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HYPERTENSION IN TRANSLATIONAL CARDIOLOGY

A HIPERTENSÃO E A CARDIOLOGIA TRANSLACIONAL

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ABSTRACT

The acceleration of the transfer of knowledge to application began symbolically in the 1940s, with the development of the atomic bomb by a notable group of physicists. In that same period, the knowledge transferred from Stanford University led to the creation of Silicon Valley, where the electronic industry was developed with the application of transistors. Soon afterwards, major universities created incubators and technology parks in order to accelerate the transfer of knowledge to application, inaugurating the concept of Translational Research. In the field of Medicine, the transfer systematization process began in 2000, with important funding from the US National Institute of Health, creating Translational Medicine. In this review, two examples of Translational Medicine (Translational Cardiology) from research by our Hypertension team of the Heart Institute (InCor) are presented. The first illustrates the feedback between basic and clinical research, studying the influence of the hyperactivity of the angiotensin converting enzyme in the development of clinical cardiac hypertrophy (polymorphism of the ACE gene) and in mice with one, two, three and four copies of the converting enzyme gene, submitted to swimming or aortic coarctation. The second illustrates the transfer of knowledge obtained in the clinical investigation to clinic practice with a multicenter trial (25 centers in Brazil) on the prevalence of resistant hypertension in the Brazilian population, and the comparison of clonidine and spirolactone as a forth drug to be administrated in resistant patients: Multicenter Study of Patients with Arterial Hypertension for Identification of Resistant Patients and Standardization of the Therapeutic Regimen. Both examples illustrate the importance of institutions (in this case, InCor) in providing a favorable environment and conditions for professionals from different disciplines (clinicians, physiologists, molecular biologists, bioengineers, nurses, nutritionists, physiotherapists, physical educators, etc.) to work in an integrated way and practice Translational Cardiology.

Keywords: Hypertension; Basic research; Research translational.

RESUMO

A nova fase de aceleração da transferência de conhecimento para a aplicação foi, simbolicamente, iniciada na década de 40, com o desenvolvimento da bomba atômica por um grupo notável de físicos. Na mesma época, o conhecimento transferido na Universidade de Stanford cria o Vale do Silício, onde se desenvolveu a indústria eletrônica com aplicação dos transistors. Logo, importantes universidades criam incubadoras e parques tecnológicos para acelerar a transferência do conhecimento para a aplicação, inaugurando-se a assim chamada Pesquisa Translacional. Na Medicina, só a partir do ano 2000, e com importante financiamento do National Institute of Health dos Estados Unidos, é que se inicia o movimento, sistematizando a transferência e criando-se a Medicina Translacional. Nessa revisão, apresentaremos dois exemplos de Medicina Translacional (Cardiologia Translacional) provenientes de pesquisas do nosso grupo de Hipertensão do Instituto do Coração (InCor). O primeiro ilustra a retroalimentação entre a pesquisa básica e a clínica, estudando a influência da hiperatividade da enzima conversora da angiotensina no desenvolvimento da hipertrofia cardíaca clínica (polimorfismo do gene da ECA) e em camundongos com uma, duas, três e quatro cópias do gene da enzima conversora, submetidos a natação ou coarctação da aorta. O segundo ilustra a transferência do conhecimento obtido na investigação clínica para a prática médica, com um estudo multicêntrico (25 centros do Brasil) sobre a prevalência da hipertensão resistente na população brasileira e a comparação da clonidina e espirolactona como quarta droga a ser administrada nos pacientes resistentes: Estudo Multicêntrico de Pacientes com Hipertensão Arterial para Identificação de Pacientes Resistentes e Padronização de Esquema Terapêutico. Os dois exemplos ilustram a importância das instituições (no caso, o InCor) propiciarem condições e ambientes favoráveis para que os profissionais de diferentes disciplinas (clínicos, fisiologistas, biologistas moleculares, bioengenheiros, enfermeiros, nutricionistas, fisioterapeutas, educadores físicos etc) trabalhem integrados e pratiquem a Cardiologia Translacional.

