenosis, because the stenosis of the left venous bed, venous hypertension, sclerosis (cardiac pneumosclerosis). This stasis leads to thrombosis, pulmonary, heart attack, stagnant pneumonia.

5. Hyperkinetic (Hyper perfusion) pathogenetic form. This form occurs in connection with pathologically increased perfusion, sometimes combined increases volume of blood circulation. This form is manifested in two clinical variants: a cordial and outside of the heart. The first option occurs when, in connection with certain congenital heart defects arterial and between the ventricular walls, cleft batalova duct, complete, or incomplete arterial – ventricle channel anastomosis between the lung and the subclavian artery, as well as operations: stenosis of the mouth of the pulmonary artery (operation bunting), shunt between artery system and arterial blood circulation. The second variant is associated with diseases involving acceleration of blood flow: hyperthyroidism, anemia etc. On both versions, the pressure in the small circle increases slightly.
6. It should be noted, however, that in the conditions of clinic, isolated pathogenic variant, is observed, if the latter is due to organic etiological factor. Pathogenic form, such clinical variants and styles, due to functional factor, usually, to a certain extent, combined, are intertwined. Therefore, it begs the appropriateness of the allocation of mixed pathogenetic form. The following tables present a classification scheme for hypertension in the pulmonary circulation.

MICROBIOLOGICAL CHARACTERISTICS OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH LYMPHO-PROLIFERATIVE DISEASES

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OBJECTIVE:

to assess the degree of contamination by opportunistic infections in lymphoproliferative diseases.

MATERIAL AND METHODS

The post evaluation analysis of 230 patient records diagnosed with lymphoproliferative diseases has been carried out, 74 patients of which are with Hodgkin's lymphoma (HL), 87 with non-Hodgkin's lymphoma (NHL), 39 with erythroid myeloma (EM) and 30 with chronic lymphatic leukemia (CLL). All patients underwent the standard examination, which was necessary for diagnosing according to current demands. The morphological and clinical variant of the core process course was determined on the results of the indicated examination. The patients were given the initiating therapy, and then the course of chemotherapy. Manifestations of OI were assessed on all treatment stages with the help of clinical, laboratory-based and microbiologic methods for the determination of manifestation infection fact and its agent.

RESULTS

On the whole OI agents structure was commensurable in all four groups of patients with different types of lymphoproliferative diseases. The leading position went to mycology and "mixed infection", the next was virus infection and the last were the infections, induced by bacteria in all the groups.

The maximum frequency of mycotic infection was presented in the patients with lymphoma (52% with HL and 51,1% with NHL). This index was statistically-valid higher as compared to the results in the patients with EM – 35,0% and CLL – 25,2%. In the OI structure, induced by mycology, the agents of Candida spp group predominated with the different forms of hamoblastosis. They are identified in 62,7% of cases and Aspergillus in 37,3%. Most of the patients had infectious complications of mycotic character in the form of mucositis with the predominant digestive system (77,9%) and respiratory system (12,2%) involvement. 16 strains of aspergillosis were identified as a part of the mycological examination of the orinasal pharynx biological material. In the vast majority of cases A.fumigatus was identified in 32,43% of them in the expressed fungi strains. A.flavus was expressed in 5,4% of cases.

The application of the up-to-date methods in diagnostics and examination allowed determining the extension of the infection, induced by viral etiology. The incidence of viral infections in patients with the different characters of lymphoproliferative diseases was not statistically different and was as follows: 21,0% with EM, 22,1% with CLL, 23,3% with NHL and 24,1% with HL.

In the agents of viral etiology the leading position in incidence went to cytomegalovirus infection (CMV) – 19,6% of the total number of OI manifestations in the patients with chronic lymphoproliferative diseases and 72,4% of the total amount of OI with viral etiology. In 4,0% CMV infection had generalized character. Herpetic infection, induced by Herpes simplex, was in 4,9% of cases.

Bacterial infections in the structure of all infectious complications took the last place. Bacterial infection was more often associated with CLL in 29,5% of cases. The lowest frequency of bacterial infections was found in the patients with NHL – in 13,5% of cases. In the whole the patients with lymphoma (HL and NHL) showed less affinity to bacterial infections, then the patients with EM and CLL.

The infections were more often determined, induced by the following bacteria: Streptococcus (19,39%), Staphylococcus (24,49%), Enterococcus (7,14%), Pseudomonas (4,60%), Klebsiella (9,18%), Escherichia (2,04%), Acinetobacter (1,02%); and also such enterobacteria as Enterococcus spp. (8,16%) and Pseudomonas spp. (4,76%).

CONCLUSION

1. The most common OI is fungal infection, the most expressed pathogen of which is yeast fungi Candida. Candida infection in the patients with lymphoproliferative diseases reaches to 52%. These patients are in the high-risk group. Received data are consistent with literature data.

2. The identification of OI agent is the important fact in the effective treatment of hemoblastosis infectious complication in order to increase survival capability of oncohematological patients and improve their quality of life.

DER EINFLUSS DER GENE POLYMORPHISMUS THROMBOGENITÄT AUF DIE REPRODUKTIVE FUNKTION DER FRAUEN

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EINLEITUNG

In den letzten Jahren vermindert sich die Bevölkerungszahl des Russlands auf 1 Million Menschen pro Jahr. Die Durchschnittszahl der Kinder in den Familien ist kleiner in 2 Mal als nützlich für Reproduktion. Nach den statistischen Angaben können die Zahl der Geschlechtsfamilien im Russland von 40 Millionen im Jahre 1995 bis 27 Millionen in den Jahren 2010-2020 etwa 30 % zurückgehen. Aus einem Grund, der zu der Erstunfruchtbarkeit und dem Fehlgeburt bringt, ist die Thrombophilie.

UNTERSUCHUNGSZIEL:

der Einfluss der Gene Polymorphismus Thrombogenität auf die reproduktive Funktion der Frauen in der Hanty-Mansijskij autonomen Bezirk schätzen.

Aufgaben der Forschung:

1. die Häufigkeit des Auftretens der Thrombophilie bei Frauen mit einer Geburtshilfe-gynäkologischen Anamnese schätzen.
2. die praktische Empfehlungen zu den Frauen mit der Thrombophilie und Prävention Kreislauf-Komplikationen bei diesen Patienten Entwickeln.

MATERIALIEN UND METHODEN

Die Forschung wurde im Chanty-Mansijsk Krankenhaus von 2011 bis 2013 durchgeführt. 78 Frauen wurden, deren Durchschnittsalter 32,4 Jahre ist, mit einer Geburtshilfe-gynäkologischen Anamnese (die Erstunfruchtbarkeit und der Fehlgeburt) und mit Thromboseanamnese beobachtet.

ERGEBNISSE UND DISKUSSION:

Aus der 78 untersuchten Frauen bei 19 diagnostiziert primäre Unfruchtbarkeit (24%), bei 56 ist die Fehlgeburt (69,6%), drei Frauen erhielten eine Therapie über Thrombosen unterschiedlicher Lokalisation (Thrombose der inneren Halsschlagader, transitorische ischämische Attacke, Thrombose der tiefen Venen der unteren Extremität).

Die Ergebnisse unserer Forschung zeigten, dass der Polymorphismus der Gene, wie MTRR, MTR, MTHFR 1298, gen Fibrinogen und gen-Aktivator Fibrinogen (PAI-1), im Zusammenhang mit der Verletzung der reproduktiven Frauen (primäre Unfruchtbarkeit) steht. Solche Änderungen haben in 71,5% der Fälle.

