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Volume Disorders as a Mechanism of Multiple Organ Dysfunction Syndrome and Associated Lethality

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Abstract--- *The aim of the present study was to evaluate the significance of volume status in critically ill patients for assessment of volume status influence of fluid-related sectoral disorders on the associated lethality.*

Methods. The authors studied 256 clinical cases of patients with multiple organ dysfunction syndrome aged from 18 to 78 (average age 62.4 ± 8.8) regardless of sex, hospitalized to units of resuscitation and intensive care.

The dynamics of general clinical parameters (central hemodynamics, respiratory status, pulseoxymetry parameters, hemoconcentration parameters, plasma albumins) was studied. The severity of patients conditions was assessed by three-level scale of intensive care patients condition severity, consciousness impairment – by Glasgow scale, volume status – by the severity and localization of edemas, presence of free fluid in organism cavities and central venous pressure. Body fluids and volume of circulating blood were measured by bioimpedance method. Infusion plan (volume, quality and ratio of media, fluid balance) was assessed. Multiple Organ Failure Scale along with the developed Scale of Fluid-Related Sectoral Disorders Evaluation was used for assessment of patients status in critical conditions and organ failure associated lethality.

Results. The authors identified 4 groups of patients by the severity of volume disorders: 49.6% of patients were in Group 2 (lethality in 20.8%); 27.4% were in Group 3 (lethality in 37.6%); 9.7% were in Group 4 (lethality in 72.5%); the rest patients were included into Group 1 (lethality in up to 10%). Direct correlation was identified between the severity of volume disorders and lethality. It was proved that volume disorders were one of the main consecutively determined mechanisms of multiple organ dysfunction syndrome development.

Conclusion. The infusion therapy for multiple organ dysfunction syndrome was primarily aimed at normalization of fluid-related sectoral homeostasis (normovolemia). For systematization of the parameters of fluid-related sectoral disorders, further distribution of the patients by the influence of the mentioned disorders on the disease outcome and dynamic control of volume status, the authors developed formalized scale for evaluation of volume disorders and prognosis of lethality risk in patients with multiple organ dysfunction syndrome.

Keywords--- *Volume Status, Fluid-Related Sectoral Disorders, Hypervolemia, Hypovolemia, MODS, SIRS, Lethality.*

I. INTRODUCTION

Development of critical conditions in patients, clinically manifested as critical syndromes (shock, ARDS (acute respiratory distress syndrome), ARF (acute renal failure), ARF (acute respiratory failure), acute cardiovascular

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insufficiency (ACVI), etc), is associated with non-isolated organ dysfunction of the most affected organ, and system multiple organ failure that is accompanied by consecutive secondary failure of some organs or physiological systems, including regulatory, i.e. multiple organ dysfunction syndrome (MODS) develops, wherein patients that survive acute critical condition die not from primary catastrophic pathological process, but from dynamically developing multiple organ failure [8; 10; 11].

Presently, there is no unified classical theory that would explain pathophysiological mechanism of MODS development. Numerous studies results give grounds to the definition of MODS, explanation of its mechanisms and, as a result, lead to consensus acceptance of theoretical basis of such mechanisms [8; 9; 10; 11].

Based on the analysis of numerous scientific publications dating from 1973, the authors came to the conclusion that there was no consensus on the issues associated with the development of multiple organ failure, seen as the basis of critical syndromes development. Presently, the following statements can be formulated.

The literature review revealed four main basic approaches to the investigation of MODS that were characterized by pathophysiology, clinical observations, morphology, clinical pharmacology, biochemistry and etc.

These studies primarily focused on 4 basic groups of issues:

1. Tissue systemic hypoxia.
2. Activation of cytokine cascade associated with the damage of histochemical barriers due to tissue hypoxia, cascade synthesis of inflammatory mediators and autoimmune aggression.
3. Active transmembrane transport failure due to cellular energy insufficiency – mitochondrial insufficiency.
4. Clinically significant systemic hemodynamic disorders, including fluid-related sectoral pathology – volume disorders that complete pathophysiological cascade and lead to dyshidria (in particular, hypovolemia and hypervolemia in different fluid-related sectors in a patient), acidosis and further hypoxic damage.

