

**Summary for a thesis**  
**«Pathophysiological and pathological changes in the body associated with intra-abdominal hypertension»,**  
**written by**  
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**and submitted for the degree of Doctor of Philosophy (PhD) in**  
**6D110100- Medicine**

**Timeliness**

Recent studies have shown an increase in intra-abdominal pressure is followed by: hypoxia and hypercarbia of all body tissues; oxidative stress; perfusion abnormality and abdominal ischemia, and in the end of these processes - reperfusion of the abdominal cavity; reduced cardiac output, limited pulmonary ventilation, inhibited renal function, impaired blood supply to internal organs, which results in such a high mortality rate of patients with the development of the given syndrome. When having necrotizing pancreatitis, peritonitis and other acute surgical diseases there is an increase in intra-abdominal pressure in 30% of cases while compartment syndrome occurs is developed in 5.5% of patients. Studies by Eddy and Morris (2007) showed mortality rate at 68% with determined compartment syndrome.

Analysis of domestic and foreign literature shows that there are still some open and disputed issues of proper and accurate measurement of intra-abdominal pressure, biochemical and pathophysiological processes that accompany this condition, the search of biomarkers of these processes, as well as clear criteria which make it possible to carry out early diagnosis of the intra-abdominal hypertension syndrome and its complications

**Research purposes**

Study of the dependence of the level of biomarkers and pathomorphological changes in the bodies on the extent and duration of intra-abdominal hypertension.

**Research objectives**

1. Development of an experimental model of intra-abdominal hypertension in laboratory animals;
2. Development of a device to measure the intra-abdominal pressure;
3. Detection of the correlation between the extent and duration of intra-abdominal hypertension and blood coagulation system indicators;
4. Study of the correlation between the extent and duration of intra-abdominal hypertension and pre-septicemic condition biomarker;
5. Study of the correlation between the extent and duration of intra-abdominal hypertension and biomarkers of cell apoptosis and oxidative stress;
6. Evaluation of morphological changes of internal organs related to the extent and duration of intra-abdominal hypertension;
7. Correlative analysis of the extent of pathomorphological changes of internal organs and the amount of intra-abdominal hypertension markers in blood serum.

**Scientific novelty**

- Surgery specialists were surveyed through questionnaire about the issue of intra-abdominal hypertension for the first time in Kazakhstan;

- There was developed a new simple and quickly reproduced experimental model of intra-abdominal hypertension in rats;
- There was developed new method of intra-abdominal pressure measurement during an experiment;
- For the first time there was revealed a correlation between the extent of intra-abdominal hypertension and blood coagulation system indicators, pre-septicemic condition markers, apoptosis, oxidative stress, and morphological changes of internal organs.

### **Key principles submitted for defense**

- Developed experimental model of intra-abdominal hypertension in laboratory animals through aeroperitonia is characterized by simplicity and rapidity of indicators, minimum costs and low level of invasiveness;
- Developed intra-abdominal pressure measuring device is characterized by high accuracy of measurement, versatility and operational comfort through plugging it to any computer;
- There is a direct correlation between the level of fibrinogen and SFMC, and extent of intra-abdominal hypertension. The increase of intra-abdominal hypertension leads to diverse changes of indicators – to hyper coagulation during 3-12 hours, and back to hypo coagulation by 24 hours which is probably related to the development of organ dysfunction and consumption coagulopathy;
- D-dimer indicator has a linear direct correlation from IAH level with a peak of amount for 3 hours of exposition;
- sCD14 protein can be considered as an early biomarker of pre-septicemic condition during intra-abdominal hypertension which indicates existence of gram-negative flora in blood as a result of enterogenous translocation of microgerms into blood flow;
- The maximum apoptotic activity of body is registered after 3 hours at any extent of intra-abdominal hypertension. Subsequently, in 12 hours and later the amount of p-53 protein and respectively apoptotic activity falls sharply, indicating a decrease in reparative activity and resistance of body, and depletion of antioxidant protection;
- Intra-abdominal hypertension of any extent causes pathomorphological changes of internal organs (from minor pathological changes in 3 hours by pericellular edema type and hyperemia of the capillaries, to major changes in 12 and 24 hours by type of necrosis foci in the brain, liver, kidneys, lungs and heart, at the same time no intestinal morphological changes during intra-abdominal hypertension were detected;
- There is a direct correlation between the concentration of the pre-septicemic condition sCD14 marker and SFMC indicator of blood coagulation ability, and the extent of pathomorphological changes of internal organs.

### **Practical significance**

Studies which are carried out in the thesis extend existing ideas about the influence of intra-abdominal hypertension on the pathophysiological processes and morphological changes in the body, namely its effect on blood coagulation system,

pre-septicemic condition markers, apoptosis, oxidative stress, and morphological changes of the brain, liver, kidneys, colon, lung and heart.

The positive experience of using the device measuring the intra-abdominal pressure makes it possible to recommend it for use in clinical practice.

Determination of content of D-dimer in the blood plasma in the intra-abdominal hypertension will help to diagnose the complications associated with impairment of blood coagulation system.

