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Perioperative assessment of metabolic status and its short, medium, and long-term effects in the oncologic patient

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Contents

Introduction

Colorectal cancer is the third most diagnosed cancer and the second leading cause of cancer-related deaths globally, affecting individuals of various ages, genders, and ethnicities.

Surgical intervention for colorectal cancer represents a cornerstone of treatment for patients diagnosed with this condition.

Administering anesthesia to oncologic patients requires a personalized approach to manage the unique challenges associated with their care. Prior to administering anesthesia, a thorough preoperative evaluation is crucial to understand the patient's medical history, cancer stage, treatment modalities, and potential side effects that may impact the anesthesia plan.

Surgical stress is a complex physiological response involving various body systems. During surgery, tissue injury, blood loss, and changes in circulating hormones can contribute to a cascade of events affecting the body's immune function and inflammatory response.

The extent of surgical stress can significantly influence the development and progression of oncologic metastases. Extensive surgical trauma and prolonged procedures can lead to a more pronounced stress response in the body, resulting in higher levels of stress hormones and inflammatory mediators. This increased systemic stress can create an environment conducive to the dissemination of tumor cells and the formation of metastases.

The assessment of surgical stress is a highly important component in the perioperative management of oncologic patients. Biomarkers play a critical role in evaluating surgical stress and its impact on the body's physiological response.

However, the biomarkers used are not yet routinely implemented in daily clinical practice, leading to a lack of objective quantification of surgical stress during surgical interventions. Currently, accurate assessment of surgical stress is primarily reserved for experimental studies.

Given these aspects, the aim of this thesis was to identify a tool that would allow for an objective, real-time, accessible, and non-invasive measurement of surgical stress. Additionally, I

aimed to provide a detailed exposition of the physiological and pathophysiological changes induced by surgical stress, specifically addressing the updating of available anesthetic techniques to modulate and minimize its effects.

To achieve these objectives, I conducted two single-center prospective studies and developed two review articles.

1.Epidemiology

According to the Global Cancer Observatory, worldwide in 2022, there were 19,976,499 new cancer cases and 9,743,832 deaths. Lung tissue, with 2,480,675 (12.4%) new cases, is the most common site, followed by breast (11.6%) and colorectal regions (9.6%). Regarding mortality, the leading cause is lung cancer (18.1%), followed by colorectal cancer (9.3%) and breast cancer (6.9%) [1]. Geographic region influences the type of cancer and prognosis. In low- and middle-income countries, oncologic pathology represents a significant challenge because, although the number of newly diagnosed cases is much lower than in developed, high-income countries, mortality is much higher. It is estimated that by 2040, the incidence of oncologic pathology will increase by 63.4%, and mortality by 71.5% [2].

In Romania, in 2022, 106,661 new cancer cases were discovered, and 56,216 deaths were recorded. Among men, prostate cancer was the most frequently diagnosed (18.2%), followed by lung cancer (14.8%) and colorectal cancer (14.1%). Breast cancer (26.8%), followed by colorectal cancer (11.6%) and cervical cancer (7.1%) were the most common oncologic pathologies in women. The leading causes of cancer-related mortality were lung pathology (18.7%), colorectal pathology (13.1%), and breast pathology (7%) [3]. Additionally, it is alarming that 33.6% of men and 23.6% of women in Romania develop cancer by the age of 75, with an incidence rate higher than the general average.

2. Perioperative Assessment of the Oncologic Patient

2.1 Neurological Evaluation

For the oncologic patient, following a detailed anamnesis, the anesthesiologist must assess the risk of ischemic or hemorrhagic stroke (CVA). The probability of ischemic stroke occurrence is higher in patients who have undergone radiotherapy sessions in the head and neck area, primarily due to the development or aggravation of carotid artery disease.

2.2 Cardiac Function Evaluation

Estimating cardiac reserve in the oncologic patient is truly challenging because it is necessary to distinguish whether the described cardiac symptoms are due to pre-existing cardiovascular diseases or a result of oncologic treatment. Currently, the recommended tool for evaluation, optimization, and management of cardiac dysfunctions is the 2022 Guidelines on Cardiovascular Evaluation and Management of Patients Undergoing Non-Cardiac Surgery, developed by the European Society of Cardiology [4].

2.3 Pulmonary Evaluation

Investigating the pulmonary status should be broad and oriented in several directions, making the evaluation of respiratory insufficiency in the oncologic patient quite difficult. Initially, if applicable, the mass effect of the tumor on the airway should be determined, anticipating a difficult intubation. Next, a complete medical history is required to decide if there is pre-existing pulmonary parenchymal involvement before starting chemotherapy or radiotherapy. In the final stage, the effects of chemotherapy and radiotherapy must be investigated.