Polymorphismus Gene MTHFR 677 und MTHFR 1298, gen Faktor XIII und ITGA2 im Zusammenhang mit dem Fehlgeburt der Schwangerschaft (47%) steht.

Die Frauen bekamen spezifische Therapie. Nach der Ausbildung bei 2 Frauen primäre Unfruchtbarkeit kam natürlich Schwangerschaft, 14 Frauen macht man extrakorporale Befruchtung, von denen 13 der Entwicklung der Schwangerschaft und mit der Geburt in der Zeit endete. In 1 Fall kam die Frau zu einer Schwangerschaft nicht.

In der Gruppe der Frauen mit der üblichen Fehlgeburt kamen 34 Frauen zu der Schwangerschaft nach der Therapie. In 13 Fällen wurde extrakorporalen Befruchtung durchgeführt. Zum Zeitpunkt der Analyse von Studien bekamen die 23 Frauen ihre Kinder. Die anderen fühlen sich gut. Die Dauer der Schwangerschaft ist 39±2 Wochen (in dreq Fallen ist Frühgeburt im Begriff 32–36 Wochen der Trächtigkeit). Das durchschnittliche Gewicht der Kinder bei der Geburt ist 3368 G, das durchschnittliche Wachstum ist 52,3. Zwei Frauen bekam die Entwicklung von Thrombosen der mesenterialen Blutgefäße mit der weiteren Entwicklung der Lungenembolie und Thrombose der Arterien der Hörnerv in der ersten Trimester der Schwangerschaft. Diese Frauen bekamen Therapie. Die Schwangerschaft wurde gespeichert und beendet die Geburt. Derzeit dauert die Behandlung der 8 Frauen mit der üblichen Fehlgeburt der Schwangerschaft.

ZUSAMMENFASSUNG

1. Die Prävalenz der Thrombophilie bei Frauen in fertilen Alter, die Ihren Wohnsitz in Hanty-Mansijskij autonomen Bezirk haben, unterscheidet sich von der durchschnittlichen Daten Russlands nicht.
2. Die frühe Diagnostik der Thrombophilie und Ihre Korrektur fördert die Schwangerschaft vor, natürlich ohne Komplikationen, verhindert die Entwicklung von Thrombosen.

THE EFFICACY OF THE INTERVAL VACUUM THERAPY DEVICE VACUMED® IN PATIENTS WITH DIABETIC FOOT SYNDROME

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KEYWORDS — diabetic foot, vacuum therapy, VACUMED®

Maira Yespenbetova, Prof., MD, PhD

Nassiba Izatullayeva, Dr.

BACKGROUND

In the morbidity structure of economically developed countries diabetes mellitus hold one of the first places. The prevalence of diabetes mellitus in general population is 1.5–6%. Lesions of the lower limbs of different genesis occur in 30–80% of persons with impaired carbohydrate metabolism. Frequently these lesions are complicated by the development of chronic ulcers that at the late diagnosis and inadequate treatment leads to amputation of the affected limb.

The objective of this study was to evaluate the efficacy of the interval vacuum therapy device VACUMED® in patients with diabetic foot syndrome.

MATERIALS AND METHODS

In a study, 50 patients (36% – male, 64% – female) with diabetic foot syndrome, mean age 60.1±12 years who underwent complex therapy with the interval vacuum therapy device VACUMED® – 10 cycles with 20-minute exposure of negative pressure at -30 – -40 mm Hg over a 48–96 hours period were analysed. All diagnosis were confirmed according to diagnostic criteria of American Diabetes Association, DIAINF Study Group. In the duration of the study was evaluated the dynamics of microcirculation indicators in lower extremities according to USDG data, arterial pressure rates and intensity of pain syndrome in lower extremities according to numerical rating scale. Analyses were performed with SPSS, version 20.0 для Windows (IBM Ireland Product Distribution Limited, Ireland).

RESULTS

After a therapy was observed restoration of microcirculation due to reduction of stenosis events, blood flow and amplitude increasing on 35% vs. initial rate 55–60% ($p<0.01$). Also was defined renewal of mainline types of blood flow in the peripheral arteries. The positive effects was detected in the normalization of systolic and diastolic arterial pressure till 120±10 mm Hg and 85±5 mm Hg vs. of initial rates of systolic 150±12 mm Hg and diastolic arterial pressure 90±5 mm Hg ($p<0.05$). The important component in the efficacy evaluation was the decreasing of acute pain syndrome in the lower extremities. Before and after vacuum therapy was made evaluation according to numerical rating scale. There was found the significant decreasing of pain more than 3 points on first days of treatment and more than 5 points on tenth day of the treatment. Beside this was detected the decreasing of such symptoms as swelling and a feeling of heaviness in the lower limbs.

CONCLUSIONS

The results of the study let to tell about the efficacy of the interval vacuum therapy device VACUMED® in patients with diabetic foot syndrome. Introduction of this method in the therapy protocol of diabetic foot syndrome would reduce the number of such effects, as amputation of the affected limb.

VERHALTENSTHERAPEUTISCHE INTERVENTIONEN IM RAHMEN MULTIMODALER SCHMERZTHERAPIE

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Bei chronischen Schmerzpatienten besteht laut aktueller Studienlage nur ein geringer statistischer Zusammenhang zwischen organischer Schädigung und wahrgenommener Schmerzstärke bzw. diesbezüglich erlebter Beeinträchtigung. Ein multimodaler Interventionsansatz hat sich in Anbetracht der Komplexität des Krankheits- und Störungsbildes als gegenwärtiger Behandlungsstandard etabliert.

Chronische Schmerzerkrankungen gehen einher mit mangelnder Befriedigung menschlicher Grundbedürfnisse. Durch fortschreitendes Schmerzleiden entsteht ein Erleben von zunehmendem Kontrollverlust über den eigenen Körper und die Weiterentwicklung individueller Lebensbedingungen. Häufige Folgen von andauernden Leistungseinschränkungen bestehen in Selbstwertzweifeln und psychosozialen Konflikten, insbesondere im Zusammenhang mit Schwierigkeiten bei der Erfüllung gewohnter sozialer Rollen.

Physiologisch fungiert Schmerz, mit einer Überaktivierung des sympathischen Nervensystems, als massiver Stressor für den Gesamtorganismus und hieraus resultierende muskuläre Verspannungszustände münden in eine teufelskreisartige sekundäre Schmerzzunahme. Auf zentralnervöser Ebene spielen im Verlauf der Schmerzchronifizierung neuroplastische Veränderungsprozesse eine bedeutsame Rolle. Durch den ständigen nozizeptiven Input entstehen neuronale Spuren mit vergrößerter Repräsentation des Schmerzgeschehens im somatosensorischen Kortex, eine Schmerzsensibilisierung und ein durch assoziative Lernprozesse zunehmend differenziertes Schmerzgedächtnis. Einerseits existiert eine Wechselwirkung zwischen aktuellem Schmerzerleben, der Schmerzbewertung sowie der Wahrnehmung von Kontrollmöglichkeiten und aufgrund der Entwicklung klassisch konditionierter Schmerzerwartungen beeinflusst der aktuelle Schmerz die zukünftige Schmerzverarbeitung. Andererseits können Verstärkungsprozesse die operante Konditionierung eines bestimmten möglicherweise maladaptiven Schmerzverhaltens bewirken.

