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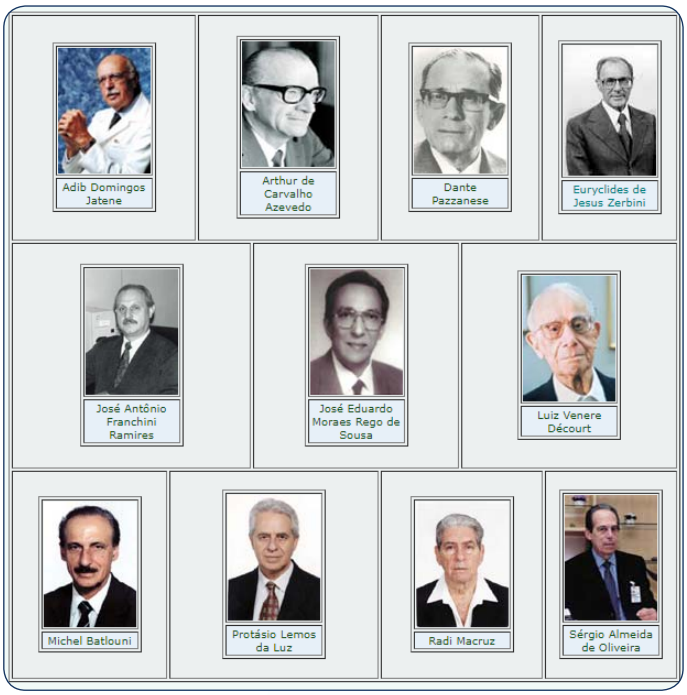

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Editorial

Arquivos Brasileiros de Cardiologia (ABC Cardiol) and the new classification Qualis of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

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The Arquivos Brasileiros de Cardiologia (ABC), the official scientific journal of the Brazilian Society of Cardiology (BSC), is currently the journal in Cardiology with the highest impact in Brazil and Latin America, with a 2018 JCR impact factor of 1.679.[1] During its history, the ABC has played an important role of publishing scientific papers produced in Brazil in journals indexed in the most prominent English-language, international databases. It thus acts as a window to the world of the Brazilian scientific production.

The mission of the ABC is to disseminate the results of national and international studies on cardiovascular diseases, to foster scientific debate on the area by means of review articles, viewpoints, editorials, letters and others, and to publish BSC scientific guidelines and standards. The journal's commitment is in line with the mission of the BSC to expand and spread the knowledge about cardiovascular science, to represent and promote the development of cardiologists and to take actions for the cardiovascular health in Brazil.

The ABC have their own regulations. The Editor-in-Chief is elected for a four-year-term, and mandate's renewal is subjected to the approval by a judging committee composed by members of the Council and published by public notice. The journal has 12 associate editors, eight of them professors of postgraduate programs, working in the respective areas: Medical Cardiology; Surgical Cardiology; Interventional Cardiology; Pediatric Cardiology/Congenital Cardiopathy; Arrythmia/Pacemaker/Noninvasive diagnostic techniques; Basic or Experimental Research; Epidemiology/Statistics; Arterial Hypertension; Ergometry; Exercise and Cardiac Rehabilitation. The editors are chosen by the Editor-in-Chief. The editorial board, composed of approximately 100 members, undergoes a complete revision every four years, considering qualitative prerequisites, such as scientific production and academic activity.

The number of articles recently published in the ABC reflects the consistency of the editorial line of the journal, with 185, 242 and 187 articles published in 2017, 2018 and in the current year, respectively. The growing interest in publishing in

Keywords

Education, Medical, Graduate/trends; Program Evaluation; Periodicals as Topic; Research Policy Evaluation; Journal Impact Factor.

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the ABC is clearly shown by the increasing number of articles submitted to the journal – 650 in 2017, 771 in 2018 and 734 so far in 2019. The current acceptance rate is lower than 20% of the articles submitted and approximately 30% of the articles rejected are transferred to other journals of the ABC group, the IJCS and the ABC *imagem cardiovascular*, contributing to the scientific quality of these Brazilian journal partners.

The number of original articles published in the ABC in 2017, 2018 and 2019, respectively, was 96 (65 of studies conducted in postgraduate programs), 98 (53 of postgraduate programs) and 40 (32 of postgraduate programs). Therefore, nearly 65% of the original articles published in the ABC are contributions from postgraduate programs. These data show that the ABC meet the strict high-quality requirements of *the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Coordination for the Improvement of Higher Education Personnel) regarding the quality of intellectual production of the Cardiology postgraduate programs, including articles published in scientific journals. To meet the criteria imposed by CAPES is a challenging task that requires the combined efforts of postgraduate programs and medical societies, aiming at making the scientific production from postgraduate programs of all academic institutions available and renown by national and international peers.

The ABC have followed an international trend of open science to give value to publications that make scientific data universally accessible. As an example, the European Community has the objective to make all the scientific production universally available by the year of 2020, similar to large research funding agencies, such as the National Institute of Health (NIH), which already requires that all scientific data produced by projects funded by the agency are openly published.

We should support national scientific journals, with the aim of improving their impact factor and their position in the global science scenario. Also, publication of national studies on cardiovascular disease should be encouraged, as they represent the main cause of mortality in Brazil and in the world. One of the aspects considered important by CAPES is the social insertion of the postgraduate programs, seeking to improve life conditions of the population. However, studies on Brazilian populations, with their particular socioeconomic characteristics, attract little or no attention from the international scientific community. These studies would then be benefited from the promotion by CAPES' evaluation system; this would construct a strong national exchange network. This social role has been played by the ABC. In this regard, it would be interesting that CAPES, by means of Qualis, evaluated the ABC, which is the main journal on the fight against cardiovascular disease, allowing the sharing of successful experiences in this sense.

Finally, the ABC are truly a "world-class" journal, with 70 years of history, high internationalization, with continuous support from the BSC, and composed mostly of articles produced in postgraduate programs. The ABC are the most important journal on Cardiology and Cardiovascular Sciences, with the highest impact factor in Brazil and Latin America. It is undoubtedly the ideal journal to publish scientific production of postgraduate programs.

The ABC is currently classified as B1 category, which discourages the submission by authors of postgraduate programs to this journal, which is based in Brazil, has renown impact factor and is highly internationalized, when compared to other national and international journals of internal medicine, with comparable impact factors, and classified in higher levels by CAPES.

Therefore, the difficulty imposed by CAPES classification restricts the use of national and specialized journals as the ABC. We believe that the A2 level encompasses journals of similar scientific reputation to the ABC and would be the most suitable to this journal.

Finally, it is the opinion of the authors of this editorial and large part of the brazilian postgraduate programs in Cardiology, that we respectfully ask the revision of the latest classification of the ABC given by CAPES, based on the potential direct benefits to the national scientific community and to the postgraduate programs in Brazil.

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Cardiology and the Cardiologist – Yesterday, Today and Tomorrow

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Carlos Chagas was the first "modern" cardiologist in Brazil.
Professor Nelson Botelho Reis
President of the SBC: 1945-1975 management

Cardiology as a medical specialty has been built from scientific knowledge derived from basic and clinical areas and from the development of technological devices that enabled us to study and understand the cardiovascular system. Two technological disruptive capacitors were: the stethoscope and the electrocardiogram, which allowed for the construction of two new "sciences", the eletroctrocardiography and the phonomecanography. Certainly, the complexity of understanding the eletroctrocardiography and its electroclinical correlation has made Cardiology to become a specialty independent from clinical medicine, in the early 20th century. In the post-war years, technical-scientific developments allowed Cardiology to be prepared to become a solid area of action, and enabled the new search for therapeutic approaches, which contributed to the increased survival rates observed in basically all cardiopathies.

The foundation of the Brazilian Society of Cardiology (SBC), on August 14, 1943, was an important mark in our country, which enabled to tie together doctors dedicated to cardiovascular teaching, research and care. Thus, since 2005, the cardiologists day has been celebrated. The SBC and its brand logos have been transformed as it searches to connect our tradition and the contemporaneity of our cardiology and its international insertion and relevance (Figure 1).[1]

The trajectory of this specialty traverses the emergence of the SBC, the propagation of training courses, the creation of the Arquivos Brasileiros de Cardiologia in 1948 and the first specialists' titles. Over the years, in association with the hospitalist practice and the great technological development, Cardiology was divided into specific specialty areas: emergency cardiology and cardiac intensivism, congenital cardiopathies, cardiac surgery, hemodynamics, echocardiography, electrophysiology, among others. In order to understand the future, it is necessary to look back into the past and realize the huge steps of this specialty, which grows worldwide, aligned with the contemporaneity of the challenges to prevent and treat cardiovascular diseases in a safe manner, based on guidelines and focusing on the patient.

Going back to remote times, we can rescue the registries of the first steps of the specialty that we call protocardiology. Leonardo da Vinci's observations, drawings and notes of the heart, made in 1490, are deemed as pioneering in the history of Cardiology. As author of the first graphic representation of the coronary arteries, he also explained the heart fluid dynamics and defined the formation of the aortic valve cusp and the sinus wall. It is possible to state that Da Vinci was a renaissance cardiologist.[2] In the mid-1500s, Andreas Vesalius published a wonderful atlas of anatomy in his "Fabricius". In this publication, he called the heart the "center of life". This publication corrects the anatomical mistakes described by Galen and, for many historians, it is the mark of modern medicine. Modern cardiology has its beginnings with the publication of the book *De Motus Cordis*, written by the English physician and scientist William Harvey, the father of Cardiology,[3] which caused a "hurricane" in science and medicine when it asserted, based on studies in animals and humans, that the blood goes from the heart through closed spaces and returns through veins into the heart.

The evolution of the history of Cardiology in Brazil was brilliantly revised by professor Nelson Botelho Reis and published in the *Arquivos Brasileiros de Cardiologia*, in 1986.[4] He reinforces that the clinical-anatomic method was the first method in clinical medicine that evolved from a simple confirmation ("findings of necropsy") or from the verification of the disease in an emerging scientific area, correlating the patient's clinical picture. Important Italian (Malpigi, Morgami); French (Vienssens, Bichat and Laennec) and German (Virchow) physicians were fundamental to the construction of this new discipline. The Anatomopathology witnessed the emergence of Histology, which brought to light the importance of examining cells and tissues, and of expanding the correlation and causal mechanisms of diseases. The physicians interested in the area of Cardiology presented a growing and e robust method to explain the abnormal cardiovascular findings and necropsy data.

In our country, the central influence of the cardiovascular anatomoclinical method was important for the formation of cardiologists until the beginning of the 1980's, initially influenced by Sylvio Carvalhal (São Paulo), Professor Luigi Bogliolo (Rio de Janeiro and Minas Gerais). Also, Professor Manoel Barreto Neto, whom I was honored to be a student of and from whom I received deep knowledge and the strength of the anatomoclinical method, along with the findings presented by Professor Raul Carlos Pareto Junior. The *Arquivos Brasileiros de Cardiologia* also publishes its traditional anatomoclinical section, an important tool for the formation of young cardiologists.

Keywords

Cardiology/history; Heart Diseases/history; History,19th Century; History,20th Century; Humans; Animals; Cardiology/trends; Brazilian Society of Cardiology/history.

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Figure 1 – *Different SBC logos throughout its history.*

In the second half of the 19th century, the third stage of Cardiology emerged: the experimental medicine, the source of the brilliance of writers such as Claude Bernard and Carl Ludwig. The German and French schools made experimental medicine an independent area and two researchers described the Frank-Starling Law, the first law of the heart. In the 19th century, scientific advances derived from new disciplines such as microbiology, immunology, histology and biochemistry. Other sciences were incorporated into the study of Cardiology, such as physics and electricity, which contributed to the discovery of the x-ray and the chord galvanometer. In the future, these would constitute the basis of cardiac radiology and electrocardiography. In the end of the 19th century, the combination of anatomoclinical data and the recording of stetho-acoustic findings using graphic methods (phonomecanographic) consolidated a new pathophysiological approach, and a detailed description was made of a growing number of cardiovascular conditions.

It is possible to assert that the official study of Cardiology, as a science and medical specialty, started with the vital contribution of Dr. Carlos Chagas' studies, who diagnosed the chagasic cardiomyopathy in 1909, and was responsible for the first translational studies and the publication of the first broad scientific study of a cardiac disease in Brazil. In addition, he was responsible for introducing the first electrocardiogram, installed in the laboratory of Manguinhos, a valuable and unequivocal contribution to Brazilian Cardiology.[4,5]

Industry development and migration from rural to urban areas, with the creation of metropolitan areas, in the early 1920s, led to a huge change in the eating and working habits of the Brazilian population, with the spread of heart diseases among the society.[6] In the same period, the dissemination of the electrocardiograph made it possible to develop specific studies, which resulted in a branch of clinical medicine that became an area of major interest for numerous physicians, who began to search for specialty programs in Brazil and abroad. This movement, throughout the 1930s, led to the emergence of the medical specialty, thanks to the particular interest of this enthusiastic group for this specific study, which caused emerging resources to be redirected to the investigation of cardiovascular diseases, through phonomechanography and electrocardiography. From this moment, a great process of creation of annual specialty courses began, which initially were offered in São Paulo and Rio de Janeiro, even before the constitution of the Chair and the formation of this Society, on August 14, 1943. The access to these great transnational networks, and the whole American continent, benefited the investigation, the learning and trainings that took place until the end of World War II, and was the result of the internationalization process of the SBC, which maintained the possibility of interchange between Brazilian and North-American doctors and, consequently, of its actions together with the American College of Cardiology.[7]

Cardiology and cardiologists experienced deep changes in the beginning of the 20th century, due to the employment of the electrocardiogram as the cornerstone of cardiovascular rationale. Another important change was the progressive loss of relevance of the French school for Cardiology and the emergence of the North-American and Mexican schools of Cardiology. The Mexican Institute of Cardiology, founded by Ignacio Chaves, in 1944, became a research and education pole in the area of electrocardiography and a model center of cardiovascular education, attracting Brazilian young people for its residence in cardiology, as well as people from other nationalities. Between the 1940's and 70's, it would become a global reference center and contribute to important advances for the pathophysiology of congenital diseases, pulmonary hypertension, hemodynamics and electrophysiology. The influence of the North-American school starts to consolidate in the post-war period, when it incorporates economic resources to professionalize clinical research and construction and new centers of cardiology, as well as into the development of cardiac catheterization and myocardial revascularization surgery. The Harvard group led by Professor Eugene Braunwald consolidates in the discovery of new mechanisms of disease and in multicenter therapeutic studies.

Editorial

In the 1980's and 90's, noninvasive cardiovascular imaging, echocardiography, myocardial scintigraphy, computerized tomography and cardiac resonance were incorporated and became increasingly indispensable for diagnostic, prognostic and therapeutic evaluation. Parallel to this, we started to incorporate the principles of evidence-based medicine into the process of clinical decision making in the therapeutic area. The Brazilian Society of Cardiology establishes clinical guidelines to guide the cardiovascular practice, incorporating and ranking the recommendations to confront several cardiovascular diseases.

Since the hospitalist practice of our cardiologists, cardiac surgery has been present and of vital importance for the development of our specialty, as well as hemodynamics, both being distinguished as the major departments in the first years of constitution of the SBC. Specialized sectors and equipment in hemodynamics and cardiac surgery, creation of specialized health care centers and units, such as the coronary unit and cardiac postoperative unit, provide specific care, adding knowledge and value to the specialty. With the arrival of the 1980's, there was the dissemination of the use of coronary angioplasty for the treatment of multiple vessel disease and acute myocardial infarction, using reperfusion techniques and thrombolytic therapy. The advances of interventionist hemodynamics through the use of pharmacological stents, valvuloplasty and prosthesis implantation emerged around the world, and quickly arrived in Brazil, promoting a huge evolution step towards the formation of the specialist in Cardiology, as well as the need for the constitution of teams dedicated to each area.[6-8]

All this movement promoted the growing and the development of the SBC, leading to the creation of the first five specialized Departments: Cardiovascular Surgery Department (1969), Pediatric Cardiovascular Department (1973), Cardiovascular and Respiratory Physiology Department (1974), Angiocardiography and Hemodynamic Department (1976) and Hypertension Department (1981).[4] Nowadays, the SBC consists of 13 active departments, where a total of 14,000 associates are distributed in 26 regional clusters throughout Brazil, being the largest society in Latin America. Cardiology, in addition to having being the first specialty to establish a Chair at universities and teaching hospitals, was also responsible for the emergence of accreditation procedures for specialist titles and, nowadays, has the support of 8,429 doctors with a specialty degree in Cardiology.

In addition, several institutions offer *lato sensu* post-graduation courses. In line with this demand for specialty courses, the SCB, alongside its regular publications *Arquivos Brasileiros de Cardiologia* (Brazilian Archives of Cardiology), *International Journal of Cardiovascular Science*, *the SBC Journal* and its guidelines, provides DE (distance education) courses, a broad schedule of events and congresses with online access. In order to respond the need for expanding translational research, the specialty counts with the possibility of network research, as in the case of stem-cell therapy, which involved several centers, the support to clinical trials and registries, in addition to epidemiologic studies on the most prevalent cardiovascular conditions in our field. In the context of standardization of conduct and creation of protocols, the SBC dedicates extreme determination for the development and publication of guidelines on approach and treatment of the main diseases with high morbidity and mortality nowadays.

In the late 20th century, Brazilian Cardiology constructed a solid legacy and international relevance, a trajectory from which renowned fellows were elected representatives of this first century of our specialty (Figure 2).

This new decade emerges with a new design for Cardiology in a digital, connected, patient-focused environment, based on major pillars – artificial intelligence, big-data, robotics, biosensors, telemedicine, devices, sensors and genomics. Together they will support the Precision Cardiology paradigm. The need to incorporate into our mindset the idea of the cardiologist approaching the world of innovation and entrepreneurship is a new challenge in the formation of our new cardiologists with emphasis on the development of female leadership in cardiology. From the assistance point of view, our integration with the population health and family doctors will increase, as well as our multidisciplinary approaches, enabling the implementation of lines of care and the monitoring of clinical outcomes and focused on patient safety. This means to know and dominate the triad formed by cardiovascular biomedical knowledge, technology (Digital medicine) and humanization. Knowledge moves forward quickly and unstoppable, in a global manner, supported and favored by numerous opportunities of knowledge exchange between peers and institutions worldwide. The technology, which promotes the evolution of Digital and Precision Medicine, favors the access to knowledge, the strengthening of diagnosis, the promotion of man-machine interaction and the possibility of personalizing therapy to its molecular level. And, finally, the rescue of essence: the humanization of such advanced and futuristic Cardiology. A new journey will be necessary into the daily practice of doctor-patient interaction in order to promote empathy, patient empowerment and sensitivity to the doctor inserted in this new context for this new decade.[9-13]

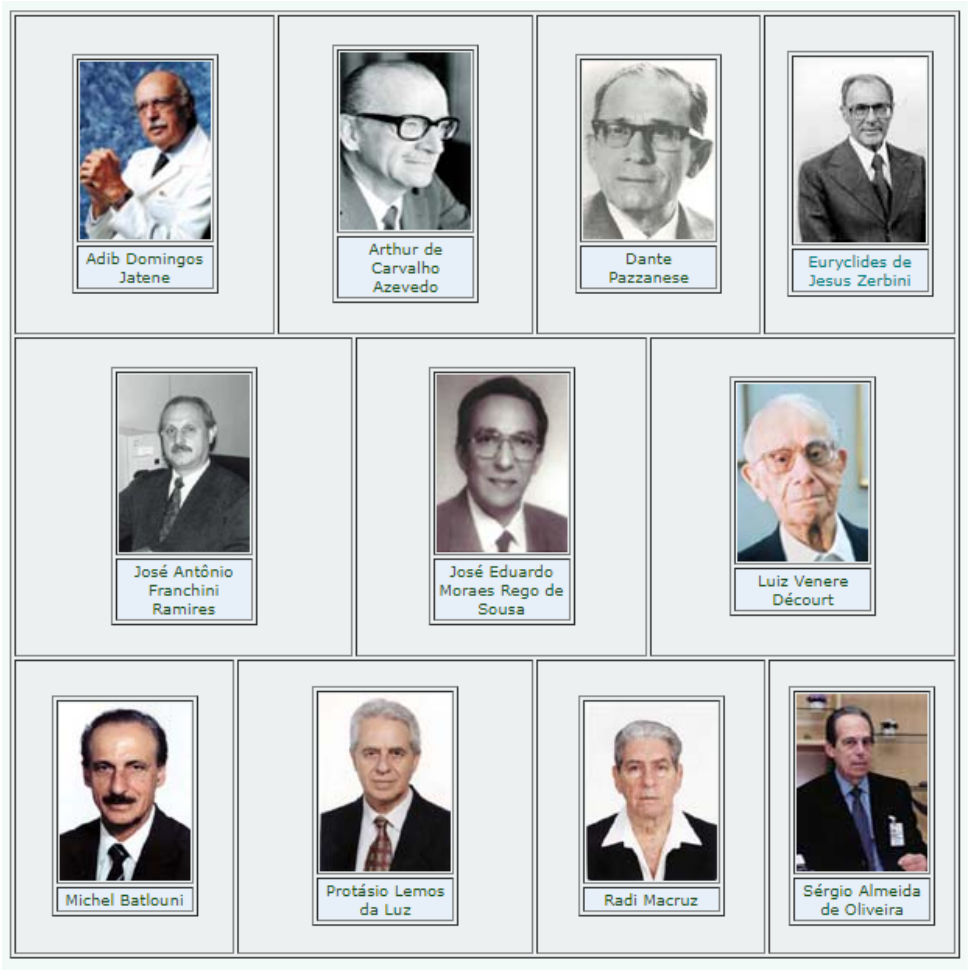

Figure 2 – *Brazilian cardiologists. Elected from SBC Partners as highlights of the 20th century.*[1]

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Paralympics – Addendum to the Update on the Guidelines for Sport and Exercise Cardiology of the Brazilian Society of Cardiology and the Brazilian Society of Exercise and Sports Medicine

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Para-athletes or athletes with disabilities

Paralympic sports include a wide group of athletic activities for individuals who have disabilities and who participate in diverse levels of competition.

The Paralympic Movement began in 1888 in Berlin with the founding of the first sports clubs for people with hearing impairments.

In 1922, the International Committee of Sports for the Deaf (CISS) was founded and the First International Silent Games were organized.

In 1989, the International Paralympic Committee was founded in Dusseldorf (http://www.paralympic.org), related to diverse federations connected to athletes with disabilities.

In 1945, Ludwig Guttmann, a doctor specializing in neurological surgery, initiated rehabilitation programs for World War II veterans with special needs at the National Spinal Injuries Centre of the Stoke Mandeville Hospital, in England. The first competition took place with 16 war veterans, on July 29, 1948, during the Opening Ceremony of the 1948 Summer Olympics in London. In 1960, the first Paralympic Games took place in Rome, with 400 athletes from 23 countries; on that occasion, Pope John XXIII referred to Guttmann as "the de Coubertin of the paralyzed." Since the Summer Games of 1988 and the Winter Games of 1992, the Paralympics have been held in the same city as the Olympics.

In Brazil, Paralympic sports began in 1958, when the wheelchair user Robson Sampaio de Almeida and the physical trainer Aldo Miccolis founded the Clube do Otimismo. Shortly thereafter, Sérgio Seraphin Del Grande, an athlete with a disability, founded the Clube dos Paraplégicos de São Paulo. The National Association for Parasports (Associação Nacional de Desporto de Deficientes [ANDE]) was founded in 1975.

In 1995, the Brazilian Paralympic Committee (http://*www.cpb.org.br*) was founded. Its headquarters, initially located in the city of Niterói, Rio de Janeiro State, moved to Brasília in 2002. The Brazilian Paralympic Committee has the following vision, mission, and principles:

"1 – **Vision:** to represent and lead the Brazilian Paralympic Movement, seeking to promote and develop high-performance sports for people with disabilities;

2 – **Mission:** To exercise the legitimate representation of Brazilian Paralympic sports; To organize Brazil's participation in continental and worldwide competitions and in the Paralympic Games; To promote the development of diverse Paralympic sports in Brazil, in conjunction with the respective national organizations; To promote universal access of people with disabilities to athletic practice on their diverse levels;

3 – **Principles:** To work in full partnership with technical areas of national associations and confederations affiliated and connected to the Brazilian Paralympic Committee, valorizing the convergence of objectives in favor of the development of every segment of Brazilian Paralympic sports."

Paralympic Medicine deals with healthcare related to athletes with disabilities.[1] As of 1994, the International Paralympic Committee, aims to bring scientific support to the Paralympics, without interfering with athletes, training, and organization of the games.[2] There are 4 core Paralympic values established by the International Paralympic Committee. They are courage, determination, inspiration, and equality.[3]

The development of specialized prostheses and equipment, such as specific wheelchairs is essential for the optimized use of parathletes' residual mechanical function.[4,5] Two-dimensional kinematic analysis of athletic gestures may be useful, given the broad diversity of parathletes' residual functional capabilities.[6] Furthermore, sports psychologists should assist parathletes in developing mental skills for stress management and consequent improvements in athletic performance.[7]

Cardiological evaluation: pre-participation and re-evaluation

All Paralympic athletes should undergo evaluation, regardless of age, sex, and associated disability; pre-participation

Keywords

Sports; Athletes/history; Athletes/legislation &jurisprudence; Disabled Persons; Physical and Rehabilitation Medicine; Hearing Loss; Vision Disorders.

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evaluation should include male and female children, adolescents, adults, and masters/elderly athletes, and it should be the sole responsibility of the attending physician (class of recommendation: I, level of evidence: C).

Evaluation should be comprehensive, considering the organism as a whole, with emphasis on physical and somatic aspects; it is necessary to bear in mind that, in physical training and athletic performance, there are interactions between physical disabilities, comorbities, and their respective sequelae (class of recommendation: I, level of evidence: C).

Frequency of re-evaluation should be at the discretion of the attending physician, in accordance with each case's characteristics; the primary aim of re-evaluation frequency should be safe athletic practice (class of recommendation: I, level of evidence: C).

Evaluation of Paralympic athletes must follow the established protocol, which is summarized in Table 1.

Following initial evaluation, based on the findings, specialized exams will be indicated at the attending physician's discretion. Examples include cardiopulmonary exercise test (CPT), echocardiogram (ECHO), vectorcardiogram (VCG), computerized tomography, magnetic resonance, ultrasound, hemoglobin electrophoresis (to investigate sickle cell anemia), cardiological evaluation, ophthalmic evaluation, (to investigate Marfan syndrome, glaucoma, and retinal detachment), and orthopedic evaluation[8,9] (class of recommendation: I, level of evidence: C).

For athletes with cerebral palsy, the spasticity assessment score (quantitative sports and functional classification [QSFC]) may be used, based on muscular conditions in the upper and lower limbs and the torso. The score may be used for clinical investigation, clinical treatment, and physical training.[10]

Athletes who use wheelchairs or prostheses should be closely and thoroughly examined for decubitus sores or sores in the region of the prosthetic implant. The presence of ulcers in these areas will make the athletes temporarily ineligible, until the local conditions of the tegument have been restored (class of recommendation: I, level of evidence: C). The practice of urinary retention should be prohibited in athletes who use wheelchairs, owing to the risk of high elevations in blood pressure and stroke. In cases of neurogenic bladder, it is necessary to pay attention to the presence of subclinical urinary infection.

The occurrence of athletic heart syndrome, considering the presence of 2 or more signs, affected 46% of Paralympic athletes. Signs of athletic heart syndrome occurred in 33% of clinical exams (murmurs and clicks), in 55% of electrocardiograms (bradycardia, incomplete right bundle branch block, overloads, T-wave alterations), in 15% dos vectorcardiogram (overloads), and in 5% of echocardiograms (cavity dimensions higher than normal). Signs occurred in 51% of athletes, with 46% of cases having 2 or more signs and 12% having 4 or more signs. ET was normal in 77% of athletes; ischemic ST segments were not found. Right bundle branch block was present in 23% of cases.[11]

The following ECG alterations, classified as athletic ECG, were found in Paralympic athletes: primary alterations in ventricular repolarization, 6%; first-degree atrioventricular block, 2%; sinus bradycardia, 6%; block of the anterosuperior division of the left His bundle branch, 2%; right His bundle branch conduction disorder, 14%; early ventricular repolarization, 29%; left atrial overload, 2%; left ventricular overload, 39%.[12]

Eight cases of late potentials were described on high-resolution electrocardiogram in 11% of athletes, and there was no evidence of heart disease in a consecutive series of 79 top athletes with disabilities.[13]

In subgroups of Paralympic athletes, significant correlations have been described involving variables related to aerobic potential, anaerobic threshold, and morphological variations evaluated by echocardiogram, proving that athletic heart syndrome may occur in Paralympic athletes.[14]

In Paralympic Judo athletes, the presence of athletic heart syndrome has been found in 64% of cases evaluated.[15]

In subjective evaluations of young Paralympic athletes, it was found that parents might report lower perceived quality of life than their children.[16]

Cardiopulmonary exercise test

The bases of cardiopulmonary exercise testing protocols include: 1) reproducibility of athletic actions, according to the principle of specificity; 2) adequacy for the athletic modality and the athlete's means of locomotion; 3) performance of tests with stability and safety, guaranteeing accuracy and reproducibility of measurements[11] (class of recommendation: I, level of evidence: B).

Special care should be taken in relation to type and degree of disability, the athlete's posture, room temperature, prior emptying of bladder, prevention of hypertension, the risk of seizures and accidents, blood pressure measurements, and

Table 1 – Protocol for evaluating Paralympic athletes, according to the Medical Department of the Brazilian Paralympics Committee (http://www.cpb.org.br)

1. Application of a standardized medical questionnaire, involving identification, personal and family history, sports history, and dietary and daily living habits;
2. Physical examination, with standardized medical form;
3. Laboratory exams: complete blood count, iron, ferritin, folic acid, vitamin B12, blood type, total lipids, cholesterol and fractions, triglycerides, uric acid, blood glucose, type I urine, creatinine, urea, sodium, potassium, testosterone, free testosterone, insulin, cortisol, free T4, free T3, T3, T4, TSH, serology for Chagas, herpes, HIV and HCV, total proteins, AST, ALT, GGT, alkaline phosphatase, calcium, and homocysteine;
4. Chest radiograph;
5. Resting ECG and ergometric test.

adequate mask sealing. Numerous factors may limit evaluation performance, including: 1) clinical factors: mental and sensorial disabilities (visual, tactile, or hearing impairments, epilepsy, autonomic dysreflexia, neurogenic bladder, sympathetic deprivation, post-polio syndrome, stress-induced tachypnea, malnutrition); 2) locomotive factors: reduced body mass, reduced muscle strength and flexibility, increased muscle tone, reduced joint mobility, reduced motor coordination, osteoarticular injuries secondary to athletic practice, amputation stump injuries; 3) cardiovascular factors: eventual associated infections; 4) physiological factors: reduced peak VO_2, anaerobic threshold, respiratory compensation point, early fatigue, physical inactivity; 4) socioeconomic and cultural factors: social exclusion, lack of funds.[8]

According to the principle of specificity, arm ergometers have been used for tennis players, throwers, weightlifters, fencers, and swimmers; bicycles for cyclists; and treadmills for all other modalities;[8] cyclists may use their own equipment, attached to a Mag 850 Minoura 180 system (class of recommendation: I, level of evidence: C).

Athletes should be encouraged to reach their "real" maximum effort. Athletes with cerebral palsy or mental disabilities require prior, detailed explanation regarding the tests, owing to inherent challenges in comprehension. It is possible to carry out the first exams of the day with athletes who have been previously evaluated on other occasions, allowing those who will undergo the test for the first time to watch and understand the execution and objectives of the test.[17]

Some precautions should be followed. In athletes with cerebral palsy, there exists a predisposition to accidents (falling), in treadmill tests, due to lack of neuromuscular coordination, especially at higher velocities. In some cases, it is necessary to increment workload using inclination rather than velocity. Due to involuntary facial movements or very acute mandibular angle, the mask or mouthpiece may not seal adequately, and escape may occur in uptake of gases. Athletes with visual impairments, in most cases, will need to maintain contact with their hands on the rail of the treadmill (without leaning on it), and they will need to receive verbal orientation on their biomechanics and spatial situation. Safety belts, which are tied to the athlete's waist and to the front rail of the treadmill, may be used in some cases.[17]

Cardiopulmonary exercise tests may be carried out following numerous specific protocols, examples of which are summarized in Table 2.

Knechtle and Köpfli's[18,19] Protocol (Institute of Sports Medicine, Swiss Paraplegic Centre) for wheelchair treadmill testing begins at a velocity of 8 km/h and an inclination of 1%, with 0.5% increments every 2 minutes and constant velocity, until exhaustion.[18,19]

There are also advantages to carrying out field tests.[20] Variations between 48% and 80% have been described in regression equations for determining physical capacity in people with paraplegia and quadriplegia. These variations may be explained by the level and degree of spinal cord injury, age, gender, physical activity, and body weight. In Brazil, values referring to aerobic potential of Paralympic athletes have been similar (Table 3).[21]

Pre-participation evaluation for leisure activities is similar, depending on physical and mental stress. In many situations, given the emotional burden involved and the lower level of training, physical and psychological stress may be highly intense, to a degree similar to that of competitions.

Preventing injuries/sudden death in sports

Injury prevention should include prevention of accidents, aggravation of pre-existing injuries and comorbidities, and sudden death.

The objectives of an athletic injury prevention protocol are based on pre-participation screening:

1. Identification of predisposing conditions, or be it, cardiovascular diseases that may potentially cause sudden death;
2. Definition of measures that may be taken to reduce risk of sudden death: "What are they?" "How should they be developed?"
3. Standardization approach to be adopted for each heart disease and discussion of the eventual disqualification of an athlete to exercise his or her profession.

Prevention of injuries and sudden deaths in sports and leisure activities is carried out considering early diagnosis and treatment of cardiovascular disorders, as well as the application of up-to-date ineligibility criteria, which are duly applied to Paralympic athletes.[23] It is imperative that competition venues have medical and paramedical resources that are properly equipped for emergency response.

In various institutions, the clinical director and/or the attending physician responsible are accountable to the respective Regional Council of Medicine regarding compliance with these norms.

Individuals who have been recently hospitalized or who have been sedentary for a long time will require progressive

Table 2 – Protocols for cardiopulmonary exercise tests for Paralympic athletes (Centro de Estudos em Fisiologia do Exercício – Unifesp/Escola Paulista de Medicina)[8]

Wheelchair treadmill CET	Initial velocity of 3 to 13 km/h and initial inclination of 0 to 2%, with increments of 0.5 to 1.0 km/h and 0.5 to 1.0% every 3 minutes
Treadmill CET	Initial velocity of 3 to 8 km/h and initial inclination of 0%, with increments of 0.5 to 1.0 km/h and 0.5 to 5.0% every 3 minutes
Exercise bicycle CET	Initial load of 25 to 50 watts, with increments of 25 watts every 3 minutes
Roller bicycle CET	Initial velocity of 30 to 33 km/h, with increments of 3 km/h every 3 minutes
Arm ergometer CET	Initial load of 25 a 37.5 watts, with increments of 5 to 25 watts every 3 minutes

CET: cardiopulmonary exercise test

Table 3 – Aerobic potential of Brazilian Paralympic athletes participating in the Atlanta Games. Silva AC, Torres FC, Oliveira Filho JA. Avaliação dos atletas paraolímpicos de Atlanta. Unpublished data. Unifesp-EPM, São Paulo, 2006[22]

Modality/disability	n	$VO_{2\,max}$ ml.kg^{-1}.min^{-1}	Variation ml.kg^{-1}.min^{-1}	LA %
Football ♂ CP	18	50.6 ± 6.70	36.5 – 62.8	70 ± 9
Swimming ♂ tetra, PM, SCI	7	36.8 ± 17.7	19.8 – 59.0	64 ± 5
Swimming ♀ para, PM, SCI	4	48.9 ± 9.90	35.3 – 61.4	56 ± 9
Basketball ♀ PM, SCI, amp	14	30.0 ± 6.00	20.0 – 40.0	61 ± 8
Tennis ♂ SCI	2		29.7 – 33.3	60
Table tennis ♂ SCI, PM	2		31.0 – 34.5	64.67
Judo ♂ VD	4	45.5 ± 12.0	36.0 – 62.0	59 ± 11
Field/wheel ♂ tetra, PM, CP	3	32.8 ± 10.0	25.0 – 44.0	60 ± 2.9
Field/wheel ♂ para, amp	2	39.0 - 42.0		47.62
Track ♂ VD	3	57.0 ± 7.0	50.0 – 65.0	80 ± 5
Track ♀ VD	2		51.0 – 59.0	46.72
Pentathlon/wheel ♂ para, PM, amp	2		44.0 – 51.0	64.81

amp: amputation; AT: anaerobic threshold; CP: cerebral palsy; para: paraplegia; PM: poliomyelitis; quad: quadriplegia; SCI: spinal cord injury; wheel: wheelchar; VD: visual disability

training with gradual increments in exercise intensity and session frequency and duration; in addition to the risks which physical injuries and sequelae present, their appearance may be a factor that discourages training, negatively impacting self-image and predisposing athletes to abandon the program (class of recommendation I, level of evidence C).

Ethical Aspects

Medical evaluation should include specialists from diverse areas, with exercise and sports medicine, cardiology, orthopedics, and physiatry standing out.

When treating athletes with disabilities, it is important to emphasize that it is the physician's exclusive competence to direct training, diagnose any eventual pathologies and sequelae, request exams, prescribe therapy, and remove athletes from athletic activities; the doctor is not allowed to delegate functions within his or her exclusive competence to individuals who are not qualified to practice medicine (Brazilian Federal Council of Medicine, Resolution nº 1236/87). On the other hand, training should be conducted by physical education instructors and physical therapists. The interaction between doctors, physical education instructors, physical therapists, physiologists, nutritionists, and psychologists is fundamental to a program's success. Training should be prescribed by means of a medical prescription that states the modality, frequency, and duration of sessions, as well as training intensity and other observations at the attending physician's discretion. This conduct has been ratified by the Brazilian Federal Council of Medicine Position 4141/2003: "In all of the above, it is the physician's exclusive competence, following diagnosis of a disease, to prescribe adequate therapy for a patient, including the prescription of physical activity in view of the disease diagnosed or to prevent diverse diseases."

In various institutions, the clinical director and/or responsible attending physician are accountable regarding compliance with these norms before their respective Regional Council of Medicine. Physicians' relationships with other professionals in the area of healthcare should be based on mutual respect, freedom, and professional independence for all involved, always seeking the interest and well-being of their patients (Brazilian Code of Medical Ethics, January 1, 1988, Article 18). Interaction between physicians, physical education instructors, physical therapists, nutritionists, psychologists, and trainers is fundamental to a training program's success, and it should be encouraged at all times.

Recommendations

Currently, given the scarcity of reports in specialized literature, criteria for attending Paralympic athletes are generally based on specialist consensus (level of evidence: C).

Determination of athletic eligibility should follow the protocol of the International Paralympic Committee Classification Code and International Standards[24] and the Brazilian Olympic Committee. In this manner, Paralympic athletes may be eligible for one activity and ineligible for another. Athletic eligibility criteria for all Paralympic activities are defined by the respective international federation. Physicians, trainers, and Paralympic athletes should be aware of the risks of eventual and involuntary doping.[25] Since 2000, an overall incidence of < 1% of violations related to doping has been reported in Paralympic competitions. These are generally detected by urine tests during competition periods, comprising a total of 60 violations, 37 of which were in weightlifters.[26]

Recommendations for attending Paralympic athletes are listed in Table 4. The practices of doping and boosting are to be severely prohibited. Spinal cord injuries lead to changes in autonomic and cardiovascular function, thus interfering with athletic performance. In these cases of spinal cord injuries at or above level T6,[27] boosting may occur. Boosting intentionally induces autonomic dysreflexia during

Table 4 – Recommendations for attending Paralympic athletes (class of recommendation: I, level of evidence: C)

1. All Paralympic athletes should undergo evaluation, regardless of age, sex, and associated disability.
2. Pre-participation evaluation should include male and female children, adolescents, adults, and elderly athletes, and it should be the sole responsibility of the attending physician.
3. Re-evaluation frequency should be at the discretion of the attending physician, in accordance with each case's characteristics; the primary aim of re-evaluation frequency should be safe athletic practice.
4. Evaluations should follow the protocol of the International Paralympic Committee, and they should by specific for each athletic activity and individualized for each athlete.
5. Clinical and cardiological evaluations should be coordinated and carried out by physicians; physical education instructors, physical therapists, physiologists, nutritionists, and psychologists should participate in evaluation, and the integration of physicians and other healthcare professionals is of great value.
6. Clinical evaluation should include all parts and systems of the organism, and it should be performed by a multi-professional team involving diverse medical specialties.
7. Cardiovascular evaluation follows the same general eligibility criteria for athletes without disabilities.
8. Pharmacological prescriptions should always be guided by the WADA's latest policies, which are periodically updated.

WADA: World Anti-Doping Agency

competition.[28] For the purpose of obtaining rapid elevations in blood pressure, some athletes who use wheelchairs might induce a state of autonomic dysreflexia, a reflex which occurs in the lower part of the body.[29] Boosting leads to an increase in circulating catecholamines, blood pressure, and heart rate, and it leads to a 9.7% improvement in racing time for 7% to 10% of athletes.[30] The practice of boosting, however, exposes athletes to serious risks during competitions, and it is officially banned by the International Paralympic Committee.[30] In order to obtain a rapid increase in blood pressure athletes who use wheelchairs have been reported to provoke a state of autonomic dysreflexia by exposing the lower part of the body to painful stimuli, which include keeping one's bladder full, tying belts or straps around one's legs, sitting on pointed objects, sitting on one's own scrotum, closing one's catheter tube in order to fill the bladder, bending one's feet in the wheelchair, and provoking the fracture of toes.[29] Only Paralympic athletes with high-level spinal cord injuries may experience episodes of autonomic dysreflexia.[31]

During medical care, special attention should be paid to musculoskeletal injuries, which accounted for 44.6% of 2,590 accredited medical encounters.[32] Considering any musculoskeletal complaint which led athletes to seek medical attention, the occurrence of sports injuries during the Winter Paralympic Games was 9.4% in 2002, 8.4% in 2006, and 24% in 2010. This proportion was similar in men (22.8%) and women (26.6%).[33]

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Original Article

Rheumatic Fever: A Disease without Color

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Abstract

Background: Brazil has approximately 30.000 cases of Acute Rheumatic Fever (ARF) annually. A third of cardiovascular surgeries performed in the country are due to the sequelae of rheumatic heart disease (RHD), which is an important public health problem.

Objectives: to analyze the historical series of mortality rates and disease costs, projecting future trends to offer new data that may justify the need to implement a public health program for RF.

Methods: we performed a cross-sectional study with a time series analysis based on data from the Hospital Information System of Brazil from 1998 to 2016. Simple linear regression models and Holt's Exponential Smoothing Method were used to model the behavior of the series and to do forecasts. The results of the tests with a value of $p < 0.05$ were considered statistically significant.

Results: each year, the number of deaths due to RHD increased by an average of 16.94 units and the mortality rate from ARF increased by 215%. There was a 264% increase in hospitalization expenses for RHD and RHD mortality rates increased 42.5% (p-value < 0.05). The estimated mortality rates for ARF and RHD were, respectively, 2.68 and 8.53 for 2019. The estimated cost for RHD in 2019 was US$ 26.715.897,70.

Conclusions: according to the Brazilian reality, the 1-year RHD expenses would be sufficient for secondary prophylaxis (considering a Benzatin Penicillin G dose every 3 weeks) in 22.574 people for 10 years. This study corroborates the need for public health policies aimed at RHD. (Arq Bras Cardiol. 2019; 113(3):345-354)

Keywords: Rheumatic Fever; Rheumatic Heart Disease; Cardiovascular Surgical Procedures/mortality; Hospitalization/economics; Antibiotic Prophylaxys/economics; Public Health Policy.

Introduction

According to the Brazilian Institute of Geography and Statistics (IBGE), Brazil has 10 million cases of pharyngotonsillitis every year, leading to approximately 30.000 cases of Acute Rheumatic Fever (ARF).[1] Rheumatic Heart Disease (RHD) has a low incidence in developed countries, with 0.1 to 0.4 cases/1,000 school children in the US, while in Brazil these values are 7 cases/1.000 school children, showing that it is directly associated with environmental and socioeconomic factors.[2] Approximately 70% of the patients with acute RF develop carditis and a third of the cardiovascular surgeries performed in Brazil are due to of RHD sequelae.[3,4] RF was responsible for 5.1 million potential disability-adjusted life years (DALYs), resulting from 280.000 deaths in 2004, and it was the seventh and eighth causes of mortality and morbidity due to neglected diseases, respectively.[5]

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Rheumatic fever is a disease with a cross-linked autoimmune nature triggered by susceptible host response after pharyngotonsillitis by Group A β-hemolytic *Streptococcus*.[6–8] The implementation of treatment for pharyngotonsillitis by Group A β-hemolytic *Streptococcus* with Benzathine Penicillin G (BPG) within nine days of symptom onset can eradicate the infection and prevent a first outbreak of acute RF[3] or a new outbreak,[9] which was already advocated by the WHO in 1955.[10] Unfortunately, the expected infection eradication rates do not seem to have been reached in Brazil, as shown by our analyses of data from the Health Information System (SIH) from the Brazilian National Health System (SUS).[11]

SUS guarantees universal and egalitarian access to health care and services to everyone in the national territory. Therefore, Brazil's health policies include care by the public (SUS) and the private sectors (supplementary healthcare, or private health plans), plus care by the private sector within the public sector (complementary health) and by the public sector within the private sector (regulation, inspection, surveillance). Herein, we disclose the cost analysis of health care and services related to RF and RHD incurred by SUS, i.e. under public management, which is different from that of the private systems.