2.4 Renal Evaluation

Renal impairment can occur either directly through a renal or bladder tumor or indirectly through the effects of chemotherapy. The most common manifestations of renal toxicity include acute kidney injury, nephrotic syndrome, kidney stones, Fanconi syndrome, thrombotic microangiopathy, and the syndrome of inappropriate antidiuretic hormone secretion [5].

2.5 Metabolic Nutritional Evaluation

Preoperative assessment of metabolic and nutritional status is essential, as complications associated with surgical treatment are reduced if the patient is metabolically balanced [6].

3. Response to Surgical Stress

3.1 Physiology and Pathophysiology of Surgical Stress

When a stressor acts upon the body, multiple mechanisms are activated to restore homeostasis, preserve life, and ensure the perpetuation of the species [7]. The physiological and pathophysiological changes that occur in response to surgical stress can be divided into two main categories: neurohormonal response and immunological response. During surgery, disturbances activate two major mechanisms as part of the neurohormonal response: the hypothalamic-pituitary axis and the sympathetic adrenergic nervous system. Immunologically, there is initially a bimodal reaction: an exaggerated inflammatory response phase – systemic inflammatory response syndrome (SIRS) – followed a few days later by a compensatory anti-inflammatory response (CARS).

3.2 Effects of Surgical Stress on Oncologic Prognosis

After undergoing curative colorectal oncologic surgery, up to 30% of patients who did not have metastases at the time of surgery develop metastases within the first five years [8]. Numerous studies have also reported that, regardless of the type and location of the primary tumor (stomach, liver, breast, lung, ovarian), metastases or local recurrences can occur distant from the initial tumor excision [9-14]. During surgery, the release of stress hormones and cytokines can promote changes in the tumor microenvironment that support the survival and spread of cancer cells. For example, inflammation induced by surgical stress can contribute to remodeling the extracellular matrix, making it easier for cancer cells to invade surrounding tissues and enter the bloodstream or lymphatic system [15]. Additionally, stress hormones can modulate the activity of immune cells, potentially compromising the body's ability to detect and destroy circulating tumor cells.

3.3 Methods for Quantifying Surgical Stress

The first method for evaluating surgical stress is the determination of specific biomarkers; the second method involves using scores or intraoperative monitoring of parameters used as surrogates for the response to applied surgical stress. The biomarkers used are divided into two main categories: serum inflammatory markers and markers that reflect neurohormonal changes induced by surgical stress. Serum inflammatory markers can be grouped into acute phase markers

(CRP and procalcitonin), mediators of immune system activity (tumor necrosis factor, interleukin-1, interleukin-6, interleukin-8, interleukin-10), and markers that reflect cellular activity.

The second major category of biomarkers used in evaluating the extent of surgical stress includes neuroendocrine biomarkers such as cortisol, catecholamines, insulin, growth hormone, and copeptin.

Another method for quantifying the body's response to stress is through scores and mathematical calculations. The E-PASS (Estimation of Physiologic Ability and Surgical Stress) score is a tool designed to assess surgical stress and the risk of postoperative complications.

3.4 Indirect Calorimetry and Energy Consumption

Indirect calorimetry is the most commonly used method for determining energy expenditure, both in clinical studies and in everyday practice. It is a non-invasive tool with acceptable cost and high accuracy. It is well known that human energy comes from chemical energy, which is obtained through the oxidation of various food substrates.

Currently, indirect calorimetry is predominantly used in patients admitted to intensive care units, but I believe that such a useful tool can also find its utility in the operating room, monitoring the body's response to the stress induced by surgical procedures.

II. Personal Contributions

4. Working Hypothesis and General Objectives

Study 1: Energy Expenditure, a New Tool for Monitoring Surgical Stress in Patients with Colorectal Cancer: A Monocentric, Prospective Study

Working Hypothesis: The intensity of surgical trauma influences mortality, morbidity, and the occurrence of distant metastases in patients with colorectal cancer. The body's response to surgical stress in colorectal oncologic surgery involves a neurohormonal and inflammatory response, which impacts the oncologic prognosis. Energy expenditure represents the energy consumed by the body to maintain homeostasis.

Specific Objectives: This study aims to evaluate surgical stress through energy expenditure by comparing the recorded EE values during the intraoperative period with the dynamics of serum cortisol in the perioperative period.