Die moderne multimodale Schmerztherapie definiert dementsprechend Schmerz als bio-psychosoziales Phänomen mit Interventionsansätzen auf den Ebenen des Körpers, der Gedanken und Gefühle sowie des beobachtbaren Verhaltens.

USE OF ENDOSURGICAL TECHNIQUES IN THE TREATMENT OF PATIENTS WITH TUMOUR-LIKE OVARIAN FORMATIONS

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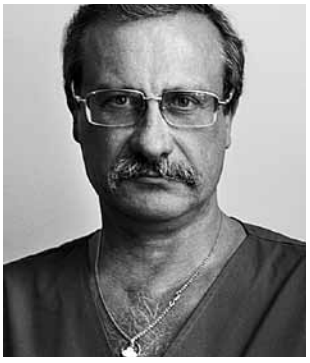

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Ovarian tumours and tumour-like ovarian formations remain one of the most urgent problems in the modern clinical medicine. In the first place, it is caused

by the incidence rate of this pathology and difficulties in the differential diagnostics between malignant and benign ovarian tumours. As D.N. Demidov and B.I Zykin point out in their work (2), ovaries of women of the reproductive age often have functional cysts, follicles and yellow bodies at different development stages.

As a rule, screening examination methods available in the wide clinical practice, e.g. abdominal rectovaginal examination and ultrasound, do not make possible to characterise a pathological process in the ovarian area according to the degree of malignancy.

For this reason, when having indistinct palpatory data and ambiguous results of echographic examinations, many authors, e.g. G.M. Savelieva (3), L.V. Adamyan et.al. (1), A.N. Strizhakov, A.I. Davydov (1991), Saksetall (1985), Bouttevilleetall (1087), are of the opinion that it is possible to use laparoscopic techniques to determine the character of ovarian tumours and surgical treatment more accurately.

In "Dr Paramonov's Clinic" we observed and treated 67 women with various tumour-like ovarian processes (class IX of the World Health Organisation Histological Classification of Ovarian Tumours, 1973) (4). The patients were between 21 and 34 years old. The average age was 26.5±2.1.

Ovarian pathology was diagnosed by means of a traditional scheme which included taking of medical history, general clinical and gynaecological examination and a series of additional procedures. In order to eliminate metastatic ovarian cancer, we examined the condition of the gastrointestinal tract by means of fibro-gastroduodenoscopy or stomach fluoroscopy, rectoromanoscopy and colonoscopy. To determine the content of the tumour marker CA^{125} in the blood serum, we used a monoclonal antibody method. During our work we used reagents and equipment by Olimpus (Japan) and SorinBiomedica (Italy). None of the examined women had any pathological changes of the gastrointestinal tract or any significant increase of the CA^{125} content.

The medical history showed that before hospitalisation 28 (41.8%) women received combined therapy in regard to ovarian inflammatory disease and 25 (37.3%) women received combined oral contraceptive pill in the course of 2–3 menstrual cycles. 14 (20.9%) patients did not receive any conservative treatment due to the fact that the tumour diameter was larger than 6 cm or because there was a strong tendency to a cyst with a twisted pedicle.

All the patients underwent a dynamic examination of small pelvis organs. We used real-time equipment SiemensSonolineVeraPro (Germany), 3.5 MHz convex and linear sensors and a 6.5 MHz intra-vaginal convex sensor. Operative laparoscopy was performed under combined endotracheal anaesthesia using standard techniques with three protocols. We used equipment by "Cabotmedical", "AutoSutricalInstruments", «Johnson & Johnson» (USA) and "Endmedium" (Kazan). Pneumoperitoneum was created by CO_2.

During laparoscopic surgery, we took a sample of the abdominal cavity contents for a further bacteriological and virologic analysis for the presence of predominantly sexually transmitted pathologic agents.

When detecting a tumour-like formation in the ovarian area, the cyst was removed without pouring the contents into the abdominal cavity, if possible.

For this purpose, the tumour-like formation was enucleated from the surrounding tissues and placed into a special rubber tank (airtight reservoirs from glove rubber). Only after this we performed a cyst aspiration with the smallest amount of the contents getting into the abdominal cavity. Monopolar and bipolar coagulation were used for the mobilisation of the formation and hemostasis.

When the ovarian pathology was combined with a significant adhesive process (in 14 –20.9% – patients), we performed adhesiostomy, fimbryolysis, uterine tubes patency recovery (salpingostomy, salpingoneostomy), usually by means of sharp dissection using monopolar electrocoagulation.

Postoperative regimen management was very active. In the first hours after recovery, patients received general massage, respiratory exercises, physical therapy. 3–4 hours after the surgery the patients were transferred from the resuscitation department to the general hospital ward. Narcotic analgesics were only given to the patients once and were combined with antihistamines. There were no drinking limitations for the patients. The food intake was optional and took place in accordance to the patient's state.

According to our data, the average duration of surgery was 44±6 minutes, the blood loss in all the cases was very low and did not exceed 50ml. The use of laparoscopic surgery made it possible to reduce the patients' stay in the hospital, which lasted 4.3±0.4 days on average.

The size of the extracted formations varied between 3 and 11 cm in diameter and was 4.8±0.6 cm on average.

The histological verification of the extracted formation showed that 18 (26.8%) women had follicular cysts, 13 (19.4%) — multiple follicular cysts (polycystic ovaries), 23 (34.3%) — corpus luteum cysts, 6 (8.9%) — surface epithelial inclusion cysts (germinal inclusion cysts) and 7 (10.4%) — paraovarial cysts.

The patients were advised to have sexual abstinence until their next period and use condoms in the course of at least 3 months after the surgery.

There were no complications during the surgery or in the postsurgical period. We agree with the opinion of L.V. Adamyan et. al. that, when treating patients

with ovarian tumours, operational laparoscopy might have the following complications: the possibility of pouring out the formation contents into the abdominal cavity and the possibility of the process dissemination which is characterised by the absence of guarantee of the complete capsule removal and the impossibility of the precise histological analysis of the removed tissues due to coagulation or tissue vaporisation.

However, taking into account the insignificant frequency of ovarian tumour malignization — 1.8 out of 100 (Andlf E. AstedB., 1986) — we think that it is possible to use laparoscopy for the treatment of tumour-like ovarian processes after the preliminary elimination of the malignant character of the formation (the principle of the oncological alertness).

For this purpose, we dynamically determined the tumour marker CA^{125} by means of the ultrasound and examined the condition of the gastrointestinal tract. It is necessary to emphasize that an atrophic form of the chronic gastritis A+B (5) detected during the fibrogastroduodenoscopy is one of the increased risk factors for the ovarian cancer.

Furthermore, we think it is advisable to treat patients with tumour-like processes with monophasic birth control pills in the course of three months according to the method of Granberg et. al. (1989). And only in case this treatment is inefficient, it is necessary to perform an endoscopic surgery. The exception is made in the case of women with tumour-like formations, the diameter of which is more than 6 cm due to the fact that this category of patients has a high risk of acute complications in the course of the ovarian tumour, e.g. twisted pedicle or rupture of the cyst capsule.

Therapeutic laparoscopy is particularly advisable for women who plan a pregnancy in the nearest future or have various types of tuboperitoneal infertility, because the surgery makes it possible to both modify the condition of the fallopian tubes and reduce the frequency of the postsurgical adhesion — the main infertility factor — to the minimum.