Descritores: *Hipertensão; Pesquisa básica; Pesquisa translacional.*

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INTRODUCTION

The relationship between knowledge and translational application of knowledge has always existed. Our hunter ancestors were successful in the creation of agriculture about ten thousand years ago through a long process of maturation and transmission of knowledge accumulated for generations. Only with the Greek miracle at 300 years BC, with Aristotle as its prime example, did mankind systematically begin to seek knowledge for the sake of knowledge, in order to better understand who we are and our place in nature, without the concern for immediate application of such knowledge. The accumulation of knowledge in the Middle Ages was slow until the Scientific Revolution led by Galileo in the sixteenth century, when the Scientific Method and Experimentation, as we know it today, were created. Experimentation was a powerful instrument that exponentially increased the store of practical knowledge and led to the Industrial Revolution in the eighteenth century. With Louis Pasteur (1822-1895) we have a fine example of the same process of creation of knowledge (he is considered the father of microbiology) with its application in Agriculture (food fermentation) and Medicine (vaccines).

The atomic bomb created in the 40s, during the Second World War, gave symbolic birth to a new phase in the temporal relationship among creation, knowledge, and application. Notably, it was the integration of physicists from different disciplines who together accelerated the transfer of basic knowledge to create the atomic bomb. At the same time, there was a need to create new technologies with military applications (transistor) that spurred the creation of Silicon Valley in San Jose, California, with knowledge coming from nearby Stanford University. Since then, major universities began to focus in a more systematic way on transferring knowledge to application. Hence, incubators and industrial parks were born alongside university campuses. Consequently, the time between the creation of knowledge and its application was shortened by the development of a new concept called Translational Research. Since 2000, the National Institutes of Health (NIH) of the United States has led a program to accelerate the translation of knowledge obtained in the laboratory to application in the clinic (bench-to-bedside). In a second phase, the NIH has accelerated the translation of knowledge obtained in clinical research to application in the Health Care System to improve the overall quality of medical care. Thus, the concept of Translational Medicine was created.

In Hypertension, great advances in the past were gradually achieved through basic and clinical research.[1] The great discovery by Harry Goldblatt (1891-1977) in 1934, showing that chronic hypertension could be induced in dogs through controlled constriction of the renal artery, only occurred long after Richard Bright (1789-1858) postulated through clinical observation that there was an association between renal disease and cardiac overload (hypertension). This discovery was more in the direction of the bedside to bench. Another example with a temporal lag – now from the bench to the bedside – was the discovery and application of angiotensin-converting enzyme inhibitors. It was Sergio H. Ferreira (1934-2016) who – working with collaborators from 1965 to 1971 – demonstrated in a series of experiments the existence and synthesis of peptides in the venom of the jararaca viper that simultaneously evoked the potentiation of bradykinin and inhibited the conversion of angiotensin I to angiotensin II through inhibition of angiotensin-converting enzyme.[2] In 1977, Cushman and Ondetti, based on the discovery by Ferreira, finally produced a new molecule, i.e., captopril, which initiated a new phase in the treatment of hypertension and cardiac insufficiency.[3,4]

Below, we present examples of how Translational Cardiology is presently applied in the field of Hypertension.

FEEDBACK LOOP BETWEEN BASIC RESEARCH AND CLINICAL RESEARCH (CROSS-TALK)

Population data obtained for 1,507 individuals in the MONICA project showed cardiac hypertrophy, as measured with the Sokolow-Lyon index, in patients with polymorphism for the angiotensin-converting enzyme DD+DI in comparison with those expressing genotype II.[5,6] This would indicate that the polymorphism determining enzyme inhibitor hyperactivity produces more angiotensin II in patients with the DD+DI genotype, and that this would be responsible for hypertrophy. To prove that excessive angiotensin-converting enzyme activity causes an increase in ventricular mass, mice with one, two, three, or four copies of the angiotensin-converting enzyme gene were subjected to swimming experiments. Mice with more copies of the angiotensin-converting enzyme gene showed no difference from those with fewer copies, in part because the increase in angiotensin-converting activity determined by the increasing number of copies of the gene was offset by a decrease in the concentration of plasma renin, thereby preventing an increase in the concentration of angiotensin II. Under physiological conditions, therefore, cardiac overload caused by swimming did not lead to increased cardiac hypertrophy in mice with additional copies of the angiotensin-converting enzyme gene.