Determination of sCD14 marker concentration in the blood plasma at the intra-abdominal hypertension makes it possible to diagnose the pre-septicemic condition in a timely manner before the active bacteremia occurs.

### **Practical implementation**

Certificate of intellectual property “Experimental model of intra-abdominal hypertension in laboratory animals” № 0359 written by Turgunov Ye.M., Matyushko D.N., Koishybayev Zh.M., Mugazov M.M., and Kaliyeva D.K. was issued on 25.02.2016 (see Appendix A).

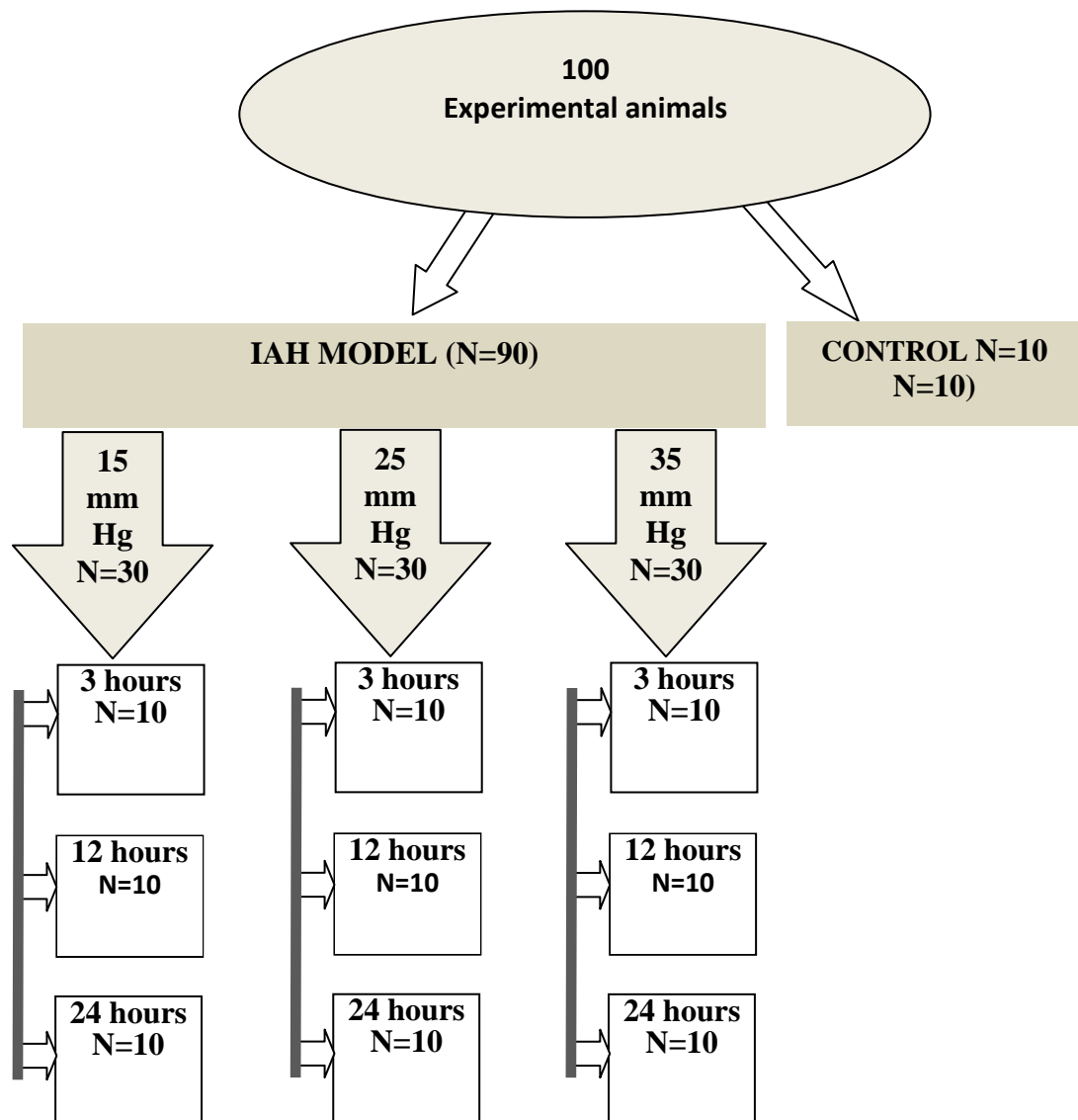
Certificate of intellectual property “Intra-abdominal pressure measuring device” № 0360 written by Turgunov Ye.M., Matyushko D.N., Kolesnikov V.A. Baysagov Ya. Zh. was issued on (see Appendix A).

Developed intra-abdominal pressure measuring device was implemented into the practice in Regional clinical hospital of Karaganda, Regional perinatal centre of Karaganda, Regional obstetric-gynecologic centre of Karaganda as implementation of results of “Diagnostics of intra-abdominal pressure through modified method with use of devices” scientific and research work (Appendix B).