DIE DIAGNOSTIK UND BEHANDLUNG ANALER INSUFFIZIENZ BEI KINDER

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Einleitung

Analatresie und Atresie des Rektums machen über 80% aller anorektaler Mißbildungen bei Kindern aus (Korol E.F, 2005; Lenushkin A.I. 1999; Rintala R. 1994)) Anale Inkontinenz gehört zu den schwierigsten Pathologien im Kindesalter. Die Stuhlinkontinenz führt zu schweren seelischen Leiden beim Kind und Eltern. (Fomenko O.J 2007; Sulajmanov A.C. 1984; Nicastro A. 2006) Trotz vielen Forschungsarbeiten und trotz der Entwicklung neuer plastischen Rekonstruktionstechniken, ist das Ergebniss in 15% bis 60% der Fälle nicht zufriedenstellend. (Dultsev J.V. 1993; Evans D. 2005) Die Erfolgsrate chirurgischer Behandlung bei Analatresie hängt vom Stadium, Form der Atresie, Kindesalter und der Art der Rekonstruktion ab. In den letzten Jahren hat man sich viel bemüht um die Ergebnisse der operativen Behandlung der angeborenen kolorektalen Mißbildungen und insbesondere der Analatresie zu verbessern. Nichtdestotrotz bleibt die Frage der Erfolgsrate Rekonstruktioneingriffe bei Analatresie offen.

In der Proktologie wendet man immer häufiger die Operation nach Feierman bei der Neubildung des analen Sphinkters an, außerdem führt man die Sphinkteroplastik aus der Fascia lata nach Vredin, aus M.gluteus maximus nach Aminov usw durch. In diesem Zusammenhang bleibt eine qualitative Verbesserung der Behandlung bei Kinder mit Stuhlinkontinenz wichtig.

Ziel der Studie

Verbesserung der Ergebnisse der Rekonstruktiv-plastischer Eingriffe bei Kindern mit analer Atresie

Materialien und Methoden. Wir haben die Ergebnisse der Behadlung von insgesamt 31 Kinder mit Stuhlinkontinenz von 2006 bis 2013 ausgewertet. Die Kinder waren im Alter von 2 bis 14 Jahren. Alle Kinder waren im Zustand nach Operationen der anorektaler Mißbildungen: Analatresie (8), anorektale Atresie (19), Rektumatresie (4). Von 31 Kindern hatten 24 (77,41%) Fisteln, Anusatresie mit Fistel bei 13(54,16%), Dammektopie bei 2(8,3%), Uretralfistel bei (16,66%), Harnfistel 2(8,33%) и und Scheidenfistel bei 3(12,5%) der Kinder. Hohe rektale Atresie lag bei 7(22,5%) vor, Zwischen — 4(12,9%) und tiefe Atresie bei 20(64,5%). Von 31 Kindern wurde bei 13(41,9%) kombinierte Peritoneum- und Dammplastik durchgeführt und bei 18(58,1%) proktologische Dammplastik. Die Diagnose der analen Insuffizienz wurde anhand von Klinik, radiologischen Untersuchungsergebnissen, Koloskopie, Myographie und Sphinktometrie gestellt. Aber um die Funktion des inneren und äußeren Sphinkters, der puborektalen Muskulatur und des Analkanals nach den Eingriffen einzuschätzen, braucht man spezielle Untersuchungsmethoden. Heutzutage sind Kolonkontrasteinlauf und radiologische Untersuchungen die einfachste und die informativste Methode. Je nach Länge des Analkanals (bei Gesunden führt eine Dehnung des Rektums durch 10–30 cm^3 Luft zur reflektorischen Kontraktion und anschließender Relaxation des inneren Sphinkters und zu Kontraktion des äußeren Sphinkters) unterscheiden man funktionelle Grade der Insuffizienz I(3), II(4), III(24 Die Kinder waren im Alter von 2 bis 14 Jahren. Die Patienten wurden auf zwei Gruppen verteilt: die Kontrollgruppe, wo die Operation nach Feiermann Plastik des Sphinkters durch Glutealmuskulatur oder durch Muskulatur des inneren und äußeren Schließmuskels (12) durchgeführt wurde; und die Hauptgruppe die Plastik nach Feiermann modifiziert nach unerer Klinik (19) erhalten hat.

Die Plastik nach Feiermann modifiziert nach unerer Klinik sieht folgendermaßen aus: der erste Schritt ist ein Schnitt der Innenseite des linken oder rechten Oberschenkels in der Projektion des M. gracilis von dem oberen Drittel des Oberschenkels bis zum Einsatz der Muskulatur. Dann folgt eine vorsichtige Präparation des M.grazilis und eine Durchtrennung an dem Sehnenansatz unter Erhalt von versorgenden Gefäßen, selbstverständlich unter Einsatz des Operationsmikroskop. Im zweiten Schritt führt man zwei Schnitte beidseits vom Anus im Abstand von 3 cm und ein Schnitt median am Damm hinter dem Anus 3 cm lang, dann folgt die Untertunnelung der Haut am Oberschenkel und um den Analring, M.grazilis wird in zwei gleiche Hälften durchtrennt und und wird durch das Tunnel beidseits geführt. Zuerst die erste Hälfte der Muskulatur und dann die zweite werden gegenläufig um den Anus herum gelegt. Auf jeden Fall zu beachten ist, dass die beiden Muskelbäuch völlig spannungsfrei übereinander im Tunnel liegen. Danach werden beide Enden des Muskels im Sehnenbereich miteinander vernäht, im dritten Schritt vernäht man die Wunde am Oberschenkel und am Anus.

Ergebnisse und Diskussion.

Bei Aufnahme zeigte sich bei Kindern mit Sphinkterinsuffizienz Grad 2 и 3 ein klaffender Anusm fehlender Tonus des Sphinkters, bei Grad 1 geringe Muskelkontraktionen, bei Grad 2 и 3 fehlend, also eine komplette Inkontinenz von Stuhlmassen. Bei Insuffizienz Grad 2 -3 lag bei Kindern im Zustand nach einem operativen Eingriff bei angeborener Mißbildung der Druck im Rektum bei 5–10 cm^3. Je nach Grad der analen Insuffizienz und der vorangegangener OP führten wir bis 2004 folgende Arten der Proktoplastik durch: OP nach Feiermann y 2 детей Plastik mit Glutealmuskulatur y 5, Plastik durch die Muskulatur des inneren und äußeren Sphinkters y 5. Postoperative Komplikationen nach OP nach Feiermann traten als Stuhlinkontinenz y 2, Plastik mit Glutealmuskulatur y 3, Plastik durch die Muskulatur des inneren und äußeren Sphinkters trat ein Rezidiv bei 2 Patienten. Wie die Analyse der Ergebnisse in der Kontrollgruppe zeigt lag die Quote der Komplikationen bei 58,3%, was insgesamt eine untzureichende Wirksamkeit zeigt.

Die Plastik nach Feierman modifiziert nach unserer Klinik wurde bei 16 Patienten durchgeführt. Drei von 31 Kinder mit der Stuhlinkontinenz Grad I wurden konservativ behandelt: Elektostimulation, Physiotherapie, Massagen, Krankengymnastik. Der Zustand der Kinder hat sich deutlich verbessert, allerdings blieb Schmierinkontinenz bei weichen Stühlen.

