# Journal of Biomedical and Medial Sciences

ISSN 2667-9507

## EDITORS (INTERNATIONAL AND NATIONAL ASSOCIATES)



## PROJECT AUTHOR

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# Content

# Letter of Editor-in-Chief

*Dear authors, reviewers, readers and all those interested!*

*On behalf of the Editorial Board, we are pleased to present refereed Journal of BIOMEDICAL AND MEDICAL SCIENCE.*

*This Journal is a scientists' and researchers'-run journal who strive to allow famous scientists, recognized and young researchers, specialists and teachers of biomedicine and medical area from all over the World to share fundamental, applied knowledge, innovations, new and the newest methods of research and educations with the audience. We believe it is critical to have the opportunity to share their research and make knowledge transferable. It is a main goal and mission of science.*

*The editorial board and editorial staff dedicated a monumental amount of time and energy towards making and developing the journal, and we hope, our tireless efforts will be a great success in this year and it will stay unchanged in the future.*

*Despite pandemic in the World and despite many challenges one had to overcome related to the situation, we reached the goal.*

*We received a number of excellent submissions and it was wonderful to see modern, innovative, basic topics, as well as multidisciplinary. The independent experts, who were selected by the council, reviewed all articles. You can see the best ones in this issue. Scientific articles in this volume truly represent the breadth and depth of perspectives of authors.*

*Protection of copyrights, implementation of an anti-plagiarism campaign, knowledge of bioethical norms in the administration of research, using Open Access are the most important aspects for us. Together with the originality, innovation, historical insight of biomedicine issues are the most important criteria for publication in a peer-reviewed journal of BIOMEDICAL AND MEDICAL SCIENCE.*

*I would like to express special gratitude to my colleagues, co-editors and editorial board members, as well as to all authors who sent their applications. The European University deserves special thanks from all of us, which brought together scientists from all over the world and made it possible to create the journal.*

*Personal thanks to Lasha Kandelakishvili and Tamar Zarginava. They are the owners and gold sponsors of "BIOMEDICAL AND MEDICAL SCIENCE". They assisted us in every possible way and initiated not only the publication of Journal of BIOMEDICAL AND MEDICAL SCIENCE, but also helped us to make research in the direction of "COVID-19".*

*A special place in this issue is given to the New Coronavirus problem. This global problem has united scientists in the field of biomedicine and medicine and once again made it clear to the world community how important the work of medics and biomedics is.*

*You can find list of topics, rules for authors on the pages of the journal. The journal is published 2 times a year. You can find electronic versions on http://bmms.ge/en.*

***Best regard, your Maka Mantskava***

# Focus and Scope

We refer, peer-review and publish science articles about original study and clinical trial, theoretical reviews, preview and report of researcher project, preliminary data and the describing of new and the newest hypothesis, essay in next directions.

- All about COVID-19
- Epidemiology methods. Infection Diseases and Non-infection Diseases. Vaccinations
- Prevention of Epidemic. Prevention of Pandemic
- Multidisciplinary Approaches of Modern Science
- Polyprofile Medicine
- Biomedicine, Biorheology and Biotechnology
- Biochemistry and Biophysics in Fundamental and Applied Medicine. Micro- and Nanobiomechanics
- Innovative Methods. Bioinformatics. Biological Models. Mathematical Models, etc.
- Economic and Strategic Aspects of Biomedicine
- Blockchain and programming languages in Medicine. Digital Medicine. Chatbots
- The Role of Biomaterials in Biomedicine
- Theoretical, Clinical and Environmental Toxicology
- Radiology and Radiation Safety
- Nutritionology. Food, Biologically Active Substances, Medicines and Health. Enzyme Research
- Balneology, Wellness and SPA. Physical Education
- Beauty Industry
- Medical Physics. Medical chemistry
- Evidence Medicine. Medical and Biological Statistics
- Health Care and Policy
- Clustering in Biomedicine. Management systems in Biomedicine Areal. Strategic Communication in Biomedicine
- Ethics. Informed Consent. Doctor-Patient Relationship. Strategy and Using Instruments for Conflict Avoidance
- Grant application. Grant Management. Funding Science. Donors. Sponsors
- Mental Health. Defectology. ADD and ADHD
- Pharmacy and Pharmacology
- Reproductive Sciences and Sexual Medicine
- Cell Membranes, Structures and Function. Genome. Mechanisms of Aggregation and Deformation. Genome
- Blood, Blood Flow. Anatomy, Physiology and Pathophysiology of Blood Circulation
- Mechanisms of Thrombus and Stasis Formation
- Theoretical Hemodynamics and Hemorheology
- Clinical Hemorheology

- Rheology of Petroleum Products, Oils, Food and Construction Materials
- Neonatology. Pediatrics
- Gerontology and Geriatrics
- The Brain and its Functioning
  - ◊ Sleep-wakefulness Cycle
  - ◊ Pain and Analgesia
  - ◊ Behavioral and Cognitive Functions
  - ◊ Stress
  - ◊ Experimental and Clinical Neurology
  - ◊ Neurophysiology
  - ◊ Ultra- and Nanoarchitectonics
  - ◊ Alzheimer's Disease
  - ◊ Parkinson's Disease
  - ◊ etc.

- Kinesiology and Biomechanics
  - ◊ Rehabilitation
  - ◊ Sports Medicine
  - ◊ Prosthetics
  - ◊ Occupation Disease
  - ◊ etc.

- Alternative medicine
  - ◊ Chinese medicine
  - ◊ Acupuncture
  - ◊ Chinas Medicine
  - ◊ etc.

- Surgery
  - ◊ Planned Operations
  - ◊ Urgent Operations
  - ◊ Postoperative Shock
  - ◊ Plastic Surgery
  - ◊ Reconstructive Surgery
  - ◊ etc.

- New Approaches and Challenges for the Medical Education System
- Authorization, Certification, Licensing Issues in Health Care Institutions, University
- etc.

DOI 10.51231/2667-9507-2021-001-01-8-16

# Programmatic Management of Tuberculosis during COVID-19 Pandemic in Georgia

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## Abstract

The article reveals the real problems caused by the pandemic associated with the new coronavirus. The problems affected the implementation of the National Tuberculosis Program. It is important for National TB Programs to put all efforts in active case detection, treatment adherence and preventive treatment implementation in response to COVID-19 impact on TB epidemics.

KEY WORDS: diagnosis of tuberculosis, treatment of tuberculosis, prevention of tuberculosis

## Introduction

Georgia has decreased the Tuberculosis (TB) burden by more than 50% over the last 10 years compared to 2009, however TB disease burden still remains high with 2,590 and 2,448 reported cases of TB in 2018 and 2019 respectively, resulting in the notification rates of 69.4 and 65.7 per 100 000. On average, TB incidence in Georgia has been decreasing by approximately 10% per year. In 2019, the proportion of TB cases with rifampicin-resistant or multi-drug resistant TB (RR/MDR-TB) was 12.1% of new cases and 32.1% of previously treated cases. In absolute numbers, among all TB cases (pulmonary or extrapulmonary) notified in 2018 and 2019, the total numbers of laboratory-confirmed

RR/MDR-TB cases were 311 and 319 respectively, with 35% and 27% exhibiting fluoroquinolone drug resistance. Georgia detects 100% of the WHO estimates of RR/MDR-TB, but remains among the high Multi-drug resistant Tuberculosis (MDR-TB) priority countries within the WHO European region [1,2].

Diagnosis, treatment and prevention of tuberculosis is free of charge in Georgia is covered by the state and the Global Fund grant funding. According to the Law of Georgia on State Budget, the amount of funding for the TB State Program is determined annually for the diagnostic and treatment services provided to high risk groups and people confirmed with TB. The state budget covers for the inpatient and outpatient treatment services, active drug safety monitoring (aDSM) activities, and post-treatment follow-up (once every 6 months for 24 months most treatment) funded through the per capita voucher system for the outpatient level and based on the DRG for the inpatient level. 100% of First line anti-TB drugs (FLDs) and 80% of Second Line anti-TB Drugs (SLDs) are also covered by the state budget, with remaining 20% covered by the Global Fund.  TB is not part of the health insurance schemes and the free of charge services are supported through the state TB program funding to the private health care facilities, as the latter represent 99% of the healthcare facilities in Georgia. RR/MDR-TB patients receive monthly incentives for good adherence, partly covered by the state and partly by the Global Fund. Patients also receive DOT related transportation reimbursement and android cell phones for accomplishing the VTS both covered by the Global Fund grant.

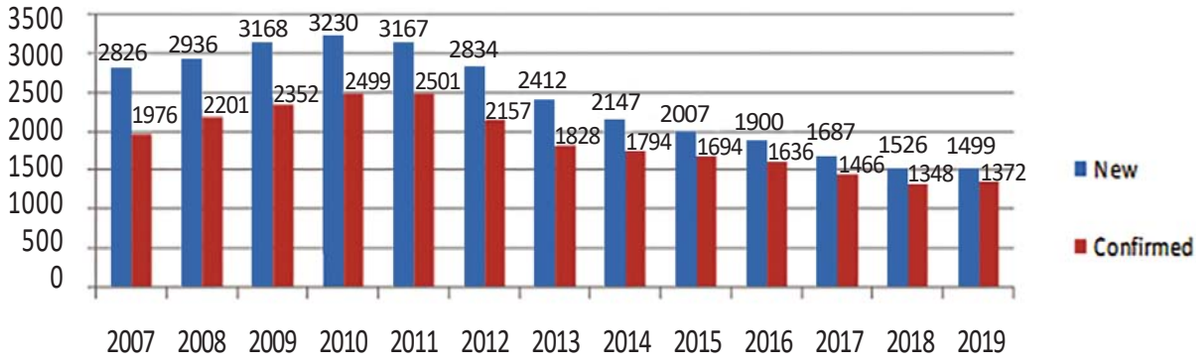
The National Center for Tuberculosis and Lung Diseases (NCTLD), in Tbilisi serves as a TB reference clinic and as a methodological center within National Tuberculosis Program (NTP) of Georgia. The National Reference Mycobacteriology Laboratory (NRL) is a structural part of the NCTLD. The NRL has a capacity to perform the below listed tests with the following turnaround time from sample collection to results submission (Table 1).

The national TB diagnostic algorithm ensures that every person investigated for TB in Georgia is tested using a WHO-recommended rapid molecular test such as GeneXpert and or HAIN LPA. Culture and DST is performed for every person diagnosed with TB. Every RR-TB patient is tested using HAIN MTBDRsl test and phenotypic DST to SLDs listed in the table above. Georgia has increased the proportion of bacteriological confirmation of TB cases over the last 10 years and in 2019 is 92% (picture 1) [3,4].

**Table 1**. The National Reference Mycobacteriology Laboratory capacity

| Test Name | Test turnaround time |
|---|---|
| Ziehl-Neelsen (ZN) staining | 24 hours |
| LED fluorescent microscopy | 24 hours |
| Culture on solid Löwenstein-Jensen (LJ) media | 21- 56 days |
| Culture on liquid media in MGIT (Mycobacteria Growth Indicator Tube) on Bactec 960 system | 5-14 (positive) 42 (negative) days |
| Genotype MTBDRplus Assay, HAIN Lifescience | 2-3 days |
| Genotype MTBDRsl Assay, Hain Lifescience | 2-3 days |
| DST on 1st line drugs (SIRE) on Bactec 960 system | 7-14 days |
| DST to 2nd line drugs: Ofloxacin, Moxifloxacin (2 concentrations), Kanamycin, Capreomycin, Bedaquiline, Levofloxacin, Linezolid, Clofazimine, Amicacin; Delamanid (validation in process) on Bactec 960 system | 7-14 days |
| Xpert MTB/Rif and Xpert MTB/Rif Ultra | Same day |

**Picture 1**. Bacteriological confirmation among pulmonary TB cases in Georgia 2007-2019



Monthly smear microscopy and culture is used to monitor the treatment effectiveness, along with the rapid molecular and phenotypic DST to monitor for drug resistance amplification.

A majority (80%) of RR/MDR-TB patients in Georgia start treatment at the NCTLD hospital. However, s the average length of stay is 29 days, after which patients are discharged to the community where patients receive treatment and monthly monitoring based on the nationally approved protocols. Decision on the treatment initiation, or regimen modification and the model of care is made by the Central DR-TB Clinical Committee (DRC) based on the available national policy.

Georgia is widely using the innovative modes of treatment observation and follow-up such as Video Supported Treatment (VTS) with almost 80% of MDR-TB patients and 30% of drug-susceptible TB (DS-TB) patients receiving the fully oral treatments through this mode at the outpatient level of care. Other option of DOT, such as facility based, home based by a nurse and home based by a family member for pediatric patients also exist and are implemented whenever needed.

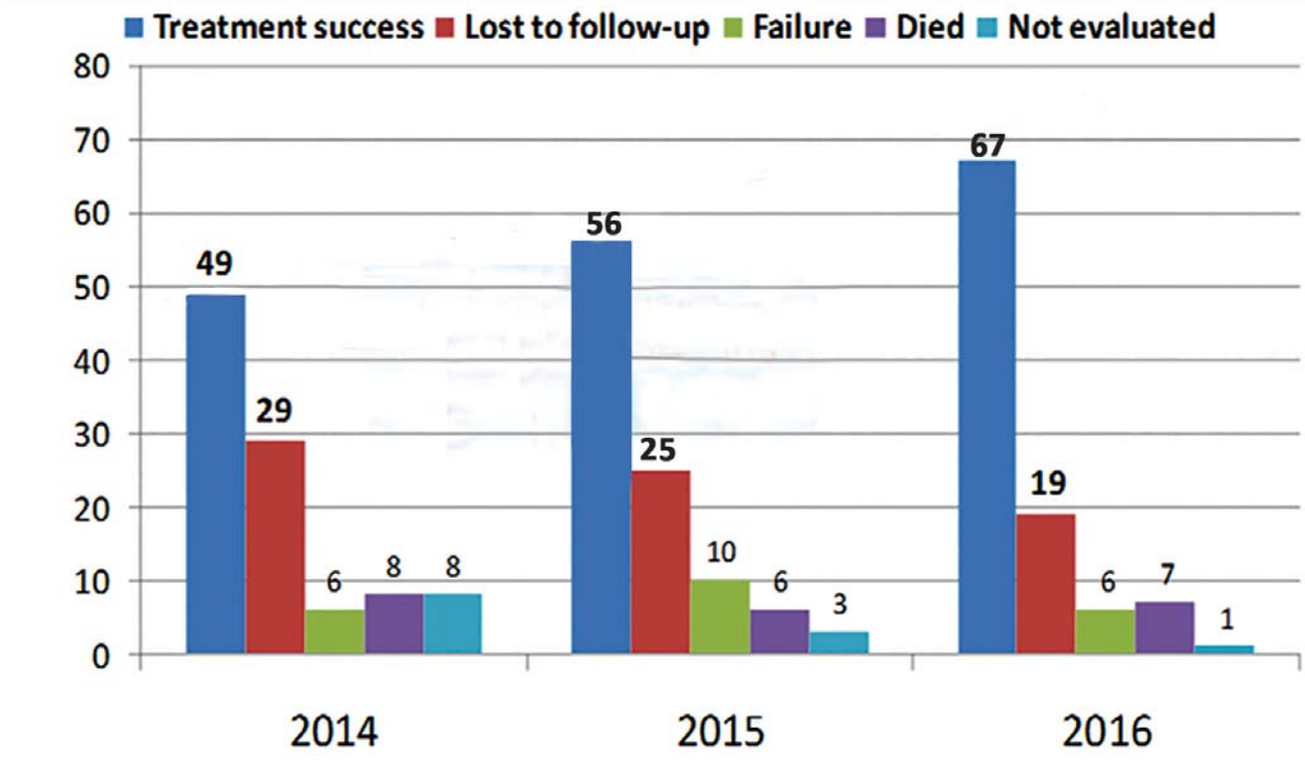
Treatment policy documents are regularly updated by the NCTLD in line with the WHO guidelines and recommendations. Current national TB treatment and management guideline includes chapters and separate protocols on Drug Sensitive (DS) and Drug-resistant (DR) TB diagnosis, treatment, treatment monitoring and follow-up, models of TB care, criteria for hospitalization and discharge, TB and HIV management, TB and HCV management, TB and other co-morbidities management, active drug safety monitoring and management, management of adverse events and drug toxicities, extra-pulmonary TB (EPTB), TB and pregnancy, TB and Surgical management, LTBI diagnosis and TB prevention strategies. The guideline and protocols were endorsed by the Ministry of health in June 2019 and includes WHO recommended fully oral longer regimens and also a mechanism to implement modified shorter treatment regimens with focus on data collection for the OR purposes. The guideline implementation started since June 2019. The major revisions in the guideline that target adults and children include: a) themodified fully oral shorter regimen of 9 months BDQ/Lzd/Lfx/Cfz/Cswith DLM the first drug to substitute in case of toxicity and used in case of children under 6 years of age in RR-TB patients with the same inclusion and exclusion criteria as listed for the WHO mSTR OR, and b) longer 18-20 month regimens for all other patients, e.g. quinolone resistance, extensive TB disease with a backbone of BDQ/Lzd/Lfx/Cfz, with additional drugs based on treatment history and drug resistance patterns.