Considering the presented data and the absence of a national RF and RHD prevention program, the objective of this

study was to analyze the historical series of mortality rates and disease costs, projecting future trends to offer new data that may justify the need to implement a public health program for RF. In addition, we estimate the annual costs of the diseases and their comorbidities in Brazil. Moreover, the RHD mortality rate was compared with breast (BC) and prostate (PC) cancer mortality rates, which already have implemented public health programs, such as the case of the Pink October[12] and the Blue November,[13] respectively.

Methods

A cross-sectional ecological study with a time series analysis was developed to analyze the historical series of mortality rates and disease, using data from the SIH/SUS[11] from 1998 to 2016. The year 2017 was not included in this study because the data were still subject to updates.

To estimate the annual cost of the diseases and their comorbidities in Brazil, first we determined the costs associated to the diagnosis of ARF, primary and secondary prophylaxis of RHD, as well as public expenses associated to the consequences of RHD, such as interventional procedures and hospitalizations for heart failure, atrial fibrillation, ischemic stroke and infective endocarditis. For this purpose, the data were obtained as follows: the procedures required for the diagnosis of ARF and Jones Criteria, which have been reviewed at irregular intervals by the American Heart Association (AHA), adjusted for RHD. For hospitalization costs, we considered the mean length of hospital stay of 7 days for ischemic stroke, heart failure 4 days, 4 days for atrial fibrillation and 17 days for infective endocarditis.[14] The data related to cost of the procedures required for the diagnosis of ARF/RHD and hospitalizations due to consequences of RHD were taken from the database of the Table Management System of Procedures, Medical drugs, Orthotics, Prosthetics and Special Materials of SUS (SIGTAP)[14] and the Drug Market Regulation Chamber (CMED) of the National Agency of Sanitary Surveillance (ANVISA).[15] These data are available at the Hospital Information Systems - SIH/SUS -Brazilian Health System. Second, we developed a hypothetical scenario based on the current panorama of rheumatic fever in Brazil, crossing data from the Brazilian Institute of Geography and Statistics with data from the REMEDY study[16] with their respective morbidities in numbers, to estimate the number of cases. The REMEDY study involved 25 sites in 12 African countries, Yemen and India. Countries were grouped into three income categories: low-income countries (Ethiopia, Kenya, Malawi, Rwanda, Uganda and Zambia), low-middle income countries (Egypt, India, Mozambique, Nigeria, Sudan and Yemen) and middle-income countries (Namibia and South Africa).[16] The costs obtained were multiplied by the number of cases of group A Streptococcus (GAS) infection, ARF, RHD, and RHD morbidity.

Moreover, the RHD mortality rate was compared with breast (BC) and prostate (PC) cancer mortality rates, which was performed taking in account the period of 18 years (1998 to 2016), using data from the Mortality Information System's (SIM) of SUS – DATASUS,[11] responsible for the maintenance of mortality data in Brazil. For this comparison, a simple linear regression was adjusted to each case (RHD, PC, and BC).

The present study used only secondary data obtained from public access sources. The approval of this study was waived by the Research Ethics Committee, as established in Resolution 510 of the National Health Council (CNS) of April 7, 2016.

Statistical analyses

To evaluate the trend of the historical series, simple linear regression models were adjusted. When working with time series, it is common to find problems of heteroscedasticity and autocorrelation. In order to deal with these problems and to allow the performance of valid inferences for the adjusted models, as well as to guarantee the robustness of the models, the HAC (Heteroskedasticity and Autocorrelation Consistent) was used for the covariance matrix of the estimated coefficients.[17] To model the behavior of the series and make predictions, Holt's Exponential Smoothing Method was used.[18] R software (version 3.2.4) was used for the statistical analysis. The results of the tests with a value of $p < 0.05$ were considered statistically significant. The limitation of this study was the analysis of the SIH (SUS) database,[11] of which data are entered every two months or more, limiting confidence only to total annual data.

Results

Mortality rates from Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) showed an increasing pattern throughout the analysis period (Figure 1). The ARF mortality rate increased from 0.80 in 1998 to 2.52 in 2016, a growth of 215%, with an increase of 0.12 units, on average, with each passing year (Figure 1A). The RHD mortality rate was 5.77 in 1998, increasing to 8.22 in 2016 (a growth of 42.5%), showing an average rate increase of 0.15 units per year (Figure 1C). Using Holt's Exponential Smoothing, it was possible to perform mortality estimates for ARF and RHD. The predicted values for ARF mortality rate for 2018 and 2019 were, respectively, 2.59 and 2.68, while the predicted values for RHD mortality rates were 8.43 for 2018 and 8.53 for 2019.

Although these numbers may be underestimated de to the lack of a health surveillance strategy, which will be discussed later, 732 deaths were recorded in 2003 and after a linear regression (p-value < 0.005) of the entire studied period, it is observed that the number of deaths increases on average 16,94 units each year.

Regarding the cost analyses, Table 1 shows a detailed description of the obtained costs for ARF diagnosis, the most common interventional procedures in RHD, and the costs of hospitalization due to the consequences of RHD, for a hypothetical patient in the context of the Brazilian public health system.

With an average of 30,000 ARF cases per year in Brazil, in a hypothetical scenario based on the REMEDY study,[16] we would have the scenario shown in Figure 2. According to this hypothesis, there would be 21.000 cases of RHD per year, which would lead to approximately 7.014 new patients with heart failure, 4.578 cases of atrial fibrillation, 1.491 cases of stroke, 8.904 cardiac surgeries and 840 cases of infective endocarditis.

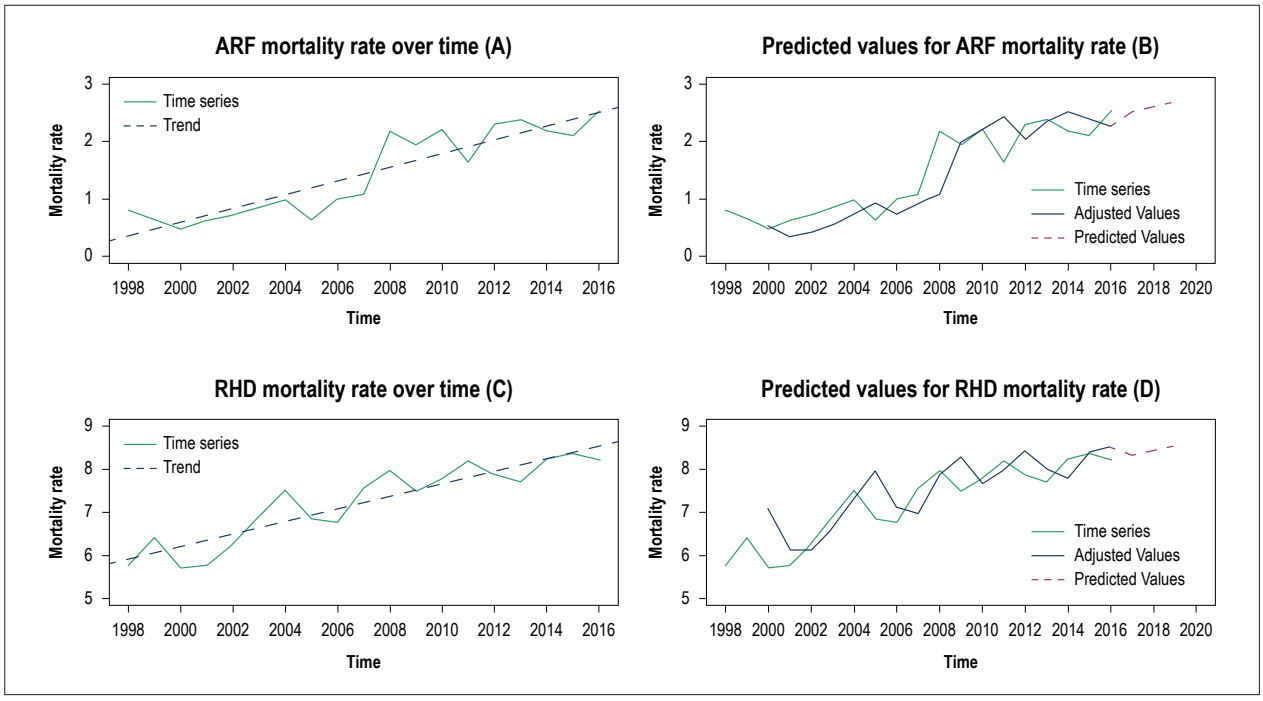

Figure 1 – *Growth trends and predicted values for Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) mortality rates. The model equation for the trend of the ARF (A) mortality rate was ARF_{MT} = –237,79 + 0,12* Year, whereas for the trend of the RHD mortality rate (C) it was RDH_{MT} = –286,11 + 0,15* Year. It should be noted that all trends were significant (p-value < 0.050), evidencing the increasing trend of the series over time.*

Table 1 – A detailed description of the costs associated with the diagnosis of Acute Rheumatic Fever, as well as the costs of interventional procedures and hospitalizations due to Rheumatic Heart Disease in the context of the public health system of Brazil (values set for 2016)

Diagnosis and treatment	Procedures	Individual cost per procedure	
		(R$)	(US$)†
Procedures needed for the diagnosis of ARF*	Medical consultation	10.00	3.04
	Electrocardiogram	5.15	1.56
	CRP	2.83	0.86
	ESR	2.73	0.83
	ASO	2.83	0.86
	Oropharyngeal Culture	5.72	1.74
	Transthoracic echocardiogram	39.64	12.03
	Rapid antigen detection test for GAS	4.33	1.31
Interventional procedures in RHD*	Valve repair	6,061.70	1,840.33
	Valve replacement	6,321.74	1,919.28
	Multiple valve replacement	7,277.56	2,194.28
	Percutaneous mitral valvuloplasty	1,739.19	528.01
Hospitalization due to the consequences of RHD*	Ischemic stroke	1,635.55	496.55
	Heart failure	699.46	212.35
	Atrial fibrillation	219.65	66.68
	Infective endocarditis	880.00	267.68

*ARF:acute rheumatic fever; RHD: rheumatic heart disease; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; ASO: antistreptolysin O; GAS: group A β-hemolytic Streptococcus. *Data from Jones Criteria, reviewed by the AHA. † The values in US dollars (US$) were obtained on February 8, 2018. One Brazilian Real (R$) was equivalent to US$ 0.3036. Source: The authors.*

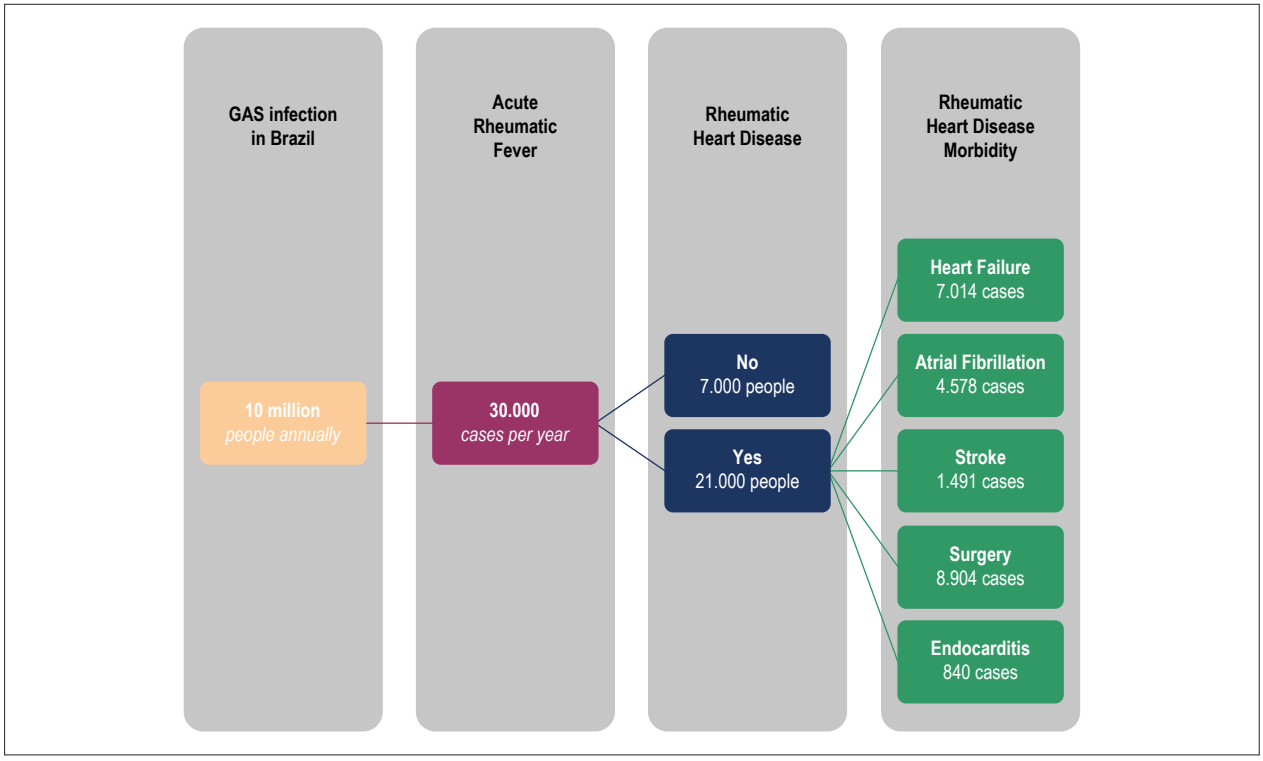

Figure 2 – *GAS: Group A β-hemolytic Streptococcus. Hypothetical scenario based on the current panorama of rheumatic fever in Brazil, after crossing data from the Brazilian Institute of Geography and Statistics with data from the REMEDY study,[16] showing the evolution of Acute Rheumatic Fever to Rheumatic Heart Disease, with their respective morbidities in numbers.*

As shown in Figure 3A, total expenditures with hospitalization in Brazil for RHD increased by 264% in the analyzed period, from R$ 23.077.356,65 (US$ 7.006.288,21) in 1998 to R$ 84.080.772,39 (US$ 25.526.924,01) in 2016. The costs in the analyzed period were recorded in 2013 (R$ 99.476.203,42 or US$ 30.200.975,35). Therefore, applying Holt's Exponential Smoothing method, the predicted values for total costs related to RHD (Figure 3B) were R$ 86.691.610,00 (US$ 26.319.572,79) and R$ 87.997.028,00 (US$ 26.715.897,70) for 2018 and 2019, respectively.

Considering this hypothetic scenario, where all the morbidities required at least one hospitalization and the regular values of cardiac surgeries, the expenses for the Brazilian public health system would have a minimum annual cost of R$ 56.726.131,10 (US$ 15.981.534,55), as shown in Figure 4.

Taking as reference the mortality rates from two diseases with a high global prevalence, breast cancer and prostate cancer, of which magnitude generated the preventive task force established by worldwide campaigns (Pink October and Blue November), RHD mortality behaves in a similar manner (Figure 5). In this sense, we highlight that growth trends of RHD and BC are significant; however, there are no significant differences between them, which is demonstrated by the overlap of confidence intervals. Moreover, the PC trend was not statistically significant (p-value = 0.334) for the comparison of confidence intervals.

Discussion

Rheumatic heart disease (RHD) is one of the leading noncommunicable diseases in low- and middle-income countries and accounts for up to 1.4 million deaths annually. There are few contemporary data systematically collected on disease characteristics, treatments, complications, and long-term outcomes in RHD patients.[16]

Despite the magnitude of the problem, Brazil does not have a specific database for this pathology. Thus, because we did not have weekly or monthly data, it was not possible to statistically evaluate disease seasonality. Although these numbers may be underestimated by the lack of a health surveillance strategy during the entire studied period, it is observed that, each year, the number of deaths increases on average 16.94 units, as obtained from the model equation for the trend of the RHD mortality rate (Figure 1C and D). Indeed, ARF and RHD are included in the Brazilian list of preventable death causes for children under 5 years and for the age group of 5 to 75 years. The avoidable or reducible causes of death are defined as those totally or partially preventable by effective health care services, accessible at a certain place and time. Herein, this mortality rate refers to the overall Brazilian population, without distinction of age, with predictive values for 2019 at the magnitude of 8.53 for RHD and 2.68 for ARF, which are higher than the ones from 2017[11] (6.70 for RHD and 1.94 for ARF), representing an increase of 27.3% and 38.1% for the respective pathologies.

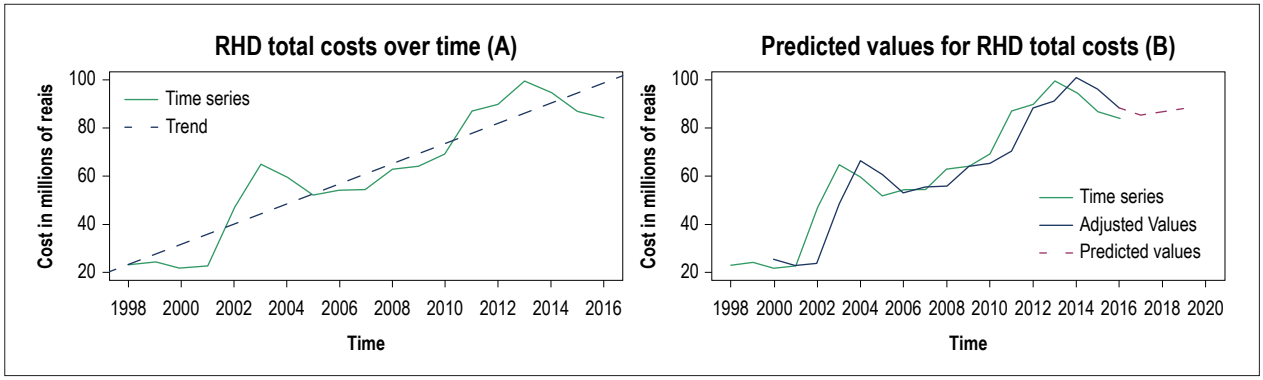

Figure 3 – *Growth trends (A) and predicted values (B) for total costs with RHD. The model equation for the total costs with RHD (C) was RDH_{TC} = –8346,31 + 4,19* Year. It should be noted that all trends were significant (p-value < 0.050), evidencing the increasing trend of the series over time.*

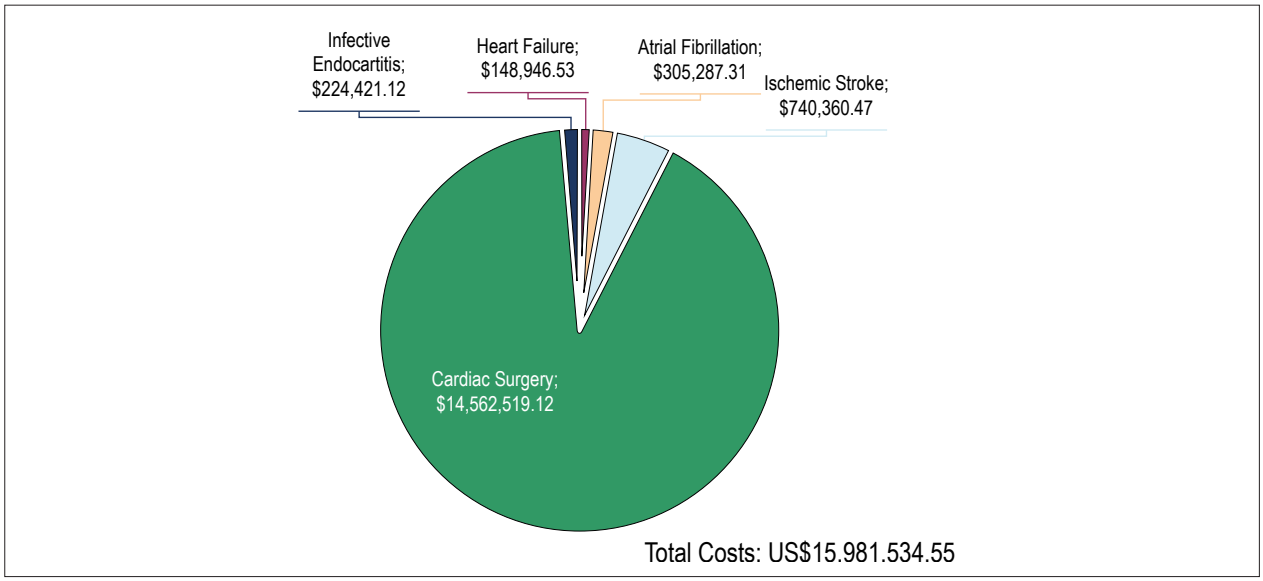

Figure 4 – *Projection of estimated minimum annual costs in US dollars for Rheumatic Heart Disease morbidities. The final values were calculated based on the case estimates made in Figure 2, multiplying by the values detailed in Table 1, taking into account only one procedure or one hospitalization for each patient over time.*

The proposal of the World Health Organization (WHO), to reduce mortality from RHD and other NCDs (noncommunicable diseases) by 25% by the year 2025, requires an understanding of the contemporary characteristics and the use of proven interventions in patients living in endemic countries.[19] Taking into account our projections, this WHO proposal is far from our reality, which could be associated to the fact that ARF and RHD are diseases of poverty. Moreover, although ARF and RHD have largely disappeared from affluent parts of the world, they remain an important cause of morbidity and mortality in low-income countries and among marginalized sections of society in high-income countries.[20]

These conditions had an impact on the costs of the National Health System, with a remarkable 264% increase in total expenditures with hospitalization for RHD from 1998 to 2016. Considering the current scenario, our predicted values point out the increment of 5.4% for the period from 2017 to 2018 and 1.5% from 2018 to 2019.

The WHO defines secondary prophylaxis as "the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or well-documented rheumatic heart disease. The purpose is to prevent colonization or infection of the upper respiratory tract with GAS and the development of recurrent attacks of rheumatic fever".[4] The internationally accepted dose for secondary prophylaxis with BPG in adults is 900 mg (1.2 million IU) intramuscularly. There is some uncertainty regarding the optimal frequency of administration; some studies suggest 2-weekly administration, whereas others report very good outcomes with a 3-weekly regimen[21] as established by the last Brazilian guideline.[1]

Meanwhile, the value standardized by ANVISA's Drug Market Regulation Chamber for Benzathine Penicillin G is R$ 14.75 or US$ 4.48.[15] Considering the number of cases due to the evolution of ARF into RHD with its complications (Figure 2) multiplied by the respective costs of procedures (Table 1) we reached the hypothetical value spent in 1 year

Figure 5 – *Comparison between the increase of mortality rates for Rheumatic Heart Disease (RHD), Prostate Cancer (PC) and Breast Cancer (BC). According to the adjustment of a simple linear regression for each of the series, the trends for RDH (0.15 [0.12, 0.17]) and BC (0.14 [0.07, 0.22]) were significant (p-value < 0.050) and did not show any significant difference, as the confidence intervals overlapped. The trend for PC (0.04 [-0.04; 0.12]) was not significant (p-value > 0.050).*

(R$ 56,726,131.35 or U$ 15,981,534.55; Figure 4). Thus, we highlight that this amount would be enough to carry out secondary prophylaxis of RHD (considered a BPG dose every 3 weeks) in 22,574 people for 10 years. Unfortunately, the low BPG accessibility is not a Brazilian problem, only. Minimal access to BPG was reported in almost all 24 countries in Africa, the Asia-Pacific region, and Central and South America in 2011,[22] with some respondents indicating no access to BPG at all. Of 39 respondents, 35% indicated that their BPG supply is inadequate to treat all of their patients using the recommended prophylaxis schedules.[22] Although there are no national data on access to BPG in Brazil, the concern about its lack of availability has increased in recent years.[23] This lack of an acceptable domestic supply of BPG is a significant problem in several global sites where RF/RHD is prevalent. Without consistent access to an inexpensive and high quality supply of BPG, children in areas with a high prevalence of RF/RHD will remain at risk of developing this crippling and life-threatening condition.[22]

The increasing trend in the RHD and ARF mortality rates, with increments of 27.3% and 38.1% respectively (2017-2019), as well as the comparison between the total costs of the RHD morbidities and the use of BPG, indicates the need for public policies and programs for ARF / RHD control, leading to the early diagnosis and the prevention of disease development and its morbidities. Despite the lack of ARF/RHD control programs in Brazil, this prevention strategy has been already applied in many countries with positive responses, as evidenced by the following data. The 10-year program in Pinar del Rio (Cuba) dramatically reduced morbidity and premature mortality in children and young adults and was cost-effective.[24] A study carried out in Zambia has shown that understanding public perceptions and behaviors related to neck pain is critical to informing health programs aimed at eliminating new cases of RHD in endemic regions. This cross-sectional study found that pharyngitis is common among school children and adolescents, with women reporting significantly more episodes of sore throats than males. Parents/guardians have varying knowledge of the frequency of sore throats in their offspring, and management of pharyngitis may be suboptimal for many children, with more than one quarter receiving treatment without a qualified evaluation, providing a view of the need for public awareness campaigns aimed at reducing RHD,[25] which further reinforces the need for greater visibility regarding RHD in Brazil, with program implementation, considering the alarming perspectives of mortality shown in this article.

This increase in mortality may be a matter of discussion considering the possible development of factors, such as better diagnosis, mortality notifications and BPG accessibility. Merely approximately 5% of all carriers of rheumatic fever have a symptomatic acute phase, whereas the majority of patients with severe cardiac rheumatic sequelae are diagnosed only in the final phase of the disease. In fact, these figures may be underestimated, and of these 5% symptomatic individuals, only about 5% need hospitalization,[26] according to DATASUS data. In Brazil, the PROVAR study[27] (the country's first large-scale screening program) was implemented in 2014 and revealed an echocardiographic prevalence of 42/1.000 in the preliminary assessment, contrasting with the IBGE prevalence of 7/1.000[1]. This shows that populational screening policies are needed to identify these asymptomatic patients, and it partially explains the increase in prevalence due to better diagnostic methods, but more studies are required to understand the real causes of this increase. The same study shows that although the prevalence of RHD has declined in high-income countries, lack of social and

economic development and precarious primary prevention - especially in low- and middle-income countries - perpetuate an environment in which RHD remains endemic and with increasing trends. Moreover, the increased mortality rate is largely due to the stage at which the disease is diagnosed, a classic example being the young woman who discovers severe mitral stenosis only when an acute pulmonary edema is identified during pregnancy.[28]

This progressive increase was also confirmed by another national study,[27] which justifies the greater availability of echocardiography, with more sensitive criteria, especially for subclinical RHD. In these subclinical cases, echocardiography plays a crucial role because it can establish the diagnosis or even raise suspicion of a possible case in those patients who are going through the last phase of the disease, from the acute manifestations of RFA to the last complications of RHD.[29]

When analyzing our data on mortality from RHD, we see, to a certain extent, the results of non-diagnosed ARF and the cases that were adequately treated in the past. This gap can last 10 to 20 years.[28] Similarly, by implementing population screening measures to identify the individuals that occupy this gray area, the results will also come after at least a decade.[29]

As in Brazil, the proportion of reports of ARF and RHD in the Pacific islands has increased in recent years, where GAS disease rates seem to be unstoppable.[30] In the same study, where the annual incidence of ARF was 155 per 100,000, a 41% increase was reported between 2004 and 2009, attributed to improved case detection and reporting of a record and a health program coordinator. However, raising awareness and case reporting is unlikely to account for the high rates of ongoing ARF in this population, as the disease became notifiable in Australia in 1996, an example that should be followed in Brazil, not only notifying hospitalized cases, but compulsorily notifying all cases, allowing greater prophylaxis use. Rates are likely to remain high because of the failure to adequately address socioeconomic determinants of health, increasing the already high rates of infection. Consequently, this remains a significant concern for public health that deserves more attention.

RHD presentation (considering a 10-20 year latency), in the absence of a history of ARF, actually suggests that detection, accurate diagnosis and reporting of ARF remain below ideal. Contributing factors may include lack of training or awareness among health staff, transient health professional staff in remote areas, poor access to medical services, and lack of use of health services due to many factors.[20]

Differences between echocardiographic criteria considerably affect the apparent prevalence of rheumatic heart disease in screening surveys, and emphasize the difficulties in the diagnosis of subclinical disease. Some might argue that there is a wide range of definitions of normality and that echocardiography screening might lead to over- diagnosis. Although controversial, evidence supports a link between mild valvular lesions, detected by echocardiography, and rheumatic heart disease, particularly the substantially higher case detection rates of such lesions in populations at risk for acute rheumatic fever.[31]

Sustained control of rheumatic heart disease at a population level requires a high-functioning health system that meets the needs of vulnerable people. In high-income settings, rheumatic heart disease demonstrates persistent inequality.[32] For instance, indigenous Australians in the Northern Territory under 35 are 122 times more likely to have rheumatic heart disease than their non-indigenous peers in the same region, reinforcing that a greater focus on RHD prevention and control by strengthening the existing record-based programs (or the development of such programs where they are absent) in countries with high disease burden, improving primary care and raising awareness about ARF and RHD, is critical. Governments, as well as clinicians, should prioritize RHD control to ensure continued funding and recognition of large regional organizations.[30]

In a challenging clinical setting characterized by high ARF/RHD rates, as in Brazil, an Australian study showed a significant improvement in care for people with ARF/RHD in association with the implementation of a continuous improvement quality (CQI) based on participatory research principles. Key findings include improvement in key clinical care indicators, including the administration of scheduled injections of BPG, scheduling injections at the recommended 4-week interval, and periodic review of documentation by a medical specialist, whereas significant improvements in record keeping were also related to ARF/RHD.[33]

Another study carried out in Bangladesh showed that rheumatic fever and rheumatic heart disease are the most common cardiovascular diseases in young people < 25 years of age and are important contributors to cardiovascular morbidity and mortality. It also shows that chronic RHD continues to prevail, and the real burden of disease may be much higher, indicating that large-scale epidemiological and clinical research is needed to formulate evidence-based national policies to address this important public health problem in the future.[34] As in Brazil, RHD continues to demand a high health and economic rate in African countries, but evidence-based prevention and treatment measures are currently underutilized.[35]

An initial step for Brazil could be based on the report of the African Union Commission (AUC) Social Committee, which described actions that governments must take to eliminate ARF and eradicate RHD: (a) create prospective disease records in sentinel sites (b) decentralization of technical knowledge and technology for the diagnosis and management of ARF and RHD (including echocardiography), (c) establishment of national and regional centers of excellence for cardiac surgery, and (d) promoting international partnerships to mobilize resources and expertise.[36]

Preventive task forces already well established, with the impact of worldwide campaigns, including Brazil, are Pink October and Blue November. We highlight that these two programs are related to prevention of breast cancer (BC) and prostate cancer (PC) mortality, of which magnitude is similar to that of ARF and RHD mortality.

The Blue November began with a movement called *Movember* in Australia in 2003, taking advantage of the celebrations of the World Day to Fight Prostate Cancer, held

on November 17, starting its activities in Brazil in 2008. Despite the support of several non-governmental entities, the movement, especially regarding its aspect related to prostate cancer, is repudiated by the Ministry of Health of Brazil and the National Cancer Institute due to the lack of scientific indications for the screening.[37]

Pink October's history dates back to the last decade of the 20th century. In 1997, entities from the cities of Yuba and Lodi in the United States began effectively celebrating and promoting actions aimed at breast cancer prevention, called Pink October. All actions were and are directed towards the prevention and early diagnosis. From 1989-2015 (most recent data available), breast cancer mortality decreased by 39 percent (preventing more than 320,000 deaths).[38] The first initiative seen in Brazil in relation to the Pink October, was carried out in 2002, and is currently disseminated throughout the country, where there is the involvement of the health teams and the population.[12]

The campaign against rheumatic heart disease needs a strong political will, driven by the awareness and effort of health professionals. The principles that underlie the control of this disease in high-income countries might not apply to developing countries. Where health care finances are very scarce and health is often provided by non-governmental organizations (NGOs), rheumatic heart disease might not be perceived as a priority.[39] Three successful approaches originating from Central America and the Caribbean, in different economic and political contexts, showed the efficiency of combined strategies consisting of education and primary and secondary prophylaxis.[31]

Some initiatives in this sense have already been taken in Brazil, such as the PROVAR (Rheumatic Valvular Diseases Screening Program) program, being the first large-scale echocardiographic screening program in Brazil, using echocardiography to estimate the prevalence of latent RHD in asymptomatic children between 5 and 18 years of age attending public schools in the underserved areas of cities such as Belo Horizonte, Montes Claros and Bocaiúva, in the Brazilian state of Minas Gerais.[40]

Conclusion

The analysis of mortality rate trends in Brazil by ARF and RHD are alarming. At the advent of the new millennium, we know little about our real situation due to the lack of a more complete database aimed at this condition. The existing disease load may represent only the tip of the iceberg, since the analyzed data may be underestimated. On a large scale, preferably, national surveys and clinical studies should be conducted to determine the different aspects of RF and RHD in Brazil. The information added by this research would thus help to encourage the real need to formulate national policies to address this public health problem more efficiently in the future. Moreover - why not give a color to rheumatic fever?

Author contributions

Conception and design of the research, Statistical analysis and Critical revision of the manuscript for intellectual content: Figueiredo ET, Azevedo L, Rezende ML; Acquisition of data: Figueiredo ET, Alves CG; Analysis and interpretation of the data: Figueiredo ET, Azevedo L, Rezende ML, Alves CG; Writing of the manuscript: Figueiredo ET, Azevedo L, Rezende ML, Alves CG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Rheumatic Fever in Brazil: What Color Should It Be?

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Short Editorial related to the article: Rheumatic Fever: A Disease without Color

Rheumatic fever (RF) and its valvular sequela rheumatic heart disease (RHD) have been a scourge on humanity for ages, and it is only relatively recently that high-income countries have seen rates of RF decline dramatically. Yet, the Global Burden of Disease Study estimates that more than 275,000 deaths due to RHD still occur every year around the world, especially in low and middle-income countries including Brazil.[1]

In this issue of the journal, Figueiredo et al.[2] have presented ambitious modeling of the disease burden and costs of RF and RHD in Brazil. Using data from the Hospital Information System of Brazil, their central findings are that mortality rates for RF and RHD have increased by 215% and 42.5% respectively from 1998 to 2016. Additionally, the estimated cost for procedures related to RF/RHD diagnosis, interventions such as valve surgery, and hospitalizations for RHD complications like stroke and endocarditis was nearly $27 million USD in 2019.

Although staggering, these figures are – by the authors own admission – likely underestimated. There are several reasons for this. First, the authors acknowledge an inadequate disease reporting and surveillance strategy as one possible source of error in the mortality estimates. In addition, the cost analysis only considered direct costs to the medical system, which does not include the indirect costs to the larger economy from lost productivity. Compared to diseases of the elderly (e.g. heart failure), these indirect lost productivity costs are greater for diseases like RF and RHD that claim the lives of children and young adults with a potential lifetime of productive work ahead of them.

In addition to a full assessment of cost burden, studies are needed to assess the cost-effectiveness of interventions to reduce RF/RHD in Brazil. In general, interventions that improve appropriate diagnosis and treatment of group A strep infections (i.e. primary prevention) and benzathine penicillin for all patients with a history of RF/RHD (i.e. secondary prevention) have been shown to be cost-effective in a variety of contexts, including low- and middle-income countries.[3,4] Assumptions used in the cost-effectiveness modeling should, however, be tailored to the Brazilian context. Is it possible that some Brazilian innovations could improve the cost-effectiveness of RF/RHD prevention? One example is the use of telemedicine for remote ECG diagnosis and appropriate referrals for acute myocardial infarction in Minas Gerais.[5] This group has already implemented a telemedicine-based strategy for echocardiographic screening for RHD through the PROVAR initiative.[6]

Figueiredo et al.[2] have included a thoughtful and thorough discussion of the many other issues facing countries who seek to implement a national RF/RHD control program. These include problems with the global penicillin supply chain and the daunting task of addressing social determinants of RF/RHD such as poverty and overcrowding. Yet, missing from their discussion is mention of the World Health Organization's resolution on RF/RHD issued in April 2018.[7] This historic resolution calls on the Member States from endemic regions to take eight specific actions: (1) implement a national RHD control program; (2) improve diagnosis and treatment of group A strep pharyngitis; (3) implement secondary prevention monitoring programs; (4) ensure a consistent supply of benzathine penicillin at no cost to patients; (5) educate professionals and the public about RF/RHD prevention; (6) improve access to tertiary care for severe RHD; (7) address known social determinants of RF/RHD; and (8) develop bilateral, regional, and multilateral collaboration and resource mobilization. The resolution also calls on the WHO Secretariat to launch a coordinated global response to RF/RHD, to provide technical assistance to the Member States, to work with pharmaceutical manufacturers to ensure a secure penicillin supply chain, and to convene stakeholders to advance research priorities in vaccine development, disease pathogenesis, and long-acting penicillin formulation. The WHO resolution represents the cresting of a new wave of enthusiasm for RF/RHD prevention among clinicians, policymakers, and – most importantly – affected persons living with RHD. The moment is now to convince governments to invest in this mission. Technical resources are available through organizations such as RHD Action (http://rhdaction.org/) or Reach (www.rheach.org) to assist the Member States in building comprehensive control programs.

The authors are right to compare RF/RHD to other diseases that have similar disease burdens or costs, in order to shine a spotlight on how much less is invested in RF/RHD prevention compared to other diseases. Breast cancer and prostate cancer were highlighted in this analysis; but one could also consider the disease burden and funding that has been dedicated to global infectious diseases. For example, annual global mortality from malaria is only three times greater than RF/RHD, but research and development funding for malaria is over 500 times greater.[8] The disparity is even worse for HIV/AIDS.

Keywords

Rheumatic Fever/ecomomics Heart Disease/economics, Cardiovascular Surgical Procedures/mortality; Hospitalization/economics; Antibiotic Prophylaxys/economics; Public Health Policy.

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The voice of the RHD community in Brazil and around the world is getting stronger and demanding the attention of public health experts. Breast cancer has Pink October and prostate cancer has Blue November, so what color should be given to a RF/RHD public health campaign in Brazil? Red – to reflect the urgency and severity of the situation? Perhaps it would get confused with HIV/AIDS. Green – to reflect the tropical areas that are so afflicted by the disease worldwide? But this color lacks the sense of urgency required. What about orange, the universal color of warning signs? Ultimately, it is for Brazil to decide, and the global RF/RHD community will be there to support you when you do.

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High Residual Platelet Reactivity during Aspirin Therapy in Patients with Non-St Segment Elevation Acute Coronary Syndrome: Comparison Between Initial and Late Phases

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Abstract

Background: High platelet reactivity (HPR) during therapy with acetylsalicylic acid (ASA) is a poor prognostic factor in acute coronary syndromes (ACS). The prevalence of HPR during ACS is greater than that reported in stable diseases. However, it is unclear whether this prevalence of HPR is a transient phenomenon or a characteristic of this high-risk population.

Objective: The main objective is to compare the effects of ASA on platelet function in the initial and late phases of ACS in a single population. Secondary objectives are: correlation between the tests between themselves and the relationship between the tests and the variation of the inflammatory markers (C-reactive protein and interleukin-6).

Methods: Seventy patients with non-ST segment elevation (NSTE) ACS in use of 100-200 mg of ASA per day for at least 7 days were prospectively studied. Platelet function was assessed in the first 48 hours and subsequently after 3 months using four methods: VerifyNow™ (VFN), whole blood platelet aggregation (WBPA) with arachidonic acid (AA) and collagen as agonists, and platelet function analyzer (PFA). The level of statistical significance considered was < 0.05.

Results: According to the more specific methods (WBPA with AA and VFN), the incidence of HPR was significantly higher in the early phase than in the late phase: WBPA with AA: 31% versus 13%, p = 0.015; VFN: 32% versus 16%, p = 0.049. The other methods tested, which were less specific for ASA, did not show significant differences between phases. The correlation between the methods was weak or moderate (r ranging from 0.3 to 0.5, p < 0.05), and there were no significant associations between HPR and inflammatory markers.

Conclusion: The prevalence of HPR during AAS therapy, assessed by specific methods for cyclooxygenase 1 (COX-1), is higher during the acute phase than in the late phase of NSTE ACS. (Arq Bras Cardiol. 2019; 113(3):357-363)

Keywords: Acute Coronary Syndrome; Platelet Aggregation/drug effects; Myocardial Ischemia; Aged; aspirin/therapeutic use; Aspirin/adverse effects.

Introduction

Acetylsalicylic acid (ASA) is widely used as first-line antiplatelet therapy for acute coronary syndromes (ACS) and is recommended by the guidelines of the American Heart Association and the American College of Cardiology,[1] European Society of Cardiology[2] and the Brazilian Society of Cardiology[3] for patients with non-ST segment elevation acute coronary syndromes (NSTE ACS).

AAS has been tested with proven efficacy in several randomized clinical trials across the spectrum of both acute and chronic coronary artery disease.[4-7] However, some studies have demonstrated high variability in the individual antiplatelet response to ASA in different populations and scenarios.[8] This variability may contribute, at least in part, to the high rate of recurrence of ischemic events in patients with coronary artery disease.[9,10]

The prevalence of high platelet reactivity (HPR) in patients using ASA depends, among other factors, on the laboratory test and cut-off point used, as well as on the clinical picture. In patients with chronic arterial disease, the prevalence ranges from 0 to 57% (24%, on average).[10-13] More importantly, patients with HPR have been described to have a poorer clinical outcome, with a higher incidence of serious cardiovascular events, including mortality.[10,11,14]

In ACS, the estimated prevalence of HPR is supposedly higher.[15] Previous studies have suggested that atherosclerotic load and systemic inflammation may have a significant influence on platelet reactivity.[16,17] However, it is not clear whether this high prevalence of HPR is a transient acute phase phenomenon or a permanent characteristic of this

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high risk population, since, to the best of our knowledge, no study has analyzed the response to ASA during the acute and chronic phases in the same population. The present study was designed to give a definitive answer on this important question.

Methods

Study population

Prospective inclusion of 70 consecutive patients admitted to the emergency department (ED) of a tertiary cardiology hospital with a diagnosis of NSTE ACS, with initial evaluation at admission (acute phase) and subsequently 3 months after discharge (late phase). Patients were considered eligible for inclusion if aged ≥ 18 years, had been diagnosed with unstable angina or non-ST segment elevation myocardial infarction within the first 48 hours of clinical onset, and were using 100 mg to 200 mg of AAS for at least 7 days prior to the event.

The main exclusion criteria were the use of another antiplatelet agent in addition to ASA, oral or parenteral anticoagulation, percutaneous coronary intervention (PCI) in the last 30 days or myocardial revascularization surgery in the last 90 days. Other exclusion criteria were hemoglobin < 10 g/dL; platelets < 100,000/mm^3 or > 500,000/mm^3; creatinine clearance < 30 mL/min; decompensated heart failure (Killip III or IV); current use of inotropes or vasopressors; and known hematological or neoplastic diseases.

Model

Patients were evaluated at two different moments: initially, at admission to ED, prior to the administration of any other antithrombotic treatment except ASA, and 3 months after hospital discharge, when they should also be on ASA as the only antiplatelet agent. At each evaluation, patients were evaluated and interviewed, and underwent blood collection 1 to 4 hours after the use of ASA. Adherence to ASA treatment was systematically evaluated during face-to-face medical interviews. The study is in accordance with the Helsinki Declaration and was approved by the local Ethics Committee; patients provided their informed consent.

Objectives

The primary objective of the study was to compare platelet aggregation in patients with NSTE ACS in the acute phase (the first 48 hours of the clinical picture) in relation to the late phase (3 months after) using four different methods of evaluating platelet aggregation: VerifyNow™ aspirin (VFN) (Accumetrics, Inc., San Diego, California, USA); whole blood platelet aggregation (WBPA) using arachidonic acid (AA) (Sigma-Aldrich, Saint Louis, Missouri, USA) and collagen (Chrono-Log®; Chrono-Log Co., Havertown, Pennsylvania, USA); PFA-100® Platelet Function Analyzer with collagen/ADP cartridge (COL/EPI) (Siemens Healthcare Diagnostics, Newark, Delaware, USA). Secondary objectives were the correlation between the four tests in the acute phase and the relationship between each of the tests with inflammatory markers (C-reactive protein and interleukin-6).

Blood collection

All blood samples were collected through antecubital venous puncture with a 21 gauge needle between 10:00 am and 1:00 pm. The four tests were performed within two hours of the collection.

Definition of HPR

The cut-off values used to define HPR were: PFA-100®, closure time (CT) < 150 seconds;[18] VFN, aspirin reaction units (ARU) ≥ 550 (according to the manufacturer); WBPA with AA, Ω ≥ 3;[19] WBPA with collagen, Ω ≥ 10.[20]

Statistical analysis

The sample size was calculated based on the expected mean result of the PFA-100® test, which was 191 seconds ± 100[21] during the acute phase, and the 25-second reduction estimate of that value in the chronic phase. According to the McNemar test, with 80% power and alpha of 0.05, 70 patients were required. The continuous variables were evaluated for their distribution (Gaussian or not) using the Kolmogorov-Smirnov test.

Parametric continuous variables were presented as mean ± standard deviation, and nonparametric variables as medians and interquartile ranges (25-75). The unpaired Mann-Whitney (non-Gaussian variables) or Student's T (Gaussian variables) tests were used with the Welch correction when indicated. When comparing two different moments, the Wilcoxon test was used for the non-Gaussian variables and the paired Student's T for Gaussian samples. The categorical variables were presented in relative and absolute frequencies. Contingency distribution tables were analyzed using the chi-square test and Fisher's exact test. Analysis of the correlation between the tests was done with Spearman's correlation coefficient. Values of $p < 0.05$ were considered statistically significant. The software used was SPSS (IBM Corporation), version 11.