Alle Patienten erhielten eine Therapie, um die rheologischen Eigenschaften von Blut, die Regeneration des Gewebes und den Immunschutz zu verbessern, Krankengymnastik und Übungen des neu erschaffenen Sphinkters.

Die Untersuchung der langfristigen Behandlungsergebnisse bei 16 Patientin nach einem Zeitraum von 5 bis 10 Jahren zeigte bei 3 (18,7%) der Kinder nach der modifizierten Operation nach Feiermann zeigte Komplikationen wir Schmieren und Insuffizienz bei weichem Stuhl.

Also zeigte die Analyse der Beobachtungen eine Wirksamkeit der vorgeschlagenen Methode bei Stuhinkontinenz, obwohl die Narben an der Innenseite der Oberschenkel und um den Anus kosmetisch auf-

fallen. Bei dem modifiziertem Eingriff nach Feierman wurden gute Ergebnisse bei 10 Kinder (62,5%), zufriedenstellende bei 3(18,7%) und unzureichende bei 3(18,7%) erreicht. Dieser Eingriff ist wirksam bei Kindern über 10 Jahre. Zur Vorbeugung der Komplikationen ist eine Anwendung vom medizinischem Ozon als Bestandteil der komplexen medikamentösen Therapie und Krankengymnastik sinnvoll.

Fazit

1. Die Modifikation der chirurgischen Korrektur konnte kurzfristige und langfristige Ergebnisse in der Behandlung der Stuhlinkontinenz verbessern.
2. Die Gesamtheit der konservativen Therapiemethoden vor und nach dem Eingriff und eine rehabilitative Therapie bei Kindern mit Stuhlinkontinenz verbessern die Funktionalität des Sphinkters.

SURGICAL PREPARATION OF WOMEN WITH GENITAL PATHOLOGIES FOR EXTRA-CORPOREAL FERTILISATION

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Infertility is a problem that occupies a particular place in medicine. It is very important to know the reasons which complicate the onset of pregnancy. The main reasons are a commissural process which occurs as a result of external and internal genital endometriosis and inflammatory diseases of fallopian tubes, fibrimyoma uterus of various localisations. In 90 % of cases, surgical correction is performed by endoscopic methods. The probability of pregnancy after the surgical preparation for the extracorporeal fertilisation increases by 12%.

The objective of the research was the endoscopic surgical preparation which makes it possible to increase the percentage of infertility treatment.

Materials and methods

917 couples with infertility problems turned to our centre in 213. 417 of them required extracorporeal fertilisation. 217 patients of the first group received laparoscopy and hysteroscopy before the extracorporeal fertilisation.

200 patients of the second group received extracorporeal fertilisation without the preceding surgical preparation. The effectiveness in the first group was 51.8% and it was 40% in the second group.

Surgical correction before extracorporeal fertilisation has several objectives:

1. Removal of the negative hydrosalpinx influence on the implantation and embryogenesis processes;
2. Risk reduction of the ectopic pregnancy when performing extracorporeal fertilisation;
3. Removal of small pelvis pathologies which can might have a negative influence on the results of the procedure.

In general, we single out 2 types of surgeries:

1. Plastic-reconstructive, in order to restore uterine tubes patency before natural conception;
2. Surgeries directed towards the creation of appropriate conditions for the extracorporeal fertilisation (removal of hydrosalpinx, ovarian cysts, paraovarian cysts) and creation of conditions for ovariocentesis (salpingoovariolysis, ovariopexy).

Clinical case

In October 2013 patient N. was accepted into the extracorporeal fertilisation programme with the diagnosis of infertility of the first endocrine genesis. Her medical history revealed appendectomy in childhood. Due to an intense commissural process in the small pelvis, anatomical shortening of the broad ligaments of uterus and uteroovarian ligaments, the transvaginal ovariocentesis was accompanied by technical difficulties. We only managed to obtain one oocyte and the pregnancy did not occur.

In November 2013 the patient had laparoscopy, salpingoovariolysis, ovariopexy and the anatomical position of the uterine appendages was restored.

In January 2014 the patient returned to the extracorporeal fertilisation programme; the transvaginal ovariocentesis was carried out without any technical difficulties. We received 11 oocytes and there was a single pregnancy.

Conclusion

Endoscopic surgical procedures (laparoscopy and hysteroscopy) make up a final and obligatory stage of diagnostics and infertility treatment for women with genital pathologies and before extracorporeal fertilisation.

TRANSFER STRATEGY: CHOOSING THE NUMBER OF EBMRYOS FOR TRANSFER

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Patients who turn to Russian Reproductive Medicine clinics often ask how many embryos are going to be transferred. In the dawn of the auxiliary reproductive technologies, 3–4 or even more embryos were transferred. Then, this transfer strategy was justified. However, the number of multiple-fetus pregnancies (twins, triplets or more) was gradually increasing, which made doctors to strictly reduce the number of the transferred embryos (Fig. 1).

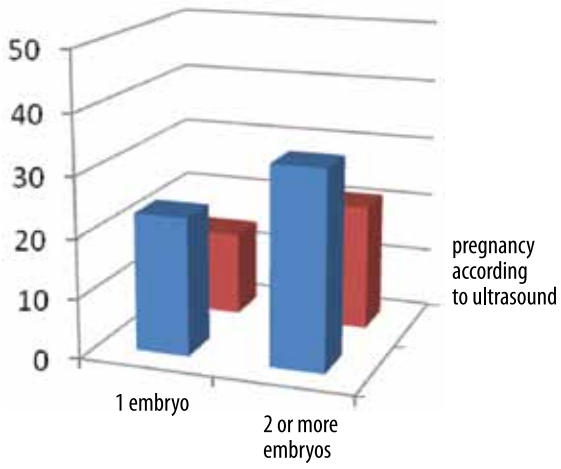

Fig. 1. *Transfer at the blastomere stage*

The main problems of multiple-fetus pregnancies are:

- Premature birth is more frequent (from 40 up to 80%);
- Newborns' weight in case of multiple-fetus pregnancies is significantly lower than in case of single pregnancies (from 800 to 1500 g);
- Newborns require resuscitation activities in the postpartum;
- The cases of disability are more frequent;
- Infant mortality is much higher in the group of multiple-fetus pregnancies than in case of single pregnancies;
- High cost of medical aid.

It is necessary to say that there are many cases of successful completions of twin pregnancies in Reproductive Medicine clinics, however, the statistics is inexorable – multiple-fetus pregnancies have higher risks for both mother and child. So what is the solution? How can we reduce risks connected to multiple pregnancies? The only right solution is the transfer of only one embryo. The data of embryo transfer at the blastomere stage shows different parameters (Fig. 2): the number of births is equal when transferring 1 or 2 or more embryos.

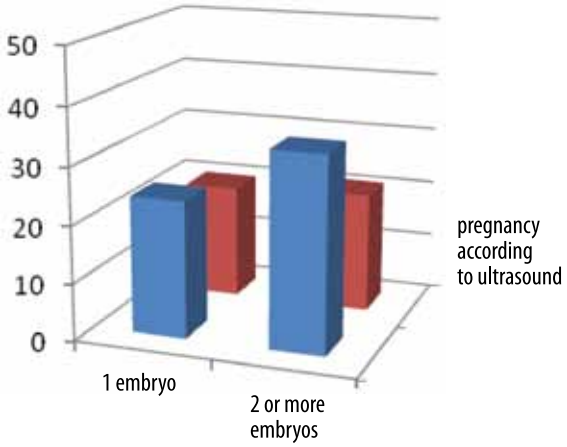

Fig.2. *Transfer at the blastomere stage*

Conclusion

It is obvious that the transfer of 2 or more embryos only influences the effectiveness of pregnancy determined by means of ultrasound. The number of births is equal in both cases. Therefore, it is advisable to transfer only one embryo at the blastomere stage.