Another series of experiments was planned to determine whether the number of copies of the angiotensin-converting enzyme gene and the consequent increase in the concentration of angiotensin in the myocardium could influence the development of hypertrophy. Mice were now submitted to thoracic aortic coarctation and consequent cardiac overload. Three to six weeks after constriction of the aorta, the association between blood pressure above the ligature with left ventricular mass was greater in mice with three copies of the angiotensin-converting enzyme gene than in those with one or two copies (Figure 1). It was also verified that the blockade of AT1 receptors by losartan eliminated this difference, indicating the importance of an increase in the concentration of angiotensin II in mice with three copies in causing greater hypertrophy. The data showed that upon pressure overload (hypertension), unlike that associated with physiological hypertrophy induced by swimming, the increased number of copies of the angiotensin gene positively influenced hypertrophy development. These data led to a review of the results obtained in clinical research on polymorphism of the angiotensin-converting

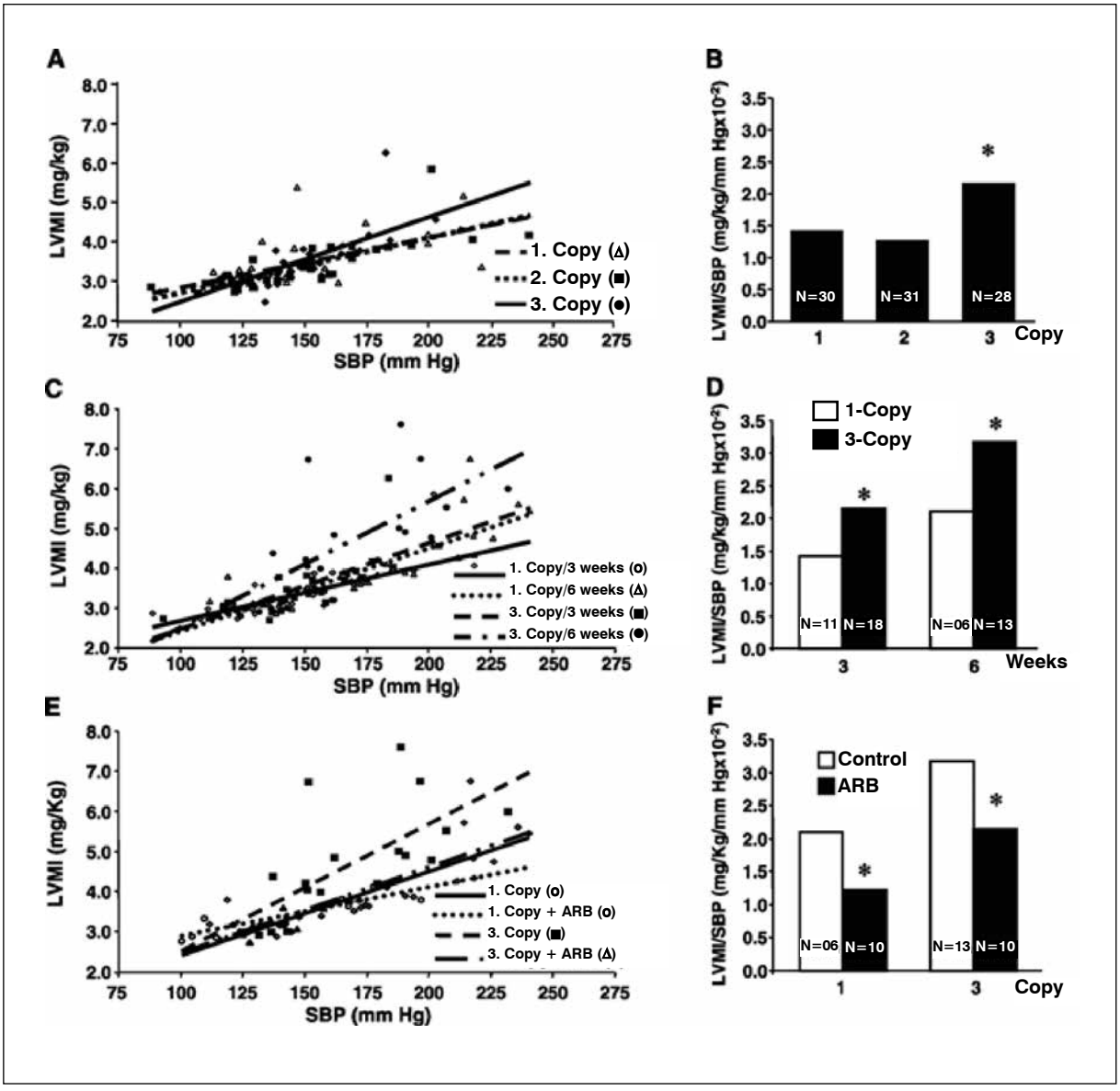

Figure 1. Association between left ventricular mass index (mg/kg)/systolic pressure (A, C and E) and slope of linear regression (B, D and F) in mice with 1, 2, or 3 copies of the angiotensin-converting enzyme gene, subjected to 3 and 6 weeks of coarctation of the aorta. The carriers of 3 copies had approximately 50% greater hypertrophy than those with 1 copy after 3 and 6 weeks of coarctation (D). An angiotensin receptor blocker (ARB) eliminated the differences. Adapted from reference 6.

