

**MECHANICAL CHARACTERISTICS  
OF VESSELS AND PROINFLAMMATORY  
CYTOKINES IN PATIENTS  
WITH RHEUMATOID ARTHRITIS  
AND ARTERIAL HYPERTENSION**

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The cardiovascular pathology develops much earlier in patients with the rheumatoid arthritis (RA) than in the population in general, which is determined to a large extent by an accelerated development of the atherosclerotic vascular disease. Nowadays, it is believed that the advance of atherosclerosis is caused mainly by the lipid metabolism disorders and the vessel wall inflammation, also due to chronic autoimmune disease. In this respect, it is worthy of analyzing how the level of proinflammatory cytokines correlates with disorders of the mechanical properties of the vascular bed under condition of RA associated with arterial hypertension (AH).

**The aim of the study:** to determine the serum level of proinflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , IL-6) and the arterial elasticity in patients with the AH.

**Materials and conclusions.** During the study, 84 patients (female), who had AH stage 1-3 against the background of an advanced RA (seropositive, stage II), were observed. The arterial hypertension was diagnosed using criteria suggested by the Russian Scientific Society of Cardiologists, 2008. The average age of the patients was  $51,3 \pm 4,5$  years old. In all the patients the AH was diagnosed after the RA development. The control group consisted of 18 healthy donors. The level of cytokines in blood serum was measured by the enzyme immunoassay method («Cytokines LLC», Russia). The mechanical properties of the vessel wall were assessed using arterial pressure monitor «Petr Telegin», Russia.

**Results and discussion.** In patients with the AH on the background of the RA, we could identify a reliable increase of the proinflammatory cytokine content compared with the control group. At the same time, it should be mentioned that the highest concentrations of IL-1 $\beta$  ( $241,5 \pm 14,3$  pg/ml,  $p < 0,001$ ), IL-6 ( $297,4 \pm 17,4$  pg/ml,  $p < 0,001$ ), TNF- $\alpha$  ( $321,8 \pm 16,4$  pg/ml,  $p < 0,001$ ) was registered in patients with the AH stage 3, which reliably differed from the respective values of the RA patients with the AH stage 1 and 2. In patients with the RA accompanied by the AH, a higher rigidity of vessel wall was observed, which was evident through higher pulse wave velocity (PWV) and

augmentation index (A|x). The revealed disturbances in the mechanical characteristics of arterial wall were apparent at the most in the RA patients with the AH stage 3. Their PWV was 12,5% ( $p < 0,05$ ) higher than in patients with the AH stage 2, and 28,6% ( $p < 0,001$ ) higher than the respective value in the RA patients with the AH stage 1. The A|x was also higher, its maximal value ( $-9,8 \pm 1,1$ ) was registered in the RA patients with the AH stage 3. We found a reliable direct correlation between the level of IL-1 $\beta$ , IL-6, TNF- $\alpha$  and the PWV, A|x under condition of the RA-HA combination.

To sum up, the conducted research ascertained that the number of proinflammatory cytokines grows along with the AH severity under condition of RA. The revealed correlations prove indirectly the pathogenic role of proinflammatory cytokines in advance of disorders of the vessel wall mechanical properties in the RA patients with the AH.

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**MODERN NECHNOLOGIES  
OF INFERTILITY TREATMENT  
IN WOMEN WITH OPERATED OVARIES**

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Unfavorable demographic situation, which has been formed in Russia, is nowadays examined as serious problem for the public health, society and country. Nowadays in our country there were registered more than 5 million infertile married couples, from them the majority needs the cure with the methods of auxiliary reproductive technologies (ART).

The aim of research – defining of the effectiveness of ART methods of women of reproductive age with operative intervention at the ovaries.

**Materials and methods.** Into clinical research there were included 975 sick people with the new formations of ovaries, which are at the treatment in the department of VRT CCH RAS city of Moscow and gynaecological departments of city of Izhevsk UR. The average age of sick people was  $32,33 \pm 9,73$  years (DI 95% 31,72; 32,04;  $m=0,31$ ).

At the first stage all sick people were clinically-laboratory examined, there were defined their levels of CA-125, the estimation of ovarian reserve, ultrasonic research with Doppler velocimetry (by the indicators there was carried out the magnetically-resonance tomography). While the revelation of some new formations of ovaries (till 4–5 sm), low level CA-125, positive results of Doppler velocimetry there was carried out conservative treatment, which includes anti-inflammatory and hormonal therapy.