ENTERAL ANTIHYPOXIC THERAPY OF THE INTESTINAL FAILURE IN DIFFUSE PERITONITIS PATIENTS

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One of the main reasons which have a direct influence on the outcome of an open cavitary surgery in the abdominal cavity organs in the case of diffuse peritonitis patients is the intestinal failure which develops in the early postoperative period. One of the intestinal failure treatment techniques in the case of diffuse peritonitis is one or another type of gastrointestinal decompression. The most frequently used technique is a nasointestinal drainage used for the intestinal decompression, early enteral nutrition and introduction of pharmaceutical substances. Over the last few years, this concept of the intensive intestinal failure therapy has outlined a new approach which foresees an incorporation of pharmaceutical antihypoxic agents which actively stimulate organ metabolic processes in the intestine [1, 2, 3].

On the base of the pharmaceutical research and manufacturing enterprise "Astlek" we have developed an oxygenated water technology "OxyEnergy". This product is a specially prepared and purified water, enriched with pure oxygen molecules in the amount of 250000 ppm. This water has not been previously used for the treatment of intestinal failure patients.

The objective of the research was to improve the results of intestinal failure patients with diffuse peritonitis.

The research was conducted among 86 patients with diffuse purulent peritonitis who were treated in the General Surgery Unit of the Astrakhan State Medical Academy on the base of the State Budget Healthcare Institution of the Astrakhan Region "City Clinical Hospital №3" in Astrakhan. The age of the patients was between 19 and 82. Mannheim peritonitis index was 21.5 on average.

The following describes the treatment method for the intestinal failure with the diffuse purulent peritonitis, first developed by us. After the removal of the peritonitis source and sanitation of the abdominal cavity we placed a nasointestinal tube and removed intestinal contents, thus reaching complete decompression. Then the intestine was cleaned with a saline solution until the water was clear. During and after the operation we also introduced the oxygenated water in the amount of 100 ml by means of the nasointestinal tube, with the subsequent tube occlusion for the duration of 60 minutes. The oxygenated water was introduced twice a day every 12 hours in the course of 3–5 days [4].

In order to monitor the effectiveness of the technique, we analysed the acid-base balance and blood gas with the help of the Medica Edsy Blood Gas analyser (USA, selective electrode technique). The tests were taken before the introduction of the oxygenated water (initial indexes); 30 minutes after its introduction we analysed blood samples from the superior mesenteric vein and the central vein. 60 and 120 minutes after the introduction of the oxygenated water we took more blood samples from the central vein. We then calculated the arithmetic mean value by means of the method of moments to estimate the certainty value of the mean and relative values according to the Student's t-tests.

We applied this technique in the group of 46 patients with diffuse peritonitis. The obtained results were compared to the results of the other group of 40 patients who did not receive any oxygenated water. The groups were identical according to their gender, age, severity of the pathology and character of surgical procedures. There were no complications when using the above technique.

The research results are shown in Table 1.

The research showed that all the patients with diffuse peritonitis suffered from acidosis, hypercapnia and hypoxia before the oxygenated water introduction. There was a significantly faster reduction of the hypoxia symptoms in the group of patients who received the oxygenated water, which was confirmed by the

Table 1. *Indicators of acid-base balance and gas composition of blood in the groups*

Indicators	Group of interest (n-14)				Control group (n-15)			
	start	30 min	60 min	120 min	start	30 min	30 min	120 min
pH	7,27	7,38	7,30	7,32	7,26	7,23	7,1	7,16
pCO_2	45,5	44,4	38,5	35,4	51,2	51,0	50,5	45,4
pO_2	32±1,1	63±1,2	68±1,1	91±1,5	36±0,9	42±0,8	58±1,1	59±1,3
TCO_2 %	22,3	22,2	20,9	17,9	24,7	23,4	20,9	17,9
HCO_3 mmol/l	21	20,8	19,3	16,5	23,1	21,8	19,3	16,5
BE в mmol/l	-5,9	-6,1	-9,3	-12,0	-4,6	-6,2	-9,3	-12,0
BE ect mmol/l	-6,0	-6,1	-9,1	-12,2	-4,1	-5,8	-9,1	-12,2
SO_2 %	54,1±1,5	75,9±1,1	82,4±0,9	88,5±1,1	59,8±1,2	60,1±1,1	66,4±1,2	62,5±1,3
O_2 stand. %	12,1±0,3	15,4±0,2	16,8±0,4	22,1±0,3	12,2±0,4	13,9±0,4	12,8±0,3	11,1±0,2
R 1	40	49	30	34	51	45	30	32

Additional information: in the indicators pO_2, SO_2, O_2 standard accuracy changes ($p<0,05$)

increase in the oxygen partial pressure in the superior mesenteric and central veins.

The average duration of the nasointestinal tube presence and the relief of the intestinal failure in the main group was 3.8 days and 5.8 days in the control group. In the main group, 3 patients died from the progressing intoxication and multiple organ failure. 6 patients deceased in the control group. On average, the patients of the first group stayed 15.8 days in the hospital and those in the second group – 18.5 days.

In addition to the acid-base balance and blood gas tests, we also analysed other biochemical and immunological oxidative stress markers. The results of these tests were not included into this article, however, they correlated with the final research results.

This way, against the background of the combined therapy, the introduction of the oxygenated water by means of the nasointestinal tube in the case of patients with diffuse peritonitis makes it possible to relief the hypoxia of the intestinal wall and the intestinal failure symptoms within a shorter period of time. When using our technique, the nasointestinal drainage lasts 2 days less, thus reducing the complications connected to it. Our technique is simple, does not require any additional equipment and ultimately leads to a cost reduction due to the shorter stay of the patient in the hospital. Furthermore, our method reduces the lethality of patients with diffuse peritonitis.

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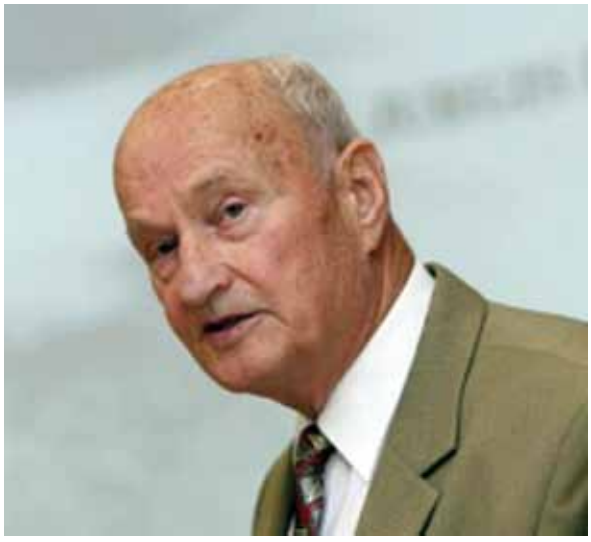

PROF. Bredikis Urgis Uoso

turning 85 on the 30.04. 2014

Born in 30.04.1929. Surgeon. Academician of the Academy of Medical Science (1986; correspondence-clerk 1969). Graduated from the Kaunas Medical Institute (1952), clinical internship at the same institution at the hospital therapy department and post graduated studies at the department of operative surgery and topographic anatomy 1 MMI (1957). Assistant (1957), associate professor (1961), Head of Department (1964), professor (1966) of operative surgery at the Kaunas Medical Institute. His main scientific work is dedicated to experimental and clinical heart surgery, the development and application of new electronic devices and mathematic methods of processing information, medical cybernetics affairs.