Study 2: Intraoperative Oxygen Consumption and Postoperative Immune Response in Colorectal Oncologic Surgery: A Monocentric, Prospective Pilot Study

Working Hypothesis: Surgical resection is one of the pillars of treatment for colorectal cancer, and the magnitude of tissue trauma is one of the key factors that can influence oncologic prognosis. The body's response to surgical stress involves an immune response that generates a cascade of immunological events, including the generation of NET complexes, the reduction of NK cells, and the activation of platelets, which can influence both the immediate postoperative prognosis and the oncologic prognosis.

Objectives: In this study, we aim to investigate the degree of correlation between intraoperative oxygen consumption and the dynamic variation of neutrophils, lymphocytes, and platelets in the perioperative period to identify an intraoperative tool that could predict immunological changes in the postoperative period.

Study 3: Pain in Colorectal Surgery: How Does It Occur, and What Options Do We Have to Combat It?

Working Hypothesis: Pain is a complex entity with harmful effects on the entire body. Inadequate pain management during the intraoperative and postoperative periods affects patient outcomes and is associated with increased morbidity, a decrease in quality of life, and impaired functional recovery.

Objectives: The first section of this literature review aims to expand knowledge about the physiology of pain, focusing on the mechanisms of pain onset and the pathways of pain sensation transmission. The second part aims to highlight the available options for the anesthesiologist to prevent and block pain at different stages of its transmission.

Study 4: The Body's Response to Surgical Stress and Anesthesia: A Literature Review

Working Hypothesis: The human physiological response to stress includes all metabolic and hormonal changes produced by a traumatic event at the micro or macroscopic cellular level. The main goal of the organism is to maintain homeostasis, but non-specific perioperative adaptation can often be harmful and can cause a systemic inflammatory immune response characterized by a hypercatabolic and hypermetabolic state.

Objectives: The first part of this narrative review aims to provide a detailed description of the (neurohormonal and immunological) changes that occur in response to tissue trauma. The final part of this work aims to review the methods described in the specialized literature to modulate the response to surgical stress.

5. General Research Methodology

To improve oncologic prognosis in patients diagnosed with colorectal cancer, this work approached two research directions. The first research direction aimed to understand the physiology and pathophysiology of the onset of surgical stress as well as highlighting various anesthetic techniques to minimize its magnitude.

The second research direction focused on finding a non-invasive, easy-to-use tool that could provide early information about the intensity of surgical stress. To this end, two prospective studies were conducted that successfully identified instruments capable of quantifying the body's response to tissue trauma and predicting certain immunological dysfunctions.

6. Study 1: Energy Expenditure, a New Tool for Monitoring Surgical Stress in Patients with Colorectal Cancer: A Monocentric, Prospective Study

Working Hypothesis: The intensity of surgical trauma influences mortality, morbidity, and the occurrence of distant metastases in patients with colorectal cancer. The body's response to surgical stress in colorectal oncologic surgery involves a neurohormonal and inflammatory response, which impacts the oncologic prognosis.

Specific Objectives: This study aims to evaluate surgical stress through energy expenditure (EE), comparing the recorded EE values during the intraoperative period with the dynamics of serum cortisol in the perioperative period [16].

6.1 Introduction

The response to surgical stress in colorectal surgery consists of a neurohormonal and immunological response, influencing oncological outcomes. The intensity of surgical trauma affects mortality, morbidity, and the occurrence of metastases in colorectal neoplasia. Energy expenditure (EE) represents the energy consumed by the body to maintain homeostasis and can be calculated or measured through direct or indirect calorimetry. The purpose of the present study was to evaluate the response to surgical stress using EE measurements and compare it with the dynamics of postoperative cortisol.

6.2 Materials and Methods

A prospective, monocentric study was conducted over a one-year period in the Anesthesia Department, including 21 patients from whom serum cortisol values were collected in the preoperative period and on the first postoperative day. EE was measured and recorded every 15 minutes during surgery using the indirect calorimetry method. The study compared the dynamics of EE values recorded 30 minutes after intubation and 30 minutes before extubation (after abdominal closure) with the perioperative dynamics of cortisol.

6.3 Results

We included 21 patients and recorded 84 measurements, comprising 42 serum cortisol samples and 42 EE measurements. The mean value of the first serum cortisol measurement was 13.60±3.6 µg, and the second was 16.21±6.52 µg. The mean value of the first EE recording was 1273.9±278 kcal, and for the second recording, it was 1463.4±398.2 kcal. Bivariate analysis showed a good correlation between cortisol variation and EE variation (Spearman coefficient=0.666, $p<0.001$, CI=0.285, 0.865). In nine cases (42.85%), the cortisol value at 24 hours reached the baseline value or below the preoperative baseline value. In eight cases (38.09%), the EE at the end of the procedure was lower than that recorded at the beginning of the surgery.

