The congress highlights up-to-date theoretical and practical aspects of the internal medicine, neurology, surgery and related fields that will bring together experts of the scientific research with clinical practitioners through a range of interactive sessions.

Venue: Hanover Congress Center, Andor Hotel Plaza, June 5-6

Please contact: Georg Tyminski, MD, Olga Tyminski, MBA
Tel.: +49 (0) 511 390 80 88, Fax: +49 (0) 511 390 64 54
info@eu-eco.eu, info@eamx.de

www.congress-euromedica.de
Dear Colleagues!

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.
CONTENTS

F. Bätje
EXTRACORPOREAL SHOCKWAVE THERAPY (ESWT) IN OSSEOUS NON-UNIONS – A GERMAN COHORT STUDY ..........2

N. Buyanova
TREATMENT OF PATIENTS WITH CERVICAL DISEASES COMBINED WITH HPV INFECTION ..........7

THE PROGNOSIS FOR PATIENTS WITH ISCHEMIC HEART DISEASE AND CONCOMITANT ATRIAL FIBRILLATION AFTER AN OPERATION OF RADIOFREQUENCY ABLATION ..........9

E. Dommes, P. Georgiewa, R. Klingebiel
GREY MATTER VOLUME DIFFERENCES IN OBESE AS COMPARED TO NORMAL-WEIGHT INDIVIDUALS: A Voxel-BASED MORPHOMETRIC STUDY ..........11

T.N. Doronina, N.S. Cherkasov
THE IMPORTANCE OF COMORBID ILLNESSES IN CHILDREN WITH CONGENITAL HEART DISEASES IN THE POSTOPERATIVE PERIOD ..........17

I.A. Filina
INNOVATIVE PAY SYSTEM FOR PHARMACISTS ..........19

N.V. Gabrielyan, M.A. Danilova, M.S. Koshel
THE FUTURE DEVELOPMENT OF THE GLOBAL PHARMACEUTICAL CLUSTERS ..........20

Charalampos Giannopoulos
ARZNEYMITTELHERAPIE IM FORTGESCHRITTENEN LEBENSLALTER ..........21

G.T. Glembotskaya, V.V. Mubkova
CURRENT APPROACHES TO THE DEVELOPMENT AND IMPLEMENTATION OF THE CONCEPT OF DRUG IN THE MARKETING INNOVATIONS ..........24

I. Maev, D. Andreac, Yu. Kuecherianyi, D. Dicheva
MOLECULAR MECHANISMS OF HELICOBACTER PYLORI ANTI-BACTERIAL RESISTANCE ..........27

O.V. Marzoeva, E.D. Bespalova, O.A. Pitirimova
PROGNOSTIC SIGNIFICANCE OF REVERSE BLOOD FLOW IN DUCTUS VENOSUS IN A FETUS DURING THE FIRST TRIMESTER OF PREGNANCY FOR EARLY CHD DIAGNOSIS CLINICAL OBSERVATION ..........30

S.V. Nagumanov, A.A. Zhidovinov, V.V. Sidirov, S.I. Paskova, L.V. Petrukhina
OPTIMIZATION OF DIAGNOSTICS AND TREATMENT OF A SYMPTOM OF ENTERAL INSUFFICIENCY AND SYMPTOM OF THE SYSTEM INFLAMMATORY RESPONSE IN THE ACUTE PERIOD OF BURN DISEASE ..........32

S. Schink
HÄUFIGKEIT KARDIOCHIRURGISCHER WUNDHEILUNGSSTÖRUNGEN ..........35

J. Schulz, S. Heymann, U. Fuchs, M. Sturm, R. Klopp
INDIVIDUELLE SYSTEMISCHE BIOKORREKTUR – ADJUVANTES BEHANDLUNGSVERFAHREN BEIM DIABETES MELLITUS TYP II ..........40

W.N. Vance
UROLOGISCHE KOMPLIKATIONEN BEI QUERSCHRITTGELÄHMTEN PATIENTEN ..........45

A.A. Glukhov, N.T. Alexeeva
MORPHOLOGICAL ASSESSMENT OF THE HEALING OF SKIN WOUNDS WITH DIFFERENT METHODS OF REGIONAL TREATMENT ..........53

A.A. Karlitskaya, N.D. Bunyatan, L.M. Krasnykh, G.F. Vasilenko
QUANTITATIVE ANALYSIS OF MEMANTINE IN BIOLOGICAL FLUIDS ..........53

D.J. Korshunova, M.A. Djebudzhe
MICROCIRCULATORY BED IN ORGANS SUPPLIED BY DRAINING DUCTS: FOUR COMPARTMENTS INSTEAD OF THREE ..........54

N. Zakharova, O. Vetchnikova, L. Ivantsova
CYTOMORPHOLOGICAL FEATURES OF PARATHYROID GLANDS AT HYPERPARATHYROIDISM ..........55

N.B. Bulieva
THE ETOLOGY OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH NON-HODGKIN’S LYMPHOMAS ..........55

E.A. Shliakhtunov
BREAST CANCER AND EPSTEIN-BARR VIRUS INFECTION ..........56

V.V. Vinov, M.M. Ilkovich, K.S. Karchevsky, O.V. Isaulov
THERAPEUTIC Apheresis IN THE TREATMENT OF ACUTE LUNG INJURIES ..........57
EXTRACORPOREAL SHOCKWAVE THERAPY (ESWT) IN OSSEOUS NON-UNIONS — A GERMAN COHORT STUDY

Frank Bätje, MD
Private General Medicine-Office, Hannover

ABSTRACT
Background — Shockwave therapy is less or more established as an alternative treatment to surgical interventions for impaired osseous healings like delayed or non-unions after fractures or arthrodeses. This cohort study looked for own results and best practice of focused shockwaves in adequate cases.

Materials & Methods — Between 2001 and 2010 381 unselected bone fractures or stiffed joints with persistent impaired healing as delayed or non-unions were included in this pilot study. Details about outcomes were received by questionnaires, X-ray-evaluations and transmitted informations from doctors or these patients. Only hard facts concerning bony consolidation in the gaps have been of interest to assess bony healing.

Results — Overall 239/381 cases (63%) showed sufficient bony consolidation after ESWT. Cases of impaired fracture-healing showed better (66%) success rates than those of impaired arthrodesis-healing (47%). Healing-rates in impaired unions ranged from 93% after scaphoid-fractures to only 23% after talocalcaneonavicular arthrodeses.

Conclusion — So long as inconsistent pseudarthrosis-definitions and non-comparable results of post-surgical outcomes in cases of impaired osseous healing exist the ESWT is an alternative to surgery in selected indication-subgroups because of their satisfying success rates in selected groups of impaired bone healing.

Discussion — As the ESWT demands to exist as a serious alternative to surgery in cases of impaired bone healings all doctors who use this option must be certificated and have to use comparable shockwave devices in the interest of improvement of successful therapy protocols for different bone healing-complications.

KEYWORDS
extracorporeal shockwave therapy, ESWT, fracture, arthrodesis, impaired bone healing, delayed union, non-union, pseudarthrosis, bone healing, bony consolidation

METHODS & MATERIALS
In a cohort design a total number of at last 381 different bone fractures (n=326) and stiffed joints (n=55) with persistent impaired healing after three months (139 delayed fracture and 29 delayed arthrodesis-unions) or after six months (187 fracture-non- and 26 arthrodesis-non-unions) were included in this pilot study after exclusion of 72 cases (62 cases without sufficient follow up and 10 cases as drop outs). All treatments were performed in a ten-year-period (2001 – 2010) by the author of this study. The evaluation was retrospective: most results were obtained in 2011.
107 cases belonged to women and 284 to men (drop outs included) — some patients had several localisations. 232/381 cases were complications after formerly occupational accidents. The mean interval between last surgery resp. immobilisation after fracture or osteotomy and begin of ESWT was 4.1 (range 3–5) months in the delayed union and 10.9 (range 6–47*) months in the non-union-group resp. 3.9 (3–5) and 11.8 (6–43) in these groups after arthrodesis. Distinct patterns of prior treatment in both groups were evident as conservative treated (n=55) or surgical treated (n=327); of course, all arthrodesis-cases had surgery. Main criterias for shockwave therapy were full gap- or joint-stability due to osteosynthesis resp. immobilization and patient’s compliance for distinct follow ups after ESWT.

For fractures a total number of 2.4 ESWT-sessions (range 1–6) of middle-to high energetic focused shockwaves (mean 6984) and for arthrodeses a total number of 2.4 ESWT-sessions (range 1–3) of middle-to high energetic focused shockwaves (mean 6740) were applied with two different shockwave devices:

- Modulith SLK with an optoelectronic navigation tool (n=268) or Duolith SD1 without this computer-assisted navigation (n=89) or both (n=24) – all devices from STORZMEDICAL™ / Switzerland.

According to the subdivision in delayed or non-unions each treatment in delayed union-cases was started later than three and each in non-union-cases later than six months following last surgical resp. non-invasive way to stabilize the gap or joint. In all cases it was a specialist for orthopaedic surgery who diagnosed the kind of healing-disturbance and stayed involved in follow up after ESWT. In all cases these physicians who were responsible for follow up as well as the patients received written medical reports and therapy protocols. We had a continues overview of some cases since beginning of our ESWT activities (databank) to get sufficient informations to improve the own running ESWT-practice. In May 2011 we started one single follow up-procedure: by questionnaires (IBH- and IAH-scores, see below), X-ray-evaluations, patient’s or doctor’s informations. We were only interested in hard facts like total or sufficient bony / joint consolidation after five months at the latest; weaker criterias like “improvements”, “better range of motion”, “lower pain level” or “obviously consolidated gap” were considered as unhealed cases.

**RESULTS**

Basically in 239/381 cases (63%) a sufficient bony consolidation was achieved: 52% in females and 65% in males. Our 326 cases of impaired fracture-healing showed better results (65%) than our 55 cases of impaired arthrodesis-healing (47%). We have seen no serious adverse effects nor ESWT-related complica-
eswt-study 2011 – IBH (Impaired Bone Healing Score)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Healed (all pat.)</th>
<th>Healed (women)</th>
<th>Healed (men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed fracture-union</td>
<td>139</td>
<td>99</td>
<td>71.2</td>
</tr>
<tr>
<td>Non-fracture-union</td>
<td>187</td>
<td>114</td>
<td>60.1</td>
</tr>
<tr>
<td>Total nr.</td>
<td>326</td>
<td>213</td>
<td>65.3</td>
</tr>
</tbody>
</table>

% 52.3 64.8

All surgical treated fractures (after 1st, 2nd or 3rd procedure) were considered as healed in 52% (171/326). Tibia-fracture-complications were most frequent and showed bony consolidation in 53/90 cases (59%). Related to other anatomical subgroups within all impaired fracture-unions (n=326) we achieved different results from a 93%-healing rate in scaphoids to only 54% in femurs.

eswt-study 2011 -results (1)

eswt study 2011 -results (2)

Talocrural arthrodesis in different stages of impaired osseous healing were most frequent and showed bony consolidation in 8/16 cases (50%). Related to other anatomical subgroups within all impaired arthrodesis-unions (n=55) we also achieved different results from a 79%-healing rate in tarsometatarsal arthrodeses to only 23% after stiffness of talocalcaneonavicular joints.
eswt study 2011 -results (3)

<table>
<thead>
<tr>
<th>studygroup</th>
<th>delayed arthrodesis-union</th>
<th>nonarthrodesis-union</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nr.</td>
<td>%</td>
</tr>
<tr>
<td>talocrural joint: healed</td>
<td>29</td>
<td>3/7</td>
</tr>
<tr>
<td>talocalcaneonav. joint: healed</td>
<td>3/9</td>
<td>3/13</td>
</tr>
<tr>
<td>tarso</td>
<td></td>
<td>0/3</td>
</tr>
<tr>
<td>(metatarsal) joint: healed</td>
<td></td>
<td>4/6</td>
</tr>
<tr>
<td>(crico) metacarpal joint: healed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESWT-specific results:

When the hospital-device STORZ Modulith SLK (almost used for long bones) was used, 62% (166/268) were considered as healed compared with 71% (63/89) of those cases, where the doctor’s office-device STORZ Duolith SD1 (almost for smaller bones and joints in hands and feet) was used; if both devices were used for treatment (almost in cases of metatarsal-fractures or ankle-arthrodesis) 67% (16/24) showed bony consolidation.

eswt study 2011 -results (4)

<table>
<thead>
<tr>
<th>studygroup</th>
<th>delayed fracture-union</th>
<th>non-fracture-union</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nr.</td>
<td>%</td>
</tr>
<tr>
<td>healed with STORZ Modulith SLK</td>
<td>166</td>
<td>61.9</td>
</tr>
<tr>
<td>healed with STORZ Duolith SD1</td>
<td>26</td>
<td>66.7</td>
</tr>
<tr>
<td>total nr.</td>
<td>381</td>
<td></td>
</tr>
</tbody>
</table>

Fracture-delayed unions, -non-unions and arthrodesis-delayed unions showed highest percentages of bone-healing after three (and more) sessions (32%) compared with 28% after two and 12% after one single ESWT-session. In our smaller group of arthrodesis-non-unions two ESWT-sessions were more successful (31%) than three (19%) or only one (4%) treatment.

eswt study 2011 -results (5)

<table>
<thead>
<tr>
<th>studygroup</th>
<th>delayed fracture-union</th>
<th>non-fracture-union</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nr.</td>
<td>(mean nr.)</td>
</tr>
<tr>
<td>ESWT-sessions</td>
<td>139</td>
<td>2.4</td>
</tr>
<tr>
<td>healed after 1 session</td>
<td></td>
<td></td>
</tr>
<tr>
<td>healed after 2 sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>healed after &gt;3 sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total nr.</td>
<td>381</td>
<td>36/23/9</td>
</tr>
</tbody>
</table>

eswt study 2011 -results (6)

<table>
<thead>
<tr>
<th>studygroup</th>
<th>delayed fracture-union</th>
<th>non-fracture-union</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nr.</td>
<td>months since surgery</td>
</tr>
<tr>
<td>healed with mean nr. shockwaves</td>
<td>139</td>
<td>4.1 (3-5)</td>
</tr>
<tr>
<td>healed with mean nr. shockwaves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unhealed with mean nr. shockwaves</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More benefit for arthrodesis-non-unions could be watched in cases with shorter intervals between surgery and begin of shockwave therapy (mean 7.6 months in healed vs. mean 17 months in unhealed joints. In cases after fractures this difference couldn’t confirmed.

eswt study 2011 -results (7)

<table>
<thead>
<tr>
<th>studygroup</th>
<th>delayed fracture-union</th>
<th>non-fracture-union</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nr.</td>
<td>months since surgery</td>
</tr>
<tr>
<td>healed after mean nr. shockwaves</td>
<td>139</td>
<td>4.1 (3-5)</td>
</tr>
<tr>
<td>healed with mean nr. shockwaves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unhealed with mean nr. shockwaves</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

Is ESWT as successful as the classic technique, the surgical intervention in cases of delayed or non-unions after fractures or arthrodeses? And what is the best practice? Unique datas about success rates after...
surgery in earlier or later stages of impaired bone healing concerning different bone- or joint-localisations are not existing as we think to know. According to the most optimistic comments in literature (97% healing rate) the ESWT isn’t a serious alternative. According to our personal overview with the fact that many cases will have repeated surgery without a positive outcome we recommend the ESWT as one other hopeful option. With our ESWT-experience -second purpose-we are optimistic to offer good alternatives in selected cases because of the high acceptance in patients, the unserious adverse effects of the procedure and the low risks (no complication seen in all treatments). Secondly, our study showed us where we could distinguish between better and poorer prognosis for good results: better in smaller bones and joints, in foot-and hand-bones, in delayed fracture-unions and arthrodesis-non-unions, in patients with shorter intervals after fracture or arthrodesis (and obviously in non-smokers – not evaluated here). And, important, our recommendation for orthopaedic surgeons to initiate the ESWT in the delayed-union-stage after fractures and not to wait for the non-union-stage.

**DISCUSSION**

The treatment of impaired bony healing after surgical or conservative treated bone fractures or in problem-cases of arthrodeses with focused and high-energetic (energy flux density > 0.30 mJ/mm²) shockwaves is quite good established since 1999. The purpose is to offer a good alternative to the usual procedure of consecutive surgical interventions in cases of pseudarthroses and re-pseudarthroses which is the golden standard in industrial nations. Shockwave-centers in Austria, Colombia, Italy and Taiwan published encouraging results of ESWT in those indications with success-rates of approximately 80%. Since the knowledge about comparable success-rates after classic surgery is poor, it seems that this percentage of healed cases is encouraging and should be copied by others. The scientific shockwave – societies like the ISMST and the DIGEST enables their members the sharing of experiences and study-results since more than ten years and improves the comparability of the use of different shockwave-devices. Here some standards are important: possibility to apply high-energetic and focused shockwaves which are able to send this focus to the targeted bone localisations in depths up to 15 cm underneath the skin surface, if possible (or necessary) with computer-assisted target-navigation-tools. All high-energetic ESWT-sessions have to be performed by specialized, surgical-skilled medical doctors with certification and good skills for this treatment. Some patients need special advices for defined post-treatment-periods like temporary immobilisation. Smaller bones or joints need two to three, bigger ones up to five months for complete healing – like after surgery. Our overall success rate is poorer than those results received in centers in Austria or Italy. Comparisons of therapy protocols and cohorts are necessary to evaluate the own results. But some subgroups of patients certainly realized a very good benefit of our ESWT. So we recommend that ESWT is a good alternative but not yet the next golden standard for the treatment of every non-union but for some selected cases of course. Our spectrum of treated fracture- or arthrodesis-complications is too large in comparison to the quantity of treated cases to get sufficient prior datas about ideal inclusion criterias and ideal therapy protocols.

Bätje © 2011
In Russia, there are no standardized approaches to the treatment of patients with diseases of the cervix in the presence of human papillomavirus. [2] There are attempts to observe such patients. Probably, such optimism is based on the recent foreign studies, which showed that in 90% cases of young women infected with nononcogenic HPV types and 70% cases of those infected with oncogenic HPV types, there may happen a spontaneous disappearance of the infection [Bauer HM, Kaufman RH, Adam E., 2002]. According to WHO (2001, 2006), [6] in the absence of confounding factors in the last three years, the LSIL containing HPV are subject to regression in 50-70% cases. According to other authors, the spontaneous cure of HPV occurs even more frequently and at a young age occurs as often as in 90% cases [3,4,5]. What happens later? What are the long-term results of the initial presence of HPV, even after its disappearance? Unfortunately, in most cases the disease only develops further.

Molecular methods of research carried out over the last two decades have proved the etiological role of oncogenic HPV types (Nos. 16 and 18) in the development of stratified squamous epithelial dysplasia of the cervix. Such dysplasia can develop to preinvasive and invasive cancer of the cervix. The key proof of such a pathogenic connection was the separation of DNA of HPV from tissue of genital condylomata, from tissue of cervical cancer tumor, and from cell lines of cervical cancer [zur Hausen, 2000, 2008]. In 2008, this discovery was awarded with the Nobel Prize.

Indications for the conization of the cervix:

- Identified hyperplasia or endocervical polyps in combination with HPV in patients without colposcopic changes in ectocervix.
- Pseudo-erosion and leukoplakia of the cervix in patients with identified hyperplasia or endocervical polyps in combination with HPV.
- Flat condyloma or CIN of types I and II in patients with identified hyperplasia or endocervical polyps with or without HPV.

