REVIEW

From Prof. Dr. Ivo Spassov Petrov, MD,
Medical Director and Head of the Clinic of Cardiology and Angiology at Acibadem City Clinic Cardiovascular Center EOOD,

elected a member of the Scientific Jury for awarding the scientific and educational degree "Doctor of medicine", determined by order №19-10 / 10.01.2022 of the Executive Director and Procurator of Acibadem City Clinic University Hospital Tokuda EAD, under a public protection procedure of the dissertation

To Dr. Assen Stefanov Keltchev,
PhD fellow at the Clinic of Cardiac Surgery, Acibadem City Clinic UMHAT Tokuda EAD,

Regarding PhD thesis "Surgical pulmonary thrombectomy as a method of treatment for acute pulmonary thromboembolism"

Scientific adviser: Assoc. Prof. Dr. Dimitar Nikolov, Ph.D.

for awarding the scientific and educational degree "Doctor of medicine"in the field of higher education - 7. Health and sports, professional field - 7.1. Medicine, doctoral program "Cardiovascular Surgery"

Scientific organization: Acibadem City Clinic UMBAL Tokuda EAD
Professional field 7.1. Medicine
Qualification and professional path:

- He graduated from high school in 1997 at 125 Boyan Penev High School with a degree in French.
- In 2004 graduated from the Medical University - Sofia
- In 2013 board certified in "Cardiac Surgery"
- In 2018 board certified in "Vascular Surgery"
- In 2018 acquired master's degree in Health Management

Assen Stefanov Keltchev In 1998 was admitted to the Medical University of Sofia, graduating from medical school. Since 2001 he has been working as a nurse in ICU at UMHAT "NI Pirogov" and then in KARIL at UMHAT "St. Catherine", where during his state internships he is a volunteer at the Clinic of Cardiac Surgery. It is from our joint work at St. Ekaterina Hospital that I know Dr. Keltchev, where in 2005 he was appointed a resident doctor at the same clinic, where he worked until April 2007. In 2005 he won a competition and was enrolled in a specialization program in General Surgery. In May 2007 he started working as an intern at the Department of Cardiac Surgery at Tokuda Hospital in Sofia. In 2008 he won a competition and was enrolled in the specialization program in cardiac surgery at the Medical University of Sofia.

Acquired the specialty "Cardiac Surgery" in 2013. In 2018 he completed a master's degree in health management at Hospital "Neofit Rilski". In 2018 acquires the specialty "Vascular Surgery". From May 2018 heads the Cardiac Surgery Department at Acibadem City Clinic Cardiovascular Center. From 2019 is a part-time assistant at the Medical Faculty of Sofia University "St. Kliment Ohridski". Married, has one child. He has attended a number of courses and trainings abroad (Germany, France, Switzerland, Romania, Greece and Belgium). He speaks French and English.

Structure of the dissertation:

The dissertation contains 149 pages, of which 134 pages main text and 15 pages bibliography. It is illustrated with 50 figures, 43 tables. The bibliography includes 242 literary sources, of which 10 in Bulgarian and 232 by foreign authors. The chapters covering the literature review, research methodology, research results, discussion of the results and conclusions and recommendations are clearly presented in detail, and the structure of the study meets the generally accepted requirements. Contributions are presented only in the Abstract, where a list of publications and scientific communications on the topic is attached.

Structure of the scientific work:

- Introduction - 3 pages
- Literature review - 56 pages
- Materials and methods - 13 pages
- Results - 24 pages
- Discussion of the results - 20 pages
- Conclusions - 2 pages
- Bibliography - 15 pages

Relevance of the problem:

Acute pulmonary thromboembolism (PTE) is the third most common cause of death in the modern world. Due to the diverse clinical picture, its diagnosis and clinical risk evaluation is based on differentclinical score systems, determining the potential risk of its occurrence and its potential prognosis. Imaging is key to confirming or rejecting a diagnosis, as well as the risk of complications, including mortality. According to the Recommendations of the European Society of Cardiology (ESC) from 2019, depending on the hemodynamic profile of the patient, patients with acute pulmonary thromboembolism are divided into low-risk, those with intermediate or moderate risk and high risk of death. According to the recommendations, moderately high-risk and high-risk patients need hospital treatment and aggressive therapy (fibrinolysis or surgical embolectomy). Patients at high risk of PTE who are in shock need urgent reperfusion therapy, while in those at moderate risk the decision to escalate (fibrinolysis or surgical embolectomy) or use anticoagulant therapy alone is still controversial.
In modern medical practice, the multidisciplinary team determining the most appropriate approach in the diagnosis and treatment of acute pulmonary thromboembolism is commonly referred to as PERT (Pulmonary Embolism Response Team). This team includes a pulmonologist, interventional

cardiologist, cardiac surgeon, vascular surgeon, imaging specialist, hematologist, anesthesiologist and cardiologist.