The present study focused only on understanding the mechanism and perspectives of intensive therapy for generalized consecutive cascade physiological pathology of multiple organ insufficiency – fluid-related sectoral dysfunction or volume disorders [3; 4; 7].

This does not imply that volume disorders at MODS are the main mechanisms that form clinical picture and pathophysiological background. Clinically, in this particular case it is impossible to identify and evaluate the primary mechanism of MODS, and it does not make sense either to do it by the definition of the process itself – consecutive multiple organ dysfunction with any organ or physiological system where it starts. Hence, all the possible basic pathophysiological mechanisms of MODS should be accounted during the diagnostics and intensive therapy [5; 7; 18].

At the initial stage of critical symptoms development, organs and systems failure is primarily functional and, as a rule, they are reversible after intensive therapy based on pathophysiological picture. Along with systemic multiple organ failure, organs and systems damage acquires decompensated irreversible character increasing the risk of lethality [10; 11].

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Prevention of MODS in critically ill patients by intensive therapy based on deep understanding of pathophysiological processes, including the respective therapeutic measures (for example, active surgical approach), systemacity and logics of MODS development as a universal pathophysiological basic of critical conditions is more efficient than highly specialized approach of narrow field specialists that often cannot understand and accept the extra disciplinary nature and general pathophysiological mechanisms of MODS regardless of the initial critical condition. This explains the necessity in multidisciplinary approach to prevention and treatment of MODS [5; 13].

Multiple Organ Dysfunction Syndrome (MODS), closely associated with Systemic Inflammation Response Syndrome (SIRS), remains the main cause of death in 72-83% of patients in the unit of resuscitation and intensive care [1; 14; 16].

Reduction of tissue perfusion with oxygen utilization failure due to mitochondrial insufficiency, systemic hypoxia, oxidative stress, cytokine storm and secondary immune cascade autoaggression lead to metabolism pathology and histochemical barriers (membranes) damage that maintain homeostasis, which results in intersectoral volume disorders [2; 6; 11].

The main pathophysiological part of multiple organ dysfunction mechanism is hypoxia and associated mitochondrial insufficiency. Under hypoxic condition, aerobic ATP synthesis switches to anaerobic one. From energy metabolism point of view, anaerobic ATP synthesis has low efficiency and leads to lactic acid accumulation and development of intracellular acidosis (tissue acidification), which results in vascular spasm intensification and microcirculatory crisis associated with the development of hypoxia.

Reperfusion also leads to the development of reperfusion damages associated with oxidative and cytokine stress. This stressor mediators damage histochemical barriers at all the levels – extracellular, organ (endothelium, epithelium), cell membranes and intracellular structures (mitochondria, lysosomes, DNA) [8; 11].

Under hypoxic conditions, activation of all the systems of homeostasis protection from hyperergic excessive activation is observed. These excessive activation processes are characterized by damaging effect, including actual physiological cachexy and activation of the synthesis of aggressive proinflamatory and anti-inflammatory cytokins, pain and inflammation mediators (prostaglandins, prostacyclin, tromboxan-A, toxic oxygen radicals, NO, TNF, etc.). They activate cellular immunity with autoaggression, which generally can be characterized as “metabolic storm” or cascade cytokine crisis that is known as systemic inflammation response syndrome (SIRS), which, in its turn, acts as a trigger mechanism and pathophysiological basis of MODS.

Homeostasis pathology is expressed as a damage of histological barriers, cease or complication of active transmembrane transport due to energy metabolism disorder, albumin outflow into interstitial space via the damaged barrier, which leads to osmotic gradients and physiological constants disturbances [11; 13; 20].

All the mentioned processes activate redistributive mechanisms of fluid volume regulation, dyshidria and volemic status disorders, which lead to formation of persistent fluid-related sectoral disorders that aggravate tissue perfusion insufficiency and systemic hypoxia.

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Hence, volemic status disorders at MODS lead to hypoperfision, tissue hypoxia, metabolic acidosis and consecutive organ dysfunction [1, 2; 14].