All patients (38 patients with HPV in total, of whom 35 patients had ectocervical disease, and
3 patients did not) went through conization of the cervix (Figure 1). The conization was conducted on an outpatient basis immediately after the menstrual period up to the 10th day of menstrual cycle, using the standard method for this operation with paracervical anesthesia. The surgical intervention was carried out using the full and adequate local anesthesia. The patients were completely awake. One third of patients showed a slight bleeding from the wound during the surgical intervention. Hemostasis was conducted by coagulation of blood vessels with the ball electrode of Surgitron. After the surgery the patient could leave the clinic in a satisfactory condition, without the need to take sick leave.

In all patients with HPV, the histological examination of the removed tissue showed koilocytosis and CIN type I. In all patients with HPV without colposcopic changes in the cervix, but with hyperplastic processes in the cervix, that have gone through conization of the cervix, morphological analysis also revealed koilocytosis and CIN type I.

The results of the epithelialization process is shown on Figure 2.

Thus, the epithelialization processes of the removed tissues in all patients with and without HPV were 100% complete by the 60th day. In patients with HPV, the epithelialization was slower.

Fig. 1. Cone Biopsy (Conization) of the Cervix

Fig. 2. Complete epithelization

RESULTS OF CASE-CONTROL STUDIES AFTER THE TREATMENT

We conducted the Pap test with all patients after the full and complete epithelialization, and appearance of the normal colposcopic picture. The Pap test showed 1-2 types of the smear. After 2 months we conducted the quantitative estimation of HPV with all patients with the method Digene Hybrid Capture System II (97.9% cases were negative)

REFERENCES


THE PROGNOSIS FOR PATIENTS WITH ISCHEMIC HEART DISEASE AND CONCOMITANT ATRIAL FIBRILLATION AFTER AN OPERATION OF RADIOFREQUENCY ABLATION


Regional Clinical Cardiological Dispensary, Tver State Medical Academy, Military Hospital, Tver, Russian Federation

INTRODUCTION
The most perspective method of treatment and preventive measures for cardiovascular complications with patients with atrial fibrillation is radiofrequency ablation of hyper-automatic focuses [5, 8]. At this, the combination of treatment strategies of general cardiovascular pathology and arrhythmia syndrome cause the disappearance of arrhythmia attacks, reduction of congestive heart failure class and improving of patients’ states [7]. Finally, the authors connect the increase of patients’ life quality after the interference with reverse structural and geometric remodeling, decrease of dependence on arrhythmia and constant administration of anti-arrhythmic drugs [9]. Alongside with that, in most publications it is pointed out at the necessity of additional discussion of clinical and functional characteristics and prognosis for patients with atrial fibrillation who had radiofrequency ablation of hyper-automatic focuses [1, 8].

OBJECTIVE
Study the indices of prognosis for patients with ischemic heart disease and concomitant atrial fibrillation after an operation of radiofrequency ablation.

MATERIAL AND METHODS
We included 64 patients (average age 52.7±3.9) with ischemic heart disease that shows as strokes of stable angina of I–II functional class into our research “occurrence–control”. All the patients had a paroxysmal form of atrial fibrillation confirmed earlier. They underwent radiofrequency ablation of hyper-automatic focuses. The patients follow-up after the operation was on the average 3.6±1.2 years. We considered as the combined end point of unfavourable prognosis: appearance of AF relapses after the operation and development of cardiovascular complications. Its beginning was registered with 22 patients (34.4%). They made the 1st group. 42 patients (65.6%) didn’t have arrhythmia relapses after the operation. They were included into the 2nd group. The groups were matched according to sex, age and concomitant pathology. The checkup included: the analysis of complaints of chest pains, dyspnea, intermissions in heart function, appearance of weakness; history taking; physical examination; registration of standard electrocardiography (ECG); Holter monitoring of ECG; transthoracic echocardiography (EchoCG) and Doppler cardiology. We were doing the research in the setting of sinus rhythm at frequency of heart beats 60–70 per minute. On ECG we studied indices of atrial complex: Pmax and Pmin – maximum and minimum of P-wave length, Pdisp – P-wave dispersion [9]. During EchoCG we estimated: A-P dimension, volume of a left atrium. Left ventricular diastolic function was studied by trans-mitral flow markers. The data analysis was performed with the help of the application program package “Statistica 6.1”. The obtained numeric data were stated in SI-units. We were defining the indices: average minimum, maximum, error of arithmetical mean, rms deviation. Parametric (paired and unpaired Student’s t-test for dependent and independent samples, Pearson’s linear correlation coefficient) and nonparametric (Fisher’s test, Mann-Whitney U-test, χ² with Yates adjustment) were applied. The analysis of discrete parameters frequency was accomplished with the appliance of contingency tables, Pearson’s χ² test and McNemar’s χ² test. For estimation of connection between variables we used Spearman rank correlation coefficient. To compare the indices in initial and prospective
researches we used Wilcoxon paired difference t-test. Studying of prognostic value of clinical laboratory data were done according to the indices: sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR). The level of statistical significance was taken as 0.05 [2].

RESULTS AND DISCUSSION
The patients in the 2nd group (compared with the 1st) showed decrease of P-wave dispersion, size and volume of the left atrial (all \( p < 0.05 \)). One can expect that it indicates the efficiency of the operation and the development of processes of reverse myocardium remodeling without atrial fibrillation relapses [3, 6, 7, 9]. Besides, in the 2nd group we observed decrease of the level of left ventricular diastolic dysfunction [3]. This observation can indicate the good prognosis with such patients. However, literature data about predictive validity of the mentioned indices are not so identical. Despite the obtained results, one can expect that the question about atrial fibrillation predictors needs more detailed the trial [6]. The results of the analysis of prognosis indices of patients with ischemic heart disease and concomitant atrial fibrillation after an operation of radiofrequency ablation are shown in table 1.

Table 1. Prognosis indices of patients with ischemic heart disease and paroxysmal atrial fibrillation and those who had radiofrequency ablation

<table>
<thead>
<tr>
<th>Indices</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>OR (c.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pains</td>
<td>75.0</td>
<td>85.7</td>
<td>75.0</td>
<td>14.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>28.5</td>
<td>62.5</td>
<td>40.0</td>
<td>50.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Intermissions in heart function</td>
<td>55.6</td>
<td>40.0</td>
<td>66.7</td>
<td>40.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Weakness</td>
<td>44.4</td>
<td>60.0</td>
<td>55.6</td>
<td>45.4</td>
<td>1.2</td>
</tr>
<tr>
<td>( P_{\max} )</td>
<td>50.0</td>
<td>50.0</td>
<td>55.5</td>
<td>55.5</td>
<td>1.0</td>
</tr>
<tr>
<td>( P_{\min} )</td>
<td>37.5</td>
<td>60.0</td>
<td>60.0</td>
<td>62.5</td>
<td>0.9</td>
</tr>
<tr>
<td>( P_{\text{dis}} )</td>
<td>63.6</td>
<td>60.0</td>
<td>63.6</td>
<td>40.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Left atrial</td>
<td>45.4</td>
<td>50.0</td>
<td>55.6</td>
<td>60.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunc-</td>
<td>54.5</td>
<td>58.3</td>
<td>54.5</td>
<td>71.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

As it appears from the table data, maximum prognostic value was shown by: chest pain and intermissions in heart function, P-wave dispersion, left ventricular diastolic dysfunction; average – appearance of weakness and increase of maximum P-length; low – complaints of dyspnea and decrease of a left atrial size.

CONCLUSION
So, when determining the prognosis for patients with ischemic heart disease and concomitant atrial fibrillation who had a radiofrequency ablation, one should take into account A-P dimension time course and a left atrial size. The appearance of left ventricular diastolic dysfunction can indicate high probability of development of relapses of the mentioned arrhythmia after the operation. The indices of electric remodeling of atrial myocardium and anamnesis, such as P-wave dispersion combined with complaints of weakness, intermissions in heart function and chest pains have predictive validity of cardiovascular complications development.

REFERENCES
GREY MATTER VOLUME DIFFERENCES IN OBESE AS COMPARED TO NORMAL-WEIGHT INDIVIDUALS: A VOXEL-BASED MORPHOMETRIC STUDY

Esther Dommes¹, Petra Georgiewa¹, Randolf Klingebielc

¹ Neurologische Rehabilitationsklinik Beelitz-Heilstätten, Germany
² Charité University Medicine, Center for Internal Medicine and Dermatology, Department of Psychosomatic Medicine, Germany
³ Klinik Im Park, Zürich, Switzerland

ABSTRACT

Background: Signs of declined cognitive function as well as cerebral volume reduction can be found in obese individuals earlier and to a greater extent than in the normal-weight population. We aimed at finding cerebral volume differences in young adults when using Magnet Resonance Imaging (MRI)-based volumetry to compare normal-weight and obese individuals.

Material/Methods: Twenty-four young (mean age 28.4±5.9 yrs.) female adults (12 obese patients, mean BMI 36.6±12 controls) underwent isotropic 3D-MPRAGE MR imaging in a 1.5T scanner. Image data were then post-processed by using the VBM-DARTEL algorithm and compared for subtle volume differences using a two-tailed t-test (p<0.05).

Results: VBM-based regional brain volume differences were encountered in the cingulate gyrus, orbitofrontal cortex, parts of the temporal lobe and the cerebellum. Neither total intracranial volumes (TIV) nor cerebrospinal fluid (CSF) volumes or brain volumes differed when a whole brain approach with conventional volumetric analysis was applied.

Conclusion: Our findings suggest that measurable effects of obesity on brain volumes appear already in young adults. Focal grey matter thinning involves cingulate gyrus, orbitofrontal cortex and also partially affects the temporal lobe and cerebellum.

Keywords — Obesity, Volumetry, Cingulate Gyrus, Voxel-based Morphometry (VBM), Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL), MRI

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health; BMI>25 (BMI= kg/m²) is defined as overweight, BMI>30 as obesity (WHO-definition). Obesity has been described to be associated with reduced brain volumes in late adulthood. A trend of functionally reduced skills concerning planning, goal-oriented behaviour and decision-making as assessed by cognitive testing have been shown in child, teen and adult obese individuals (Smith 2011). Even though these findings are controversially discussed, we hypothesized that structural differences might already be found in younger adults when using MRI-based volumetry. Voxel-based morphometry (VBM) is a mean by which even subtle volumetric differences can be detected where conventional volume analysis does not show volume effects yet.

Obesity is becoming one of the major epidemics of the 21st century. The prevalence amounts to about 50% in Western Europe. More than one in ten of the world’s adult population is obese. It is globally the 5th leading risk factor for death (WHO Fact sheet N°311, 2013). Obesity may lead to a substantial decrease in quality of life and is considered as a risk factor for a number of diseases such as hypertension, diabetes and Alzheimer disease (AD). Reasons for obesity are seen in generally changes of life styles, with increased intake of energy-dense food and decreased expend of energy. However, this is true for many more people than those suffering from obesity but only a certain percentage of people at risk finally fall ill.

CT-based volumetric studies showed a correlation between BMI and higher risk for atrophy in temporal lobes during aging in obese patients (Gustafson, 2004). An MRI-based volumetric study resumed a general reduction in brain volume with higher BMI (Ward, 2005). Recently published studies using more precise VBM-techniques showed focal volume reductions of gray matter (GM) in various brain regions of obese patients (Pannacciulli et al., 2006; Taki et al., 2008; Maayan et al., 2011).

There are only sparse studies based on MRI-based morphometry data in obese individuals, even less with respect to young obese adults. The purpose of this
study was to evaluate possible volume differences between normal-weight and obese young adults in order to detect obesity-related volume effects while excluding age-related decline.

**METHODS**

**Subjects**

We examined 24 young adult female subjects, 12 obese patients (mean age 29.3 ± 7.3) with a mean BMI 36.3 ± 4.8 and 12 normal-weight (age-matched) subjects (mean age 27.5 ± 4.3 yrs., mean BMI of 20.9 ± 1.7), all right-handed (Oldfield, 1971). Exclusion criteria comprised a history of severe pain, stroke, epilepsy or other neurological illnesses, diabetes, substance abuse or addiction, hypertension, claustrophobia or any psychiatric illnesses. For further details see table 1. None of the study subjects had a binge eating disorder. Prior to scanning, both groups had their last meal 1.5 hours before the experiment. Hence, they were neither hungry nor just satiated. Recruitment of the subjects was done through newspaper advertisement. Written informed consent was obtained from all participants prior to scanning. The study was approved by the local Human Subjects Committee and adhered to the Declaration of Helsinki.

**Data acquisition**

MRI measurements were performed on a 1.5 T scanner (Siemens Magnetom Vision, Erlangen, Germany) with a standard head coil. Head motion was minimised by using a vacuum pad. Subsequent to the scout scan, structural data were acquired using a T1-weighted sagittal 3D magnetization-prepared rapid gradient-echo (MP-RAGE): TR/TE 11.4/4.4ms, flip angle 15°, FOV= 256 mm, voxel size 1mm³, no gap. Prior to processing, all data sets were inspected for artifacts and structural pathologies.

**Data analysis**

Imaging data were analyzed using SPM8 (Statistical Parametric Mapping), Welcome Department of Imaging Neuroscience, University College London, UK running under the MATLAB R2010a environment (Mathworks, Inc., Natick, MA, USA).

The origin of all source images was set on the anterior commissure (AC). A Native Space Analysis was performed to get global tissue volumes, GM-, White Matter (WM)-, cerebrospinal fluid (CSF)-volumes. First, we segmented all correctly aligned data by the SPM tool "VBM-estimate and write" function. The specific volumes of the native spaces of each individual were read out by the VBM8 function "read raw volumes" (as described in the VBM8 Manual). The raw data volumes were then statistically analyzed with SPSS 18 (SPSS Inc, Chicago, IL, USA) by using two-tailed t-tests with the significance level set to p<0.05.

Afterwards we performed a VBM-DARTEL analysis. VMB-DARTEL is an algorithm implemented in a toolbox of the SPM8 algorithms; it is able to detect very sensitively systematic differences in GM including subvole volume differences (Ashburner, 2001). Additionally, the VBM-DARTEL algorithm has been shown to improve precision of inter-subject alignments compared to conventional VBM algorithms (Takahasi, 2010).

Basically, the VBM-DARTEL analysis was performed as described by Ashburner (2010 “VBM tutorial”). As far as no other values are mentioned we used the default values of SPM8. Rigidly transformed tissue classification as well as accurate warping of individual brains into GM population templates were performed. Smoothing was done with a Gaussian kernel of 8 mm full width at half maximum (FWHM). Data were spatially normalized to MNI. Within the framework of the general linear model (GLM) the data were analyzed in SPM8. Statistical Analysis was performed using a two-tailed t-test. No confounding covariates were identified. Results were thresholded at p <0.05; corrected for multiple comparison using false discovery rate (FDR). This last correction guarantees that no more than 1% of the significant voxels are false positive. The VBM data was masked using an absolute threshold of 0.2 as recommended in the Ashburner tutorial. No a priori identification of a region of interest was done as VBM-DARTEL provides a whole brain analysis.

Testing was performed for two hypotheses:

Hypothesis 1: K > P (controls have more GM volume than obese); a minimal number of contiguous voxels was set at a cluster size of 25.

Hypothesis 2: K < P (controls have less GM brain volume than obese), cluster size of 25 voxels. Additionally, one analysis was done by using a cluster size of 5 voxels in order not to overlook any effect.

For better anatomical depiction the resulting statistical data were visualized by using the program MRicro (Chris Rorden).

**RESULTS**

Table 1 shows anthropometric and metabolic data of the study groups. The two groups differed significantly in BMI values (p< 0.001). Obesity was prevailing since 17 ± 8.9 yrs. in the obese subjects group. All examined subjects were right-handed. The two groups did not differ significantly with respect to age, gender, and medication. No other illness than obesity was present in the study participants.
Global volume changes

No significant differences in the global volume parameters (TIV, GM, WM and CSF) were encountered (see Table 2). The TIV was about equal in both groups, with approximately 1.3 litres each.

Region-specific GM changes evaluated by VBM

The VBM-study showed some regional foci, where GM volume was significantly reduced (see Figures 1 and Table 2). Region-specific significant volume reduction (p < 0.05) in GM in obese participants was found in four major clusters, including the cingulate gyrus, orbitofrontal cortex, parts of the temporal lobe and the cerebellum. Table 3 displays MNI-coordinates of the most significant statistical values together with their localization and corresponding cluster sizes. When regarding cluster sizes, most extended volume differences in GM were observed in the anterior cingulate gyrus (255 R + 96 L voxels), followed by the orbitofrontal gyrus (274 voxels), the right cerebellar hemisphere (245 voxels) and the left cerebellar hemisphere (192 voxels).

Table 1. Anthropometric Group Data

<table>
<thead>
<tr>
<th>all data, mean (SD)</th>
<th>Normal-weight group (n=12)</th>
<th>Obese group (n=12)</th>
<th>T or Z value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>27.5 (4.3)</td>
<td>29.25 (7.28)</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>BMI, years</td>
<td>20.9 (1.7)</td>
<td>36.3 (4.8)</td>
<td>T(24)=-10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Handedness (right)</td>
<td>12</td>
<td>12</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Current medication</td>
<td>none</td>
<td>none</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Time since suffering from obesity, in years</td>
<td>none</td>
<td>17.2 (8.9)</td>
<td>-</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 2. Comparison of NATIVE SPACE VOLUMES between obese and controls

<table>
<thead>
<tr>
<th>all data, mean (SD)</th>
<th>Normal-weight group (n=10)</th>
<th>Obese group (n=13)</th>
<th>T or Z value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV (ml)</td>
<td>1359.83</td>
<td>1316.42</td>
<td>0.94</td>
<td>0.36</td>
</tr>
<tr>
<td>GM volume (ml)</td>
<td>641.90</td>
<td>613.55</td>
<td>1.32</td>
<td>0.20</td>
</tr>
<tr>
<td>WM volume (ml)</td>
<td>526.26</td>
<td>525.47</td>
<td>0.03</td>
<td>0.98</td>
</tr>
<tr>
<td>CSF volume (ml)</td>
<td>191.69</td>
<td>177.47</td>
<td>2.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Neuparenchym (ml)</td>
<td>1168.16</td>
<td>1139.01</td>
<td>0.64</td>
<td>0.53</td>
</tr>
<tr>
<td>grey of total (in %)</td>
<td>47</td>
<td>47</td>
<td>0.52</td>
<td>0.61</td>
</tr>
<tr>
<td>white of total (in %)</td>
<td>39</td>
<td>40</td>
<td>-0.93</td>
<td>0.37</td>
</tr>
<tr>
<td>CSF of total (in %)</td>
<td>14</td>
<td>14</td>
<td>1.03</td>
<td>0.31</td>
</tr>
</tbody>
</table>

DISCUSSION

Following a hypothesis of Peters (2009) decreased brain volumes might be an effect of an insufficient metabolic supply of this organ. Especially reduction of grey matter or neurons might be explained by energy deficits as neurons are the most energy demanding cells. This hypothesis is supported by results of a phosphorus 31 magnetic resonance spectroscopy (31p MRS) study that showed an inverse correlation between BMI and intracranial adenosine triphosphate (ATP) levels (Schmoller 2009). Also, well-documented increases of cytokines and other inflammatory mediators in obese subjects might contribute to brain volume reductions (Rizvi 2010). A correlation between elevated fibrinogen levels and diminished brain volumes in orbitofrontal cortex was demonstrated in a recent study by Cazettes and co-workers (Cazettes 2011). Also, our results indicate subtle GM volume effects rather than extended volume differences between obese and control subjects.