The individual approach to the choice of therapy is the basis of good short-term and long-term results. The optimal treatment of PTE includes all types of therapy, but the possibility of providing them in full spectrum is only available in large hospitals with the necessary set of specialists and equipment. The development of endovascular medicine and a number of devices for thrombofragmentation and thrombaspiration, allows in clinical practice to increasingly use selective fibrinolysis, in which the total dose of fibrinolytics is reduced and thus reduces the risk of hemorrhagic complications, including intracerebral hemorrhage. . On the other hand, in recent years, with the improvement of extracorporeal circulation equipment, including the development of mobile devices for extracorporeal membrane oxygenation (ECMO), surgical pulmonary thrombectomy has become an increasingly low-risk procedure in patients with high-risk PTE and high-risk intermediates. in which fibrinolysis is contraindicated or has no effect.

Literature review:

In the present literature review, the author examines in detail the etiology and predisposing factors for the development of acute pulmonary thromboembolism, as well as its consequences. The laboratory abnormalities, the clinical picture and the diagnostic tests necessary for the diagnosis are considered. Attention is paid to the point systems having diagnostic and prognostic value in acute pulmonary embolism. Drugs needed to treat this disease are listed, namely vasoactive drugs to maintain hemodynamics and the various groups of anticoagulants underlying the therapy. The different types of reperfusion therapy (systemic fibrinolysis, local fibrinolysis with thrombus fragmentation and thrombaspiration, surgical thrombectomy) are discussed in detail, mentioning the advantages and disadvantages of their use.

Goals and tasks of the scientific work:

*The aim of the present study was to determine the criteria for selecting patients suitable for surgical pulmonary thrombectomy as a method of treatment for acute pulmonary thromboembolism (*PTE*) in order to improve the prognosis and reduce mortality from this disease.*

In order to achieve this goal, the author has identified the following tasks:

1. Examination the level of efficacy and safety of surgical pulmonary thrombectomy in the treatment of acute PTE compared with systemic venous fibrinolysis.
2. Based on the clinical picture, non-invasive and invasive studies, determination of a set of criteria for selection of patients suitable for surgical pulmonary thrombectomy
3. Determining the optimal surgical technique to achieve the best possible results from the application of surgical pulmonary thrombectomy.
4. Determining the optimal pre- and postoperative intensive care and the role of ECMO (extracorporeal membrane oxygenation) in patients with surgical pulmonary thrombectomy.

5. Development and implementation of an algorithm for selection of patients suitable for surgical pulmonary thrombectomy, as well as building a multidisciplinary team involved in deciding on the optimal therapeutic approach (PERT - Pulmonary Embolism Response Team).

Material and methods:

The study included 100 patients with acute massive pulmonary thromboembolism who were treated with reperfusion therapy with systemic fibrinolysis or surgical pulmonary thrombectomy.

Patients were divided into two groups according to the reperfusion therapy used, as follows: Group 1, comprising 36 patients treated with fibrinolysis and Group 2, consisting of 64 patients treated with surgical pulmonary thrombectomy.

The analysis of the data throughout the period is retrospective, based on the hospital database for the respective patients. The diagnostic and therapeutic algorithm of behavior in the diagnosis and treatment of these patients is based on the recommendations for good medical practice at the time of the study. After diagnosing PTE and assessing the need for reperfusion therapy, the type of reperfusion therapy is determined depending on which clinic the patient was admitted to.

Results and discussion:

The current study included a total of 100 patients with acute pulmonary thromboembolism treated with fibrinolysis or surgical pulmonary thrombectomy in the Pulmonology and Cardiac Surgery wards of Tokuda hospital between 2007 and 2021. Patients were divided into two groups depending on the reperfusion procedure. The first group included 36 patients treated with fibrinolysis, and the second group included 64 patients treated with surgical pulmonary thrombectomy. In the present study, the large number of surgical thrombectomies relative to the number of patients treated with fibrinolysis is impressive. The reason for this is that in the clinic of Cardiac surgery at Acibadem City Clinic UMHAT Tokuda hospitalizes patients from various hospitals in the country, directed directly to surgical treatment. Statistically, men in the present study were slightly more likely to be affected by acute pulmonary embolism than women, and the difference was not statistically significant in either study group. The mean age in the group with surgical pulmonary thrombectomy was significantly higher than the mean age in the fibrinolysis group, and no statistically significant association between age and mortality was found in the present study. The presence of preoperative hypotension was statistically significantly more common in patients undergoing pulmonary thrombectomy. The presence of hypotension is a sign of an increased risk of adverse outcomes in pulmonary thromboembolism. This determines the choice of more aggressive therapy in these patients. However, it should be noted that hypotension is a risk factor for death in the group of patients with surgical pulmonary thrombectomy. It is interesting to note that after analyzing the data, no statistically significant relationship was found between mortality and the existence of concomitant procedures. Unlike other studies, mortality in the present study did not depend on the development of postoperative respiratory failure. As in other studies, there was a relationship between mortality and preoperative tachycardia and