At the second stage to the 923 there was carried out surgery operation. Operative cure was carried out as laparoscopic – in 82,34%±0,01 (760/923 cases), and also laparotomic access – in 17,66%±0,01 (163/923 cases). Practically all operations were carried out by plan – 75,84%±0,01 (700/923 cases). Exceptions were extraordinary situations, which appeared at the stage of examination and preparation to the operative treatment – 24,16%±0,01 (223/923 cases). These are disruptions of the cysts of ovary – 143 cases out of 923 (15,49%±0,01) and abnormalities of blood supply of the tumors of ovary while the distortion of last – 30 from 923 (3,25%±0,005). Indication to the carrying out the plan operative cure of the patients with cysts and benign tumors of ovaries is the presence of one or some new formations in the ovary, sizes are more than 5 sm in the diameter, the absence of the effect from the conservative therapy. The volume of operation had straight correlated dependence on the age ( $r=0,089$ ); urgency of carrying out of operation ( $r=0,166$ ); intraoperational diagnosis ( $r=0,152$ ). And reverse correlated dependence on the belonging of new formation to defined morphological group ( $r=-0,175$ ); on the composition of new formation with other pathology of organs of small pelvis ( $r=-0,166$ ) or with outward genital endometriosis ( $r=-0,230$ ), and also on the necessity of carrying out extra operation at the second ovary while the two-side process ( $r=-0,232$ ). Thereby, while the general analysis of received facts, we noticed that independently from the type of access and urgency of carrying out operation while the presence of intraoperational conditions we carried out organ-saving operations, which were directed to the saving of reproductive function of patients. As while the timorous formations of ovaries – 45,5%±0,02 (334/734 cases), that also while benign tumors of ovary – 43,38%±0,04 (82/189 cases) surely frequent that were cystectomy ( $p<0,001$  and  $p=0,02$  accordingly).

At the third stage with the aim of restoration of reproductive function 784 from 923 operated

sick people (84,94%±0,01) at the post-operational period, with the taking into account of histological conclusion and changes of hormonal status, there was appointed antioxidant (vitamin E) and metabolic therapy (vitamins A, B, C), combined oral contraceptives, progestagens, preparations for the substitutive hormonal therapy, agonists of gonadotropin releasing hormone, immuno-modulating and system enzymotherapy.

At the four stage while the inefficiency of offered complex cure sick people, who desired to continue therapy, were included into a program of auxiliary reproductive technologies (ART). For this aim there was formed a group of 85 people, what was 8,72%±0,009 from the initial number of sick people (85/975 cases) or 10,72%±0,01 from the number of sick people, who received post-operational cure (85/793 cases). The average age of patients of the group, which was included into a program ART, was 32,6±5,28 years (DI 95% 31,46; 33,74;  $m=0,57$ ). The group of comparison was compound of 30 sick people with infertility, which connected with male factors.

72 female patients out of 85 72 (84,71%±0,04) was immunohistochemically examined. The sampling of material was carried out at the waited “window of implantation” on the 21–24 days of 28-daily menstrual cycle. With the help of hysteroscopy with the use of apparatus «Karl Storz» (Germany) there was carried out Pipell biopsy of endometrium or, by the indicators, separate curettage of mucous membrane of cervical channel and uterine cavity. Immunohistochemical reactions were carried out at the stepped paraffin cuts by peroxidase-antiperoxidase method with demasking of antigens in the SHF-oven. For the visualization of reactions there were used the universal peroxidase tool LSAB+kit («Dako», USA). The intensity of immunohistochemical reactions to the  $\alpha/\beta$ -receptors of oestrogen and progesterone at the nuclei of cells of epithelium of the glands and stoma were estimated by the method of histological count H-score (McClelland R.A. et al., 1991). The degree of evidence of expression of receptors were estimated by following way: 0-10 points – absence of expression, 11–100 – weak expression, 101–200 – moderate expression, 201–300 – expressed expression. The intensity of immunohistochemical reactions to the protein Ki 67 was calculated in the percents (quantity of tinged nuclei to 100 cells).

With the aim of improvement of results of cure by methods of auxiliary reproductive technologies (ART), depending on the results of immunohistochemical research of endometrium, to

the female patients with an abnormality of steroid receptiveness and proliferative activeness was carried out hormonotherapy during 3 months till the including to a program ART. The stimulation of superovulation was carried out while the dynamic examination and observation. The fertilization was carried out by the methods of ECO and IKSI.