TIV= intracranial brain volume

Regarding total brain volumes, no significant volume difference was found in our study collective of young adult women between obese and normal-weight participants. Their WM/GM-ratios did not differ significantly from each other. Following a study of Groeschel et al. (2010), in which brain development from birth through the age of 30 were analyzed using...
algorithms based on voxel-based morphometry (VBM), we conclude that all study participants were at about the same level of brain maturity. Our TIV findings are also in accordance with other studies showing no volume differences on macroscopic levels between obese and normal-weight women such as the study of Peters et al. (2011), underlining the need for advanced imaging techniques, such as VBM.

Our findings of GM diminishment in obese subjects are supported by various other studies (Maayan et al., 2011, Walther et al., 2010, Raji et al., 2010, Taki et al., 2008, Gunstad et al., 2008 and Panacciulli et al., 2006), even though different study designs hamper their comparability. In contrast to Taki et al. (2008) who did not detect brain volume differences but in men solely, we found BMI-associated parenchymal volume differences in women. By examining exclusively right-handed young adults with neither prior CNS illnesses nor medication, we were able to rule out confounding variables such as aging or drug related effects and attributed brain volume changes to the BMI differences of our study groups.

The nature of GM volume reduction in VBM studies has not been described on a cellular level yet. It remains unclear whether the described selective volume effects are due to apoptosis of neurons or just represent neuronal volume shrinkage. Also, the reversibility of GM volume differences has not been established up to now, i.e. the beneficial effects of dietary measures and weight reduction in obese patients. A recent study suggests that salutogenesis/reduction in brain volume in the obese seems possible when an adequate therapy is applied (Matochik 2005a); in that study leptin-deficient patients showed increasing grey matter volumes after Leptin-substitution. It might also be speculated that the selective GM volume changes

TABLE 3. VOXEL BASED MORPHOMETRIC, Obese < controls. Two-tailed t-test, p < 0.05; FDR

<table>
<thead>
<tr>
<th>Region</th>
<th>H</th>
<th>BA</th>
<th>T</th>
<th>Z</th>
<th>MNI-coordinates</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingulate Gyrus; Limbic Lobe</td>
<td>R</td>
<td>24</td>
<td>13.22</td>
<td>6.88</td>
<td>11; 13; 33</td>
<td>255</td>
</tr>
<tr>
<td>Cingulate Gyrus; Limbic Lobe</td>
<td>R</td>
<td>24</td>
<td>7.98</td>
<td>5.41</td>
<td>8; -5; 35</td>
<td>96</td>
</tr>
<tr>
<td>Cingulate Gyrus; Limbic Lobe</td>
<td>L</td>
<td>24</td>
<td>5.55</td>
<td>4.87</td>
<td>-9; 22; 24</td>
<td>96</td>
</tr>
<tr>
<td>Orbital Gyrus, Frontal Lobe</td>
<td>R</td>
<td>11</td>
<td>9.90</td>
<td>6.05</td>
<td>12; 36; -28</td>
<td>274</td>
</tr>
<tr>
<td>Sub-Gyral; Temporal Lobe</td>
<td>R</td>
<td>37</td>
<td>8.24</td>
<td>5.51</td>
<td>48; 48; -9</td>
<td>30</td>
</tr>
<tr>
<td>Gyrus fusiforme; Temporal Lobe</td>
<td>R</td>
<td>37</td>
<td>5.85</td>
<td>4.95</td>
<td>50; -41; -13</td>
<td>245</td>
</tr>
<tr>
<td>Culmen; Anterior Lobe</td>
<td>R</td>
<td>Cerebellum</td>
<td>11.54</td>
<td>6.49</td>
<td>11; -39; -4</td>
<td>156</td>
</tr>
<tr>
<td>Culmen; Anterior Lobe</td>
<td>L</td>
<td>Cerebellum</td>
<td>10.0</td>
<td>6.08</td>
<td>-12; -35; -6</td>
<td>36</td>
</tr>
<tr>
<td>Cerebellar Tonsil; Posterior Lobe</td>
<td>L</td>
<td>Cerebellum</td>
<td>6.60</td>
<td>4.85</td>
<td>-27; -54; -34</td>
<td>36</td>
</tr>
<tr>
<td>Anterior Lobe;</td>
<td>L</td>
<td>Cerebellum</td>
<td>5.31</td>
<td>4.72</td>
<td>-18; -54; -28</td>
<td>36</td>
</tr>
</tbody>
</table>

TABLE 4. VOXEL BASED MORPHOMETRIC, Obese > controls. Two-tailed t-test, p < 0.05; FDR

<table>
<thead>
<tr>
<th>Region</th>
<th>H</th>
<th>BA</th>
<th>T</th>
<th>Z</th>
<th>MNI-coordinates</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle Frontal Gyrus; Frontal Lobe</td>
<td>R</td>
<td>10</td>
<td>7.27</td>
<td>5.14</td>
<td>12; 52; 6 R=3</td>
<td>9</td>
</tr>
<tr>
<td>Middle Frontal Gyrus; Frontal Lobe</td>
<td>L</td>
<td>10</td>
<td>6.63</td>
<td>4.87</td>
<td>-11; 46; 6 R=1</td>
<td>16</td>
</tr>
</tbody>
</table>
in obese subjects are a constitutive factor rather than a sequel of BMI increases.

**Anatomical and physiological context**

In the following, we address the potential functional impacts of subvolume differences of the brain parenchyma in obese patients as compared to healthy controls.

**Cingulate gyrus**

We found a significant volume reduction of GM in obese individuals as compared to control subjects bilaterally in the anterior cingulate gyrus. These findings are in agreement with the studies of Raji et al. (2010) and Taki et al. (2008) in which volume reductions in the cingulate gyrus were detected as well. Representation of sense and flavour can be found in the anterior cingulate cortex, as well as in the orbitofrontal cortex and the insular taste cortex (Grabenhorst 2007).

Neurons of the cingulate gyrus express leptin receptors. Leptin seems to be essential in several differentiating steps of fetal neurons and may maintain neuronal stem cells (Udagawa et al., 2006). In Leptin-deficient mice an elevated number of pycnotic cells could be found in cingulate gyrus with reduced sizes of cerebrum and cerebellum. The authors hypothesized that leptin deficiency leads to an elevated rate of neuronal apoptosis (Udagawa, 2006). In addition, leptin is secreted by adipocytes and regulates food intake and homeostasis of metabolism as could be shown in some knock out mutations (Udagawa 2006). Leptin deficiency as well as -resistance of receptors is associated with elevated weight. Leptin-deficient mice show elevated body weights, reduced brain weight, reduced grey matter, maturation deficits of neuronal and glial cells and an elevated tendency towards neurodegeneration (Sriram 2002). The role of Leptin in idiopathic obesity is less clear, yet leptin seems to have trophic effects on brain tissue and at least in some cases sustained GM volumes increases could be shown in leptin-deficient patients by VBM measurements, following replacement therapy of recombinant methionyl human leptin (Matuchik 2005a). Altogether, these findings suggest a context between leptin metabolism, obesity and pathomorphology of the cingulate gyrus, that fits into our current study findings.

**Orbitofrontal cortex (OFC)**

The prevailing study showed reduced OFC volumes, which has also been reported in obese subjects by Maayan (2011). The OFC plays a key role in impulse control as indicated by functional studies (Rothemund 2007, Weygandt 2013) and impulse control in turn does have an important impact on food uptake.

Some cerebellar regions showed reduced volumes in obese young women as compared to controls. The cerebellum is not only involved in the control of movement but also in that of visceral activity (Triarhou 2008) and it participates in modulating the function of higher centres. Direct cerebello – thalamic projections have been described. Finally also homeostatic undergoes cerebellar modulation (Schmahmann 2007).

**Middle frontal gyrus/temporal lobe**

Volume reductions in the temporal lobe have been described to a greater extent in an CT -based study on elderly women (Gustafson, 2004), showing that elevated body weight leads to disproportional volume decreases in this region throughout the process of aging. Our results in young female adults only showed sparse comparable effects, yet further decline within following decades might be expected for obese participants.

**LIMITATIONS**

A major limitation of this study is the relatively small sample size, resulting in reduced statistical power. All participants were young adult women, making our findings less generalizable, even though this fact in turn strengthened the statistical power by reducing the within sample variation.

Data acquisition itself is a potential source of imprecision of VBM studies; usage of different scanners can have a negative effect on data analysis (Focke et al. 2011). To avoid this, we made only use of a data sample made on one single scanner within a time span where acquisition conditions could be kept stable even though this in turn limited the study period and thus the number of patients to be included.

The comparability of our results with previously published VBM studies on the obese also suffers from the varying study designs.

**CONCLUSION**

Comparison of global brain tissue volumes in obese versus normal-weight young women showed no significant differences.

Yet, our data suggest subtle foci of reduced gray matter volumes in the cingulate gyrus, orbitofrontal gyrus, temporal lobe, fusiform gyrus, anterior lobe and in the cerebellum of young, adult, obese females, some of these regions have previously been put into context with control of food intake.

**ACKNOWLEDGEMENT**

This work was done in memory and gratefulness of our colleague Yvonne Rothemund, who ceased during the preparation of this manuscript.
REFERENCES


Ashburner, 2010 VBM Tutorial

Ashburner 2007 DARTEL


Gustafson, D; Lissner, L; Bengtsson, C; Björklund, A; Skoog, I; Tham, A. Relationship between body mass index and grey matter volume from infancy to adulthood. Int. J. Neurosci. 2008 Nov;118(11):1582–1593.


The Importance of Comorbid Illnesses in Children with Congenital Heart Diseases in the Postoperative Period

T.N. Doronina, N.S. Cherkasov

Astrakhan State Medical Academy, Astrakhan, Russia

Abstract — The peculiarities of extracardiac pathology have been studied in 52 children after atrial septal defect correction. It was determined that in patients with the SPLT in the structure of the accompanying pathology the leading place belongs to the hypoxic-ischaemic encephalopathy, repetitive respiratory infections and combinations of these diseases. The dynamics of monitoring in 6 months after the cardio-surgical correction showed a significant reduction in the frequency of occurrence of extracardiac diseases. It was stated that in children with the studied heart disease in early postoperative period associated comorbid diseases increase the number of violations of the heart activity.

Keywords — congenital heart disease, atrial septal defect, children, comorbidity.

It is known that in recent years there has been an increase in the number of operations on correction of congenital heart defects (CHD) in children during the first years of life due to advances in Pediatric Cardiac Surgery and it is associated with the expansion of early surgical care, improving of the quality of the used equipment, etc. [1, 2]. The state of the operated child, as well as the duration of rehabilitation therapy, is not only determined by the peculiarities of cardio-vascular system, the volume and specific features of intervention, but by the presence of concomitant pathology.

Under modern conditions, great attention is paid to comorbid diseases in various somatic pathology [3]. Different authors describe the presence of various diseases which accompany CHD. At the same time, there has been no detailed study of the structure of extracardiac pathology in certain heart diseases after operations, and its importance in children, especially infants has not been determined either [4, 5].

The aim of the investigation: to set the importance of the accompanying pathology in CHD after surgical corrections in children in the first year of life.

The children is characteristics and methods of investigation. Under our supervision were 52 children, ranging in age from 3 months to 1 year who undergone cardio-surgical correction of secondary atrial septal defect (SASD). Clinical picture of congenital heart disease was characterized by the classic signs. The children were divided into two groups. The first consisted of 21 children with comorbid diseases, among which the leading ones were: hypoxic-ischaemic encephalopathy (HIE) with various syndromes; losing anemia of low level; repeated respiratory infections; gyptrophy of the 1 degree. The second included 31 patients with various combinations of the associated pathology.

Results of the study

CHD in 48.5% were diagnosed antenatal (from the anamnestic data), in other cases - in the first months of life. We have analysed the accompanying pathology in 1 and 6 months after cardio-surgical correction of congenital heart disease carried out under relatively similar conditions.

In the structure of the associated pathology in the first group in a 1 month after the surgery the leading ones were HIE and losing anemia (table). 6 months later the frequency of concomitant pathology decreased considerably with relatively high numbers of levels of repeated respiratory infections (13.5%). This shows that successful operative correction CHD cardio surgery on the heart, normalization of the hemodynamics, rehabilitation therapy in 6 months reduce the frequency of comorbid illnesses. Reduction in the frequency of occurrence of comorbid diseases in the second group is also due to the normalization of hemodynamic conditions and ongoing therapy. The high frequency of respiratory diseases (15.4%) is probably connected with the continuing enrichment of the pulmonary circulation in these patients even after the operation, and reducing of the immune protection factors. In some cases, they are probably caused by the
availability of seasonal peaks and contacts of these children.

We were especially interested in the condition of cardiac activity in the children in compared groups in the postoperative period. At first (in a 1 month after the heart surgery) clinical manifestations in the first and second groups were not significantly different. It was stated that in the second group in 6 months after the operation bradiaritmia was met twice as often as in the first group. The muffling of heart tones at this time was noticed in two children of the first group and in the compared group in — 9. In a few cases in both groups a systolic murmur was determined (Table 1).

**Table 1. The frequency of comorbid diseases (%) in SASD in children early after the operation**

<table>
<thead>
<tr>
<th>Comorbid diseases</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-group</td>
<td></td>
</tr>
<tr>
<td>a) HIE</td>
<td>In 1 month</td>
</tr>
<tr>
<td>b) Gypotrophy of the 1 degree</td>
<td>7</td>
</tr>
<tr>
<td>c) Closing anemia of low level</td>
<td>20</td>
</tr>
<tr>
<td>d) Repeated respiratory infections</td>
<td>15</td>
</tr>
<tr>
<td>II group: different combinations of these diseases</td>
<td>34,9</td>
</tr>
</tbody>
</table>

ECG detected bradiaritmia (17), rarely recorded moderate tachycardia (5), single extrasystolia; in addition there were blockades of the right leg of the beam of Guisa (13), half full (7) and full (3) atrioventrikuliar blockades. The violations of the heart rhythm and conductivity on the ECG in 6 months were significantly more common in the second group (36,2%) than in the first one (12,3%).

On Echocardiography the presence of valvular dysfunction was seen in three children of the first group and in 12 patients of the second one. Moderately expressed manifestations of valve dysfunction were more often diagnosed in 41,4% of the patients long after heart surgery. This comparative analysis shows that the heart disorders are most often found in 6 months than in a 1 month after the Cardio-surgical correction of congenital heart defect. High level of frequency of these disorders in patients in the second group can be explained by the influence of concomitant accompanying pathology.

Thus, it was determined that in patients with the SPLT in the structure of the accompanying pathology the leading place belongs to the hypoxic-ischaemic encephalopathy, repetitive respiratory infections and combinations of these diseases. The dynamics of monitoring in 6 months after the Cardio-surgical correction showed a significant reduction in the frequency of occurrence of extracardiac diseases. It was stated that in children with the studied heart disease in early postoperative period associated comorbid diseases increase the number of violations of the heart activity.

**REFERENCES**


In the face of fierce competition in the pharmaceutical market it is highly relevant to introduce innovations to the activities of pharmacy, ensuring the formation of stable and long-term competitive advantages. As a result of questioning conducted among the pharmacists, we have identified priorities of the importance of work for specialists. It was found that the first place is salary (85%), the second place is the staff (66%) and the third is position (34%). Thus, the financial reward is the most important stimulus for work. The result of our research was the development of an innovative pay system for pharmacists based on the process approach, which includes: location of the main business processes in subdivisions of pharmacy, standardization of the structural units at the level of sub processes, the development of estimates of employees' labor activity for each department of pharmacy, development of bonus forms of payment for pharmacists.

We have developed a form of bonus pay for pharmaceutical professionals based on estimates of labor by using the multi-criteria analysis. The method of multi-criteria analysis of the labor activity consists of four stages. At the first stage the most important functions are allocated that workers carry and their indicators of evaluation are determined. At the second stage the duties of employees are converted into points. The activity of each employee is evaluated on a 100-point scale. Each function has a range from one to ten points. At the third stage the daily results of each worker a manager enters in an electronic database. At the fourth stage at the end of the month the results are summed up and the issue of encouraging each employee is addressed.

The system of estimates allows to allocate the functions performed by employees every day in every structural unit of pharmacy. Functions, in turn, correspond to sub processes, which any business process in pharmaceutical company can be divided to. To the group of key business processes we included the following: the process of ordering, receiving and product pricing, product release to the public; supply of goods to medical organizations; the process of manufacturing of dosage forms; the system of quality control in pharmacies. We have developed a system of estimates of pharmacists’ labor for each business process, including business process “Product release to the public” (table 1).

<table>
<thead>
<tr>
<th>N</th>
<th>Function</th>
<th>Indicator</th>
<th>Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Determination of residues of goods</td>
<td>Number of items</td>
<td>Minimization of denials</td>
</tr>
<tr>
<td>2</td>
<td>Determining the need</td>
<td>Number of items</td>
<td>Minimization of denials</td>
</tr>
<tr>
<td>3</td>
<td>Forming the order</td>
<td>Number of items</td>
<td>Minimization of denials</td>
</tr>
<tr>
<td>4</td>
<td>Reception of goods to the department</td>
<td>Number of items</td>
<td>Recharge outs</td>
</tr>
<tr>
<td>5</td>
<td>Placing goods under storage sites</td>
<td>Number of items</td>
<td>Adherence to storage</td>
</tr>
<tr>
<td>6</td>
<td>Display of goods in the showcases</td>
<td>Number of items</td>
<td>Advertising goods</td>
</tr>
<tr>
<td>7</td>
<td>Making price tags</td>
<td>Number of items</td>
<td>Pharmaceutical order</td>
</tr>
<tr>
<td>8</td>
<td>Product release to population</td>
<td>Number of items, checks, total amount</td>
<td>The increase in turnover</td>
</tr>
<tr>
<td>9</td>
<td>Registration of cash receipts</td>
<td>Number of documents</td>
<td>Pharmaceutical order</td>
</tr>
<tr>
<td>10</td>
<td>Preparation of reports</td>
<td>Number of documents</td>
<td>Pharmaceutical order</td>
</tr>
</tbody>
</table>

Work on the release of product to the population is expressed in points, depending on the planned turnover. Amount of planned turnover is divided into fixed rate for each function (10 points), determined its significance in the amount, which is 1 point. If an employee scored more than 10 points, his efforts should be encouraged. In product release to population the number of checks and commodity positions is also taken into account. Also, the number of commodity items determines the performance of other functions.

We developed the program that allows to quantify the involvement of every employee in the business process, to form a financial motivation of pharmaceutical professionals, increase employee satisfaction index, extend the range of the measured parameters of the organization and balance these parameters with the financial results of pharmacy, business processes, information about the quality of customer service.
We estimate that the three largest pharmaceutical clusters today (measured by employment in pharmaceutical headquarters, offices and research facilities) can be found in the areas around London, New York and Zurich/Basel. The large pharmaceutical firms tend to have offices and distribution facilities all around the world but currently they base the majority of head office functions in these clusters.

We expect that the key global trends affecting the pharmaceutical industry will be rising prosperity and demographic shifts. The former will provide a growing market for pharmaceutical products as wealthier households especially in emerging markets will buy more healthcare or demand greater government provision.

The effects of demographic shifts will be more complex. Aging populations in the developed world and increasingly China, South Korea and other emerging nations will increase overall demand for health related products and services considerably. The mixture of demand will also change. Currently much care is focussed on control of infectious diseases (which disproportionately affect the young and developing nations). This will shift to a focus on management of chronic disease (which affect older people and developed nations more).

Management of chronic disease tends to be far more costly than control of infectious disease (which can often be eliminated through a vaccination costing a few dollars). In a world where the population will be larger, older and wealthier; management of chronic disease will provide an enormous market for pharmaceutical companies.