One of the first in the USSR he developed and used the method of electro stimulation on the heart. Board member of the Lithuanians Society of Surgeons. Board member of the international Society of Medical Technique. Member of the international Society of Surgeons. National prize of the USSR(1986) for the development and introduction to the clinical practice of new diagnostic methods as well as surgery treatment with the tachyarrhythmia.

National prize Lithaunians USSR for his work on coronary insufficiency. Active member of the EANS(2013). Honorable European Inventor (2013), Honorable science figure of the EANS(2014), Distinguished Inventor of the Fatherland (2012), Honorable Inventor AMTS (2013).

Chief of the international cardiologic center (1984-1990), Health minister of Lithuanians (1993-1994), Diplomat Lithuanians in Czech Republic, Hungary, Turkey (1995–1998).

Creator and up to date president of board of the Society "Svisuva" (analog to the existing Lithuania society "Znanie") as well as president of the fond "Science and Society" of the Lithuanian Academy of Science.

Medizinisches Kompetenzzentrum in Neurologie und Rehabilitation

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→ Fachkrankenhaus für neurologische Frührehabilitation
→ Neurologisches Fachkrankenhaus für Bewegungsstörungen/Parkinson

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- → **Neurologische Spätrehabilitation** aller neurologischer Krankheitsbilder, Anschlussheilbehandlung
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  Rehabilitation neuroimmunologischer Erkrankungen in Kooperation mit der Charite`- Universitätsmedizin Berlin, Campus Mitte
  Schwerpunkt Dystonie und Spastik im Funktionsbereich Neuroorthopädie mit individuellen spezifischen Therapieangeboten
- → **Akutbehandlung von Patienten mit Parkinson-Erkrankungen und Bewegungsstörungen**

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Zustand nach Schädel-Hirn-Trauma, Hirninfarkt oder intrakranieller Blutung, Operation von Hirntumor, Nervenverletzung, entzündliche Hirn- oder Rückenmarkerkrankung, Querschnittlähmung, Parkinson, Dystonie, hypoxische Hirnschädigung, chronisches Guillain-Barré-Syndrom/Polyneuritis/Polyneuropathie, Multiple Sklerose, Epilepsie, degenerative Hirn- und Rückenmarkerkrankung mit akuten Veränderungen

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Unterbringung

Die Kliniken befinden sich in modern rekonstruierten, historischen Gebäuden eines einzigartig architektonischen Ensembles von Gebäude- und Landschaftsarchitektur. Helle und freundliche, durchgehend barrierefreie Zimmer sowie ein aufmerksames, fachlich hochkompetentes Team von Ärzten, Pflegekräften, Therapeuten, Service- und Verwaltungsmitarbeitern sorgen für Ihren angenehmen Aufenthalt. Unser Personal spricht englisch und teilweise russisch; internationale Gäste sind also willkommen.

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Beelitz-Heilstätten liegt in unmittelbarer Nähe zu Potsdam und im Nahverkehrsbereich Berlin. Mit stündlicher Zuganbindung ist das Stadtzentrum Berlins in 45 Minuten erreicht. Die Mittelmark mit Wald- und Seenreichtum hat einen hohen Erholungs- und Freizeitwert und zeichnet sich durch Ruhe und naturbelassene Landschaften aus. Eigener Regionalverkehrsbahnhof und eigene Ausfahrt an der BAB 9 direkt vor dem Berliner Ring sorgen für eine hervorragende Verkehrsanbindung. Die internationalen Flughäfen Berlin-Tegel und Berlin-Schönefeld sind in kürzester Zeit erreichbar.

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Medizinische Hochschule Hannover

KLINIK FALLINGBOSTEL

Fachklinik für Rehabilitation

Durch unsere Partnerschaft mit der Medizinischen Hochschule (MHH) können wir allen Patienten eine effiziente Behandlung auf höchsten Niveau in fast allen Fachgebieten anbieten. Wir überprüfen gemeinsam mit der MHH die Behandlungsmöglichkeiten und führen die notwendigen Voruntersuchungen durch. Zur Operationen werden die Patienten in der MHH stationär aufgenommen und sobald wie möglich wieder zurück in die Klinik Fallingbostel verlegt.

Die Klinik Fallingbostel ist ein Zentrum für spezialisierte Rehabilitation aller Herz- und Gefäßkrankheiten, der post-operativen Nachsorge mit Wundbehandlung und der Rehabilitation chronischer Krankheiten z.B. durch orthopädische oder neurologische Krankheiten.

Die Rehabilitationsbehandlung wird aus einem breiten, modernen Angebot von anerkannten Therapieverfahren individuell auf die Bedürfnisse und Fähigkeiten des einzelnen Patienten abgestimmt. Alle Patienten erhalten täglich 5-6 Behandlungen, jeweils 20-30 Minuten. Der Sonntag steht den Patienten zur freien Verfügung.

Die Patienten werden vom Flughafen oder vom Hauptbahnhof (Hannover, Hamburg oder Bremen) direkt abgeholt. Wir haben englisch und russisch sprechende Ärzte und Fachpersonal und bieten eine rund-um-die-Uhr Versorgung d.h. auch nachts und am Wochenende.

Unterbringung
In unserem barrierefreien Haus wohnen die Patienten in hellen und freundlich eingerichteten Zimmern. Es kann zwischen unterschiedlich großen Einzelzimmern bis zum 4-Raum-Appartment mit Balkon, Dusche, WC, Safe, Telefon, russisches Fernsehen und Internetanschluss gewählt werden.
Selbstverständlich können Angehörige und Betreuer den Patienten begleiten und auch auf Wunsch im Zimmer oder Appartment des Patienten wohnen oder ein extra Zimmer in der Nähe erhalten.

Unsere Klinik befindet sich am Rande der Kleinstadt Bad Fallingbostel in Norddeutschland (zwischen Hamburg, Hannover und Bremen) und liegt am Rande des Kurparks mit kurzen Wegen zum Ortszentrum. Der Ort ist sicher und ruhig und es gibt ausreichend Geschäfte für den täglichen Bedarf.

Weitere Informationen über uns und unsere Möglichkeiten können über unser Aufnahmebüro unter 05162/44-605 erfragt werden. Gerne schicken wir auch Informationsmaterial zu. Auch im Internet unter www.klinik-fallingbostel.de würden wir uns über einen Besuch freuen.