Results

Patients' characteristics

The demographic and baseline characteristics of the patients are summarized in Table 1. Almost half of the patients reported a previous history of diabetes. The majority (64%) had a classification for thrombolysis in myocardial infarction (TIMI) with risk for non-ST segment elevation ACS equal to 3 or 4 on admission. All patients were on 100 to 200 mg ASA as the only antiplatelet agent in the last 7 days prior to the collection of the tests, both in the acute phase and in the late phase.

Primary objective

Platelet aggregation tests were divided into COX-1-specific (WBPA with AA and VFN) and COX-1-nonspecific (WBPA with collagen and PFA-100®). COX-1-specific tests were associated with higher platelet reactivity in the acute phase, compared to the late phase (Figure 1). Comparisons between the phases by the nonspecific COX-1 tests did not show

Table 1 – Demographic and baseline characteristics of patients

Number of patients	70
Age, years (mean ± SD)	64.2 ± 9.7
Female, n (%)	38 (54.3)
Medical history	
Diabetes mellitus, n (%)	34 (48.6)
Hypertension, n (%)	61 (87.1)
Dyslipidemia, n (%)	58 (82.9)
Current smoking, n (%)	11 (15.7)
Obesity, n (%)	16 (22.9)
Family history of CAD, n (%)	28 (40)
AMI, n (%)	41 (58.6)
SMR or PCI, n (%)	38 (54.3)
CHF, n (%)	6 (8.6)
Type of ACS	
Unstable angina, n (%)	54 (77.1)
NSTE AMI, n (%)	16 (22.9)
TIMI risk score	
0 to 2, n (%)	15 (21)
3 to 4, n (%)	45 (64)
≥ 5 (%)	10 (15)
Previously used medications	
PPIs, n (%)	32 (45.7)
Beta-blockers, n (%)	55 (78.6)
Calcium channel blockers, n (%)	10 (15)
ACEIs/ARBs, n (%)	45 (64.3)
Aldosterone antagonists, n (%)	3 (4.3)
Laboratory tests	Median ($25^{th}/75^{th}$)
Hemoglobin, g/dL	13.7 (12.8/14.7)
Leukocytes × 1.000/mm^3	8.0 (6.5/9.2)
Platelets × 1.000/mm^3	220 (179/273)
Creatinine, g/dL	1.0 (0.9/1.2)

ARBs: angiotensin receptor blockers; SMR: Surgical myocardial revascularization; CAD: coronary artery disease; AMI: acute myocardial infarction; PPIs: proton pump inhibitors; CHF: congestive heart failure; PCI: percutaneous coronary intervention; ACEIs: angiotensin converting enzyme inhibitors; ACS: acute coronary syndrome; NSTE: non-ST segment elevation; TIMI: thrombolysis in myocardial infarction.

significant differences (PFA = 215.9 ± 83.75 seconds *versus* 200.51 ± 84.63 seconds, respectively, in the acute and late phases, p = 0.233; WBPA with collagen, 7.19 ± 5.64 Ω *versus* 6.46 ± 5.09 Ω, p = 0.658).

When the results were categorized according to pre-established cutoff values for HPR diagnosis (Table 2), COX-1-specific tests were associated with significant differences between the acute and late phases (WBPA with AA, 31.4% *versus* 12.8%, p = 0.015; VFN, 32.1% *versus* 16%, p = 0.049), whereas nonspecific tests did not show significant differences (PFA, 34.2% *versus* 40%, p = 0.50; WBPA with collagen, 33.8% *versus* 30.8%, p = 0.86).

Secondary objectives

Correlation between platelet tests

In the acute phase, the analyzed methods correlated significantly (Table 3). However, the magnitude of this correlation was only moderate (r > 0.4) between WBPA with AA and WBPA with collagen. The correlation between the other methods was only weak (r > 0.2 and < 0.4).

Variation of inflammatory markers and platelet reactivity between acute and late phases

C-reactive protein (CRP) levels differed significantly between the acute and late phases [median CRP = 2.84 mg/dL (1.54 to 8.41) *versus* 1.41 mg/dL (0.73 to 5.64), p = 0.006], whereas interleukin-6 (IL-6) did not differ between the two phases [median IL-6 = 2.1 pg/mL (2.0 a 5.68) *versus* 2.0 pg/mL (2.0 to 3.25), p = 0.110]. When CRP (acute/late) variation was compared to the variation of the methods in the two phases analyzed, a weak but significant correlation (Figure 2) was demonstrated between CRP and VFN (r = 0.29, p= 0.03).

Discussion

Our data demonstrate significant differences in response to ASA during the acute and late phases of acute coronary disease.

Previous studies have unequivocally documented that ASA reduces the occurrence of cardiovascular events in patients with CAD.[4-7] Even with the advent of the new antiplatelet agents that act by blocking the P2Y12 receptor, the role of ASA remains unchanged as it is considered, in all guidelines, a routine treatment in this population.[1-2] However, it has been well established that there is significant variability in residual platelet function during ASA therapy, especially in the context of ACS, in which the prevalence of HPR is more evident.[8,17] The reason for this variability is not fully understood. One hypothesis is that HPR is present in a subpopulation of patients with chronic CAD, leading to a decrease in the efficacy of ASA and, as a consequence, increasing the likelihood of developing ischemic cardiovascular events. Another hypothesis is that HPR develops during the acute ischemic episode, as a consequence of the increase in platelet reactivity due to phenomena occurring in the acute phase (increased inflammatory activity, increased rate of platelet renewal, activation of the coagulation system, among others).

To our knowledge, this study was the first to test both hypotheses in the same population of patients with NSTE ACS. Our results showed that, for most patients, HPR is labile, with a higher prevalence observed during the acute phase compared to the late phase. These results are consistent with the data reported by Hobikoglu et al.,[21] who analyzed two different populations (one group of patients hospitalized with ACS and another group of patients with chronic CAD).

The present demonstrations can have a significant therapeutic impact, since approximately one third of our patients showed HPR during the initial phase of ACS, and new regimens, including change of dosage and use of more potent antiplatelet agents, may be proposed to reduce the risk of ischemic events. Neubauer et al.[22] evaluated a therapeutic regimen of dose escalation of ASA and clopidogrel in

Table 2 – Comparison of HPR by different platelet tests between the acute and late phases

Test	Acute Phase	Late Phase	p
	HPR	HPR	
PFA	34.2%	40%	0.503
WBPA with AA	31.4%	12.8%	0.015
VFN	32.1%	16%	0.049
WBPA with Col	33.8%	30.8%	0.860

WBPA: whole blood platelet aggregation; AA: arachidonic acid; Col: collagen; PFA: Platelet Function Analyzer (PFA-100®); VFN: VerifyNow™; p: p value.

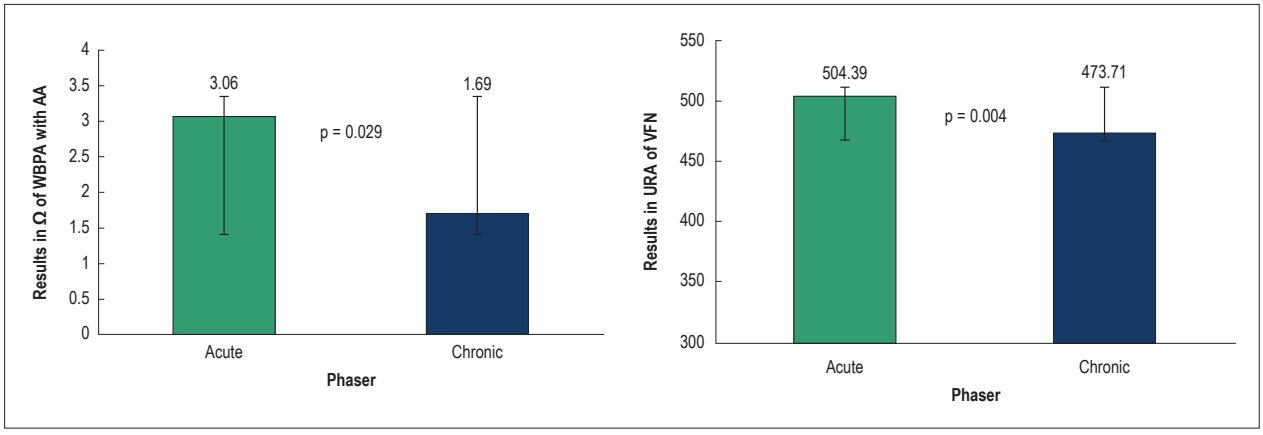

Figure 1 – *Comparison of COX-1-specific tests (WBPA with AA and VFN) between the acute and late phases. WBPA: whole blood platelet aggregation; AA: arachidonic acid; VFN: VerifyNow™; URA: units of reaction to acetylsalicylic acid.*

Table 3 – Correlation between platelet tests in the acute phase

		WBPA with AA	WBPA with Col	VFN
PFA	r_s	–0.429*	–0.281*	–0.279*
WBPA with AA	r_s		0.498*	0.393*
WBPA with Col	r_s			0.318*

** p < 0.05, AA: arachidonic acid; Col: collagen; WBPA: whole blood platelet aggregation; PFA: PFA-100®; r_s: Spearman correlation coefficient; VFN: VerifyNow™.*

patients with ACS or unstable angina undergoing PCI and considered nonresponders by WBPA with AA and adenosine diphosphate (ADP). Patients considered nonresponders to ASA were treated with increasing doses of 100 mg to 300 mg per day, and up to 500 mg, if necessary, with improved therapeutic response.

On the other hand, our data demonstrate that, although there is a significant decrease in the incidence of HPR during the chronic phase, a significant percentage of the population still present HPR at this stage.

The high rate of platelet turnover that occurs in several situations (including ACS) could be one of the explanations for our findings; however, this mechanism was not analyzed in the present study. As demonstrated in previous studies in diabetic patients in the postoperative period of cardiac surgery,[23-25] the number of circulating immature platelets increases as a consequence of increased platelet consumption, leading to an exponential increase in the platelet turnover rate. In a study by Dillinger et al.,[26] comparing different doses of ASA twice daily in diabetic patients with CAD and at least one risk factor, twice daily use of the drug reduced HPR rate when compared to the same dose administered once a day. However, in the CURRENT study, the use of a double dose of ASA showed no benefit when compared to the conventional dose.[27]

Another possibility would be the influence of the inflammatory process, which is characteristic of the acute phase, on platelet function, resulting in increased platelet activation and increased HPR in response to ASA. In the present study, there was a significant but weak association between inflammation and platelet reactivity, analyzed by PCR and VNF, respectively ($r = 0.293$, $p = 0.03$). In a stable CAD population, Bernlochner et al.[28] showed a significant, positive and independent association between CRP levels and platelet aggregation, which were assessed by WBPA with ADP. Similarly, Tantry et al.[29] reported a significant correlation between inflammatory markers

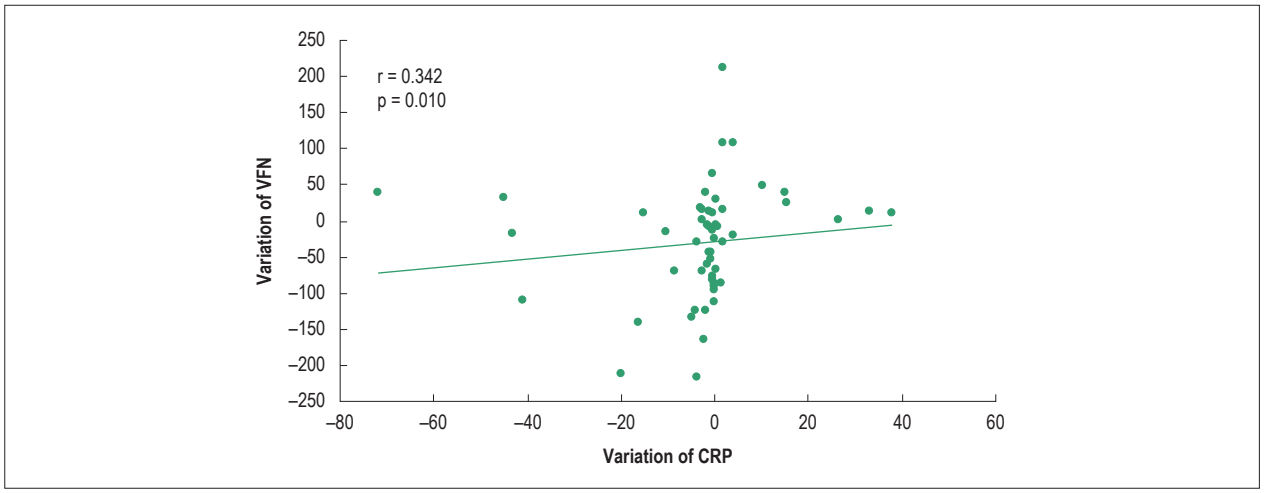

Figure 2 – *Correlation between the variation of CRP and VFN (acute/late). CRP: C-reactive protein; VFN: VerifyNow™; r: Spearman's coefficient.*

(including CRP), markers of hypercoagulability and platelet function in different CAD spectra (asymptomatic, stable CAD and ACS). However, contrary to these findings, Ziegler et al.[30] demonstrated that in patients with peripheral arterial disease, there was no significant correlation between CRP and platelet aggregation measured by PFA-100®. These conflicting results can be attributed, at least in part, to methodological differences.

In our study, different methods of determining platelet function were used simultaneously. The correlation between the tests during the acute phase was significant, but the magnitude of these correlations was only weak or moderate. Unexpectedly, even the methods classified as COX-1-specific showed medium to low correlation with each other. These findings are consistent with findings from previous studies: Lordkipanidzé et al.[19] studied 201 patients with stable CAD undergoing aspirin therapy[19] using six different tests. The prevalence of HPR varied from 4% when analyzed by optical aggregometry with AA, to 59.5%, when analyzed by PFA-100® (COL/EPI). In this study, as in ours, there were weak correlations between methods for determining platelet function, including COX-1 specific methods. The present study was the first to analyze different methods of platelet aggregation during the acute and late phases, in the same population of patients with NSTE ACS.

In summary, our findings may have important therapeutic implications in demonstrating that one-third of the patients showed HPR in the acute phase, leading to the hypothesis that new dosing regimens should be tested in this population. In addition, despite the fact that there is a significant decrease in the incidence of HPR during the chronic phase, a significant percentage of the population still presents HPR at this stage.

Study limitations

Firstly, our study had a relatively small sample size, but it was adequate to assess the primary outcome. However, the secondary results should be considered as hypothesis generators and interpreted with caution. Secondly, all patients were on chronic ASA use at a dose of 100 mg/day to 200 mg/day, but individual doses were not collected and may have influenced the results obtained.[25] Lastly, in recent times, the role of young (immature) platelets has been valued; if they had been assessed in the present study (which was not done), they could have added important information.

Conclusion

In conclusion, the prevalence of HPR during ASA therapy measured by COX-1-specific methods is higher during the acute phase than in the late phase of patients with non-ST segment elevation ACS. However, the relationship between inflammation as indicated by CRP and IL-6 and platelet reactivity in these two phases is weak, suggesting that the variability in the inflammation state may not play a role in the temporal changes in platelet reactivity in this population.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Dracoulakis MDA, Martins HS, Nicolau JC; Acquisition of data: Dracoulakis MDA; Statistical analysis, Obtaining financing and Writing of the manuscript: Dracoulakis MDA, Nicolau JC; Critical revision of the manuscript for intellectual content: Dracoulakis MDA, Gurbel P, Cattaneo M, Martins HS, Nicolau JC, Kalil Filho R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAPPESQ - HCFMUSP under the protocol number 0992/08. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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High Residual Platelet Activity in Response to Acetylsalicylic Acid in Acute Coronary Syndrome: A New Challenge for Antiplatelet Treatment?

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Short Editorial related to the article: High Residual Platelet Reactivity during Aspirin Therapy in Patients with Non-St Segment Elevation Acute Coronary Syndrome: Comparison Between Initial and Late Phases

Cardiovascular diseases (CVD) are the leading cause of death in the world, with coronary heart disease being the main etiology, accounting in 2016 for 31% of global deaths.[1] Myocardial infarction (MI) is usually due to changes in the arterial wall or thrombotic occlusion of a coronary vessel caused by the rupture of a vulnerable plaque.[1,2] Instability in the atherosclerotic plaque is the result of local and systemic oxidative stress, thus leading to platelet activation and formation of aggregates in the circulation.[3] The major function of platelets is as part of the homeostatic mechanism, halting blood loss after tissue trauma, but in oxidative conditions, they are associated with various CVD such as hypertension, heart failure, stroke, diabetes and atherosclerosis.[3]

Previous studies have shown the importance of aspirin in reducing cardiovascular events in patients with coronary artery disease, hence the importance of anti-platelet aggregation in acute and chronic coronary syndromes.[4-7] However, in this issue of the *Arquivos Brasileiros de Cardiologia*, Dracoulakis et al.[8] demonstrate the high residual variability in response to aspirin in patients with non-ST-elevation acute coronary syndrome, comparing acute and late phases, correlating with laboratory evaluation tests of platelet aggregation and the variation of inflammatory markers (C-reactive protein and interleukin-6). In this study, the authors demonstrate statistically significant differences in response to aspirin during the acute and late phases of acute coronary disease.

Oxidative stress represents an imbalance between the production of reactive oxygen species (low density oxidized lipoproteins - oxLDLs and the catalytic subunit of NADPH oxidase - NOX2, among others) and the cellular antioxidant system (ascorbate / a-tocopherol pair, glutathione, glutathione peroxidase (GPx), heme oxygenase 1, superoxide dismutase 1 and 2 -SOD1 and SOD2, and catalase, among others), contributing to the development of atherosclerosis that eventually leads to thrombosis, the main cause of heart attacks and strokes.[1,9-12] Reactive platelet oxygen species are mainly generated by the reduction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[3,9] NOX2 is a platelet-expressed NADPH oxidase isoform and an important thrombosis regulator associated with platelet activation.[3] Thus NOX2 has a prominent role as shown by the antiplatelet effects caused by the inhibition of NOX2 activity, resulting in impaired production of platelet, lower calcium mobilization and GPIIb/IIIa activation and usually inhibition of platelet aggregation.[9] There is an increase in P-selectin and sCD40L plasma levels associated with increased NOX2 activity, oxLDL triggering foam cell formation and accumulation in atherosclerotic plaques, leading to platelet activation.[1] Thus, platelets are oxidized by LDL, with activation via specific oxLDL receptors, both effects being mediated by NOX2 activation.[13] However, there are complex enzymatic and non-enzymatic pathways involved in the formation of reactive oxygen species by cells, as demonstrated by Eduardo Fuentes et al.[1] A Genetic deficiency of the enzyme is associated with a very rare illness (chronic granulomatous disease - CGD), which is characterized by the absence at NOX2 (X-linked CGD) or more rarely by lack of cytosolic subunits such as p47phox.[9] This has been corroborated by the discovery of NOX2 on the platelet surface and by the demonstration, that as with leucocytes, platelet NOX2 is essential for the production reactive oxidant species. Accordingly, platelets from patients with NOX2 hereditary deficiency not only reduced F2-isoprostanes but also enhanced nitric oxide generation.[10] Furthermore, NOX2 is important for platelet aggregation because O_2^- is rapidly dismutated to H_2O_2.[10] Animals treated with apocynin, which hampers $p47^{phox}$ translocation to NOX2, disclosed reduced platelet H_2O_2 formation and age-related thrombosis.[10] Studies have revelated the importance of H_2O_2 as a trigger of platelet activation and thrombosis, including the role of GPx, another enzyme that destroys H_2O_2. Animals over-expressing GPx1, platelet activation as well as platelet-related thrombosis were significantly inhibited.[10] These data indicate that NOX2 plays a major role in platelet activation via different mechanisms: formation of F2-isoprostanes, inhibition of NO and production of H_2O_2.[10] Patients with coronary atherosclerosis have a higher platelet reactivity, which may represent an increased risk of periprocedural MI. Approximately one-third of patients presenting an acute ST-segment elevation MI, even with coronary stenting, develop a "no-reflow" phenomenon that is associated with increased platelet activity or inadequate platelet inhibition at the time of MI.[1] Therefore, oxidative stress may be associated with increased platelet aggregation due to a diminished response to antiplatelet therapy.[1]

Multiple pathways contribute to platelet activation and aggregation by reflecting, as independent signals, thromboxane A_2 (TXA_2), adenosine diphosphate (ADP) and activated

Keywords

Acute Coronary Syndrome; Oxidative Stress; Plaque, Atherosclerosis; Aspirin/therapeutic use; Platelet Aggregation Inhibitors.

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thrombin.[13] These represent goals in therapeutic modulation such as cyclooxygenase-1 inhibitors, P2Y12 inhibitors, protease-activated receptors (PAR) 1 inhibitors and interindividual variability in drug responses.[14] Platelets are heterogeneous in volume and density, biological variables that determine platelet function, playing an important role in the development of intravascular thrombus. Large platelets are metabolically and enzymatically more active than small platelets, which is reflected in the increase in mean platelet volume (MPV).[15] In the study by Hilal Bektas et al.,[16] the MPV value above 10.4 is a predictor of severe atherosclerosis with a sensitivity of 39% and specificity of 90% (ROC curve: 0.631, 95% CI: 0.549-0.708, p = 0.003), and can be used as a predictor of cardiac risk in patients with disease coronary artery. Another pathway includes impaired biosynthesis or inactivation of NO and/or enhanced the formation of isoprostanes, which may represent a future target of antiplatelet drugs.[17]

Antiplatelet therapy is important in the prevention of MI, and despite its proven efficacy in both acute and chronic phases, there is still a high recurrence rate of ischemic events in patients with coronary artery disease.[1,17] Aspirin resistance may be present in 5% to 75% of patients.[1] In a systematic review, Hovens et al.[15] demonstrated the high variability in individual response to aspirin in different populations. There are laboratory methods such as VerifyNow (VFN), total blood aggregometry (TBA) and platelet function analyzer (PFA-100) that can assess this platelet variability.[19-21] Oxidative stress may be associated with increased aggregation due to diminished response to antiplatelet therapy.[1] However, the reason for this high platelet variability is still unclear despite the routine use of aspirin and the relative contribution of NOX2 as a key target of different platelet activation pathways in the treatment of acute and chronic coronary disease. Specific antioxidants may, therefore, represent a new approach to limit platelet-related vascular complications due to the presence of NOX2.

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Clinical Characteristics and Adverse Events in Acute Coronary Syndrome Patients with a History of Peripheral Arterial Disease

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Abstract

Background: In clinical observation, patients with acute coronary syndrome complicated with peripheral artery disease have poor prognosis, so the relationship between the diseases and clinical characteristics need to be further explored.

Objective: This study aims to investigate clinical characteristics and independent risk factors for in-hospital adverse events in acute coronary syndrome patients with a history of peripheral arterial disease (PAD).

Methods: A total of 5,682 patients with acute coronary syndrome were included into this study. These patients were divided into two groups according to the presence or absence of a history of PAD: PAD group (n = 188), and non-PAD (control) group (n = 5,494). Then, the clinical characteristics and incidence of in-hospital adverse events were analyzed; $p < 0.05$ was considered statistically significant.

Results: The age of PAD patients was higher than that in the control group (65.5 ± 10.3 years vs. 58.6 ± 11 years, $p < 0.001$), and the proportion of PAD patients with diabetes history and stroke history was higher than that in the control group (73 [39%] vs. 1472 [26.8%], $p = 0.018$; 36 [19.3%] vs. 396 [7.2%], $p < 0.001$). The multivariate logistic regression analysis between groups based on in-hospital adverse events revealed that a history of PAD (OR = 1.791, $p = 0.01$), a history of diabetes (OR = 1.223, $p = 0.001$), and age of > 65 years old (OR = 4.670, $p < 0.001$) were independent risk factors for in-hospital adverse events.

Conclusion: A history of PAD, advanced age, and a history of diabetes are independent risk factors for in-hospital adverse events in patients with acute coronary syndrome. (Arq Bras Cardiol. 2019; 113(3):367-372)

Keywords: Acute Coronary Syndrome; Atherosclerosis; Mortality; Peripheral Arterial Disease; Hospitalization/complications; Diabetes Mellitus; Risk Factors.

Introduction

Atherosclerosis is a systemic vascular disease and one of the main causes of death and disability among Chinese residents. It mainly occurs in the coronary and cerebral arteries and affects the peripheral arteries (upper extremity, lower extremity, mesenteric and carotid arteries).

Peripheral artery disease (PAD) is a general name that refers to vascular diseases, except for cardio-cerebrovascular diseases. The narrow concept of PAD mainly refers to atherosclerotic stenosis or occlusion of the lower extremities, which causes symptoms of chronic or acute ischemia in the lower extremities.[1] PAD patients have a high risk of cardiovascular disease. A study[2] revealed that the risk of myocardial infarction in patients with PAD increased by 20-60%, and the risk of death caused by coronary artery disease (CAD) increased by 2-6 times. Therefore, similar to CAD), PAD can be a powerful predictor of death induced by myocardial infarction, stroke and other vascular diseases,[3] and is closely correlated with the occurrence of death for cardiovascular events.[4] Since the proportion of patients with lower extremity arterial disease is high in patients with PAD, in the present study, the lower extremity arterial disease was included into the concept of PAD and was investigated and discussed.

Methods

Subjects: A total of 5,682 patients with acute coronary syndrome (ACS), who were admitted to the Department of Cardiology, Beijing Anzhen Hospital from April 2002 to August 2016, were included into the present study. Among these patients, 188 patients had a history of PAD. The age of the patients ranged from 36 to 84 years, with a median age of 64 years old; 143 patients were male (76.1%) and 45 patients were female (23.9%). The remaining 5,494 ACS patients without PAD were assigned as the control group. The age of these patients ranged from 25 to 90 years old, with a median age of 59 years old; 3,972 patients were male (72.3%) and 1,522 patients were female (27.7%).

Inclusion and exclusion criteria: Patients diagnosed and treated for ACS, with history of PAD were included into the study. The diagnostic criteria for ACS were based on the 2015 European Society of Cardiology diagnostic criteria.[5]

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Exclusion criteria: patients with previous admissions for myocardial infarction, patients with acute myocardial infarction caused by embolus shedding, intravascular operation, or other diseases; patients who presented with cardiogenic shock, cardiac arrest and gastrointestinal bleeding upon admission; patients with acute infectious disease, malignant tumors and autoimmune diseases; pregnant women.

Diagnostic criteria for related diseases: diabetes mellitus was diagnosed based on the Guidelines for the Prevention and Treatment of Diabetes in China (2013 Edition).[6] The criteria for diabetes diagnosis were based on the typical symptoms of diabetes in addition to random blood glucose ≥ 200 mg/dL and/or fasting blood glucose ≥ 126 mg/dL and/or blood glucose level at two hours after glucose load ≥ 200 mg/dL. Hypertension was diagnosed according to the Chinese Guidelines for the Management of Hypertension in China (2015 revised edition).[7] The patient was diagnosed with hypertension when systolic blood pressure (SBP) was ≥ 140 mmHg (1 mmHg = 0.133 kPa) or diastolic blood pressure (SBP) was ≥ 90 mmHg. Dyslipidemia was diagnosed according to the Guidelines for Prevention and Treatment of Dyslipidemia in Chinese Adults (2016 revised edition):[8] triglyceride (TG) ≥ 150 mg/dL, total cholesterol (TC) ≥ 201 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 131 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 38 mg/dL, and smoking ≥ 10 cigarettes per day for more than one year.

Clinical data acquisition: (1) baseline clinical and demographical data of patients were recorded, including gender, age, body mass index, smoking history, alcohol consumption, family history of CAD, and past history of diabetes, hypertension, and dyslipidemia; (2) clinical indicators were recorded within 24 hours after admission, including heart rate, SBP and DBP. Fasting blood samples were collected in the morning of the next day after admission for the laboratory tests – blood routine test (complete blood count and platelet count) was performed using an automatic blood cell analyzer; blood lipid profile (triglyceride triacylglycerol, TC, LDL-C, and HDL-C) was determined using an automatic biochemical analyzer; brain (B-type) natriuretic peptide concentration was determined by radioimmunoassay, and troponin I was determined by mass spectrometry. The echocardiographic indexes included left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter. The coronary angiography results were recorded after admission. In-hospital adverse events included acute left heart failure, cardiogenic shock, cardiac arrest and death.

Statistical analysis

Statistical analysis was conducted using the statistical software SPSS 22.0. Normally distributed data were expressed as mean ± standard deviation, and non-normally distributed measurement data were expressed as median and interquartile range (P25, P75), and counts expressed as percentage. Data with normal distribution were compared using independent sample *t*-test, non-normally distributed continuous variables were evaluated using Mann-Whitney U-test, and discrete variables were compared using Chi-square (X^2) test. The multivariate logistic regression analysis between groups for in-hospital adverse events was performed. A two-sided test was used in the present study, and a $p < 0.05$ was considered statistically significant.

Results

Comparison of baseline data: mean age of PAD patients was 65.5 ± 10.3 years old and mean age of patients in control group was 58.6 ± 11 years old, with a statistically significant difference ($p<0.05$). The proportion of patients with diabetes mellitus in the PAD group was 39%, while that in the non-PAD group was 26.8%, and the difference was statistically significant. The analysis of clinical data after admission revealed that the levels of creatinine, TC and LDL-C were significantly higher in the PAD group than in the non-PAD ($p < 0.05$, for all; Table 1).

Characteristics of the coronary artery: coronary angiography was performed for all included patients. Multi-vessel disease was defined as the presence of two or more main branches of the coronary artery or its major branches with ≥70% stenosis.[8,9] According to these features, the disease was divided into three types: left main coronary artery disease (≥50% stenosis in the left main trunk), total occlusion (100% vascular stenosis), and calcification. The proportion of patients with multi-vessel stenosis was 12.1% in the PAD group, significantly higher than the non-PAD group ($p < 0.05$). In terms of left main CAD, occlusion, calcification and bifurcation lesions, the proportion of patients with these diseases was higher in patients with ACS combined with stroke, than in patients without stroke; but the difference was not statistically significant (Table 2).

Comparison of in-hospital adverse events: adverse events during in-hospital treatment included death, cardiogenic shock, acute left heart failure and cardiac rupture. In-hospital mortality rate was statistically significantly higher in ACS patients in the PAD group (1.1%), compared with patients in the control group (0.4%) ($p < 0.05$, Table 3).

After the patients were grouped according to the presence of the above events, the variables were selected for multivariate logistic regression analysis. The results revealed that history of PAD (OR = 1.791, p = 0.01), history of diabetes (OR = 1.223, p = 0.001), and age of >65 years old (OR = 4.670, $p < 0.001$) were independent risk factors for in-hospital adverse events (Table 4).

Discussion

There is a close correlation between atherosclerotic heart disease and PAD.[10] Patients with PAD have more extensive atherosclerosis, and the lesions are often more serious. Therefore, the risk of atherosclerotic events in this group is further increased. In the GRACE trial, approximately 9.7% of 41,108 ACS patients had PAD.[11] In the present study, 5,682 ACS patients were included; 188 of them (3.3%) had a history of PAD, and this proportion was lower than the proportion reported in the GRACE trial.

The occurrence and development of atherosclerosis are closely correlated to age. A study revealed that PAD patients were older and had higher risk of cardiovascular disease.[12] Furthermore, the present study revealed that patients with ACS complicated with PAD was older than patients in the control group. The multivariate logistic regression analysis

Table 1 – Baseline data of acute coronary syndrome patients with and without a history of peripheral arterial disease admitted to hospital

Items	ACS with a history of PAD (n = 188)	ACS without a history of PAD (n = 5,494)	p
Age (years)	65.5 ± 10.3	58.6 ± 11.0	< 0.001
Male (%)	143(76.1)	3972(72.3)	0.472
History of hypertension (%)	123(65.9)	3175(57.8)	0.129
History of diabetes mellitus (%)	73(39)	1472(26.8)	0.018
Dyslipidemia (%)	24(12.5)	890(16.2)	0.464
History of smoking (%)	104(55.7)	3044(55.4)	0.987
History of alcohol intake (%)	30(15.9)	1170(21.3)	0.464
History of stroke (%)	36(19.3)	396(7.2)	< 0.001
SBP (mmHg)	126.36 ± 20.25	124.47 ± 26.67	0.389
DBP (mmHg)	72.47 ± 12.01	74.02 ± 13.03	0.233
HR (bpm)	76.09 ± 14.03	74.44 ± 19.37	0.280
WBC (10^9/L)	7.3(5.9,9.7)	7.3(5.9,9.6)	0.801
RBC (10^{12}/L)	4.3(3.9,4.6)	4.5(4.1,4.8)	0.001
PLT (10^9/L)	205.04 ± 69.76	206.88 ± 66.03	0.795
ALT(U/L)	26.0(17.0,41.0)	26.0(17.0,44.0)	0.510
Creatinine (mg/dL)	0.97(0.75,1.24)	0.87(0.75,1.02)	0.021
AU (mg/dL)	5.91 ± 1.89	5.78 ± 2.13	0.545
Fasting plasma glucose (mg/dL)	106.3(93.7,147.7)	108.1(93.7,136.9)	0.381
TG (mmol/L)	123.9(79.7,159.4)	132.8(88.5,185.9)	0.079
TC (mg/dL)	166.3(139.2,189.5)	154.6(127.6,170.1)	0.002
LDL-C (mg/dL)	100.62(81.3,123.8)	89.0(73.5,108.4)	0.004
HDL-C (mg/dL)	34.8(27.1,46.4)	34.8(30.9,46.4)	0.586
D-dimer (umol/L)	99.0(50.0,196.2)	105.0(50.0,188.0)	0.832

Data expressed as mean ± standard deviation or median (interquartile range). ACS: acute coronary syndrome; PAD: peripheral arterial disease; SBC: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; WBC: white blood count; RBC: red blood count; PLT: platelet count; ALT: alanine aminotransferase; AU: albumin in urine; TG: triglycerides; TC: total cholesterol; LDL-C: low density lipoprotein; HDL-C: high density lipoprotein.

of in-hospital adverse events between the groups revealed that an age of ≥65 years old is an independent risk factor for in-hospital adverse events (OR = 4.670, p < 0.001). The older the age, the higher the incidence of the adverse events, which is consistent with existing literature. Therefore, for elderly ACS patients with a history of PAD, more attention should be given to changes in patient condition. In the present study, although the incidence of stroke in ACS patients with a history of PAD was higher (19.3%) than in controls, further analysis revealed that it did not affect in-hospital adverse events.

Dyslipidemia has been considered an important risk factor for atherosclerosis.[13] Existing studies have shown that cholesterol is closely related to the occurrence and development of PAD. In the formation and development of atherosclerosis, LDL-C plays an important role. Furthermore, evidence supporting the relationship between LDL-C and PAD has been found.[14] The present study also revealed that the level of LDL-C was higher in the PAD group than in the control group. Therefore, lipid-lowering therapy should be strengthened for patients with PAD complicated with ACS. Among the common risk factors for atherosclerosis, diabetes has been well-recognized as an independent risk factor for atherosclerosis. The ARIC study[15] revealed that, as compared with patients with a 0-5-year course of diabetes, the risk for PAD in patients with a course of diabetes of ≥ 6 years significantly increased, and the relative risk was 1.24. The present study also revealed that a history of diabetes was an independent risk factor for in-hospital adverse events (OR = 1.223, p < 0.001). Long-term hyperglycemia affects the elasticity and stiffness of the blood vessel walls, which leads to endothelial dysfunction and microcirculatory dysfunction. Therefore, controlling blood sugar is a necessary measure to reduce the incidence of ACS and PAD.[16]

Analysis of the characteristics of coronary arterial lesions revealed that compared with left main coronary artery disease, bifurcation lesions and calcification, and other serious CADs, ACS patients with PAD are more frequently affected by multivessel disease in coronary arteries. Also, atherosclerosis was characterized by extensive vascular involvement in coronary arteries. Therefore, multivessel lesions tend to indicate extensive wall motion abnormalities, leading to poor prognosis. This study has also confirmed this.

Table 2 – Characteristics of coronary artery lesions in acute coronary syndrome patients with and without a history of peripheral arterial disease [case(%)]

Items	ACS with a history of PAD (n = 188)	ACS without a history of PAD (n = 5494)	p
Left main coronary artery disease	9(4.8)	206(3.7)	0.777
Multivessel stenosis	22(12.1)	478(8.7)	0.015
Bifurcation lesion	27(14.4)	917(16.7)	0.782
Occlusion lesion	18(4.3)	191(3.6)	0.511
History of diabetes Calcified lesions	3(0.7)	15(0.2)	0.656

ACS: acute coronary syndrome; PAD: peripheral arterial disease.

Table 3 – The incidence of adverse events in acute coronary syndrome patients with and without a history of peripheral arterial disease [case(%)]

Items	ACS merged with PAD history (n = 188)	ACS not merged with PAD history (n = 5,494)	p
Death	5(2.6)	23(0.4)	0.035
Cardiogenic shock	6(3.1)	203(3.7)	0.435
Acute left heart failure	7(3.7)	174(3.2)	0.355
Cardiac rupture	0(0)	2(0.03)	0.707

ACS: acute coronary syndrome. PAD: peripheral arterial disease.

Table 4 – Multivariate Logistic regression analysis based on in-hospital adverse events

Items	SE	OR	95%CI	p
History of PAD	0.220	1.791	1.05-2.88	0.010
History of hypertension	0.169	1.112	0.79-1.55	0.529
History of diabetes mellitus	0.082	1.223	1.01-1.41	< 0.001
Age > 65 years old	0.181	4.670	3.21-6.44	< 0.001
Multivessel disease	1.015	0.625	0.08-4.57	0.643

PAD: peripheral arterial disease.

In the present study, analysis of in-hospital adverse events revealed that in-hospital mortality in ACS patients with PAD was 1.1% (p = 0.035), and the difference was statistically significant when compared with the control group. A meta-analysis revealed that after 2.7 years of follow-up for patients with acute myocardial infarction complicated with a PAD history, cardiovascular deaths occurred in 17.8% of patients, and 52.3% of these patients, and only 28% of patients without PAD experienced re-hospitalization caused by nonfatal myocardial infarction, nonfatal stroke and heart failure. Therefore, PAD is an independent risk factor for predicting poor outcomes.[17]

Thus, it can be concluded that patients with a history of PAD are more likely to experience many adverse events. In the present study, mortality due to adverse events was lower than that reported in the literature. The reasons for these differences may be that the subjects included in the present study were ACS patients, including low-risk patients such as patients with unstable angina. Furthermore, patients were not followed-up, and only in-hospital cardiovascular deaths were counted.

The limitation of the present study was that it had a single-center, retrospective design, and a single-center study may have bias in case selection. Furthermore, our sample (ACS population) included patients with unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction. The difference in severity between these conditions may have led to observation bias.

Conclusion

Patients with ACS complicated with a history of PAD have extensive coronary disease and high in-hospital mortality. A history of PAD is an independent risk factor for in-hospital adverse events.

Author contributions

Conception and design of the research: Yun-Peng K, Li-Ying C, Wen-Xian L; Acquisition of data and Analysis and interpretation of the data: Yun-Peng K, Li-Ying C, Tie-Duo K; Statistical analysis: Tie-Duo K, Wen-Xian L; Writing of the manuscript: Yun-Peng K, Li-Ying C; Critical revision of the manuscript for intellectual content: Yun-Peng K, Tie-Duo K, Wen-Xian L.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Characteristics and Adverse Events in Acute Coronary Syndrome Patients with a History of Peripheral Arterial Disease

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Short Editorial related to the article: Clinical Characteristics and Adverse Events in Acute Coronary Syndrome Patients with a History of Peripheral Arterial Disease

Cardiovascular diseases (CVD) are the leading cause of death in the world,[1] with increasing numbers of cases in low and middle-income countries. In Brazil, it is estimated that 350,000 patients die each year due to CVD.[2] The relationship between acute coronary syndrome (ACS) and peripheral atherosclerotic disease (PAD) is well established.[3,4]

Cross-sectional studies carried out in countries with genetic characteristics different from ours help us to evaluate the possible relationship between the characteristics of the patients evaluated and the increase in cardiovascular risk, and, despite their limitations, are good hypothesis generators.

The present study[5] analyzed the characteristics of patients with ACS and PAD, showing that advanced age, diabetes, worse lipid profile and multiarterial disease were more prevalent in patients with ACS and PAD than in patients with ACS and without PAD. In addition, it suggested that patients with such an association have a worse prognosis.

Limitations of the present study were the facts of its retrospective analysis and the exclusion of patients at higher risk (prior acute myocardial infarction, acute myocardial infarction caused by thrombus detachment, intravascular surgery, patients with cardiogenic shock and post-cardiac arrest and gastrointestinal bleeding on admission), which could have shown an even higher risk in such patients, considering that generally patients with associated PAD have greater complications and worse prognosis. It is also worth noting that it was carried out in a single center.

However, the present study has great value for showing once again, as previous studies have demonstrated,[6] the worsening of the prognosis of patients with ACS and PAD and which risk factors are most prevalent in this population, making possible the detection of subgroups of patients with ACS and PAD are more susceptible to a worse outcome and in this way emphasize their strict control. It is also necessary to offer the best treatment evidenced in the literature to such patients since real-life studies have shown that despite the higher risk of patients with ACS and PAD, they frequently receive less drugs with established benefit.[7]

Keywords

Cardiovascular Diseases; Acute Coronary Syndrome; Peripheral Arterial Disease/complications; Diabetes Mellitus; Myocardial Infarction; Risk Factors.

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Stress and Food Consumption Relationship in Hypertensive Patients

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Abstract

Background: Stress is a state of threat to the balance of the organism, which can cause biological and psychological changes. In hypertensive patients, stress can interfere with blood pressure levels, influence on food choices and neglect of the diet.

Objective: This study aims to describe the relationship between stress and dietary intake of hypertensive patients.

Methods: A transversal study was carried out at the Arterial Hypertension Clinic of the Cardiology Institute of Rio Grande do Sul, Brazil. The participants were aged ≥ 18 years and hypertensive. Blood pressure, food consumption and anthropometric measurements were collected. The variables related to stress were evaluated by the Lipp's Stress Symptoms Inventory (LSSI) for adults. Significance level of 5% has been considered for all analyzed data.

Results: The number of participants was 100. There was a higher prevalence of the female sex (67%), the mean age of the study population was 55.87 ± 12.55 years. Among the participants, 86% were classified in some of the stress phases, on which 57% were in the resistance phase. It was observed that there was no correlation between the presence of stress (as well as their actions), pressure levels and food consumption. The consumption of foods rich in lipids and individuals with a prevalence of psychological symptoms of stress displayed a significant association.

Conclusions: Rich in fat dietary has been the first choice in patients with psychological symptoms of stress. Further studies regarding remodeled dietary intake and blood pressure levels in relation to the stress phases are suggested. These findings are important to contribute to the development of prevention and treatment strategies for cardiovascular diseases. (Arq Bras Cardiol. 2019; 113(3):374-380)

Keywords: Hypertension; Food Consumption; Stress, Physiological; Dietary Fats/metabolismo; Body Weights and Measures; Metabolism.

Introduction

Stress is considered any force or experience that breaks the psychological homeostatic balance of an organism by activating a chain reactions cascade that increases blood flow through adrenaline release by adrenal glands and stimulates tachycardia, dilation of muscles and brain blood vessels and constricts blood vessels that supply the organs of digestion.[1]

According to the World Health Organization, stress affects more than 90% of the world's population and about 70% of Brazilians. Stress is a special situation where the development of considerable blood pressure changes may occur.[2,3]

Exposure to stress can lead to qualitative and quantitative changes in food consumption pattern,[4] with higher and easier consumption of hyperpalatable foods. They have high-calorie density and are rich in fats and sugars, providing not only weight gain, but also contributing to the increase of chronic non-communicable diseases. Most of the time, stress promotes an increase in the consumption of this type of food, consequently decreasing the intake of fruits and vegetables.[5] Emotional feeding may be related to behavioral and metabolic changes in the stress response.[4,6]

The effect of stress on a diet seems to modify the metabolism of various nutrients, such as B complex vitamins, C vitamin, calcium, magnesium, iron and zinc.[7,8] Furthermore, when stress affects the patient, there is a tendency of neglecting the diet, aggravating pathological conditions by inadequate intake of nutrients. Among nutritional deficiencies, it stands out that mineral deficiencies are connected to a wide variety of metabolic dysfunctions.[8]

If the stress is continuous and intense, besides causing damage to the endocrine and immune system,[9] it may lead to changes in lipid metabolism, blood pressure, heart rate, increased myocardial oxygen consumption and, as a consequence, reduction in peripheral vascular resistance.[6] Progressively these problems lead to an increase in cardiovascular diseases.[10,11] There is evidence that the major

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triggering factor for hypertension is precisely the stress exerted in moments of stress and anxiety that alter the entire hormonal and systemic configuration of the organism.[7]

Therefore, this study aims to evaluate the relationship between stress, food choices and food consumption in hypertensive patients.

Methods

A cross-sectional study took place at Arterial Hypertension Clinic of the Cardiology Institute of Rio Grande do Sul, Brazil, between 2013 and 2015. Hypertensive patients of both genders, older than 18 years old, from Basic Health Units, with uncontrolled hypertension, in current use of antihypertensive medication and with an average diagnosis of hypertension of five years. Exclusion criteria were patients with secondary hypertension, congenital heart disease, surgical and acute myocardial infarction, as evidenced by the clinical file. The flowchart of patients invited to participate in the study is described in Figure 1.