The world's current largest clusters in New York, London and Zurich/Basel may be well placed to benefit from these shifts – they are already geared to serve the older and wealthier consumers in the developed world; the type of customers who will become more common in the developing world over the next 30 years. The pharmaceutical majors are already increasing their access to emerging markets through direct investment or strategic alliances with, and acquisitions of, generic medicine producers based there.

Another reason we expect the developed world to retain the largest clusters is the importance of linkages between world class tertiary education and pharmaceutical’s facilities. Whilst emerging nations are making great strides in developing world class educational facilities, the best university in China is ranked 226th in the world and only one BRIC university makes the top 100 (Moscow State in 77th).

The exception to this rule could be Shanghai. With a growing complement of pharmaceutical offices, and some of the few major facilities outside of the developed world, we believe Shanghai is well placed to be the key cluster serving Chinese and wider regional markets. Investors also share this sentiment: Shanghai has attracted over US$1 billion in pharmaceutical foreign direct investment over the last five years.

London, New York, and Zurich/Basel will remain major clusters and centres of research excellence in the pharmaceutical industry – however a new centre will be needed closer to the largest markets in Asia. We expect Shanghai to be this centre.

We expect strong growth in each of the pharmaceutical clusters on account of the older and wealthier world population. London and Zurich/Basel are projected to roughly double in size by 2040. We see New York more than doubling in size as its strong academic linkages and ability to attract both foreign and domestic investment in the sector mean that it is the best placed of the three developed market clusters.

REFERENCES

ARZNEIMITTELThERAPIE IM FORTGESCHRITTENEN LEBENSALTER

Charalampos Giannopoulos
Klinik für neurologische Frührehabilitation, Beelitz-Heilstätten


Eine Vielzahl dauerhaft eingenommener Medikamente mit kaum mehr überschaubaren Summationswirkungen in Ziel- und Nebenwirkungen sind die Folge. Zwangsläufig steigt auch die Zahl der unerwünschten Wirkungen (UAW) bis hin zu schweren und sogar tödlichen Komplikationen.

Bessere Erfassung der Individualmedikation und Dokumentation für jeden behandelnden Arzt sowie der sensible Umgang mit Medikamenten bei der geplanten Verordnung unter Abwägung der Besonderheiten der Organfunktion - insbesondere von Herz, Nieren, Leber und Hirn - beim älteren Mitbürger sind zwingend Voraussetzungen dafür, um UAW’s zu reduzieren und soweit als möglich zu vermeiden. Es geht also um eine besondere und sehr spezifische Nutzen/Risikoabwägung bei der Arzneimitteltherapie im höheren Lebensalter.

Die Thematik gewinnt zunehmend an Bedeutung, weil
1. der Altersdurchschnitt der Bevölkerung der Industrieländer steigt und damit vorwiegend ältere Bürger in das Netzwerk ambulanter und stationärer Gesundheits- und -fürsorge gelangen.
2. die auf dem Markt befindlichen Arzneimittel vor ihrer Zulassung an ausgewählten gesunden Probanden im „Durchschnittsalter“ (nicht > 60 Jahre) getestet wurden.
3. das Patientenkollektiv der zukünftigen Jahre wird im Bereich der chronisch Kranken und Multimorbidem zu sehen sein

Unerwünschte Arzneimittelwirkungen (UAWs) betreffen alte Menschen viel häufiger als junge. Die Multimorbidität mit konsekutiver Multimedikation spielt ursächlich eine Rolle, andererseits aber auch die eingeschränkte Fähigkeit des älteren Organismus, Medikamente zu eliminieren bzw. die zum Teil höhere Sensitivität gegenüber Arzneimitteln.

Bei der Betrachtung schwerwiegender UAWs, die zu Krankenhausneinweisungen führen, fällt auf, dass Herz-/Kreislaufmedikamente und Antidiabetika eine führende Rolle einnehmen. Gerade diejenigen Arzneimittel wie Digitalisglykoside oder Diuretika, deren geringere therapeutische Breite bei Alten bekannt ist, sind im hohen Alter oftmals ursächlich für UAWs.

Nichtberücksichtigung grundlegender Aspekte der Pharmakotherapie im Alter, d.h. Beachtung des Körpergewichts, der Körperzusammensetzung, der Nieren- und Leberfunktion und der Komedikation stellt eine häufige Ursache für UAWs dar.

Etwa 30-40 % der UAWs werden als vermeidbar eingeschätzt, dies entspricht auch Zahlen aus internationalen Studien.

Bei Heimbewohnern weisen Demenzkranké ein sehr hohes UAW-Risiko auf. Neuroleptika werden bei Heimbewohnern nicht nur häufig verordnet, sondern stellen auch die Substanzgruppe dar, die am häufigsten mit UAWs verbunden sind (in 33 %).

Bei der Analyse der UAWs in Altenheimen tritt ebenfalls zutage, dass neben einer inadäquaten Dosierung fehlendes Monitoring von Arzneimittelwirkungen häufig zu UAWs führt. Ob und inwieweit elektronische Verordnungshilfen und/oder der Einsatz geriatrischer Care-Teams eine signifikante Abnahme der UAW-bedingten Morbidität und Mortalität älterer Menschen bewirken kann, ist in Deutschland noch nicht umfassend nachgewiesen.

Eine Auswertung von 3664 Klinikeinweisungen durch unerwünschte Arzneimittelwirkungen zwischen 2000 und 2006 wurde von Frau Prof. Dr. Petra Thürmann vom Lehrstuhl für klinische Pharmakologie der Universität Witten/Herdecke durchgeführt.

530 der UAW waren durch Insuline und deren Analoga verursacht,
446 durch NSAR,
437 durch Phenprocoumon,
316 durch Digitalis (90 % durch Digitoxin),
285 durch Beta-Blocker,
267 durch orale Antidiabetika und
262 durch Diuretika.

KEYWORDS — Demografischer Wandel, Multimorbidität, Arzneimitteltherapie, Unerwünschte Arzneimittelwirkungen, Komplikationen
59 % der UAW traten bei Patienten über 70 Jahre auf.

Gegenwärtig geht man davon aus, dass bei circa 5 % der medikamentös behandelten Patienten UAW auftreten und dass bei etwa 3–6 % aller Patienten, die auf internistischen Stationen aufgenommen werden (geschätzt 50.000–300.000), eine UAW-Ursache für diese Aufnahme ist.

Etwa 2,3 % der aufgenommenen Patienten versterben als direkte Auswirkung der UAW.

Unerwünschte Wirkungen waren somit für den Tod von 0,15 % der im Krankenhaus behandelten Patienten verantwortlich (0,1 bis 0,2 %).

49,6 % der tödlichen UAWs wurden mit einer inkorrekten Anwendung der Arzneimittel begründet.

Problemlösemöglichkeiten wären z. B.:

Das TheraOpt® – ein Therapiekontroll- und Überwachungssystem. (Prof. Frölich, Hannover)

Es handelt sich um eine elektronische Dokumentation und Verordnung der Medikation

**Berechnet automatisch**
- Dosierung
- (Teilbarkeit der Tablette)
- CrCL/GFR
- Tagesterapiekosten
- Stellplan

**Überprüft**
- Aufnahmemedikation
- Umsetzung auf KH-Liste
- Entlassmedikation
- Empfehlung nach SGB V
- und ist

**Warn vor**
- AM-Allergie
- Kreuzallergie
- Interaktionen
- Ampelsystem
- Kontraindikationen

**Koppelbar mit**
- KIS, UDS
- Umsetzung auf KH-Liste
- Entlassmedikation
- Empfehlung nach SGB V

**CONCLUSION**
- Max. 3–4 Medikamente, regelmäßig Indikationsprüfung (auch bei Verlegung)
– Berücksichtigung von Lebensqualität, aktiver Lebenserwartung, Lebensumständen
– Beachtung (nicht kritiklose Anwendung) von Evidence der Diagnostik und Therapie im Alter-Nutzen/Risiko-Abwägung
– Einmalgabe des Präparates und einmaliger Applikationszeitpunkt zur Compliancesicherung
– Kombipräparate (Nachteil: Fixkombination, Vorteil: Reduzierung der Tablettenzahl, keine Teilmengen)
– Produktanpassung (Verpackung, Applikation, Galenik, Schriftgröße), klare Farbcodierung, Piktogramme fordern
– Assessment zu Fähigkeitsstörungen
– Gute Aussage bezüglich funktioneller Reserve, Lebenserwartung
– Reduktion des Medikamentenverbrauches


Besondere Beachtung muss der bereits physiologisch geänderten Organfunktion von Niere, Leber und auch den Besonderheiten der homöostatischen Verhältnisse (Lösungsmedium) im Alter geschenkt werden. Erst recht dann, wenn diese zusätzlich durch entsprechende Organpathologie akzentuiert werden.
One of the key factors of the successful development of the pharmaceutical business is investment in innovations. Over 20% of all investments in the innovative development of the planet are made in the world pharmaceutical industry. They play an important role in building a healthy and productive society, as well as a sustainable and healthy economic system. Over the past 100 years, pharmaceutical innovations have made a significant contribution to the improvement of social well-being and economic growth. The increase in life expectancy during this period was largely due to the fact that new, improved treatment possibilities were introduced in the drug market.

In accordance with the Government-approved Strategy for the development of the pharmaceutical industry for the period up to the year 2020, it is planned that after 10 years, domestic medicines will cover 50% of the market, 60% of them being innovative products. The fundamental factors for implementing innovations in Russia are as follows: an open dialogue with the State, cooperation of Russian and international market players, an optimal procedure for registration and providing availability of drugs, as well as selecting the best ways to market innovative drugs. According to the leaders in the pharmaceutical industry, basing on the results of 2012, the Russian market is already approaching the global Top 10, being second in Europe only to Germany and Italy. The Russian pharmaceutical market is growing rapidly: together with Brazil and China, it demonstrates the fastest growth rate, while many mature markets have stalled their progress. As recently as 6–7 years ago, the share of public funds in venture capitals available to innovators accounted for more than 70%, whereas today it dropped to under 5%. In 2012, the Dow Jones VentureSource declared Russia the fastest growing venture capital market in Europe, and the fourth largest in terms of investments. Bloomberg ranked Russia 14th among the 50 most innovative countries in the world.

Research and practice have proven that for the product development process to be viable, it is imperative that it is focused on the pharmaceutical market [1]. Proceeding from the concept of innovative marketing, development and introduction of a new product is a step-by-step process of transformation of ideas into a product, and then into a commodity. Modeling the new drug launch process should be preceded by market research, which is its foundation. (Fig. 1)

The understanding of drugs as commodities should be based on specific types of commodity attributes:

- social (compliance with individual and social needs);
- functional (compliance with its function and consumption purpose);
- ergonomic (provision of convenient administration of the drug; rationality of the dosage form; rationality of packaging);
- anthropometric (compliance with the anthropometric characteristics of the human body, for example, the size of the oral pills);
- physiological (compliance with the physiological characteristics of the human body, for example, the isotonicity of eye drops with the fluid medium of the eye);
- psychophysiological (compliance with the peculiarities of the sensory organs, such as smell and taste of drugs);
- hygienic (compliance with the temperature, humidity and gaseous exchange parameters of the microbiological medium in the human body);
- psychological (compliance with the perception of the drug as a product capable of improving and strengthening health).
Fig. 1.

Fig. 2.
— aesthetic (compliance with aesthetic human needs, for example, the package design);
— ecological (compliance with the requirements of environmental safety during administration and storage);
— reliability (storability within the established shelf life);
— safety (physical — in terms of physical properties; chemical — in terms of the active substance; biological — in terms of organic origin) [2].

In earlier research conducted under the leadership of G.T. Glembotskaya, it was scientifically proved that the drug becomes a commodity, when, along with physical, chemical, and pharmacological properties, it acquires consumer characteristics and recognition of the intermediate users — demand [3]. Thus, the drug becomes a commodity, when it acquires elements of the marketing environment. If a drug successfully passes all the stages of development, trials, registration, formation of the marketing environment, then comes the stage of implementation, including mass production and market launch. We adapted an algorithm for assigning consumer characteristics to drugs (Fig. 2).

Under the current state of the pharmaceutical market, it is no longer enough to develop a safe and effective drug of optimum composition and available technology. In addition to these essential qualities, new drugs should be biosimilar to substances, original products, as well as have sufficient competitive advantages over existing drugs on the market. In considering the feasibility of launching an MP onto the market nowadays, the question inevitably arises not only about comparable equivalent efficacy and high safety, but also about affordability for the consumer. For the consumer, comparison of prices is an extremely important factor influencing the purchase, and this factor often determines his choice.

The proposed methodological approaches to rationalizing demand for new drugs were tested on the example of Depantol suppositories and Panavir eye drops. These approaches will receive further development in an ongoing study of the Organizational and technological rationale of the prospects for developing improved locally applied pharmaceutical forms as an individual approach to treatment in gynecological practice. The need of the gynecological practice in a new individual approach to treatment has been identified, and structural elements of the operational model of the approach have been developed.

Thus, the conceptualization of the process of launching a new drug is dynamic and constantly improving with account of the turbulent (changing) external conditions.

REFERENCES


Nowadays the growth of *Helicobacter pylori* (*H. pylori*) strains, resistant to the main medications that are used in the schemes of the first-line therapy, is regarded as the chief reason for failure of the infection treatment. In the world population prevalence rates for *H. pylori* resistant strains vary within wide range in different geographical areas, correlating with the total worldwide frequency of antibiotics application [1]. The mechanisms of the development of *H. pylori* resistance to antimicrobials are mainly based on the point mutations, causing the change of the mechanisms of antibiotic action. The spectrum of mutations are extremely heterogeneous, as determined by different application points (targets) of antibiotics, used in eradication therapy schemes of the infection [2].

Studies of *H. pylori* resistance mechanisms to clarithromycin revealed the presence of the point mutations in the chromosomal region, encoding peptidyl transferase (the main target of macrolides) in V domain of 23S rRNA [3]. The most common variations of such mutations are the replacement of the nucleotide sequences at the positions 2142 (A2142G and A2142C), 2143 (A2143G) [3, 4]. The replacement of nucleotides in these sequences leads to reducing the affinity of macrolides to the ribosomes of the bacterial cell, thereby developing a resistance. Today other point mutations have been also described: A2115G, G2141A, T2117C, T2182C, T2289C, G224A, C2245T, C2611A, though their clinical significance in the context of antibiotic resistance has not ascertained yet, except for T2182C and C2611A, associated with low-level resistance to clarithromycin [3, 5, 6].

In addition to mentioned above changes the expression of efflux pumps of RND-family may play the role in the development of clarithromycin resistance [2, 7]. Efflux pumps are protein complexes that provide a rapid translocation (release) of medication from the bacterial cell outside, thus preventing contact of antibiotic with the ribosome [8]. The possible interaction of proton pump inhibitors (PPIs) with efflux pumps of the RND-family due to their structural analogy is of certain interest. Particularly, in addition to suppression of acid output PPIs may have an inhibitory effect on efflux pumps, reducing resistive potential of *H. pylori* [3, 9]. However, this point still does not have a substantial evidence.

Mechanisms of *H. pylori* resistance to nitroimidazole derivatives (metronidazole, tinidazole) are poorly studied. It is considered that the main reason for this resistance to the group of medications is the impossibility of antibacterial compound to transform to the active form [2]. The reasons for this phenomenon may be mutations of the RdxA gene, encoding oxygen-insensitive nitroreductase, and the FrxA gene, encoding flavin oxidoreductase [10]. Inactivation of these genes leads to the reduction in transformation (recovery) of metronidazole into the active derivatives (NO₂⁻ and NO₃⁻), that have a damaging effect on the structure of DNA (fig. 1) [3]. Nevertheless, cases of *H. pylori* resistance to the nitroimidazole derivatives, not associated with mutations in the RdxA and FrxA genes have been described [11]. It is assumed that some of them may be result from low activity of the NADH-oxidase and efflux mechanisms [2, 12].
The main reason of *H. pylori* resistance to amoxicillin is the mutation in the resistant pbp1A gene, encoding penicillin binding protein 1A (PBP1), responsible for catalyzing the terminal stage of peptidoglycan development of the bacterial cell wall [3, 13, 14]. Three variations of replacement of amino acids (Ser414 to Arg, Thr556 to Ser, and Asn562 to Tyr) in the structure of protein are the most frequently associated with amoxicillin resistance. Point mutations of the genes, encoding others of penicillin-binding proteins (PBP2, PBP3 and PBP4) are described as well. However, their role in the development of amoxicillin resistance is considered as additive [3, 14, 15].

Apart from it, the mechanisms referred to reducing the permeability of the microorganism may play a certain role in the development of *H. pylori* resistance to amoxicillin. The last biological characteristic is associated with the alteration of protein functions of *H. pylori* outer membrane, that are encoded by genes hopB and hopC [16].

The main reason of *H. pylori* resistance to tetracyclines consists in mutations in the genes, encoding 16S rRNA (*rrnA* and *rrnB*) [13, 17]. The most frequent mutation is considered to be substitution of the nucleotide triplet AGA_{926–928}→TTC, that leads to reducing antibiotic affinity to the ribosome by 24–52% [3, 18]. Other mechanisms of resistance to tetracycline include activity of the protein Tet(O), which is an antagonist of the antibiotic, preventing its interaction to the ribosome and subsequent stop of the protein synthesis [19].

Fluoroquinolone (levofloxacin) resistance is associated with changes in nucleotide sequences in the *gyrA* gene (in positions 87, 88, 91) encoding the A subunit of bacterial DNA gyrase [2, 20, 21]. The value of the *gyrB* gene mutations in the development of resistance to fluoroquinolones is minimal [22].

Mechanisms of resistance to rifabutin and nitrofurans (furazolidone) are poorly studied. It is assumed that the mechanism of rifabutin resistance is associated with point mutations in the *rpoB* gene, encoding β-subunit of the bacterial RNA polymerase [3, 23]. Conversely the nitrofurans resistance may be mediated by mutations in the porD and oorD genes, encoding β-subunits of the pyruvate flavodoxin oxidoreductase and 2-oxoglutarate reductase respectively [24].

Thus, in the basis of antibiotic resistance to *H. pylori* lies single point mutations and efflux mechanisms, causing an alteration of the antibacterial medication effect. The introduction of molecular genetic methods for identification of the described above mutations into clinical practice will allow for more individually approach to the treatment of *H. pylori* infection.

**REFERENCES:**


ABSTRACT — Considering the low detection rate of CHD in the first trimester of pregnancy, and often in the second one, as well as a high postnatal mortality rate, there is need to develop new methods for early diagnosis. A large number of researches is devoted to developing additional methods for early CHD detection in fetuses with normal nuchal translucency thickness and normal karyotype. According to pooled data from the world literature, the anomalous blood flow in ductus venosus in early pregnancy may be a marker of CHD.

One clinical CHD observation in a fetus with normal nuchal translucency thickness, but with abnormal blood flow in the ductus venosus in the first trimester of pregnancy is presented in our paper.

KEYWORDS — fetus, pregnancy, fetal CHD, common open atrioventricular canal, prenatal diagnosis, ductus venosus.

INTRODUCTION

Ductus venosus (DV) is direct communication between the umbilical and the central venous system, through which well oxygenated blood is flowing bypassing the hepatic circulation [1]. Diameter of fetal DV at 11–14th gestation weeks is several times smaller than that of umbilical vein, and its length is approximately 2–3 mm. However, despite such a small size, the DV has an important role in regulating arterial blood volume flowing through it. At Doppler scanning, unidirected flow in the form of the three-phase curve should be recorded in DV into all phases of cardiac cycle. Anomalous blood flow in ductus venosus in early pregnancy in fetuses with normal nuchal translucency thickness may be a marker of CHD [2]. Firstly this diagnosis method was used by T. Huisman et al. in 1997 [3]. The study was performed in a fetus of twins with trisomy 18 and dilated nuchal translucency.