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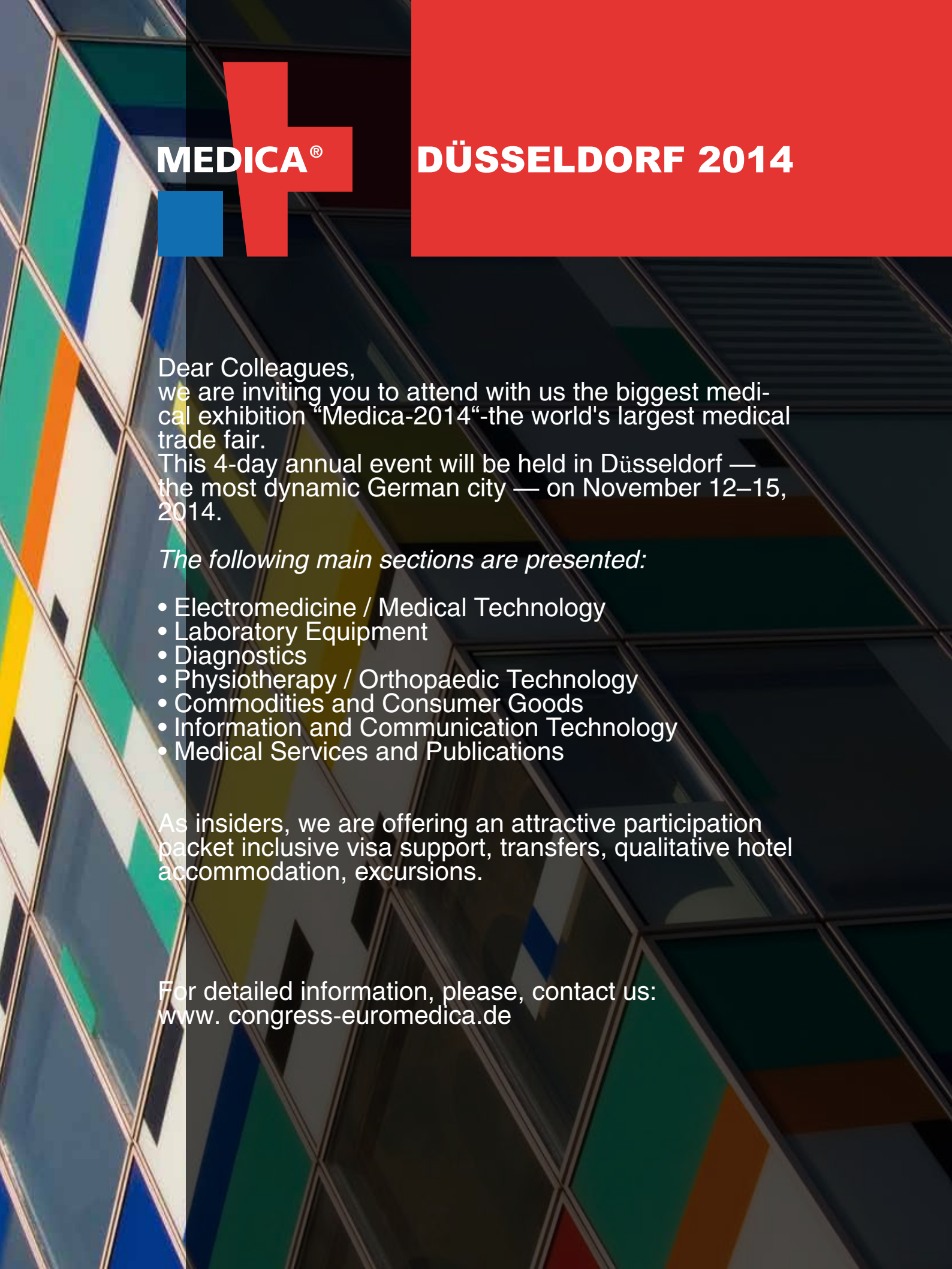

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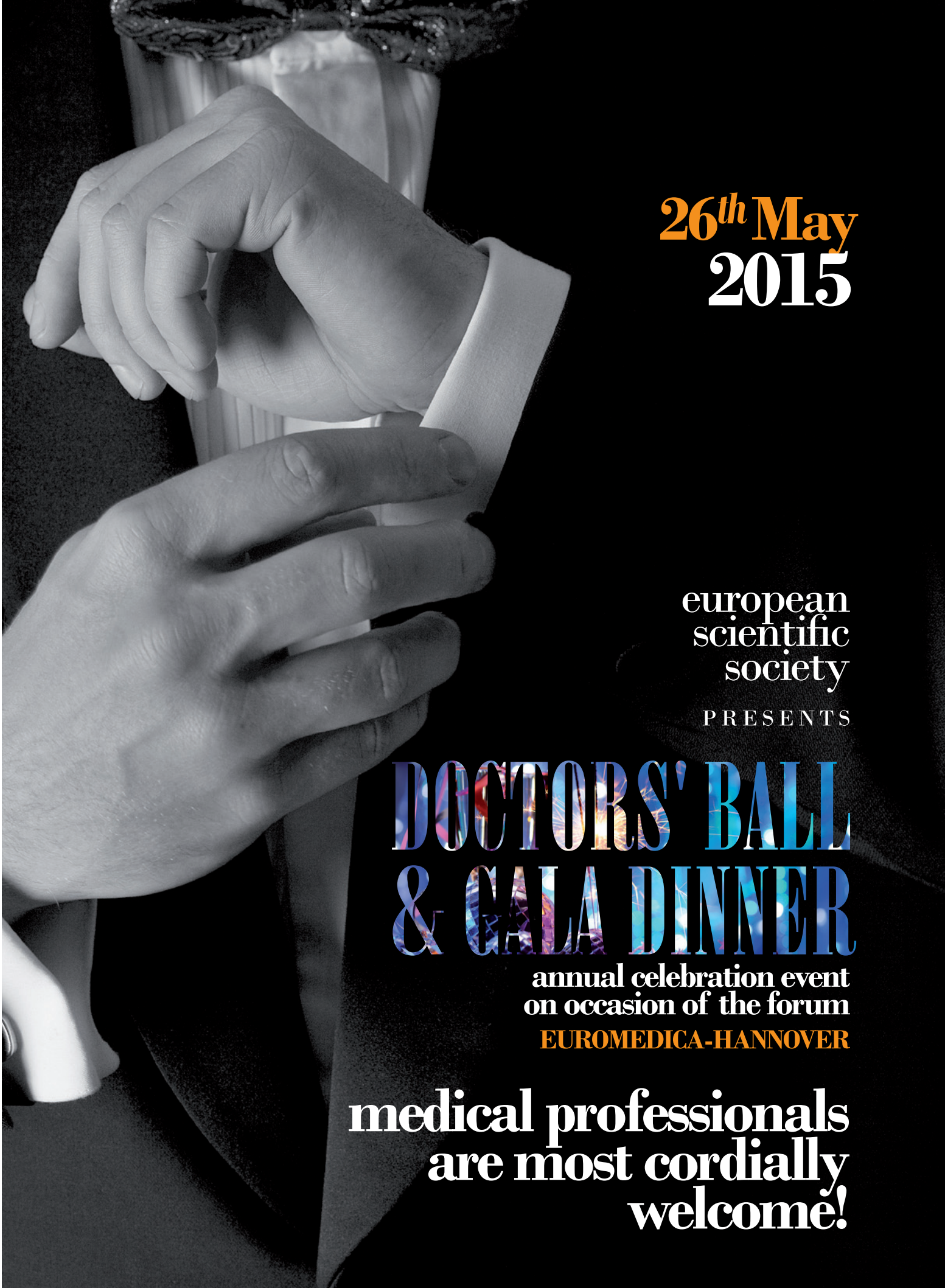

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