enzyme gene. In calculating the ratio of systolic blood pressure using the Sokolow-Lyon index, it was found that only pressures above normal (fourth quartile) showed a difference in the degree of hypertrophy in carriers of the DD+DI polymorphism (which results in hyperactivity of the converting enzyme) (Figure 2), when compared with carriers of genotype II. In normotensive individuals, hyperactivity of the angiotensin-converting enzyme gene (DD + DI) does not cause hypertrophy similar to that observed in normotensive mice subjected to swimming and carriers of a greater number of copies of the angiotensin-converting enzyme gene (hyperactivity of the enzyme). This example shows the importance of Translational Cardiology performed with the same research objective, facilitating the transfer of knowledge from the bench to the clinic and vice versa (*cross-talk*).

TRANSFER OF KNOWLEDGE TO MEDICAL PRACTICE (HEALTH CARE SYSTEM)

Resistant hypertension is defined as that which does not normalize even when treated with optimal doses of the three main categories of antihypertensive drugs (ACE inhibitors, calcium channel blockers, and a diuretic). It is important to know the prevalence of the disease in our country, and to determine which fourth drug should be administered to patients with resistant hypertension. Therefore, a multicenter study was designed by the leaders of research on hypertension in Brazil to evaluate the prevalence of resistant hypertension in patients who are treated by the SUS and treated with medications available in the Network. The study