The static treatment of received material was carried out with the help of program of the treatment of electronic tables Statistica 6.0 with the use of generally accepted parametric and nonparametric statistic methods.

Received results. 139 sick people out of 784 (15,06%±0,01), who received after operation complex therapy, the pregnancy appeared at the natural cycle in 1-2 months after the beginning of cure. With the infertility from them there were 56,83%±0,04 (79/139 cases). The average age of sick people with appeared independent pregnancy was 29,77±5,46 лет (DI 95% 28,85; 30,69;  $m=0,46$ ). Among the sick people with appeared pregnancy 25 out of 139 female patients (17,98%±0,03) were with the initial infertility, and 54 out of 139 (38,85%±0,04) with repeated. After the ending of carrying out the post-operational therapy the pregnancy, at the time constraints from 1 till 6 months appeared of 196 from 975 sick people (20,1%±0,01). The average age of these sick people was 30,78±4,99 years (DI 95% 30,08; 31,48,  $m=0,36$ ). Among the sick people with appeared pregnancy 20,41%±0,03 (40/196 cases) were with initial infertility, and 25,0%±0,03 (49/196 cases) with the repeated and 54,59%±0,04 (107/196 cases) with normal fertility.

At the four stage of cure in connection with inefficiency of offered complex cure 85 sick people were included into a program ART. The group of comparison was compound of 30 sick people with an infertility, which is connected with male factors. From the 72 sick people 39 (54,17%±0,06) had female infertility, which was connected with tubal factor, 17 out of 72 (23,61%±0,05) suffer from the female infertility, which was connected with abnormality of ovulation and 16 out of 72 sick people (22,22%±0,05) had infertility, which was associated with an endometriosis.

In the result of carrying out of immunohistochemical research, we revealed, that steroid receptiveness of endometrium of women with the tubal factor of infertility ( $p=0,008$ ) and with an infertility, which was associated with an endometriosis ( $p<0,001$ ) was reliably changed. While these factors of infertility the level of expression of receptors of progesterone at the glands of endometrium was rather lower that the level of expression

of  $\alpha$ -receptors of estrogen, in comparison with the group of sick people with the male factors of infertility. While the comparison of groups with different factors of infertility between them there were not revealed essential peculiarities of reception to the estrogens and progesterone. At the glands the number of  $\alpha$ -receptors to the estrogens and progesterone was a little bit higher while the tubal factor, and at the stroma the reception to the estrogens and progesterone had a tendency to higher indicators of women with the abnormalities of ovulation ( $p<0,001$ ), than in the groups of tubal infertility and infertility, which is associated with an endometrium. Proliferative activity (expression of protein Ki 67) considerably prevailed while the tubal factor of infertility ( $p<0,001$ ) and in glands, and in stroma, at the same time while the infertility, which is connected with the abnormality of ovulation the proliferative activeness was higher ( $p<0,001$ ), than while the infertility, associated with endometrium.

Reliable and bright differences of proliferative activeness at the glandular and stromal cells while different factors of infertility objectively reflect inadequacy of proliferative processes and degree of their deflection from the norm. Taking into consideration received facts, to the sick people with infertility, which is connected with tubal factor and associated with endometrium, before the program ART was carried out the preparation with the preparation of substitutive hormonal therapy, which contains estradiol in combination with progesterone – didrogesterone during 3 months.

Carrying over of embryos was carried out to 64 out of 85 sick people (75,29%±0,05). Carrying over was carried out average at the 17,7±1,76 day (DI 95% 17,32; 18,08;  $m=0,19$ ). Finally, the pregnancy biochemical was registered of 27 out of 85 sick people (31,76%±0,05), clinical of 33 (38,82%±0,05). Reliable differences by the number of sick people with clinical pregnancy at the base groups of examination were not revealed. Among the patients with the initial infertility the clinical pregnancy appeared of 16 out of 33 sick people (48,48%±0,09), with the repeated infertility of 17 out of 33 sick people (51,52%±0,09). From the group with tumorous formations of ovaries the pregnancy clinical was of 26 out of 734 sick people (3,54%±0,007) and benign tumors of ovaries of 7 out of 189 sick people (3,70%±0,01).