In order to obtain the sample number to perform the study, the calculation was performed with 80% power, 95% confidence level and an expected correlation of r = 0.25 between the phases of stress and food consumption, totalizing a sample composed of 97 patients.[12]

Patients were invited to participate in the study after explaining the objectives, justification and methods that would be used in the data collection. After the acceptance, the patients signed two copies of the Free and Informed Consent Form, which was approved by the IC / FUC Research Ethics Committee, under No. 4843/13. It is important noticing that the study protocol complied with all ethical guidelines recommended by the National Health Council.

The data collection was conducted by training professionals in the Cardiology Institute settings during a single scheduled consultation in the multidisciplinary outpatient clinic of Systemic Arterial Hypertension. Variables of age, gender, blood pressure, anthropometry, food consumption and stress symptoms were collected.

The nurse team performed measures of blood pressure in accordance with the VII Brazilian Guidelines for Hypertension.[2] Anthropometric measurements were taken by the nutritionist. Weight and height variables were collected using an anthropometric scale (Welmy®), with a capacity of 200 kg and with anthropometric ruler coupled up to 2 meters. For weighing, all patients were instructed to be barefoot to remove objects from their pockets, watches and excess clothing. The patient was placed in the center of the platform, with arms extended along the body. For height measurement, the patient remained barefoot and standing upright, with his head held high, arms hanging at his side, heels and back against the vertical plane of the rod. In sequence, the patient was instructed not to shrink when the stem was placed on the head, the support of which remained

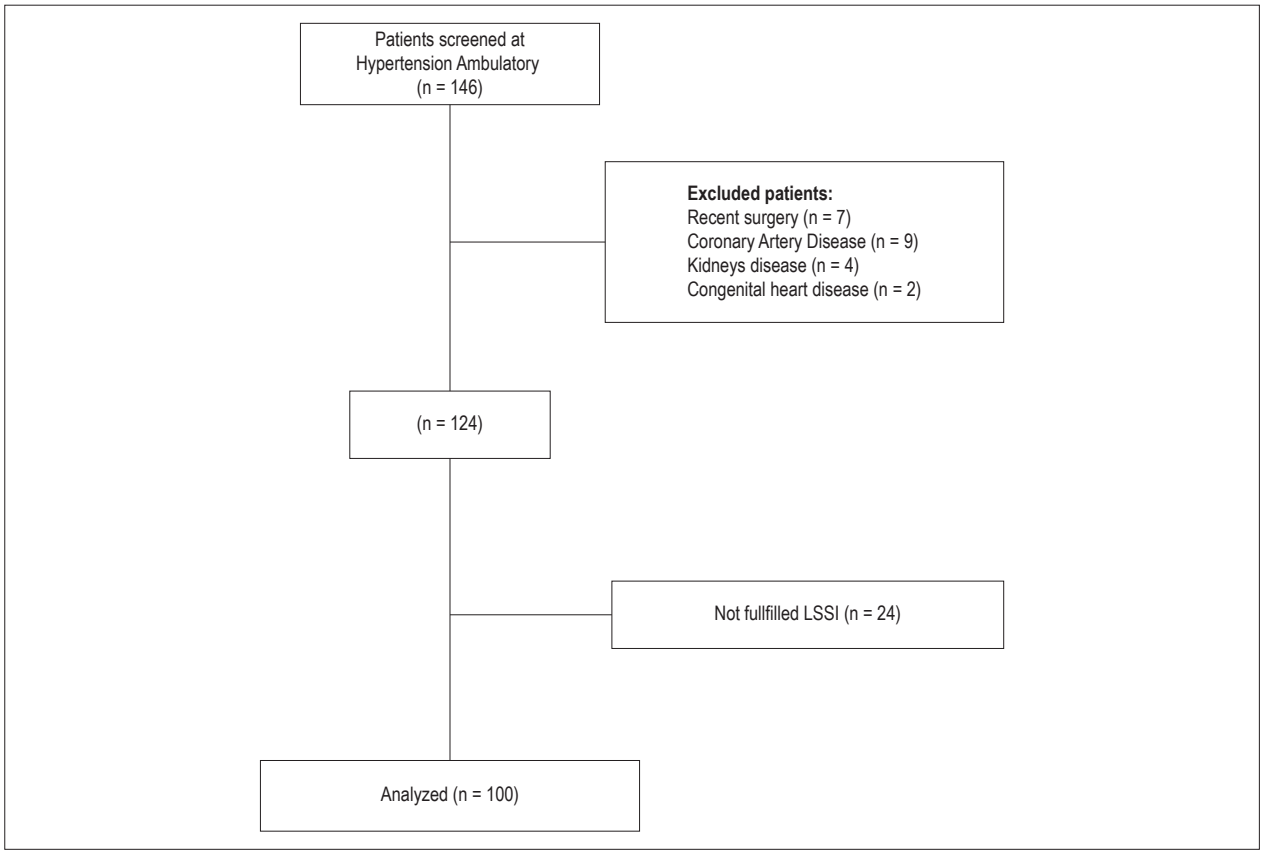

Figure 1 – *Flowchart of Participants. LSSI: Lipp stress symptoms inventory.*

on the scalp, avoiding contact only on the hair. Weight and height data were used to calculate body mass index (BMI) and the following cutoff points were used for adults: Low weight < 18.5 kg/m²; Eutrophic 18.5 - 24.9 kg/m²; Overweight 25 - 29.9 kg/m² and Obesity ≥ 30 kg/m²; [3] and for elderly: Low weight: < 22 kg/m²; Eutrophic: 22 - 27 kg/m² and Excess weight: > 27 kg/m² according to Lipschitz (1994).[13]

For the qualitative evaluation of food consumption, food frequency questionnaire adapted from Ribeiro et al.,[14] was applied in order to analyze the frequency of food consumption. The interpretation of this questionnaire was carried out through the stratification of the consumed food groups, being evaluated the following groups: ultra-processed foods, *in natura* foods, rich in carbohydrates, proteins and lipids.

Lipp's stress symptoms inventory (LSSI) for adults was applied by a psychologist to evaluate the symptoms of stress. This inventory is an objective measure of stress symptomatology in individuals over 15 years of age. LSSI is composed of 37 somatic and 19 psychological items whose symptoms, if repeated, differ only in intensity and severity. This instrument is divided into 3 sets: the 1st with 15 items refers to the physical or psychological symptoms that the patient has experienced in the last 24 hours; the second, composed of ten physical and five psychological symptoms, and is related to the symptoms experienced in the previous week; the third, with 12 physical and 11 psychological symptoms, refer to the situation of the previous month.[15]

Statistical analysis

Data tabulation was performed in the Microsoft Excel 2013 for Windows. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 22.0. Variables with normal distribution were described in mean ± standard deviation. Variables with normal distribution were described in mean ± standard deviation and variables with asymmetric distributions such as median and interquartile range (25th and 75th percentile).

In order to correlate dietary intake of different food groups (carbohydrates, lipids, proteins, *in natura* and ultra-processed foods) with the stress phases, the Spearman correlation coefficient was used.

For the comparison of continuous variables concerning the presence or absence of stress, the Mann-Whitney test (food intake) and Student's t-test (blood pressure) were used for independent samples. In regards to the types of stress symptoms (physical/psychological/mixed) the tests used were Kruskal Wallis (food consumption) and ANOVA One-way (blood pressure). Significance level of 5% ($p < 0.05$) was considered.

Results

The sample consisted of 100 patients with a mean age of 55.87 ± 12.55 years and 67% (n = 67) were females. The mean values of blood pressure were 182.38 ± 28.01 mmHg for systolic and 94.95 ± 12.42 mmHg for diastolic. Regarding the stress variable, 86% (n = 86) of the participants were included in some of the phases, of which 57% were in the resistance phase (Table 1).

No correlation was observed between the different stages of stress, blood pressure and food consumption (Table 2).

Table 3 shows the comparison of the food consumption profile with the presence or absence of stress and blood pressure.

Among the food groups investigated, there was a significant association with foods rich in lipids and psychological symptoms of stress, according to Table 4.

Discussion

This study aimed to describe the relationship between stress and food consumption in hypertensive patients. Analyzing the consumption of foods rich in lipids in individuals with stress and predominance of psychological symptoms, we found a significant association between the variables.

Regarding the predominance of women, it is believed that a more significant number of them seek care assistance and show higher health concerns when compared to the men.[16]

In a review of stress-induced eating, Greeno and Wing[17] have shown that different stress stimuli cause different reactions, taking into account the individuality of the patients, but stress can affect the quality of food choice.

Nguyen et al.[18] demonstrated in his study on stress-induced eating with 517 students that perceived stress was a significant correlate of "emotional eating" and also added in their results that this factor is independent of BMI, suggesting there is no relation between stress-induced eating; and people who are overweight and obese.

In the present study, we did not observe a significant positive relationship between food consumption in different stages of stress with the presence or absence of stress. The divergences found in this study concerning those mentioned above can be attributed to the diversity of the analyzed variables, which suggests a more detailed investigation, as it is well documented by Sousa et al.[19] that the stimuli and physiological responses differ in each phase of the stress.[19]

Regarding stress, in the resistance phase (57%), it is in agreement with the results obtained by Wottrich et al.,[20] in which the predominance of the individuals evaluated was predominant in the endurance phase. These findings are in agreement with data from the study described by Malagris[21] and Rosseti [22] whose results were similar in their research.

Lipp et al.[23] also emphasizes that the resistance phase is associated with excessive fatigue, memory problems and doubts about oneself, which can significantly compromise the individual's quality of life.

Pecoraro et al.[24] and Zellner et al.[25] stated that in order to minimize stress symptoms, it is common to eat tasty foods, mostly high in fat, as a form of comfort and "self-medication". In another study with adolescents conducted in London, it was found that a high degree of perceived stress was related to high intakes of fat and large amounts of unhealthy meals.[5] In this study, a positive association between the consumption of rich foods in lipids in patients classified with some level of stress, with a predominance of psychological symptoms.[5]

It is important to point out that fat in the food promotes greater palatability being also more caloric. The fact that

Table 1 – Characterization of participants

CARACTERÍSTICAS	n	%
Gender		
Women	67	67%
Men	33	33%
Age (mean ± standard deviation)	55.87 ±12.55	
(minimum- maximum)	(19 a 80)	
BLOOD PRESSURE		
SBP	182.38 ± 28.01	
DBP	94.95 ± 12.42	
ESTRESSE – LSSI		
Alert	2	2%
Resistence	57	57%
Almost exhaustion	11	11%
Exhaustion	16	16%
No stress	14	14%
Nutritional State – BMI		
Eutrophic	31	31%
Overweight	69	69%

LSSI: Lipp Stress Symptom Inventory; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index.

Table 2 – Correlation of the Stress phases with food consumption and blood pressure

	LSSI Phases	SBP	DBP
SBP	0.023 (p = 0.821)	-	-
DBP	0.134 (p = 0.185)	0.449 (p > 0.01)	-
Ultraprocessed	-0.059 (p = 0.563)	-0.003 (p = 0.980)	0.070 (p = 0.490)
Carbohidrates	0.008 (p = 0.938)	-0.074 (p = 0.467)	-0.115 (p = 0.253)
Proteins	-0.154 (p = 0.125)	-0.044 (p = 0.663)	-0.064 (p = 0.524)
In natura	-0.002 (p = 0.987)	-0.113 (p = 0.262)	-0.083 (p = 0.413)
Lipids	0.160 (p = 0.313)	-0.193 (p = 0.220)	0.003 (p = 0.987)

Spearman Correlation Coefficient - correlation between stress phases (alert, resistance, near exhaustion and exhaustion) with food consumption (carbohydrates, proteins, lipids, ultra-processed and in natura foods) p < 0.05. LSSI: Lipp Stress Symptom Inventory; SBP: systolic blood pressure; DBP: diastolic blood pressure.

psychological symptoms are predominant may reveal that the individuals were worried, with low self-esteem and irritated, therefore, with their psychological conditions compromised, seeking for some compensation and well-being in food. It is known that emotions can determine food choices and preferences and foods are associated with the emotional context in which they are usually consumed.[26,27]

Considering that primary prevention of blood pressure elevation can be achieved by controlling risk factors including changes in lifestyle, multimodal interventions are indicated to integrate education on healthy lifestyle and medical resources, physical activity, stress management and counseling on psychosocial risk factors.[28]

The present study presented some limitations, we highlight the application of the questionnaire of the frequency of food consumption. This method requires greater precision to remember the foods consumed in the different frequencies evaluated, which could potentially be considered a memory bias. However, among the types of validated food consumption protocols, this is considered to be more reliable and representative of food when compared to the 24-hour food recall or food diary. Another difficulty observed was the small number of scientific studies on the subject, which made it difficult to deepen the discussion of the data.

In the population of hypertensive patients, it is necessary to explore team strategies for better management of stress, as well as to prescribe a reduction in the intake of fatty foods and to accompany them, which will imply the effectiveness of disease control, risk control related to comorbidities and better quality of life.

Table 3 – Food consumption and blood pressure according to the classification of present or absent Stress

	LSSI		p
	Absent	Present	
Ultraprocessed	3 (1.1; 3.5)	2.4 (0.7; 3.4)	0.295
Carbohydrates	0.3 (0.2; 0.9)	1.1 (0.3; 2.3)	0.099
Proteíns	2.5 (2; 3.2)	2.4 (1.7; 3.1)	0.522
In natura	3.5 (2.7; 3.9)	3.3 (2.7; 4.2)	0.761
Lipids	4.3 (3.5; 6.5)	7 (3.6; 7)	0.367
SBP (mmHg)	168.07 ± 27.31	174.36 ± 26.58	0.416
DBP (mmHg)	90.93 ± 15.83	93.51 ± 15.56	0.568

Mann-Whitney and SBP (systolic blood pressure) and PAD (diastolic blood pressure) were used for food consumption (consumption on days of the week). Test T. LSSI: Lipp Stress Symptom Inventory for Adult.

Table 4 – Comparison of frequency of food consumption and blood pressure in relation to the types of stress symptoms

Outcomes	LSSI			p
	Physical	Psychological	Mixed	
Ultraprocessed	1.9 (0.5; 2.8)	3.4 (1.3; 4.9)	2.4 (0.8; 2.9)	0.065#
Carbohidrates	1.1 (0.3; 2.5)	1.1 (0.3; 1.7)	1.4 (0.2; 2.7)	0.573#
Proteins	2.3 (1.6; 3)	2.4 (1.7; 3.2)	2.4 (1.6; 3.2)	0.848#
In natura	3.3 (2.6; 4)	3.6 (2.9; 4.2)	3.1 (2.6; 4.2)	0.608#
Lipids	5 (3.5; 7)	7 (7; 7)	5 (3.3; 7)	0.026#
SBP	170.66 ± 27.1	182.38 ± 28.01	177.92 ± 23.82	0.226*
DBP	91.92 ± 15.74	94.95 ± 12.42	100.15 ± 18.81	0.226*

*#Kruskal Wallis Test – Values presented as mediana/interquartile interval. *ANOVA – Values presented as Mean (M) ± Standard Deviation (SD). LSSI: Lipp Stress Symptom Inventory; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

As future work, we intend to evaluate the relationship between altered dietary intake and blood pressure levels regarding specific stages of stress. Indeed, the analysis of this study shows itself useful for hypothesis assessment for future researchers.

Conclusion

Changes in dietary choices were evidenced by higher consumption of high-fat foods in individuals with a prevalence of psychological symptoms. However, more studies are needed the alteration of food consumption and blood pressure levels in relation to certain stages of stress. Because hypertension is a multifactorial disease, it requires a multi-area treatment approach to achieve better results. These findings are essential to contribute to the development of new strategies for the prevention and treatment of diseases, thus minimizing the risk factors for the progression of cardiovascular diseases.

Author contributions

Conception and design of the research: Dalmazo AL, Goldmeier S, Irigoyen MC, Pellanda LC, Osório DRD; Acquisition of data: Dalmazo AL, Goldmeier S, Osório DRD; Analysis and interpretation of the data: Goldmeier S, Pellanda LC, Barbosa ECD, Osório DRD; Statistical analysis: Fetter C, Moreira TR; Obtaining financing: Irigoyen MC; Writing of the manuscript: Dalmazo AL, Fetter C, Moreira TR, Osório DRD; Critical revision of the manuscript for intellectual content: Fetter C, Goldmeier S, Irigoyen MC, Pellanda LC, Barbosa ECD, Moreira TR, Osório DRD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the IC-FUC under the protocol number 4843/13. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Hypertension: Pathophysiological Aspects, Psychosocial Stress and Food Preference

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Short Editorial related to the article: Stress and Food Consumption Relationship in Hypertensive Patients

Arterial hypertension is highly prevalent in developed and developing countries. Together with high blood glucose levels, hyperlipidemia, overweight and obesity, it is considered a consequence of behavioral risk factors such as physical inactivity, tobacco use, harmful alcohol use and inadequate diets.[1] The cause of arterial hypertension in most of the cases (over 90%) is unknown. The activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system and an abnormal pressure-natriuresis curve play an important role in the pathophysiology of hypertension.[2] Oxidative stress has also been identified as an intermediate phenotype in the development of arterial hypertension.[3] Experimental and epidemiological studies point to psychosocial stress as a possible trigger that causes the autonomic imbalance (increased sympathetic activity) in hypertensive patients.[4] This autonomic imbalance can be observed even before the arterial hypertension onset in children born to hypertensive parents.[5] In addition to psychosocial stress, an unhealthy diet contributes to the development of arterial hypertension and higher cardiovascular morbidity/mortality.[6]

If, on the one hand, diet plays an important role in the pathophysiology of arterial hypertension, on the other hand, adopting a healthy diet can result in better blood pressure control. The DASH (Dietary Approach to Stop Hypertension) diet, mentioned in worldwide guidelines, was evaluated by Appel et al.[7] and it was the first scientifically tested diet to result in a significant blood pressure reduction in hypertensive patients. The DASH diet consists of easily accessible foods such as vegetables, fruits, nuts, lean meat, and low-fat milk and dairy products. In a study of obese hypertensive patients,[8] we tried to elucidate the possible mechanisms involved in blood pressure reduction after the consumption of the standard DASH diet. In this study we demonstrated that the consumption of a standard DASH diet results in improved antioxidant capacity, especially in obese hypertensive patients. Since oxidative stress plays a role in the pathophysiology of arterial hypertension, this is one of the possible mechanisms for reducing blood pressure in those individuals who consume the DASH diet foods in adequate proportion.

Although there is a previously tested diet with a positive impact on blood pressure reduction, as in the case of the DASH diet, there is a tendency among humans to preferentially consume some types of food. Previous studies, mainly experimental ones, have evaluated the association of stress exposure and emotional state with preference for some specific foods.[9]

In the article by Ulrich-Lae et al.,[9] they describe the association of eating high-fat and sweet foods with stress improvement in animals. As the stressed animals and human beings prefer more caloric foods (carbohydrates and fats), the tendency is to develop obesity. Obesity is known to be directly related to arterial hypertension.[10]

In this issue of the Brazilian Archives of Cardiology, Dalmazo et al.[11] demonstrated the association of stress levels with a higher consumption of high-fat foods in patients with arterial hypertension. The findings of this study indicate the importance of a multidisciplinary approach in hypertensive patients, especially those with high levels of psychosocial stress.

Keywords

Hypertension; Obesity; Diabetes Mellitus; Dyslipidemias; Sedentary Behavior; Oxidative Stress; Healthy Diet; Indicators of Morbidity and Mortality.

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Prevalence of Systemic Arterial Hypertension in Quilombola Communities, State of Sergipe, Brazil

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Abstract

Background: The quilombolas are groups formed by black ancestry individuals, living in a context of social vulnerability due to low socioeconomic level, which influences health care and the development of chronic diseases.

Objective: To assess the prevalence of systemic arterial hypertension and its association with cardiovascular risk factors in the quilombola population in the State of Sergipe, Brazil.

Methods: Study design was cross sectional, involving the administration of a questionnaire to individuals aged ≥ 18 years, in 15 quilombola communities of the State of Sergipe, Brazil. A value of two-sided $p < 0.05$ was considered statistically significant.

Results: sA total of 390 individuals were evaluated, 72.3% of whom were women, with a mean age of 44.7 years. The prevalence of hypertension was 26% (with a confidence interval of 95% [95% CI]: 22-30), with no significant sex-related differences. The age was associated with arterial hypertension (95% CI: 1.03-1.06), systolic (95% CI: 1.04-1.07) and diastolic (IC 95%: 1.01-1.04) arterial hypertension. The level of body mass index was associated with arterial hypertension (95% CI: 1.00-1.11) and diastolic arterial hypertension (95% CI: 1.03-1.17). Economic class was associated with diastolic arterial hypertension (95% CI: 1.22-5.03).

Conclusion: The prevalence of arterial hypertension in the quilombola communities was high. Its association with cardiovascular risk factors indicates the need to improve access to healthcare services. (Arq Bras Cardiol. 2019; 113(3):383-390)

Keywords: Cardiovascular Diseases; Hypertension; Prevalence; Public Health; Risk Group; African Continental Ancestry Group; Health of Specific Groups.

Introduction

The quilombolas are groups formed by black ancestry individuals, due to their African origin, trafficked to Brazil between the XVI and XIX centuries. They were brought to work as slaves in the sugar plantations under precarious conditions. After the abolition of slavery, numerous quilombola communities arose in Brazil; nowadays there are 2,958 communities throughout the country, and 35 are located in the State of Sergipe. The States of Bahia, Maranhão, Pará, Minas Gerais and Pernambuco have a higher number of communities in their territories.[1] The land demarcated as quilombola territories ensure the physical, social, economic and cultural reproduction of the remaining members of the Quilombo communities.[2]

The quilombola communities are inserted in a context of social vulnerability due to low socioeconomic level, which directly influences healthcare and the development of chronic diseases.[3] Studies have shown that systemic arterial hypertension (SAH) is one of the most relevant diseases among the quilombola populations, and can be associated with genetic factors. However, Brazilian studies could not associate genetic polymorphism with increased blood pressure levels among the quilombolas, which may be associated with the intense Brazilian miscegenationa.[4,5]

The prevalence of SAH among quilombola communities has ranged from 38.4%[6] to 45.4%,[7] which represents a higher percentage rate compared to the general Brazilian population.[8] The risk factors for the development and grievance of arterial hypertension are diseases like dyslipidemia, abdominal obesity, glucose intolerance, diabetes mellitus (DM), in addition to modifiable factors, such as socioeconomic determinants and inadequate access to healthcare services.[9] SAH can cause permanent damage to individuals through the onset of cardiovascular, cerebrovascular and kidney diseases.[10]

Thus, the aim of this study was to identity the prevalece of SAH and its association with cardiovascular risk factors in the quilombola population of the State of Sergipe, Brazil.

Methods

The study design and sample

This is a cross sectional study, carried out in quilombola communities in the State of Sergipe, Brazil, in the period between September 2016 and April 2017. The sample delineation

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was performed through random selection in the quilombola communities, using the existing proportion of the population in the communities. These data were provided by the National Institute of Colonization and Agrarian Reform (INCRA).[1]

A random sample of clusters was selected in two stage cluster sampling. There are 35 quilomobola communities registered in the State of Sergipe, distributed in eight territories, of which four were randomly selected. Out of these four territories, 15 communities were randomly selected from a total of 19. Between 15% and 20% of the adult population voluntarily participated. For each stage, once the territories and the quilombola communities were registered, the random sampling without replacement was performed using the Stata® version 15.1 software.

The communities studied are far from the city headquarters, in areas of difficult acess. Certain communities (Resina and Pontal da Barra) surround the main river in the region and the sea, respectively. The other communities (Mocambo, Canta Galo, Pirangy, Terra Dura, Forte, Caraíbas, Bongue, Patioba, Ladeiras, Alagamar, Aningas and Quebra Chifre) are situated in large land properties. The quilombola community "Maloca" is the only one that is located in urban area among the other remaining communities in the state.[1]

The target population of the research, according to oficial registries,[1] was estimated in 1,979 adult individuals, inhabitants of the 15 quilombola communities. Sample size calculations were done using the G*Power 3 software,[11] respecting the following parameters: 80% power; two-sided alpha = 0.05; covariable distribution pattern; log-normal distribution; potential correlation between predictors, 0.80; expected prevalence of arterial hypertension in the general population (20.4%).[8] According to these parameters, about 350 individuals would be necessary to detect an odds ratio ≥ 1.5 for differences between categorical predictors, in multiple regression logistic analysis. With the aim of preserving these characteristics in a potential situation of missing data, the sample size was increased to about 10%, totalling 390 individuals.

The inclusion criteria adopted for individual selection were: age ≥ 18 years; and being registered as quilombolas in the communities where they belong and in the INCRA. The exclusion criteria were: practice of physical exercise in the last 60 minutes; ingestion of alcoholic drinks, coffee or food; use of cigarette or consumption of other substances within the 30 minutes prior to blood pressure measurement; pregnancy; and amputated upper limbs.

Clinical and Sociodemographic Data Collection

The data were collected using individual interview. The interviewers were trained for this procedure. The interview instrument used was a semi-estructured questionnaire adapted from the following studies: the Brazilian Ministry of Health's Food Guide [12] and the Evaluation of Physical Activity Program Effectivity in Brazil,[13] both published by the Brazilian Ministry of Health; the National Household Sample Survey ;[14] the criteria of economic classification of the ABEP (Brazilian Association of Market Research Firms), which divides society into economic classes A, B1, B2, C1, C2, D-E, considering household assets, education level and the public services available.[15] The questions related with licit and illicit drugs were based on the Brazilian version of ASSIST (Alcohol, Smoking and Substance Involvement Screening Test)[16] The previous history of diseases was based on the questions asked for admission to hospital due to primary care-sensitive conditions.[17]

Then, three blood pressure measurements were perfomed (with a 1-minute interval between each measurement). A Welch Allyn DuraShock™ DS44 (Welch Allyn, Curitiba, Brazil), internationally validated, Aneroid Sphygmomanometer, with nylon cuff and metal clasp, was used. The measurements were performed at the end of the interview.

During BP measurements, the individuals remained seated, with their legs uncrossed, feet flat on the floor, back supported by the back of a chair and relaxed. The individual's left arm was positioned for measurement, followed by the right upper limb. The third measurement was performed on the limb that presented the highest value, always with the arm rested on a table, at heart level.

For analysis, the mean of the three measurements was calculated, which corresponded to the research criteria, being considered hypertensive those individuals who had systolic arterial pressure ≥ 140 mmHg and/or diastolic arterial pressure ≥ 90 mmHg.[9] These more conservative measurements have been adopted because the three measurements of the blood pressure were performed in only one day. For this reason, the classification of the American Heart Association was not adopted.[18]

The Body mass (BMI) index [kg/m^2] was estimated to evaluate the anthropometric measurements (weight and height). The BMI found was categorized according with the following measures: low weight, < 18.5 kg/m^2; normal weight, 18.5 to 24.5 kg/m^2; overweight, 25 to 29.9 kg/m^2; level I obesity, 30 to 34.9 kg/m^2; level II obesity, 35 to 39.9 kg/m^2; and level III obesity, > 40 kg/m^2.[19]

Statistical analysis

Categorical variables were expressed as absolute numbers and percentage. The continuous variables were expressed as mean and standard deviation. To produce robust estimates independent from the distribution pattern of the variables, some tests were specifically adopted. sThe comparisons between continuous variables and two groups were performed using the unpaired student t-test with adjustment for heterogeneity of variance and degrees of freedom using the Satterthwaite method. Comparisons between continuous variables and more than three groups were estimated using the Kruskal-Wallis test. Several logistic regression models for AH were used, starting from the choice of predictors with $p < 0.20$ in unadjusted analyses. The model's potential increment was assessed after inclusion of squared terms and interaction of predictors. The comparison of the increased prevalence between the quilombola communities and the population in general was performed using the chi-squared adjustment test. To adjust the analysis for the differences between groups and the potential of heteroskedasticity in the quilombola communities, the Huber-White method was used to estimate clustering, robust standard errors, according with the 15 communities.

The estimate of the effect size was presented in odds ratio with 95% confidence interval. The Hosmer-Lemeshow test and C-statistics (area under the receiver operating characteristic curve, or ROC curve) were used to assess the potential calibration and discrimination of the model, respectively. A value of two-sided $p < 0.05$ was considered statistically significant and the Stata® version 15.1 software (Stata Corp, College Station, TX, EUA), was used for data analysis.

Results

A total of 408 volunteers participated in the research; out of these, 18 were excluded: four of them who reported being pregnant, and 14 because they had consumed alcohol. A total of 390 individuals were deemed eligible, 72.3% women and 27.7% men. There were no missing data. The age ranged from 18 to 101 years, with a mean equal to 44.7 ± 19 years. The skin color was self-reported, according to the criteria of the Brazilian Institute of Geography and Statistics (IBGE), which indicated that 50% of the individuals were brown-skinned. The most prevalent level of education was illiterate/incomplete primary education I (58%). In the economic field, classes D and E obtained greater representation (76.41%). Table 1 presents the frequency of the main sociodemographic characteristics of the quilombola communities studied.

A prevalence of 26% (95% CI: 22-30) was observed for SAH; systolic arterial hypertension in 22% (95% CI: 18-26) and diastolic arterial hypertension in 16% (95% CI: 12-20) of the cases. A chi-square test was performed to compare the prevalence of SAH in the quilombola communities and in the general population of Sergipe (20.4%),[8] and the quilombola communities had a significantly higher prevalence ($p = 0.0071$).

The mean number of years with a previous SAH diagnosis was 9.59 (standard deviation = 8.66). The diagnosis of the disease had been made at a minimum age of 18 years and at a maximum age of 55 years.

There was no significant sex-related differences between the subclassifications of blood pressure. In women the average value of systolic pressure was 125.35 mmHg (95% CI: 122.7-127.9), whereas in men the average value was equal to 129.53 mmHg (95% CI: 125.3-133.7); $p = 0.09$. The average diastolic pressure value estimated for women was 78.88 mmHg (95% CI: 77.1-80.6); as for men, the average value was 78.57 mmHg (95% CI: 76.3-80.7); $p = 0.83$.

Among the behavioral variables reported by the participants, the following percentages were obtained: smoking, 37.18%; having alcohol drinking habits, 60.77%; and being physically inactive, 44.10%.

The participants responded that they consumed high quantities of sodium chloride (salt) everyday (17.69%). In relation to the anthropometric parameters, about 60.01% of the population presented with overweight or classes I, II and III obesity, with a smaller number of normal weight individuals (37.17%) (Table 2).

Table 1 – Distribution of the demographic and socioeconomic variables in quilombola comunities in the State of Sergipe, Brazil, 2016-2017

Variables	N	%
Age		
18 to 49	245	63
50 to 79	133	34
> 80	12	3
Sex		
Female	282	72.31
Male	108	27.69
Skin Color/Race		
Black	150	38.46
Brown	209	53.59
White	31	7.95
Level of Education		
Illiterate/Incomplete Primary Education I	226	58
Complete Primary Education I/Incomplete Primary Education II	64	16.43
Complete Primary Education II/Incomplete High School	50	12.83
Complete High School/Incomplete Higher Education	45	11.54
Complete Higher Education	5	1.20
Economic classification		
B2	5	1.28
C1	18	4.62
C2	69	17.69
D-E	289	76.41

Table 2 – Distribution of behavioral variables, lifestyle, anthropometric profile and risk fators in quilombola communities in the State of Sergipe, Brazil, 2016-2017

Variables	N	%
Smoking		
Yes	145	37.18
No	245	62.82
Alcohol consumption		
Yes	237	60.77
No	153	39.23
Dyslipidemia		
Yes	71	18
No	318	82
Diabetes Mellitus		
Yes	36	9.23
No	354	90.77
Physical activity		
Light	172	44.10
Moderate	77	19.74
Vigorous	141	36.16
Fatty food consumption		
< 1 time/week	130	33.33
1 or 2 times/week	113	28.98
3 or 4 times/week	147	37.69
Candy consumption		
< 1 time/week	185	47.44
1 or 2 times/week	108	27.69
3 or 4 times/week	97	24.87
Daily intake of high-sodium foods		
Yes	69	17.69
No	321	82.31
Adds salt to served food		
Yes	49	12.56
No	341	87.44
Body mass index categories		
Underweight	11	2.82
Normal weight	145	37.17
Overweight	139	35.64
Classes I, II and III obesity	95	24.37

In the univariate logistic regression analysis, the risk factors associated with arterial hypertension were: smoking ($p = 0.02$) and BMI ($p = 0.04$). In the multivariate analysis, the the odds ratio with statistical significance for arterial hypertension were found for the predictors age and BMI. For systolic arterial hypertension alone, the only significant statistic preditor was age; as for diastolic arterial hypertension, the predictors were age, BMI and, primarily, economic class (Table 3).

The logistic regression model enabled us to identify the probability of developing arterial hypertension through increased BMI. Among the sexes, the number of women was higher. According with the age and sex, it was noticeable that, as the quilombola population grows older, the number of hypertensives tends to increase, especially among women (Figure 1).

The Hosmer-Lemeshow test showed good adjustment/calibration of the final model ($p = 0.14$). To assess the discrimination capacity of the model, the C-statistics was performed through calculation of the area under the ROC curve, presenting a value equal to 0.77, which was considered a satisfactory value.

Table 3 – Predictors of systemic arterial hypertension in quilombola communities in the State of Sergipe, Brazil, 2016-2017

Variables	AH			SAH			DAH		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.05	1.03-1.06	< 0.001	1.06	1.04-1.07	< 0.001	1.02	1.01-1.04	< 0.001
Sex									
Female (ref.									
Male	0.71	0.38-1.33	0.29	0.67	0.36-1.24	0.24	0.98	0.48 -2.01	0.97
ABEP									
B2-C2 (ref.)									
D-E	1.75	0.93-3.28	0.07	1.38	0.74-2.56	0.29	2.47	1.22-5.03	0.01
BMI	1.05	1-1.11	0.04	1	0.95-1.05	0.84	1.10	1.03 -1.17	0.02

AH: arterial hypertension (systolic, diastolic or both); SAH: systolic arterial hypertension (alone); DAH: diastolic arterial hypertension (alone); OR: odds ratio; CI: confidence interval; ABEP: Brazilian Association of Market Research Firms; BMI: body mass index.

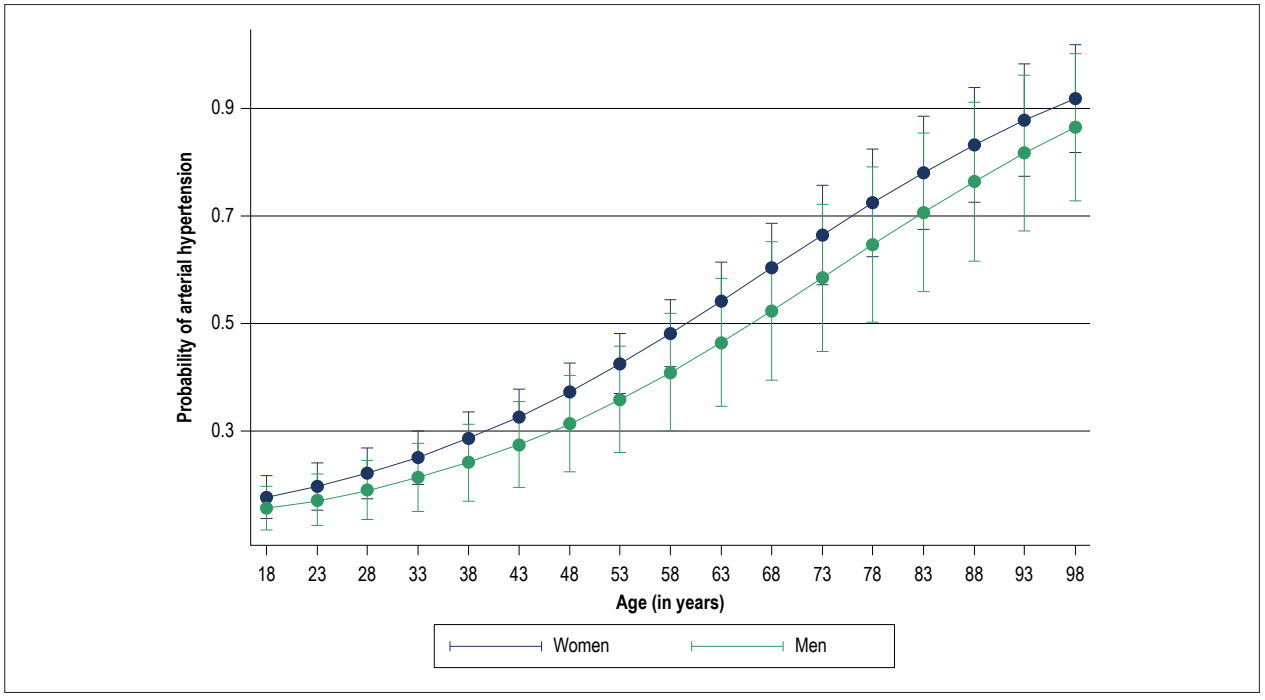

Figure 1 – *Probability of arterial hypertension in Quilombola communities according to age and sex.*

Discussion

The prevalence of SAH in the quilombola communities in the State of Sergipe (26%) was high, when compared with the estimates of the population in general (20.4%) in the same State,[20] in similar age ranges.

In accordance with other studies in the general population developed in Brazil[21] and in other multiracial countries,[22,23] the prevalence of SAH was associated with increased age. The black ethnicity showed a higher predisposition to arterial stiffness than the other ethnicities.[24,25]

aAlthough the prevalence of arterial hypertension was higher when compared to the general population, our results found a lower prevalence than other studies.[6,7] This difference may be due to methodological issues (such as the number of measurements and the conditions under which they were performed), regional variations (for example, alcohol consumption and sodium ingestion) or even ethnic issues which remain unclear, beyond the scope of this study.

In this study, no significant sex-related differences were observed in the occurrence of SAH or its subclassifications (systolic and diastolic) among the quilombolas. This data stands in contrast to what is found in the literature in the context of the general population[26] and the quilombola population.[27]

Concerning the modifiable variables, increased BMI was one of the major predictors associated with arterial hypertension. Cross sectional studies have shown such association and the damage to the health of the quilombola population,[3] whose inadequate lifestyle choices may be a result of low income and education.[28]

The prevalence of physical inactivity is this study was high. Probably, the idleness in rural areas promotes physical inactivity for most part of the months, when it is not harvest or planting time. This data corroborates with researches developed in rural[29] and quilombola[30] populations. This fact may have contributed for obesity and physical inactivity to foster the onset of arterial hypertension in the quilombola communities studied here.

It should be stressed that, when salt consumption was measured, low salt intake in this population may not have been accurately asessed, since sodium intake through processed or ultra-processed foods consumed everyday was not taken into consideration.[31]

The observed association between smoking and hypertension was significant in this study, which corroborates the results of other population-based studies.[27,32] Another important data was alcohol consumption, which showed a high prevalence. However, this factor was not associated with arterial hypertension, corroborating the results of other studies developed in the quilombola communities.[21,30]

Among the limitations of this research, we can mention the fact that the participants were volunteers, that is, the communities were randomly selected and the sample size was determined in advance, but the the enrolment was voluntary. In addition, part of the male population was not accessible, because they were working in the fields or fishing when the visits took place. The presence of diabetes and dyslipidemia has not been investigated, since glucose and lipid measurements, respectively, were not performed and the mere response of the individuals enrolled was avoided, because it could lead to biased information.

Future research should adequately assess these risk factors among the quilombolas to obtain better comprehension, since, as far as we know, this is the first study to approach this issue in the quilombola communities of the State of Sergipe.

Conclusion

The prevalence of arterial hypertension among the quilombolas was higher than in the general population. Age and increased BMI were the major predictors. This finding sugests the need for greater health care for the quilombolas, and serves as a baseline for the Brazilian government's development of health strategies in line with the the needs of ethnoracial communities.

Author contributions

Conception and design of the research: Santos DMS, Almeida-Santos MA; Acquisition of data: Santos DMS, Prado BS, Oliveira CCC; Analysis and interpretation of the data and Statistical analysis: Almeida-Santos MA; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Santos DMS, Prado BS, Oliveira CCC, Almeida-Santos MA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Tiradentes under the protocol number 1.685.357. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Short Editorial: Hypertension in Special Populations: An Epidemiological Challenge

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Short Editorial related to the article: Prevalence of Systemic Arterial Hypertension in Quilombola Communities, State of Sergipe, Brazil

Arterial hypertension (AH) is the most prevalent chronic disease worldwide and the main risk factor for most cardio-cerebrovascular diseases.[1] The true prevalence in Brazil is still unknown, and the available data are from the Vigitel Study, where the information is obtained by telephone contact. The prevalence of hypertension in Brazil is estimated at around 31% in adult individuals.[2] In recent data from the Vigitel Study, the prevalence was 25.7% of the adult Brazilian population.[3] Knowledge of the real prevalence and geographic distribution is not only important for prevention and treatment measures, but also contribute to the knowledge of the genesis of the disease.

In some populations, particularly individuals of African descent, AH has its own characteristics, including prevalence, therapeutic response and severity.[4,5] The multifactorial aspect of AH is only understood when assessing special populations considering their own habitats and habits, as in the case of *quilombolas*, where individuals with African ancestry still retain some genetic and cultural characteristics of the African origin.[6] The analysis in this context is important, since we can detect aspects inherent to factors related to AH development.

In this study,[6] the prevalence of hypertension in the *quilombola* communities of Sergipe was 26%, with the authors reporting that the mean value in the state is much lower (20.4%).[7] However, the values are very similar to those found in the Vigitel Study, which attempts to represent the Brazilian population. Regarding the risk factors for AH, in this population with a certain degree of vulnerability, the study disclosed inadequate lifestyle habits, especially physical inactivity, smoking and alcohol consumption. The quantification of salt in the diet was not accurate, as more complex tests are needed to determine the values, and the authors justify the fact by the study's own limitation.[8]

Knowledge of these risk factors for both hypertension and cardiovascular events is important for the planning of health actions in these at-risk populations. This study[6] has a very significant epidemiological value, as it allows social considerations and extrapolation to other *quilombola* communities, so that health team interventions can achieve a better cardiovascular prevention.

Keywords

Hypertension/epidemiology; Hypertension/prevention & control; African Continental Ancestry Group/genetics; Risk Factors; Tobacco Use Disorder; Alcoholism.

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Salt Preference is Linked to Hypertension and not to Aging

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Abstract

Background: Seasoning is one of the recommended strategies to reduce salt in foods. However, only a few studies have studied salt preference changes using seasoning.

Objectives: The aim of this study was to compare preference for salty bread, and if seasoning can change preference in hypertensive and normotensive, young and older outpatients.

Methods: Outpatients (n = 118) were classified in four groups: older hypertensive subjects (OH) (n = 32), young hypertensive (YH) (n = 25); older normotensive individuals (ON) (n = 28), and young normotensive (YN) (n = 33). First, volunteers random tasted bread samples with three different salt concentrations. After two weeks, they tasted the same types of breads, with seasoning added in all. Blood pressure (BP), 24-hour urinary sodium and potassium excretion (UNaV, UKV) were measured twice. Analysis: Fisher exact test, McNamer's test and ANCOVA. Statistical significance: $p < 0.05$.

Results: Systolic BP, UNaV, and UKV were greater in HO and HY and they had a higher preference for saltier samples than normotensive groups (HO: 71.9%, HY: 56% vs. NO: 25%, NY; 6%, $p<0.01$). With oregano, hypertensive individuals preferred smaller concentrations of salt, with reduced choice for saltier samples (HO: 71.9% to 21.9%, and HY: 56% to 16%, $p = 0.02$), NO preferred the lowest salt concentration sample (53.6% vs. 14.3%, $p < 0.01$), and NY further increased the preference for the lowest one (63.6% vs. 39.4%, $p = 0.03$).

Conclusions: Older and younger hypertensive individuals prefer and consume more salt than normotensive ones, and the seasoned bread induced all groups to choose food with less salt. Salt preference is linked to hypertension and not to aging in outpatients. (Arq Bras Cardiol. 2019; 113(3):392-399)

Keywords: Aged; Aging; Salt Tolerance; Food Preferences; Sodium Chloride,Dietary/adverse effects; Flavoring Agents.

Introduction

Although the relationship between high salt intake and hypertension is well established[1-4] and salt consumption by the world population is known to be higher than recommended,[4-7] only a few studies have assessed the preference for salty foods and studied the preference changes using seasoning among hypertensive and normotensive individuals.[8,9] Many countries are adopting different strategies to reduce salt intake by the population worldwide. The current public health recommendations in most countries are to reduce salt intake from about 9-12 g/day to 5-6 g/day.[10-12]

The 2010 World Health Organizations (WHO)[3] global status report on non- communicable diseases urged member states to take immediate actions to reduce salt intake. To this end, the WHO recommended a 30% reduction in salt intake by 2025, with an eventual target of 5 g per day for adults and lower levels for children based on calorie intake.[13]

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Sodium chloride is added to processed foods for palatability, preservation and processing reasons.[14,15]

One of the recommended steps to lower salt intake by the Food and Drugs Administration[16] is to flavor food with pepper and other herbs and spices instead of salt.