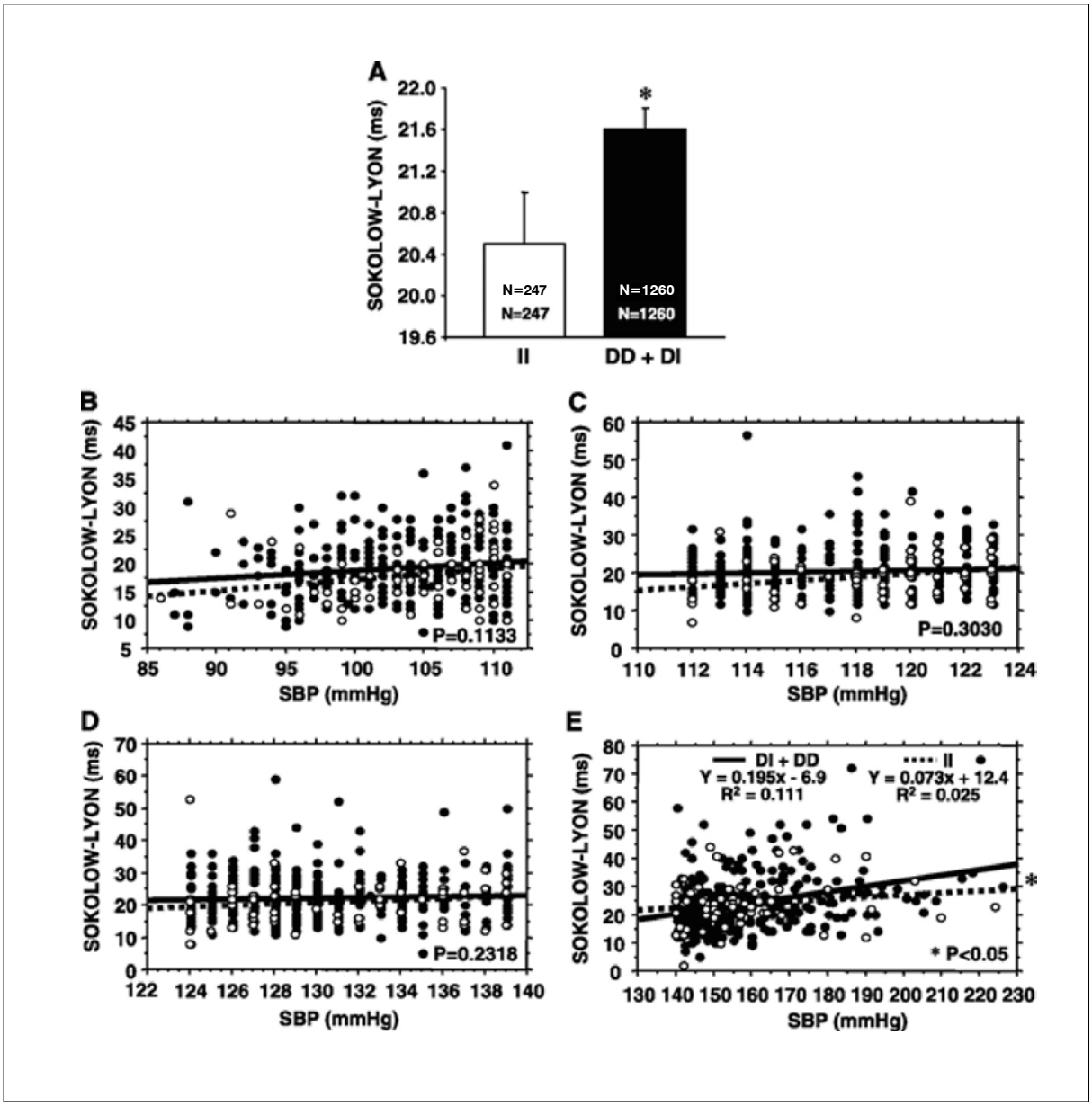

Figure 2. Higher Sokolow-Lyon index in individuals with DD +DI polymorphism in comparison with the those with genotype II (A). The relationship between the Sokolow-Lyon index and systolic pressure only showed a difference in the degree of hypertrophy in the fourth quartile (E), with systolic pressure above 130 mmHg. Adapted from reference 6.