6.4 Conclusions

The intraoperative variation of EE correlated well with the perioperative dynamics of cortisol and was highlighted in this study as a valuable and accessible predictor of surgical stress in colorectal surgery.

7. Study 2: Intraoperative Oxygen Consumption and Postoperative Immune Response in Colorectal Oncologic Surgery: A Monocentric, Prospective Pilot Study

Working Hypothesis: Surgical resection is one of the pillars of treatment for colorectal cancer, and the magnitude of tissue trauma is one of the key factors that can influence oncologic prognosis.

Objectives: This study aimed to investigate the correlation between intraoperative oxygen consumption and the dynamic variation of neutrophils, lymphocytes, and platelets in the perioperative period to identify an intraoperative tool that could predict immunological changes in the postoperative period [17].

7.1 Introduction

Surgical resection is the key treatment for colorectal cancer, but the extent of surgical trauma has been implicated as a key factor for oncologic outcomes. This study aimed to investigate the correlation between intraoperative oxygen consumption (VO2) and the dynamic variation of neutrophils, lymphocytes, and platelets in the perioperative period to identify an intraoperative tool that could predict the postoperative immune response.

7.2 Materials and Methods

Twenty-six oncologic patients undergoing colorectal surgery were included in a prospective, observational, monocentric study over an 18-month period. Serum values of neutrophils, lymphocytes, and platelets were collected in the preoperative period and on the third postoperative day. Oxygen consumption was measured and recorded every 15 minutes during surgery using indirect calorimetry. We compared the oxygen consumption measurements recorded 30 minutes after anesthesia induction (VO2a) and the first value recorded after closing the abdominal wall (VO2b) with the perioperative variations in the absolute number of neutrophils (ANC), lymphocytes (ALC), and platelets (APC).

7.3 Results

Our results showed a significant correlation between the variation in VO2 and the perioperative dynamics of neutrophils as assessed by ANC (correlation coefficient = 0.547, $p < 0.01$, confidence interval (CI) = 0.175, 0.783). We also observed a correlation between APC and VO2 (correlation coefficient = −0.603, $p < 0.01$, CI = −0.815, −0.248). No correlation could be demonstrated between VO2 and the variation in ALC ($p = 0.39$).

7.4 Conclusions

The intraoperative variation of VO2 measured through indirect calorimetry correlates well with the perioperative dynamic variations in the number of neutrophils and platelets. It can be used as an early prognostic marker for the postoperative immune response and surgical outcome in colorectal oncologic surgery.

8. Study 3: Pain in Colorectal Surgery: How It Occurs and What Options We Have to Combat It?

Working Hypothesis: Pain is a complex entity with harmful effects on the entire organism. Inadequately managed pain during the intraoperative and postoperative periods affects patient outcomes, associated with increased morbidity, decreased quality of life, and impaired functional recovery.

Objectives: The first section of this literature analysis aims to expand knowledge about the physiology of pain, focusing on the mechanisms of pain onset and the pathways of pain sensation transmission. The second part aims to highlight the available options for the anesthesiologist to prevent and block pain at different stages of its transmission [18].

8.1 Introduction

Pain is a complex entity with harmful effects on the entire organism. Poorly controlled postoperative pain affects patient outcomes, associated with increased morbidity, inadequate quality of life, and deficient functional recovery. In the current surgical environment, with increasingly less invasive surgical procedures and a trend towards rapid patient discharge after surgery, it is necessary to continuously reassess analgesic strategies.

8.2 Materials and Methods

We conducted a narrative analysis consisting of a description of the anatomical pathways of acute surgical pain and the connection between pain and the response to surgical stress, followed by a review of multimodal analgesia methods in colorectal surgery presented in recent literature.

8.3 Results and Discussions

We described various regional analgesia techniques and effective medications in the treatment of pain, highlighting their advantages and concerns. Additionally, we attempted to identify current knowledge gaps that require further research.

8.4 Conclusions

Our conclusion is that surgical pain has specific characteristics that make its management complex, involving a consistent and multimodal approach targeting both peripheral and central pain pathways.

9. Study 4: The Body's Response to Surgical Stress and Anesthesia: A Literature Review

Working Hypothesis: The human physiological response to stress includes all metabolic and hormonal changes produced by a traumatic event at the micro or macro-cellular level.

Objectives: The first part of this narrative review aims to provide a detailed description of the changes (neurohormonal and immunological) that occur in response to tissue trauma. The final part of this work aims to review the methods described in specialized literature to modulate the response to surgical stress [19].

