

Cardiomyopathies: Yesterday, Today, and Tomorrow

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The interest in myocardial damage is very old, but only in recent decades has there been a reasonable advance in greater knowledge thereof. Ancient peoples were limited to rudimentary observations on the morphology and physiology of the circulatory system, but with special interest directed to the heart. Texts in cuneiform scripts from Sumer, considered the first civilization in human history; others from the Library of Ashurbanipal, with inscriptions on clay tiles, discovered intact under the sands at Nineveh; Egyptian hieroglyphs in stone and ink; and writings by the Mayans, the only people in the Americas to leave reports in their alphabet as well as books, of which we have only copies in some cases (the Spanish invaders took it upon themselves to destroy and burn many originals) all demonstrate an ancient interest in human anatomy and the heart. With the limitations of their times, they demonstrated curiosity about the constitution of the human body, reaching academic-level descriptions by Leonardo da Vinci's time. Recent developments have brought us new knowledge about the etiopathogenesis and pathophysiology of the diseases that affect the heart, but they are not sufficient to generate greater therapeutic advances. There are reasons for this.

As these diseases are predominantly clinically treated, cardiology has spent the past few decades committed to understanding and disseminating themes considered more relevant in surgical areas, such as coronary, congenital, and valve diseases, which were and are subjected to highly developed treatments in the recent past, with more immediate results. The drug and equipment industries have understood the size of the doors open to their interests, actively participating in research associated with academic institutions. There is no doubt that the evolution in these fields has been enormous, with remarkable material interests, massively concentrating research, symposiums, congresses, and publications on these themes. Spaces for cardiomyopathies were very limited, due to almost total lack of interest, and therapy in these fields was limited to digitalis and diuretics, indicated for heart failure, and not for underlying diseases. It was a world apart within cardiology. It took a long time for new drugs to be studied and released on the market, but only for the treatment of

dysfunction as a syndrome. There was a long delay in creating laboratories to promote understanding of the etiological factors of myocardial aggression, in an attempt to understand, reduce, or eliminate the lethality of these diseases, many of which are still little known, and to attempt to develop specific treatments for each cause. Unfortunately, we are still a long way from this goal. As an example, I cite the old and current Chagas cardiomyopathy. We treat the consequences, heart failure, thromboembolisms, and arrhythmias, but to date we do not have any truly effective specific treatment, in a society that contains a significant part of the infected population. Even prevention, which is inexpensive, given that it simply uses insecticides, is carried out on a modest scale. It has become conventional to use the terminology “disease of the poor” to justify this lack of interest. Nonetheless, this delay generates a huge social cost in the health area.

This disease was described at the beginning of the last century by Carlos Chagas, a source of pride for Brazilian and world medicine, in a long and masterful text, in which he observed the transmitting insect, parasitized by the etiological agent, the transmission of the vector to the human being, and its clinical consequences, which vary from individual to individual, in its multiple forms of presentation. This is perhaps the moment of greatest brilliance in his studies. With his curiosity and power of observation that characterize a good researcher, he originally commented on the three phases of an infectious-contagious disease, a pioneering feat in medicine. This earned him nominations for the Nobel Prize, nominations that were sabotaged by colleagues, armed with the worst things that human beings can carry in their minds. It is a shame, because to date Brazil has yet to receive this award. Nevertheless, he gave rise to highly productive lines of research in Brazil and worldwide, which are of interest to numerous specialties. In clinical cardiology, study centers multiplied, enriching Brazilian medical literature. It would be unfair to mention only groups coordinated by names like Décourt and Pareto (Figure 1A and 1B), leaving many others out of these comments. That is not the purpose of this text.

The lack of importance initially given to cardiomyopathies has been very well illustrated since the Heart Institute of the University of São Paulo (Incor, acronym in Portuguese) was founded almost 50 years ago. It was necessary to divide the beds in our wards in order to form study groups. On that occasion, few were allocated to a unit considered of small importance within the organization chart. It was referred to as “General Cardiology”, or “Cardio-General”, as it was known internally, generic terminologies, which said nothing, and its need was often questioned. The name itself demonstrates the lack of interest in this group. Thanks to the immense