Villela et al.[9] compared the preference for salty foods between elderly hypertensive and normotensive subjects and showed that hypertensive individuals prefer and consume more salty foods than normotensive individuals. Some studies have shown that older people prefer more pronounced flavors than young people since the number of papillae and taste buds decreases with age.[17,18]

The INTERSALT study[19] suggested a strong relation between salt intake and a progressive increase in blood pressure (BP) with age up to 4 mm Hg per year for a 6 g/day salt intake. A reduction in salt intake is therefore likely to attenuate the rise of BP with aging, in addition to having an immediate BP lowering effect.[20]

Since raised BP throughout its range is a major cause of cardiovascular disease, a reduction in salt intake, if it lowered BP, would reduce cardiovascular risk.[1] Scientific research on this topic is scarce and only a limited number of studies have been performed in an experimental real-life setting.[14]

The aim of the present study was to compare the preference for salty foods among elderly and young individuals and hypertensive and normotensive ones and to determine if

seasoning food can change the preference for salt. Another aim was to assess the habitual consumption of sodium and potassium, as well as BP and body mass index (BMI) in the different groups.

Methods

This was a double-blind experimental investigation in which the sensory parameters were assessed by a convenience sample of 118 untrained tasters from a public healthy center who gave written informed consent to participate. This healthy center is responsible for the secondary care of an area with about 180,000 inhabitants, descendants of diverse ethnicities and coming from many regions of the country.The study was approved by the Ethics Committee of the Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo (Protocol no. 464/CEPCSE- FMRP-USP; 09/11/2011) and met the guidelines of the responsible governmental agency.

Exclusion criteria were: (1) food intolerance, (2) urinary incontinence (3), renal insufficiency, (4) presence of flu, colds, or any oral disease that would affect taste on the day of the experiment, (5) alcohol abuse (intake of more than 14 alcoholic drinks per week), (6) cognitive deficit (7), taking medications that might alter gustatory sensitivity such as chemotherapeutic drugs, penicillin, metronidazole, hydrochloride, amphotericin, nortriptyline, hydrochloride, carbamazepine, biguanide, etambutol, phenylbutazone, fluorouracil, allopurinol, penicillamine, or levodopa; (8) pregnancy (9), and having been submitted to radiotherapy of the head and/or cervical region.

After the exclusions, and factoring individuals who refused to participate, four groups of both genders were studied: 32 older hypertensive individuals aged 60 to 80 who were under treatment (OH), 28 older normotensive volunteers aged 60 to 80 years (ON), 25 young hypertensive subjects aged 30 to 50 years (YH), and 33 young normotensive subjects aged 30 to 50 years (YN). The experiments was conducted over 10 consectives months.

Procedures

The general data of each volunteer were obtained using a semistructured questionnaire, including previous diagnoses, use of medications, smoking status, and alcohol consumption. Weight and height were measured and BMI was calculated for all participants.

As a reference of daily sodium and potassium intake, 24-hour urinary sodium and potassium excretion was determined on each of the 2 days preceding the experiment.[21] Urine collection started with voiding and discarding the first urine in the morning after waking up. Subsequently, the urine excreted during the next 24 hours, up to and including the first voiding of the following day, was collected. A second 24-hour urine collection was performed 2 weeks later before the second experiment, for futher determination of sodium and potassium excretion.

Blood pressure was measured with a semiautomatic instrument (Omron HEM-431 CINT), with 3 measurements on the upper right limb and 3 measurements on the upper left limb after the patients rested in the sitting position for 5 minutes. The measurements were repeated after 2 weeks.

On the first day of the experiment, 3 samples of french bread rolls of the same composition except for different amounts of salt were prepared. Salt (1.4%, 2.0%, and 2.7%) was added to each kg. French bread habitually sold in this community contains, on average, 2% salt in its composition. Therefore, we provided a sample of bread with less salt (1.5% salt; 30% less salt than ordinary bread), a sample with the usual percentage of salt (2.0%), and a sample of bread with higher salt content (2.7% salt; 30% more salt than usual bread).

The three bread samples were prepared on the day of the test and offered to the volunteers in a random manner in disposable paper bags coded with random 3-digit numbers so that the investigator involved in the test would be unaware of the salt content of each sample. For the tasting, the samples were tested from left to right with a standard size of 10 to 15 g each in order to provide uniformity. The patients drank mineral water at room temperature between samples in order to help remove the taste. At the end of the test, the volunteers, who did not know that the bread samples contained different amounts of salt, were asked to state which sample they preferred. The participants were asked to avoid eating and drinking 2 h before the experiment.

In the second experiment, two weeks later, the participants were asked to again taste the 3 samples of french bread containing the same different amounts of salt as in the first experiment (1.5%, 2.0% and 2.7%), but now also containing oregano as an added spice (0.23 g/100 g of bread) and to state their preference. There were no changes in medication between the first and the second tests.

Data analysis

Firstly, an exploratory analysis of the data was performed. Continuous variables with normal distribution are reported as mean + standard deviation and categorical variables are presented as absolute numbers and percentages. The Fisher exact test was used to compare categorical variables, the McNamer's test was used to evaluate the effect of the intervention and ANCOVA was proposed to compare the groups and to verify the effect of the covariates.[22] This analysis assumes that its residues have a normal distribution with mean 0 and variance σ^2 constant. Transforms were used in response variables that did not reach the assumption. Differences were considered to be statistically significant when $p < 0.05$. The SAS system (version 9; SAS Institute, Cary, NC) was used for all statistical calculations.

Results

Gender and alcohol consumption distribution was similar in all groups ($p = 0.63$; $p = 0.26$). There was a higher percentage of smokers among young patients than elderly ones ($p < 0.001$) (Table 1).

Urinary sodium excretion was higher in the hypertensive groups (young and older subjects) than in the normotensive groups (young and older volunteers) ($p < 0.05$) (Table 1), and was higher in men than in women (men: 170.9 ± 73.6 mEq/24 h

Table 1 – Characteristics and Distribution of clinical data of the volunteers included in the study

	Young Hypertensive Subjects (YH); n = 25	Young Normotensive (Y) Subjects; n = 33	Older Hypertensive Subjects (OH); n = 32	Older Normotensive Subjects (ON); n = 28	P Value
Sex					**p = 0.63**
Male	11(44.0%)	13 (30.3%)	9 (28.1%)	10 (35.7%)	
Female	14(56.0%)	20 (60.7%)	23 (71.9%)	18 (64.3%)	
Use of Alcohol					**p = 0.26**
Yes	9 (36.0%)	15 (45.5%)	8 (25.0%)	7 (25.0%)	
No	26 (64.0%)	18 (54.5%)	24 (75.0%)	21 (75.0%)	
Smoking Habit					**p < 0.001**
Yes	6 (24.0%)	4 (12.2%)	0(0%)	1(3.5%)	
No	19 (76.0%)	29 (87.8%)	32 (100%)	27 (96.5%)	
Age, years	40.8 ± 6.2	35.6 ± 4.4	73.6 ± 6.3	71.4 ± 7.8	
SBP, mmHg	137 ± 15	116 ± 11	134 ± 16	125 ± 12	**p < 0.05***
DBP, mmHg	86 ± 9	75 ± 9	79 ± 9	75 ± 7	**p < 0.05****
UNaV, mEq/L	181.0 ± 74.2	127.6 ± 36	177.3 ± 62.3	129.6 ± 3 6.6	**p < 0.05***
UKV, mEq/L	46.2 ± 13.4	40.3 ± 12.8	45.2 ± 14.5	35.2 ± 10.1	**p < 0.05*****
BMI, kg/m^2	29.1 ± 5.0	25.9 ± 4.0	29.1 ± 5.1	27.0 ± 4.0	**p = 0.02***

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; UNaV: 24-hour urinary sodium excretion; UKV: 24-hour urinary sodium excretion; p: hypertensive groups vs. normotensive groups; p**: young hypertensive group vs. other groups.*

vs. women: 142.6 ± 46.0 mEq/24 h, p = 0.01). Volunteers who consumed alcohol had higher sodium excretion than those who did not (p = 0.02). Mean urinary potassium excretion was lower in normotensive elderly subjects than in the other groups (p < 0.05) (Table 1). Systolic BP was higher in the hypertensive groups (young and older subjects) compared to the non-hypertensive groups (young and older subjects), with p < 0.05. Mean diastolic BP was significantly higher in the group of YH subjects compared to all other groups of volunteers (p < 0.05) (Table 1).

BMI was higher in the hypertensive groups than in the normotensive ones (p = 0.02) (Table 1).

On both days of the experiment, men preferred the saltier samples compared to women (p < 0.01 in the first experiment and p = 0.01 in the second one).

Alcohol consuming volunteers preferred more often the saltier samples in the first experiment than the other volunteers (p = 0.04) but this difference no longer existed when oregano was added to the samples (second experiment) (p = 0.10). No difference was observed between smokers and nonsmokers.

On the two days of the experiment, gender, alcohol consumption and smoking did not show any differences in the elderly groups (hypertensive and normotensive), whereas differences were observed between the younger groups. In the first experiment, women in the YN group preferred more often samples with less salt, while men preferred more often saltier samples (p < 0.01). In the second experiment (oregano addition), the distribution was similar between genders, with a nonsignificant trend to a change in preference for less salty samples among men (p = 0.06). In the YH group, those who consumed alcohol in the first experiment more often preferred the saltier samples, and in second experiment (oregano addition), they began to prefer less salty bread samples (p = 0.04).

On the first day of the experiment, there was a different preference between the elderly hypertensive and normotensive groups (p < 0.01), with the elderly hypertensive group showing a greater preference for saltier samples which persisted in the second experiment (p = 0.02).

The YH group showed greater preference for samples with higher salt concentrations compared to YN subjects (p = 0.02), with this difference persisting in the second experiment (p < 0.01). The groups of elderly and YH had a similar distribution in the first and second experiment (p = 0.27 and p = 0.25), and the elderly and YN groups did not differ in preference (p = 0.11 and p = 0.34).

Comparing the first and second experiments, there were significant changes in all groups. In the hypertensive groups (young and older subjects), there was a predominance of preference for saltier samples in the first experiment (Figure 1), whereas a change in preference for standard bread samples and samples with a lower salt concentration (p < 0.01 for the hypertensive elderly group and 0.04 for the YH group) was observed in the second experiment (Figure 2). In the group of ON volunteers, in the first experiment the preference was more common for standard bread samples (Figure 3), whereas a greater preference for the sample with a lower salt concentration as observed in the second experiment (with the addition of oregano) (p < 0.01) (Figure 4). In the first experiment, YN subjects showed a higher preference for the samples with lower salt concentrations (Figure 3), with an increase in this preference in the second experiment (p = 0.03) (Figure 4).

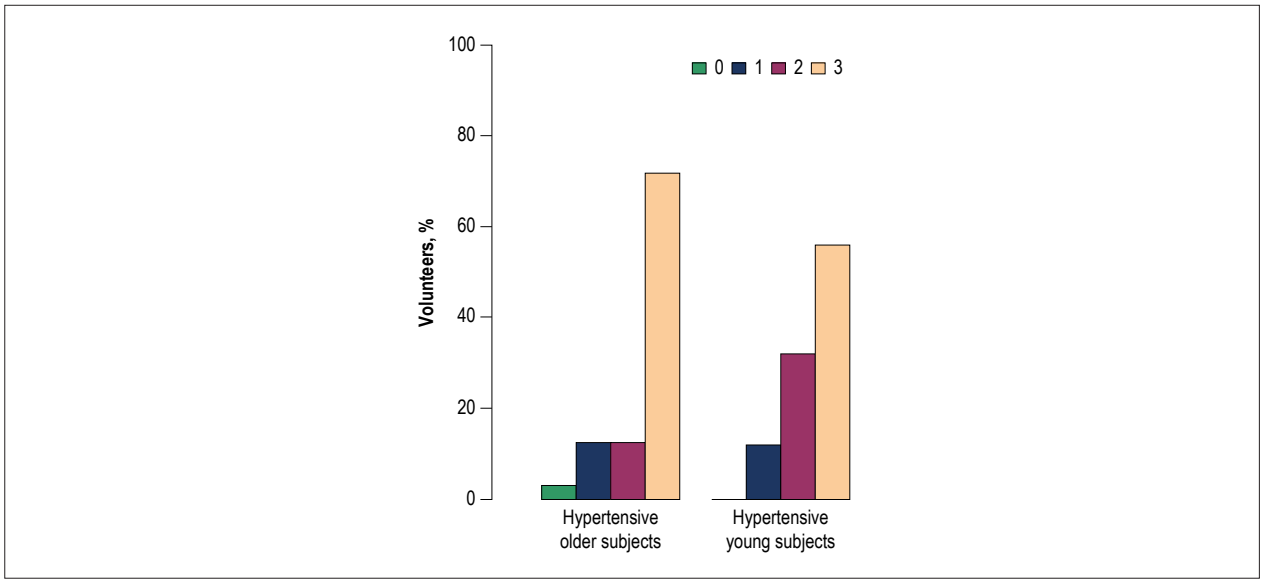

Figure 1 – *Distribution of the preference for bread samples among hypertensive volunteers in the first experiment, without the addition of oregano. 0: did not perceive a difference; 1: preferred the sample with 1.5% salt; 2: preferred the sample with 2.0% salt; 3: preferred the sample with 2.7% salt.*

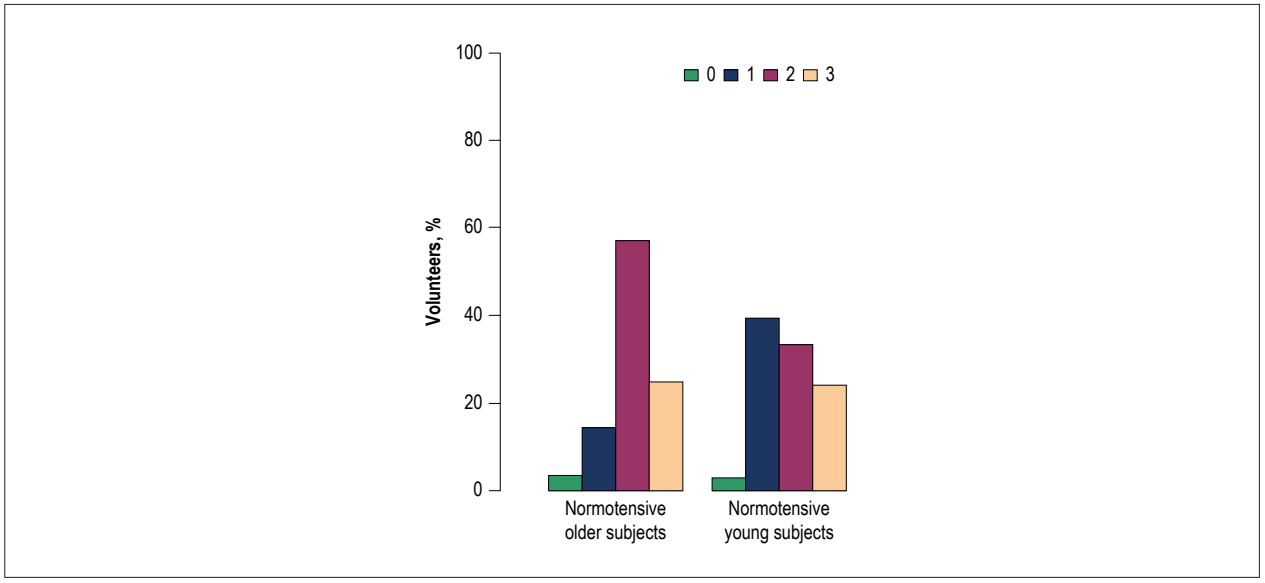

Figure 2 – *Distribution of the preference for bread samples among normotensive volunteers in the first experiment, without the addition of oregano. 0: did not perceive a difference; 1: preferred the sample with 1.5% salt; 2: preferred the sample with 2.0% salt; 3: preferred the sample with 2.7% salt.*

Oregano seems to contribute to the failure to differentiate flavors, with the total number of volunteers who did not notice a difference between samples increasing from 3 (3.13%) to 18 (15.25%), with $p < 0.001$.

Discussion

We found a clear predominance of salt preference in hypertensive participants compared to the non-hypertensive groups. In this study, we used a sensory analysis to investigate salt preference using a method similar to that employed by Shepherd et al.,[23] who compared the preference of hypertensive individuals for soup samples with three different salt concentrations. In the cited study, there was a greater preference for the sample with lower salt concentration, in contrast to what was observed in the present study. However, all of the participants in the Shepherd study were hypertensive, with no comparison with normotensive subjects.

The preference for high salt intake can be caused by physiological, genetic and psychological factors and by changes occurring during human development.[24] Evidence indicates that the taste of salt is inherently attractive to humans by making the flavor of the foods more palatable compared to the same foods without salt.[24,25]

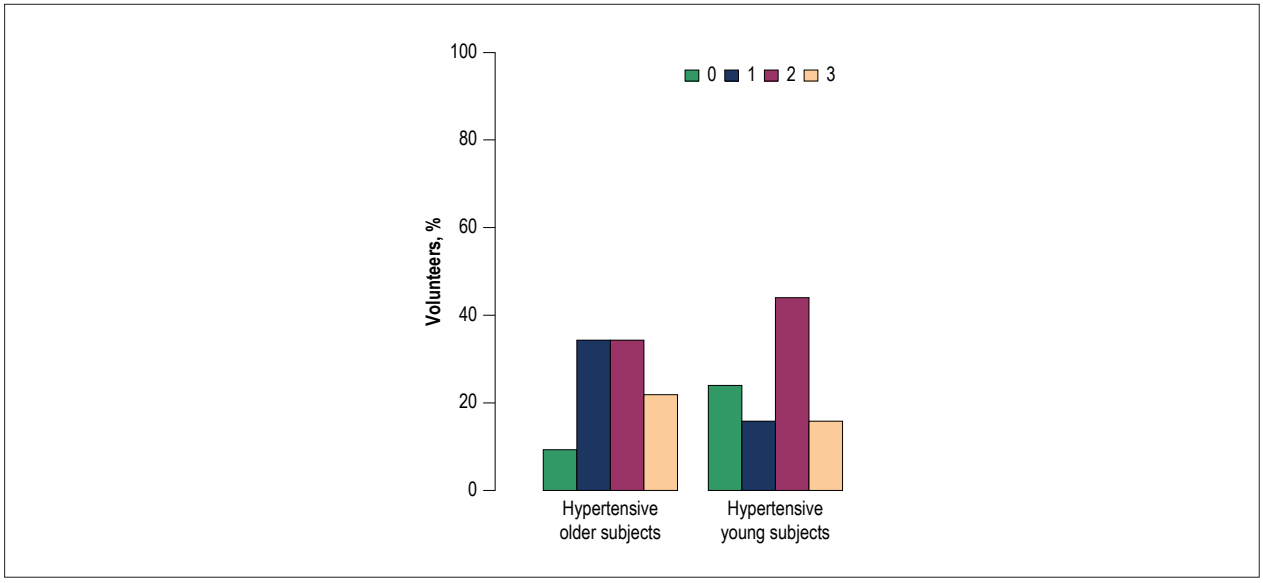

Figure 3 – *Distribution of the preference for bread samples among hypertensive volunteers in the second experiment, with the addition of oregano. 0: did not perceive a difference; 1: preferred the sample with 1.5% salt; 2: preferred the sample with 2.0% salt; 3: preferred the sample with 2.7% salt.*

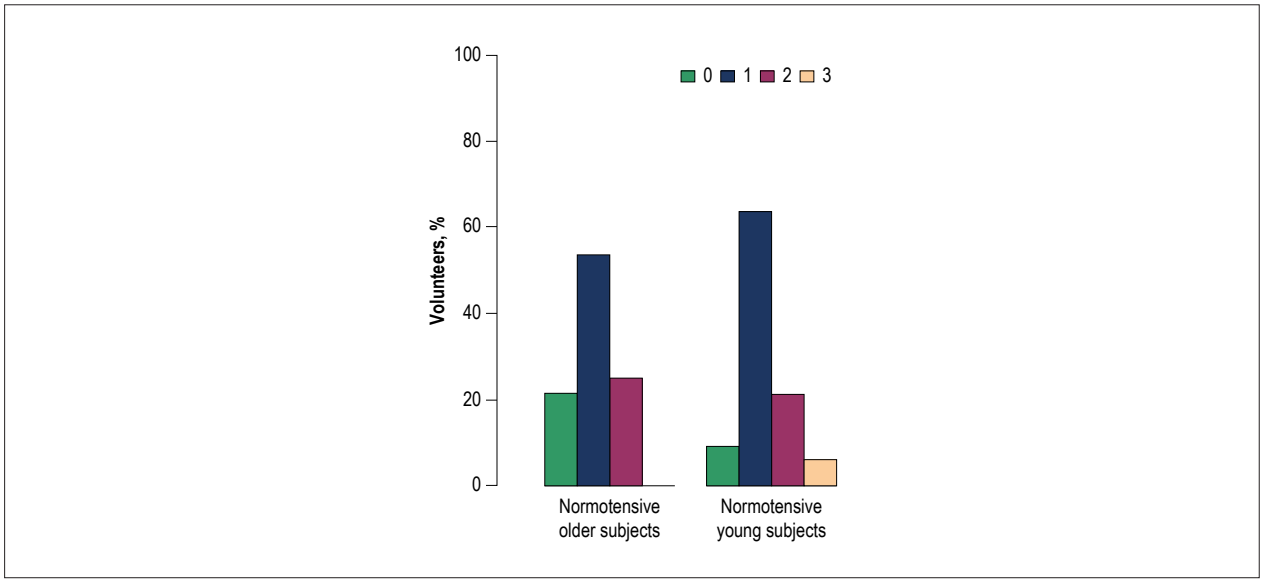

Figure 4 – *Distribution of the preference for bread samples among normotensive volunteers in the second experiment, with the addition of oregano.0: did not perceive a difference; 1: preferred the sample with 1.5% salt; 2: preferred the sample with 2.0% salt; 3: preferred the sample with 2.7% salt.*

Regarding age, there were no differences in preference for salt samples and salt intake. The same result was reported by Khadeja & Leshen,[26] who compared salt appetite in the elderly (65-85) and in middle-aged (45-58) people to determine possible age-related changes. To estimate salt appetite, the participants were tested for preferred amounts of salt in the soup, followed by a test with oral sprays of NaCl. Between the taste tests, the participants were interviewed to complete a dietary, seasoning and preference questionnaire. The authors found no clear difference in salt preference in elderly participants compared to middle-aged participants.

Regarding gender, men usually prefer more salt than women.[27] It is well established that salt intake is lower in women as a function of their lower absolute caloric intake and that women add less salt to soups than men.[27] The present study also showed a higher salt consumption among men.

The variables that significantly influenced the preference for samples of saltier breads were the presence of hypertension, male gender and alcohol consumption. These were maintained even in the presence of oregano, except for subjects with higher alcohol consumption, for which the preference for saltier samples ceased to exist when oregano was added to bread.

Contrary to our hypothesis, we found no relationship between sodium intake and age, BMI or tobacco use, but sodium intake was significantly higher among volunteers who consumed alcohol. These volunteers preferred saltier samples and showed an average larger amount of sodium excretion in 24hour urine, in agreement with data reported by Gibson & Margaret[28] who showed that high alcohol intake is one of the major features among high salt consumers. It is important to note that one of the exclusion criteria for the present study was alcohol abuse so that the effect of alcohol on salt preference could have been underestimated if individuals with greater consumption had been included. Alcohol consumption has been associated with increased BP and an increased risk of hypertension in many observational studies and clinical trials, demonstrating that these associations are causal.[29] Hypertensive volunteers had higher mean BP and higher average urinary sodium excretion compared to normotensive volunteers, in agreement with the association between increased sodium excretion and increased arterial BP reported in several studies.[19,20,30,31] Thus, it was observed that hypertensive patients had higher mean BP even when treated, with a greater preference for salt intake and with higher urinary sodium excretion compared to normotensive subjects.

These results support recommendations for the reduction of high salt intake in the population for prevention and control of adverse BP levels.[20]

Despite the small percentage of smokers included in this study (9.3%), no significant differences were identified as to their preferences. Recent research in Germany has shown that smoking did not present a risk to gustatory commitment, although food preferences were not compared and the average age of individuals who participated in the study was 56 years.[32]

For potassium intake, the present study found increased urinary potassium excretion in the hypertensive groups, in contrast to the study of Galletti et al.,[33] which showed low potassium excretion in 24hour urine in 1232 hypertensive Italians from 47 volunteer centers of the Italian Society of Hypertension. Observational studies have shown an inverse relationship between potassium intake and BP.[19] The electrolyte excretion in 24-hour urine analysis and BP in the INTERSALT study[19] showed that potassium excretion was negatively correlated with BP. Cappuccio et al.[34] performed a meta-analysis of 19 studies with oral potassium supplementation involving 586 participants. The results showed that oral potassium supplementation significantly reduced both systolic and diastolic BP and that reductions in BP were higher in hypertensive patients than in normotensive individuals. Perhaps the finding in the present investigation differing from other studies could be explained by the fact that the volunteers had been regularly monitored at a secondary level health center for many years, having received nutritional guidance regarding a balanced diet rich in fruits and vegetables, and greater potassium intake.

It is important to emphasize that this study did not evaluate long-term adherence to bread with oregano, only preference in a tasting test in a small sample. A larger, longer, and randomized clinical trial is needed to confirm the benefits of an intervention contributing to the reduction of daily sodium intake, by adding spice to food.

The volunteers were followed up at a public health center, not being able to extrapolate the results to different populations.

Conclusions

The present study demonstrated a greater preference for salt and more salt consumption in hypertensive than normotensive individuals regardless of age. The intervention of adding oregano to food led to a preference for samples with lower salt content in all groups, i.e., hypertensive, normotensive, young or old subjects. A higher preference for salt was found to be associated with male gender and alcohol consumption.

Author contributions

Conception and design of the research and Writing of the manuscript: Villela PTM, Moriguti JC, Lima NKC; Acquisition of data: Villela PTM, de-Oliveira EB, Villela PTM, Bonardi JMT, Bertani RF; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Villela PTM, de-Oliveira EB, Villela PTM, Bonardi JMT, Bertani RF, Moriguti JC, Ferriolli E, Lima NKC; Statistical analysis and Obtaining financing: Ferriolli E, Lima NKC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This article is part of the thesis of Doctoral submitted by Patrícia Teixeira Meirelles Villela, from Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo under the protocol number 464. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Original Article

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Salt Appetite and Aging

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Short Editorial related to the article: Salt Preference is Linked to Hypertension and not to Aging

The Villela et al.[1] study showed greater preference and salt intake by hypertensive individuals over the normotensives one regardless of age.

A relationship between higher salt preference and male gender and alcohol consumption was observed. Most sensitivity to salt is the elderly and afro-descendant hypertensive people.

Salt sensitivity increase with advancing age.[2] One of the reason is that the kidney is less able to either conserve sodium in response to dietary restriction or remove sodium after excess intake.[3,4] Both aging rats and humans have a blunted ability to excrete an acutely administered sodium load.[3,5,6]

It has long been recognized that reducing dietary salt content has better blood pressure control. Also, it is now known that there are different degrees of salt sensitivity in the hypertensive and normotensive population. Therefore, in non-pharmacological treatment of hypertension, salt reduction is one of the most important interventions.[4] However, diets restricted in salt are not well tolerated by most patients. Many attempts to substitute salt for other substances have been employed. The addition of oregano to the foods in the Villella's study resulted in the preference for the lower salt samples in all groups studied.

Just as hypertension is a multifactorial disease, the phenomenon of salt sensitivity is also multifactorial involving genetic, environmental and aging-related aspects. Therefore, salt sensitivity also increases with age and is more marked in African Americans, obese, and patients with metabolic syndrome and/or chronic kidney disease.[6] Thus, excess salt intake over many years may probably play a greater role in the development of hypertension in these groups. Salt-sensitive normotensives may be more likely to develop hypertension.

The mechanisms of salt sensitivity are not yet fully understood. The lower activation of the renin-aldosterone mechanism may explain the greater fall in BP with reduced sodium intake among the elderly, African Americans, and patients with CKD. Impairment of renal sodium excretion may initially lead to volume expansion and then hypertension.

Multiple genes have been implicated in the pathogenesis of hypertension, including those that regulate sodium absorption, which should undoubtedly participate in the phenomenon of salt sensitivity.

Therefore, the conclusions of the study by Villela et al.[1] bring new information about the salt preferences of different extracts of our population as well as the possibility of decreasing the salt content in foods with substitution by other spices such as oregano.

Keywords

Hypertension; Salt Tolerance; Food Preferences; Sodium Chloride, Dietary/adverse effects; Aged; Aging.

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Acute Physical Stress Preconditions the Heart Against Ischemia/Reperfusion Injury Through Activation of Sympathetic Nervous System

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Abstract

Background: Stress is defined as a complicated state that related to homeostasis disturbances, over-activity of the sympathetic nervous system and hypothalamus-pituitary-adrenal axis responses. Cardiac preconditioning reduces myocardial damages.

Objective: This study was designed to assess the cardioprotective effects of acute physical stress against ischemia/reperfusion (I/R) injury through the activation of the sympathetic nervous system.

Methods: Thirty-two male Wistar rats were divided into four groups; (1) IR (n = 8): rats underwent I/R, (2) Acute stress (St+IR) (n = 8): physical stress induced 1-hour before I/R, (3) Sympathectomy (Symp+IR) (n = 8): chemical sympathectomy was done 24-hours before I/R and (4) Sympathectomy- physical stress (Symp+St+IR) (n = 8): chemical sympathectomy induced before physical stress and I/R. Chemical sympathectomy was performed using 6-hydroxydopamine (100 mg/kg, sc). Then, the hearts isolated and located in the Langendorff apparatus to induce 30 minutes ischemia followed by 120 minutes reperfusion. The coronary flows, hemodynamic parameters, infarct size, corticosterone level in serum were investigated. $P < 0.05$ demonstrated significance.

Results: Physical stress prior to I/R could improve left ventricular developed pressure (LVDP) and rate product pressure (RPP) of the heart respectively, (63 ± 2 versus 42 ± 1.2, $p < 0.05$, 70 ± 2 versus 43 ± 2.6, $p < 0.05$) and reduces infarct size (22.16 ± 1.3 versus 32 ± 1.4, $p < 0.05$) when compared with the I/R alone. Chemical sympathectomy before physical stress eliminated the protective effect of physical stress on I/R-induced cardiac damages (RPP: 21 ± 6.6 versus 63 ± 2, $p < 0.01$) (LVDP: 38 ± 4.5 versus 43 ± 2.6, $p < 0.01$) (infarct size: 35 ± 3.1 versus 22.16 ± 1.3, $p < 0.01$).

Conclusion: Findings indicate that acute physical stress can act as a preconditional stimulator and probably, the presence of sympathetic nervous system is necessary. (Arq Bras Cardiol. 2019; 113(3):401-408)

Keywords: Stress, Mechanical; Sympathetic Nervous System; Hypothalamo-Hypophyseal System; Ischemia; Sympathectomy.

Introduction

Ischemic heart disease is the major health problem in the world.[1] Although reperfusion, which refers to the rapid reestablishment of blood flow, can be one of the most effective methods against lethal injuries,[2] it is associated with additional myocardial damage.[3] Many methods have been proposed to diminish the deleterious effect of ischemia/reperfusion (I/R) injuries and increase cardiac endurance. Based on these advances, induction the short-term episodes of I/R or using the pharmacological agents earlier than prolonged I/R period induces cardiac preconditioning which can successfully attenuate cellular necrosis and conserve high levels of energy.[4,5]

Sympathetic nervous system and hypothalamus-pituitary-adrenal (HPA) axis are two coordinated defence systems. They can mediate two-way brain-body communication during stressful situations.[6] Autonomic system activation contributes to behavioral responses in animals and enables them to regulate homeostasis and improve endurance.[7] Stress is characterized as a general HPA axis response against potential and deleterious stimuli.[8] In fact, stress through increasing the activity of HPA axis and corticosterone release plays a critical role in coordinating of neuroendocrine, autonomic and behavioral functions and leads to adaptive responses.[9,10] The activity of the sympathetic nervous system increases and neurotransmitter secretion alters during the occurrence of stress.[11] Several body systems such as nervous, cardiovascular and immune systems are influenced by stress. Moreover, significant changes in hemodynamic parameters such as; heart rate (HR) and blood pressure are observed during stress which ultimately may lead to heart diseases.[12] On the other hand, the release of norepinephrine from the sympathetic nervous system is increased during lethal ischemia and it has a role for inducing of I/R injuries through the generation of hydroxyl free radicals. This current study was designed to evaluate the role of the sympathetic nervous system in mediating acute stress-induced cardioprotection against I/R injury in isolated rat heart.

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Methods

A total of 32 male Wistar rats (200-250g) were kept in an air-conditioned room on a 12 hours light-dark cycle, at 22 ± 2°C, with free access to water and food. The experimental protocols followed in this study conformed to the Guidelines for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996) and were further approved by the institutional ethical committee of Tehran University of Medical Sciences (Tehran, Iran).

Stress box apparatus was used for physical stress exposure. It contained stainless bars at the bottom, connected to electroshock device using a connecting cable. Physical stress was induced using electrical foot shock (1mA) for 10 seconds with 50 seconds intervals for one hour. After that, animals were anaesthetized with sodium thiopental (60 mg/kg, i.p),[13] put on a surgical board. The chest was opened and the surgical silk suture (6-0) placed under the root of the left anterior descending coronary artery (LAD). Finally, the heart was removed from the chest and connected to Langendorff-perfusion apparatus. Heart was perfused in a retrograde manner using Krebs–Henseleit bicarbonate buffer (in mmol/l): sodium bicarbonate = 25, sodium chloride = 118.5, potassium chloride = 4.7, magnesium sulfate = 1.2, glucose = 11, gassed with 95% O_2 and 5% CO_2 (pH = 7.3-7.4 at 37°C). Thereafter, the ends of the suture were passed through a plastic tube to create a snare for ischemia induction. Reperfusion was performed by releasing the snare. Latex fluid- filled balloon was inserted inside the left ventricle and connected to a pressure transducer (Harvard, March-Hugsteten, Germany), the biolab apparatus was used for recording the ventricular pressures. During the surgical procedure, recording was done during three designated periods: 20-30 minutes of the baseline (a period without any manipulation), 30 minutes of the local ischemia and 120 minutes of the reperfusion. After reperfusion, LAD was occluded again; Evans Blue dye (3 mL of 1.5% solution) was administrated to discriminate ischemic zone (the area at risk; [AAR]) from non-ischemic zone.[14] After freezing (−20°C for 24 hours), heart tissue was sliced into 2mm transverse sections and kept in 1% 2, 3, 5 triphenyltetrazolium chloride (TTC in 0.1 M phosphate buffer, pH = 7.4 Sigma) solution for 15–20 min at 37°C to delineate ischemic from infarct zone.[15] At the end of the experiments, the ratio of AAR and infarcted size (IS) were calculated by the Photoshop program.

Animals were allotted in 4 groups:

1. IR group (n = 8): Rats were kept in stress box device (without stress exposure) for 1 hour and then, hearts were removed from the chest and subjected to ischemia and reperfusion.
2. Acute stress (St+IR) group (n=8): Rats were exposed electrical feet shock in the stress box for 1 hour and then, hearts were removed from the chest and subjected to ischemia and reperfusion.
3. Sympathectomy (Symp+IR) group (n = 8): chemical sympathectomy was done by injection of a 6-hydroxydopamine (6-OHDA, 100 mg/kg, sc) 24 hours prior to I/R induction.[16]
4. Sympathectomy- physical stress (Symp+St+IR) group (n = 8): chemical sympathectomy was done 24 hours prior to physical stress and I/R induction.

We measured serum corticoesterone levels by ELISA method. Moreover, systolic blood pressure was measured via non-invasive technique (Tail Cuff and power lab) to confirm chemical sympathectomy (n = 4).

Statistical analysis

The sample size and group divisions were defined based on our previous studies.[17] All data are reported as means ± S.E.M. Normality was checked using Kolmogorov-Smirnov test, SPSS software version 20. One way ANOVA and Tukey post hoc test was done for comparison of parameters between different groups. Analysis of changes in mean values over three times was done using repeated measurement ANOVA within each group. Sample t-test was used to compare systolic blood pressure before and after sympathectomy. Significant changes were considered as $p < 0.05$.

Results

Effect of acute physical stress on coronary flow and heart rate

Figure 1 shows coronary flow (CF) at the end of the baseline, ischemia and reperfusion periods. There are significant differences for CF at the end of ischemia and reperfusion when compared to the end of the baseline period within groups ($p < 0.01$). HR was significantly decreased at the end of both ischemia and reperfusion in comparison with the end of baseline period within groups ($p < 0.01$), but no significant change were observed between different groups (Figure 2).

Effect of acute physical stress on cardiac hemodynamic parameters

The left ventricular developed pressure (LVDP, the difference between intraventricular systolic and diastolic pressures), rate product pressure (RPP, LVDP multiplied by HR) and were diminished at the end of reperfusion in comparison to the end of baseline period among groups,

The amount of RPP and LVDP in acute stress group were extremely increased in comparison to IR group ($p < 0.05$ in induction of chemical sympathectomy before physical stress were considerably decreased RPP and LVDP in comparison to physical stress group $p < 0.05$, but there is no marked difference between sympathectomy group when compared to IR group (Figure 3).

Effect of acute physical stress on infarcts size (%IS/AAR)

Figures 4 shows the size of the infarct (%IS/AAR) in different groups.

Infarct size was greatly deacreased in acute stress group as compared to the IR group ($p < 0.05$), but there was no considerable change in chemical sympathectomy group as compared to the control group. Chemical sympathectomy prior to acute physical stress represented no extermly change

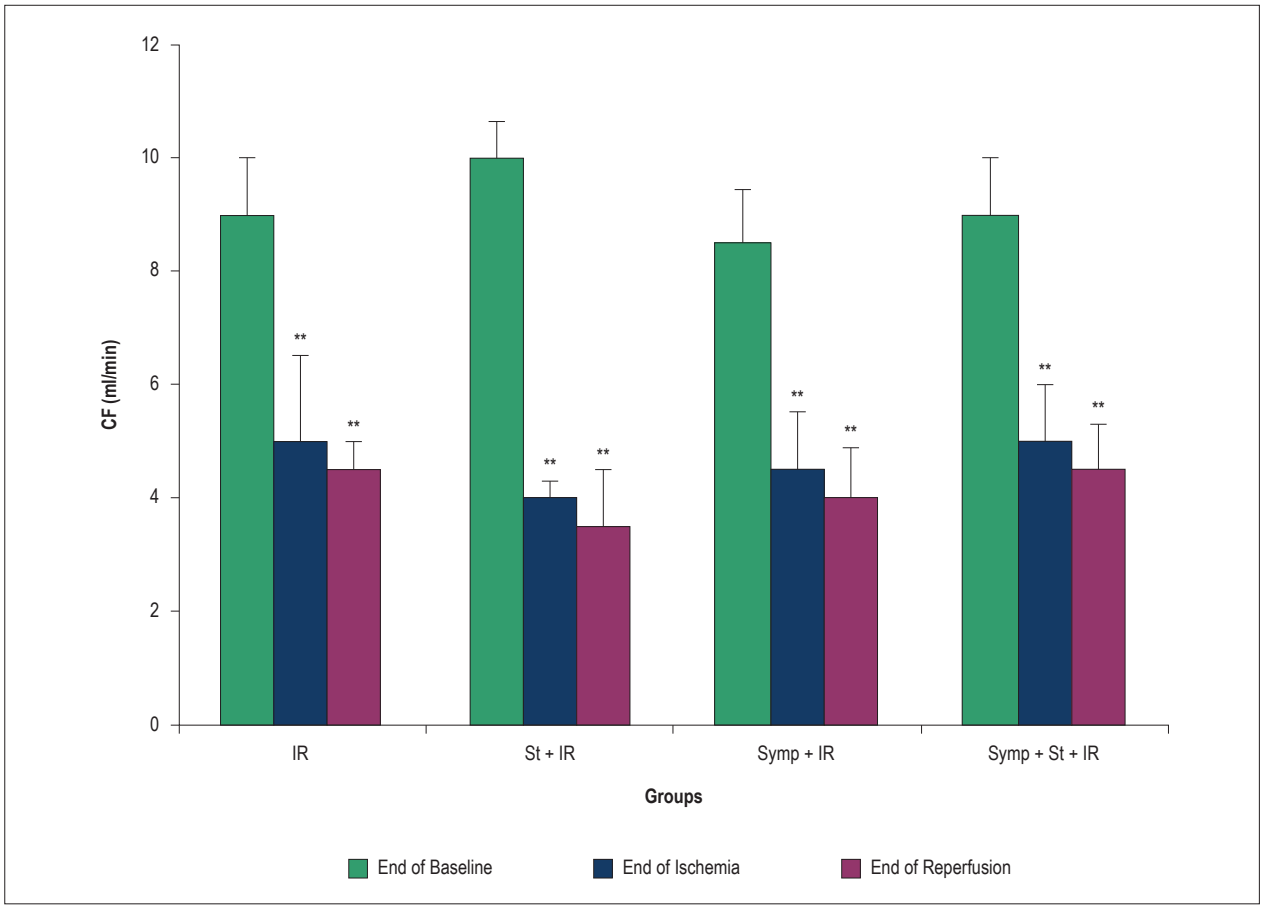

Figure 1 – *Coronary flow (CF) at the end of baseline, ischemia and reperfusion periods. IR: Ischemia/reperfusion; St: Physical stress; Symp: Symapathectomy. ** p < 0.01 vs baseline phase within the same group.*

as compared to IR group, while it has been shown significant reduced infarct size as compared with acute physical stress alone ($p < 0.01$).

Effect of acute physical stress on corticosterone level in serum

Figure 5 shows the serum level of corticosterone in different groups. Induction of acute physical stress without or with chemical sympathectomy in St and St+Symp+IR groups could increase the amount of serum corticosterone as compared to the IR group, ($p < 0.01$).

Effect of chemical sympathectomy on Systolic blood pressure

Figure 6 represents the significant reduction of systolic blood pressure after induction of chemical sympathectomy ($p < 0.05$).

Discussion

Nowadays daily life is associated with stress that is divided to acute stress and chronic stress, based on exposure duration.[18] Acute stress mediates several neurogenic pathways.[19] Electrophysiological recordings revealed that acute stress manifests good effects such as favour heightened arousal and increases cognitive flexibility in an attentional set-shifting task.[20] In the other view, stress is divided into physical and psychological. A physical stressor such as surgery, trauma and heavy physical activity can trigger many cardiac events.[21] Psychological stress can affect the cardiovascular system through metabolic, inflammatory and hormonal factors.[22,23] In this study, we evaluated the effects of acute physical stress prior to sympathectomy on ischemia-reperfusion injuries in isolated rat heart.