To ensure adequate guideline implementation the relevant training of the TB program doctors and programmatic staff has been conducted in May-June 2019. In addition to training NCTLD holds a central supervision team, which conducts regular supportive supervision to treatment facilities countrywide and NCTLD in- and out-patient units.

Georgia started programmatic implementation of new and re-purposed TB drugs since early 2015. Since 2016 Georgia implemented the active Drug Safety and Monitoring and Management (aDSM) framework to ensure safe administration of new treatment regimens. All baseline and monthly laboratory and instrumental investigations are covered by the State TB Program funding for all RR/MDR/XDR-TB patients in Georgia. Information on SAEs and AEIs are routinely collected by the NCTLD pharmacovigilance system. The

treatment outcomes of RR-TB patients have improved with the implementation of new drugs and are shown in the picture below (Picture 2).The key driver for the improved treatment outcomes seems to be the better tolerance of new treatment regimens, hence better adherence and less loss to follow-up (LFTU), which was and still is the major challenge for treatment in Georgia. However, the country has progress in decreasing the number of the LTFU patients and hopefully with the implementation of the fully oral longer and mSTR regimens the impact on LFTU will be significant [5].

**Picture 2**. RR/MDR-TB Treatment Outcomes 2014-2016




## Interventions

The anti-COVID-19 interventions started since mid January 2020 in Georgia. By the time when the first case of COVID-19 was detected on February 26th 2020, Georgia was in the phase of active disease surveillance and risk mitigation with: airport and other border screening, closed flight communications with China and Iran, established capacity to transport countrywide samples and conduct PCR testing at the Lugar Center of the National Center for Disease Control and Public Health (NCDC), elaborated recommendations and trained key personnel and operational overarching “COVID-19 Coordination Council”.

In parallel, the National Tuberculosis Program started training of health care workers and other staff by epidemiologists on key infection control and self protection measures, revised the distribution and the utilization rules of existing in stock N95 respirators and initiated the process of developing a TB and COVID-19 co-infection screening and clinical management guide. It is worth mentioning that as fully oral injecting agent free DR-TB treatment regimens have been programmatically implemented since June 2019 in Georgia, the country was already widely using the innovative modes of treatment observation and follow-up such as Video Supported Treatment (VST) with almost 80% of MDR-TB patients and 30% of Drug Sensitive TB (DS-TB) patients receiving the fully oral treatments through this mode. With the glooming COVID-19 pandemic, measures were taken to protect already diagnosed and on treatment TB patients from contracting the COVID-19. Specifically, since March 16, 2020, all patients at the outpatient level are given one month stocks of drugs on hand; the remaining MDR-TB patients were moved to VST, with very few exceptions of six patients to whom a TB nurse was delivering drugs weekly. The drug sensitive patients not on VTS are receiving drugs at home without observation. Every newly diagnosed TB patient is receiving free of charge COVID-19 PCR or antigen based testing.

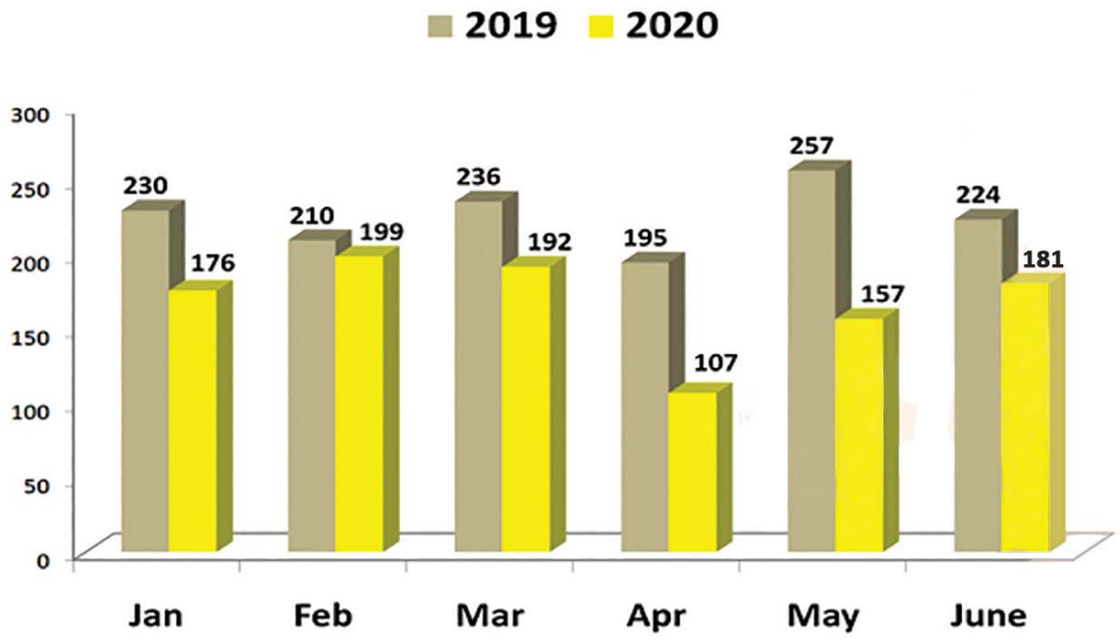
In April 2020 NCTLD in collaboration with the Infectious Diseases, AIDS and Immunology Research Center (IDACIRC) has developed a protocol on management of Tuberculosis and COVID-19 co-infected cases. The protocol has been approved by the Ministry of Health in May 2020 and was the first such protocol in the EU region.

The National Center for TB and Lung Diseases (NCTLD) and its staff has been involved in the different aspects of COVID-19 control since the emergence of the epidemics. Since mid-March to mid-April, the pediatric TB department of the NCTLD which is a separate isolated building within the NCTLD campus was closed and transformed to a quarantine facility. A team of TB doctors and nurses were within NCTLD were transferred from TB activities and assigned to work for the COVID-19 quarantine space. Since mid-April through the end of May the same pediatric TB department was assigned to function as a so called “Fever Center”, where patients with fever were evaluated for COVID-19 as COVID-19 suspect cases. Inpatient DS and DR-TB doctors (8 doctors) were removed from daily TB practice, including the night shifts and allocated to the fever center for the full time work. With decreased referrals to TB clinics, the inpatient wards where the doctors worked were not as busy as usual, thus this temporary shift in functions did not impact much the TB care within the NCTLD. Since September 1st 2020, with increased number of COVID-19 cases in Georgia, the pediatric department was re-profiled to the COVID clinic and is performing this function since then. The 20 bed department is always full of patients, with beds being occupied immediately after a patient is discharged.

# Impact of COVID -19 on tuberculosis in Georgia

Talking about the preliminary trends at the country level in terms of the impact of COVID-19 pandemic on the TB health indicators, it is important to understand the restrictive measures implemented by Georgia. Based on the national TB Data Base, number of TB cases detected during the first six months of 2020 have been decreased by overall 25% in comparison to 2019 (Graph 1). This decrease is unexpected and lies outside the statistically significance range of 10%.

**Graph 1.** TB cases enrolled in the TB program in January-June 2019-2020.



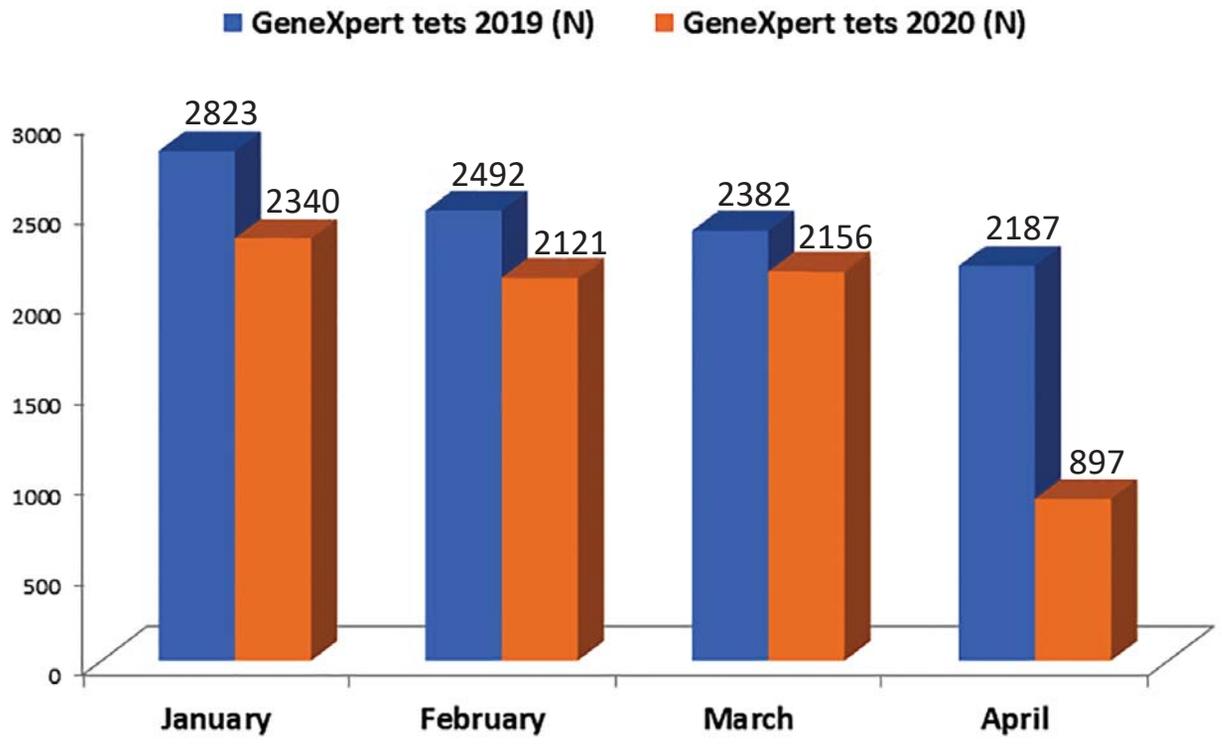

So, the preliminary trend of TB detection indicates that COVID-19 might have impacted greatly and that might have translated into further disease transmission and spread. It is early to explore the impact of the epidemics on the treatment retention and hence the TB treatment outcomes. However, with all the measures the TB program undertook, it should be estimated that the impact on the treatment outcomes will be less dramatic than the impact on the case detection.

The sole TB laboratory capacity and function has not been impacted by the COVID-19 epidemics. Also was not impacted the sample transportation capacity, because the latter is accomplished by the Georgian Postal Service since 2014 and the postal service vehicles transportation was not restricted during the lock down and curfew periods mentioned above. Also, the laboratory personnel were working in shifts covering the need as usual. Georgian government has made a direct communication with Cepheid to ensure the rapid supply of SARS-Cov-2 express cartridges that were planned to be used on the 3 of the

existing GeneXpert machines, one outside TB program in Lugar Center and 2 within TB Program. However, the selection of machines was made in a way that it could not impact the TB program diagnostic needs.

The TB diagnostic algorithm in Georgia implies conducting the GeneXpert MTB/Rif testing for every TB suspect. On average the NTP performs 25,000 Xpert test per year with a plan to increase the number of tests in line with the roll out of extra GeneXpert machines. The analysis of the Xpert testing trends in 2019 and 2020 is shown in graph 2 below:

**Graph 2.** GeneXpert testing in Jan-April 2019-2020 in Georgia




As the graph shows there is on average 14% drop in Xpert tests in Jan-March and extreme 59% drop in April. Not surprising, as the source of the test samples are from the TB suspects visiting the health facilities, but with complete lock down in April persons with mild symptoms would be postponing their visits to health care facilities as the only way to get to the clinic would be either by walking or ambulance. With the ease of the lock down measures it is expected to see increased number of TB suspects tested using GeneXpert for next 6 months until another wave of the restrictions goes in force.

## Conclusion

COVID-19 has proven to be a real challenge for every sector and program, including the National Tuberculosis Program as well. It has also impacted the functionality of the non-governmental and community organizations. However the representatives of the community organizations in Georgia did manage to transform their modus operandi in a way that had allowed them to still deliver their services to at least certain categories of patients. In line with measures taken within NTP in response to COVID-19, many of the TB patients were left without daily in-person interaction with health care workers and peers that could have impacted the treatment adherence and overall psychological well being of the patients.

The decreased case detection of TB due to COVID-19 will have long term negative impact on TB epidemics globally and nationally. WHO estimates, that COVID-19 will decrease the case detection by 50% and that this major disruption will result in additional 400,000 lives lost globally. It is important for National TB Programs to put all efforts in active case detection, treatment adherence and preventive treatment implementation in response to COVID-19 impact on TB epidemics.

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DOI 10.51231/2667-9507-2021-001-01-17-23

# Hepatoprotective Therapy for Disease and Diabetes

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## Abstract

Our work is devoted to the treatment of non-alcoholic fatty liver disease as a complication in patients with complex cardiovascular pathology and type 2 diabetes mellitus. The data of the study of the effect of the drug Hepa-Merz® on the functional state of the liver, endothelium, rheological properties of blood, the state of capillary blood fl ow, markers of endotoxicosis and clinical state in this category of patients are presented. The results obtained confirm the possibility of using the drug Hepa-Merz® for liver functional disorders in patients with cardiovascular diseases and complex type 2 diabetes mellitus.

KEY WORDS: diabetes mellitus, cardiovascular pathology, hepatoprotectors

## Introduction

For many years, diseases of the cardiovascular system have been leading in the ranking of the main causes of mortality in the population. According to experts, one of the important reasons for the discrepancy between the expected effectiveness of modern methods of therapy and real results is the lack of adherence to the principles of optimal therapy when choosing treatment regimens. Optimal drug therapy involves the appointment of a combination of drugs that allows you to achieve the maximum positive result with a minimum risk of side effects and complications. With a desire to achieve this efficacy, it is limited to the appointment of standard treatment regimens without taking into account

the individual characteristics of interaction, metabolism, bioavailability, speed and completeness of neutralization and elimination of drugs. At the same time, it is these factors, especially in conditions of comorbid pathology, that have a decisive influence on both the effectiveness and safety of the prescribed therapy.

The main body that regulates the state of pharmacokinetics and pharmacodynamics of drugs and determines the nature of drug-drug interactions is the liver. In the liver, among other things, the metabolism of almost all major classes of drugs that are included in the standards of treatment of cardiovascular pathology occurs: antiplatelet drugs and anticoagulants, beta-blockers, a significant number of ACE inhibitors and blockers of angiotensin II receptors, calcium channel antagonists.

In different countries, the treatment standards for these diseases differ, but are mostly similar to each other [1,2,3,4].

In turn, the pathogenesis of major diseases of the cardiovascular system is associated with changes in the structural and functional state of the liver. The highest risk of developing liver cirrhosis is in women over 45 years of age with metabolic syndrome, type 2 diabetes, arterial hypertension (AH) and signs of cytolysis syndrome during laboratory tests.

In connection with the foregoing, it is evident that therapeutically the event I in the treatment of coronary heart disease, type 2 diabetes, particularly complicated with hypertension should include correction of the functional state of the liver.