In all at the result of our clinical observation and carrying out of complex therapy pregnancy appeared of 377 sick people, what was 38,67%±0,02 from all 975 observed sick people. Among the patients with the infertility the preg-

nancy appeared of 206 out of 317 sick people with the infertility ( $64,98\% \pm 0,03$ ): from them in  $85,92\% \pm 0,02$  (177/206 cases) the patients with operated tumorous formations of ovaries and in  $14,08\% \pm 0,02$  (29/206 cases) the patients with operated benign tumors of ovaries.

Resume. Thereby, modern technology of curing the infertility of women with the pathology of ovaries consists in the early revealing of reason and successive carrying out of cure stages. While the absence of positive effect from the traditional ways of curing the infertility during 1 year, it's reasonable to recommend the overcoming of infertility by the methods of ART. Modern higheffective methods of curing of infertility (hormonal preparations, endoscopic methods and methods of auxiliary reproductive technologies) are the links of one circuitry, the final aim of which is maximal rapid realization of reproductive function of woman.

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**CHANGES OF FUNCTIONAL CONDITION OF ENDOTHELIUM AND MECHANICAL BEHAVIOR OF VESSELS OF SICK MEN WITH THE ARTERIAL HYPERTENSION WITH METABOLIC SYNDROM UNDER THE INFLUENCE OF THERAPY**

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Metabolic syndrome (MS) at the last years owing to wide spread is called "epidemic of highly developed countries". The components of MS in aggregate with arterial hypertension (AH) cause the development of cardiovascular complications.

By the researches of last years there is established the connection of pathological changes, which are connected with mechanical behaviors of the wall of artery and frequency of appearance of cardiovascular complications. It was revealed that increase of speed of developing of pulse wave (SPW) is registered at early stages of sick men with cardiovascular pathology. There is noted the multifactorial essence of rising of rigidity of vessel and the role of endothelial dysfunction, as one of the base mechanisms of progressing of cardiovascular pathology. Therefore as perspective there

is considered the assessment of influence of anti-hypertensive therapy to the indicators of endothelial function and rigidity of vessels with the aim of studying the possibilities of opposite development of these abnormalities, what can lead to the decrease of the risks of development of vascular catastrophe of AH sick men with MS.

The aim of work: study of interconnection between the indicators of endothelial function and characteristics of elastic behaviors of vascular channel of sick men with arterial hypertension in combination with metabolic syndrome.

Materials and methods. There were examined 98 sick men with AH of 2 stage with the metabolic syndrome at the age of 40-60 years, 78 men and 20 women. The presence of metabolic syndrome was defined by the criterions of WHO. AH was defined in correspondence with the classification of All-Russian Scientific Society of Cardiologists (2008). The group of control was formed by 20 clinically healthy persons, the group of comparison was formed by 30 sick men without metabolic syndrome. The level of endothelin-1 (ET-1), the Willebrand factor (fW) were defined by immunofluorescent method. Elastic behaviors of vascular wall were estimated with the help of twenty-four-hour monitor of arterial pressure of company "Petr Telegin" (Russia). Static treatment of the results of research was carried out with the use of standard package of applied programs Statistica.

Results and their discussion. The assessment of functional condition of endothelium of vessels of AH sick men showed reliably big concentration ET-1 ( $59,8 \pm 2,3$  ng/l) and fW ( $169,8 \pm 5,2\%$ ), being laboratorial markers of endothelial function, of examined sick men in comparison with control. In the group of sick men with a combination of AH and MS there was revealed maximal high concentration of ET-1 ( $78,9 \pm 3,8$  ng/l) and fW ( $189,3 \pm 6,1\%$ ). AH sick men in combination with MS have definitely reliable decrease of time of development of pulse wave (RTT) by 31% in comparison with control ( $165,8 \pm 4,8$  m/s) and by 26% by patients with AH without MS. Maximal speed of increase of arterial pressure (dPdt)max, which indirectly reflects the load to the wall of vessels during the passing of pulse wave, was lowered in 2,1 times with the AH sick men. The index of rigidity (ASI) of patients with Ah by 28% ( $p < 0,01$ ) exceeded control values and by 13% of AH sick men with MS, and index of augmentation (A|x) in 3,4 and 1,6 times accordingly ( $p < 0,01$ ). Revealed changes testify to the presence of endothelial dysfunction and decrease of elastic behaviors of vessels of AH