9.4.1 Introduction

The human physiological response to "stress" includes all metabolic and hormonal changes produced by a traumatic event at the micro or macro-cellular level. The primary goal of the body's initial response to trauma is maintaining physiological homeostasis.

9.4.2 Materials and Methods

We conducted a narrative analysis consisting of a description of the changes that occur as a result of the response to surgical stress (neurohormonal and immunological response), followed by a review of the methods found in published studies to modulate the perioperative surgical stress response. We described various perioperative measures cited in literature as reducing the burden of surgical trauma.

9.4.3 Results

This article reviews anesthetic medications and techniques that impact the response to surgical stress and demonstrate immunomodulatory effects. We also attempted to identify current knowledge gaps that require further research.

9.4.4 Conclusions

Our analysis concludes that appropriate preoperative measures, adequate general anesthesia, multimodal analgesia, early postoperative mobilization, and early enteral nutrition can reduce the surgical stress response and facilitate patient recovery. Anesthetics and analgesics used in the perioperative period can modulate the innate and adaptive immune system, as well as the inflammatory system, with subsequent impact on cancer recurrence and long-term outcomes.

10. Conclusions and Personal Contributions

10.1 General Conclusions

Within this thesis, two major research areas were explored. The starting hypothesis that surgical intervention is an essential element in the oncologic treatment of patients diagnosed with colorectal neoplasms led to the first research direction aiming to understand the concept of surgical stress. This involved analyzing the impact of surgery on the body, identifying various anesthesia techniques that can modulate surgical stress, and evaluating its influence on oncologic prognosis. Recognizing the significant effects that surgical stress can have on oncologic prognosis, a second research direction was outlined. This targeted the identification of a tool capable of objectively quantifying the impact a surgical intervention can have on the body.

10.2 Personal Contributions

The first study in this thesis was conducted in the Anesthesia and Intensive Care Unit of the "Carol Davila" Central Military Hospital, involving a group of 21 patients. According to the proposed objectives, we managed to identify a device capable of real-time quantification of surgical stress. Through an in-depth exploration of the specialized literature, it is concluded that this study marks the first use of energy expenditure, determined by indirect calorimetry, during a surgical intervention for this specific purpose. It can be stated that this work opens new horizons for assessing surgical stress. However, numerous additional studies are necessary to confirm our observations.

In the second prospective study, conducted over about a year and a half, we demonstrated that by monitoring the evolution of intraoperative oxygen consumption, we can deduce and predict how the immune system will react in the postoperative period. Showing that the use of a simple tool can foresee the immunological evolution of the patient during the functional recovery period provides the clinician with the advantage of taking early measures to modulate the immune system response, thereby improving the patient's prognosis.

The next two articles, review types, significantly contribute to the list of personal contributions. The main contribution in the pain-centered review lies in updating the analgesia techniques that can be used to combat surgical pain. Through careful and meticulous research of the specialized literature, it is believed that a document was created to assist the anesthesiologist,

and others as well, in formulating appropriate treatment schemes, so that the sensation of pain has a minimal impact on the patient in the immediate postoperative period.

The implementation of adequate analgesia not only improves quality of life in the short and long term after surgery (chronic pain being a major issue of the 21st century) but, more importantly, influences oncologic prognosis.

Through the second review, the mechanisms by which the body tries to maintain homeostasis in the perioperative period are structured and described. These pathophysiological details are essential for all medical staff involved in treating an oncologic patient, as these modifications inevitably occur following surgical treatment, often necessary for curing the oncologic disease. Understanding how surgical stress occurs and its effects on the entire body is a first step in modulating it. In the second part of the article, a comprehensive description of ways to minimize surgical stress was conducted, making this work a valuable tool for clinicians and, implicitly, for oncologic patients.

All four published articles, although analyzing and presenting various variables, had the same goal: identifying means to support the physician in patient treatment, so that complications arising after surgical interventions or after oncologic treatment are significantly reduced, and long-term oncologic prognosis is improved.

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List of published papers

1. **Ivascu, R**.; Dutu, M.; Bucurica, S.; Corneci, D.; Nitipir, C. Intraoperative Oxygen Consumption and Postoperative Immune Response in Colorectal Oncological Surgery: A Prospective, Monocentric Pilot Study. J. Pers. Med. 2024, 14, 594. https://www.mdpi.com/2075-4426/14/6/594

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4. **Ivascu, R**.; Dutu, M.; Stanca, A.; Negutu, M.; Morlova, D.; Dutu, C.; Corneci, D. Pain in Colorectal Surgery: How Does It Occur and What Tools Do We Have for Treatment? J. Clin. Med. 2023, 12, 6771. https://doi.org/10.3390/jcm12216771.