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Figure 1 – A) Professor Luiz Venere Décourt, B) Professor Raul Carlos Pareto Junior, C) Professor Claudio Rapezzi, D) Professor Elliot, E) Laboratory of Genetics and Molecular Cardiology, Incor/HC/FMUSP, F) Projeto Renômica – National Network of Cardiovascular Genomics, G) Diane Ávila and Professor Claudio Tinoco Mesquita of Universidade Federal Fluminense (UFF) – Healthscience laboratory, 3-dimensional printed hearts (developed in partnership with Professor Marcus Simões of the Faculty of Medicine of Universidade de São Paulo, Ribeirão Preto).

dedication and production of our human resources, history has corrected this blurred vision that was present at that time. It became the first center for the study of diseases of the myocardium, pericardium, and endocardium in Brazil, with notable didactic, scientific, and care production. When the postgraduate program was established, it was the group most sought by students. It trained specialists and doctors, many of whom are now professors in their hometowns, creating highly productive centers and spreading the culture of studying these diseases. Those who came here to receive information went on to become opinion makers. The school spawned other schools.

In Portuguese, myocardial diseases have always been referred to as “*miocardiopatias*”. Decades ago, a text whose author muses about terminologies proposed changing to “*cardiomiopatias*”. At that time, we questioned the reasons they did not propose changing “*pericardiopatias*” to “*cardioperipatias*” and “*endocardiopatias*” to “*cardioendopatias*”. We did not receive a response. This need that we have to change titles and names is interesting.

The first official description of cardiomyopathies was provided by Krehl, in 1891, but the term was introduced in the medical literature in 1957, by Bridgen, in the article “Uncommon myocardial diseases. The non-coronary cardiomyopathies”, published in *The Lancet*, which discussed the difficulty of classification and the diversity of the disease. At that time, they mainly focused on dilated forms. In the 1960s, Goodwin¹ defined them as primary myocardial diseases. But what are primary diseases of the myocardium? Do they exist? The authors had noteworthy difficulties.² We believe that any aggression should be considered a cardiomyopathy. Afterwards, an etiological classification was attempted which, as it is immense, serves only to guide the search for causes. Perhaps the most clinical is the division between dilated, hypertrophic, and restrictive, however much criticism it may receive. As an example of complexity, I cite hypertrophic cardiomyopathies, which include diseases of the fibers, interstitium, and vessels, thus, a universe of causes, which increase thickness according to the affected compartment, even without an increase in the number of muscle fibers. The term

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hypertrophic should be modified in the near future to something that simply means increased thickness. The term restrictive follows a pathophysiological pattern common to all of them. The disease began to be better known when European doctors were called to visit some countries in Africa to promote further understanding of a heart disease that was highly prevalent in their regions, causing high mortality rates. In these patients, unlike the dilated forms, right heart failure predominated. Endomyocardial fibrosis was thus described, resulting from environmental and parasitic factors, therefore typical of underdeveloped countries. Rare cases have been described in developed countries, becoming curiosities in these locations. This heart disease opened doors to the knowledge of other restrictive forms, which are now much studied.

Scholars face difficulties in creating an objective and didactic classification that, at the same time, encompasses a large number of presentations. Today, we have several, all of which have their faults and undergo frequent changes as knowledge advances. As Goodwin said, "Any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding."

Cardiology is translational and personalized, with therapeutic targets increasingly differentiated in cardiomyopathies. Based on phenotypes, there are beta-blockers, calcium channel blockers, and disopyramide. There are others based on mechanisms, such as an allosteric inhibitor of myosin adenosine triphosphatase, which is specific for the heart in hypertrophic cardiomyopathy. Based on the genotype, there may be an indication for implantable cardioverter-defibrillator, and, based on protein or enzyme, there is enzyme replacement therapy, such as chaperone therapy in Fabry disease and even, for example, protein stabilization, such as transthyretin tetramers

in amyloidosis. Future possibilities also include molecular targets such as monoclonal antibodies, PCSK9 inhibitors in dyslipidemia at high cardiovascular risk, the selective oral inhibitor of mitogen-activated protein kinase p38 in dilated cardiomyopathy related to the lamin A/C gene, and even xenotransplantation (Figure 2).³⁻⁵