Modern approaches for prevention and treatment include: weight loss, restoration of insulin sensitivity (metformin), correction of lipid metabolism (statins) and the use of hepatoprotectors. If these items in most cases are counted by cardiologists and endocrinologists, district of hepatoprotective choice usually has difficulties.

It should be noted that today there is no generally accepted classification of hepatoprotectors. Several groups of hepatoprotectors are distinguished depending on the chemical structure and origin:

- herbal preparations;
- preparations of animal origin;
- preparations containing essential phospho-lipids (EPL);
- amino acids or their derivatives;
- antioxidant and vitamin-like vitaminsconnections;
- drugs of different groups [5].

Herbal products are most often used in clinical practice [6]. There is an opinion that any drug presented as a hepatoprotector is a priori effective and safe in the prevention and treatment of any disease. At the same time, practice shows that not all drugs of this class have convincing evidence of an improvement in the histological picture of the liver.

The aim of the study was to study the effect of Hepa-Merz® on the functional state of the liver, endothelium, rheological properties of blood, the state of capillary blood flow, markers of endotoxicosis, as well as the clinical state of patients with complex cardiovascular pathology, type 2 diabetes mellitus and chronic heart failure.

## Material and methods

Study design intended to study the dynamics of the liver functional state of the endothelium, blood rheology, condition of capillary blood flow markers of endotoxemia prior to administration Hepa-Merz®, after the first (day pery therapy) and fifth (the fifth day of therapy) infusions. The drug is in a single dose of 10 ml (1 ampoule). 45 patients aged 60-74 years (main age 68.4 ± 4.2 years) with a diagnosis of ischemic heart disease: stable exertional angina ( main group) were examined.

Randomly these patients were divided into two groups: the first group (15 patients) received conventional therapy, the second group (30 patients), according to the study design, standard therapy of full assignment original preperate L-ar – Nitin-L-aspartate the form of infusion at a dose of 10 ml 1 time per day. The examination was carried out one day after the first infusion and at the end of the course of treatment (after five infusions).

Selection into groups was carried out on the basis of anamnesis and clinical, instrumental and laboratory examinations (ECG, EchoCG, blood and urine tests). Clinical examination of patients was carried out in accordance with accepted diagnostic standards. The functional state of the endothelium sc e NIWA by laser Doppler flowmetry (LDF) for dual laser Doppler flowmetry [7].

The aggregation activity of venous blood platelets was studied using a two-channel laser analyzer of platelet aggregation. The level of spontaneous and induced platelet aggregation was assessed.

The rheological properties of blood were investigated using a rotational viscometer at shear rates of 10 $s^{-1}$, 20 $s^{-1}$, 50 $s^{-1}$, 100 $s^{-1}$, 200 $s^{-1}$ with the calculation of the erythrocyte deformability index (IDE) and the erythrocyte aggregation index (IAE).

The state of microcirculation of the bulbar conjunctiva was studied using a Zeiss television slit lamp (Germany). Images were recorded using applied computer programs.

The indicators of the microcirculation system obtained by morphometric analysis were also analyzed. P was calculated vascular conjunctival index, extravascular conjunctival index and intravascular conjunctival index, as well as the general conjunctival index, which is equal to the sum of the scores of all indices.

## Results

According to the results obtained, the first infusion of Hepa-Merz® led to a significant decrease in the level of liver enzymes. And although a pronounced cytolysis syndrome is not typical for cardiovascular pathology and the level of these indicators in the examination group slightly exceeded the standard indicators, the data presented can be regarded as a positive effect of the drug on the functional state of hepatocytes, a decrease in congestion in the biliary tract. Also, against the background of therapy with Hepa-Merz®, the level of fibrinogen, total cholesterol and triglycerides was significantly reduced. See Table 1, which confirms the

high hepatoprotective and anti-inflammatory efficacy of the drug. An increase in the volumetric blood flow rate of the skin at the peak of the creation of reactive hyperemia, which manifests itself from the first infusion and reaches clinically significant values while taking the drug, indicates an improvement in the vasomotor function of the endothelium and confirms the presence of the endothelioprotective effect of the drug Hepa-Merz®. See Table 2.

## Discussion

The indicated changes in the state of hemovascular homeostasis indicators, associated with the restoration of the balance of the molecular components of the plasma, the fluid properties of the membranes of the blood corpuscles and the protective properties of the endothelium, became a prerequisite for an increase in the perfusion blood flow of organs and tissues, assessed by the microcirculation index and capillaroscopy data. The level of microcirculation index before treatment was poor, and after – was better. The improvement of capillary blood flow during therapy with the original L-ornithine-L-aspartate is also evidenced by the results of capillaroscopy of the bulbar conjunctiva and the nail bed, according to which, with the introduction of the drug, there was an increase in the velocity and homogenization of blood flow, a significant decrease in stagnation in the capillaries. The improvement in hemorheological parameters led to a decrease in the intravascular conjunctival index [7,8].

Given that systemic capillary tropical failure is the leading cause of death in patients with severe heart failure observed during therapy with the drug Hepa-Mer® increase in the microcirculation, indicating an increase in the number of erythrocytes, passing per unit time through a unit of fabric, it confirms the possibility of gaining metabolic processes in tissues, not only due to the participation of drug components in metabolic cycles, but also due to an increase in oxygen delivery to ischemic organs and tissues.

As it is known, the main mechanism of cell death in chronic hypoxia and intoxication is apoptosis. It is obvious that improving blood supply while reducing the level of endogenous intoxication and toxic effects of free radicals creates conditions for improving the viability of body tissues, which is manifesting a decrease in the activity of cell apoptosis. During therapy with Hepa-Merz®, a significant decrease in spontaneous and induced apoptosis of mononuclear cells, as well as the apoptosis index, which characterizes the potential cell viability, was observed. It is possible that the latter is evidence of the potential for a positive effect of the drug on the life expectancy of this category of patients [8,9].

This conclusion is supported by the improvement in the clinical condition of the examined patients. The results of this study indicate the advisability of including the drug Hepa-Merz® in the therapy of patients with complex cardiovascular pathology and type 2 diabetes mellitus.

The results obtained confirm the possibility of influence of the preparation Hepa-Merz® on the functional disorders of the liver in patients with complexes c hydrochloric cardiovascular disease and type 2 diabetes.

Taking into account the fact that the clinical effect of Hepa-Merz® begins to manifest itself from the first infusion, patients with cardiovascular pathology can be prescribed a short course of the drug in a daily dose of 10 ml 1 time per day for five days of therapy with further transfer to the granular form original L-ornithine-L-aspartate.

## Conclusion

The following can be considered valuable conclusions of this work. Already the first infusion of Hepa-Merz® leads to a significant decrease in the level of liver enzymes; During therapy with Hepa-Merz®, the level of fibrinogen, CRP, total cholesterol and triglycerides is significantly reduced, which confirms the high hepatoprotective and anti-inflammatory efficacy of the drug; The level of endogenous intoxication with the use of the minimum therapeutic dose of Hepa-Merz® decreases by 12%, which indicates a decrease in tissue hypoxia and an improvement in the functional state of hepatocytes; Against the background of therapy with Hepa-Merz®, a significant decrease in spontaneous and induced apoptosis of mononuclear cells, as well as the apoptosis index, which characterizes the potential viability of cells, up to 30% is observed.

## Note

Our research is purely scientific. The data cannot be interpreted as marketing or post-marketing.

**Table 1.** The level of markers characterizing the functional state of the liver in the examination group during therapy with original L-ornithine-L-aspartate. (*=p<0.05)

| Parameters | Group (n = 30) | | | Group (n = 15) | |
|---|---|---|---|---|---|
| | Before | Day 1 | After 5 days | Before | After 5 days |
| Fibrinogen | 5.1 ± 0.7 | 4.5 ± 0.3 | 3.5 ± 0.2 * | 4.5 ± 0.3 | 4.0 ± 0.3 |
| Total cholesterol | 4.8 ± 0.3 | 4.46 ± 0.30 | 3.92 ± 0.20 * | 4.66 ± 0.30 | 4.44 ± 0.40 |
| Triglyceride | 3.2 ± 0.1 | 2.7 ± 0.2 | 2.2 ± 0.2 * | 3.21 ± 0.30 | 3.2 ± 0.2 |

**Table 2.** The vascular markers in the examination group during therapy with original L-ornithine-L-aspartate. (*=p<0.05)

| Index | Main group | | Comparison group | |
|---|---|---|---|---|
| | Before starting treatment | On the fifth day of therapy | Before starting treatment | On the fifth day of therapy |
| Vascular conjunctival index | 10.53 ± 0.20 | 9.03 ± 0.20 * | 11.03 ± 0.30 | 10.78 ± 0.20 |
| Extravascular conjunctival index | 1.00 ± 0.01 | 1.10 ± 0.01 * | 1.10 ± 0.01 | 1.10 ± 0.01 |
| Intravascular conjunctival index | 3.71 ± 0.10 | 1.71 ± 0.20 * | 3.82 ± 0.10 | 3.79 ± 0.10 |
| General conjunctival index | 15.43 ± 0.50 | 12.27 ± 0.22 * | 15.11 ± 0.50 | 15.21 ± 0.40 |
| Arteriole diameter, μm | 10.04 ± 0.20 | 11.57 ± 0.10 * | 9.7 ± 0.3 | 10.5 ± 0.5 |
| Venule diameter, μm | 29.3 ± 0.4 | 27.6 ± 0.5 * | 29.3 ± 0.4 | 28.9 ± 0.2 |
| Arteriolovenular coefficient | 0.41 ± 0.01 | 0.44 ± 0.01 * | 0.42 ± 0.01 | 0.42 ± 0.01 |
| The number of functioning capillaries in 1 $mm^2$ | 8.0 ± 0.1 | 8.0 ± 0.2 | 8.0 ± 0.1 | 8.0 ± 0.1 |

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DOI 10.51231/2667-9507-2021-001-01-24-28

# Some Aspects of Research on Interpersonal Relationships and Motivations of Healthcare Professionals

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## Abstract

The modern theory and practice of medicine, as well as a number of other edological (helping) disciplines and practices, have been supplemented by a very productive area called "evidence-based medicine". Its occurrence is associated with a large number of bioethical problems, including the problem of the conflict of interests between a doctor and a patient. A conflict of interest is born as a result of conflicting motives of relationships and interactions between the activities of a medical worker. The contradiction of interests and motives of activity is manifested in the phenomena of professional psychological burnout and professional deformations. The article highlights the main motives contributing to the conflict of interest, as well as ways of preventing and correcting conflicts of interest in connection with the implementation of these motives. Among the main motives, one can name the motives associated with the unresolved personal and interpersonal problems of a specialist: his need for power and control, for confirmation and for belonging.

KEY WORDS: motivation, health care, doctor-patient relationship

## Introduction

The problem of healthcare efficiency is one of the most significant problems of modern society. This is a multifaceted problem that unites different aspects. This problem manifested itself especially sharply during the COVID-19 pandemic. But in this work, we will consider the traditional problems that exist. These are the doctor-patient relationship, efficiency, motivation, etc. In modern World a doctor-patient relationship (DPR) is considered as a main issue. It shows us the meaning of our work as a doctor and psychologist. Due to the relationship, psychologist owes a responsibility to the patient to proceed toward the ailment or conclude the relationship successfully. Very important direction is doctor-patient relationship in health care. A lot of medical reviews have covered ways to form a relationship between a psychologist and a patient. But our research is very interesting and our approach gave very high remark in the International meetings [1,2]. Very essential features are important for maintaining a healthy DPR communication, doctor empathy, trust, professional boundaries, informed consent: This is based on the moral and legal arguments of the patient's autonomy (independence in decision making). In relation to trust, the psychologist needs to be honest with the patient and his family to provide a genuine assessment of favorable and unfavorable outcome probabilities, along with the suggested therapy. One of the most important issues related to solving the problems of increasing the productivity of medical care is the issue of motivation for work and career growth of specialists. The problem of the motives of specialists in the field of medicine is relevant. It is very important to prevent and resolve conflicts of interest problems. In the structure of the conflict of interest in medicine and other branches of science, the vital functions of medical personnel in general are important. The appearance of a conflict of interest is due to the fact that a person relies not so much on reality as on a subjective understanding of it. When a conflict of interest arises, people usually inadvertently interpret the circumstances of the situation in such a way that the decision-making emphasizes their competence. This is due to the lack of moral education. Therefore, sometimes they talk not about conflict, but about competition and competing interests. The professionalism of the doctor, his honesty towards himself and the world, sincerity, morality, balance and harmony, etc. – ethical characteristics that control vital activity, as well as the correspondence between the declared and real semantic motives of professional activity. One of the most important issues related to solving the problems of increasing the productivity of medical care is the issue of motivation for work and career growth of specialists. The problem of motives from specialists in the field of medicine is relevant. It is very important to prevent and resolve conflicts of interest. In the structure of the conflict of interest in medicine and other branches of science, the vital functions of medical personnel in general play an important role. The emergence of a conflict of interest is due to the fact that a person relies not so much on reality as on a subjective understanding of it. When a conflict of interest arises, people usually inadvertently interpret the circumstances of the situation in such a way that the decision-making emphasizes their competence. This is due to the lack of moral education. So sometimes they do not speak about the conflict and about the competition and competing interests or motives (competing interests) [3]. The professionalism of the doctor, his honesty towards

himself and the world, sincerity, morality, balance and harmony, etc. – ethical characteristics that control vital activity, as well as the correspondence between the declared and real semantic motives of professional activity. For the first time, the problem of motivation was posed by A. Smith, who believed that people are governed by selfish motives. Today, it is noted that the orientation of employees to achieve health goals is the main task of the management of medical personnel. Due to changes in the health care system (automation and informatization of health care), the management of health care facilities has become more complicated. Ong and de Haes distinguish three different concepts of labor motivation [4].

## Materials and methods

The research was carried out on the basis of the Kursk State University. Several health authorities were included in the study. We investigated the external and internal motivators of the activity of doctors of different ages. We used statistical programs. And also the standard skills of the doctor were investigated by special original questionnaires.

## Results

Part of our results you can see in Table 1.

## Discussion

Based on our research, it turned out that the regulators of motivation and the main motivators were in the following relationship. Motivation regulators are work, environment, remuneration, personally safety. The main motivators are involvement in the process, interest. Details of our research you can see in the table. Some authors show that incentivizing workers is a major problem for most managers. The art of management plays an important role in the effectiveness of the organization. Motivation is an important causal factor in an individual's performance. Lack of coordination between the doctor and the head of the hospital, polyclinic leads to an increase in economic and professional inefficiency. Furthermore, large corporate executives are not interested in the maximum profit of their companies, as it is associated with increased risk. Therefore, to maintain their position, managers choose development options focused on short-term and stable income. Pod the influence of a complex socio-economic conditions of the degree of activity and physician base on the

labor motivation. Complementary trends in the development of incentive systems. On one hand, the need of taking into account the specific social needs of different groups of workers is obvious. However, at critical, extreme, unexpected moments in the functioning of organizations, which provoke non-competitiveness of external and internal assessments, these methods lose their positive qualities. This requires the development of situational complexes, methods that provide efficient operation in unusual circumstances [5,6,7].

## Conclusion

It is important to note that the motivation of activity affects not only the life of the specialist himself, but also those with whom he is connected, with the life of the organization, its partners and patients. That is why the motivation of professional activity and the career of a specialist is one of the key problems of optimizing medical care. Research in this direction is now especially important when the work of doctors in particular is associated with pandemic – the new coronavirus.