was sponsored by the Ministries of Health and Science and Technology, FAPESP, and Hospital Samaritano. The study was entitled "Multicenter Study of Arterial Hypertension for Identification of Resistance and Standardization of Therapy," and was published as "*Spironolactone versus clonidine as fourth drug therapy for Resistant Hypertension: the Resistant Hypertension Optimal Treatment (ReHOt) Randomized Study*.[7,8] Twenty-six centers were included in the study, representing the five regions of the country (Figure 3). The first phase detected patients with BP above 160/110 mmHg, with resistant hypertension after 3 months of treatment. The criterion for standardization was determined by the consultation pressure as determined by the Ambulatory Blood Pressure Monitoring (ABPM). Resistant patients (less than 12% of the total) were randomized for treatment with clonidine or spironolactone for 3 more months (Figure 4). In addition to routine laboratory examinations, the recording of an electrocardiogram with natural frequency appropriate for spectral analysis and the determination of the components of the renin-angiotensin system were also standardized in different centers. This enables correlation of the results of BP treatment with hyperactivity of the sympathetic system (spectral analysis) and/or the renin-angiotensin system. The study was completed and published recently for submission to the SUS, and will be used for standardization of the treatment of hypertension, particularly in the administration of the fourth drug to be included in the treatment of resistant hypertension. It is, therefore, a study typical of the second phase of Translational Cardiology when the knowledge gained in academic research is transferred into the health care system.

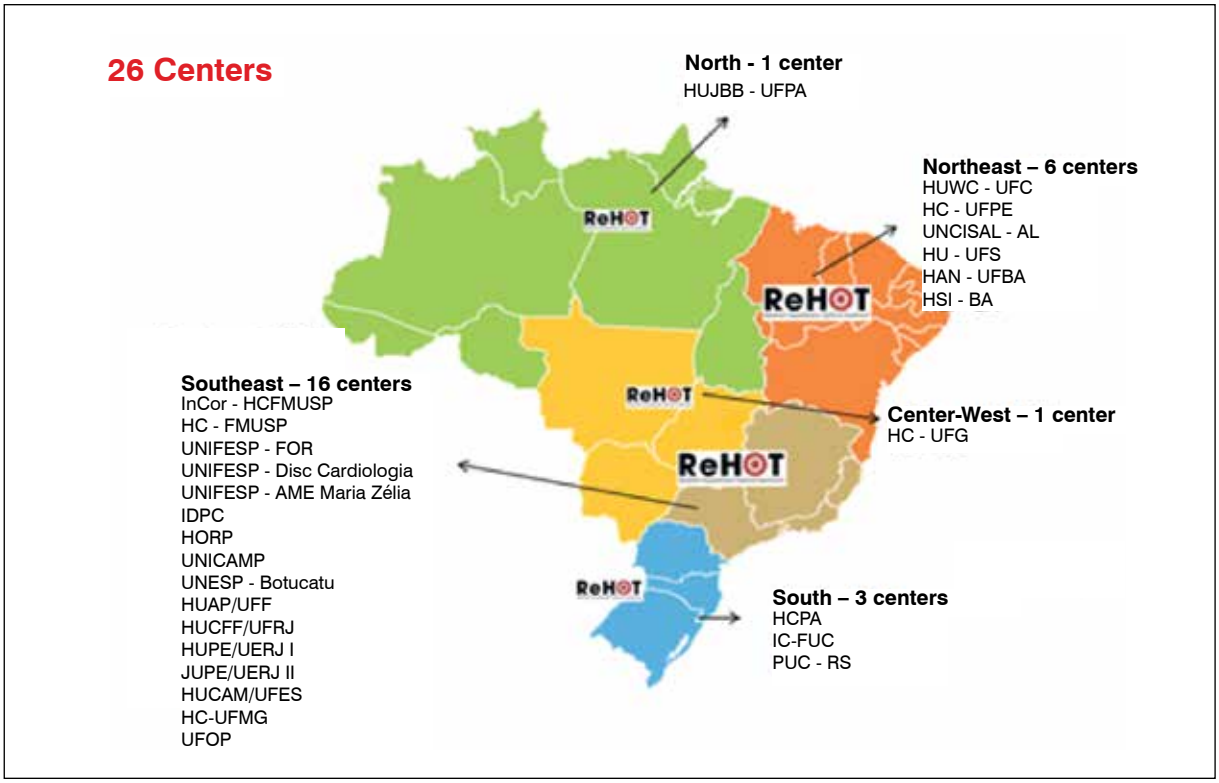

Figure 3. Distribution by region of the centers that participated in the project. The proportion of patients was close to the proportion of inhabitants in each region. North (5.9% -8.3%), Northeast (22.7% - 27.8%), West (2.8% - 5.5%), Southeast (57.6% - 42.1%), South (11% - 14.4%).