Currently, DV blood flow study is carried out in fetuses at high risk of chromosomal abnormalities or CHD only, particularly in those with dilated nuchal translucency. We present the observation of CHD screening based on the detection of reverse blood flow in DV in the absence of other prognostic factors.

CASE HISTORY

29-year-old gravida with assumption of fetal rhythm disturbance was examined at the 12th gestation week. From history, her husband is known to have underwent the Fallot’s tetralogy correction in early childhood.

According to biochemical screening, low risk of developing chromosomal abnormalities was determined in this fetus.

US and Doppler ECG fetal examination (GE VOLUSON 730 Pro, Fetal Cardio and Obstetrics Program) with convex probe 3.5–5 MHz in the mode of 2D+Doppler from abdominal approach on the base of measuring the coccyx-parietal size showed...
gestational age corresponded to 12–13 weeks. Nuchal translucency thickness was 2.1 mm, being the norm for this gestational age. Furthermore, anomalous (reverse) blood flow in DV was found (Fig. 1). Fetal nasal bone length was 3.1 mm, being the norm for this gestational age; other fetal parameters corresponded to gestational age.

Sighting Doppler ECG revealed common open atrioventricular canal in the fetus (Fig. 2).

Considering great percentage of compatibility of this heart disease with the presence of chromosomal abnormalities in the fetus, the woman was recommended to make fetal karyotyping, which she refused, citing the high risk of miscarriage.

Despite the heart disease complexity and the risk for fetal chromosomal pathology, the family had decided to prolong the pregnancy. Previously established diagnosis was confirmed by the number of dynamic examinations at 16–17, 21–22 and 30–31 weeks, as well as postnatally and intraoperatively.

**DISCUSSION**

Given the high prevalence as well as low detectability of the CHD in early pregnancy in fetuses with normal nuchal translucency thickness, the need for introduction of new diagnosis methods increases. The literature describes a large number of studies on the development of additional predictive methods for early detection of heart defects [2]. According to pooled data, anomalous blood flow in the ductus venosus in early pregnancy may be a marker of chromosomal abnormality in a fetus, as well as presence of the CHD in it. The above described clinical case demonstrates that Doppler blood flow in DV may be considered as an additional criterion, allowing more efficient US-screening in the first trimester of pregnancy for early CHD diagnosis in a fetus. This method is particularly actual in cases of borderline and normal values of nuchal translucency thickness. Echographic study of blood flow in ductus venosus is methodologically available that allows to introduce it in standard obstetric US-examination to identify fetuses at risk for developing CHD.

![Fig. 1. Dopplerograms of blood circulation curves of blood flow in the ductus venosus. Arrow — the reversible blood flow in the ductus venosus. Pregnancy 12 weeks](image1)

![Fig. 2. US scanning in grayscale. The projection of the four heart chambers. White double-headed arrow, common open AV canal in the fetus of 22 gestation weeks, black arrow — ventricular septum defect, dotted arrow — primary interatrial septum defect.](image2)
Patients with burn pathology represent a certain interest in the context of studying changes of permeability of intestinal canal and risk of development of polyorgan insufficiency as according to various authors from 3.3 to 22% of adult patients have various complications from a gastrointestinal tract, the part of patients among children is even higher [3, 6, 7]. On some evidence, the burning injury can result also in incompetence of barrier mechanisms of a gastro-intestinal tract, with the subsequent invasion of pathogenic and opportunistic microorganisms in blood. Also, intestinal canal is given one of the leading roles in development of the systemic inflammation response syndrome and polyorgan insufficiency [1, 2]. The lethality from polyorgan insufficiency takes a dominating position among other reasons of mortality at a burning injury at children, and makes more than 50% from total number of cases [11]. It should be noted that, according to many researchers at the heart of sepsis development including burning, the complex of the reactions developing in an organism of the patient in reply to a microbic invasion are placed. The main starting factor of development of systemic inflammation response syndrome is considered release by endotoxin by gram-negative microorganisms, main active principle is liposaccharide (LPS) [5, 10].

The aim of the research is improvement of results of treatment of children with a heavy burning injury by means of effective diagnostics of a syndrome of intestinal insufficiency and a syndrome of the system inflammatal response syndrome and optimization of performed therapies.

**MATERIALS AND METHODS.**

The results of treatment of 24 injured children with the burning injury, passing treatment in anesthesiology and intensive care department No. 1 of Regional children’s clinical hospital named after Silishcheva N.N. in the city of Astrakhan are studied in the work. All observations were made during the prospective study carried out from 2009 to 2012. The clinical methods of research including an assessment of complaints of the injured child, the general condition, detailed, physical examination were used in the work. The area of burn wounds determined by rules of “nine” and “palm”. Depth of burnings was defined according to classification of the 27 congress of surgeons in the USSR (1961). For an objectification of an assessment of weight of a burning injection the area and severity index, offered by H. Frank (1960) was used. The assessment of weight of burning shock, was carried out on A.A.Popova’s classification (in modification of N.P. of Shen) [9]. In total 24 injured children had a shock-producing, burning injury of the I–II degree, with an index of Frank from 25 to 45 c.u. The age of the surveyed children made from 1 year to 3 years. Damaging thermal factor in all cases is boiled water. As criteria of an exception the patients having accompanying diseases of the gastro-intestinal tract before...
receiving a burning injury. Circumstances of an injury and localization of burnings weren’t considered in the work. From injured children 2 groups on 12 children were created groups (basic and control), similar on age, sex, the area and depth of damages (Table 1). The domestic enterosorbent of “Polisorb MP” was included in the scheme of treatment of the early period of a burning disease to children from the main group.

Table 1. Characteristics of injured children (M±m)

<table>
<thead>
<tr>
<th>index</th>
<th>Basic group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of burning injury</td>
<td>18,2 ± 2,5%</td>
<td>20,5 ± 1,5%</td>
</tr>
<tr>
<td>Index Frank</td>
<td>28,6 ± 3,4 c.u.</td>
<td>29,2 ± 2,2 c.u.</td>
</tr>
<tr>
<td>age</td>
<td>1,5 years±1,3 month</td>
<td>1,7 years±1,2 month</td>
</tr>
</tbody>
</table>

As a perspective marker, for studying of violation of permeability of intestines at a burning disease at children, we chose sCD14 definition (dissolved CD14 of a receptor) in serum of blood of the patient. The research sCD14 was conducted with the help of a ‘sandwich’ method of the solid-phase immunofermental analysis. Research was conducted by means of ‘Hbt human sCD14 ELISA’ set (HyCult biotechnology b.v. Netherlands). Also it was carried out microbiological researches of excrements of children with a burning injury. Microbiological researches of quantitative and qualitative composition of excrements were carried out according to methodical recommendations in the Russian Federation [8].

RESULTS OF THE RESEARCH AND THE DISCUSSION

The analysis of the conducted research showed that throughout the early period of a burning disease the sCD14 level in serum of patients of control group exceeded the sCD14 level in serum of patients of the basic group against enterosorbtion application. At the end of the first days average values of indicators of sCD14 of the basic and control groups exceeded the limit of standard parameters specified by manufacturing firm of a laboratory set (2–4 ng/ml). In the basic group average sCD14 value made 4,17±0,29 ng/ml that was reliable below, in comparison with control group where this indicator equaled to value 6,65±0,64 ng/ml (P<0,05). At the end of 3 days, the sCD14 levels reached the peak values in both groups and made 7,57±0,78 ng/ml (the basic group) and 9,71±1,57 ng/ml (control group). Further, gradual decrease in indicators of sCD14 is noted, for the 5th days after the got burning injury average values basically and control groups made 5,2±0,27 ng/ml and 7,03±0,52 ng/ml respectively. For the 7th day of a burning disease the maintenance of sCD14 in the basic group (5,4±0,2 ng/ml) was authentic less (p< 0,05), in comparison with control group (6,79±0,72 ng/ml), however both indicators considerably exceeded laboratory standards (Fig. 1).

Results of microbiological researches revealed the following changes. By the end of the first day after the got burning injection in the basic group it wasn’t noted violations of a fecal microbiocenosis, in comparison with control group where at 16,6% of patients changes in a microbiocenosis were recorded. These changes were shown, in the form of reduction of quantity of an coliform organism with normal properties (10⁵–10⁶) that corresponded to dysbacteriosis of the I degree. In the researches which have been carried out on the 10th days, in the basic group 16,6% of patients with changes of a microbic landscape of intestines characteristic for dysbacteriosis of the 1 degree are recorded, for comparison the number of patients with similar violation in control group made 33,3% from number of patients in the group. Dysbacteriosis of the II degree was noted at 8,3% of patients from the basic group and 25% of patients from control group respectively. Violations were shown in the form of decrease in quantity of lactobacilli (10⁵) and bifid bakterium (10⁷), a coliform organism with normal properties, increase in quantity of a coliform organism possessing hemolytic properties. Half of patients of control group with dysbacteriosis of the II degree had moderate increase of representatives of the sort Proteus (10⁴–10⁵). Dysbacteriosis of the 3 degrees was diagnosed only in control group for 8,3% of patients. Violations of a fecal
microbiocenosis were shown in the form of considerable decrease in lactobacilli (<10⁵) and bifidobakterium (10⁵), increase of quantity of a coliform organism with the reduced enzymatic activity (10⁸), a coliform organism possessing hemolytic activity (10⁷). Increase of representatives of the genus Pantoea, Citrobacter, Proteus (10⁵–10⁶) was noted, emergence of mushrooms of the genus Candida was noted at these patients (Table 2).

**CONCLUSION**

1) On the basis of the undertaken research, we suppose that increase of the concentration of sCD14 in serum of blood can be used as a test for identification of “a translocation syndrome” and intoxication of an organism of LPS of gram-negative bacteria at a burning disease at the children.

2) Studying of dynamics of the concentration of sCD14, showed that the greatest body burden from LPS of gramo-negative bacteria falls on the third day after receiving a burning injection.

3) Inclusion in therapy of the early period of a burning disease of an enterosorbent of “Polisorb MP” showed the efficiency in the form of sCD14 level reduction in blood serum, and also severity of violation of a fecal microbiocenosis.

**REFERENCES**


7. **Mandalas Barun Kumar, Grigorev O. I.** Erosive and ulcer defects of a gastrointestinal tract at patients with thermal burnings / Collection of scientific works of the II congress combusiologists of Russia. – Moscow, 2008. – P. 164–166.


---

**Table 2. Comparison of the statement of microbiocenosis of intestinal canal at the children**

<table>
<thead>
<tr>
<th>Day of a burning disease</th>
<th>Group</th>
<th>Number of injured people</th>
<th>Degree of disbacteriosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>1st day</td>
<td>Basic group</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>1st day</td>
<td>Control group</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>10th day</td>
<td>Basic group</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>10th day</td>
<td>Control group</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>
HÄUFIGKEIT KARDIOCHIRURGISCHER WUNDHEILUNGSSTÖRUNGEN

Siegfried Schink MD
Rehabilitationsklinik Fallingbostel, Bad Fallingbostel

ABSTRACT

In einem Jahr sahen wir bei 9,0% (178) der 1967 herzoperiert Patienten behandlungsbedürftige WHS, eine chirurgische Wundversorgung erfolgte bei jedem Dritten dieser Patienten.

25% der WHS wurden bei der Aufnahmeuntersuchung festgestellt, 31% in der ersten, 26% in der zweiten und 18% in der dritten Woche der stationären Rehabilitation. Eine Leukozytose oder ein CRP-Wert unter 10 mg/dl waren in beiden Gruppen gleich häufig, ein CRP-Wert über 10 mg/dl trat bei 20% der WHS und 6% der Kontrollgruppe auf.


Nach der Herzklappendenoperation kam es seltener zu WHS als nach Bypass- oder kombinierten Operationen. Eine Leukozytose oder ein CRP-Wert über 10 mg/dl trat bei 20% der WHS und 6% der Kontrollgruppe auf.

Die Prüfung der Merkmalsverteilung Geschlecht und Alter zeigte eine gute Übereinstimmung zwischen den beiden Gruppen, so daß die Kontrollgruppe als repräsentativ angesehen werden kann.

9,0% (178) der herzoperierten Patienten erhielten eine dokumentierte Wundbehandlung, bei 6 fehlenden Daten umfaßt die Studiengruppe 172 Patienten. Wir zogen zufällig aus den 1789 herzoperierten Patienten des Jahres 2002 ohne Wundbehandlung eine gleich große Kontrollgruppe und verglichen die klinischen Daten dieser beiden Gruppen miteinander.

Geschlecht

9.0% (178) der herzoperierten Patienten erhielten eine dokumentierte Wundbehandlung, bei 6 fehlenden Daten umfaßt die Studiengruppe 172 Patienten. Wir zogen zufällig aus den 1789 herzoperierten Patienten des Jahres 2002 ohne Wundbehandlung eine gleich große Kontrollgruppe und verglichen die klinischen Daten dieser beiden Gruppen miteinander.

Die Prüfung der Merkmalsverteilung Geschlecht und Alter zeigte eine gute Übereinstimmung zwischen der Kontrollgruppe und der Gesamtpopulation herzoperierter Patienten ohne Wundbehandlung, so daß die Kontrollgruppe als repräsentativ angesehen werden kann.

1. STUDIENDESIGN


9,0% (178) der herzoperierten Patienten erhielten eine dokumentierte Wundbehandlung, bei 6 fehlenden Daten umfaßt die Studiengruppe 172 Patienten. Wir zogen zufällig aus den 1789 herzoperierten Patienten des Jahres 2002 ohne Wundbehandlung eine gleich große Kontrollgruppe und verglichen die klinischen Daten dieser beiden Gruppen miteinander.

Die Prüfung der Merkmalsverteilung Geschlecht und Alter zeigte eine gute Übereinstimmung zwischen der Kontrollgruppe und der Gesamt population herzoperierter Patienten ohne Wundbehandlung, so daß die Kontrollgruppe als repräsentativ angesehen werden kann.

2. ERGEBNISSE

<table>
<thead>
<tr>
<th>Geschlecht</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Männer</td>
<td>90</td>
<td>126</td>
<td>0,7</td>
</tr>
<tr>
<td>Frauen</td>
<td>82</td>
<td>46</td>
<td>1,8</td>
</tr>
</tbody>
</table>
Formal ist das Risiko der Frau für eine postoperative Wundheilungsstörung um das 1,8fache erhöht. Allerdings zeigt sich in der Subanalyse eine deutlich divergierende Verteilung klinischer Merkmale: Die Frauen sind 2,8 Jahre älter, weisen häufiger einen BMI über 35 (11 Frauen : 7 Männer) auf. 26 Frauen versus 2 Männer haben einen insulinpflichtigen oder mindestens 10jährigen Diabetes mellitus Typ 2. Die Verteilung der OP-Arten ist annähernd gleich.

**Alter**

<table>
<thead>
<tr>
<th>Alter</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arithm. Mittelwert</td>
<td>69,8 Jahre</td>
<td>67,4 Jahre</td>
<td></td>
</tr>
<tr>
<td>Standardabweichung</td>
<td>8,8</td>
<td>9,6</td>
<td></td>
</tr>
<tr>
<td>kl/gleich 60 Jahre</td>
<td>21</td>
<td>32</td>
<td>0,7</td>
</tr>
<tr>
<td>gr/gleich 80 Jahre</td>
<td>23</td>
<td>11</td>
<td>2,1</td>
</tr>
</tbody>
</table>

(Hier für Veröffentlichung auch Daten 60–70 /70–80)

Die Patienten mit Wundheilungsstörungen sind im Durchschnitt 2,4 Jahre älter, der Anteil von sehr alten Patienten ab dem 80. Lebensjahr ist doppelt so hoch.

**Gewicht**

Am Aufnahmetag wurde in unserer Klinik der BMI gemessen.

<table>
<thead>
<tr>
<th>Gewicht</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arithm. Mittelwert</td>
<td>29,4</td>
<td>27,1</td>
<td></td>
</tr>
<tr>
<td>Standardabweichung</td>
<td>4,5</td>
<td>3,6</td>
<td></td>
</tr>
<tr>
<td>Kleiner/gleich 20</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>20 kl/gl 25</td>
<td>28</td>
<td>44</td>
<td>0,6</td>
</tr>
<tr>
<td>25 kl/gl 30</td>
<td>79</td>
<td>96</td>
<td>0,8</td>
</tr>
<tr>
<td>30 kl/gl 35</td>
<td>41</td>
<td>27</td>
<td>1,5</td>
</tr>
<tr>
<td>Über 35</td>
<td>18</td>
<td>1</td>
<td>18</td>
</tr>
</tbody>
</table>

Die Patienten mit Wundheilungsstörungen sind im Durchschnitt 2,3 kg schwerer. Wegen der kleinen Fallzahl kann die Gruppe „BMI unter 20“ nicht berücksichtigt werden. Es zeigt sich ein deutlicher Risikoanstieg mit zunehmendem BMI, wobei der BMI von 30 die Schwelle darstellt: Die Patienten mit einem BMI unter 30 zeigen ein erniedrigtes und über 30 ein erhöhtes Risiko. Dieser Zusammenhang wird in einer Vier-Felder-Tafel geprüft:

**Vier-Felder Tafel: BMI unter /über 30**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unter 30</td>
<td>105</td>
<td>144</td>
</tr>
<tr>
<td>Über 30</td>
<td>59</td>
<td>28</td>
</tr>
</tbody>
</table>
|           | 164           | 172            | 336

Der y-Wert ist mit 16,9 hochsignifikant, d.h. Der Unterschied im WHS-Risiko zwischen BMI kleiner und größer 30 ist signifikant. Klinisch relevant wird das erhöhte Risiko erst ab einem BMI von 35, das Risiko ist hier stark erhöht.

**Postoperative Verweildauer in der operierenden Klinik**

<table>
<thead>
<tr>
<th>Alter</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
</tr>
</thead>
<tbody>
<tr>
<td>KHB-arithm. Mittelwert</td>
<td>8,5 Tage</td>
<td>8,3 Tage</td>
</tr>
<tr>
<td>KHB-Standardabw.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR- arithm. Mittelwert</td>
<td>16,6 Tage</td>
<td>14,8 Tage</td>
</tr>
<tr>
<td>KHB-Standardabw.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Die AR-Patienten mit WHS kommen durchschnittlich 1,8 Tage später zur Aufnahme als Patienten ohne WHS. Dies resultiert aus der deutlich höheren Rate postoperativer Komplikationen (siehe unten), die einen längeren Aufenthalt in der operierenden Klinik erfordert.

**Operationsarten**

Bei der Einteilung wurde die Bypass-OP mit arteriellem Graft besonders berücksichtigt, da nach früheren Untersuchungen diese OP-Technik häufiger zu Wundheilungsstörungen führt.

<table>
<thead>
<tr>
<th>Operationsart</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Re-Herzoperation</td>
<td>4 (2,3%)</td>
<td>5 (2,9%)</td>
<td></td>
</tr>
<tr>
<td>2. MIDCAB</td>
<td>5 (2,9%)</td>
<td>4 (2,2%)</td>
<td></td>
</tr>
<tr>
<td>3. OPCAB</td>
<td>1 (0,6%)</td>
<td>1 (0,6%)</td>
<td></td>
</tr>
<tr>
<td>4. art.Bypass +/-</td>
<td>104 (58%)</td>
<td>82 (46%)</td>
<td>1,3</td>
</tr>
<tr>
<td>venöser Bypass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. venöser Bypass.</td>
<td>23 (13%)</td>
<td>17 (10%)</td>
<td>1,4</td>
</tr>
<tr>
<td>6. Klappenop. +/-</td>
<td>20 (11,2%)</td>
<td>14 (7,7%)</td>
<td>1,6</td>
</tr>
<tr>
<td>Bypass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Klappenop.</td>
<td>15 (8,4%)</td>
<td>49 (27%)</td>
<td>0,3</td>
</tr>
</tbody>
</table>

Die Spalte 1-3 (Re-Operation, MIDCAB, OPCAB) können wegen der geringen Fallzahl nicht ausgewertet werden.