The effects of stress

Our results showed that induction of acute stress prior to ischemia-reperfusion period led to a decrease in the infarct size, improve hemodynamic parameter and increase in the plasma corticosterone level as compared to IR group and Symp+IR group. Two paradoxical theories have been proposed to explain both advantage and disadvantage effect of stress on the heart. Extremely elevated HR, cardiac contractility and peripheral resistant due to exposure to acute stress can increase the cardiac load and oxygen consumption. In contrast, emerging evidences indicate the opposite effect, for example; cold restraint stress induces cardiac cell protection[24] and it can diminish infarct size as a main parameter of cardiac damage.[25]

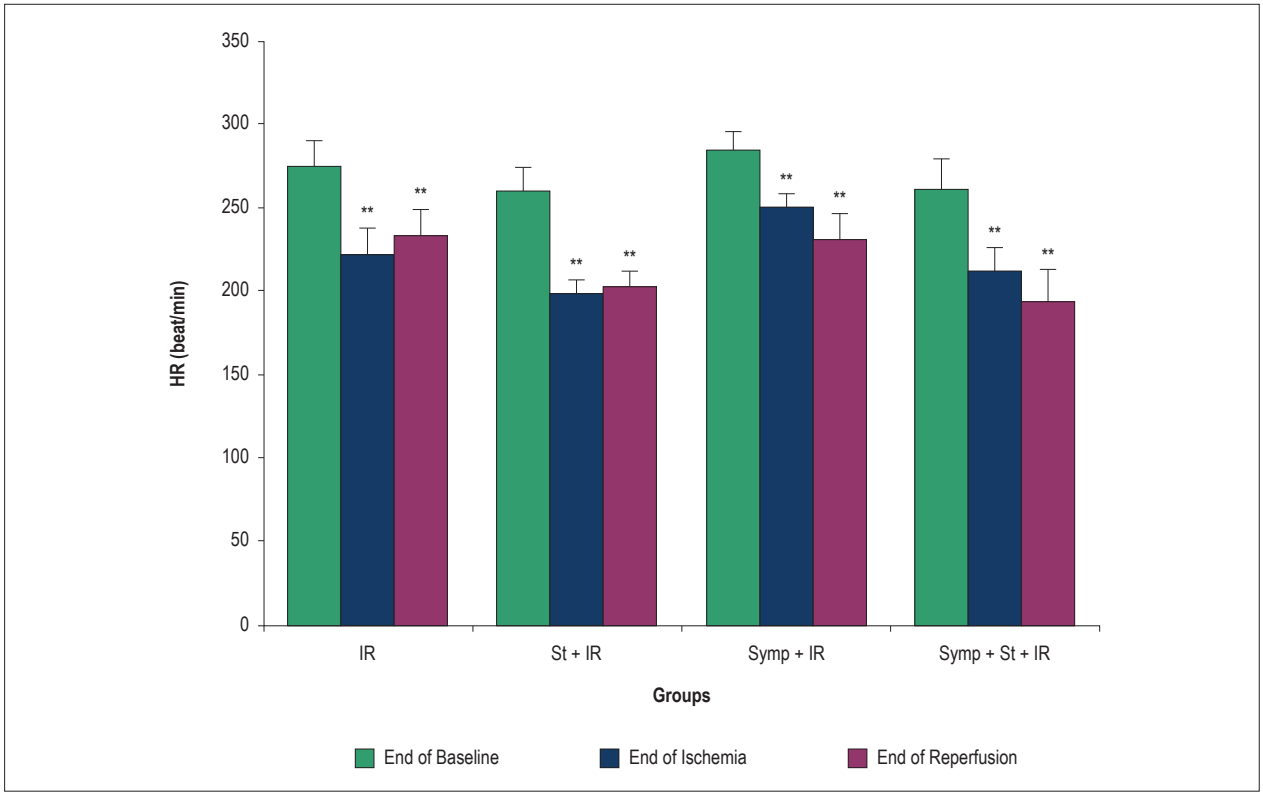

Figure 2 – *Heart rate (HR) at the end of baseline, ischemia and reperfusion periods. IR: Ischemia/reperfusion; St: Physical stress; Symp: Symapathectomy. ** p < 0.01 vs. baseline phase within the same group.*

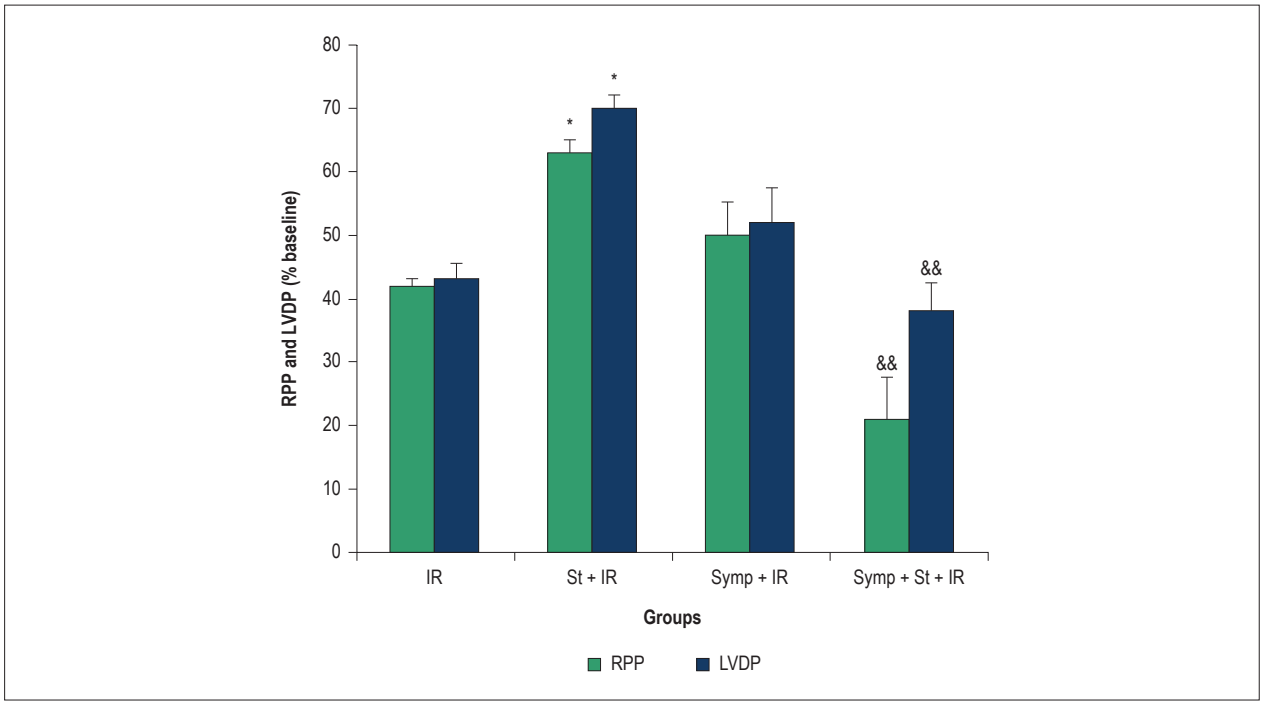

Figure 3 – *Left Ventricular Developed Pressure (LVDP) and rate product pressure (RPP) at the end of reperfusion period. IR: Ischemia/reperfusion; St: Physical stress; Symp: Symapathectomy. * p < 0.05 compared to IR, && p < 0.01 compared to St + IR.*

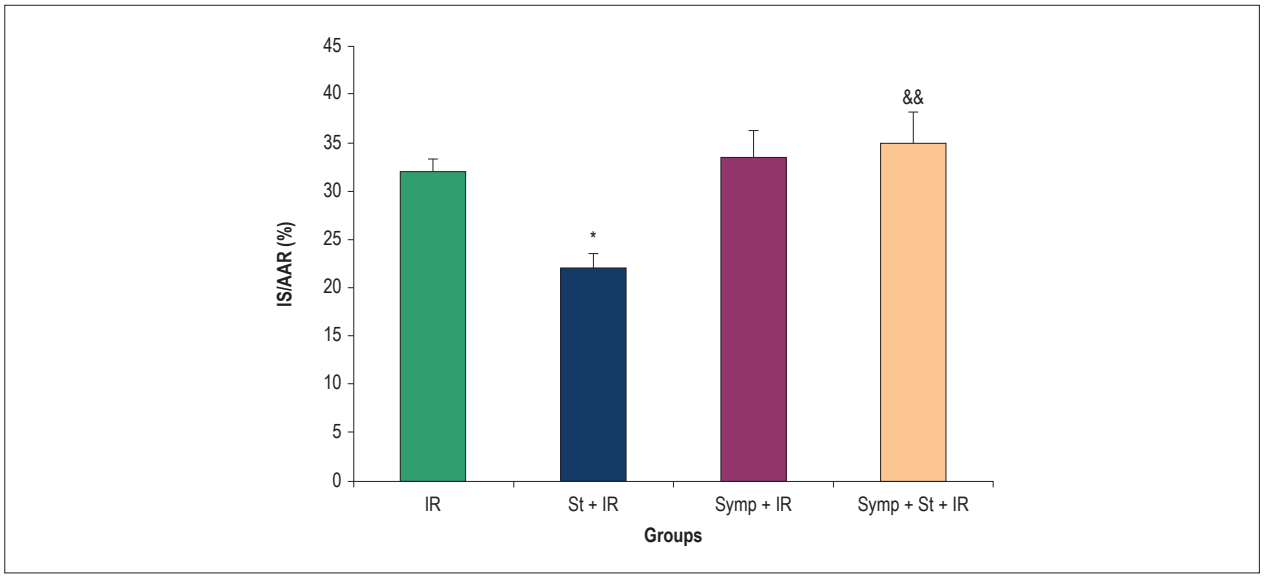

Figure 4 – *The percentage of infracts size (IS/AAR %). IR: Ischemia/reperfusion; St: Physical stress; Symp: Symapathectomy. * p < 0.05 compared to IR, && p < 0.01 compared to St+IR.*

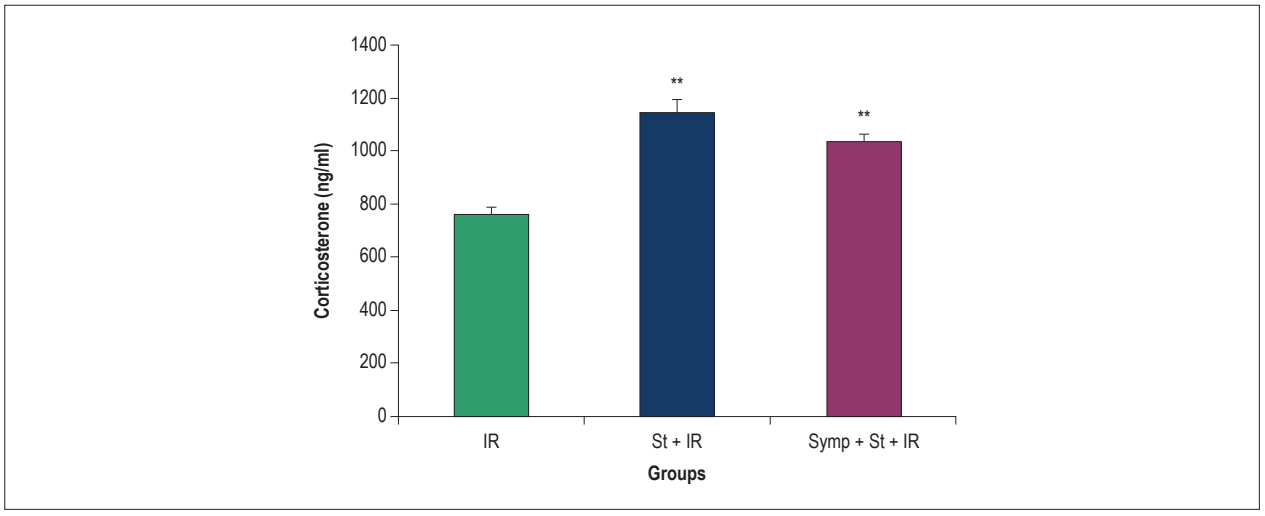

Figure 5 – *Corticosterone level in serum. IR: Ischemia/reperfusion; St: Physical stress; Symp: Symapathectomy. ** p<0.01 compared to IR.*

In this regard, Abe et al. demonstrated that acute stress attenuates ischemia-reperfusion injury in the kidney through the activation of sympathetic and anti-inflammatory pathway.[26]

Moreover, exposure to intermediate stress involves in cell protection against subsequent lethal ischemia, as a concept, preconditioning phenomenon.[27,28] It seems that acute physical stress exposure as a preconditioning agent protects the heart against I/R. We observed an increase in RPP and LVDP amounts due to acute stress induction in St+IR group as compared with IR group that indicates acute stress would trigger mechanisms to prepare the body for suitable responses to stimuli because the improvement of the cardiac function is important. Therefore, it seems that the effectiveness of stress induction is associated with; 1. nature of the stressor, 2. stress episode duration, 3. intensity of the stimulus and 4. stress predictability or unpredictability. In fact, each of the above factors effects on the neural and hormonal responses to stress. Our results showed that corticosterone is elevated after stress induction, and in Symp+St+IR group is higher than the IR group. It is well established that stress enhances the activity of the HPA axis which results to increase corticosterone secretion[22,29] that can be protective as it prepares the organism to deal with challenges. Based on our results sympathectomy did not effect on stress-induced elevated corticosterone possibly because stress affects HPA axis through different mechanisms such as changes in metabolic and inflammatory factors in addition to increased sympathetic nervous system.[22] Furthermore, this hormone induces changes in immune cells redistribution that enhance immune function.[30] We showed that infarct size is decreased in St+IR group in comparison to the IR group and

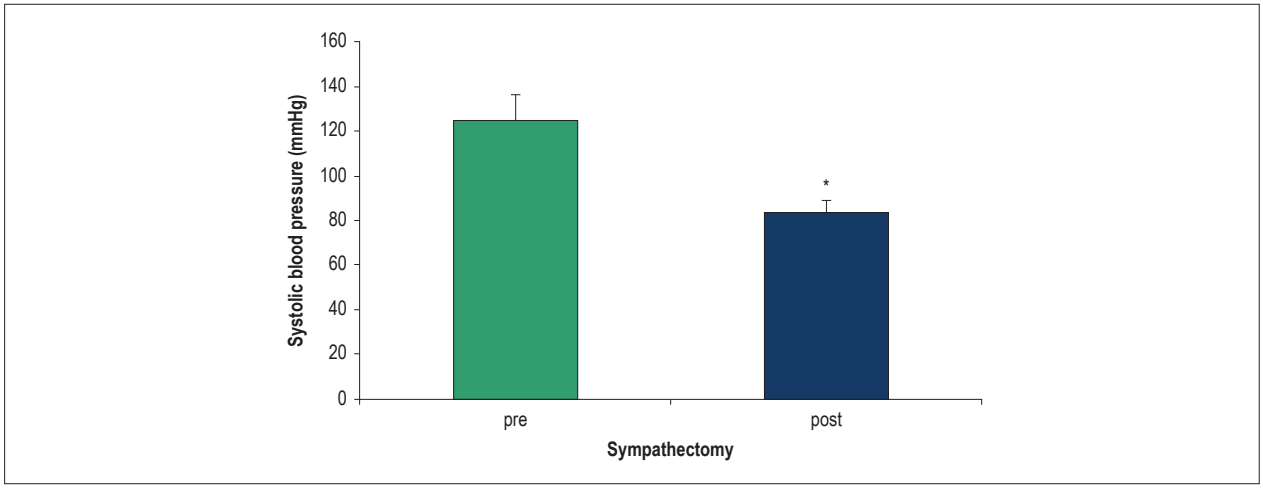

Figure 6 – *Systolic blood pressure before and after chemical sympathectomy. *p < 0.05 compared to before sympathectomy.*

the hemodynamic parameters are improved in St+IR group in compare to the IR group. Diminished infarct size led to reducing in cardiac arrhythmia occurrence[31,32] and also improved cardiac contractility.[33] It seems the beneficial effects of acute stress induction may relate to the improvement of immune system function due to elevated corticosterone level encounter inflammatory factors, which trigger I/R injuries.

The effects of sympathectomy

It has been established that exposure to stressful conditions increase autonomic nervous system activity.[30] The cardioprotection of sympathetic activity has been investigated[34] and we used chemical sympathectomy after acute stress induction to confirm the protective effects of the sympathetic nervous system. Animals in Symp+IR group were subjected to chemical sympathectomy before induction of I/R and there was no significant change in infarct size in comparison to IR group, indicating that chemical sympathetic denervation has no effect on IR injury. In addition, chemical sympathectomy prior to physical acute stress removed the cardioprotection effect of acute stress on infarct size in Symp+St+IR group that emphasizes the presence of sympathetic system is necessary for cardioprotective effects of acute stress. We found that acute stress induction after chemical sympathectomy could overcome harm effects of deleted sympathetic system on hemodynamic parameters in Symp+St+IR group when compared to Symp+IR group that indicates the essential role of sympathetic system physiological activity in regulating HR, pressure and flow.[35] Hara and Abiko declared norepinephrine has two opposite effects on ischemia damages according to the duration of ischemia, means that it could protect the heart with short ischemia and increase the injuries with prolonged ischemia.[28] Positive and negative properties of the sympathetic nervous system are associated with the duration of stimulus exposure. At the long term ischemia, large quantities of norepinephrine are released from the sympathetic nervous system, acting as a source of the free radical and subsequent generation of OH free radical.[36] Protective effect of norepinephrine can be emerged by producing energy for cardiac muscle in short term ischemia episode.[37] Moreover, Yohimbine (as an alpha2 receptor antagonist) administration reduced the incidence of arrhythmia through increasing sympathetic norepinephrine release.[37,38] According to our previous studies, pretreatment with alpha receptor agonist such as phenylephrine could protect the cardiomyocytes against I/R damages in isolated HR.[39] Activation of protein kinase-C (PKC) signalling pathway[40] and NO release[41] by norepinephrine, are involved in the opening of mitochondrial KATP channels, which in turn can reduce mitochondrial calcium load[42] and will lead to attenuation of norepinephrine beneficial effects. Also, we showed that systolic blood pressure declined after chemical sympathectomy that is compatible with this fact that muscle sympathetic outflow is responsible for the regulation of blood pressure.[43] The limitations of this study were the method of induction physical stress does not commonly occur in daily life. Unfortunately, the data of corticosterone level in Symp+IR group were missed so we can't discuss the effect of sympathectomy on corticosterone level and comparison between St+IR group and Symp+St+IR group is not significant. In consistence with our results, Lowrance et al. showed that stress-induced corticosterone level didn't change following pharmacological sympathectomy.[44]

Conclusion

The present study showed that induction of physical acute stress before I/R led to cardioprotection and chemical sympathectomy removed this beneficial effect of physical acute stress.

Acknowledgements

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Author contributions

Conception and design of the research: Imani A, Faghihi M; Acquisition of data: Rakhshan K, Golnazari M; Analysis and interpretation of the data: Imani A, Parsa H, Chookalaei LG, Faghihi M; Statistical analysis and Writing of the manuscript:

Imani A, Parsa H, Chookalaei LG; Critical revision of the manuscript for intellectual content: Imani A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Alireza Imani, from Tehran University of Medical Sciences.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Tehran University of Medical Sciences under the protocol number 30486. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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The Role of Sympathetic System as a Therapeutic Option in the Ischemia/Reperfusion Injury

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Short Editorial related to the article: Acute Physical Stress Preconditions the Heart Against Ischemia/Reperfusion Injury Through Activation of Sympathetic Nervous System

Coronary artery disease is the leading cause of mortality and the most resource-consuming health pathology in industrialized countries.[1] In the United States, it is believed that more than 12 million individuals have ischemic heart disease.[2]

It is estimated that approximately 1 million cases of acute coronary syndrome occur annually in the United States, demonstrating that this syndrome occurs in epidemic proportions.[2] Few pathologies have evolved as radically as AMI, with a marked reduction in mortality as a result of changes in treatment over the past 30 years, particularly cardiac reperfusion.[1,3]

In fact, with the introduction of myocardial reperfusion, 30-day mortality has been reduced from about 14% to about 3% in several clinical trials.[3] In addition to this benefit, early and sustained reperfusion results in lower cardiac morbidity, lower incidence of ventricular fibrillation and tachycardia, conduction disorders and less development of congestive heart failure.[1]

Despite the unequivocal benefit, an undesirable event of this strategy is the phenomenon of reperfusion injury. This phenomenon is defined as the injury that occurs as a direct result of coronary blood flow restoration. This phenomenon may have important clinical implications, because it may be responsible for 30-50% of the final infarct size.[4] Thus, several strategies have been studied with the objective of attenuating the ischemia/reperfusion (I/R) injury phenomenon.

In this issue of the Arquivos Brasileiros de Cardiologia, Imani et al.[5] assessed the cardioprotective effects of acute physical stress against I/R injury, through the activation of the sympathetic nervous system. They used the isolated heart preparation, with the Langendorff apparatus. The hearts were subjected to 30 minutes of ischemia, followed by 120 minutes of reperfusion. Physical stress prior to the I/R improved left ventricular developed pressure and reduced infarct size when compared with the I/R alone.[5] In addition, chemical sympathectomy before physical stress eliminated the protective effect of physical stress on I/R-induced cardiac damages. The authors concluded that the presence of the sympathetic nervous system is necessary for the beneficial effects of acute physical stress on I/R injury.[5]

It is important to emphasize that knowledge about the pathophysiological mechanisms involved in I/R injury is critical, as this allows the creation of therapeutic strategies to attenuate or prevent cardiac damage. On the other hand, we must consider that cardioprotection strategies in I/R models are the main model used to exemplify the difficulties of translational medicine, since positive results from experimental studies are obfuscated by the fact that to date, cardioprotection strategies in clinical studies have shown negative results.[6]

Therefore, although provocative, the role of the sympathetic system as a therapeutic option in the I/R injury remains to be confirmed in future studies.

Keywords

Stress, Mechanical; Simpathetic Nervous System; Hypothalamo-Hpophyseal System; Ischemia; Sympathectomy.

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Physical Activity Levels in Peripheral Artery Disease Patients

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Abstract

Background: **Increases in daily physical activity levels is recommended for patients with peripheral artery disease (PAD). However, despite this recommendation, little is known about the physical activity patterns of PAD patients.**

Objective: **To describe the physical activity patterns of patients with symptomatic peripheral artery (PAD) disease.**

Methods: **This cross-sectional study included 174 PAD patients with intermittent claudication symptoms. Patients were submitted to clinical, hemodynamic and functional evaluations. Physical activity was objectively measured by an accelerometer, and the time spent in sedentary, low-light, high-light and moderate-vigorous physical activities (MVPA) were obtained. Descriptive analysis was performed to summarize patient data and binary logistic regression was used to test the crude and adjusted associations between adherence to physical activity recommendation and sociodemographic and clinical factors. For all the statistical analyses, significance was accepted at $p < 0.05$.**

Results: **Patients spent in average of 640 ± 121 min/day, 269 ± 94 min/day, 36 ± 27 min/day and 15 ± 16 min/day in sedentary, low-light, high-light and MVPA, respectively. The prevalence of patients who achieved physical activity recommendations was 3.4%. After adjustment for confounders, a significant inverse association was observed between adherence to physical activity recommendation and age (OR = 0.925; $p = 0.004$), while time of disease, ankle brachial index and total walking distance were not associated with this adherence criteria ($p > 0.05$).**

Conclusion: **The patterns of physical activity of PAD patients are characterized by a large amount of time spent in sedentary behaviors and a low engagement in MVPA. Younger patients, regardless of the clinical and functional factors, were more likely to meet the current physical activity recommendations. (Arq Bras Cardiol. 2019; 113(3):410-416)**

Keywords: **Motor Activity; Exercise; Waling; Peripheral Arterial Disease; Intermittent Claudication.**

Introduction

Patients with peripheral artery disease (PAD) and symptoms of intermittent claudication have walking impairment, several comorbid conditions and increased cardiovascular risk,[1,2] due to the disease characteristics and severity. Supervised exercise training has been considered a cornerstone in the clinical therapeutic approach in PAD patients,[3] as it improves several components of physical function and quality of life.[4-6] Similarly, positive effects of device-monitored, home-based exercise training programs to improve the walking capacity in these patients have also been reported.[7] However, these interventions are available for a restricted number of patients, limiting applicability in the public health context. Therefore, recommendations to increase physical activity levels remain the most often used approach in clinical practice.

Current physical activity recommendations for the overall population, including PAD patients, consists of practicing at least 150 min of moderate or 75 min of vigorous physical activities or an equivalent combination of moderate-vigorous physical activities (MVPA) per week.[8] Furthermore, it has been recommended that MVPA should be performed in bouts with at least a 10-minute duration.[8] Surprisingly, there are no data indicating the number of symptomatic PAD patients who achieve these physical activity recommendations. Given that most of symptomatic PAD patients are older, have several comorbidities, and that symptoms of intermittent claudication are the main barrier for physical activity practice in these patients,[9] by limiting their walking and functional capacity, it is expected that only a small percentage of the patients would achieve the recommended physical activity levels.

Thus, in this study we aimed to describe the physical activity pattern of Brazilian patients with PAD and symptoms

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of intermittent claudication according to the recommendations for physical activity practice, providing objective information regarding the time spent in sedentary behavior, light physical activity and MVPA. Moreover, we tested the association between adherence to physical activity recommendations and sociodemographic and clinical factors in Brazilian patients with symptomatic PAD.

Methods

Study design and ethical issues

This descriptive study was approved by Local Ethics Committee. Prior to data collection, patients were informed about the methodological and logistic procedures required to participate in the study, as well as the risks and benefits, and signed a written informed consent form before participation.

Participants

The overall sample consisted of symptomatic PAD patients, recruited at a tertiary center specialized in vascular disease, between September 2015 and November 2017. The tertiary center is a specific unit designed to treat PAD patients with intermittent claudication symptoms. There, physicians instruct patients to: stop smoking, control their risk factors, and increase their physical activity levels. In the present study, no additional instructions were given, and patients were asked to keep their physical activity routine. To be included in the present study, patients should: have PAD (Fontaine Stage II), ankle brachial index (ABI) <0.90 in one or both legs and undergo the six-minute walking test (6MWT). Patients with non-compressible vessels, amputated limbs and/or ulcers, previous diagnosis of neurological or psychiatric disorders, or those classified as illiterate were excluded.

Measurements

Clinical data

A standardized face-to-face interview was performed, including assessment of social and demographic information, co-morbid conditions (self-reported), and medications. Social and demographic variables included age and gender (male or female). Time of disease diagnosis was obtained through the question "*How long have you had the disease?*". Data on smoking habits (ex- or current smoker, or non-smoker), obesity (body mass index (BMI) ≥ 30 kg/m^2), diabetes (doctor-diagnosed or hypoglycemic drugs), hypertension (systolic/diastolic blood pressure >140/90 mmHg or antihypertensive drug use), dyslipidemia (doctor-diagnosed or hypolipidemic drug use), coronary heart disease, heart failure and history of cancer (self-reported or analysis of medical records) were obtained.

Disease severity

PAD severity was obtained by calculating the ABI in accordance with the guidelines.[10] All measures were carried out by a single and trained evaluator, using vascular Doppler (Medmega DV160, Brazil) and aneroid sphygmomanometer.

Walking capacity

The 6MWT was performed on a 30-meter long corridor, following the previously described protocol.[11] Briefly, patients were instructed to complete as many laps as possible. Patients were encouraged to "walk at the usual pace for six-minutes and cover as much ground as possible". Patients were informed that they could rest, if necessary. At the end of each minute, patients received feedback on the elapsed time and standardized encouragement in the form of statements such as "you are doing well, keep it up" and "do your best". Total walking distance was defined as the maximum distance which the patient could walk during the test, with or without leg pain. In addition, the self-reported ambulatory ability was assessed using the Brazilian versions of Walking Impairment Questionnaire (WIQ)[12] and the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire.[13]

Objectively measured physical activity

Physical activity was assessed using a GT3X+ triaxial accelerometer (Actigraph, Pensacola, FL, USA). Each participant was instructed to use the accelerometer for seven consecutive days, removing it only for sleeping, bathing or performing activities in the water. The device was attached to an elastic belt and attached to the right side of the hip. Data reduction was performed using the Actilife software, version 6.02 (Actigraph, Pensacola, FL, USA), with a 60Hz sample frequency and 60s epochs. Periods with consecutive values of zero for 60 min or longer were interpreted as "accelerometer not worn" and excluded from the analysis. Physical activity data were included only if the participant had accumulated a minimum of 10 hours/day of recording for at least four days, including one weekend day. The average of total time spent in each intensity of physical activity was calculated using the cutoff points specific for elderly individuals,[14] adapted by Buman et al.,[15] considering sedentary time (SED) as 0 – 99 counts/min; low-light physical activities as 100–1040 counts/min, high-light physical activities as 1041-1951 counts/min and MVPA as ≥ 1952 counts/min using the vertical axis, and analyzed in min/day, adjusting for the time and number of days the device was worn. The total time spent in SED bouts and the time spent in bouts of at least high-light physical activities and MVPA were analyzed by the sum of minutes spent in SED, high-light physical activities and MVPA, respectively, in periods lasting ≥10 minutes. Additionally, we calculated the percentage of patients that met the current physical activity recommendations (≥ 150 min/week) considering MVPA bouts.

Statistical analysis

The sample size was calculated by estimating an effect size of 0.3 in the chi-square analysis, considering an alpha error of 5% and a power of 80%. The sample size required for the study was 143 participants. The data were stored and analyzed using the Statistical Package for the Social Sciences (SPSS, version 17.0, SPSS Inc, Chicago, IL). Descriptive analysis was performed to summarize the patients' data using means, standard deviation or frequency distribution (absolute and relative), as appropriate. Binary logistic regression was used to test the crude and adjusted (age, time of the disease

diagnosis, ankle-brachial index, and six-minute walking distance) association between adherence to physical activity recommendation and sociodemographic data and clinical factors. The results are expressed as odds ratios (OR) and their respective 95% confidence intervals (95%CI). For all the statistical analyses, significance was set at $p < 0.05$.

Results

The overall characteristics of patients are shown in Table 1. The mean age of all patients was 66.7 ± 9.0 years and, on average, patients had moderate disease (ABI: 0.61 ± 0.18). Most patients had hypertension (88.9%), dyslipidemia (85.2%) and diabetes (52.4%),and used antihypertensive (78%) (i.e. thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers), lipid-lowering (89%) (i.e. statins) and antiplatelet agent drugs (85%) (i.e. irreversible cyclooxygenase inhibitors, adenosine diphosphate receptor inhibitors). Forty-three percent of the patients used antidiabetic (i.e. sulfonylureas, metformin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides), 29% used vasodilator (i.e. hydralazine and minoxidil) and 20% used antidepressant drugs (i.e. sertraline, fluoxetine, citalopram, escitalopram, paroxetine).

Figure 1 depicts the distribution of time spent in sedentary, low-light, high-light and moderate/vigorous activities. Patients, aged between 43 and 96 years, spent in average 640 ± 121 min/day, 269 ± 94 min/day, 36 ± 27 min/day and 15 ± 16 min/day in sedentary, low-light, high-light and moderate/vigorous physical activities, respectively. Most patients (52.9%) spent less than 10 min in moderate/vigorous physical activities (sporadic, non-bouted) per day.

Table 2 depicts data about sedentary bouts (< 100 counts), bouts of high light and MVPA (≥ 1041 counts) and bouts only of MVPA (≥ 1952 counts). Ninety percent of patients spent at least 10 bouts in sedentary behavior per day and, on average, the total duration of this bout was 413.7 ± 151.1 min/day. On the other hand, sedentary breaks lasted 174.4 ± 51.4 min/day. Thirty-one percent of patients did not accumulate 10 or more consecutive minutes a week, at least, in high-light physical activities. Considering only MVPA, 67.7% of patients did not accumulate 10 consecutive minutes (bouts) or more at this intensity of physical activity during a week. Among those patients who spent at least one bout of MVPA, the duration of this bout was 9.7 ± 9.6 min/day.

The prevalence of patients who achieved physical activity recommendations for the overall population (≥ 150 min/week of MVPA in bouts of 10 minutes or more) was only 3.4%. Stratifying by age (Figure 2), this prevalence was 11.1% in those under 60 years old, 2.9% in those between 60 and 64 years old, and 1% in those over 65 years. No patients over 70 years old achieved the physical activity recommendations for the overall population.

Table 3 shows crude and adjusted association between adherence to physical activity recommendations and sociodemographic and clinical characteristics in PAD patients. After adjustment for confounders, an inverse and significant association was observed between adherence to physical activity recommendation and age (OR = 0.867; p = 0.011), which means that for each year of life, the odds are ~13% less to meet the physical activity recommendations. Time of disease diagnosis, ABI and total walking distance were not associated with this adherence criterion ($p > 0.05$).

Table 1 – Characteristics of peripheral artery disease patients according to gender (n = 174)

	Values
Age (years)	66.7 (9.0)
Gender (% men)	61.5
Still working (%)	20.5
Time of disease diagnosis (yrs.)	7.9 (5.8)
Ankle-brachial index	0.61 (0.18)
Claudication distance (m)†	135.9 (82.4)
Six-minute walking distance (m)	326.6 (92.7)
WIQ distance (score)	22.7 (22.2)
WIQ speed (score)	23.2 (15.6)
WIQ stairs (score)	30.7 (25.3)
WELCH (score)	27.3 (19.1)
Comorbidities and risk factors	
Charlson index (score)	3.0 (1.7)
Current smokers (%)	18.1
Hypertension (%)	88.9
Dyslipidemia (%)	85.2
Diabetes (%)	52.4
Obesity (%)	28.6
Coronary artery disease (%)	34.5
Heart failure (%)	13.6
Cancer (%)	14.9
Medications	
Antihypertensive (%)	78
Antidiabetic (%)	43
Vasodilator (%)	29
Lipid-lowering (%)	89
Antiplatelet agent (%)	85
Antidepressants (%)	20
Medications	
Cardiac (%)	24
Vascular (%)	12

WIQ: Walking Impairment Questionnaire; WELCH: Walking Estimated-Limitation Calculated by History.

Discussion

The main findings of the present study were: a) Brazilian PAD patients with intermittent claudication symptoms spent most part of the day in sedentary behaviors with a short time in MVPA; b) only 3.4% of the patients met the physical activity

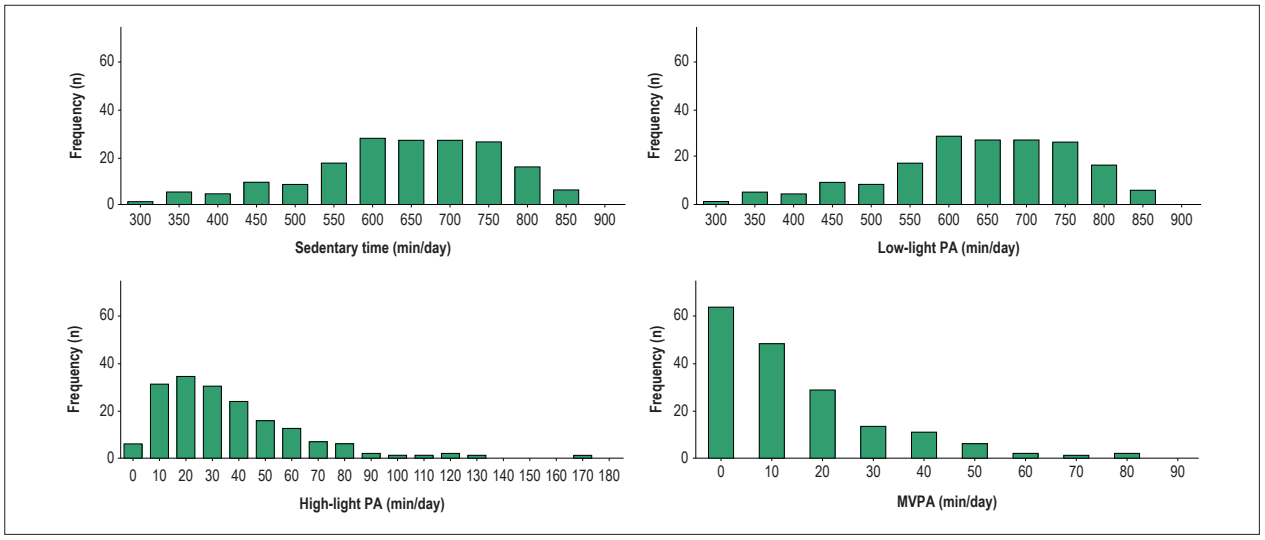

Figure 1 – *Time spent in sedentary, low light, high light and moderate-to-vigorous (MVPA) physical activities (PA).*

Table 2 – Total time spent in sedentary, high light or MVPA and MVPA bouts and sedentary breaks per week and per day in PAD patients (n = 174)

Variable	In a week (mean ± SD)	In a day (mean ± SD)
Total SED bouts	120.1 ± 32.6	17.2 ± 4.7
Total time in SED bouts (min)	2895.6 ± 1057.3	413.7 ± 151.1
Total SED breaks	118.7 ± 32.6	17.0 ± 4.7
Total time in SED breaks (min)	8543.9 ± 2518.0	174.4 ± 51.4
Total high light and MVPA bouts	5.7 ± 7.8	0.8 ± 1.1
Total time in high light and MVPA bouts (min)	84.01 ± 123.8	12.1 ± 17.7
Total MVPA bouts	1.5 ± 3.1	0.22 ± 0.44
Total time in MVPA (min)	22.7 ± 50.3	3.2 ± 7.2

SED: sedentary; MVPA: moderate/vigorous physical activity.

recommendations for the overall population; c) younger patients, regardless of clinical or physical factors, were more likely to meet the current physical activity recommendations for the overall population.

The cutoff used in the present study considered, in addition to "sedentary" and "moderate-to-vigorous physical activity", the "low-light" and "high-light" categories.[15] This decision was based on the following aspects: a) light physical activities are the physical activities most often performed by the elderly, especially those with functional capacity limitations (i.e. patients with PAD); b) light physical activity was broadly unspecified to account for all activity between sedentary and moderate-to-vigorous physical activity (100–1,951 counts/minute); c) the association between light physical activity and health parameters increases when those light physical activities with high energy expenditure (high-light physical activity), that are closer to the classification of moderate-to-vigorous physical activities than sedentary activities, are considered.[15]

In the present study, our sample of PAD patients with intermittent claudication symptoms spent 640 min/day and 15 min/day in sedentary behavior and MVPA, respectively, which represents 66.7% and 1.5% of the waking hours of the day. This pattern is similar to that observed in patients with other cardiovascular diseases, including coronary heart disease, congestive heart failure, myocardial infarction[16] and stroke survivors.[17] In these populations, sedentary behavior ranged from 576 min/day[16] to 606 min/day,[16,17] while MVPA ranged from 8.6 min/day to 11.4 min/day. Interestingly, although pain symptoms (intermittent claudication) during exercise have been reported as a main barrier for physical activity practice in PAD patients,[9] their physical activity patterns seem to be similar to cardiac patients without walking impairment. The current physical activity recommendation for the overall population includes 150 min/day of MVPA in bouts of at least 10 min. The results of this study indicated that a very small percentage (3.4%) of our sample met the current physical activity recommendations. These values are lower than those of previous studies generally carried out with adults (~10%),[18] older adults (12%)[19] and osteoarthritis patients (13% men and 8% women)[20] who usually also have physical limitations. The reduced number of patients who met the physical activity recommendations could be explained by the difficulty of

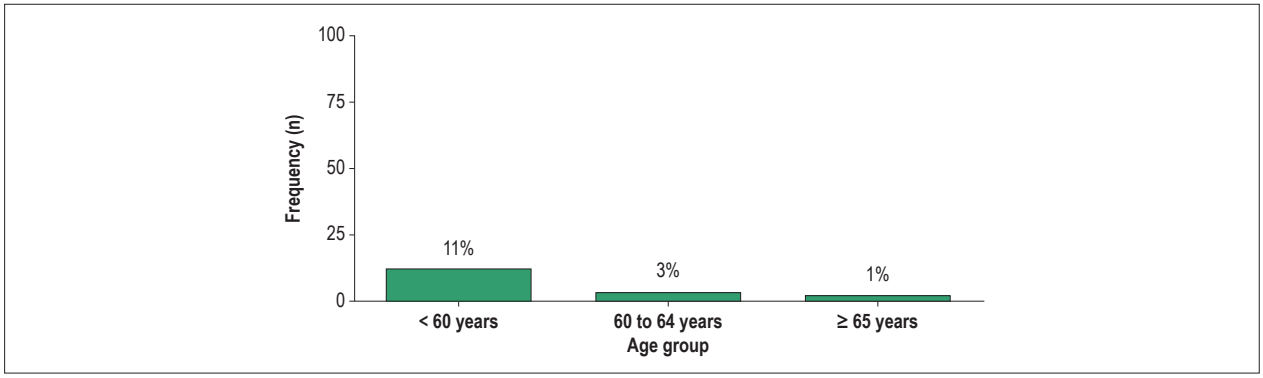

Figure 2 – *Frequency of PAD patients who achieved the current physical activity recommendations according to age group.*

Table 3 – Crude and adjusted association between adherence to physical activity recommendations and sociodemographic or clinical characteristics in PAD patients (n = 174)

Variable	Crude analysis		Adjusted analysis*	
	OR (95%CI)	p	OR (95%CI)	p
Age	0.87 (0.79; 0.97)	0.01	0.88 (0.80; 0.98)	0.02
Time of disease diagnosis	0.94 (0.78; 1.12)	0.46	0.98 (0.83; 1.16)	0.82
Ankle-brachial index	0.19 (0.02; 153.41)	0.77	1.14 (0.07; 173.68)	0.96
Six-minute walking distance	1.01 (0.99; 1.02)	0.12	1.00 (0.99; 1.02)	0.32

**Adjusted by age, time of the disease diagnosis, ankle brachial index, and six-minute walking distance.*

PAD patients to perform moderate and/or vigorous physical activities. In fact, as higher-intensity physical activities may precipitate the occurrence of intermittent claudication symptoms, PAD patients commonly perform lower-intensity physical activities to avoid the symptoms.

In the present study, we also analyzed the frequency of patients who achieved the current physical activity recommendations according to age group. We observed that no patients over 70 years old met the current physical activity recommendations for the overall population. This result was confirmed by the multivariate analysis, which revealed that younger patients are more likely to achieve the current physical activity recommendations. These results are in accordance with previous studies carried out with a representative sample of adults from the United States[21] and with older adults in a population-based sample from Brazil,[19] which showed an inverse relationship between age and the amount of time spent in MVPA physical activities. The decrease in physical activity with increasing age might be due to a worsening in physical functions associated with the presence of the comorbid conditions, leading to an increase in sedentary behavior and functional capacity impairment.

The ABI, considered one of the best prognostic indexes in PAD,[22] and walking capacity, a main clinical marker of PAD associated with endothelial function[23] inflammation[24] and several clinical indicators,[2,25] were not associated with the meeting of physical activity recommendations. These results are not surprising, since ABI[26] and walking capacity have been poorly associated with physical activity in patients with PAD.[27]

Previous studies showed that low levels of physical activity and high levels of sedentary behavior were associated with several risk factors, such as high blood pressure,[28] increased arterial stiffness,[29] increased waist circumference and reduced HDL cholesterol,[30,31] in healthy and clinical populations. In symptomatic PAD patients, a study carried out by Garg et al.[32] reported that reduced physical activity was associated with increased mortality and cardiovascular events. In other words, patients who attempted to control or eliminate their intermittent claudication symptoms by reducing their physical activity, worsened their risk of myocardial infarction, stroke, and death. Thus, the finding of our study that the majority of PAD patients did not attain the current physical activity recommendations highlights the necessity of interventions to increase physical activity in these patients. Future studies are necessary to describe whether different forms of exercise, home-based programs or wearable physical activity monitors are more effective to help patients to attain the current physical activity recommendations.

The present study has several limitations. Although the accelerometer has been considered a gold standard method to measure physical activities in free-living conditions, it was not possible to measure the type and the context in which the physical activity was performed, which hinders the analysis of what kind of activities were most often performed by these patients. In addition, the accelerometer does not assess physical activities such as water gymnastics and resistance training, which are commonly performed by elderly patients, and could underestimate the real physical activity levels of our sample. Given that there are no specific physical activity recommendation

for PAD patients, we employed the current physical activity recommendations for the overall population. However, whether this approach is ideal for PAD patients is unknown. The study was performed in São Paulo, Brazil, and our results may not be extrapolated to other patients with different cultures and lifestyle. We did not include a matched overall population group to compare the prevalence of physical activity between non-PAD and PAD patients. Finally, we did not analyze the type of physical activity performed by these patients, or the difference in physical activities over the year. Some patients assessed during colder/rainier months could be less active than those assessed in the summer months.

Conclusion

This study showed that the pattern of physical activity of Brazilian PAD patients with intermittent claudication symptoms are characterized by a high amount of time spent in sedentary behavior and a low engagement in MVPA, with only 3.4% of these patients meeting the current physical activity recommendations for the overall population. Moreover, younger patients, regardless of clinical and functional factors, are more likely to meet the current physical activity recommendations.

Author contributions

Conception and design of the research: Zeratti AE, Puech-Leão P, Wolosker N, Ritti-Dias RM, Cucato GG; Acquisition of data: Correia MA, Oliveira PML, Palmeira AC, Domingues WJR; Analysis and interpretation of the data: Gerage AM; Statistical analysis: Gerage AM, Correia MA, Ritti-Dias RM, Cucato GG; Writing of the manuscript: Gerage AM, Correia MA, Oliveira PML, Palmeira AC, Domingues WJR, Ritti-Dias RM; Critical revision of the manuscript for intellectual content: Zeratti AE, Puech-Leão P, Wolosker N, Cucato GG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Israelita Albert Einstein under the protocol number CAAE: 42379015.3.0000.0071. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Aspects of Non-Pharmacological Treatment in Peripheral Arterial Disease

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Short Editorial related to the article: Physical Activity Levels in Peripheral Artery Disease Patients

Peripheral arterial disease (PAD) is one of the main atherosclerotic diseases in the elderly population[1] which limits the performance of physical activity. Patients with PAD who have intermittent claudication may have gait impairment, which compromises daily living activities.[2] In addition, these patients have other comorbidities that may increase cardiovascular risk.[1,3] Regular exercise is a non-drug treatment recommended for the prevention and treatment of cardiovascular disease. On the other hand, maintaining adherence to a physical training program becomes a major challenge.

The present study[4] exposes the physical activity pattern of patients with PAD and demonstrates the high rate of a sedentary lifestyle with aging. In fact, the disease itself leads to physical limitation, which in turn is also a worsening factor of the disease, since the recommendation of vigorous physical activity has therapeutic effects that contribute, in addition to the chronic use of arterial vasodilator drugs. In addition, chronic arterial vasodilation due to the use of medications may lead to reduced long-term peripheral flow, as arterial vasodilation promoted by medication further reduces perfusion pressure in the lower limb peripheral muscles and intensifies the low level of physical activity in patients with PAD, according to current physical activity recommendations.

The assessment of the degree of physical activity was performed by a device over a period of 7 days, and the data are relevant in classifying the degree of physical limitation with aging, as well as, demonstrating the significance of sedentary lifestyle, may corroborate to further aggravate the disease and cardiovascular risk. On the other hand, the device does not evaluate or quantify localized muscular resistance training (strength), which may underestimate the results pointed out by the study.

Clearly, the importance of developing strategies for these patients to engage in regular exercise. The main reason for these patients with PAD not progressing with physical training is pain related to increased muscle energy demand, called intermittent claudication, especially in the calf region during walking.[5] Moderate to vigorous exercise can precipitate the symptoms of intermittent claudication and this becomes a barrier for these patients to engage in physical activity. Thus, low intensity and progressive aerobic exercise can be used as a strategy to delay these symptoms. In addition, patients with intermittent claudication have muscle atrophy, and reduced muscle strength and endurance in the lower limbs increase the fragility of these patients, especially with aging.[6] In this aspect, strength exercises and peripheral muscular endurance (bodybuilding) should be used.

Although the literature recommends exercises with aerobic characteristics, such as walking, as the main exercise modality for these patients with PAD, muscle overload exercises have also been recommended as part of a physical exercise program in this population.[7,8]

Regular exercise should be used as a non-pharmacological tool for the treatment and prevention of cardiovascular disease in patients with PAD and intermittent claudication, so it is important to develop a specific exercise program, especially to delay the onset of symptoms. intermittent claudication, because, besides preventing the onset of pain and the interruption of exercise, it can be a motivational factor that will imply the adherence of these patients to physical activity.

Keywords

Peripheral Arterial Disease/physiopathology; Peripheral Arterial Disease/drug therapy; Aged; Intermittent Claudication; Ankle Brachial Index; Exercise; Prevention and Control.