**Table 1**. Activities and orientations: activity-semantic motivation for the work of doctors of different ages (experience). YD – counts of young doctors, MD – counts of mature doctors, T – total counts

| Type | YD | MD | T |
|---|---|---|---|
| Transformative activities | 80 | 54 | 67 |
| Communicative activity | 56 | 34 | 45 |
| Utilitarian-pragmatic activity | 68 | 82 | 70 |
| Cooperative activities | 56 | 64 | 60 |
| Competitive activity | 48 | 54 | 52 |
| Achievement activities | 62 | 42 | 52 |
| Procedural orientation | 72 | 68 | 66 |
| Resulting orientation | 28 | 32 | 34 |

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DOI 10.51231/2667-9507-2021-001-01-29-35

# Investigation of Microcirculatory in Resistive Arteries

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## Abstract

The article shows the physiological significance of resistive arteries in relation to blood flow. The article describes a new non-invasive method for assessing the functional state of resistive arteries, which indicates the resistance of resistive arteries. Microcirculation coefficient – resistance of resistive arteries is an easy-to-use diagnostic method for assessing circulatory problems. The article shows new normative indicators of the microcirculation index in young healthy men. And also shows the rheological indicators for the same group.

KEY WORDS: resistance index, resistive arteries, rheological properties

## Introduction

The cardiovascular system consists of the heart and blood vessels – arteries, arterioles, capillaries, venules and veins, arterio-venous anastomoses. Its transport function lies in the fact that the heart ensures the movement of blood along a closed circuit of blood vessels. From the point of view of biomechanics, vessels are elastic tubes of various diameters. Distribution of total blood volume: 84% – in the systemic circulation, 9% – in the lesser circulation, 7% – in the heart [1]. In terms of elasticity, arteries are of the Elastic type. This is the aorta, the pulmonary artery; Muscular-elastic type – these are sleepy, subclavian, vertebral arteria; muscle type – these are the arteries of the limbs, trunk, internal organs. Veins are of the Fibrous type. They are muscleless. Veins of the hard and soft meninges (without valves); retina of the eye; bones, spleen, placenta. Veins are of the Muscular type: with muscle elements. These are the superior

vena cava and its branches, veins of the face and neck; Veins are with an average development of muscle elements. These are the veins of the upper extremities. Veins are highly developed with strong muscle development. This is the inferior vena cava and its branches and veins of the lower extremities. The structure of arteries and veins is as follows: intima is the inner shell, media is the middle, and adventitia is the outer. All blood vessels are paneled from the inside with a layer of endothelium. All vessels have elastic, collagen and smooth muscle fibers. Their number in different vessels is different. They are not in true capillaries. Depending on the function performed, the following groups of vessels are distinguished: 1. Amortizing vessels – aorta, pulmonary artery. The high content of elastic fibers in these vessels causes a shock-absorbing effect, which comprises smoothing out of periodic systolic waves. 2. Resistive vessels – terminal arterioles (precapillaries) and, to a lesser extent, capillaries and venules. They have a small lumen and thick walls with developed smooth muscles, and offer the greatest resistance to blood flow. 3. Vessels-sphincters – terminal sections of precapillary arteriol. The number of functioning capillaries, that is, the area of the exchange surface, depends on the narrowing or expansion of the sphincters. 4. Exchange vessels – capillaries. The processes of diffusion and filtration take place in them. Capillaries are incapable of contractions, their diameter changes passively following pressure fluctuations in pre – and post-capillary resistive vessels and sphincter vessels. 5. Capacitive vessels are mainly veins. Due to their high elongation, veins are able to accommodate or eject large volumes of blood without significant changes in blood flow parameters, and therefore they play the role of a blood depot. 6. Bypass vessels – arterio-venous anastomoses. When these vessels are open, blood flow through the capillaries either decreases or stops completely [1,2,3]. We, as specialists in the study of hemodynamics and blood rheology, showed particular interest in the incomplete functional signs of resistive arteries that have been investigated. From the point of view of hemodynamics, blood circulation taps, which regulate the adequacy of blood circulation and ensure the required blood flow. Hemodynamic bases. The flow of blood through the vessels. The driving force of blood flow is the pressure difference between different parts of the vascular bed. Blood flows from a high-pressure area to a low-pressure area, from the high-pressure arterial section to the low-pressure venous section. This pressure gradient overcomes the hydrodynamic resistance due to internal friction between the liquid layers and between the liquid and the vessel walls, which depends on the size of the vessel and the viscosity of the blood. The flow of blood through any part of the vascular system can be described by the formula for the volumetric blood flow velocity. Volumetric blood flow velocity is the volume of blood flowing through the cross-section of a vessel per unit time (ml/s). Volumetric blood flow velocity Q reflects the blood supply to a particular organ. $Q= (P_2 – P_1)/R$, where Q is the volumetric blood flow velocity, $(P_2 – P_1)$ is the pressure difference at the ends of the vascular system, R is the hydrodynamic resistance. The volumetric blood flow velocity can be calculated based on the linear blood flow velocity through the cross-section of the vessel and the area of this section $Q = V \times S$, where V is the linear velocity of blood flow through the cross-section of the vessel, S is the cross-sectional area of the vessel. In accordance with the law of flow continuity, the volumetric blood flow velocity in a system of tubes of various diameters is constant regardless of the cross section of the tube. If a liquid flow

through the tubes at a constant volumetric velocity, then the speed of movement of the liquid in each tube is inversely proportional to its cross-sectional area: $Q=V_1 \times S_1 = V_2 \times S_2$. The viscosity of blood is a property of a liquid, due to which internal forces arise in it that affect its flow. If the flowing liquid comes into contact with a stationary surface (for example, when moving in a tube), then the layers of liquid move at different speeds. As a result, a shear stress arises between these layers: the faster layer tends to stretch in the longitudinal direction, while the slower one retards it. Blood viscosity is determined by blood cells and plasma proteins. Under physiological conditions, a laminar blood flow is observed in almost all parts of the circulatory system. The liquid moves as if in cylindrical layers, and all its particles move only parallel to the axis of the vessel. Separate layers of liquid move relative to each other, and the layer immediately adjacent to the wall of the vessel remains motionless, the second layer slides along this layer, and the third layer over it, and so on. The result is a parabolic profile of the velocity distribution with a maximum in the center of the vessel. The smaller the diameter of the vessel, the closer the central layers of the liquid are to its stationary wall and the more they are inhibited as a result of viscous interaction with this wall. Due to the mean blood flow velocity is lower in small vessels. In large vessels, the central layers are located farther from the walls, therefore, as they approach the longitudinal axis of the vessel, these layers slide relative to each other with increasing speed. As a result, the average blood flow velocity increases significantly [2]. Under certain conditions, the laminar flow turns into a turbulent one, which is characterized by the presence of vortices, in which fluid particles move not only parallel to the vessel axis, but also perpendicular to it. In turbulent flow, the volumetric blood flow velocity is proportional to the square root of the pressure gradient. There are legalized principles of ultrasound examination. When studying them, the following are assessed: vessel permeability, vessel geometry, wall pulsations, vessel diameter; thickness, structure, uniformity of the wall; vessel lumen state.

Quantitative parameters are very important for clinical practice:

- peak systolic blood flow velocity (S);
- end diastolic blood flow velocity (D);
- time-averaged maximum blood flow velocity (TAMX);
- time-averaged mean blood flow velocity (Fmean, TAV);
- peripheral resistance index, or resistivity index, or Pource-lot index (RI). RI=S–D/S;
- pulsation index, or index, or Gosling index (PI). PI=S–D/Fmean;
- spectral expansion index (SBI). SBI=S–Fmean/S x 100%;
- systolic-diastolic ratio (SD).

The spectrogram is characterized by many quantitative indicators, however, most researchers prefer the analysis of the Doppler spectrum based on not absolute, but relative indices [2]. Described by us, above is the features of the study of hemodynamics in the arterial network. Features of hemodynamics in the veins are as follows. Fluctuations in the velocity of blood flow in the great veins are associated with breathing and cardiac contractions. These fluctuations increase as you approach the right atrium. Fluctuations in pressure and volume in veins located near the heart (venous pulse) are recorded by non-invasive methods (using a pressure transducer) [1,4,5,6]. Compression of the vein

lumen by the sensor leads to complete compression of the lumen. In the case of partial or complete thrombosis, the lumen of the vein is not completely compressed by the sensor or not compressed at all. In the study of the venous system, in contrast to the arterial, fewer parameters are assessed. In our early works, we paid special attention to the intimate media layer for the evaluation of blood in general. All the methods described are especially laborious, requiring special additional qualifications and experience from the meeting. For these methods, sophisticated equipment, specialized clinics and offices are required. The methods are financially expensive. But not only had these questions prompted us to develop a particularly interesting method for evaluating blood circulation. This is a method for studying the functional state of resistive arteries. In our early work, we paid particular attention to the intimate media layer for blood flow assessment [7]. But this is a very painstaking process. At the moment, all methods are laborious, requiring special additional qualifications and experience from the doctor. These methods require sophisticated equipment, specialized clinics and offices. The methods are financially expensive. These and other questions prompted us to develop a new method for assessing blood circulation. This method is based on the study of the functional state of resistive arteries, determines the coefficient of microcirculation. This article is methodological, overview and includes experimental data. The article presents a new method for studying the functional states of resistive arteries in order to diagnose somatic health in young men.

## Methods

The study included 53 healthy young people aged 22.4 ± 5.4 years. By means of special questionnaires, according to the analysis of the general blood picture (HumanCount, Germany), as well as by measuring the total arterial pressure (“Pulse” manometer, Russia), the condition of all volunteers was assessed, which corresponded to the definition of somatic health (“practically healthy”). The apparatus was used to study the functional state of resistive arteries at the site of pulsation using a standard test, measuring the coefficient of resistance of resistive arteries.

The coefficient of resistance of resistive arteries was denoted by the letter M, was calculated by the formula $M=(V_{pix} / V_{phon}) \times 100\%$, where $V_{pix}$ is the volumetric blood flow velocity at the site of pulsation on the wrist after a standard ischemia with a duration of 1 min; $V_{phon}$ is the rate of volumetric background blood flow at the site of pulsation on the wrist without exposure. The coefficient of resistance of resistive arteries was measured as a percentage [7]. The measurement was based on a comparison of the blood flow velocity in postischemic (reactive) hyperemia resulting from a standard 60 cessation of local blood flow with the background blood flow at the site of pulsation at the wrist. Standardized ischemia was induced by compression of the brachial artery, the blood flow curve was analyzed using a texture analysis apparatus (TAS-plus, Germany). Following the Helsinki convection about scientific research, the participants were informed about the inclusion of the depersonalized method in the study, an informed

consent was drawn up, which was signed by all volunteers included in the study addition to measuring the functional state of resistive arteries, we investigated the intravascular state of the blood, which forms the flow laminarity, or its turbulence [8]. Specifically, we measured the rate of erythrocyte aggregation [9], the rate of erythrocyte deformability in [10], plasma viscosity according to existing certified techniques [11].

## Results

When solving this problem, we studied a group of actually healthy young people. We examined all members of the group, the resistance of resistive arteries, the index of erythrocyte aggregation [EAI], the index of erythrocyte deformability [EDI], plasma viscosity. This comprehensive study enables us to study the vascular and extravascular factors that shape microcirculation and blood flow. The statistically processed data showed that EAI, EDI and blood viscosity in the group of young people corresponded to the existing control (normative) values. See table 1. Also, a homogeneous series of values of the functional value of resistive arteries was obtained, i.e. the resistance coefficient series did not have extrema and the scatter of values was minimal. This gave us the opportunity to conclude that the study of the functional state of the arteries is a diagnostic tool. To check the validation of our new method, we examined patients with hemodynamic disorders with arterial obstruction syndrome: patients with stenosis (n = 8) and patients with occlusion (n = 9). All patients were examined for resistance of resistive arteries. 1. Syndrome in violation of arterial patency of varying degrees: patients with stenosis (n = 5) and patients with occlusions (n = 5); 2. Syndrome of arteriovenous shunting (n = 6); 3. Syndrome of arterial vasodilation (n = 5).

## Discussion

According to the literature, a decrease in the linear blood flow velocity can be recorded up to the deformation zone, and the peripheral resistance indices can be increased. In the deformation zone, there is an increase in the blood flow velocity, more often during bends, or multidirectional turbulent flow – in the case of loops. Behind the deformation zone, the blood flow velocity increases, the peripheral resistance indices decrease. Since deformities develop for a long time, adequate collateral compensation develops.

As a result, the resistance measured by our method turned out to be adequate, the one that was investigated by complex technological methods.

It occurs in the presence of arteriovenous fistulas, malformations. Changes in blood flow are noted in the arterial and venous bed. In the arteries proximal to the shunting site, an increase in the linear blood flow velocity, both systolic and diastolic, is recorded, the

peripheral resistance indices are reduced. A turbulent flow is observed at the shunting site, its value depends on the shunt size, the diameter of the adducting and draining vessels. In the draining vein, the blood flow velocity is increased, often noted “arterialization” of venous blood flow, manifested by a “pulsating” Doppler curve. Having determined the resistance of resistive arteries in these patients with a new method, we obtained the same results.

This leads to a decrease in peripheral resistance indices and an increase in blood flow velocity in systole and diastole. It develops in systemic and local hypotension, hyper perfusion syndrome, “centralization” of blood circulation (shock and terminal states). In contrast to arteriovenous shunting syndrome, arterial vasodilation syndrome does not cause characteristic disorders of venous hemodynamics [1, 2]. Research by our method showed similar results.

Thus, within the framework of the grant, the results obtained can be interpreted as confirmation of a new diagnostic method with the aim of introducing and expanding this method into clinical medicine. Knowledge of the structure of the walls of blood vessels, their functions, the characteristics of hemodynamics in the arteries and veins is necessary for the successful prevention of hemodynamic disorders and proper treatment. Work in this direction is very timely, since the latest approaches in biomedicine include minimizing financial costs, patient safety and reducing the risk of errors on the part of the doctor. A new method for assessing the resistance of resistive arteries by examining the functional state of resistive arteries is safe, easy to implement and does not require large expenses against the background of high information content.

**Table 1**. Rheological properties in young men group. M – arithmetic mean of a row; m – arithmetic mean deviation from the mean of row. Row consists of 53 healthy young men

| Parameters | M | m |
|---|---|---|
| **EAI** | 23.5 | 0.2 |
| **EDI** | 2.0 | 0.02 |
| **Plasma viscosity** | 1.2 | 0.015 |

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DOI 10.51231/2667-9507-2021-001-01-36-40

# From Full-Time Traditional Education to a Distant Form Due the Pandemic Caused by COVID-19

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## Abstract

The article presents data on the prerequisites of different countries on the issue of distance education. In the article the percentage valuation of the distance form of education in relation to the full-time traditional form was shown before the pandemic caused by the new coronavirus and after. In connection with the COVID-19 pandemic, a change in these proportions occurred due to an increase in the partial part of distance learning against the background of a suspended full-time traditional education. In a number of countries, distance learning has become the only one, absorbing all other educational approaches and systems. This provided the education system with special significance and attention from state structures and the government. The relevance of the work is caused by the fundamental nature of the issue of education, as such in general and specifically now, in a pandemic situation. Against the background of WHO recommendations on universal social distance and strict restrictions on mass events, which are an integral part of full-time traditional education, the urgency of the emergency transition from full-time traditional education to distance learning is especially great. The relevance of the issue is increasing due to the uncertainty caused by the expectation of the second wave of coronavirus, which is expected in October and coincides with the beginning of the first semester of the 2020/2021 academic year.

KEY WORDS: distance education, full-time traditional education, emergency transition, pandemic, COVID-19, student's sympathies, scientific skills

## Introduction

The purpose of the article is to compare the effectiveness of traditional full-time education in a normal academic situation and distance learning in an emergency forced transition caused by the COVID-19 pandemic by comparing students' perceptions of basic subjects and the scientific component. Online and distance learning has steadily grown in popularity. We focused comparing online versus traditional education side-by-side comparison on key areas. Model "blended learning" is very interesting. Flexibility is one of the key components to consider when weighing the options is the amount of time. Self-discipline is very important direction, we should thing about this, when we talk about inline education. Both traditional and online education certainly require some discipline to succeed, but there can be significant differences in how learning is structured. Self-motivation is veri important factor too. In these directions traditional education has an advantage in the eyes of many. The structured schedule of attending class a handful of times per week and having routine face-to-face interactions with instructors can help keep students on task. Students in traditional, on-campus settings have more opportunities to be reminded of upcoming assignments, which can help if you tend to procrastinate on large, time-consuming assignments. Social interaction is a big plus for educations. In this direction, traditional education has a great advantage. Our experiments will show which teaching methods are more effective.