Die koronare Bypasschirurgie (Spalte 4 + 5) weist ein leicht erhöhtes Risiko für WHS auf, einen Einfluß des art. Graft fanden wir nicht.

Bei der Herzklappenoperation mit koronarem Bypass (6) ist das Risiko erhöht.

Die Herzklappenoperation ohne Bypass zeichnet sich formal durch ein niedrigeres Risiko aus, es ist jedoch zu berücksichtigen, dass hier keine Saphenektomienarbe vorliegt. Unter Berücksichtigung der Wundverteilung (40% Sapenektomienarben) dürfte das korrigierte relative Risiko bei der Herzklappenoperation 0,5 betragen.
Zusammenfassend fanden wir bei der koronaren Bypassoperation keinen Einfluß des arteriellen Graft auf die Wundheilung, ein erhöhtes Risiko bei der kombinierten Herzklappen-Bypass-Operation und eine verminderte Risiko bei der reinen Herzklappenoperationen.

Postoperative Komplikationen

Bei 46%(82) Studienpatienten und 29%(51) Kontrollpatienten wurden im Verlegungsbericht der operierenden Klinik postoperative Komplikationen erwähnt.

<table>
<thead>
<tr>
<th>Komplikation</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wundheilungsstörungen, -infekte</td>
<td>27 (16%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Vorhofflimmern</td>
<td>25 (15%)</td>
<td>14 (8%)</td>
<td></td>
</tr>
<tr>
<td>Durchgangssyndrom</td>
<td>11 (6%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Akutes Nierenversagen</td>
<td>10 (6%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Respiratorische Insuffizien</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Revisions-OP (meist Sternum/ Nachblutung)</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Kardiales Versagen</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Kammerflimmern/AV-Block</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Neurolog. Komplikation</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Perikarderguss,-Pleureraerguss</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sonstige</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>


Bereits in der operierenden Klinik auftretende Wundheilungsstörungen sind in der Studiengruppe naturgemäß deutlich häufiger vertreten, da bei uns die Wundbehandlung fortgesetzt wurde.

Typische postoperative Komplikationen (Rhythmusstörungen, renale und pulmonale Insuffizienz, Durchgangssyndrom) treten in der Studiengruppe bis 2mal häufiger auf. Postoperatives kardiales Versagen war mit 8 Patienten ausschließlich in der Studiengruppe vertreten.

Revisions-Operationen sind mit keinem erhöhten Risiko behaftet.

Diabetes mellitus


<table>
<thead>
<tr>
<th>Komplikation</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diab.mell. Typ 2</td>
<td>81</td>
<td>42</td>
<td>1,9</td>
</tr>
<tr>
<td>Bis zu 10 Jahre, keine Insulingabe</td>
<td>48</td>
<td>33</td>
<td>1,5</td>
</tr>
<tr>
<td>Mehr als 10 Jahre oder Insulingabe</td>
<td>28</td>
<td>6</td>
<td>4,7</td>
</tr>
<tr>
<td>Fehlende Daten</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Der Diabetes Typ 2 ist in der Studiengruppe 1,9fach häufiger vertreten, die Patienten mit einem über 10 Jahre bestehenden Diabetes weisen ein 4,7fach erhöhtes Risiko auf.

Begleiterkrankungen

Die häufigsten Begleiterkrankungen, die unabhängig und bereits vor der Herzoperation bestanden, wurden erfaßt.

<table>
<thead>
<tr>
<th>Komplikation</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>13</td>
<td>18</td>
<td>0,7</td>
</tr>
<tr>
<td>pAVK</td>
<td>28</td>
<td>19</td>
<td>1,5</td>
</tr>
<tr>
<td>Niereninsuffizien</td>
<td>40</td>
<td>30</td>
<td>1,3</td>
</tr>
</tbody>
</table>

Aufnahmebefund

Immerhin wiesen 43%(74) der Studienpatienten bei der Aufnahme reizlose Wundverhältnisse auf.

Wundlokalisation

Bei 137 (80%) Patienten wurde eine Wunde behandelt, bei 35 Patienten (20%) mehrere Wunden. Es bestanden bei 112 (65%) Patienten Sternotomie-, 75 (44%) Saphenektomie- und 17 (10%) Drainage-Wundheilungsstörungen. Seltenere Lokalisationen waren die Leiste (6 Pat.), linker Rippenbogen- (2 Pat. mit anterolat. Thorakotomie) und der Unterarm (2 Pat.).

Wundabstrich

Bei 52 (29%) der Patienten wurde ein Wundabstrich (im Mittel am 28.postoperativen Tag) durchgeführt: 19 Staphylokokkus aureus, 15 grampositive
Kokken, 7 Staphylokokkus epidermidis, 6 MRSA-Staphylokokken, 5 Enterokokken, 4 koagulasenegative Staphylokokken, 3 gramnegative Stäbchen, 3 E.coli, 3 Pseudomonas. Weitere Bakterien weniger als 3mal diagnostiziert, teilweise bestand Mehrfachbesiedlung, in 5 Fällen kein Keimwachstum.

**Wundbehandlung**

Die Intensität der Wundbehandlung wurde in drei Gruppen eingeteilt: Bei 83 (48%) Patienten wurde eine einfache Wundbehandlung (spülen, Oberflächenreinigung) durchgeführt, bei 55 (32%) Patienten wurde eine erweiterte Wundbehandlung mit Abtragung von Nekrosen, Eröffnung von Verbandsstreifen, Entfernen von tiefen Fäden/Cerclagen im Verbandszimmer. Die intensivste Wundbehandlung mit allgemeinchirurgischer Vorstellung und erweitertem Wunddebridement erfolgte bei 34 (19%) der Patienten.

Neben der Wundbehandlung wurden 125 (70%) Patienten antibiotisch behandelt.

10 (6%) Patienten stellten sich ambulant beim Operateur vor, 22 (12%) Patienten wurden in die operierende Klinik zur weiteren Wundbehandlung verlegt. Kein Patient ist an den Folgen der Wundinfektion gestorben, 1 Patient erlitt einen Sekundenherzinfarkt.

Bei 26 (15%) der Patienten konnte das Wundprotokoll während des stationären Aufenthaltes beendet werden. 101 (59%) der Wundflächen verkleinerten sich bis zur Entlassung, 14 (8%) blieben unverändert, 19 (11%) vergrößerten sich.

**Beginn der Wundbehandlung**

Das Datum der ersten Wundbehandlung (=Anlegen des Wundprotokolls) gibt den Zeitpunkt wieder, an dem die Behandlungsbedürftigkeit erkannt wird. Im Durchschnitt wurde das Wundprotokoll am 22. postoperativen Tag bzw. dem 7. Tag nach der Aufnahmeverifikation angelegt, die Standardabweichung betrug 6,4 Tage.

In der 1. Woche wurden 56% (97) der Wundprotokolle angelegt, in der 2. Woche 26% (44) und in der 3. Woche 13% (23), in der 4. Woche 5% (8).

**Labor**

Beim CRP und Leukozyten wurde der Aufnahmewert, Maximalwert und Entlassungswert ausgewertet.

<table>
<thead>
<tr>
<th>CRP</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aufnahme-Mittelwert</td>
<td>4,3</td>
<td>2,9</td>
<td>1,5</td>
</tr>
<tr>
<td>–Standardabweichung</td>
<td>4,3</td>
<td>Wird berechnet</td>
<td></td>
</tr>
<tr>
<td>Maximal-Mittelwert</td>
<td>6,7</td>
<td>4,2</td>
<td>1,6</td>
</tr>
<tr>
<td>–Standardabweichung</td>
<td>7,0</td>
<td>Wird berechnet</td>
<td></td>
</tr>
<tr>
<td>Entlassung-Mittelwert</td>
<td>2,8</td>
<td>1,4</td>
<td>2,0</td>
</tr>
</tbody>
</table>

Aufnahme bis 5 | 117 | 146 | 0,8 |
5–10 | 34 | 20 | 1,7 |
10–15 | 11 | 3 | 3,7 |
über 15 | 5 | 2 | 2,5 |

Maximalwert bis 5 | 92 | 120 |
5–10 | 39 | 26 |
10–15 | 14 | 6 |
über 15 | 19 | 4 |

Leukozyten

Beim CRP und Leukozyten wurde der Aufnahmewert, Maximalwert und Entlassungswert ausgewertet.

<table>
<thead>
<tr>
<th>Leukozyten</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aufnahme-Mittelwert</td>
<td>9,8</td>
<td>9,5</td>
<td>1,0</td>
</tr>
<tr>
<td>–Standardabweichung</td>
<td>2,9</td>
<td>Wird berechnet</td>
<td></td>
</tr>
<tr>
<td>Maximal-Mittelwert</td>
<td>10,6</td>
<td>10,2</td>
<td>1,0</td>
</tr>
<tr>
<td>–Standardabweichung</td>
<td>3,2</td>
<td>Wird berechnet</td>
<td></td>
</tr>
<tr>
<td>Entlassung-Mittelwert</td>
<td>8,3</td>
<td>7,8</td>
<td>1,1</td>
</tr>
</tbody>
</table>

Aufnahme bis 12.000 | 136 | 140 | 1,0 |
12–15.000 | 26 | 22 | 1,2 |
über 15.000 | 6 | 7 | 0,9 |

Maximal bis 12.000 | 118 | 133 | 1,0 |
12–15.000 | 31 | 27 | 1,2 |
über 15.000 | 12 | 10 | 1,2 |

**Verteilung der operierenden Kliniken**

<table>
<thead>
<tr>
<th>Klinik</th>
<th>Studiengruppe</th>
<th>Kontrollgruppe</th>
<th>rel. Risiko</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>30</td>
<td>1,2</td>
</tr>
<tr>
<td>–2</td>
<td>36</td>
<td>19</td>
<td>1,9</td>
</tr>
<tr>
<td>–3</td>
<td>12</td>
<td>7</td>
<td>1,7</td>
</tr>
<tr>
<td>–4</td>
<td>14</td>
<td>23</td>
<td>0,6</td>
</tr>
<tr>
<td>–5</td>
<td>55</td>
<td>76</td>
<td>0,7</td>
</tr>
<tr>
<td>–6</td>
<td>19</td>
<td>17</td>
<td>1,1</td>
</tr>
</tbody>
</table>
3. DISKUSSION

Inzidenz

Infolge des steigenden Anteils herzchirurgischer Eingriffe bei Risikopatienten und der kurzen Krankenhausverweildauer treten postoperative Wundheilungsstörungen (WHS) zunehmend während der Anschlussrehabilitation auf. Wir führten bei 9,0 % der herzoperierten Patienten eine Wundbehandlung der Operationsswunden durch, wobei in dieser Zahl 27 Patienten (1,4 %) enthalten sind, die bereits mit einer Wundheilungsstörung von der operierenden Klinik verlegt wurden. Davon 112 (5,7 %) Patienten mit Wundheilungsstörungen der Sternotomie- und 75 (3,8%) der Saphenektomienaht.

Risikofaktoren für Wundheilungsstörungen

Die bekannten Faktoren Diabetes (1) und Adipositas (3,5) mit negativen Auswirkungen auf die postoperative Wundheilung können wir bestätigen:

– In unserem Kollektiv ist das Risiko einer Wundheilungsstörung beim langjährigen Typ 2 Diabetiker um das 4,7 fache erhöht. (Literatur 1 z.B. 2,3) Interessant ist die Subanalyse nach zeitlicher Dauer des Diabetes, bei Diabetes ohne Insulintherapie bzw. unter 10 Jahren ist das Risiko nur 1,5fach erhöht.


Das weibliche Geschlecht ist in unserem Kollektiv mit einem 1,8fachen Risiko behaftet, wie auch Ferraris (4) berichtete. Allerdings ist dies kein Einfluss des Geschlechtes, sondern die deutliche Häufung von langjährigem Diabetes bei den untersuchten Frauen.

Die Begleiterkrankungen Niereninsuffizienz und pAVK zeigen ein 1,3 bzw. 1,5fach erhöhtes Risiko – dies war nicht statistisch signifikant.

Die WHS zeigte sich bei 56% der Patienten in der ersten Woche, bei 26% bzw. 18% in der zweiten bzw. dritten Woche. Eine Leukozytose oder ein CRP-Wert bis 10 mg/dl hatte keinen prädiktiven Wert, bei 20% der Patienten mit WHS bestimmten wir einen CRP-Wert über 10 mg/dl, in der Kontrollgruppe bei 6% der Pat.


Bei 15% der Patienten wurde die Wundbehandlung bis zur Entlassung abgeschlossen, bei 59% zeigte sich eine deutliche Verbesserung des Lokalbefundes, 19% blieben unverändert oder verschlechterten sich. Eine Mediastinitis zeigte sich nicht. 22 Patienten, also 1,1% aller herzoperierten Patienten unserer Klinik, wurden zur Wundbehandlung zum Operateur zurückverlegt.

LITERATUR

EINLEITUNG


Zusätzlich leisten die ungesättigten Fettsäuren wertvolle Hilfe als Biokorrektivium. Sie machen nicht
nur die Zellmembranen beweglicher, sondern dienen auch als Fänger unkontrolliert wirkender freier Radikale. In der Folge wird die Akkumulation oxidativ bedingter Zell- und Molekülschäden durch freie Radikale vermindert. Die physiologische Rückführung in unbedenkliche Toleranzbereiche wird durch die Kombination der mineralischen Komponente im Nanovit® metabolic und der zusätzlichen Gabe von Omega-3-Fettsäuren befördert.

Die vom Organismus benötigte Energie wird im Wesentlichen über die Verbrennung von Kohlenhydraten und Fetten produziert.

Der Anteil, den die Fettverbrennung daran hat, hängt von der verfügbaren Sauerstoffmenge für die beteiligten Muskel- und Organzellen sowie vom Wirkungsgrad der Fettoxidation aufgrund unterschiedlich entwickelter Enzymaktivität ab. Die verfügbaren Sauerstoffmengen werden durch die Sauerstofftransportkapazität und die Makro- und Mikrozirkulation des Blutes limitiert. Diese Prozesse sind genetisch und vom aktuellen Gesundheitszustand individuell geprägt und laufen relativ stabil ab.

Um die Dominanz des Fettstoffwechsels zu sichern, muss die Sauerstoffversorgung und -verwendung im Gewebe mit einer individuell passenden Bewegungsintensität in Einklang stehen. (BioKorrektur) Damit dies gewährleistet ist, wird diese individuell passende (optimale) Bewegungsintensität aktuell über die Messung des respiratorischen Quotienten und die aufgenommene Sauerstoffmenge bestimmt (Eingangstest) und geregelt (Training).


Eine effektive Beeinflussung des Energiestoffwechselverhaltens erfordert die exakte Einhaltung der festgelegten Stoffwechselcharakteristik (RQ, Sauerstoffaufnahme) und damit die Fokussierung der Reizgebung auf die Maximierung der Energieausbeute bei der Fettoxidation über den gesamten Behandlungszeitraum. Ein Abweichen von der festgelegten Stoffwechselcharakteristik verhindert oder erschwert die angestrebte Umstellung in der Energiebereitstellung.

Da sich physiologische Vorgänge nicht linear entwickeln, und auch einer Vielzahl von Einflüssen des normalen Lebensvollzuges ausgesetzt sind, ist eine ständige Steuerung und Regelung des Trainings Voraussetzung. Durch die regelmäßige Kontrolle des respiratorischen Quotienten und der Sauerstoffaufnahme ist es möglich, die Arbeitsintensität exakt an das aktuelle individuelle Stoffwechselverhalten anzupassen.

Als physische Belastung wird das Gehen (walking) auf dem angestellten Laufband angewandt, da Gehen eine natürliche Bewegung ist, die jeder Mensch (unbewusst) beherrscht. Die definierten Vorgaben auf dem Laufband (Anstieg und Geschwindigkeit) sichern die Vergleichbarkeit aller erhobenen Messgrößen und schalten subjektive Faktoren weitgehend aus.

**Methodik**

Es wurden zwei Pilotstudien durchgeführt, um den Einfluss der individuellen systemischen BioKorrektur auf laborchemische und mikrozirkulatorische Veränderungen festzustellen.

Bei 43 Patienten mit gesicherten Diabetes mellitus Typ II wurde folgendes methodisches Design gewählt:

Vor „BioKorrektur“ Erfassung folgender Messparameter:

- Blutzucker;
- C-Peptid;
- HbA1C;
- Cholesterin;
- Triglyzeride;
- HDL;
- LDL;
- Insulin;
- antioxidativer Status;
- HOMA – Index;
- Spiroergometrie;
- Global-klinische Index (Cgl).

Durchführung der Bewegungseinheiten

- 3×30–60 Minuten/Woche;
- Dauer 3 Wochen;
- RQ-Steuerung (0,75–0,8);
- Kontrolle Herzfrequenz, pO2, Blutzucker;
- Verabreichung von Nanovit® metabolic (3×1 Kapsel) und Omega-3-Fettsäure (1×1000 mg) pro Tag;
- Training unter hyperoxischen Bedingungen.

Bei einer kleineren Patientengruppe (n=8) wurden zusätzlich Untersuchungen zur Mikrozirkulation durchgeführt und methodisch ein hochauflösend kombinierte Weißlicht-Spektroskopie und Laser-Doppler-Mikrorussmessung angewendet. Dabei wurden im Behandlungsintervall in zwei Target-Gecken gemessen (Fettgewebe Haut-Abdomen 3 mm Eindringtiefe und Skelettmuskulatur Wad 6 mm Eindringtiefe).
ZUSAMMENFASSENDEN ERGEBNISSE

In beiden Pilotstudien konnte gezeigt werden, dass die Durchführung einer individuellen systemischen BioKorrektur bei Patienten mit Diabetes mellitus Typ II positive Ergebnisse auf klinische, laborchemische und mikrozirkulatorische Befunde resultieren.


— Die Kombination einer RQ-angepassten, mindestens 45 minütigen Trainingsbelastung mit 9 Trainingseinheiten unter hyperoxischen Raumluftbedingungen und mit einer antioxidativen Zusatzbehandlung mit Nanovit® metabolic und Omega-3-Fettsäure garantiert eine Nachhaltigkeit der individuellen Ergebnisse von mindestens 3–6 Monaten.

— Eine 45-minütige Belastungsdauer ist einer 30-minütigen Belastungsdauer vorzuziehen.

— Das individuelle Training wird optimalerweise bei einem RQ von 0,75 – 0,80 durchgeführt, da unter diesen Bedingungen eine vorrangige Fettverbrennung resultiert und die Energiegewinnung nicht primär aus dem Zuckerstoffwechsel erfolgt.

— Die Hyperoxie (26Vol.% Sauerstoffanteil in der Raumluft) wirkt sich auf eine Senkung des RQ aus, was zur gewünschten erhöhten Beanspruchung des Fettstoffwechsels führt.

— Da der oxidative Stress der Zellen beim Metabolischen Syndrom und durch Trainingsmaßnahmen erhöht ist, wird die zusätzliche Verabreichung von Nanovit® metabolic und Omega-3-Fettsäuren als Antioxidanzien die Stoffwechselsituation stabilisieren und die biokorrektiven Wirkungen langfristig aufrecht erhalten.