The aim of the present study was to evaluate the significance of volemic status in critically ill patients for assessment of fluid-related disorders influence on the associated lethality in patients with multiple organ dysfunction syndrome.

II. Materials and Methods

The authors studied 256 clinical cases registered from 2004 to 2016 in patients with MODS aged from 18 to 78 (average age 62.4 ± 8.8) regardless of their sex, hospitalized to the units of resuscitation and intensive care in Volgograd (Russia).

The dynamics of the following parameters were studied:

1. General clinical parameters (central hemodynamics, respiratory status, pulseoxymetry, hemoconcentration parameters, plasma albumin).
2. Evaluation of patients condition severity by the three level scale of intensive care unit patients condition.
3. Depth of consciousness impairment by Glasgow scale.
4. Volume status (severity and localization of edemas, presence of free fluid in organism cavities, central venous pressure).
5. Body fluids volume (BFV) and circulating blood volume (CBV) were measured by bioimpedance method with BoMED NCCOM3-R7 monitor.
6. Infusion plan (volume, quality and media ratio, water balance).
7. The Scale of Multiple Organ Failure was used along with the developed clinical Scale of Evaluation of Fluid-Related Sectors Pathologies in critically ill patients and organ dysfunction associated lethality.

III. Results

Pathology of fluid-related sectors was diagnosed in 100% of patients with severe clinical picture of MODS.

The observed severity of volume disorders: 49.6% in Group 2 (lethal outcome in 20.8%), 27.4% in Group 3 (lethal outcome in 37.6%), 9.7% in Group 4 (lethal outcome in 72.5%).

Condition, close to normovolemia (Group 1), was characterized by the lowest rate of lethality – up to 10%.

In Groups 3 and 4 impairment of consciousness to deep coma developed. Respiratory support (ARDS) was needed, in Group 4 artificial ventilation (AV) was performed to 100% of patients.

Hemodynamics disturbance was registered in 66.7% of cases, wherein the rate of disturbances development directly correlated with the severity of organ dysfunction, including fluid-related sectoral disorders.

Bioimpedance monitoring in Groups 3 and 4 showed that the dynamics of CBV and BFV values increased from 7-10% (average 8.6 ± 1.2) to 15-20% (average 17.5 ± 2.2) at $p<0.001$, which was interpreted as life threatening hypervolemia.

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The obtained data indicated on direct correlation between the level of hypervolemia and lethality rate.

The obtained unstructured data did not provide general structural clear pathophysiological picture of MODS. The Scale of Volume Disorders Evaluation was developed for structuring, organization, systematization and analysis of the obtained data.

Volume disorders evaluation scale in critically ill patients.

Disorder	***If present (points)***
Edema	
Upper extremity edema	1
Lower extremity edema	1
Lumbar edema	1
Abdomen edema	1
Face edema	1
Respiratory status - acute respiratory distress syndrome (ARDS)	
No AV	1
AV	2
Volume status	
Free fluid in abdomen cavity	1
Free fluid in thorax	1
Free fluid in pericardium	1
Positive fluid balance per day from 0 to 499 ml	1
Positive fluid balance per day from 500 to 999 ml	2
Positive fluid balance per day from 1000 to 1999 ml	3
Positive fluid balance per day from 2000 ml and more	4
CVP (central venous pressure)	
Below the norm	- 1
Normal	0
Above the norm at normal cardiac output	1
Above the norm at reduced cardiac output	2
Total	

Comments on calculations:

1. Calculation was made 1-2 times per day (in dynamics).
2. Evaluation of the obtained results:

Group №	*Group 1*	*Group 2*	*Group 3*	*Group 4*
Score	0 – 5 points	6 – 10 points	11 – 15 points	16 and more points
Need in blood volemic function repair	+5 ml/kg×day	++ 10 ml/kg×day	++ 10 ml/kg×day	+++ 15 ml/kg×day
Lethal outcome prognosis, %	10	20	30-50	70-100

The present scale was used for volume status evaluation in patients with MODS before the start of intensive therapy (distribution of patients into 4 groups by the severity of volume disorders and associated lethality). The most informative data was obtained at evaluation of fluid-related sectoral disorders dynamics associated with organ dysfunction during the performed intensive therapy.