## Material and Methods

We used the original methodology. The study was a two-time survey of students of different universities of the same profile. The study included full-time students of the faculties of traditional education (in retrospect, the fall semester of the 2019/2020 academic years) and students of the same universities that studied remotely (spring semester of the 2019/2020 academic years). The significance of the experiment is determined by the fact that within the framework of the study it became possible to study the students' attitude to a particular academic subject, to a teaching during different forms of training. Moreover, the subjects and personality of the teacher in the research did not change, which makes it possible to reduce artifacts and show comparative features of only forms of learning. Perceptions were studied in relation to the basic subject and to the subject "Scientific Skills".

Detail of methods. In order to determine the effectiveness of traditional full-time education in a regular educational situation and in distance learning (with the COVID-19 pandemic), we conducted research in two directions. Students from three different universities were included in the research. All students were informed by the teacher before the start of the study and informed consent was obtained to participate in the study [1,2]. The study consisted of a double survey of students. All students included in the study were over 18 years of age (second year students who did not change institution and group during the previous semester). It should be noted that the teacher and stu-

dents did not know each other before the study, and also, the subject for students was new (students did not take this subject in previous courses and semesters). The survey of students was carried out twice in the 2nd and 7th weeks of study. The research was carried out in a blind manner. Each student in the second week of meeting the teacher and the subject answered the question: – How much and why do you like the subject and the teacher? (in the case of qualitative questions, it was necessary to choose only one correct answer; in the case of verbal answers, one answer did not exclude the other, but the maximum number of answers should not exceed two). In this paper, this study is retrospective and at the same time makes it possible to carry out new targeted studies in the field of comparing distance education with full-time education. Studies with a similar design were carried out in a distance learning setting, also in the 2nd and 7th week. The questionnaire for distance learning students was fully consistent with the questionnaire for full-time traditional students.

## Results

The main results are that the fact of assessing sympathy for the subject and for the teacher in traditional and distance education showed that at the 7th week of study there was complete agreement with respect to the basic subject and the subject “Scientific Skills”. This was preceded by the difference in the perception of the subject in the second week in the basic subject during the survey in the context of traditional full-time education compared to distance learning, an even greater difference was recorded in the assessment of the scientific component (subject “Scientific Skills”). As for the justification of sympathies, regardless of the type of syllabus, the teacher was awarded a uniform assessment in traditional full-time and distance education. On the 7th week, regardless of the type of syllabus, the teacher was awarded a uniform perception by the students. On the 7th week, when assessing the scientific component (“Scientific Skills”), there was an absolute synchronization between traditional full-time and distance learning. In the second week of full-time distance learning, the perceptions of students differed from the perceptions of students in traditional full-time studies. The article demonstrates the basic technologies of distance education, identifies the main problems, the risks of effective learning, especially when teaching the subject “Scientific Skills”. The article explores relevant approaches. In conclusion, it is concluded that with remote and full-time traditional forms of education, the student’s sympathy for a particular subject, as well as for the teacher, turned out to be the same.

## Discussion

In recent decades, Europe has been actively working on legislative and administrative projects in the field of recognition of distance education. In this direction, Georgia began to actively cooperate with European countries from the beginning of 2005. There was constant work in this direction, but the pace and aspiration of the teaching staff and departments, heads of education policy was not sufficient. And the implementation of distance learning into practice in universities did not work out [3]. The percentage dispersion of distance education in relation to the full-time traditional system is 20% to 80% at the beginning of 2020 [4]. In connection with the COVID-19 pandemic, these proportions changed due to an increase in the partial part of distance learning against the background of suspended full-time traditional education against the background of the COVID-19 pandemic. On March 11, 2020, the spread of the virus took on hyperbolic proportions, in 90% of the countries of the world there were cases of infection of the population with the COVID-19 virus and WHO in an official statement announced a pandemic [5]. During the pandemic, the main strategy of all developed states and Georgia was preventive measures: self-isolation and social distancing. In the scientific pedagogical literature, ambiguous approaches have appeared in relation to the transition to distance education. Some experts referred to a decrease in quality during a forced transition from one form to another, other authors considered this process illegal [6,7,8]. Statistical financial reports have shown that declaring an academic year academic will have a negative impact on education funding and quality of instruction. However, the implementation of full-time traditional education through personal contacts of pairs “student-teacher” during the quarantine period became impossible. Our research was very important during pandemic period.A total of 182 students were interviewed. Of these, 100 students studied subjects traditionally full-time, 82 students were interviewed during the pandemic in the context of distance learning. All students included in the research studied at three different universities with a single profile. Their teacher of basic subject and also tuter of research work was the same person. The research work involved the study of the subject “Science”, familiarization with the methodology and the implementation of a real experiment.

## Conclusion

In conclusion, it is concluded that with remote and full-time traditional forms of education, the student’s sympathy for a particular subject, as well as for the teacher, turned out to be the same. The author notes that the subject “Scientific Skills”, which is actually a scientific component, was not sufficiently perceived during distance learning. The significance of the direction has long been obvious, but this direction has gained particular relevance in connection with the current situation caused by the spread of COVID-19. The significance of the experience of the emergency transition of full-time traditional education to distance

education is obvious. Modifying, developing and developing the tactics of distance learning through the involvement of international research will make it possible to improve quality and financial issue of Hight Education Institutions.

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DOI 10.51231/2667-9507-2021-001-01-41-44

# Relevance Method to Structure of Orthosis

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## Abstract

There are many problems when treatment is needed. Such diseases occur in young and old people. The orthosis and their development have lot of problems. One way to solve this problem is to define and apply standard rules and procedures throughout the development process. We show in this work is to develop a methodology to structure the orthosis design process. A case study was used to validate the proposed methodology. It was applied to the development of an orthosis to treat a camptocormia – bent spine syndrome. This disorder is characterized by the anteroflexion of the trunk and especially affects elderly people and young non-health people with difference disease.

KEY WORDS: orthopedic devices, development of orthosis, structure of orthosis

## Introduction

The design of orthopedic devices, or orthoses, may include particular requirements and design specifications, mainly related to the patients' varying characteristics, such as morphological changes or treatment evolution. The reason is that the orthosis is in permanent direct contact with the patient's body and consequently should be adaptable and comfortable. There are no strict rules and stages that should be respected during the development process [1,2]. Consequently, orthosis development depends adapted to the user needs [3,4]. One of the current challenges in the field of orthoses is to develop a device to treat

camptocormia [5, 6]. Also known as bent spine syndrome, this pathology is characterized by the anteroflexion of the trunk in populations. Camptocormia precludes the patients from having a normal daily life since the curved posture causes contraction of the diaphragm (fatigue problems) [5], reduces walking gait, results in a lack of social visual contact, etc. The purpose of this study was to develop a design methodology devoted specifically, to the orthosis and its application during the development of a brace to treat camptocormia.

## Materials and Methods

We have used new breakdown of the design process [7,8] as a base (task clarification, conceptual design, embodiment design, and detailed design), it was possible to develop a new design methodology for the development of the orthosis. The first stage of the proposed methodology corresponds to task clarification, which may include the definition of the orthosis stakeholder,

the orthosis typology, and the orthosis life situations. Orthosis development should play mean roal is biomedical area. There are two main actors with respect to the medical domain, the doctor and the orthoprosthesist. The doctor is responsible for the diagnosis and the medical design specifications of the orthosis. The proposed methodology is composed of six stages: mechanism research; concept, displacement, and dimensional constraints; comfort adaptations; blocking definition; orthosis definition; and orthosis design qualification. These stage [7], have been revised and supplemented. These stage [7], have been revised and supplemented. the methodology proposed considers a superposition of stages for a more dynamic design process.

## Results

The methodology was then applied to the development of a brace to treat a postural pathology named camptocormia. Also known as bent spine syndrome, it is characterized by the progressive anteroflexion of the trunk during walking and in the standing position [8-16]. Contrary to other postural disorders, camptocormia is reversible, which means that the postural flexion is not permanent and same time patients are able to redress their posture [12-16]. But etiologies of camptocormia are not completely understood [12-16]. Yet, as the camptocormia is a multicasual postural disease, these causalities should were considered during the orthosis design process [12-16]. The specifications is very good, if witch correspond to the starting point of the methodology. Even if presently the etiologies of camptocormia are not completely understood by the medical community, and still exists several questions without answers, the treatment combining physiotherapy sessions with a brace has presented satisfying results [12-16]. Yet, as the camptocormia is a multicasual postural disease, these

causalities were considered during the orthosis design process. From the stakeholders' definition, the design team in accordance with the medical domain establishes the orthosis specification. These specifications correspond to the starting point of the methodology. The following stage, blocking definition, defines the mechanism blocking system which locks the orthosis in the prescribed treatment position (trunk redressed). As at the anterior stage, the technical solution depends on the possibilities available to the enterprise. In this case, in accordance with the enterprise's blocking system database, the choice rests with an obstacle blocking system. The next stage, orthosis definition, is based on the architectural design stage, which means assembling all the components of the orthosis. This stage is developed in strict contact with the user's domain since, depending on the geometry of the supports (a custom-made orthosis), the positioning of the mechanism may change. During this stage, numerical and experimental analyses are performed in order to evaluate the mechanical behavior of the orthosis. The last stage, orthosis design qualification, corresponds to an evaluation of the orthosis by the user (user's domain). As previously described, during this stage, several questions were put to the user in order to evaluate the different components of the orthosis, for example, the supports, the mechanism, the blocking system, comfort, and ergonomics. The results of these inquiries not only enabled the designer first to make any necessary improvements but also to personalize the orthosis according to the patient's needs.

## Conclusions

The development of medical devices is a demanding task, especially with respect to orthoses because of the way in which they are classified. In some cases, this results in deficient products that do not meet the patient's needs. The primary aim of the present work was to develop an orthosis design methodology based on dividing up life situations and integrating the design constraints in different knowledge domains. This methodology was then applied to the development of a new orthosis, a brace to treat camptocormia. Although several concepts emerged, in this study, only a representative group of specifications were considered, and for this reason, only one concept has been presented. The selected concept meets the main device specifications in terms of straightening the patient's posture. This straightening was possible through the link chain proposed during the conceptual design stages and allows a vertical displacement of the chest.

Concerning comfort, two aspects were considered. The first was the use of a neoprene layer between the rigid part of the supports and the body, and the second was the fact that with the proposed concept it is possible to tighten the supports to the body and consequently adjust the orthosis to the patient's morphology. The blocking system of the proposed concept was specially taken into account in terms of ergonomics. Since the developed orthosis will be manipulated by elderly people and in some cases by patients with Parkinson's disease, the fact that their fine motor skills are often reduced must be considered.

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DOI 10.51231/2667-9507-2021-001-01-45-50

# Details of Laboratory Work for Medical Students

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## Abstract

In the modern world of pandemics, a special place is occupied by the problems of education in the field of medicine. In developed countries, medical education remains combined. Practical training of students in the laboratories of the university is very important. The article describes a biochemistry laboratory class protocol.

This protocol is described in order to create an opportunity for students to apply by doing the theoretical concepts underlying biomolecules and vesicles properties, together with the principles of centrifugation and colorimetric methodologies. The aims, objectives, methodology of teaching/learning, and assessment for this laboratory class are indicated. The proposed protocol for a laboratory class described us creates the opportunity for undergraduate students to perform experiments, to reason, and to discuss some related biochemical concepts, namely protein characterization and properties of specific staining reactions; enzyme quantification by enzymatic reaction; composition and biochemical properties of exovesicles; amphiphilic biomolecules properties; and principles and applications of centrifugation methods. This work was supported by Portuguese Ministry of Science and Higher Education (MCES).

KEY WORDS: medical teaching, medical learning, laboratory task

## Introduction

Membrane cell exovesiculation is a physiological process that occurs in several situations, including apoptosis, erythrocyte aging, and storage of blood samples [1]. Different types of endogenous cellular membrane stimulus promote exovesiculation [2,3,4]. It was verified in vitro that changes in either pH or ATP, as well as the presence in incubation medium of amphiphilic compounds, induce the release of exovesicles from erythrocytes [5,6,7]. In these experimental conditions, the presence of the enzyme acetylcholinesterase (AChE) 11 is considered as a marker for the exovesiculation process [8,9].

We have proposed a method to simultaneously induce the release of the erythrocyte exovesicles, enriched in AChE and cholesterol, and label them with the fluorescent membrane probes used to induce the vesiculation: 1,6-diphenyl-1,3,5-hexatriene (DPH), 1-(4-(trimethylamino)-phenyl)-6-phenyl-1,3,5-hexatriene (TMA-DPH), or 4-heptadecyl-7-hydroxycoumarin (C17-HC) [9]. The exovesicles obtained by this method are not visible in the buffer suspensions. In the present work, we found that it is possible to visualize the exovesicle aggregates without an expensive apparatus, by the coloration of either: a) the exovesicle membrane proteins, using Coomassie blue [10]; b) the specific presence of AChE, using an adaptation of the Ellman's reagent enzyme assay [11]; or c) the phospholipids content, by phospholipase D digestion followed by phosphatidic acid coloration [12]. The importance of these coloration processes is strengthened by the fact that the most valuable method to physically evaluate the presence of the exovesicles (together with their size and shape) is light scattering spectroscopy [9], which requires an equipment not readily available in most of institutions.

The aim of the present work is to describe a biochemistry laboratory class protocol to visualize erythrocyte exovesicles, by colorimetric assays focused on their different components, based on the principles and application of centrifugation and colorimetric methods especially appropriate for undergraduate students. This is an original method that complements our recent research works [9]. Working in an innovative area of research proves stimulating for the students and encourages them to develop new solutions for practical problems.

Good teacher training is essential for quality student learning. The teacher must know all the nuances of laboratory research. For this the teacher (instuction) should have special preparation.

Previous experimental preparation. Reagents.

The fluorescent probes DPH, TMA-DPH, and C17-HC were purchased from Molecular Probes (Eugene, OR). Acetylthiocholine iodide (ASCh), 5,5-dithio-bis (2-nitrobenzoic acid) (DTNB, Ellman's reagent), 2,4-diaminophenol, and tetrahydrofuran were obtained from Sigma-Aldrich (St. Louis, MO). Coomassie brilliant blue R 250, dibutyl phtalate, dimethyl phtalate, acetone, N,N-dimethylformamide, ammonium molybdate, sodium disulfite, $NaH_2PO_4$, and $Na_2HPO_4$ were obtained from Merck (Darmstadt, Germany). The enzyme mixture used for the phospholipid's identification (phospholipase D 400 U/liter, choline oxidase 2,200 U/liter, peroxidase 3,600 U/liter, 4-aminophenazone 0.24 mM, and diclorophenol 2.1 mM, in Tris-buffer, pH 7.6, 50 mM) was obtained from Spinreact (Sant Esteves de Bas, Spain).

Solutions.

The following aqueous solutions are needed for the present experimental work: ASCh 37.5 mM, DTNB 10 mM, Coomassie blue 1 mM, ammonium molybdate 5%, 2,4-diaminophenol (amidol) reagent (2,4-diaminophenol 10 mg/ml in sodium disulfite 0.25 g/ml), and phosphates buffer, pH 7.4, 155 mM. As the three fluorescent probes are not soluble in water, their stock solutions are prepared in organic solvents: DPH 1 mM in acetone, TMA-DPH 0.5 mM in N,N-dimethylformamide, and C17-HC 10 mM in tetrahydrofuran.

Blood Samples.

Human venous blood samples were collected with anticoagulant (10 IU of heparin/ml of blood) from healthy donors, with their previous informed consent, following our protocol with the Portuguese Blood Institute. Freshly collected whole blood samples were centrifuged for 10 min at 1,000 x g in a Sorvall TC6 centrifuge (Du Pont, Bad Nauheim, Germany). Erythrocytes were isolated by plasma and buffy-coat removal, resuspended in phosphate buffer, pH 7.4, 155 mM, and divided in aliquots.

Erythrocyte Exovesicles Isolation.