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Pulmonary Hypertension in General Cardiology Practice

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Abstract

The finding of pulmonary hypertension (PH) by echocardiography is common and of concern. However, echocardiography is just a suggestive and non-diagnostic assessment of PH. When direct involvement of pulmonary circulation is suspected, invasive hemodynamic monitoring is recommended to establish the diagnosis. This assessent provides, in addition to the diagnostic confirmation, the correct identification of the vascular territory predominantly involved (arterial pulmonary or postcapillary). Treatment with specific medication for PH (phosphodiesterase type 5 inhibitors, endothelin receptor antagonists and prostacyclin analogues) has been proven effective in patients with pulmonary arterial hypertension, but its use in patients with PH due to left heart disease can even be damaging. In this review, we discuss the diagnosis criteria, how etiological investigation should be carried out, the clinical classification and, finally, the therapeutic recommendations for PH.

Introduction

In the cardiologist's routine, the echocardiographic finding of pulmonary hypertension (PH) is extremely common. PH on echocardiogram can be identified in up to 2.8% of the general population[1] and in more than half of the patients with heart failure. It is estimated that almost 100% of the individuals with symptomatic mitral regurgitation and the majority of those with major aortic stenosis show some degree of increased systolic pulmonary artery pressure.[2,3]

The diagnosis of PH has major prognostic implications, both when it is attributable to cardiovascular diseases,[4] and to pumonary diseases,[5] or even in isolated pulmonary vascular involvement. Unfortunately, it is common to initiate specific treatment indiscriminately for PH patients based only on echocardiographic data, which, in some cases, can increase mortality.[6] It is essential to perform detailed investigation to confirm the diagnosis and comprehension of the mechanisms predominantly involved in PH and, thus, determine the correct therapeutic approach. These topics will be discussed in this review.

Keywords

Hypertension, Pulmonary; Pulmonary Heart Disease; Echocardiography/methods; Pulmonary Disease, Chronic Obstructive; Pulmonary Emphysema; Pulmonary Fibrosis.

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Definition

Traditionally, PH is defined through invasive hemodynamic monitoring, with a recent review of the value assumed as pathological. Since 1973, the diagnosis of PH was arbitrarily made when mean arterial pulmonary pressure (mPAP) was equal to or greater than 25 mmHg.[7] However, recent data have shown that, even with lower mPAP values, there is an increase in mortality rates.[8] Therefore, on December 2018, a consensus resulting from the 6th World Symposium on Pulmonary Hypertension was published, which redefined PH to the situation in which mPAP is higher than 20 mmHg and pulmonary vascular resistance is greater than or equal to 3 Woods units.[9]

When, in the presence of this level of pulmonary pressure, the pulmonary artery occlusion pressure (PAOP) is equal to or less than 15 mmHg, circulatory impairment begins to occur in the pulmonary circulation, either due to pulmonary arterial hypertension (PAH), or to pulmonary thromboembolism or pulmonary parenchymal disease. If the PAOP is higher than 15 mmHg, the PH is considered postcapillary. In this case, increased pressure in the pulmonary arterial territory is due to retrograde transmission of increased left atrial hydrostatic pressure into the pulmonary veins and pulmonary capillaries and, ultimately, into the pulmonary arterial circulation. There are situations in which the PAOP is above 15 mmHg, but this fact does not seem suficient to justifify the severity of mPAP increase. These patients display a pulmonary vascular resistance greater than 3 Woods units and, usually, the diastolic pulmonary gradient is higher than 7 mmHg (GDP – the difference between the pulmonary artery diastolic pressure and the pulmonary capillary pressure).[10]

This condition is called combined pre- and post-capillary PH. This hemodynamic profile can occur in patients with left heart disease and pulmonary vascular remodelling secondary to chronic congestion, but can also be seen in severely hypervolemic patients with PAH, and reverse Bernheim effect (when PH is so severe that results in the interventricular septum bulging toward the left ventricle, thus increasing the left ventricular pressure and, therefore, the PAOP).[11]

Right heart catheterization is indispensable for the diagnosis of PH, with a morbidity of 1.1% and mortality of 0.055%, in experienced centers.[12] On the other hand, its implications for the accurateness of the diagnosis are overwhelming. In a study conducted at a referral center for PH in Brazil,[13] out of the 384 patients with echocardiography suggestive of PH undergoing right heart catheterization, only 78.6% actually had a mPAP ≥ 25 mmHg. Thus, if the diagnosis of PH is based on echocardiography alone, mistakes may occur in more than 20% of the cases. Moreover, in the same study, among the patients wih PH, 18.3% had post-capillary PH (PAOP > 15 mmHg), which has direct implications for the treatment. Without the catheterization, a quite considerable number of patients would be inadequately diagnosed and treated.

Classification of pulmonary hypertension

The current classification of PH takes into account data of clinical presentation, pathophysiology, anatomopathological findings and hemodynamic parameters,[7,9,11] and proposes a division into 5 different groups (Table 1). It should be highlighted that, since 2003, the terms "primary" and "secondary" PH are no longer listed in the WHO consensus.

Group 1

Patients with PAH. These are the patients with idiopathic PAH, heritable PAH, associated with HIV infection, connective tissue disease, portal hypertension, drugs or congenital heart diseases. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are also categorized as Group 1.[14] Schistosomiasis-associated PH has a major epidemiological relevance in Brazil, and is included in this group.[15-18] In Group 1 patients, the catheterization reveals pattern of pre-capillary HP (PAOP ≤ 15 mmHg), and does not show significant pulmonary heart disease or chronic thromboembolic HP. The histological findings are vasoconstriction, vascular remodelling with plexiform lesions and microthrombosis in the pulmonary vasculature.[19] Studies with specific medication for the treatment of PH mainly comprise this group.

Group 2

Patients with HP due to left heart disease: valvular disease, left ventricular diastolic or systolic dysfunction. These patients have hemodynamic patterns of post-capillary hypertension. In the cases where combined post-capillary PH with a pre-capillary component is observed, the prognosis is worse than that for patients with isolated post-capillary PH.[20] The identification strategy of this hemodynamic profile can be sensitized by performing fluid challenge during catheterization. Elderly patients with metabolic syndrome, atrial fibrillation or changes in the left heart, revealed by echocardiography, have a high probability that their HP will be due to the post-capillary component. In these situations, if the PAOP is ≤ 15 mmHg and > 12 mmHg, a new fluid challenge during catheterization should be considered.[21] The administration of 500mL of saline solution within 5 minutes is recommended, being the post-capillary component assumed when the PAOP, measured immediately after the fluid challenge, is greater than 18 mmHg.[21] This is the most prevalent type of PH worldwide.[22]

Group 3

Patients with HP due to pulmonary disease and/or hypoxia. For instance: chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, high altitude exposure. The hemodynamic pattern is that of pre-capillary HP.[9]

Group 4

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) or diseases of pulmonary artery obstruction such as arteritis, neoplasms, or congenital pulmonary artery stenosis, with hemodynamic pattern of pre-capillary PH.[23] The aim of the treatment in this population is to restore blood flow to the obstructed vascular territories.

Group 5

Patients with HP and unclear multifactorial mechanisms, as in the cases of renal failure, sarcoidosis, myeloproliferative disorders and hemolytic anemia.[7]

Diagnostic evaluation of pulmonary hypertension

The diagnostic suspicion is based on unspecified symptoms (dyspnea to effort and/or syncope), not always accompanied by signs suggestive of PH or right ventricular dysfunction (hyperphonesis of the second heart sound, tricuspid systolic murmur, jugular stasis, hepatomegaly and lower limb edema). Considering these findings, the non-invasive test of choice to begin the investigation is the transthoracic echocardiography.[19]

The interval between the symptom onset and the diagnosis of PH is about two years, which hinders early treatment.[7]

The investigation should begin by searching for the most frequent causal factors: left heart disease, lung disease or pulmonary thromboembolism. Only after excluding these conditions, should the presence of PAH be considered, as proposed in the algorithm (Figure 1).

CHEST X-Ray

It can show prominence of the pulmonary artery trunk, as well as of the right (> 16 mm) and/or left (> 18 mm) branches, increased right chambers (bulging of the right mediastinal contour, boot shaped heart and filling of retrosternal space).[24] These changes are usually more marked only in advanced stages of the disease.

Electrocardiography

Traditionally, the electrocardiography shows signs of overload in the right chambers – axis shift to the right and P-wave pulmonale (p ≥ 2.5 mm in DII); as in the X-ray, the electrocardiographic changes are more evident in the stages when there is cardiac structure repercussion. In up to 13% of the cases, the EGC is normal.[25]

Table 1 – Classification of pulmonary hypertension[7,9]

Group 1	Pulmonary Arterial Hypertension
Group 2	Pulmonary hypertension due to left heart disease
Group 3	Pulmonary hypertension due to Pulmonary Disease and/or Hypoxia
Group 4	Chronic thromboembolic pulmonary hypertension and other diseases of pulmonary artery obstruction
Group 5	Pulmonary hypertension with unclear multifactorial mechanisms

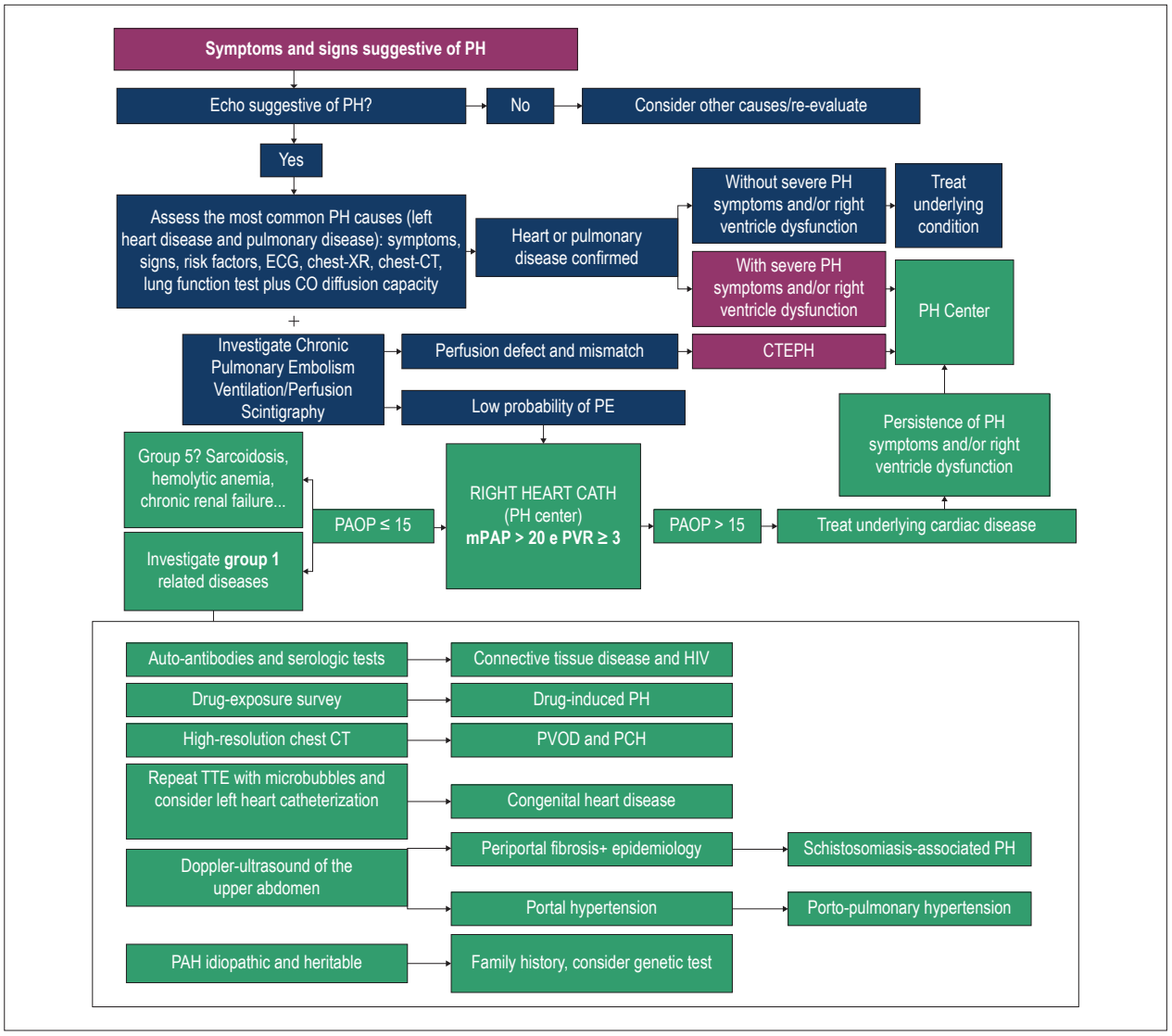

Figure 1 – *Diagnostic algorithm (adapted from Alves-Jr, et al.[19]). DLCO: Diffusing capacity of the lungs for carbon monoxide; V/Q scintigraphy: Ventilation and pulmonary perfusion scintigraphy; CTEPH: PH due to chronic pulmonary thromboembolism; RHC: Right heart catheterization; HRCT: High-resolution CT; TTE: Transthoracic doppler echocardiogram; PVOD: Pulmonary veno-occlusive disease; PCH: pulmonary capillary hemangiomatosis.*

Chest CT

Computed angiotomography of the chest plays an important role in the differential diagnosis of PH and its classification, helping to investigate diseases that affect the pulmonary parenchyma and chronic thromboembolism. It can also increase the suspicion of the diagnosis of pulmonary veno-occlusive disease. Computed tomography findings of increased pulmonary artery diameter, of secondary importance compared to echocardiography, are also suggestive of PH and, thus, can be used in indirect screening. This measurement of the pulmonary artery diameter exhibits quite high specificity for the presence of HP when the diameter is greater than 33.2 mm.[26]

Ventilation/Perfusion Scintigraphy

Ventilation/perfusion scintigraphy is essential for CTEPH screening due to its high sensitivity (96-97%), combined with a specificity of 90-95%, while chest CT angiography can have a sensitivity of up to 50%.[27] Nevertheless, dual-energy computed tomography has been shown to have the same sensitivity and specificity for CTEPH than scintigraphy.[28]

Echocardiography

It is the best non-invasive screening method for PH, but it does not establish the definitive diagnosis, nor does it make a clear distinction between the different PH groups (Table 1).

Echocardiography allows for the assessment of pulmonary artery systolic pressure – according to the direct measure of the tricuspid regurgitation speed and the estimate of right atrial pressure – in addition to assessing the right and left ventricular functions. Besides the cavity dimension, specifically in relation to right ventricular assessment, several parameters are used, such as TAPSE – tricuspid annular plane systolic excursion, the area difference between RV diastolic and systolic areas, called right ventricular fractional area change (FAC), myocardial performance index (MPI), left ventricular ejection fraction (LVEF) as measured by two-dimensional (2D) and three-dimensional (3D) echocardiography, DTI-derived tricuspid lateral annular systolic velocity (S'-wave) and longitudinal strain.[29]

Prognosis Assessment

In spite of all the advances of the last two decades, PAH remains a high-mortality disease (an approximate 25% mortality rate at 3 years, according to recent registries).[30] There are several markers associated with the prognosis of PAH which can be used in clinical practice for therapeutic follow-up of patients under specific therapy.[31] Based on the results of these prognostic markers, it is possible to decide on stabilisation of the medication or therapeutic escalation. Table 2 shows the values defined as better, intermediate or worse prognosis of each marker.[11] Recent researches have indicated the possibility of using noninvasive prognostic markers in follow-up assessments (BNP, 6-minute walk test and functional class), with a good survival prediction.[32]

Treatment

Pulmonary Arterial Hypertension (Group 1)

After definition of the diagnosis, initiation of treatment can be considered. It should be highlighted that, in patients with PH associated with HIV infection, or in patients with systemic lupus erythematosus or mixed connective tissue disease, it is necessary to treat the underlying disease, which may be sufficient to treat PAH.[24]

General measures for PH include: physical rehabilitation, avoiding excessive physical activity, psychosocial support, avoiding pregnancy, immunization against influenza and pneumococcal infection. Treatment with diuretics, O_2 therapy and digoxin are considered supportive therapy. Oral anticoagulant therapy may be considered in patients with IPAH, HPAH and anorexigen-induced PAH.[19]

Calcium-channel blockers are recommended only in cases of PAH with a positive acute vasoreactivity test. This test is performed with nitric oxide (NO) inhalation (10-80 ppm) for 10 minutes, and is indicated in the cases of idiopathic, heritable or drug-induced PAH.[7] Epoprostenol, iloproste or adenosina can also be used. The test is deemed positive when, after the vasodilator infusion, the mPAP decreases to less than 40 mmHg, with a variation of at least 10 mmHg, in association with a maintained or increased cardiac output. This assessment allows for identification of the subpopulation with PAH (about 10%) whose main pathophysiological mechanism is pulmonary vasoconstriction, with a better medium- and long-term prognosis.[33] High doses of calcium-channel blockers should only be used in this situation, because they worsen the prognosis of patients who do not respond to the test.

Group 1 PAH-specific therapy arose from the decade of 1990 on. These medications target three pathophysiological pathways of the disease: the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway (Table 3).

Endothelin Receptor Antagonists 1 (ambrisentan, bosentan and macitentan) and phosphodiesterase type 5 inhibitors (nitric oxide pathway – sildenafil and tadalafil) are more recurrent in Brazil, and are often used as monotherapy or in combination as first line in the treatment of pulmonary arterial hypertension.[15,34]

Prostanoids were the first class of medication used in pulmonary arterial hypertension and, in addition to improving morbidity and exercise capacity, epoprostenol was the ony drug to show survival improvement in a clinical randomized trial.[35] This drug class should always be considered for patients with FC-IV symptoms.[35,36]

In cases of progressive disease, or even in cases where prognostic stratification in the initial approach is already suggestive of high risk, the use of combined therapy should be considered.[36] Drugs that act in different pathways should be combined (Figure 2).[37] Once there are no more possibilities of clinical management of PAH, atrial septostomy or even lung transplantation should be considered.[11]

Pulmonary hypertension due to left heart disease (Group 2)

Pulmonary hipertension in patients with left-sided cardiomyopathy is the most frequent form of PH. It is difficult to establish its exact prevalence because most reports are based on echocardiographic findings, with no confirmation of diagnosis through catheterization. Pulmonary congestion, due to retrograde transmission of elevated filling pressures in the left heart, determines directly an increase in pulmonary artery blood pressure; what happens is that, in adittion to this passive mechanism, congestion is also associated with the activation of neuro-hormonal mechanisms and eventually with vascular remodelling. Thus, a pre-capillary component can arise, combined with the post-capillary component, characteristic of left heart disease. In this context, there might be rationale for the use of specific PAH medication; however, until now, there is no significant evidence of the benefits of such approach, as we shall see.

Epoprostenol

Twenty years ago, Califf et al.[38] carried out a study to assess the impact of epoprostenol in 471 patients with advanced heart failure (HF) (LVEF < 25%, NYHA functional class III or IV and optimized therapy for those times: ACE inhibitors/diuretics/digitalis; many in need of inotropic support).[38] In spite of clear improvement of hemodynamic parameters with the use of epoprostenol (increased cardiac index, decreased pulmonary capillary pressure and reduced systemic and pulmonary vascular resistance), the study was precociously interrupted due to increased mortality within 6 months: 48%

Table 2 – Risk assessment in pulmonary arterial hypertension – adpted from the European guidelines on pulmonary hypertension published in 2015[11]

Prognostic marker/RisK	Low risk (Estimated mortality < 5% year)	Intermediate risk (Estimated mortality 5-10% year)	High risk (Estimated mortality > 10% year)
Signs of heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Frequent
Functional class	I, II	III	IV
6MWD	> 440 m	165-440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg (> 65% pred.) VE/VCO_2 slope < 36	Peak VO_2 11-15 ml/min/kg (35-65% pred.) VE/VCO_2 slope 36-44.9	Peak VO_2 < 11ml/min/kg (< 35% pred.) VE/VCO_2 slope ≥ 45
BNP levels	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1400 ng/L	BNP > 300 ng/L NT-proBNP > 1400 ng/L
Imaging	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 l/min/m^2 SvO_2 > 65%	RAP 8-14 mmHg CI > 2-2.5 l/min/m^2 SvO_2 60-65%	RAP > 14 mmHg CI < 2.0 l/min/m^2 SvO_2 < 60%

VO_2: consumo de oxigênio; VCO_2: liberação de dióxido de carbono; Slope VE/VCO_2: equivalente respiratório para o dióxido de carbono; BNP: peptídeo natriurético cerebral; NT pro BNP: fragmento N-terminal do pró BNP; AD: átrio direito; In.C: índice cardíaco; SVO_2: saturação venosa mista de oxigênio.

Table 3 – Specific drugs available for PH treatement (modified from Galiè N, et al.[11])

Pathophysiological pathways	Class	Drug
Endothelin	Endothelin Receptor Antagonists 1	Ambrisentan
		Bosentan
		Macitentan
Nitric Oxide	Phosphodiesterase type5 inhibitors	Sildenafil
		Tadalafil
		Vardenafil
	Soluble Guanylate Cyclase Stimulants	Riociguat
Prostaglandins	Prostacyclin	Epoprostenol
	Prostacycline Analogues	Iloprost
		Treprostinil
		Beraprost
	Selective IP receptor agonists	Selexipag

vs 37%. There was no significant differences in symptoms, quality of life or walking distance. Minor studies have shown conflicting data of clinical and/or hemodynamic improvement, but they had no power to assess mortality.[39] Until today, the use of epoprostenol (or the prostanoid analogs, i.e., iloprost, treprostinil, beraprost, or even selexipag, a specific IP-receptor agonist, which acts on the same pathway as prostaglandins) is not recommended for group 2 PH.

Endothelin receptor antagonists

Blockade of ETA receptors in patients with group 2 PH can be useful not only for the well-known effects on pulmonary circulation, but also because of its potential direct benefits to the systemic circulation and myocardium. In 1998, Sütsch etal.[40] observed an increase in cardiac output, decrease in pulmonary capillary pressure and severe systemic and pulmonary vascular resistance in a small number of patients with advanced HF, randomized to receive bosentan 1 g (a non-selective inhibitor of endothelin receptors A and B).[40] Four years later, in the ENABLE study, 1,613 patients with NYHA functional class III or IV heart failure due to severe left ventricular dysfunction (EF < 35%) received bosentan (125 mg 2X/day) or placebo; there was no difference in the primary outcome (death or hospitalization due to heart failure) and there was higher fluid retention in the group who had received the medication.[41,42] In the HEAT study, 157 patients with FC III HF (and cardiac index ≤ 2.6 L/min.m^2 and PCP ≥ 12 mmHg) were randomized to receive placebo or darusentan (a selective inhibitor of endothelin receptor A). The group who received darusentan showed increased cardiac index (the study's

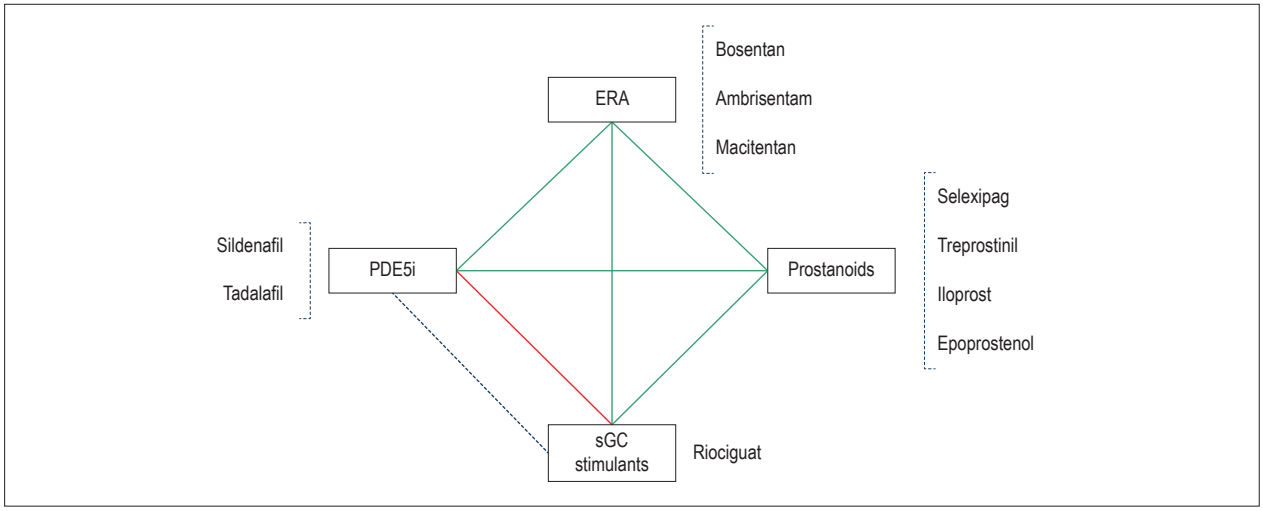

Figure 2 – *Pathophysiological pathways in pulmonary hypertension and specific therapy. Green lines: possible combinations; Red lines: Not recommended combination; Blue dotted line: Potential for substitution therapy, within the same pathway. ERA: endothelin receptor antagonist; PDE5i: Phosphodiesterase type 5 inhibitor; sGC: Soluble Guanylate Cyclase. Modified from Dos Santos Fernandes CJC, et al.*[37]

primary outcome) and decreased systemic resistance after 3 weeks of treatment, with no changes in pulmonary vascular resistance, pulmonary artery pressure or pulmonary capillary pressure (also a primary endpoint). However, the patients who received the medication had more clinical decompensation, notably the highest dose groups.[43] The same medication was studied again in 642 patients with FC II-IV HF and LVEF < 35%. There was no right heart catheterization monitoring. Patients were randomized for placebo or darusentan (5 doses) for 6 months. The primary outcome of the study was LV diastolic volume changes measured using cardiac resonance imaging. The selective inhibitor of endothelin receptor had no impact on cardiac remodelling or in the clinical parameters, again with a tendency towards higher decompensation of heart failure with moderate to higher doses of the medication studied.[44]

Another study, with bosentan, assessed the impact of the medication in high dosage (500 mg 2x/day) and for an extended period of time (26 weeks) in 370 patients with advanced HF, in FC III or IV and with LVEF < 35%. The primary outcome was clinical worsening. The study was interrupted precociously due to the high incidence of hepatotoxicity, so that less than half of the case reports had completed the 26 weeks of follow-up. This data is important since, in general, there was no difference between the bosentan and placebo groups, but for those patients who completed the 6 months of follow-up, the use of bosentan was associated with clinical improvement. We do not have the hemodynamic data of the mentioned study.[45]

So far we have discussed studies that analysed patients with LV systolic dysfunction, and mostly, though not entirely, PH registries (not always by right heart catheterization). If on one hand there seems to be hemodynamic improvement in the early stage of endothelin receptor inhibitor therapy, on the other hand, there may be clinical decompensation, probably due to hydrosaline retention. In the medium-term, sustained usage can bring clinical benefits, as suggested in the latest study discussed above.[45] Recently, the results of the MELODY-1 study (Macitentan in subjects with combined prE- and post-capiLlary PH due to left ventricular DYsfunction) can be incorporated into the discussion on the role of inhibitors of endothelin receptors in the treatment of patients with PH due to left ventricular dysfunction.[46] Although this is a pilot study, with small casuistry, it is the first study carried out from hemodynamic confirmation of group 2 PH to randomization. The authors limited the study to patients with group 2 PH, along with the hemodynamic criteria of post- and pre-capillary componentes of PH (pulmonary vascular resistance > 3 Wood units and diastolic pulmonary gradient > 7 mmHg). A total of 63 patients were randomly assigned to macitentan or placebo. There was more fluid retention or clinical worsening in the macitentan group, especially due to the first criterion: 22.6% X 12.5%. After 12 weeks, no difference was observed between the groups in relation to the hemodynamic parameters, BNP or 6 min walk test. Although the authors selected, among the patients with HF, the subgroup more likely to benefit from specific medication for PAH, they also observed worsened evolution when they used it,[47] which is nowadays one of the strongest evidence against the use of inhibitors of endothelin receptors in group 2 PH.

Phosphodiesterase type 5 inhibitors

In 2007, Lewis et al.[48] randomized 34 patients with FC II-IV heart failure and LVEF ≤ 40% to receive sildenafil or placebo for 3 months. The patients who received sildenafil improved HF functional class, aerobic capacity, the distance in the 6-minute walk test and showed significant reduction in pulmonary vascular resistance in relation to the basal values, with no increase in pulmonary capillary pressure or change in cardiac index.[48] Meanwhile, encouraging case reports were published on hemodynamic improvements through treatment with sildenafil in candidates for cardiac transplantation, with reduced pulmonary vascular resistance and cardiac outcome improvement.[49]

Other small studies have also demonstrated hemodynamic benefits in patients with LV systolic dysfunction who received silnadefil, even after the first dose.[50] Nonetheless, there are no data of randomized multicenter studies available to establish the impact of sildenafil on patients with LV systolic dysfunction. In the Sildenafil Versus Placebo in Chronic Heart Failure (SilHF) study, still in progress, patients with HF and Group 2 PH (echocardiographic criterion) and LVEF < 40% are randomized to receive sildenafil 40 mg 3x/day or placebo.[51] This will be an important study, though the lack of hemodynamic monitoring through right catheterization may be a problem for the interpretation of the results.

The impact of sildenafil when compared with placebo throughout 12 weeks was tested in patients with heart failure with preserved ejection fraction. In this multicenter study, 216 patients were randomized and there was no difference in the primary outcome (peak consumption of O_2) or in the clinical Picture.[52] We do not have the data on right heart catheterization and therefore we do not know the exact number of patients in group 2 PH.

Finally, the subgroup of patients with valvular heart disease deserves special attention. Most patients with significant aortic valvular disease and almost all patients with symptomatic mitral insufficiency have PH. Even after correction of the valvular disease, some patients remain with PH and others who did not have PH before surgical treatment can develop the disease evolutionarily. Recently, the impact of sildenafil in patients with residual PH, after heart valve surgery, was assessed in a multicenter randomized study.[3] A total of 200 patients with a mean pulmonary arterial pressure ≥ 30 mmHg and with no signficant valve injury were randomized to receive sildenafil 40 mg every 8 hours or placebo, for 6 months. The composite outcome of death, admission to hospital for decompensated heart failure or functional worsening occurred more often in the sildenafil group compared with the placebo group (OR 0.39; CI 0.22-0.67; p < 0.001), mainly at the expense of more admissions for decompensed HF. It is important to highlight that, although the etiology of the cardiomyopathy was valvular disease, and only patients with no significant residual valvular injury had been randomized, the hemodynamic data indicate characteristics of group 2 PH, with combined pre- and post-capillary PH; in a little more than half of the patients (57%), pulmonary resistance was greater than 3 Wood units.

Thus, althought early data from small case reports performed in single-centers encourage the use of sildenafil in grupo 2 PH, there is no evidence supporting its routine recommendation.

Riociguat

Riociguat acts on the same pathway as phosphodiesterase type 5 inhibitors, directlty stimulating guanylate cyclase, in addition to having an established role in the management of patients with PH due to chronic pulmonary thromboembolism (group 4) and in pulmonary arterial hypertension. Its role in group 2 PH has been recently tested in the LEPHT study.[53] The patients had symptomatic HF, with LFEF ≤ 40% and PH measured by right heart catheterization. A total of 201 patients were radomized to receive riociguat (3 different doses) or placebo. There was no difference in the mean pulmonary artery pressure between the groups (primary endpoint), but the group who received riociguat 2 mg three times daily showed increased cardiac index and reduced systemic and pulmonary vascular resistance. No difference was observed in relation to the functional class or in the composite outcome of death or admission for decompensated heart failure.

Thus, so far, there is no indication for the routine use of any of the specific medications for group 1 PH in individuals with group 2 PH. In selected cases, when, after optimization of cardiomyopathy, with special attention to volemia, PH remains with pre-capillary component apparent on cardiac catheterization, the decision upon the use of specific medication should be individualized, in a reference center, preferably, in the context of clinical study to deliver more evidence.

Pulmonary hypertension due to Pulmonary Disease and/or Hypoxia (Group 3)

It is considered the second most common cause of PH and the pulmonary diseases most commonly associated with PH are: chronic obstructive pulmonary disease (COPD), interstitial pulmonary disease and combined pulmonary fibrosis and emphysema.[54]

Although there is high prevalence of increased pulmonary artery pressure in patients with chronic pulmonary diseases, only a small minority of these patients present with severe PH, characterized by mPAP > 35 mmHg. In some patients with pulmonary disease and HP, especially in patients with mild pulmonary disease, but with severe PH, it may be difficult to determine whether PH is caused by pulmonary disease or related to concomitant pulmonary vascular disease.[55] Until now, there is no evidence that the specific medications used in PAH are beneficial for the treatment of Group 3 PH, and patients with suspected associated vascular disease should be referred to reference centers.

Chronic thromboembolic pulmonary hypertension (CTEPH) and other diseases of pulmonary artery obstruction (Group 4)

CTEPH is the main disease of group 4, and is characterized by chronic obstruction of pulmonary artery and vascular remodelling due to pulmonary thromboembolism. It is the only potentially curable form of PH, once effective pulmonary thromboendarterectomy is perfomed. For this reason, it is always necessary to investigate chronic pulmonary thromboembolism in patients with PH, and refer the diagnosed cases to a reference center.[56] In cases of contraindicated surgery or persistent PH after surgery, there is evidence in favor of the use of riociguat.[57] Macitentan also provides clinical and hemodynamic benefits for patients with CTEPH with no surgical indication.[58] Full anticoagulation is always recommended, even after surgery; diuretic and oxigen are indicated in case of heart failure and hypoxemia, respectively.[11] should be considered for patients who are not candidate for surgical intervention.[59]

Pulmonary hypertension with unclear multifactorial mechanisms (Group 5)

Group 5 includes several diseases which may behave similarly to other groups, but whose mechanisms associated with the development of PH are not clear yet. Thus, treatment is heterogeneous and essentially focused on the underlying disease.[60]

Conclusion

PH is a complex and heterogeneous condition, often wrongly diagnosed when based only on echocardiographic data. For patients with Grupo 1 PH, the use of specific therapeutic approaches are recommended. Unfortunately, for the most common forms of PH: group 2 (cardiac cause) or group 3 (respiratory causes) routine use of specific therapeutic is not indicated. The complexity of the assessment of patients with PH reinforces the need for these patients to be followed in centers with expertise in pulmonary circulation, where multidisciplinary approach allows for optimization of existing resources and treatment adequacy to current guidelines.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Calderaro D, Alves Junior JL, Fernandes CJCS, Souza R.

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Digital Health, Universal Right, Duty of the State?

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Introduction

The Brazilian Constitution establishes, in its art. 196,[1] that "health is a universal right and duty of the State, guaranteed by social and economic policies aimed at reducing the risk of diseases and other ailments, and universal and equal access to actions and services for their promotion and recovery".

In addition, article 198,[1] states that "public health actions and services are part of a regionalized and hierarchical network and constitute a single system, organized with the following guidelines: I – decentralization, with a single direction in each sphere of government; II – integral care, with priority for preventive actions, without loss to the care services; III – community participation".

From a systematic reading of these two constitutional provisions, it is possible to list the basic elements of the implementation of the right to health by the public authorities: universal and equal access, as well as integral care. Integral health care determines that "the duty of the State cannot be limited, mitigated or divided, since health as an individual, collective and development asset presupposes a complete approach to care" and providing integral care "means nothing more than privileging life to the detriment of the administration's budgetary interests – the so-called secondary public interest".[2]

Within this context, the Unified Health System (SUS) was designed to be the mechanism by which universal and equal access, as well as integral care, should be implemented. SUS must act according to these guidelines, not being able to impose any restrictions specifically directed to a particular group or class, nor can it privilege the administration's budgetary interests to the detriment of the right to life.

As observed by Resende[3] "the concept of health as a fundamental right in the international normative framework has been extended over the years to include, in addition to the negative idea of absence of disease, positive content related to the improvement in quality of life and wellbeing". According to the Bangkok Charter[4] for Health Promotion in a Globalized World, drafted at the VI Global Conference on Health Promotion in 2005, "The United Nations recognizes that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without discrimination. Health promotion is based on this critical human right and offers a positive and inclusive concept of health as a determinant of the quality of life and encompassing mental and spiritual well-being".

Access to health is a social right, guaranteed in Article 6 of the Constitution,[1] in accordance with the dignity of the human person, which is the basis of the democratic rule of law. The Constitution, said to be citizen-oriented, inaugurated a new legal order in the country that promotes the inclusion of millions of Brazilians who were excluded from any kind of healthcare.

Putting it into perspective, at the beginning of the 20th century, only those who integrated welfare funds had access to the health system. Even with the unification of the Institutes of Social Security Assistance, the so-called IAPs, and the creation of the National Institute of Social Security (INPS), there was still the exclusion of non-participants – non-taxpayers, a true legion of indigents.

SUS, observing the federative organization of the Brazilian State, was conceptually conceived as a solution, but after three decades, chronic problems of financing and management persist, jamming the gears of the world's largest system of universal access to healthcare, hampering the achievement of its original objectives. The gigantism of Brazil and the heterogeneity of the different regions impose the need for efficient management that can be capable of promoting, within the priorities of the State, the convenient allocative justice. Only with the adoption of consequent public policies and its capillarity in the whole country will it be possible to change the panorama of public health in Brazil.

In recent decades, as a consequence of the success of public policies, life expectancy has increased, and we are currently experiencing a real demographic transition. The growth in the number of elderly people is exponential, and it is estimated that this social segment will represent 25% of the Brazilian population in 20 years. The impact on social security is a challenge for the State, and requires increased attention, with the adoption of sustainable public policies, especially in the area of health.[4]

Non-communicable chronic degenerative diseases (NCDs) are responsible for more than 30% of global mortality and this context will be aggravated by the aging and sickness of the current population. As a matter of fact, there is no way to ignore that offering the resources needed for the expansion of health care, especially for the growing prevalence of NCDs, mainly in remote areas of a country such as Brazil,

Keywords

Comprehensive Health Care/legislation & jurisprudence; Personal Health Services/trends; Telemedicine; Unified Health System; Health Public Administration

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is a complex task. It will be a challenge, to be overcome, to bring health professionals – notably specialists – to the most distant corners of the country.[4]

On the other hand, there is a constant tension between the medical class and health authorities about the possible alternatives for the supply of doctors to society. This theme took on an epic battle line on the occasion of the sanction of Law 12.871, dated October 22, 2013,[5] which instituted the "*Programa Mais Médicos*" (More Doctors Program) in Brazil. The offer of doctors in the country, since the institution of this Program, has increased, mainly due to the increase in the number of medical schools opened in the country. However, the proportion of doctors per 100,000 inhabitants is still below the average of the countries in the Organization for Economic Cooperation and Development (OECD). It should be added that the distribution of these physicians is heterogeneous, aggravating this scenario.[6] In this sense, the use of information and communication technologies, through a Telemedicine network, could contribute to the universality and integrality of the health system, in line with the constitutional decree.

Telemedicine as a tool to expand universal access to health

The remarkable advancement of information and communication technologies and their application in medicine have enabled a secure transmission of data, facilitating the interaction of health professionals, opening a door for the democratization of access to medical knowledge, and strengthening collaboration among the various levels of healthcare.

Telemedicine can be conceptualized as an organized and efficient way of practicing distance medicine for the purposes of informing, diagnosing and treating individuals, alone or in groups, based on data, documents or other reliable information transmitted by means of telecommunications. Currently, the use of telemedicine has been increasing, ranging from consultations (teleconsultation), diagnosis (telediagnosis) to complex robotic surgeries (tele-surgery). All these advancements, which project the broader concept of digital health, must take place preserving the millennial postulates of medical art, always focused on the patient's best interests.[7]

Digital health interventions are not a substitute for the health systems already in place, as there are still significant limitations to what digital health is capable of addressing. However, the judicious use of this technology can contribute to improvements in health care, as long as it is based on the evaluation of its benefits, damages, acceptability and viability.[7]

When approaching the intricate subject of health-guaranteeing regulations, as a fundamental right, and of the application of information and communication technologies to promote the practice of distance medicine, the basis of Telemedicine, there is the need to defend the preservation of the patients' privacy. The inviolability of private life, such as the right to health, is also an inseparable part of the concept of the dignity of the human person.[1] Therefore, security in data transmission is imperative for the implementation of any Telemedicine program. The millennial principle of medical secrecy, valid since Hippocrates, is also a constitutional imposition.

The legal framework applicable to Telemedicine in Brazil is comprehensive, involving from the sanitary legislation to the recent internet regulatory framework to ensure its regular practice. Currently, international protocols ensure the secure transmission of data: the Health Insurance Portability and Accountability Act (HIPPA)[7] contains a set of standards that ensure the security of the data transported and of those responsible for its transmission.

Regulation of Telemedicine by the Brazilian Federal Council of Medicine

The Brazilian Federal Council of Medicine (CFM), an autarchic body established by Law 3.268, dated September 30, 1957,[8] is responsible for supervising professional ethics throughout the Republic and, at the same time, judging and disciplining the medical profession through supervisory and regulatory action. With a focus on these attributions, CFM is responsible for regulating the participation of doctors in activities related to the employment of Telemedicine throughout the country's territory.

Law 12.842,[9] dated July 10, 2013, the Medical Act, which provides for the practice of medicine, ratifies that the new medical procedures and therapies for regular use in Brazil must necessarily be evaluated by the Brazilian Federal Medical Council regarding safety, efficiency, convenience, and benefits to the patient. Telemedicine, with a myriad of employment possibilities in prevention, diagnosis, treatment and rehabilitation, as well as in health promotion, undoubtedly falls within and can be validated by CFM. Because of its innovative character, it brings a bioethical conflict potential, which imposes a zetetic – investigative – analysis of its principles, due to the clash between traditional ethics, which permeates the face-to-face relationship between doctors and patients, and the new frontier opened by the progress of information and communication technology.

The Brazilian Federal Medical Council, through Resolution CFM 1.643/2002,[10] provided for Telemedicine, defining it "as the exercise of Medicine through the use of interactive audiovisual and data communication methodologies, with the objective of health assistance, education and research". This regulation requires the use of appropriate technology and observance of the CFM's technical standards regarding data storage, handling and transmission, confidentiality, privacy and guarantee of professional secrecy. The role of doctors who participate in the professional act at a distance is restricted to emergencies, or when requested by the doctor in charge of administering in-person care.

In 2014, the CFM again expressed its views on the subject, through Resolution CFM 2.107/2014,[11] to discipline the use of Teleradiology. This Resolution updated the previous standard, published in 2009. The development of technology and the democratization of access to cellular telephony pluralized the development of applications dedicated to digital health. Current possibilities of employment of Telemedicine include several services, which include: (a) Teleconsulting, Teleinterconsulting, Telediagnosis, Tele-orientation, Telemonitoring, Tele-surgery and Medical Tele-Screening. Although part of these services is not explicitly regulated by the

CFM, there is an offer by specialized companies, especially in the scope of supplementary health, with the imperative need by such companies of their own administrative act.

In this sense, the CFM issued Resolution CFM 2.227/2018,[12] published in the Brazilian Federal Official Gazette on February 6, 2019, to update the current discipline. The resolution aimed to guarantee security to the provision of medical services mediated by information and communication technologies in Brazil. There is no doubt of the need to update the regulatory framework that disciplines the participation of doctors in the so-called Telemedicine. This measure legitimizes the doctor-patient relationship in the field of digital health. However, there was an avalanche of questions from the medical category about the form and merit of this standard.

In their article *Window to the future or door to chaos?*, Lopes et al.[13] discussed several aspects related to the legality and timeliness of Resolution CFM 2.227/2018, and the allowing of Teleconsultations was the most challenging question, precisely due to the flexibility of prescription without the direct examination of the patient, a conduct that is prohibited by the Brazilian Code of Medical Ethics.* For the authors, the regulation of CFM "should therefore represent a step forward, not a setback. Broadening access to public health is a common desire of all doctors. The major challenge of Resolution CFM 2.227/2018 would be having the effectiveness and applicability to move forward in the field of justice and deliberative ethics".

The avalanche of corporate questions from the medical category, among other reasons, motivated the revocation of this Resolution by CFM.[11] Thus, the use of telemedicine by doctors in Brazil must occur according to the provisions of Resolution CFM 1.643/2002.[10] It is noteworthy that there were problems in communication regarding the contents of the norm, generating an intense reaction from doctors in relation to the merit of the regulation.

In addition, as discussed by Lopes et al.,[13] CFM could not delegate exclusively to specialty societies the prerogative of developing guidelines on Telediagnosis. It is important to emphasize that Law 12.401, dated April 28, 2011,[9] defines that the elaboration of clinical protocols and therapeutic guidelines within SUS is a jurisdiction of the National Commission for the Incorporation of Technologies in SUS (Conitec). Therefore, CFM could not, on the basis of a normative resolution, exclude those who have legal jurisdiction to elaborate guidelines within the Brazilian health system, delegating this attribution exclusively to private entities, even if conditioned to their approval. Hence, whether in relation to Robotic Telesurgery or Telediagnosis, the revoked Resolution could be improved.

Difficulties for the implementation of digital health as a duty of the State

In this sense, we could imagine Telemedicine as a useful complementary tool to allow fair access to health for all Brazilians, regardless of ethnicity, gender, socioeconomic status and location in the national territory. It could be assumed, especially if we consider the continental dimension of Brazil, that populations living in remote areas would benefit from the State's investment in the dissemination of digital health.