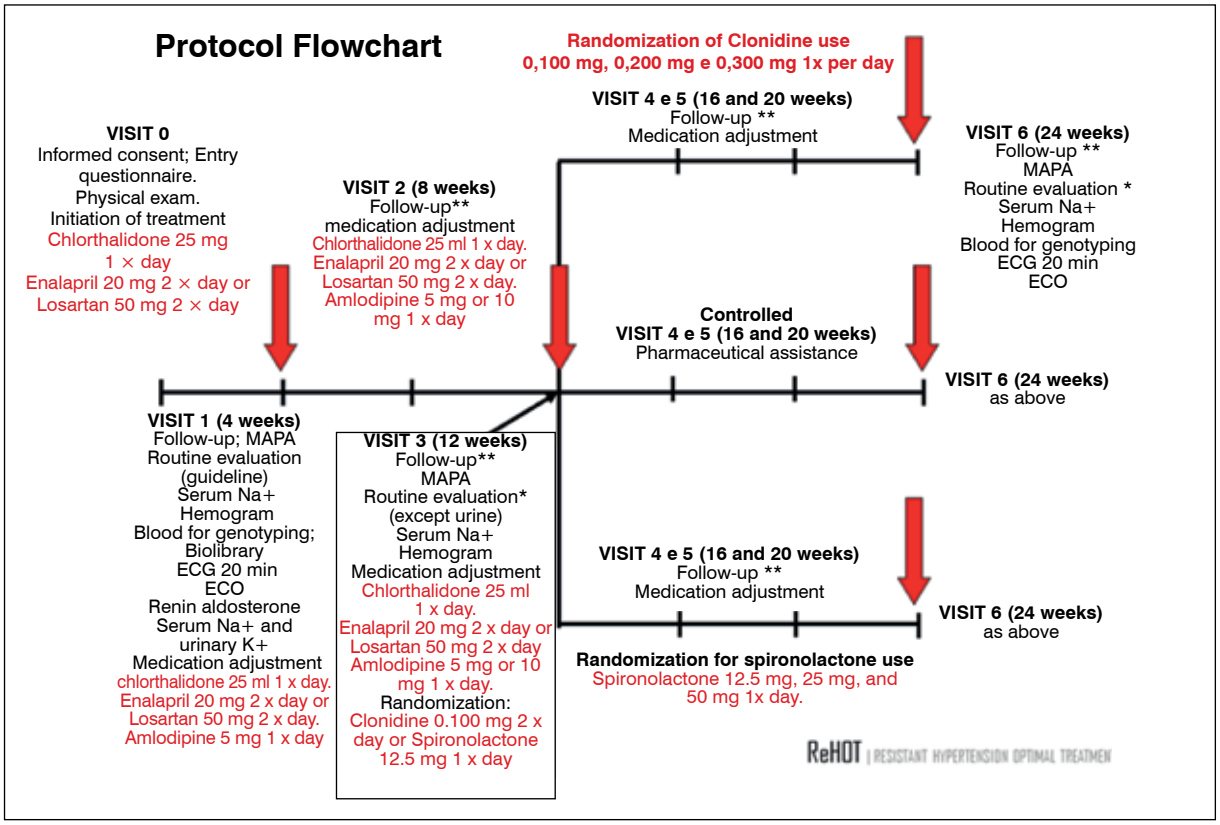

Figure 4. Flowchart of the protocol. In the first 3 months, patients with pressure above 160/110 mmHg are treated with optimal doses of three classes of antihypertensive drugs. Resistant patients evaluated by the consultation pressure and MAPA are randomized for treatment with clonidine or spironolactone for 3 more months.

The pharmaceutical industry fulfils its role in the creation of new drugs and new equipment; however, the interaction between academia (the keeper of knowledge) and the public sector (which finances the research) is essential, to establish what is practical (cost-benefit) for use in the health care system.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in conducting this study.

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