As previously described [9], erythrocyte suspension aliquots were incubated for 30 min, at room temperature, with each of the three fluorescent probes. The final total concentrations of DPH, TMA-DPH, and C17-HC were 0.22 μM in 0.037% hematocrit, 5.4 μM in 0.01% hematocrit, and 0.11 mM in 0.01% hematocrit, respectively. These values were optimized for the fluorescence measurements in erythrocytes according to the membrane/water partition coefficients [13] and fluorescence quantum yields of each probe. As the fluorescence probes reach equilibrium between the aqueous and lipid phases, and the unincorporated probes do not fluoresce [14], there was no need for a washing procedure to be done. The exovesicles were obtained on the supernatants of centrifugations (10 min, 1,000 x g) carried out 1 (t1), 24 (t24), and 48 h (t48) after the initial incubation. If the equipment is available, the exovesicles in the supernatants should be concentrated to ~2/3 of the initial volume (≈3 h at 30°C and 240 g in a micro test tubes Eppendorf concentrator model 5301, Hamburg, Germany).

## Note

We believe that even during a pandemic, the required number of laboratory sessions cannot be reduced.

These procedures, referred as “previous experimental preparation by the instructor,” can be partially or totally carried out by the students, depending on their background and experience, and on the laboratory class time available.

Experimental Procedure for Lab Class.

Both phthalate esters (dibutyl phtalate and dimethyl phtalate) and their mixtures are not miscible with water. These mixtures, used to separate erythrocytes according to their density [15], were adapted by us to the identification of the erythrocyte exovesicles and prepared following the proportions presented. It must be kept in mind that the exovesicles

suspensions are blood-derived products. Thus, proper care and handling procedures must be followed during their manipulation. Fifty-microliter aliquots of exovesicle suspensions were added to each one of the five micro test tubes, containing 1 ml of the phtalate esters mixtures. After gentle homogenization, the micro test tubes were centrifuged at room temperature for 1 min at 8,500 x g in a Heraeus Sepatech Biofuge 15 (Osterode, Germany). The process was carried out for the different exovesicles suspensions under evaluation.

Protein Coloration with Coomassie Blue.

Following an adaptation of the Bradford method [10], 10 μl of Coomassie blue 1 mM were added to each micro test tube containing the exovesicles in phtalate esters gradient medium. After gentle shaking, the tubes were centrifuged again for 2 min at 8,500.

AChE Coloration with Ellman's Reagent.

Following an adaptation of the Ellman method [11], 15 μl of DTNB 10 mM and 10 μl of ASCh 37.5 mM were added to another set of micro test tubes containing the exovesicles in phtalate esters gradient medium. After gentle shaking, the tubes were incubated at 37°C during 20 min and centrifuged at room temperature for 2 min at 8,500.

Phospholipids Digestion and Phosphatidic Acid Coloration.

Ten microliters of the enzyme mixture containing phospholipase D (to hydrolyze the phospholipids to phosphatidic acid), 10 μl of ammonium molybdate 5%, and 10 μl of 2,4-diaminophenol (amidol) reagent (for coloration) were added to a last set of micro test tubes containing the exovesicles in phtalate esters gradient medium. After gentle shaking, the tubes were centrifuged again for 2 min at 8,500.

## Results and discussion

We got colorless (unstained), blue (when stained with Coomassie blue), or yellow (when stained with Ellman's reagent or with the mixture used for phospholipid coloration) spheres at the top of the micro test tubes, in the colorless bulk of the phthalates gradient media.

These spheres are aggregates of exovesicles, which proteins are blue-stained in the presence of Coomassie blue. This coloration is due to the formation of complexes as a consequence of the dye binding to the proteins. The unbound form of Coomassie is red, with an absorption maximum at a wavelength (λ) of 465 nm. Upon protein binding, the dye shows a blue shift (λ = 595 nm), as indicated in the Bradford's method for protein quantification [10].

The yellow spheres were obtained after the addition of ASCh, which is hydrolyzed to thiocholine and acetate by the erythrocyte exovesicles AChE. The reaction of the thiol group of thiocholine with DTNB generates the yellow anion 5-thio-2-nitro-benzoic acid. These two coupled reactions were described by Ellman et al. as the principle of a rapid colorimetric method for AChE activity determination [11] and it is still largely used as a gold standard for this enzyme activity quantification [16].

The method used for phospholipid identification leads also to a yellow coloration of

the spheres. Initially, the phospholipids are enzymatically hydrolyzed by phospholipase D to phosphatidic acid. Despite the fact that the hydrolysis can also be achieved by acid treatment (e.g. with perchloric acid), this would also lead to a partial degradation of the spheres. After the hydrolysis, the phosphate group of the phosphatidic acid forms an oxidized phosphomolybdate complex upon reaction with molybdate. The reduction of this complex by the 2,4-diaminophenol reagent origins the characteristic coloration, commonly used for phospholipid quantification [12].

Further Perspectives.

This is an original method that complements our recent research works [9]. Working in an innovative area of research proves stimulating for the students and encourages them to develop new solutions for practical problems. After this laboratory class, students are invited to reach for physiological and biotechnological exovesicles applications [17,18,19]. The information obtained by them can be used for analysis and discussion on a further tutorial class.

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DOI 10.51231/2667-9507-2021-001-01-51-59

# Rheological Parameters in Patients with Brain Infarct During COVID-19

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## Abstract

In the description of the analytical clinical data of the patients with COVID-19 from difference country. In article shows detailed description of the rheological situation in patients with neuropathic during COVID-19. This data was compared with results of rheological study in analogical disease group patients without COVID-19. The article describes the effect of various anticoagulants on blood rheology, also describing protocols. In vivo, in vitro experiments, that studied a range of rheological parameters different anticoagulants. Measurement of RBC aggregation, RBC deformities, plasma viscosity were study with innovative technologies, quantitative methods. The work presents a scientific focus, after deep and increase research area is able to transport the newest conclusion to the clinical practice to treatment management of COVID-19.

KEY WORDS. COVID-19, brain infarct, neurological problems, brain infarct

## Introduction

Coronavirus infection is an acute viral disease with upper respiratory tract infection caused by a virus of the genus Betacoronavirus of the Coronaviridae family. The official names are: Disease coronavirus disease (COVID-19); Virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) [1] is a family that includes as of April 2020 40 types of RNA-containing complex viruses that have supercapsids. Combined into two subfamilies that affect humans and animals. The name is associated with the structure of the virus: from supercapsid come large spiky processes in the form of clubs, which have resemble the crown. Virions measuring 80-220 nm. A nucleocapsid is a flexible helix, which consists of a genomic plus RNA strand and a large number of nucleoprotein N molecules. It has the largest genome among RNA genomic viruses. A supercapsid is secreted in its structure, in which glycoprotein trimeric spikes (peplomer), membrane glycoprotein, small membrane glycoprotein, hemagglutinin esterase are embedded. Coronaviruses penetrate the cell membrane by simulating molecules to which transmembrane cell receptors respond. Until December 2019, it is believed that HCoV-229E, -OC43, -NL63, -HKU1 circulated among the population, which are year-round in the structure of acute respiratory viral infections, and, as a rule, cause damage to the upper respiratory tract of mild to moderate severity. Until 2002, coronaviruses were considered as agents causing mild diseases of the upper respiratory tract with virtually no fatal outcome. At the end of 2002, SARS-CoV appeared, the causative agent of SARS, which caused severe acute respiratory syndrome (SARS). This virus belongs to the genus Betacoronavirus. The natural reservoir of SARS-CoV is bats, intermediate hosts are camels and Himalayan civet. In total, over the period of the epidemic in 37 countries of the world, more than 8 thousand cases were recorded and 10% of them were fatal. In 2012, the world faced a new coronavirus (MERS-CoV), a causative agent of the Middle East respiratory syndrome, belonging to the genus Betacoronavirus. The main natural reservoir of MERS-CoV coronaviruses are bats and one-humped camels (dromedaries). Since 2012, 2,519 cases of coronavirus infection caused by the MERS-CoV virus have been registered, of which more than 30% have been fatal. All cases are geographically associated with the Arabian Peninsula. On February 11, 2020, the World Health Organization assigned the official name of the infection caused by the new coronavirus, COVID-19 (“Coronavirus disease 2019”) [2]. On February 11, 2020, the International Committee on Virus Taxonomy assigned its own name to the causative agent of COVID-19 infection, SARS-CoV-2. The new SARS-CoV-2 coronavirus is a single-stranded RNA-containing virus, belongs to the Coronaviruses family, belongs to the Beta-CoV B line. The virus is assigned to pathogenicity group II, like some other representatives of this family (SARS-CoV virus, MERS-CoV virus). Coronavirus SARS-CoV-2 is believed to be a recombinant virus between bat coronavirus and a coronavirus of unknown origin. The genetic sequence of SARS-CoV-2 is similar to the sequence of SARS-CoV [3].

The natural reservoir of the SARS-CoV-2 virus is bats. The genomic sequences of viruses found in bats are identical to those in patients with COVID-19. Currently, the main source of infection is an infected person, including those at the end of the incubation, prodromal period (the beginning of virus isolation from target cells) and during clinical

manifestations. The transmission mechanism is aspiration. Transmission: airborne and, according to many authors, contact: through water, food and objects. In fecal samples from patients infected with SARS-CoV-2, a pathogen was detected. The fact of the implementation of the artificial mechanism of SARS-CoV-2 transmission has been established. Susceptibility to the pathogen is high in all population groups. The risk groups for severe disease and the risk of death include people aged 60-70 years, patients with chronic diseases. Mortality in different countries is different and varies in different age groups. This may depend on the health system and the health of the nation in a particular age range in one particular country. SARS-CoV-2 virus is characterized by low environmental stability. Dies under the influence of ultraviolet, disinfectants, when heated to 40°C for 1 hour, to 5°C – in 30 minutes. Clinical picture. The incubation period with COVID-19: from 2 to 14 days, On average 5-7 days. Among the first symptoms of COVID-19, an increase in body temperature (90%), cough – dry or with a small amount of sputum (80%), shortness of breath (55%), myalgia and fatigue (44%), compression of the chest (20%), headaches similar to migraine (8%), hemoptysis (5%), diarrhea and nausea (3%). These symptoms are observed in the absence of an increase in body temperature [2]. Clinical options and manifestations of COVID-19: acute respiratory viral infection of the lung; pneumonia without respiratory failure; pneumonia with acute respiratory failure; ARDS; sepsis; septic (infectious toxic) shock. Hypoxemia develops in more than 30% of patients. Most patients with severe COVID-19 develop pneumonia in the first week of illness. However, it must be pointed out that in most of the literature COVID-19 is associated with pneumonia, even in the case of a middle course of the disease.

The diagnosis is established on the basis of an epidemiological history, clinical examination and laboratory results. When collecting an epidemiological history, it is necessary to take into account the patient's visits during the previous 14 days to COVID-19 countries and regions, close contacts during this time with people who arrived from endemic areas, as well as contacts with people whose diagnosis has been confirmed by laboratory tests.

General Laboratory Diagnostics: general (clinical) blood test; blood chemistry; study of the level of C-reactive protein (CRP) in blood serum; pulse oximetry with $SpO_2$ measurement to detect respiratory failure and assess the severity of hypoxemia (pulse oximetry is a screening method that allows you to identify patients with hypoxemia who need respiratory support and evaluate its effectiveness); for patients with Spo2 less than 90%, according to pulse oximetry, a study of arterial blood gases with the determination of $PaO_2$, $PaCO_2$, pH, bicarbonates, lactate is recommended; coagulogram.

Instrumental Diagnostics: computed tomography (CT) of the lungs is recommended for all patients with suspected pneumonia. CT of the lungs is a more sensitive method for diagnosing viral pneumonia. The main findings in pneumonia are bilateral infiltrates in the form of "frosted glass" or consolidations, which are predominantly distributed in the lower and middle zones of the lungs; in the absence of the ability to perform CT, a panoramic radiography of the chest organs is performed in the anterior direct and lateral projections. An X-ray of the chest reveals bilateral confluent infiltrative blackouts. Most often, the most pronounced changes are localized in the basal parts of the lungs. A small pleural effusion may also be present; electrocardiography in standard leads. Specific laboratory Diagnostics: detection of SARS-CoV-2 RNA by PCR in a smear from a nose, nasopharynx and /

or oropharynx. Also, samples can be water, which is used to wash the bronchi during fibro bronchoscopy (bronchoalveolar lavage), sputum, biopsy or autopsy lung material, whole blood, serum, and urine. Besides for differential diagnosis, PCR studies are carried out on pathogens of respiratory infections: influenza viruses of type A and B, rhinoviruses, respiratory syncytial viruses, parainfluenza viruses, adenoviruses, human metapneumoviruses, MERS-CoV. Microbiological diagnosis for Hemophilus influenzae type B, Streptococcus pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae. About disease in target groups.

Ischemic Brain Infarct. Ischemic stroke is a violation of cerebral circulation with damage to brain tissue, a violation of its functions due to difficulty or stopping the flow of blood to the place(s). It may be due to insufficient blood supply to the area of the brain due to a decrease in cerebral blood flow, thrombosis or embolism associated with diseases of blood vessels, heart or blood [3]. It is one of the main causes of death among people [4]. In recent years, mortality from diseases of the circulatory system takes first place. Mortality from stroke is in second place, second only to mortality from coronary heart disease. Total stroke morbidity and mortality rates in many countries of the world tend to increase. Ischemic strokes account for 70-85% of all cases of stroke, cerebral hemorrhage – 20-25%, subarachnoid hemorrhage – 5%. The ratio of the frequency of ischemic and hemorrhagic types of stroke is 4:1 [5]. There are various classifications of ischemic strokes, depending on the etiopathogenetic and clinical aspects, the localization of the infarction zone. By the rate of formation of the neurological deficit and its duration: transient ischemic attacks (TIA); “Minor stroke” – prolonged ischemic attack with a reverse neurological defect[eleven]; progressive ischemic stroke – characterized by the gradual development of cerebral and focal symptoms over several hours or 2-3 days with subsequent incomplete restoration of functions; completed (total) ischemic stroke is a formed cerebral infarction with stable or incompletely regressing deficiency. According to the severity of the condition of patients mild severity; moderate severity – the predominance of focal neurological symptoms over the cerebral, there are no disorders of consciousness; severe stroke – occurs with severe cerebral impairment, depression of consciousness, gross focal neurological deficit, often with dislocation symptoms.

Pathogenetic: stroke (including arterial-arterial embolism) – occurs against the background of atherosclerosis of cerebral arteries of large or medium caliber. This type of stroke develops stepwise, with an increase in symptoms over several hours or days, often debuts in a dream. Often an atherothrombotic stroke is preceded by transient ischemic attacks. Cardioembolic stroke (22%) – occurs when the embolism of the brain artery is completely or partially blocked. The onset of cardioembolic stroke is usually sudden, awake. At the onset of the disease, the neurological deficit is most pronounced. More often, a stroke is localized in the area of blood supply to the middle cerebral artery, the size of the focus of ischemic damage is medium or large, a hemorrhagic component is characteristic. A history of thromboembolism of other organs is possible. Hemodynamic stroke (15%) – due to hemodynamic factors – a decrease in blood pressure (physiological, for example, during sleep; orthostatic, iatrogenic arterial hypotension, hypovolemia) or a decrease in cardiac output (due to myocardial ischemia, severe bradycardia, etc.). The sizes of heart attacks are different, localization is usually in the zone of adjacent blood supply (cortical,

periventricular, etc.). Hemodynamic strokes occur against the background of the pathology of extra – and / or intracranial arteries (atherosclerosis, septal artery stenosis, abnormalities of the vascular system of the brain). Lacunar stroke (20%) – due to the defeat of small perforating arteries. As a rule, it occurs against the background of high blood pressure. It develops gradually over several hours. They are localized in the subcortical and stem structures (basal ganglia, inner capsule, white matter of the semi-oval center, the base of the bridge), the size of the foci does not exceed 1.5 cm. There are no general cerebral and meningeal symptoms, focal symptoms corresponding to the affected structure. In 9% of cases, a stroke develops according to the type of hemorheological micro occlusion (9%) (in some sources the term “rheological stroke” is also used [6]). Such a stroke occurs against the background of the absence of any vascular or hematological disease of established etiology. The cause of the stroke is pronounced hemorheological changes, disorders in the hemostatic system and fibrinolysis. Scanty neurological symptoms combined with significant hemorheological disorders are characteristic [7]. Patients with suspected hemorheological stroke (retrospective conclusion) participated in our studies. We tried to describe briefly cause-effect relationship between the virus and the pandemic, which claimed an incredible number of lives in these 4 months, infected almost 2 million people, endangered the economy of the whole world, also the health care system, health of world population. However, only a narrative of facts and a review are no enough. In our international collaboration, we set ourselves to find out what is the relationship between blood rheology and the course of the disease. In our international collaboration, we set ourselves the goal – to draw the attention of scientific generation to those aspects that need further study. Our scientific group consists of representatives of different specialties, different institutions of different countries, so we can describe the problems in different prisms. We will present you with unpublished data for discussion so far, we think that may be useful in terms of diagnosing and preventing complications of diseases against the backdrop of COVID-19 surveillance, and have a different health model.