According to the Brazilian Institute of Geography and Statistics (IBGE),[14] about 65% of the municipalities located in remote areas are located in the North and Midwest regions of the country. On the other hand, the study Demografia Médica no Brasil (Medical Demography in Brazil, 2018)[6] reported significant inequality in the distribution of doctors, who are predominately located in the large urban agglomerations of the South and Southeast Regions, which also concentrates the largest number of specialists, with he North and Northeast Regions having a lower medical/inhabitant density. If we also look at the issue from the perspective of care, through the National Register of Health Establishments (CNES)[15] of the Brazilian Ministry of Health, we can observe a greater concentration of medical activity in the Southeast and South Regions. It is also important to mention that there is a lower concentration of networks linked by fiber optics in municipalities in the North Region, and that mobile cellular telephone coverage for the Brazilian population is between 98 and 99%, with a higher concentration in the urban centers of the Southeast and South regions.[16,17]

It is understood that, although the demand for medical services in remote areas is an opportunity, the provision of Telemedicine services to these areas presents a great implementation challenge similar to the universal access to traditional health services. The expansion of Telemedicine would have to be preceded by improved digital technology infrastructure.

On the other hand, through the International Telecommunication Union (ITU),[18] the United Nations has been working with the World Health Organization (WHO) to stimulate the reduction of the global digital divide, with the e-health strategy, focused on digital health, via Telemedicine.

Investments in digital health have generated a number of WHO publications. Examples are the Digital Health Atlas,[19] a virtual global repository to support governments in monitoring and coordinating digital investments, BeHe@lthy, BeMobile (BHBM),[20] for prevention and control of NCDs, mHealth Assessment and Planning for Scale (MAPS), a manual for monitoring and evaluation of digital health,[21] aimed at strengthening the research and implementation of digital health, and the first WHO Digital Health Interventions Guideline.[22] The latter document[22] suggests that most of the available scientific evidence on the benefits of implementing global digital health is still not robust, and that there are numerous gaps for large-scale use, albeit in a complementary way to traditional methods. The WHO recommends that a planned process should take place, including: the feasibility of network coverage for access to remote locations, the construction of the legal framework for its implementation, the budget impact and the cost-effectiveness evaluation of each stage of the project's implementation, with the elaboration of indicators of the clinical continuum of applicability for the safety of users.

Telemedicine to reduce inequalities in the approach to NCDs

Telemedicine, if applied in its broad context, could allow access and equity, offering quality services with supposed cost-effectiveness, especially considering the increase in the prevalence and mortality of NCDs, of which cardiovascular diseases (CVD) are its main component.

There were 55.9 million deaths worldwide in 2017 in an estimated world population of 7.64 billion people.[23] Of these, 70% were due to NCDs, and are expected to continue to increase in the coming decades, especially in low- and middle-income countries, even though all-cause mortality has decreased, notably due to the reduction of infant and child mortality of children under 5 years, stabilization of mortality from 5 years to 49 years and increase in life expectancy.[23] The increase in NCDs is expected with the aging of the population, with the control of communicable diseases and with the increase of premature mortality in individuals from 30 to 70 years of age.[24]

In Brazil, NCDs were responsible for about 60% of deaths in 2017, according to the Department of Informatics of the Unified Health System (DATASUS),[25] noting that this group of diseases shares the same risk factors and social determinants. The severity of the issue is large enough to set targets for 30% reduction of premature mortality by NCDs as part of the Sustainable Development Goals (SDG) for 2030.[26,27] It is also believed that one-third of the populations of the Americas do not have access to health care, and that an additional 800,000 health workers would be needed to meet the demands of health systems in the region.[28]

The combined approach to NCDs and their risk factors was considered a cost-effective package by WHO, requiring investment of USD 1 per capita in low-income countries, USD 1.5 in low-middle-income countries, and USD 3 in average income countries, underscoring the importance of joint study of NCDs.[29] According to the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, "leveraging the power of digital technologies will be essential to achieving the Global Sustainable Development Goals, including universal health coverage, and that such technologies are no longer a luxury, but a necessity". He also suggests that we make sure that innovation and technology alleviate inequalities, and that countries must be guided by evidence to establish harmonized digital systems, and not be seduced by the novelties.[30]

The World Health Assembly resolution on Digital Health, unanimously adopted by WHO Members in May 2018, demonstrated collective recognition of the value of digital technologies in contributing to the advancement of universal health coverage, with an emphasis on NCDs, and recommended that health ministries evaluate the use of digital technologies dedicated to health, prioritizing development, evaluation, implementation and increased use of these technologies, as well as guiding their standardization, including through the promotion of digital health interventions. However, it was pointed out that, in order to reduce health inequalities, a rigorous evaluation of eHealth strategies would be necessary in order to generate evidence and promote the appropriate integration of the use of these technologies.[18]

Recommendations of the Telemedicine Directive of the Brazilian Society of Cardiology for cardiovascular health

To guide the practice of Telemedicine in CVD, Lopes et al. developed the Telemedicine Directive of the Brazilian Society of Cardiology,[31] with the objective of discussing legal and ethical support, technical conditions and priority for implementation, cost-effectiveness and budget impact for the use of Telemedicine for the cardiovascular health of the Brazilian population.

It was found that there is space for Telemedicine initiatives as a specialist matrix support for general practitioners and family health doctors in basic health units in remote areas of the Brazilian territory, especially with regard to diagnostic methods, avoiding unnecessary displacements with additional burden to the health system. The clinical and economic results obtained with public policies focused on digital health in Brazil suggest that technologies that allow patient monitoring (telemonitoring) and the issuance of remote reports (Telediagnosis) applied to cardiology can be cost-effective, with an acceptable impact on the public budget. However, the set of scientific evidence in Brazil is still limited, given the small number of patients involved, to infer that the application in subgroups of clinical interest should be generalized.

The benefits of this technology could be equally applicable to supplemental health in Brazil, even in the face of a diverse regulatory framework, and of the appropriate coverage of face-to-face social assistance. It should be noted that the majority of the beneficiaries of supplementary health reside in larger centers, where the ratio of doctors/specialists per inhabitant is appropriate, and consultations in person are a legal imposition.

Telemedicine may be an important incremental tool in supplemental health, provided there is additional regulation for its implementation. Among the possible measures to extend the scope of Telemedicine in supplementary health, as already exists in American Medicare, would be the inclusion of technologies, with scientific and legal basis, in the Health Procedures and Events List of the National Supplementary Health Agency, since coverage would be mandatory, providing equity and legal certainty.

It is recommended that the bases established by the Brazilian Code of Medical Ethics be maintained in the Telemedicine and Telecardiology procedures. Telemedicine should be considered an additional tool for the face-to-face physician-patient relationship, without ever replacing it.

Conclusion

Telemedicine as a means of increasing universal and integral access to health, backed by solid evidence, attested by the scientific community, within the budgetary capacity of the Brazilian State, expressed in legitimate public policies, integrates the existential minimum of each Brazilian citizen. It is, therefore, a universal right and duty of the State, and must be guaranteed through social and economic policies in force in the country. The remarkable advance of information and communication technologies and their application in health must be a constant focus of attention of the public authorities, being an instrument of equity and fostering the dignity of the human person. The use of technology in medicine emphasizes the duty of due care to preserve patients' privacy and the transcendent values that underlie the practice of Medicine.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of

the manuscript and Critical revision of the manuscript for intellectual content: Lopes MACQ, Oliveira GMM, Maia LM.

Potential Conflict of Interest

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Case 5/2019 — Naturally Evolving Ebstein's Anomaly of Discrete Repercussion in 24-Year-old Asymptomatic Adult

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Clinical data

Patient reports 3 episodes of paroxysmal tachycardia of up to 20 minutes, accompanied by precordial pain in the past 7 years, all with spontaneous reversal. Four years prior, the patient presented another tachycardia with signs of low output, including pallor, visual turbidity, cold extremities and mental confusion, requiring electrical reversion. On that occasion, ventricular tachycardia ablation in the right ventricular (RV) inflow tract through the right posterior accessory pathway was successfully performed. Ebstein's anomaly diagnosis was given for the first time by echocardiography scan, at that time. Ever since, the patient remained asymptomatic, living a normal life and with no medication.

Physical examination: Good general condition, eupneic, acyanotic, normal pulses in the 4 limbs. Weight: 80 kg, Height: 180 cm, BP: 110 x 70 mmHg, HR: 70 bpm, Sat O_2 = 94%.

Precordium: Apical impulse not palpated, with no systolic impulses. Normal heart sounds, with irregular splitting of the second heart sound. There were discrete systolic vibrations in the lower left sternal border. Unpalpable liver and clean lungs.

Complementary tests

Electrocardiography: Sinus rhythm with right bundle branch conduction disorder, with polyphasic QRS complexes at V1 and thickened S waves from V4 to V6. Normal ventricular repolarization. AP = + 60º, AQRS = -10º, AT+ + 60º. (Figure 1).

Chest X-ray: Normal cardiac area (CTI = 0.44) and normal pulmonary vasculature. The medial arch is rectified and the aortic knob slightly protruding (Figure 1).

Echocardiography: Normal atrioventricular connection with the tricuspid valve presenting apical implantation of its septal and posterior valves, inducing atrialization of a portion of the RV. There was a slight regurgitation of this valve and the heart cavities were normal in size. Aorta = 16, LA = 29, RV = 22, LV = 42, septum = posterior wall = 8 mm, LVEF = 60% (Figure 2).

Nuclear magnetic resonance imaging: Normal cardiac chambers. Tricuspid valve sitting low, 25 mm from the mitral annulus plane with atrialization of a portion of the RV cavity. RV diastolic volume was 53.5 ml. RV function was preserved (45%) as well as left ventricular function (73%). There was no late enhancement.

Holter: Supraventricular extrasystoles (3% of the total) and no supraventricular or ventricular tachycardias.

Ergospirometry: Maximum oxygen consumption of 40.1 ml/kg/min.

Clinical diagnosis: Ebstein's anomaly with pronounced displaced of the septal and posterior valve but with minimal tricuspid valve regurgitation in an asymptomatic adult with previous ventricular ablation of anomalous right posterior pathway.

Clinical reasoning: There were no clinical elements of diagnostic orientation of Ebstein's anomaly, given the absence of characteristic elements, mainly represented by tricuspid regurgitation. The displaced septal and posterior valves were well coupled to the extent of preventing regurgitation to the right atrium, hence the discrete repercussion of the congenital defect. The only retrospective diagnostic element was the anomalous right posterior pathway, which is common in Ebstein's anomaly, which often causes supraventricular paroxysmal tachycardia. Diagnosis was well established by echocardiography and nuclear magnetic resonance imaging.

Differential diagnosis: Other heart diseases of discreet repercussion can also be presented this way. Hence the diagnostic difficulty in acyanogenic cardiopathies, such as atrial septal defect and persistent ductus arteriosus without heart murmurs, with complementary tests showing no abnormal findings. Interventricular septal defect usually shows a characteristic systolic murmur at the left sternal border, as well as obstructive defects such as pulmonary and aortic stenosis and aorta coarctation.

Management: As the clinical repercussion it is shown to be discreet, with no harm to ventricular function or blood disorders, with good balance of pulmonary and systemic flows over time, no signs of hypoxemia and/or heart failure and good physical tolerance, clinical expectant management was considered.

Comments: The natural evolution of this patient to adulthood demonstrates favorable elements in good clinical and hemodynamic conditions, except for the presence of anomalous bundles that could be eliminated by ablation. There were no acquired characters resulting from Ebstein's anomaly, which is so common in this anomaly, from evolutionary time to adulthood. This is because this patient had no significant tricuspid regurgitation due to perfect fit of the septal and posterior tricuspid valves, although clearly sitting low in the RV cavity. Since deterioration has not been expected, expectant management is undoubtedly the most appreciated one.

Similarly rare cases have been reported, a 56-year-old atrial flutter reversed with drugs;[1] a 36-year-old with paroxysmal tachycardia controlled with drugs;[2] and a 87-year-old

Keywords

Ebstein Anomaly; Tachycardia,Paroxysmal; Cardiac Output,Low; Tricuspide Valve Insufficiency; Echocardiography/methods; Magnetic Resonance Spectroscopy/methods.

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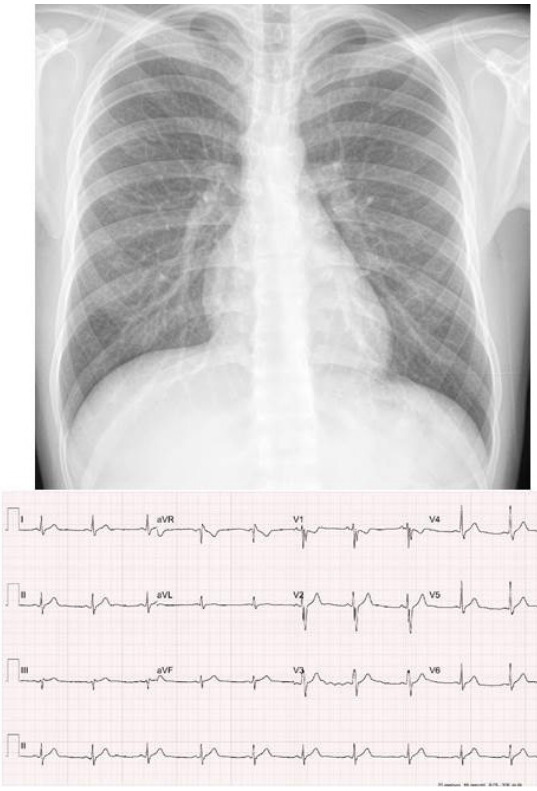

Figure 1 – *Chest X-ray emphasizes the cardiac area and the pulmonary vasculature within normal limits. The medial arch is rectified and electrocardiogram with signs of discrete final right bundle branch conduction disorder.*

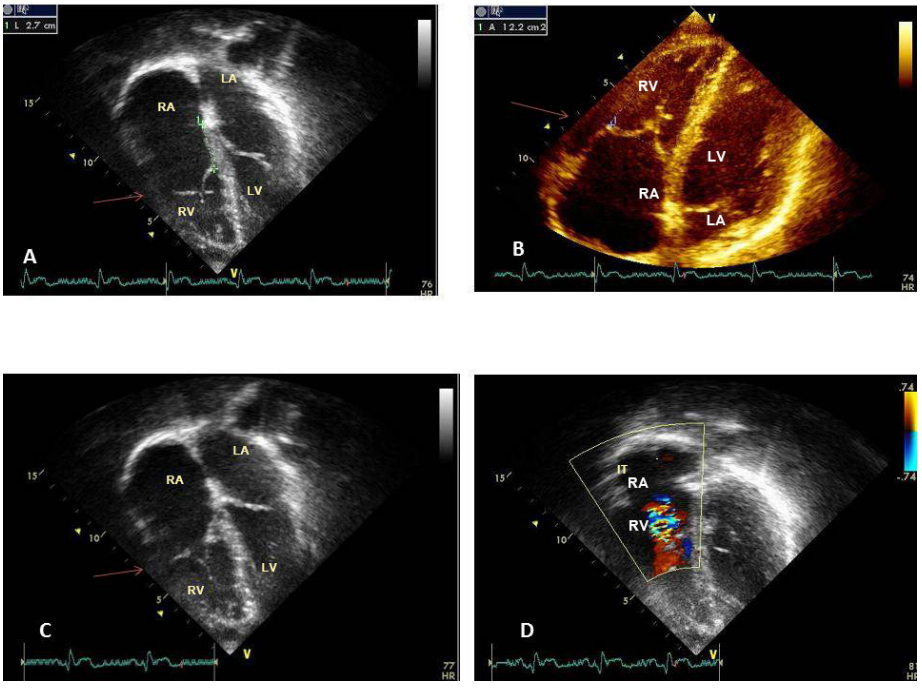

Figure 2 – *Echocardiogram shows, in the 4-chamber subcostal section, the septal and posterior valves sitting below the atrioventricular valvular plane, but with good coaptation in A, B, and C, and discrete tricuspid valve regurgitation in D. RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle.*

reversed after ablation of accessory pathways.[3] A 62-year-old asymptomatic patient, despite anatomical disorders.[4] Another one with long survival described in the literature, who decompensated with tricuspid regurgitation at 79 years of age.[5]

This unique rare case in view of good clinical evolution, despite the clear congenital anomaly, makes us think about the surgical approach adopted in similar cases and at earlier ages, which could progress in the same way.

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Immobile Tricuspid Valve: Incidental Finding in a Case of Terminal Cardiomyopathy Due to Thalassemia Major

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Introduction

Thalassemia Major is an inherited disorder caused by impaired synthesis of the B globin chain and characterized by ineffective erythropoiesis that requires regular, lifelong transfusion therapy, which creates a state of iron overload.[1] Once reticuloendothelial stores saturate, iron deposition increases in myocardium such as other parenchymal tissues.[2] Cardiac complications due to this deposition are the leading cause of death. After a silent first decade, iron deposits in the cardiac tissue lead to arrhythmias, systolic and diastolic dysfunction, and congestive heart failure in the second or third decade.[3] In this case report, we present an adolescent girl who did not receive regular iron chelation therapy and had cardiomyopathy, arrhythmia and immobile tricuspid valve secondary to thalassemia major.

Case presentation

A 14-year-old Syrian girl with Thalassemia Major presented to the emergency room with a three-month history of increasing fatigue, dyspnea, and abdominal distension. Her medical history revealed that she had been diagnosed with Thalassemia Major at the age of one year old, and she received irregular erythrocyte transfusion and iron chelation therapy in her country. It was learned that the compliance for previous blood transfusion and chelation therapy was very poor. On general examination, she was undernourished with short stature (body weight < 25 p, height < 3p) and the physical examination revealed dyspnea with a typical facial thalassemic feature without cyanosis.

Chest x-ray showed areas of consolidation on both sides of the lungs and increased cardiothoracic ratio (Figure 1). The electrocardiogram showed sinus rhythm with 70/min heart rate and prolongation of QTc value with 0.46 seconds (Figure 2-A). Transthoracic echocardiography revealed both ventricle systolic and diastolic ventricular dysfunction, left ventricle ejection fraction was 48% and fractional shortening was 24% were calculated with a mild left ventricle dilatation (Table 1). Mild-moderate mitral regurgitation and trivial pericardial effusion were also observed. Right ventricular inflow view in systole showing thickened, immobile leaflets of tricuspid valve in a fixed open position, causing mal-coaptation and severe regurgitation without stenosis (see Figure 3 and Video 1). Apical four-chamber view in diastole showed immobile leaflets of tricuspid valve in a fixed open position, as showed by the color Doppler (Video 2) (See additional files Video 3, 4 and 5). Right atrial, right ventricle dilatation and minimal pulmonary regurgitation with mild pulmonary hypertension were also observed.

After hospitalization in the intensive care unit, inotropes, diuretics and iron chelation treatment (Dopamine, Dobutamine, Furosemide infusion, Propranolol, Enalapril, Aldactone and Deferoxamine, Deferiprone therapy) started as soon as possible. Cardiac enzymes were sent to screen possible myocarditis, and D-dimer was sent to detect pulmonary thromboembolism. Results were found to be negative. On the seventh day of hospitalization, the electrocardiogram showed

Table 1 – Echocardiographic measurements of the patient

Data	Values
M-Mode Measurements	
LVID, cm	4.9
Ejection Fraction	48
Fractional shortening, %	24
RVID, cm	4.8
Doppler Measurements	
Tricuspid E, cm/s	81
Tricuspid A, cm/s	25
Tricuspid E/A	3.2
Tissue Doppler Measurements (RV)	
E' cm/s	12.1
A' cm/s	7.8
E'/A'	1.55
E/E'	6.7
S'	11.4
IVCT, ms	65
IVRT, ms	78
RV MPI	62

A: peak late diastolic velocity; A': late diastolic velocity; E: peak early diastolic velocity; E': early diastolic velocity; ET: ejection time; IVCT: isovolumic contraction time; IVRT: isovolumic relation time; LVIDd: Left ventricular internal diastolic diameter; MPI: myocardial performance index; RV: right ventricle; RVID: right ventricular internal diameter; S': systolic velocity; Tissue Doppler imaging of the tricuspid valve.

Keywords

Cardiomyopathies; beta-Thalassemia/genetics; delta-Thalassemia/genetics; Arritmias Cardíaca; Tricuspid Valve/abnormalities; Echocardiography/methods.

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Case Report

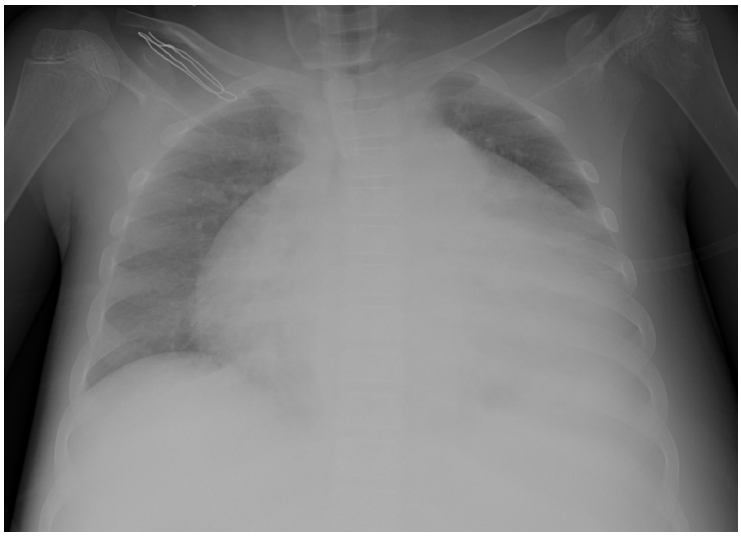


Figure 1 – *Chest X-Ray of the patient.*

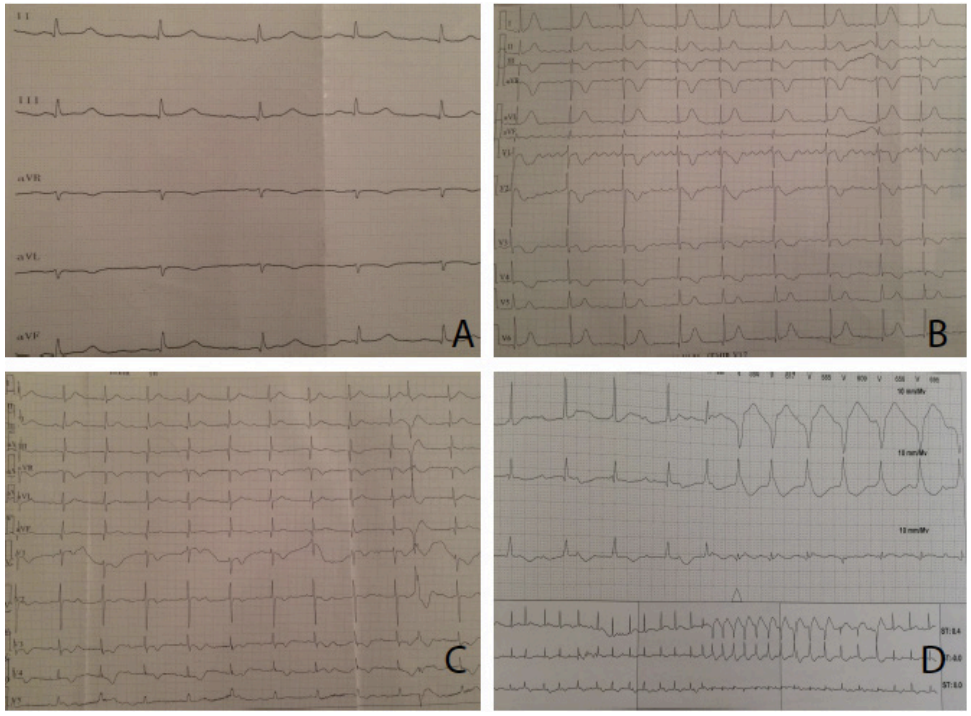


Figure 2 – *Electrocardiography of the patient. (A). Sinus rhythm with QTc prolongation (B). Atrial flutter (C). Atrioventricular dissociation and ventricular extra-systole (D). Holter monitorization revealed non-sustained ventricular tachycardia.*

atrial flutter (Figure 2-B). Therefore, digoxin and low molecular weight heparin treatment were also started. In the second week, the patient developed acute renal insufficiency and the electrocardiogram showed atrioventricular dissociation and ventricular extra-systole (Figure 2-C). Immediately after the digoxin treatment had been stopped, amiodarone infusion has started. Holter monitorization revealed atrioventricular dissociation and non-sustained ventricular tachycardia (Figure 2-D). Blood level of Digoxin was within normal reference values. Serial echocardiography was performed and no difference has been observed in the cardiac parameters during the hospitalization. Despite atrioventricular dissociation, we decided to follow-up her without pacemaker implantation due to hemodynamic stability. Although secondary prevention

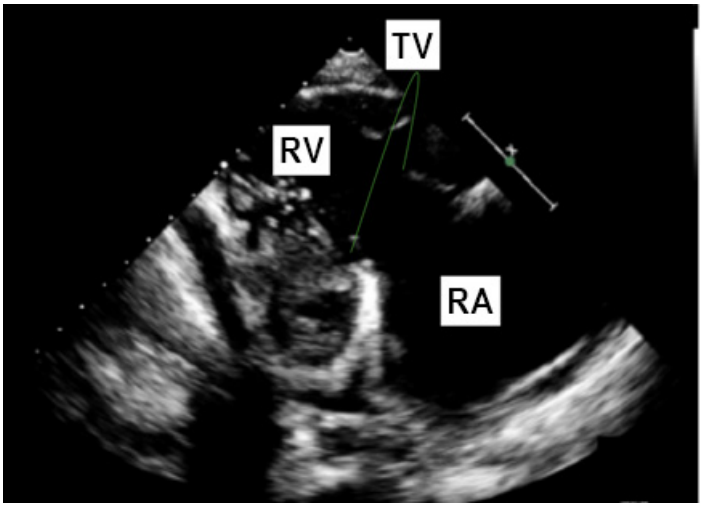
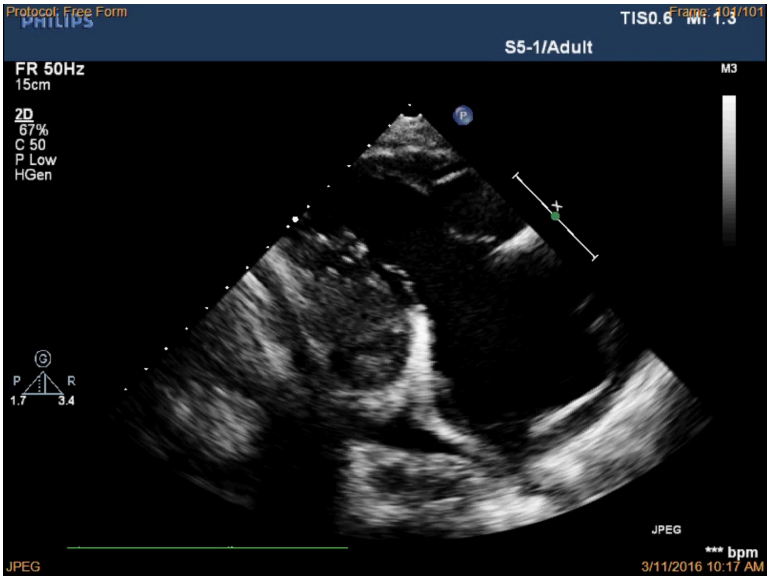


Figure 3 – *Transthoracic echocardiography from the parasternal view by tilting transducer inferomedially exploring the right atrium (RA) and right ventricle (RV) inflow tract; immobile leaflets of the tricuspid valve (TV) leading to severe insufficiency.*



Video 1 – *Transthoracic echocardiography from the right ventricular inflow view in systole showing immobile leaflets of tricuspid valve in a fixed open position, causing mal-coaptation and severe regurgitation. To view the video click on the link: https://bit.ly/2lTc6iX*

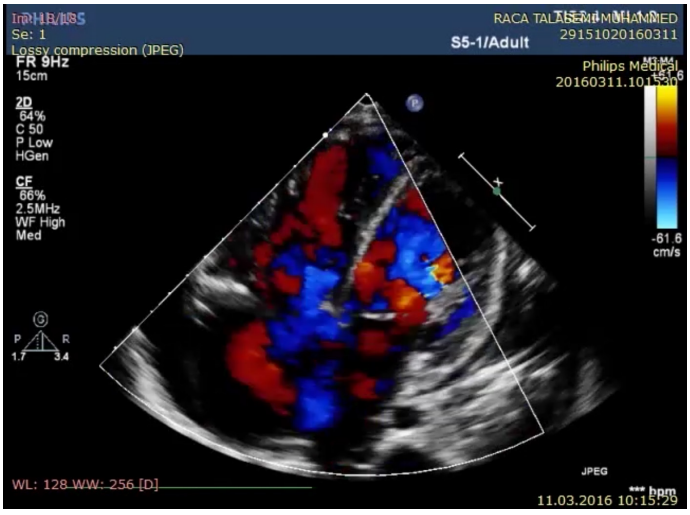
of implantable cardioverter defibrillator was decided after the patient was taken to control ventricular arrhythmias with amiodarone, she died due to ventricular tachycardia on the 22nd day of hospitalization.

Discussion

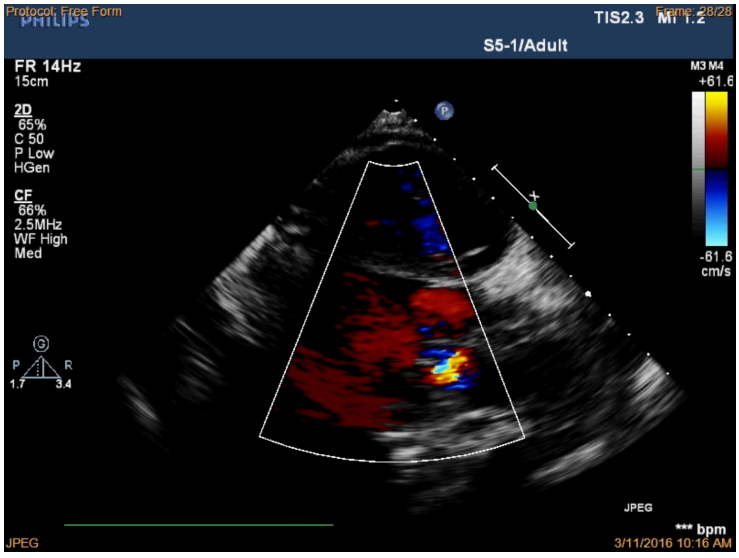
In thalassemia, cardiovascular system involvement is pivotal in the prognosis and quality of life. Iron overload cardiomyopathy is the leading cause of mortality accounts up to 67% and 71% in thalassemia.[4] As iron overload, multiple factors such as chronic anemia, hypersplenism, non-progressive restrictive lung disease also lead to cardiac complications in Thalassemia Major.[5] Iron is mainly stored in myocytes and other cells in the form of free iron, also ferritin and hemosiderin. Free iron, which is referred to as labile cellular iron, is the most toxic form of iron and also the most accessible form for chelation. The goal of iron chelation therapy is to reduce the iron deposition especially in plasma and other tissues. In some cases, these heart complications were reported as reversible with early detection of iron overload and response to regular iron chelation therapy.[6]

Cardiac magnetic resonance imaging (MRI) is the gold standard for detecting myocardial iron deposition. In our case, cardiac MRI was not performed due to lack of experienced staff in our hospital. Progressive increase of brain natriuretic

Case Report



Video 2 – *Transthoracic echocardiography from the apical four-chamber by color Doppler view showed immobile leaflets of tricuspid valve in a fixed open position. To view the video click on the link: https://bit.ly/2ITc6iX*

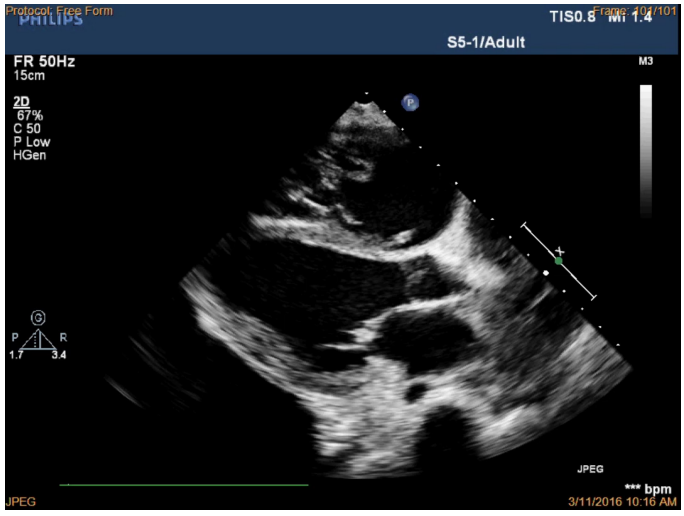


Video 3 – *Transthoracic echocardiography from the parasternal long axis view with color Doppler showing mild mitral regurgitation. To view the video click on the link: https://bit.ly/2ITc6iX*

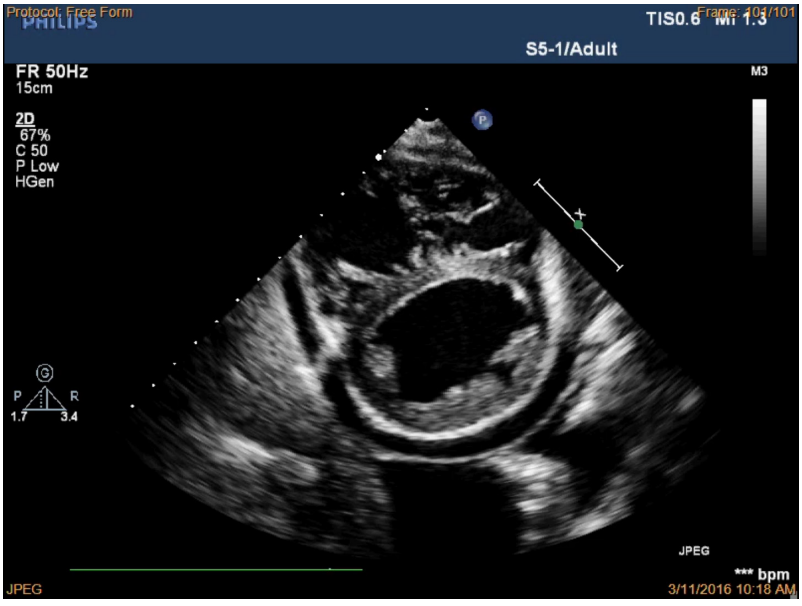
peptide assay is highly sensitive and specific in the diagnosis of heart failure. In our patient, brain natriuretic peptide levels were markedly elevated.

Conventional standard echocardiography exhibits pathologic findings at advanced stages of cardiac involvement. The assessment of the ventricular function involves two different phenotypes. The first one is 'dilated cardiomyopathy' phenotype revealed by with left-right ventricular dilatation and reduced contractility, which cause congestive heart failure. The second one is 'restrictive cardiomyopathy' phenotype revealed by restrictive left-right ventricular filling resulting in pulmonary hypertension, right ventricular dilatation, and heart failure.[7]

In this report, our patient had impaired cardiac functions similar to both dilated and restrictive patterns of cardiomyopathy. Right, and left ventricle contractility was reduced which led to congestive heart failure. Both ventricle diastolic dimensions were increased. Assessment with pulsed and pulsed tissue Doppler demonstrated left and right ventricle diastolic dysfunction. Factors that may cause pulmonary hypertension in patients with thalassemia include elevated pulmonary resistance due to high volume of blood flow, elevated shear forces, hypercoagulable state secondary to splenectomy and nitric oxide formation after chronic hemolysis. Although right heart failure may develop secondary to pulmonary hypertension, in thalassemic patients, it may also develop in the absence of elevated pulmonary hypertension.[8]



Video 4 – *Transthoracic echocardiography from the parasternal long axis view showing normal systolic function of the left ventricle and minimal pericardial effusion. To view the video click on the link: https://bit.ly/2ITc6iX*



Video 5 – *Transthoracic echocardiography from the parastrenal short axis view showed enlargement of the right ventricle and pericardial effusion. To view the video click on the link: https://bit.ly/2ITc6iX*

In our case, typical stenotic changes and doming that seen in rheumatic diseases were not present in the tricuspid leaflet. Uniformly, mildly thickened tricuspid leaflets were present with a relatively fixed valve orifice without stenosis. Cardiac carcinoid usually affects the right cardiac chamber of the heart and results in a similar presentation. However, it is not reported in the pediatric age group in the literature. Nevertheless, carcinoid tumor should also be considered as a differential diagnosis in isolated advanced tricuspid valve involvement.[9] In our case in contrast to the carcinoid tumor, the tricuspid valve did not exhibit very bright echoes secondary to fibrous plaques that are deposited on the endocardium of the leaflets.[10] Biogenic amine levels in plasma and urine samples were found to be in the normal range that excluded diagnosis of carcinoid tumor. The related literature indicates similar findings in patients with thalassemia; however, illustration of echocardiograms in children is not satisfactory. Aessopos et al.[6] reported valvular involvement including leaflet thickening (48%), endocardial calcification (20%), and left-sided valve regurgitation in adult patients with thalassemia intermedia.[6] In our case, the patient had serious dysrhythmias due to endocardial involvement, contraction and relaxation

dysfunction due to myocardial involvement, and severe leaflet disorder due to valvular involvement. We herein report an extraordinary thalassemia major patient with immobile and non-stenotic tricuspid valve that emerges as a part of the terminal phase of the cardiomyopathy.

Conclusion

Thalassemia major patients, especially those who do not receive regular chelation therapy, are under great risk of cardiac involvement. Early detection and regular treatment regimen enhance their survival and quality of life. We firstly present an immobile tricuspid valve in an adolescent girl. This very rare case of severe cardiac findings due to iron deposition is associated with endocardial, myocardial and valvular involvement. In patients with thalassemia, these end-stage complications of the cardiovascular system are irreversible despite treatment.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript abnd Critical revision of the manuscript for intellectual content: Cilsal E.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

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Double-Inlet Single Ventricle with Malposed Great Arteries

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A 62-year-old man came to the Echocardiography Service with a history of arterial hypertension and systolic murmur in the mitral area. At the subsequent evaluation, the patient reported dyspnea and fatigue on moderate exertion, but without an impact on social life. Peripheral oxygen saturation at rest ranged from 95% to 98%; extremities were warm and perfused, with no signs of peripheral hypoperfusion; cyanosis and digital clubbing were absent.

The echocardiogram disclosed a case of levocardia, with the presence of a double-inlet single ventricle with transposition of the great arteries (Figures 1, 2 and 3), with *situs solitus*, enlargement of the atrial chambers associated with significant mitral regurgitation due to annulus dilatation.

The anatomical preservation of the two atrioventricular valves was observed, as shown in Figure 1. It was not possible to define the type of ventricle from a morphological perspective, but increased dimensions and moderate contractile dysfunction were observed. The presence of pulmonary stenosis with a maximum gradient of 56 mmHg was observed, as depicted in Figure 4.

The single ventricle refers to an uncommon condition that corresponds to 1.5% of congenital heart diseases, in which a single pumping chamber receives the inflow of the two atria,[1,2] being uncommon in oligo- or asymptomatic elderly individuals, without previous surgical correction. A second rudimentary chamber may be present, but there is no functional entry.[1] Based on the morphology, location and the trabeculation pattern of the pumping and rudimentary chambers, the heart is referred to as right, left or undetermined univentricular heart,[3] as in the present report. The most common form of single ventricle is the left ventricular type, where the ventricle connections are variable;[4] in this case, there was also transposition of the large vessels.

The echocardiography was essential for the diagnosis of double-inlet single ventricle, but it is not always possible to establish the type of ventricle, i.e., whether it is right or left, since it becomes difficult to be certain there is no second rudimentary ventricle. In these cases, magnetic resonance imaging is required for diagnostic complementation.

Keywords

Transposition of great vessels/ surgery; Mitral Valve Insufficiency; Diagnosis, Imaging; Echocardiography, Doppler/ methods; Aged.

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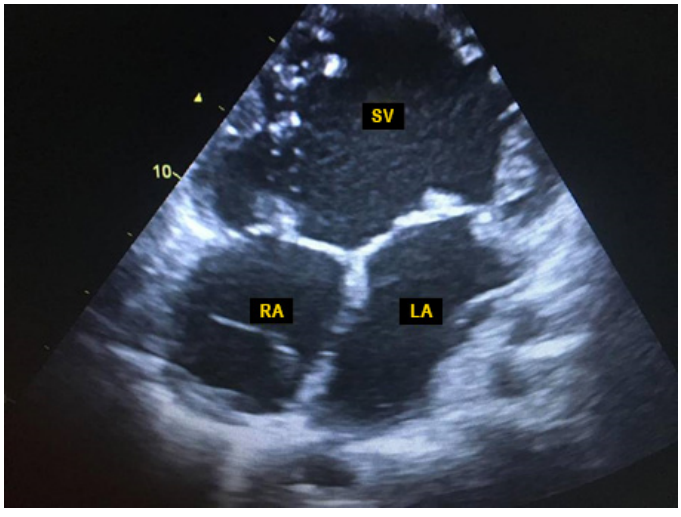

Figure 1 – *Transthoracic echocardiography: apical view, showing single ventricle and no evidence of recorded interventricular septal tissue. 254x190mm (96x96 DPI).*

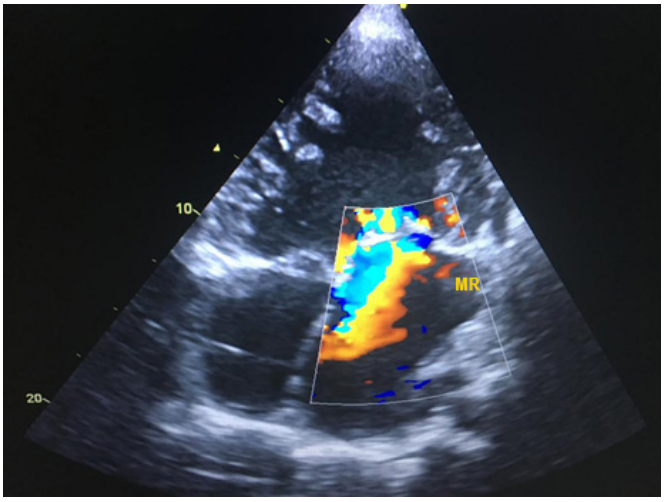

Figure 2 – *Transthoracic echocardiography: apical view, demonstrating two atrioventricular valves, interatrial septum and mitral regurgitation. 361x270mm (72x72 DPI).*

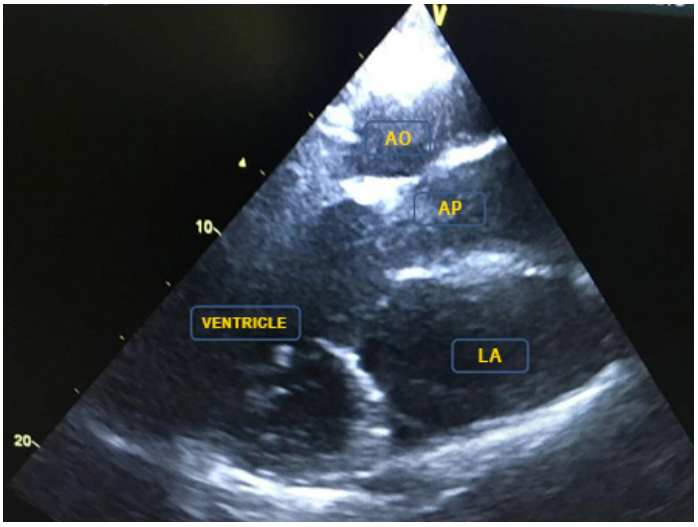

Figure 3 – *Long axis, parasternal view showing the transposition of the great arteries. 254x190mm (96x96 DPI).*

Author contributions

Conception and design of the research: Andrade P; Acquisition of data: Almeida A; Analysis and interpretation of the data: Santos D, Moreira M.

Potential Conflict of Interest

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Sources of Funding

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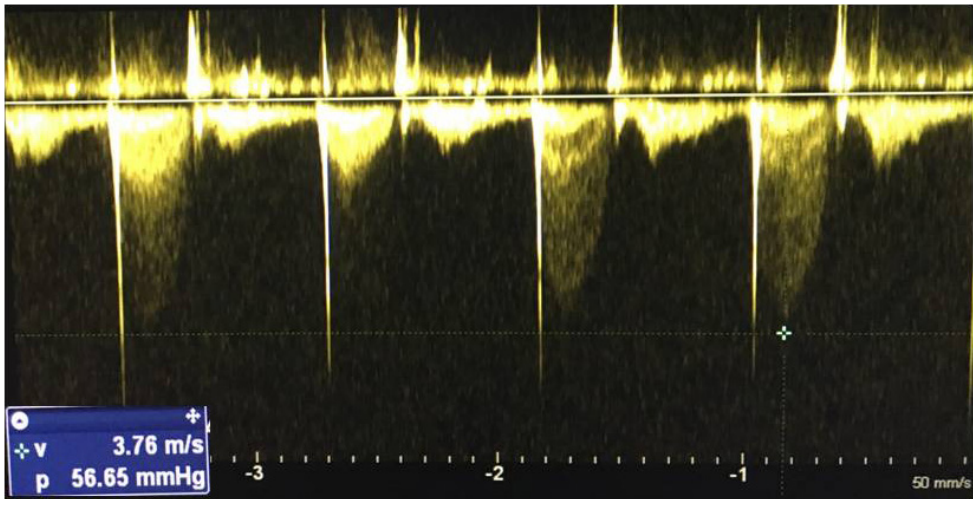

Figure 4 – *Pulmonary gradient. 254x190 mm (96x6 DPI).*

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