— Die für die individuelle systemische BioKorrektur notwendigen Voraussetzungen — Trainingsmethodik und individuelles Trainingsprogramm, RQ-gesteuerte individuelle Dauerbelastung, Schaffung einer hyperoxischen Raumluftatmosphäre, Bewahrung der Nachhaltigkeit durch Antioxidanzien und Omega-3-Fettsäuren — sind durch die ICP HealthCare GmbH entwickelt, evaluiert, standardisiert und schutzrechtlich gesichert worden.

— Im Rahmen der Studie sind folgende Einzelergebnisse festzustellen.

Vor und nach 9 Trainingseinheiten
— signifikante Senkung des Blutzuckers;
— signifikante Senkung der Triglyzeride;
— deutliche Tendenz einer HbA1C-Senkung;
— Absenkung des RQ bei gleicher Belastungsintensität.

Nach 3 Monaten (Ergebnisse der Blutwerte)
— weiterhin niedriges Blutzuckerniveau;
— weitere niedrige Triglyzeride;
— HbA1C ist gleich bliebend als Zeichen der Stoffwechselstabilität;
— Verbesserung der antioxidativen Balance.

— Als Beweis für die antioxidative Wirkung von Nanovit metabolic und Omega-3-Fettsäure wurden 10 Patienten mit Diabetes mellitus Typ II 3 Wochen lang mit 3×1 Nanovit metabolic und 100mg Omega-3-Fettsäure behandelt, ohne gleichzeitige Durchführung eines individuellen Trainingsprogrammes. Folgende Ergebnisse waren zu beobachten:

— signifikanter Abfall des Maldondialehyd;
— signifikanter Anstieg der Aktivität der Superoxid-Dismutase;
— Trend der Verbesserung der Glutathionperoxidase.

Die Ergebnisse der Mikrozirkulationsmessungen zeigten ebenfalls sehr positive Ergebnisse.

— Die venolenseitige Sauerstoffausschöpfung steigt deutlich an;
— Die relative Hb-Menge deutet auf einen deutlichen Hämodilutionseffekt hin;
— Der Strömungsfluß der roten Blutzellen nimmt erheblich zu;
— Die bessere bedarfsgerechte Verteilung des Blutes in den kapillären Netzwerken ist die wichtigste Ursache der gesteigerten Sauerstoffausschöpfung durch die Behandlung der Biokorrektur.

Diese Ergebnisse zeigen, dass die individuelle systemische BioKorrektur als adjuvante Behandlungsmethode beim metabolischen Syndrom und speziell beim Diabetes mellitus Typ II zunehmende Bedeutung erlangt. Sowohl die positiven Beeinflussungen auf die laborchemischen und mikrozirkulatorischen Parameter lassen vermuten, dass sowohl positive gesundheitsökonomische Folgen resultieren (Einsparung von Antidiabetika, Fettserker u.a.) und dass mikrozirkulatorische Folgeschäden beim Diabetes mellitus vermindert werden können.

DIE STATISTISCHEN METHODEN


Zunächst wurde die Stichprobe auf Normalverteilung geprüft. Die Sphärizität wurde mittels des Greenhouse-Geisser-Tests (siehe Anhang) berechnet,

Um unterschiedliche Einflüsse wie Gesamttrainingszeit, Geschlecht, Alter, etc. in der Auswertung zu berücksichtigen, wurde der T-Test für unabhängige Stichproben verwendet. Bei signifikanten Varianzhomogenität nach Levene, wurden die signifikanten Unterschiede der einzelnen Parameter vor und nach der Intervention mittels der Signifikanz des Welch-Tests deutlich gemacht. Andernfalls wurde die zweiseitige Signifikanz berücksichtigt.

Das Konfidenzintervall betrug stets 95%, was einem Signifikanzniveau \( \alpha \) von 0,05 entspricht. Signifikanten \( p \leq 0,05 \) wurden als signifikant (*) und Werte mit \( p \leq 0,01 \) als hochsignifikant (**) gekennzeichnet. P-Werte \( \leq 0,1 \) sind als Tendenzen (☐) vermerkt. Es wurden Korrelationskoeffizienten nach Pearson berechnet, da die Normalverteilung der Stichprobe nachgewiesen wurde.

Grafiken Pilotstudie Crivitz:

a) Ergebnisse Aktivierung des Fettstoffwechsels

<table>
<thead>
<tr>
<th>Gruppe</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{RQ prä} )</td>
<td>0,85±0,09</td>
<td>0,85±0,08</td>
<td>0,88±0,09</td>
<td>0,87±0,09</td>
<td>0,86±0,08</td>
</tr>
<tr>
<td>( \text{RQ post} )</td>
<td>0,84±0,05</td>
<td>0,78±0,05*</td>
<td>0,84±0,05</td>
<td>0,83±0,04*</td>
<td>0,82±0,03**</td>
</tr>
</tbody>
</table>

AS = anaerobe Schwelle
M = Mittelwert

b) unterschiedliche Trainingszeiten

<table>
<thead>
<tr>
<th>( \Delta \text{prä-post} )</th>
<th>HDL [mmol/l]</th>
<th>Triglyceride [mmol/l]</th>
<th>HbA1c [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>30min ( + )</td>
<td>0,08 mmol/l</td>
<td>0,13 mmol/l</td>
<td>+ 0,12 %</td>
</tr>
<tr>
<td>45min ( - )</td>
<td>0,02 mmol/l</td>
<td>0,63 mmol/l</td>
<td>- 0,16 %</td>
</tr>
<tr>
<td>( p )</td>
<td>0,019</td>
<td>&lt; 0,01</td>
<td>&lt; 0,01</td>
</tr>
</tbody>
</table>

— Glukose und Triglyceride: mittlerer Effekt nach Cohen
— HbA1c: großer Effekt nach Cohen

c) \( \text{prä-post} \)-Vergleich aller 43 Probanden im Mittel

d) Stichprobe aller 43 Probanden eingeteilt in 2 Gruppen (30 min/ 45 min)

Grafik: Durchschnittswerte des RQ zwischen den Minuten drei und zehn während der Spiroergometrie vor und nach der Intervention bei stetig ansteigender Belastung.

Abendung des RQ nach dem Trainingszyklus
— \( p < 0,01 \)
— optimierter Fettstoffwechsel
LITERATUR


Zusätzlich führten medikamentöse und operative Behandlungsverfahren zur Reduktion der Letalität und zur Erhöhung der Lebensqualität von Patienten mit neurogenen Harnblasenfunktionsstörungen (4).


In einer Untersuchung der BGU Tübingen traten bei 85,7 Prozent der querschnittgelähmten Männer und bei 97,8 Prozent der Frauen mindestens einmal, im Durchschnitt jedoch 1,9 (Männer) bzw. 3,7 Harnwegsinfekte (Frauen) während der stationären Behandlung auf. Paraplegiker erkrankten im Mittel zweimal, Tetraplegiker dreimal an Harnwegsinfekten. Inkomplette Querschnittgelähmte erlitten deutlich weniger, komplette Tetraplegiker deutlich mehr Harnwegsinfekte. Eine Altersabhängigkeit wurde nicht nachgewiesen. Bei transurethralen und suprapubischen
Harnableitungen traten innerhalb von 28 Tagen bei 98% signifikante Bakteriurien auf (5).


Bei Patienten mit intermittierendem Einmalkatheterismus ist bei 40% von einem dauerhaft sterilen Urin oder einer asymptomatischen Bakteriurie auszugehen, im ambulanten Bereich treten 1–2 Harnwegsinfekte pro Jahr auf.

Der Übergang von einer afebrilen oder febrilen Pyelonephritis zu einer Urosepsis wird auch durch das Vorhandensein oder die Vermeidung eines Pyelonephritis zu einer Urosepsis wird auch durch das infekte pro Jahr aufgeht, im ambulanten Bereich treten 1–2 Harnwegsinfekte pro Jahr auf. Bei Patienten mit intermittierendem Einmalkatheterismus ist bei 40% von einem dauerhaft sterilen Urin oder einer asymptomatischen Bakteriurie auszugehen, im ambulanten Bereich treten 1–2 Harnwegsinfekte pro Jahr auf.

Neben dem erhöhten Risiko einer Urosepsis kann der VUR mittel- bis langfristig zu druckbedingten Schädigungen der Nieren mit sonographisch nachweisbarer Parenchymreduktion der Nieren, erhöhten Nierenretentionswerten und letztlich den Folgen einer chronischen Niereninsuffizienz führen.


Das Auftreten einer autonomen Dysreflexie kann isoliert ohne urologische Funktionsstörungen vorhanden sein, aber auch durch urologische Komplikationen und Darmfunktionsstörungen ausgelöst werden. In einer japanischen Untersuchung von 571 Patienten zeigten Patienten mit regelrechter Harn- und Darmfunktion am seltensten, Patienten mit einer spinalen Reflexblase und einer Darmfunktionsstörung am häufigsten die Symptome einer autonomen Dysreflexie (11).

Die renalen Langzeitkomplikationen sind am besten bei Patienten mit Myelomeningozele zu evaluieren. Von 52 Personen mit neurogenen Harnblasenfunktionsstörungen einer dänischen Studie des Jahres 2011 zeigten 71% eine normale Nierenfunktion, 14% eine einseitige, 15% beidseits eine verschlechterte Nierenfunktion (12).

Weitere Früh- oder Spätkomplikationen sind ebenfalls mit dem Auftreten von Harnwegsinfekten assoziiert. In einer indischen Studie des Jahres 2011 (545 Patienten) traten bei 12,1% urethrale Strikturen, in 14,3% urethritische Beschwerden, bei 8,0% Epididymitiden und bei 8,2% periurethrale Abszesse auf. Bei ungefähr 4% wurden sonstige urethrale Komplikationen (z.B. Via falsa) angegeben. Auch hier traten bei Patienten mit intermittierendem Selbstkatheterismus deutlich weniger Komplikationen auf (13).


Urologische Früh- und Spätkomplikationen können durch die erfolgreiche Kombination der wichtigsten Neuerungen der letzten Jahrzehnte, d.h. den intermittierenden Einmalkatheterismus und die kontinuierliche neurourologische Betreuung, reduziert werden.

**Literatur**

2. KOCH I: Die medizinische Rehabilitation der Querschnittgelähmten. VEB Verlag Volk und Gesundheit Berlin 1980
3. MADERSBACHER H: Neurourologie – Neue Schwerpunktbildung in der Rehabilitation des Querschnitt-
Bild 1. Zystogramm einer neurogene Harnblase (Detrusor-Blasenhals-Dyssynergie) mit mehreren Divertikel, Trabekulierung und vesico-ureteralem Reflux links


14 Deluay J. Urology161 (4) / DA West Urology 53 1999
PELVIC MUSCLE TRAINING UNDER BIOFEEDBACK CONTROL IN PATIENTS WITH URINARY INCONTINENCE FOLLOWING RADICAL PROSTATECTOMY

A.Z. Vinarov, PhD., Prof., MD. E.A. Bezrukov, PhD., Prof., MD, Yu.M. Essilevsky, PhD., MD, Yu.L. Demidko, PhD, MD, D.V. Butnaru, Ph., MD., R.R. Kharchilava, PhD., MD., A.M. Bayduvaliev PhD., MD., L.S. Demidko, MD., S.A. Myannik, MD., M.V. Epifanova, MD

First Moscow Medical State University I. M. Sechenov, Research institute of uro nephrology and reproductive health, Moscow, Russia

ABSTRACT — Pelvic floor muscle training is an effective method of post prostatectomy continence recovery. Muscle training is based on the concept of plasticity of the nervous and muscular system and their capacity to acquire new abilities and reinforce the new motor skill. Using EMG biofeedback as an additional source of information about muscle performance contributes to enhanced efficacy of training. Two channels of the total EMG enable regulation of the antagonist muscles activity and development of new motor skills, in this case isolated PFM contraction. The recovery of urinary continence is a function of the ability to consciously control the pelvic floor muscles. The rate of development and reinforcement of the isolated PFM contraction may serve as a prognostic indicator of the efficacy of training and the speed of the recovery process.

INTRODUCTION

Urinary incontinence (UI) is one of the most common complications of radical prostatectomy, a surgical intervention performed to treat prostate cancer. The underlying causes of UI after prostatectomy are incompetent closure mechanism of the vesicourethral anastomosis and hyperactivity of the detrusor muscle.

It is generally held that in the early post-operative period shortly after removal of the urethral catheter it is possible for patients to experience episodes of stress incontinence. If this should happen, neither the doctor nor the patient need to be overly concerned about it. Prior to surgery the patients are briefed on the possibility that recovery of adequate voiding after radical prostatectomy may be a long-term process.

In the majority of observations, urinary continence tends to improve over time following surgical intervention. A number of researchers reported improved voiding control during the first year after radical prostatectomy. Urine leakage within a year after radical prostatectomy persists in less than 5% of patients. Men aged up to 50 years show a better recovery rate of continence function than their counterparts over 70 years old (Kundu S.D., 2004). There is a body of opinion, which holds that recovery of urinary continence function continues up to 24 months. The outcome of surgery should be assessed no earlier than nine months after its completion (Veliev E.I., 2011).

The discrepancy in data on UI could be related to different criteria used to characterize urinary incontinence (Wei J.T., 2000). Within three months after radical prostatectomy only 54% of patients do not wear absorbent products (Walsh P.C., 2000). This index tends to increase to 80% by eight months, reaching 93% after the elapse of 12 months and subsequently stays at this level.
It is worth noting that this pattern of wear is rather rigid and uncompromising because included in the patient group wearing pads are even those patients who use no more than one incontinence pad a day (Pushkar D.Yu., 2007).

It goes without saying that the underlying mechanism of urinary continence in all patients who underwent a similar operation will run a different recovery course (Pushkar D.Yu., 2007). In this context of the utmost interest is the question of the importance and intensity of age-related atrophy of the urinary bladder sphincter and neurophysiological changes in its function given post-surgery impaired innervation. When observing a group of 2415 patients over a period of 17 months to 8.5 years the percentage of patients who had a post surgical urinary incontinence level of one tablespoon per day or more was 6.65. Among males aged up to 60 years this indicator was 4%, and in those over 75 years old — 10% (Karakiewicz P.I., 2004).

Obviously, it is not only surgical techniques but also individual rehabilitation potential of the body which is conditioned to a large extent by the patient's age have a very significant effect on outcomes of radical prostatectomy (Pushkar D.Yu., 2007).

Non-surgical therapy of UI after radical prostatectomy includes changes in lifestyle, pelvic floor muscle training and electrical stimulation. Pelvic muscle training is aimed at increasing the pelvic muscle strength and tone as well as developing the perineal reflex—the ability of the patient to contract muscles in response to an abrupt increase in intra-abdominal pressure. Providing the patient with feedback on pelvic muscles functioning during training sessions (biofeedback) helps to control muscle activity and muscle strength while enhancing the efficacy of exercises.

MATERIALS AND METHODS

Pelvic muscle training under biofeedback control was employed in 87 patients who have undergone radical prostatectomy. The age of patients in the study group was 63 years (55–72)1. Clinical investigation included response to ICIQ-SF questionnaire in order to facilitate objectifying of patient complaints. During history taking situations where urinary incontinence may occur were reviewed. Clinical urinalysis was performed in all patients and the amount of residual urine was estimated. The ICIQ-SF score in the group totaled 17 (10–21). The median time of urine incontinence after prostatectomy at the onset of training was 2 months (1–22). Urinary leakage before reaching the bathroom was reported by 29 patients (33.3%), when coughing or sneezing — 63 (72.4%), while sleeping — 15 (17.2%), during physical exertion — 73 (83.9%), after a trip to the bathroom — 15 (17.2%). Loss of urine without any identifiable cause was reported by 43 patients (49.4%).

Inflammatory changes in urinalysis were found in 4 patients (4.6%). None of the patients had post-void residual urine. The main problem associated with pelvic floor muscle training is that 40 to 60% of patients are unable to selectively isolate and contract the muscles of the pelvic floor, especially given that these muscles are anatomically obscure (Ivanovsky YuV., 2003). Rather than activating their levator ani muscle, the patients would normally contract antagonist muscles—the rectus abdominis muscle, the gluteal, thigh muscles, thereby contributing to increased intra-abdominal pressure. Clearly such exercises apart from being ineffective may also lead to ongoing urinary incontinence.

The goal of isolated pelvic floor muscle training can be accomplished only through the use of biofeedback techniques because in this case visual feedback information is relayed directly to the patient which enables them to monitor the accuracy of exercise performance.

The efficacy of pelvic floor muscle training with use of biofeedback resides in its ability to help the patients develop the feeling of being in control over the pelvic floor. This has the effect of reducing their fear, anxiety, a sense of isolation and hopelessness (Tries J., 1990).

The training of pelvic floor muscles and monitoring patients’ performance were carried out under biofeedback control with a dual-channel EMG. The first channel monitored the electrical activity of pelvic floor muscles displaying it as total EMG while the second channel measured abdominal muscle activity. In a healthy individual abdominal and pelvic floor muscles will contract simultaneously when sneezing, coughing, changing body posture and during voluntary exertion. However, the exertions of abdominal and pelvic floor muscles produce a different effect — when pelvic floor muscles contract the closing function is executed and reinforced whilst during abdominal muscle contraction there is an increase in intra-abdominal pressure.

Therefore the goal of training under a dual-channel EMG control was to acquire the habit of isolated contractions with minimal involvement of anterior abdominal wall muscles. During the training process the patients were learning to consciously control groups of muscles and regulate the intensity of their contraction. In this way they acquired a new behaviour and learnt a new motor skill. A similar technique was introduced by Caufriez M. (1997) into gynecologica practice and gained a wide acceptance in Europe. 42

---

1 Hereinafter the median, 5th and 95th percentiles are shown.
patients (48.3%) have developed the skill of isolated contractions of the perineal muscles with minimal involvement of anterior abdominal wall muscles in the course of 2 or 4 training sessions. 45 other patients (51.7%) had to rely on dual-channel EMG biofeedback support to enable them to perform this type of exercises. They performed exercises once a week.

The primary efficacy endpoint of treatment was reduced frequency of UI episodes, longer intervals between voidings and an increase in excreted urine volume. The use of one small absorbent pad per day to protect against accidental leaks was considered a measure of recovery.

RESULTS

The patient group with sustainable skill of isolated contractions of perineal muscles could exercise on their own gradually augmenting the frequency and duration of training sessions. The efficacy and effort tolerance were monitored once a month by evaluating the dynamics of total EMG of perineal and abdominal muscles.

While exercising the patients learnt to correctly identify the pelvic floor muscles and consciously perform the exercises. Abdominal muscle training has contributed to behaviour change and regulation of work loads during exercise which helped minimize the loss of urine. The results of exercises are given in Table 1.

Dynamics of urinary continence recovery after radical prostatectomy with use of pelvic floor muscle exercises under biofeedback control is shown in diagram 1.

The median time to recover urinary continence after training pelvic floor muscles with biofeedback was 5.1 months.

A major focus of patient training being development of the ability for isolated contractions, the impact of this skill on training outcomes was duly assessed (diagram 2).

Of the 45 patients with post prostatectomy incontinence who trained with biofeedback control to perform corrective exercises, 18 patients have regained continence or improved their voiding function. 27 patients showed no signs of improvement secondary to pelvic muscle training and had an artificial urinary sphincter implanted. The median time of improved health status in this group was 9.5 months.

Of the 42 patients who acquired the skill of isolated floor muscle contraction, 29 patients reported some degree of improvement and recovery, while 13 patients experienced no change in their condition (an artificial urinary sphincter and a sling implanted). The median time of improvement in this patient group was 4 months. Differences in improved health dynamics between these groups were statistically significant (p=0.003).