## Material and Methods

Our protocol and studies are fully consistent with the Ethical principles for medical research involving human subjects [8]. We used “Georgian methods” [9,10].

## Results

Our results showed that in all cases when a patient with COVID-19 developed neurological changes (rheology ischemic brain infarct), a violation of the rheological status of the blood was uniform, i.e. RBC aggregation index, RBC deformability index, blood plasma

viscosity changed. Changes in this group corresponded and were 10-15% different from those from the same group of patients with a similar diagnosis without COVID-19. RBC aggregation index was 58,0 ± 6,2%; RBC deformability index was 2,70 ± 0,05 RBC deformability index, Plasma viscosity 1,60 ± 0,05 sP in patients with neuroscience problems (without COVID-19). RBC aggregation index was 63,8 ± 5,2%; RBC deformability index was 2,90 ± 0,05%; RBC deformability index; Plasma viscosity 1,75 ± 0,05 sP in patients with neuroscience problems (without COVID-19).

## Discussion and Conclusions

Although a study was conducted in China on almost 60,000 thousand patients with COVID-19, the list of symptoms did not include heart attacks, strokes, hemorrhages, as manifestation and display of infection, but death in some cases was associated precisely with these diseases.

Over the past month, medical reports, scientific articles with arguments about the causal relationship of COVID-19 with neurological syndromes appeared (by the time this article is published, the amount of information will probably increase), but much remains unknown at this point in time. We began to become interested and monitor how many people in our countries have neurological problems

Here we make a reservation that in the results section of this article we did not include data from patients with hyposmia and anosmia during COVID-19. Here we announce that we will publish these data in the next publication, which is now being done by this expanded research group.

Our train of thought provoked the fact that neurological diagnoses, despite their absolute pathophysiological autonomy, have one very important similarity. This is the presence of a rheological mechanism. More commonly, COVID-19 always or almost always entails pneumonia. And pneumonia is a vivid example of such a pathophysiological state as an inflammation with all stages inherent in inflammation.

Despite the fact that the tissues of which organ are inflamed, inflammation always as a pathophysiological process comes with a mandatory violation at the level of microcirculation.

Thus, we hypothesized that violations of blood hemorheology lead to disturbances in microcirculation, which in turn disables the main arteries. In confirming our thoughts, the anatomical structure of the virus helped us. As you know, the virus has a very large size and is not particularly elastic. Thus, the physical movement of the virus, in addition to other effects on the blood flow, can cause the destruction of blood flow not only in the small arteries, but also in the large arteries, since the parabolic equilibrium of the blood profile will leave the stationary-laminar state due to loss erythrocytes impulse in the array near the virus. Rheology is one of the most priority systems of the body, which primarily ensures blood flow (together with the coagulation / anticoagulation system), provides trophic function, oxygenation of the body. In addition, the rheological system of the body includes not

only the issues of macro and microcirculation, I provide the movement of other biological fluids and gases through various systems and organs, including in the intercellular space, in the alveoli, etc. Rheology is, on the one hand, a separate system that, regardless of various factors, is leading in connection with blood circulation, but on the other hand, rheology plays a special role in microcirculation. this is due to the fact that in rheology is mainly regulated by formed elements, in particular RBC. RBC often have larger sizes than the capillaries themselves, so it is necessary to cram the elasticity, normal aggregation and other factors so that they do not have obstacles for penetration into the microvessels. In our studies, we saw that for any disease with COVID-19, the rheological status is violated due to a strong change in the aggregation of erythrocytes. In the last century, it was believed that rheological studies are only priced in the microvasculature, when the size of the red blood cell is several times larger than the diameter of the capillaries where the red blood cell must pass. In this approach, there is common sense when it comes to erythrocyte deformability and plasma viscosity, but if you pay attention to the aggregation of red blood cells, this is a very valuable descriptive physical argument and diagnostic parameter both in macro and micro circulation. Why did erythrocyte aggregation always be disturbed with COVID-19 even when in a similar situation without COVID-19 patients did not have an increased erythrocyte aggregation coefficient? The virus can get into macrocirculation in the following ways, either the virus enters the large vessel from the smaller vessel, which is at an acute angle, with great force, or it is pushed for a long time due to its roughness and non-elasticity and is thus ejected into the blood stream, or the virus enters the laminar blood stream at right angles. All other cases are a mathematical approximation and the vector sum of these cases. Some types of movement come down to rotary, oscillating, linear and reciprocating, irregular motion. Each one moves in a slightly different way and each type of achieved different. any movement of the virus can be determined by a combination of different types of movements, precisely because of this there are violations of the velocity vector of red blood cells, their impulses and angular momentum. All this happens due to a collision with the virus, or the fact that red blood cells have to accelerate and move along the “path broken by the virus”. This causes an unexpected collision of red blood cells in the plasma, which, in turn, moves with glides at different times near the parietal layer of blood vessels. This contributes to the bonding, monetization and, most importantly, the aggregation of red blood cells. Thus, the presence of a new coronavirus promotes the formation of aggregates not only immediately during erythropoiesis, not only in the microvasculature, as usual, but also in macrocirculation. All this causes an explosion of rheological disturbances in COVID-19. In terms of blood circulation, the rheological system is completely self-sufficient. But with regard to turnover, necessary here fusion and interaction of two different systems: rheological and coagulation/anticoagulation. A very interesting fact is that the coagulation and anticoagulation systems usually balance each other being mutually exclusive and interconnected at the same time. But even with physiological processes, the anticoagulation system is depleted faster than the coagulation system. This imbalance is enhanced in parallel with the consumption of the adaptive energy of the body, despite this physiological process (for example, pregnancy, aging) or pathophysiological (inflammation and any disease). As for the rheological system of the body, there is no antipode, which for example (reduced aggregation, increased deformability, etc.). There is

no so-called “anti-rheological” compensatory reactions. But the modern clinical approach and treatment tactics are aimed at ensuring that exogenous therapy helps and determines optimal conditions for normal blood flow, regardless of the factors that disrupt this normal current. There is some recommendation that application of heparin in COVID-19 has good answer reaction because of the risk of disseminated intravascular coagulation and venous thromboembolism. However, its efficacy remains to be validated.

Coagulation results, medications, and outcomes of consecutive patients being classified as having severe COVID-19 in China were analyzed. The mortality between patients who given heparin and patients who did not heparin, as was a different risk of coagulopathy, which was stratified by the sepsis-induced coagulopathy (SIC) score or D-dimer result.

This result shows that in patients with severe COVID-19 who took for 7 days or longer heparin, their D-dimer and prothrombin time were better, change of platelet count was negatively, correlated with monthly mortality in multivariate analysis. No difference in monthly mortality was found between heparin users and nonusers. But if patients have D-dimer was very more than limit of normal and they took heparin, these patients monthly mortality have low. Also, anticoagulant therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer. However, as we studied the marker of thromboembolism, it became clear that it can be used to determine neurological conditions (stroke, subarachnoid hemorrhage). The results of studying the correlation of serum D-dimer levels with the results of intracerebral hemorrhage (spontaneous or after rupture of cerebral artery aneurysm) are reliable [11].

A high level of peripheral blood serum D-dimer in patients shortly before admission to the hospital after cerebral hemorrhage or rupture of aneurysm is a statistically significant harbinger of the development of early severe neurological disorders, adverse outcomes or deaths. Reassessing D-dimer levels can help identify patients at high risk for adverse outcomes and make adjustments to treatment tactics [12,13]. All this speaks in defense of these and other studies of these factors for the purpose of forecasting.

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DOI 10.51231/2667-9507-2021-001-01-60-74

# Myocardial Ischemia and Diabetes Mellitus. Approaches and Recommendation

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## Abstract

The outlook epidemiological auguring an increase considerable the number of subjects with diabetes and cardiological problem during diabetes, and the recent progress registered in the explorations and the treatment of coronary are necessary for to continue research. Since long been recognized as a factor of risk vascular age, the diabetes can be regarded as a genuine vascular disease in because of the frequency and in the severity. The share growing, observed and expected, of the population of diabetics, whose prognosis life is dominated by the complication's coronary up the diabetes mellitus among the priorities of health public in France. The specific features of diabetic coronary artery disease, marked by the often-insidious nature of its development, place silent myocardial ischemia (IMS) and possible atheromatous involvement of the epicardial coronary artery trunks at the center of the diagnostic and therapeutic approach. The progress, drug and instrumentals, the treatment of the inadequacy coronary lead naturally to reconsider the treatment, and therefore the screening early to IMS in the aim of reducing the morbidity and the mortality heart of patients with diabetes.

KEY WORDS: treatment, new treatment approaches, clinical trials

## Introduction

The interest prognostic and therapeutic potential of the identification of the crumb ischemyocardial in the diabetic symptom has not yet been the subject of extensive studies prospective multicentre enabling of to this day of the pipes to keep clear and formal, common to diabetics, cardiologists and general practitioners [1-5]. It is therefore in a field diagnostic and therapeutic still controversial and in the absence of evidence strong, that the group of work has attempted to bring the consensual answers to questions that control the search for a possible ischemic myocardium in a diabetic asymptomatic. Our goals were researches in this areal. Find a) the potential therapeutic benefit of an early diagnosis of IMS; b) the most appropriate examinations for carrying out this screening; c) the developments after the search for an IMS.

It is to go to work wearing specifically on the cohorts limited diabetics usually type 2 or from more extensive studies dedicated to coronary artery disease in which the diabetic does represent feel that a subgroup casual than the group of work has tried to write these recommendations. These codes of good practice not would know be formal and will be later the subject of evaluating prospective bringing the two disciplines. These recommendations are essentially on the diabetes of the type 2.

The diabetes mellitus is an entity defined by its phenotype biological marked by an upper glucose or equal to 1.26 g / L (7 mmol / L) observed twice after 8 hours of fasting in a subject apparently healthy. The current etiopathogenic classification distinguishes [6]:

- the diabetes of the type 1 response to a destruction of origin the most often autoimmune, the cells pancreatic officials usually a deficiency of insulin absolute.
  This diabetes affects preferentially in subjects aged of less than 40 years and requires the implementation in road early one insulin;
- the diabetes of the type 2, more frequent and affecting the subjects more aged, characterized by the association variable of a resistance to the action of insulin and a deficiency of insulin secretion;
- exceptionally, the diabetes knows other causes, genetic by default to the function of cells or of the action of insulin, pancreatic, endocrine, toxic and infectious.

This new classification also defines two clinical and biological situations likely to bring into play type 2 diabetes:

- hyperglycemia moderate close of intolerance to glucose, defined by a glyceryl crumb to fasting placed between 1.10 and 1.26 g / L which exposes also the risk vascular and can evolve to diabetes mellitus in 50% of cases about [7];
- the syndrome metabolic, into which fits typically the diabetes of the type 2, and which, according to the National Cholesterol Education Program [8, 9], is defined by the association of at least three of the following criteria: an abdominal obesity (waist circumference > 102 cm in man and 88 cm in the female), of triglycerides “1.5 g / L, an HDL cholesterol < 0.4 g / L in humans and 0.5 g / L at the woman and 135 mmHg for the systolic and” 85 mmHg for the diastolic.

The frequency of diabetes is in constant progression. The projections of the WHO pre see the doubling of the population of diabetics in 2025, notably by reason of the increase

of diabetes in the country by way of development [10] In France, today, the population of diabetics is estimated at 2 million and a half with a prevalence of 90% approximately of diabetes of the type 2. The number of diabetics undetected is estimated between 300 000 and 500 000 subjects, or 15 to 25% of all of the diabetic population. In addition, the number of individuals with abdominal adiposity excessive, conducive to the development of a diabetes of the type 2, is considered around 10 million.

Two to three times more frequent than in the subject not diabetic, [11] the complications cardiovascular make the prognosis of diabetes and contribute to shorten the expectation of life of a diabetic for 8 years for the subjects of 55 to 64 years [12]. The death of a subject with diabetes is of natural cardiovascular in approximately 65 to 80% of the cases [13,14]. The accidents heart, and more parcularly myocardial infarction (MI), are more common and more severe in the diabetic than in the non-diabetic [15,16]. After a procedure of myocardial revascularization, cardiac events are more numerous in the diabetic. In the register American of the NHLBI, the survival estimated at 9 years after an angioplasty coronary nary, by balloon the most often, is of 68% in the diabetics against 83.5% among non-diabetics [17]. The share of diabetic in the activity of the services of cardiology is growing. Their proportion in the population of patients hospitalized for MDI can reach 33% [18]. It is 20 to 30% in one of the coronary subjected to an exploration angiographic [19]. The diabetes is well for a long time recognized as a factor of risk cardiovascular sys – independent [20,21]. Classically, the coronary mortality of a non-coronary diabetic is identical to that of a non – diabetic coronary artery patient [22]. The most recent observations, although correcting this assertion by a less pessimistic conclusion, confirm well as the risk cardiovascular (RCV) of a diabetic is greater than that of a subject non – diabetic [23,24].

The specific anatomical, functional and biological are the severity of the coronary ropathie of diabetic. Although that aspect morphology of lesions will be no separate, infiltration parietal is more diffuse, more distal and more calcified in the subject diabetic as in evidenced the comments coronarographic [25] and as it confirms the findings autopsy [26]. The dysfunction endothelial, who participates in all the stages of the development of atherosclerosis, is worse in the diabetic by the hyperglyce – crumb and insulin resistance [27]. With the disorders of hemostasis related to platelet aggregability [28] and the imbalance in the balance fibrin-training-fibrinolysis [29] character – tics of diabetes, the dysfunction endothelial renders account of the evolution accelerated the process atheromatous in the diabetic. The disorders of hemostasis and the dysfunction endothelial contribute also to abnormalities in the microcirculation that, in the absence of a breach of trunks epicardial, can make account of IMS [30]. The neuropathy heart is common in diabetics and explains in large part the character often silent in ischemia myocardial [31].

## Silent myocardial ischemia

The alteration transient of the perfusion myocardial as well as the disorder consecutive pro – visional of the function and of the activity of the muscle heart, developed in the absence of pain chest or of any equivalent angina, is a definition pathophysiologic theory of IMS, whose clinical assertion is naturally less formal. Under the circumstance's clinics, it is agreed to distinguish three kinds of IMS: Type 1 in the subjects asymptomatic without antecedent clinic of coronary artery disease; Type 2 in the patients asymptomatic with history of heart attack of myocardium; Type 3 in the coronary angina who also of episodes of IMS [32]. Clinically, the IMS to the type 1 is defined as an abnormal electrocardiographic (and/ or scintigraphy and /or echocardiography), silent and transient, observed at the occasion of a stress in the subjects which the electrocardiogram of rest is strictly normal.

The IMS of the type 1 is more frequently observed in the diabetic than in the diabetic non in a ratio of 2 to 6 according to the series [33]. In the diabetic, the prevalence IMS varies widely from 10 to 30% depending on the mode of pre-screening of individuals and according to the acuity of screening [34,35]. It is more frequent in diabetics with two other cardiovascular risk factors and can then be noted in a third of cases [36,37]. This great variability underscores the low rentability of a screening systematic of IMS in any diabetic and puts into light the need for a selection prior rigorous of patients to go to the assessment of the overall RRS each diabetic.