The patent request “Intra-abdominal pressure measuring device” was submitted; authors Turgunov Ye.M., Matyushko D.N., Kolesnikov V.A. Baysagov Ya. Zh.

### **Materials and research methods**

The experimental study was performed on 100 adult outbred rats weighing 160 to 210 g. All experimental animals were divided into 4 groups. The first (control) group had intact healthy animals. In the second, third and fourth groups (main groups) they simulated intra-abdominal hypertension of varying degrees (15, 25 and 35 mm Hg, respectively.). Intra-abdominal hypertension was simulated by creating an aeroperitonium. Each major group was divided into three subgroups, respectively, the extent of exposure of intra-abdominal hypertension - 3, 12, 24 hours. Thus, laboratory values and morphological changes of organs were assessed in the absence of intra-abdominal hypertension in three degrees of intra-abdominal hypertension - 15, 25 and 35 mm Hg and 3 exposures of intra-abdominal hypertension - 3, 12 and 24 hours. After the above mentioned time intervals after intra-abdominal hypertension air desufflation of the abdominal cavity was performed. The blood and internal organs were taken for laboratory analysis and for morphological studies under anaesthesia.



Methods applied:

- Intra-abdominal pressure measurement method;
- Morphological studies;
- Enzyme multiplied immunoassay (SCD14 , heme-oxygenase -1, p-53);
- “Manual” methods of determination of blood coagulation system indicators;
- Statistical methods

### Summary

The following summary can be made based on the results of the thesis:

1. Developed experimental model of intra-abdominal hypertension in laboratory animals through aeroperitonia is characterized by simplicity and rapidity of indicators, minimum costs and low level of invasiveness.
2. Developed intra-abdominal pressure measuring device is characterized by high accuracy of measurement, versatility and operational comfort through plugging it to any computer via USB-port.
3. There was revealed a linear direct correlation between level of fibrinogen and SFMC, and on the degree of intra-abdominal hypertension. At all levels of IAH the fibrinogen content was significantly higher than in the controls ( $p < 0,01$ ); with an increase in IAH duration there was observed a diverse change indicators - to hyper

coagulation during 3-12 hours, and back to hypo coagulation by 24 hours which is probably related to the development of organ dysfunction and consumption coagulopathy; rate of D-dimer is also directly dependent on the linear IAH level with a peak of amount for 3 hours of exposition, with more than double rise in the level of D-dimer statistically significant ( $p < 0,01$ ) at all levels of IAH.

4. The increase in intra-abdominal pressure causes a statistically significant increase in the content of sCD14 pre-septicemic condition marker for all degrees of intra-abdominal hypertension by 1.2 - 11 times compared to the control ( $p < 0,01$ ); the duration of intra-abdominal hypertension from 12 to 24 hours causes a statistically significant increase in the concentration of sCD14 ( $p < 0,01$ ) at all values of intra-abdominal pressure; thus, the sCD14 protein can be regarded as an early biomarker of protein state at intra-abdominal hypertension, indicating the occurrence of a gram-negative flora in the blood as a consequence of translocation of enterogenous microorganisms in the bloodstream.

5. Activation and statistically significant increase in p-53 protein levels by 1.2-1.6 times ( $p < 0,01$ ) and as a consequence high apoptotic activity of the body is recorded in the earliest period of time (3 hours) from the beginning of impact of IAH at any degree. Subsequently, after 12 hours and later its content falls sharply, reflecting a decrease of reparative activity and the body's resistance and depletion of antioxidant protection.

6. Diverse changes of heme-oxygenase-1, depending on the time and extent of intra-abdominal hypertension demonstrate the importance of this enzyme as a protein-adaptogen. The absence of clear changes in the content of heme-oxygenase-1 in serum most likely indicates the absence of the positive impact of this enzyme in the production of anti-inflammatory, cytoprotective factors in intra-abdominal hypertension.

7. IAH of any level causes various pathomorphological changes of internal organs. Pericellular edema, congestion of the capillaries and veins, single focal hemorrhages appear in the groups with IAP of 15 mm Hg for 3 hours, the most striking and significant changes were observed on the part of the heart - necrosis and fragmentation of cardiomyocytes, focal hemorrhages in the myocardium; lungs – dis- and atelectasis, fibrinoid necrosis; liver - congestion of central vein of liver lobules, necrosis of hepatocytes; kidneys - bleeding in the medullary areas and / or cortical layers of the kidney, renal tubular epithelial degeneration; brain - gliosis, encephalomalacia foci. The statistical significance of the irreversible changes in the internal organs is registered mainly at the IAP of 25 and 35 mm Hg at any exposure, peaking at 35 mm Hg groups. during 12 and 24 hours. No morphological changes in intestines were detected at the IAH.

8. There was revealed a direct correlation between the severity of pathological changes of internal organs and concentration of "presepsin" sCD14 ( $p < 0,01$ ) marker; the correlative relationship between the content of SFMC and pathomorphological changes of internal organs: focal hemorrhages in the myocardium and lungs, congestion of the veins of the liver, pericellular edema of the brain ( $p < 0,01$ ).

**Preparer Matyushko D. N.**