The analysis of the parameters dynamics during infusion therapy showed that administration of volume expanders by the method of continuous low volume infusion at the rate of 5-15 ml/kg/day for 3 – 8 days [5; 12; 13] contributed to the reduction of fluid-related sectoral disorders to the level of normovolemia (provided there were no acute renal failure, there was adequate diuresis, and no extracorporeal methods of treatment were required), which

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allowed the authors to redistribute the patients from Group 3 to Group 1, i.e. reduced lethality outcome rate from 30-50% to 0-9% was registered.

The analysis of the systemized data showed that one of the main pathophysiological mechanisms of multiple organ disorder syndrome (MODS) in critically ill patients was the development of volume (fluid-related sectoral) disorders in different combinations [1; 6; 19]. Based on the above mentioned information, volume status normalization at MODS should be considered as the aim of the infusion plan.

It is evident that not only volume based treatment but also other aspects of intensive therapy contributed to the decrease of lethality rate. Still, the factor of volemic disorders at MODS manifested itself as the main one for positive disease outcome.

IV. DISCUSSION

The role of hypervolemia, including of iatrogenic etiology, remains underestimated, while the rate of organ dysfunction in patients with hypervolemia is higher than in patients without hypervolemia. The rate of clinically significant ARDS at MODS with associated hypervolemia was 39.4% [1]. The survival rate in patients with hypervolemia was by 9% lower than in patients without hypervolemia [1].

Fluid overload by more than 7–10% from the body weight at MODS lowered the index of oxygenation and survival rate by 20% [14].

Normalization of volume status is the main aim of infusion therapy in patients with multiple organ disorder syndrome.

The obtained data showed that fluid-related sectoral disorders in critically ill patients were the main parts of MODS development and were observed in 100% of cases.

The study results showed that volume disorders in critically ill patients resulted in endothelial dysfunction under systemic inflammation response (SIRS) with the development of multiple organ dysfunction syndrome with further pathophysiological mechanism:

1) Histochemical membranes damage with the damage of intestine and lung epithelium, endothelium of microvascular system and uncontrolled development of fluid redistribution in fluid-related sectors (volume disorders) with the change of ventilation and perfusion ratio.
2) Oxygen supply failure with mitochondrial insufficiency.
3) Cellular energy metabolism failure with complicated or ceased active transmembrane transport that maintains homeostasis and physiological osmotic gradients alterations.
4) Progressing, cascade, clinically significant, fluid-related sectoral (volume) disorders due to the influence of the first three factors that lead to the harmful circle of fluid balance disorder development by physico-chemical laws, and not by biological mechanisms of active transport due to high-energy compound degradation and micro and macrocirculation damage, that require blood volemic function correction.

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Therefore, from the point of view of pathophysiology and taking into account 100% rate of intersectoral volume disorders, critical conditions should be considered as multiple organ disorder that realizes universal general biologic mechanism SIRS – MODS.

The obtained data highlight the relevance of the methods of volume disorders evaluation during monitoring of volume status as one of the main mechanisms of MODS development. It is necessary for infusion plan correction for volume and homeostasis normalization and for the prognosis of the disease outcome in patients with MODS as a criterion of MODS volemic mechanism inhibition [2; 17; 20].

V. CONCLUSION

1. Verification of patients condition and their volume status under MODS development requires the evaluation scale feasible for further statistical processing.
2. The developed formalized scale for evaluation of volume dysfunction and prognosis of the associated lethal outcome risk at MODS allowed the authors to determine direct correlation between the severity of volume disorders and lethality. The obtained data significantly correlated with bioimpedance test results [15] and the results of the study conducted by Bouchard J. et al [14].
3. The proposed scale can be used for clinical monitoring of volume status in critically ill patients and for making a decision on indication of blood volemic function correction for volume normalization.
4. The main purpose of infusion therapy at MODS is fluid homeostasis normalization [7] to normovolemia based on volume status evaluation.
5. Volume disorders are the main, consequently determined mechanisms of MODS.

The present study was approved by the Ethical Committee of Volgograd State Medical University of the Ministry of Healthcare of the Russian Federation, Volgograd (Russia).

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