Premonitory of the occurrence of secondary cardiovascular events, IMS is a factor of poor prognosis [38]. In fact, in the studies devoted to the follow-up of diabetics, it appears that IMS is regularly associated with the risk of occurrence of a major coronary accident [39-42]. After 60 years, several studies have shown that the risk relating to occur later an event cardiac major is 3.2 times higher in the diabetic with an IMS that among the diabetic without IMS [40,42].

The correspondence between the IMS and the (or the) stenosis (s) coronary (s) angiographic (s) significant stage (s) is unclear and not compulsory. In fact, in the short series reported, coronary angiographic exploration of an IMS reveals the presence of one or more angiographic strictures equal to or greater than 70% in 30 to 60% of cases [36,42]. The alteration of the reserve coronary secondary to the microangiopathy intramyocardique, the disturbance of the vasomotor by dysfunction endothelial and the disorder of the hemostase can associate to render account of this discrepancy functional and angiographic in the diabetic. However, it seems that the prognosis of IMS is closely dependent on the existence or not of angiographic coronary stenosis. Indeed, two French studies have recently shown that the presence of significant stenosis is a strong predictor of major cardiac events at 2 and 3.5 years in patients with IMS, while patients with abnormal scintigraphy but without coronary stenosis have a prognosis similar to that of subjects without IMS [16,42]. The discovery of IMS justified, reasonable today, the research of coronary stenoses by the practice of a coronary angiography in the respect of the rules of own safety in this type of examination in a diabetic.

The severity of the prognosis Heart of diabetes should lead to take to load the diabetic asymptomatic in a logic of prevention secondary.

More frequent in the diabetic than in the non-diabetic, IMS is a factor of poor prognosis, promonitoire of the occurrence of events Cardiac major.

The prevalence of IMS is high when other vascular risk factors are associated with diabetes.

An IMS can appear without reaching the big trunks coronary epicardial. However, the prognosis of IMS is dependent on the presence of angiographic coronary stenosis.

The search of the IMS does should not be systematic in the diabetic. It should be guided by the assessment of the overall cardiovascular risk of each diabetic.

The discovery of an IMS justifies the practice of a coronary artery exploration while respecting the safety rules specific to diabetic patients.

By its high prevalence and its potential prognostic severity, IMS Center ‘s approach diagnosis and therapy in the diabetic symptoms. Point of encounter natural between the diabetologist and the cardiologist, IMS led to question first on the benefit therapeutic potential of a screening early, then on selecting suitable for diabetics at risk cardiovascular high under a such research of same as on the choice of examinations appropriate and finally on the strategies diagnosis and to follow the gaze of the results of this screening.

## Stenosis and atheromatous lesion – current data

The relationship between on the one hand angiographic coronary stenosis greater than or equal to 70%, and on the other hand ischemia myocardial and the prognosis in the long term are long established. Prognostic index, defined from the follow large cohorts of patients anginal stable or asymptomatic, oppose, according to the severity of the infringement angiographic, the patients with low and high risk myocardial. If the risk of coronary mortality at 5 years is estimated at 7.5% for the monotrunk patient without involvement of the anterior ventricular, this same risk is evaluated at 40% for the intravascular coronary artery (obviously with an involvement of the anterior ventricular) [43,44]. These data angiographic and scalable have chaired the development of treatments of revascularization surgery and interventional [43-45].

In vivo, the progress of the exploration morphological, functional and organic of atheroma allow a better understanding of the evolution of the process atherosclerotic sclerotic. Discontinuous, the development of atherosclerosis combines the phases of stability and instability governed by the degree of vulnerability of lesions atheromatous. The plate atheromatous is the seat constant an activity histological and biochemical which involved either in the stable, or at the destabilizing. Rich in material lipid-cell and poorly contained by a fibrous cap slender, vulnerable lesions are threatened with instability and exposed to the risk of the cracking and to erosion with formation of a thrombus endoluminal more or less occlusive [46,47]. Multifactorial, the determinism of the instability of the plaque vulnerable based on of many mechanisms dent interdependent of natural mechanical (the burden of heart lipid-cell), biological (metalloproteases Teases), vasomotor (dysfunction endothelial), hemodynamics (strengths of shear) and inflammatory [48,49]. These factors of instability

of the plate atheromatous are exacerbated by the diabetes. There is no parallel between the qualitative character of the vulnerability of the plaque and the quantitative character of the angiographic stenosis.

Some comments coronarographic suggest that the plaque unstable, responsible sand of a syndrome coronary acute, will determine not of stenosis significant. In fact, coronary angiography, occasionally practiced before the establishment of an IDM, show that the artery coronary, responsible for the necrosis, not present initially as angiographic lesions less than 50% in 60% of cases [50,51]. The low volume of the unstable lesion and the phenomenon of parietal remodeling render account in these cases, the character bit stenosing of objectified abnormalities in the coronary angiography [52]. In addition, in the framework of a syndrome coronary acute, the observation ultrasound endovascular show that the plates unstable are multiple in 75% of cases [53]. It thus appears that the phenomenon of lesional instability can be multifocal and diffuse and that, although a single plaque can cause acute coronary syndrome, many other lesions can remain asymptomatic in however, remaining exposed to the risk of an evolution either paroxysmal by an acute or subacute occlusion, or insidious with the development of an angiographic stenosis of a scarring nature.

The complexity of the development of the process atheromatous makes good account of the difficulties of screening clinic for atherosclerosis coronary and explains the limits of functional and morphological explorations. In asymptomatic diabetic lesion parietal atherosclerotic little or no significant, but potentially vulnerable by reason in particular of the dysfunction endothelial and the disorder of hemostasis specific of diabetes, cannot cause IMS to the effort and can also escape to coronary angiography. The value of diagnostic of these exams, which put the day preferentially of stenosis coronary fixed and tight, is therefore not categorical. The floor of lesions not stenotic at risk high instability, by the resonance magnetically nuclear tick, intravascular ultrasound, thermography, palpograhie and OCT (optical coherence tomography) still belongs to the field of research clinical. In the practice clinic, it is therefore less of detecting the lesions atherosclerotic risk of instability that identify the topics to RCV high. In addition, a cardio – logical assessment only explores the instant of a progressive and unpredictable disease: either quiescent, paroxysmal or insidiously stenosing. The predictive value of the tests, when they are negative, is therefore not formal, and by therefore the evaluations cardiologiques complementary must be repeated in the monitoring of a diabetic at risk in the research of evolution silent stenosis.

At plane therapeutic, the knowledge more thoroughly the mechanisms of installations ion and evolution of atheroma gives all its meaning to measures of pre – vention, pharmacological and dietary, who can participate in to many ways complementary to the stabilization preventive and curative of the vulnerable plaque.

The dissemination and the seat of stenosis coronary angiographic define the high and the low risk myocardique.

However, the progressive severity of atherosclerosis depends as much on the instability of the lesions as on the severity of the strictures.

The lesions not stenotic, potentially unstable, can escape the explorations functional and mortal phologiques.

The diagnostic and predictive value of stress tests and coronary angiography is therefore not categorical.

However, the installation of a stenosis can be done on the fashion insidious evaluation cardiology complement commentary will be repeated in the monitoring of a diabetic at risk.

It is more significant and helpful to identify the subjects at risk as to detect the lesions atheromatous potentially unstable and stenotic.

## Potential therapeutic benefit

The advantages therapeutic a screening early and systematic of IMS are not yet formally demonstrated in the diabetic. They are suggested by the results of therapeutic interventions applied to diabetic patients with a coronary disease clinically proven and well in subjects asymptomatic Sou put at risk atheromatous, diabetic or not diabetic. The profit potential is based on three measures therapeutic potential: the setting in implementing a treatment anti-ischemic, the strengthening of measures to prevent cardiovascular and in need, the practice of an act of revascularization.

## Anti-ischemic treatment

The setting in the day of IMS can and must lead to the implementation in road a treatment medi – anti-ischemic early camenteux. In asymptomatic coronary patients and with an IMS study ACIP has already demonstrated the effectiveness of a treatment anti-ischemic on the reduction of the severity and the number of episodes of ischemia sicious and, at this time, has confirmed the superiority of blockers on the inhibitor's calcium [54]. In patients with coronary artery disease, the efficacy of blockers is alsoproven. In the BIP study, the risk of cardiac mortality in diabetics was significantly reduced by 44% in the group of patients receiving a B-blocker [55]. This effect positive is more marked the waning of an IDM and in the presence of an alteration moderation ESR of the function ventricular left [56].

## Reinforcement of preventive measures

The discovery of an IMS places the diabetic in a logic of secondary prevention. The precocity of the diagnosis may lead to the setting in work early and reinforced measures lifestyle modifications and therapy with a control more strictly the fac – tors of risk associated with the prescription agents' drug which have already proved their effectiveness in the field of the prevention.

The statins have accumulated a large amount of evidence in favor of their efficacy in the diabetic. In the field of the prevention side, the big trials have proven the efficacy of a lower treatment of cholesterol with, for 5 years, a reduction of 55% of the risk related events coronary major in the diabetic hyper cholesterol treated by simvastatin in the study 4S [57] and of 25% in the diabetic normo cholesterol put under pravastatin in testing CARE [58]. In a population of 5 963 diabetics, HPS confirmed these results with a reduced significantly by 22% of the risk relative, identical to that observed in the cohort of patients non diabetics [59]. With a reduction of the risk relating to 33%, the benefit is also noted in the group of 2912 diabetic symptoms. This gain prognostic is registration what that are the kind of diabetes, its length and the quality of its control glycemic, which that are age and the sex and finally what as are the levels initial of the pressure arterial (PA), the cholesterol total and the LDL-cholesterol (LDL-C). Although having attracted less testing, the fibrates have also proven their efficiency in secondary prevention in the diabetic [60].

In the diabetic with two other factors of risk as in the coronary out, the threshold of interventions is set to 1.3 g/L of LDL-C to the Affrays with a value target of 1 g/L for the latest European recommendations [61].

The control participates also to improve the prognosis vascular. In the trial, the decrease of pressure systolic and diastolic of respectively 10 and 5 mmHg is associated with a reduction of 5% to 8 years of risk absolute occurrence of an accident vascular brain or a death of vascular origin [62].

Other studies devoted to the prognosis and the treatment of hypertensive report of results similar in the subgroup of diabetic patients [63].

Thus, in the diabetic hypertensive, a PA less to 130/80 mmHg is currently defined as the goal to reach in the past recommendations [61,64]. A square privileged must be reserved for angiotensin converting enzyme as recommendation ADA, especially in the diabetic with a proteinuria or an alteration of the function ventricular left [65]. This class drug has actually proven its effectiveness in the diabetic. In the suites immediate of IDM, the 6 weeks was significantly more low in the diabetic treated by lisinopril (8.7 against 12.4% in the group placebo) in the trial [66]. Among the diabetics who already had an accident cardiovascular or accusing one other factor of cardiovascular risk, the ramipril decreases significantly from 25% in 4 years the risk related to occurrence of a cardiovascular event in the subgroup of diabetics in the study [67].

Recently, testing EUROPA has confirmed the effectiveness of perindopril, associated to a B-blocker, in the reduction of risk vascular in the coronary steady with, in the population of diabetics, a trend favorable that reaches however not the threshold significance [68].

Aspirin, in the meta-analysis of several trials comparative, has also proven effective in the reduction of risk vascular as well in the diabetic than in the non-diabetic [69]. Among the diabetics suffering a retinopathy and who have no signs of coronary artery disease, the prescription of aspirin is associated with a reduction of 15% in 7 years of risk relative to occurrence of an IDM [70].

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The presence of achieving blood clinic, peripheral, coronary or cerebral, the clopidogrel is revealed more effective than aspirin in the subgroup of patients with diabetes CAPRIE with a reduction of 2.1% absolute risk annual occurrence of a major arterial event [71].

The control strict and attentive to the blood sugar is involved also to improve the vascular diabetic prognostic tic. In the aftermath of an IDM, DIGAMI the trial showed that the recourse to insulin, since the phase of hospital until the third month of development to a minimum, allowing a reduction of the mortality of 29% at 1 year [72]. Finally, in the UKPDS trial which recruits asymptomatic type 2 diabetics, it appears that any increase in the level of glycated hemoglobin (HbA1c) of 1% above the threshold of 6.2% is accompanied at 10 years an exaggeration of 11% of the risk coronary [73].

The affirmation of IMS may well lead to a decision in support strict and continues the RRS overall by the setting in game of medications tailored to each case. At the high vascular risk men and having an IMS affirmed by an exercise test positive, these measures attentive engaged to reduce significantly the mortality cardio vascular from 61% to 7 years [74] In diabetic type 2, with albuminuria micro, a decision in support therapeutic aggressive (control glycemic strict control blood pressure at the level of 135/80 mmHg and prescription of statin and aspirin) reduces the risk vascular to 7 years of 50% with respect to the treatment conventional and casual of factors of risk associated [75].

## Myocardial revascularization

The discovery of IMS and the setting in evidence of coronary artery disease with coronary stenosis tight and commanding a wide territory myocardial may lead to consider a gesture of revascularization. Without testing specifically dedicated to the revascularization of diabetic, including asymptomatic, and the fact of the constant evolution of methods surgical and interventional, the principle even of the revascularization and its terms are still controversial. The major trials have however allowed to identify some lines guidelines helpful in making therapeutic vis-à-vis of ischemic myocardium in the diabetic.

At the coronary stable efficiency of revascularization surgery has been proven in the group of patients at high risk myocardial having a stenosis of the trunk com – mon left a damage multivessel involving the first segment of the IVA and alteration of the function ventricular left [76]. Among the patient's single vessel at low risk myocardial, a revascularization with angioplasty will affect not notable – lies the risk of occurrence of an event cardiac major, but it improves significantly the become functional, especially in the presence of a breach of the IVA proximal male [77].

In the stable coronary artery, the efficacy of surgical revascularization has been proven

in the group of patients at high myocardial risk with stenosis of the left common trunk, multivascular involvement involving the first segment and an alteration of left ventricular function [76]. In monotronic patients with low myocardial risk, revascularization by angioplasty does not appreciably influence the risk of a major cardiac event, but it significantly improves the functional outcome, especially in the presence of a disease of the heart [77]. In coronary patients, trials tend to demonstrate the superiority of myocardial revascularization over anti-ischemic medical treatment alone. Although lacking in power, the study [78] demonstrated in subjects revascularized by bypass surgery a reduction in subclinical ischemic manifestations and above all a significant reduction in mortality at one year (0 against 1.6% in the group treated with anti-ischemic agents).

In multivascular diabetics selected for revascularization, the results of large comparative trials argue in favor of the surgical option [79]. At 7 years, the trial [80] reported lower mortality in the group treated with surgery (24.5 versus 44% in the balloon angioplasty group) with a clearer benefit in subjects revascularized by the artery. internal breast. The stent is not enough to bridge the gap between angioplasty and surgery. In the trial, the mortality at one year was 6.3% in the “stent” group compared to 3.1% in the “surgery” group in diabetics [81]. However, the registers recruiting less selected populations of diabetics do not show significantly different long-term results between the 2 methods [82]. Thus, the choice of revascularization in multivascular diabetics remains open and is based, on a case-by-case basis, on an assessment of the etiological context, in particular with age and associated pathologies, and on the analysis of coronary artery lesions.

When the indication for angioplasty is retained and the angiographic conditions are favorable, placement of a stent should be preferred. The risk of restenosis, particularly high in diabetics [83], is significantly reduced by the implantation of a stent [84] to reach, in the best case, a threshold identical to that of non-diabetic patients [85]. Finally, the results obtained with active stents seem promising today, and if they are confirmed, will lead to facilitating angioplasty in diabetics and possibly broadening the indications for revascularization in these patients [88]. In the population of diabetics in the study (26% of the total number), the rate of new supported coronary revascularization was 22.3% in the “inactive stent” group and 6.9% in the “inactive stent” group the sirolimus “covered stent” group [89].

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