Comparison of outcomes of pelvic floor muscle training in patients who acquired the skill of isolated

Table 1. Results of pelvic floor muscle training with biofeedback control (n=87)

<table>
<thead>
<tr>
<th>Result</th>
<th>Number, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>28 (32.2%)</td>
</tr>
<tr>
<td>Improvement</td>
<td>19 (21.8%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>36 (41.4%)</td>
</tr>
<tr>
<td>Sling placement</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Artificial urinary sphincter implantation</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>87 (100%)</td>
</tr>
</tbody>
</table>

Table 2. Ability to identify pelvic floor muscles and results of treatment of urinary incontinence (n=87)

<table>
<thead>
<tr>
<th>Result of pelvic muscle training with biofeedback control</th>
<th>Ability to identify pelvic muscles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no available</td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>7 (8.0%)</td>
<td>21 (24.1%)</td>
</tr>
<tr>
<td>Improvement</td>
<td>11 (12.6%)</td>
<td>9 (9.2%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>26 (29.9%)</td>
<td>10 (11.5%)</td>
</tr>
<tr>
<td>Sling</td>
<td>2 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Artificial urinary sphincter</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>45 (51.7%)</td>
<td>42 (48.3%)</td>
</tr>
</tbody>
</table>
PFM contraction and those who failed to learn the skill are shown in table 2.

There were significantly fewer patients who showed no changes in their condition and a significantly greater number of those who made a full recovery (p=0.002) in the patient group that acquired the skill of biofeedback-assisted isolated pelvic muscle contraction. Clinical symptoms and signs of disease were seen to resolve within 5.1 months\(^2\).

In patients with sustainable skill of isolated PFM contraction the median time to recover urinary continence was 4 months. In the absence of lasting skill to perform isolated contractions median time to continence recovery was 9.4 months (p=0.001)\(^3\).

**REFERENCES**


---

\(^2\) Hereinafter the median is shown.

\(^3\) The long-rank test is applied.
Unser Team

Durch die intensive Zusammenarbeit mit angrenzenden Fachgebieten und durch die große Erfahrung unserer Operateure besitzt unsere Abteilung eine besonders hohe Kompetenz im Bereich komplizierter und schwerer Operationen (Speiseröhre, Magen, Leber, Bauchspeekeldrüse, Enddarm) auf.

Prof. Dr. Guido Schumacher, Chefarzt
MORPHOLOGICAL ASSESSMENT OF THE HEALING OF SKIN WOUNDS WITH DIFFERENT METHODS OF REGIONAL TREATMENT

A.A. Glukhov, N.T. Alexeeva

N.N. Burdenko Voronezh State Medical Academy, Voronezh, Russia

The main research areas — regenerative biology and medicine. The purpose of the study was to prove the effectiveness of the use of various regional methods of the treatment of skin wounds by evaluating the structural and functional state of the regenerate. The experiment was conducted on 98 outbred male albino rats weighing 200–220 g. The animals were divided into two blocks, since the morphological evaluation of the regenerate was performed in the treatment of aseptic and septic wounds. The first block consisted of one control and two experimental groups. Under anesthesia, the animals were given aseptic wounds (1,0x0,5 cm) on the front surface of the thigh. In the control group, there was no treatment. In the first experimental group, jet sanation (JS) by the 0.9% solution of NaCl was used to treat aseptic wounds. In the second experimental group, platelet-rich plasma (PRP) was utilized. For the animals of the second block, the modeling of purulent wounds was performed using the culture of St. aureus. The second block included one control and three experimental groups. The treatment of purulent wounds began with debridement on the third day from the onset of the experiment. Then, the methods of regional therapy were used in accordance with the selected groups. In the control group, JS was used once daily for the first three days. In the first experimental group, the wound was treated by an alternating magnetic field (AMF) after JS. In the second group, phototherapy was performed after changing bandages. In the third group, JS and PRP were utilized once daily for the first three days of the treatment. The animals were taken from the experiment under anesthesia on the 21st day. The material of nearby wound zones was taken and fixed in 10% neutral formalin. For the assessment of the strength of formed scars, the tissue was subject to rupture with fixed force. It was noted that regeneration with the formation of sufficient in strength tissues occurs by the 21st day. Tensile strength of aseptic wounds is higher (1.8N) given the treatment by PRP. High tensile strength (after application of AMF-3.1N, PRP-3.3N) is associated with the predominance of fibrotic manifestations. Thus, application of PRP strengthens collagenogenesis, improves the architectonics of fibers and provides the predominance of fibrous component over cellular one.

QUANTITATIVE ANALYSIS OF MEMANTINE IN BIOLOGICAL FLUIDS

A.A. Karlitskaya, N.D. Bunyatyan, L.M. Krasnykh, G.F. Vasilenko

Scientific Center for Evaluation of Medical Products, Center of Clinical Pharmacology, Moscow, Russia

According to published data [1] concentration of memantine in the blood plasma is low, that is why we chose high-performance liquid chromatography coupled with mass spectrometry for the quantitative analysis of memantine. Mass spectral acquisition was done in multiple reaction monitoring (MRM) mode using positive electrospray ionization (ESI). There was an intense peak in mass spectrum of memantine obtained by ionization mode in MS-MS analyzer with m/z 180. This peak corresponded to the protonated molecular ion (M+H)+ of the target substance. The best chromatographic separation was accomplished on an Agilent XDB-C18 column (2.1mm×30mm, 8µm), with acetonitrile and 0.1% formic acid (65:35, v/v) as the mobile phase at a flow rate of 0.5ml/min. Retention time of memantine was 1.35 ± 0.05 min. Plasma samples were extracted by precipitation with methanol. Quantitative analysis of memantine in plasma was performed by the method of an absolute calibration. Calibration curves were linear.
over the concentration range of 1 to 50 ng/ml. Linear calibration was obtained with correlation coefficients \(R^2 = 0.996\). The limit of detection was 1 ng/ml.

**CONCLUSIONS**

The highly sensitive and selective method of extraction and quantitative analysis of memantine in the blood plasma by high-performance liquid chromatography coupled with mass spectrometry was developed. The method is characterized by repeatability and low limit of detection (1 ng/ml). With the help of developed HPLC/MS/MS method pharmacokinetics of memantine-containing drugs (10 mg) was studied after a single oral intake of the drug by volunteers.

**REFERENCES**


---

**MICROCIRCULATORY BED IN ORGANS SUPPLIED BY DRAINING DUCTS SYSTEM: FOUR COMPARTMENTS INSTEAD OF THREE**

D.J. Kordzaia, M.A. Dgebuadze

Iv. Javakhishvili Tbilisi State University, Tbilisi State Medical University, Georgia

The paper describes the microcirculatory modules of the liver and kidney and generalizes the obtained results on microcirculatory beds of all organs, having the system of draining ducts. The research is conducted on 60 white Wistar rats (equal amount of male and female animals) using standard Histology, Histology after injection of contrast mass into tubular structures, Transmission Electron Microscopy and Scanning Electron Microscopy of Corrosion Casts of blood vessels and ductular/tubular systems.

The microcirculatory module for every given organ is specific, multiply repeated, more or less standard minimal fragment of microcirculation network. Classically it includes the finest blood vessels (arterioles, capillaries, venules), lymphatic initials (Lymphatic capillaries and post-capillaries) and interstitial spaces (channels). Taking into account the results of our research, we suggest to consider the liver and kidney (as well as other organs supplied by draining ducts system) as the basis of four different liquid circulation: blood, lymph, tissue juice and organ specific liquid — bile and urine. Correspondingly, the four compartments have to be identified in the microcirculatory beds of organs with draining duct system. Three of them are classical, but the fourth is organ specific. The organ specific compartment of the microcirculation starts blindly (in similar to the lymph capillaries) and gets its specific liquid through secretion (bile) or filtration (urine) by/through the cells, which create/border its lumen. The classical compartment of the microcirculatory network in the organs supplied by draining duct system contains two components with different architectonics: the first is typical (universal) for all organs. It is located in stroma, particularly around the ducts/tubes and contains standard arterioles, capillaries, venules, tissue channels and lymphatic capillaries; the second compartment of the microcirculatory network is sharply organ specific. It contains portal terminals and arterioles — sinusoidal capillaries — the central/sublobular venules (in liver); afferent arterioles — glomerular capillaries — efferent arterioles (in kidney). This second component is realizing the specific function of the given organ: to produce/drain the organ specific liquid (bile, urine). All four compartments of the microcirculatory modules of liver and kidney and their liquids are in dynamic morpho-functional relation to each other and reveal the great opportunities of mutual replacement; e.g. in condition of bile or urine congestion the lymphatic capillaries successfully undertake the evacuation of the mentioned liquids on the early terms of pathology.
INTRODUCTION. Studies on the analysis of the vital signs of cytormorphological parathyroid glands in patients with hyperparathyroidism (HPT) are rare.

AIM. To study the cellular and structural features of parathyroid glands at HPT.

METHODS. The study included 52 patients with primary, secondary and tertiary HPT. The analysis of 84 tissue fragments parathyroid glands obtained by fine-needle aspiration biopsy under the control of ultrasonography of the front of the neck. Used color azure-eosin by Pappenheim method and examination under microscope.

RESULTS. Most samples (81%) contained epithelial cells in sufficient quantity for cytological analysis. Established a heterogeneous population of cells of the glandular epithelium parathyroid glands. Dominated by the major dark paratirocytes — small polygonal shape with a diameter of 5–8 microns mononuclear cells with a narrow rim of cytoplasm of light basophilic stains that were located in small groups, single-layer recovery, multi-papillary structures. Less often (73%) were found larger main light paratirocytes 9–25 microns in diameter, round or polygonal shape and abundant clear cytoplasm. In some preparations (13%) were identified with large centrally located nucleus and the presence of near-nuclear enlightenment "stamped" cells. Oxyphilous paratirocytes were found in 8% of cytograms, arranged singly or in groups and had oxyphilous granules in the cytoplasm. In half of the samples was determined by a colloid-like extracellular secretion. Also determined dark polymorphic granules in the cytoplasm of epithelial cells and extracellular secretions. In secondary HPT in the tissue parathyroid glands more prevalent cytological signs of degenerative processes. Cytological features of parathyroid tissue clearly contrasted with those of the thyroid gland.

CONCLUSION. By cytormorphological criteria hyperplasia and functional activity parathyroid glands at HPT include: 1. cell population heterogeneity glandular 2. expression of cell-cell contacts in clusters paratirocytes 3. Availability dark polymorphic granules in the cytoplasm of epithelial cells and extracellular secretions. Cytological verification hyperplasia and high functional activity parathyroid glands enhances topical diagnosis at HPT.

THE ETIOLOGY OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH NON-HODGKIN’S LYMPHOMAS

N.B. Bulieva

Baltic Federal University of Immanuel Kant, the medical school, Kaliningrad, Russia

OBJECTIVE: To study the etiological characteristics of opportunistic infections in patients with non-Hodgkin’s lymphomas.

MATERIAL AND METHODS: We investigated 109 patients with non-Hodgkin lymphoma treated in the hematology hospital during the period 2006–2010. Conducted microbiological testing of biological materials of patients, followed by isolation and identification of a pure culture of the pathogen through the test systems and methods of ELISA and PCR.

RESULTS: In the analysis of the etiologic spectrum of different localization OI non-Hodgkin’s lymphoma was found the following: respiratory tract infections in patients NHL basis etiologic spectrum of bacterial infections were H. influenzae (62,9%), M. pneumoniae (51,6%), Streptococcus (30,6%). Of fungal infections dominated by representatives of the genus Candida (21,0%, of which C. albicans — 11,4%), while Aspergillus verified in 8.0% of patients. The greatest
value in patients with NHL is the viral infection, the frequency allocation Epstein-Barr virus 35.5%, Cytomegalovirus — 19.3%. Mixed infection stood at 79.0% of patients. For infections of the genitourinary system frequent pathogens were representatives of Staphylococcus (64.0%), among mycotic infections — C. albicans (28.0%). Markers of viral infections were positive for Epstein-Barr virus — 76.0%, mixed infections accounted for 92.0%. Infectious complications of gastrointestinal tract in patients with NHL were accompanied by the release of Enterococcus (52.9%), E. coli (58.8%), and Acinetobacter (58.8%). Generalized infectious complications (sepsis) in patients with NHL were verified in 5 patients and are bacterial (Streptococcus — 60.0%, H. influenzae - 60.0%, M. pneumoniae — 60.0%, Klebsiella — 40.0%), fungi (Aspergillus — 60.0%, Candida — 60.0%) flora, accompanied by positive markers for Epstein-Barr virus (80.0%), mixed infections — 100.0%.

CONCLUSIONS: The analysis of the data showed that in most cases, non-Hodgkin's lymphoma at the forefront respiratory infections caused by strains of H. influenza. Special attention should be patients with generalized infections, as the causative agent of sepsis supports the mixed infection (80–100% of cases).

OBJECTIVE: To investigate the existence retrospectively viral particles Epstein–Barr tissue mammary adenocarcinoma with the overall survival (OS) and disease-free survival (DFS), and in accordance with known prognostic factors (RE, RP, Her-2-neo, Ki–67).

MATERIALS AND METHODS. The study included 28 women diagnosed with breast cancer in 2007, I–IIIB stage. The average age of the women (M ± SD) was 56±11.3 years. Determination of the presence of Epstein–Barr virus was carried out in paraffin-embedded archival histological material immunohistochemical (IHC) method manually. We determined the presence of nuclear antigen (EBNA-1) in tumor tissue.

RESULTS. Found that in 15 out of 28 cases, which was 53.5% revealed the presence of EBNA-1 in breast cancer cells. The viral genome has been detected in tumors of various sizes, but preferably in patients with metastases in the lymph nodes (N+) and high and medium grade (G2–3), as well as Her-2-neo overexpressing cancers and high index proliferation-related activity (Ki–67 > 50%). Summary data are shown in Table 1.

Total Adjusted 5-year survival of patients with breast cancer cases registered in 2007 was 74.57%. Adjusted disease-free 5-year survival of patients with breast cancer cases registered in 2007 was 64.63%. The average time to relapse-free period were stage I, 31.36±17.36 months for stage II – 28.48±18.37 months and for stage III – 21.19±11.37 months, respectively. No patient who has found EBNA-1 in the tumor tissue is not lived for more than 3 years.

CONCLUSION. More than half (53.5%) have the presence of Epstein–Barr virus, presented in the form of EBNA-1 in breast cancer tissues. EBNA-1 in the tumor tissue of breast cancer can be considered as one of the predictor. This fact requires further study.

**Table 1. Having EBNA-1 as defined by IHC in breast cancer tissue with the TNM, G, Her-2-neo, Ki–67**

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>G</th>
<th>Her-2-neo</th>
<th>Ki–67 &gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBNA-1+</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>EBNA-1-</td>
<td>5</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Brero</td>
<td>8</td>
<td>16</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>
Acute lung injuries — respiratory distress syndrome (RDS) — rather frequent and severe complications of acute pneumonia and other diseases (acute inflammatory diseases of abdominal organs, severe traumas, burns, eclampsia, septical shock and other). RDS is the major causes of unfavorable outcomes, despite the use of most modern medicaments.

Our previous experimental studies have demonstrated that endotoxicosis developed in animals since first minutes of acute pneumonia modeling. There are many pathogenous factors of endotoxicosis: bacterial endo- and exogenous toxins, inflammatory toxic metabolites, products of proteolysis, activation of lipid per oxydation and decrease of anti-oxidation protection, toxic middle molecular weight compounds (oligopeptids), lysosomal enzymes.

As a result arise some complications of endotoxicosis: increase vascular permeability (microvascular leaking), hypoproteinemia, hypooncotic hypovolemia, low blood pressure, toxic pulmonary edema — respiratory distress syndrome, acute respiratory insufficience, disseminated vascular coagulations syndrome and, as result — multiple organ failure.

Patients and methods. We analyzed the therapy of 153 RDS patients: 99 with moderate, 44 with severe and 10 with extremely severe degree of lung injury. 67 patients received the conventional therapy only (antibiotics and other drugs, and in severe degree of RDS — mechanical lung ventilation). 76 patients received an additional detoxication therapy — hemadsorption or plasmapheresis (membrane plasmapheresis with “Hemofenix” device end exchange 1.5–2.5 l of plasma). 10 patients with extremely severe RDS were underwent the extracorporeal membrane oxigenation of the blood (ECMO) with hemoadsorption.

Results. In moderate RDS group there were no lethal outcomes. But the duration of hospital stay was significantly lower in patients underwent detoxication than in ones of control group (28.9±1.5 versus 40.3±3.3 days; p < 0.05), and there were no destructive processes in lungs.

In patients with severe RDS and only conventional therapy the lethality level attained 74% while additional using of hemoadsorption or plasmapheresis allowed to decrease it to 31%. We failed to save just patients in which detoxication was performed in more late terms after the disease onset. The extremely severe RDS degree was characterized by practically total injury of lung parenchyma and severe respiratory failure, which was not corrected with mechanical ventilation. Using ECMO during from 15 to 44 hours with 3–4 hemoadsorption procedures allowed to save 7 of 10 these patients.

Conclusion. The results of the study performed demand a radical revision of fixed therapeutic schemes for acute pneumonias and RDS, still based predominantly on antibacterial therapy. However, the most powerful antibiotic don’t eliminate the endotoxines but can even aggravate it due to massive bacteria death and lysis. However, in most of these cases the fact of progressing course of the acute respiratory syndrome indicates an initial lack of defense systems. Medicament immune stimulation is also unable to restore suppressed mechanisms of immune defense. Under these conditions is pathogenetically well-founded conducting of a special detoxication therapy based on plasma exchange with compensation of removed volume (up to 1–1.5 of circulating plasma volume) with donor plasma.
Medizinisches Kompetenzzentrum in Neurologie und Rehabilitation

Neurologische Rehabilitationsklinik
Fachkrankenhaus für neurologische Frührehabilitation
Neurologisches Fachkrankenhaus für Bewegungsstörungen/Parkinson

Leistungsangebote

- Neurologische Frührehabilitation (einschließlich beatmungspflichtiger Patienten)
  Referenzklinik für Guillain-Barré-Syndrom-Patienten
- Neurologische Spätrehabilitation aller neurologischer Krankheitsbilder,
  Anschlussheilbehandlung

Spezialabteilungen:

- Brandenburgisches Zentrum für Querschnittgelähmte (Rehabilitation
  einschließlich beatmungspflichtiger Patienten)
- Epilepsie-Zentrum Berlin-Brandenburg
- 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

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

Therapieangebote
Physio-, Ergo-, Musik-, Sport-, Hippo-, Physikalische Therapie, Logopädie, Psychologie/
Neuropsychologie, Redression, Snodezen, Diätetik, Seelsorge, Bewegungsbad, Sozialdienst

Ambulanzen
Ermächtigungsambulanz für klinische Neurophysiologie, Institutsambulanz (Physikalische
Therapie), Spezialsprechstunden Botulinumtoxin und Parkinson

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

Lage
Beelitz-Heilstätten liegt in unmittelbarer Nähe zu Potsdam und im Nahverkehrsbereich
Berlin. Mit stündlicher Zugangbindung 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 Regional-
verkehrsbahnhof 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.

Kontakt
Kliniken Beelitz GmbH, Paracelsusring 6 a, 14547 Beelitz-Heilstätten
Telefon: (033204) 200, E-Mail: info@kliniken-beelitz.de, Internet: www.kliniken-beelitz.de
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 postoperativen Nachsorge mit Wundbehandlung und der Rehabilitation chronischer Krankheiten z.B. durch orthopädische oder neurologische Krankheiten.


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.