hypotension, intraoperative duration of extracorporeal circulation and catecholamine use, and postoperative development of multiorgan failure.

Conclusions from the scientific work:

To date in Bulgaria there were no other scientific work comparing different types of reperfusion therapy for acute pulmonary embolism. Despite the very different nature of the two methods, namely drug therapy compared to surgical treatment, in the end the mortality results were not statistically significant. The author drew 15 conclusions, the most significant regarding the preoperative exclusion of chronic thromboembolic pulmonary hypertension as the main disease, as well as preparation of the operative field and the extracorporeal circulation machine before induction of anesthesia due to high risk of cardiac arrest. Individual examination of deceased patients gives us to understand that mortality depends mainly on preoperative assessment and prevention of intraoperative complications. The proposed PERT team aims at an optimal and individualized therapeutic approach in order to reduce mortality.

Contributions:

The study is the first of its kind in Bulgaria, comparing systemic fibrinolysis and surgical pulmonary thrombectomy in terms of their safety profile. A complete summary analysis of clinical, instrumental and morphological data was performed in patients with acute pulmonary thromboembolism who received reperfusion therapy using systemic fibrinolysis or surgical pulmonary embolectomy. Naturally, comparing medical and surgical treatment is a difficult task, and the main reason for this is surgical trauma, which carries with it the risk of many complications. The author's conclusion is that systemic fibrinolysis and surgical pulmonary thrombectomy have a similar safety profile, and it should be borne in mind that in both cases high-risk and high-intermediate-risk patients are included, and the results in terms of death confirm data from other authors. The introduction of a special highly qualified medical team, determining the type of therapy used, meets the standards of good medical practice. Specific recommendations based on retrospective analysis have been made that are important for clinical practice in order to reduce the risk of surgical treatment, the most important of which are:

1. Due to the increased risk of cardiac arrest during induction of anesthesia, it is recommended that the operative field be prepared and the extracorporeal circulation machine be performed while the patient is awake.
2. The use of Fogarty catheters is contraindicated due to the risk of intrapulmonary haemorrhage.
3. Dousing the operating field with CO2 during the intervention reduces the risk of air embolism in the pulmonary circulation.
4. Patients with underlying chronic thromboembolic pulmonary arterial hypertension (CTEPH) are not suitable for classical reperfusion therapy, but for highly specialized surgical treatment.

Notes and recommendations:

It should be noted that in the process of finalizing the research, the dissertant has taken into account some remarks that I had outlined in a previous preliminary opinion. The scientific work of Dr. Assen Keltchev on the surgical treatment of patients with massive PTE is extremely relevant. Not only do I agree with the conclusions and contributions that the author has drawn, but I believe that they can serve to optimize the algorithms for the treatment of PTE at the national level as part of the established clinical procedures in the National Health Insurance fund (NHIF).

As a recommendation, I would like to encourage the author to continue the scientific development by validating in a prospectively controlled protocol the optimization of the details of the surgical treatment protocol on the basis of the retrospective analyzes, which represent one of the main merits of the present scientific development.

Conclusion:

The dissertation of Dr. Assen Stefanov Keltchev on "Surgical pulmonary thrombectomy as a method of treatment for acute pulmonary thromboembolism", with supervisor: Assoc. Prof. Dr. Dimitar Nikolov, Ph.D. is up-to-date and meets the scientometric criteria, as well as the regulations for the development of the academic staff of Acibadem City Clinic UMHAT Educational and scientific degree "Doctor of Medicine".

After taking into account the critical remarks with deep respect, I recommend the esteemed members of the Scientific Jury to vote positively for the award of Educational and scientific degree "Doctor of Medicine" in the field of higher education - 7. Health and Sports. professional field - 7.1. Medicine, doctoral program "Cardiovascular Surgery" by Dr. Assen Stefanov Keltchev

With consideration:

Sofia,
07.02.2022

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Prof. Dr. Ivo Spassov Petrov, MD