Many perspectives are based on treatment focused on nucleic acids, for example, antisense oligonucleotides (etheplirsen in Duchenne dystrophy, inotersen in amyloidosis), non-specific (patisiran in amyloidosis) and specific RNA interference (in point mutations, allele-specific) and DNA interference (MYBPC3/ PKP2 truncation and CRISPR gene editing). These points of focus have been expanding for several diseases, mainly in genetic cardiomyopathies, demonstrating improved quality of life and reduced mortality. However, there is still much to learn about what really makes a long-term difference, mainly in diseases where pathophysiology still has gaps, such as wild-type transthyretin amyloidosis (Figure 2).⁶⁻⁹

Medical follow-up has included multiple specialties, following the British and Italian schools, with the great example of Professor Claudio Rapezzi (*in memoriam*, Figure 1C), in São Paulo with Incor and other centers around the world. Rapezzi's heart stopped beating on October 14, 2022. He was a great university professor who covered all fields of cardiology, ending with cardiomyopathies and cardiac amyloidosis, where he became an international opinion leader. In the British school, for instance, Professor Elliott (Figure 1D), a leading international scholar and reference in cardiomyopathies, is head of the University College London Centre for Heart Muscle Disease and leader of the Hereditary Cardiovascular Diseases Unit at Bart's Heart Centre in London.

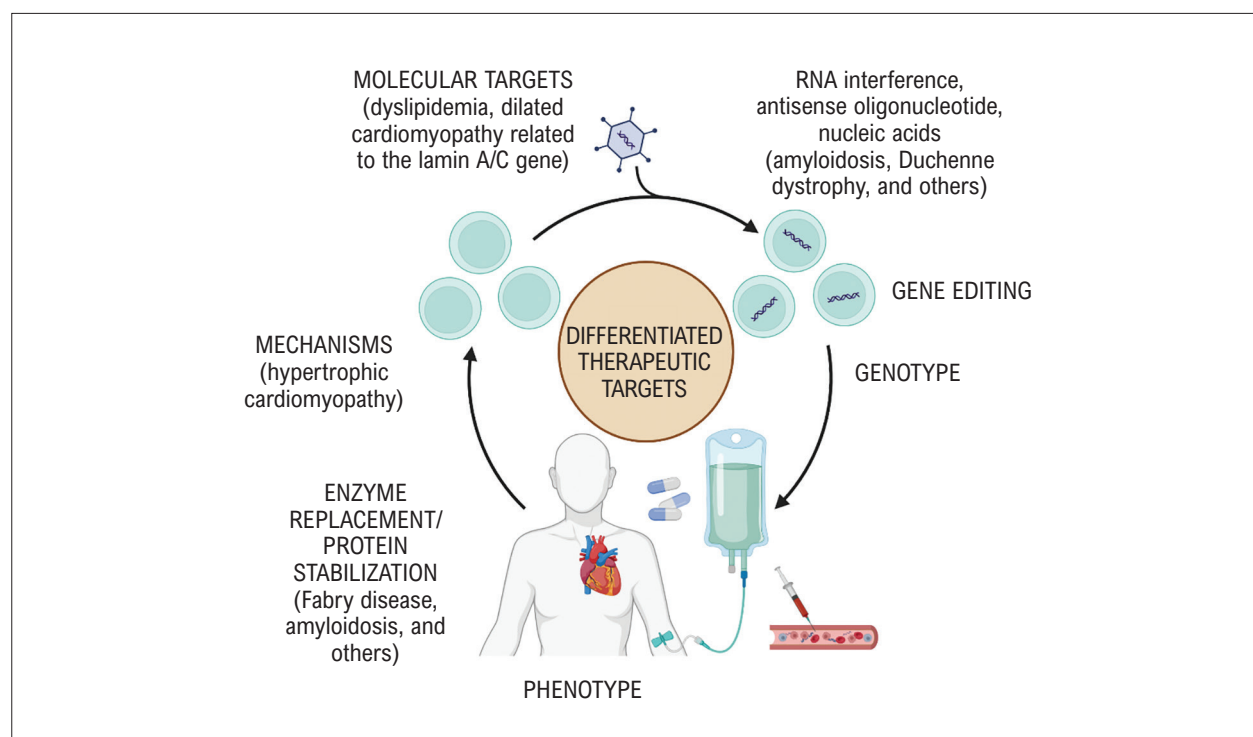


Figure 2 – Therapeutic targets and their specific actions.

Since the sequencing of the human genome and the emergence of registry tools, such as biobanks, genetic incorporation has expanded and achieved access in the private sector as well as the Brazilian Unified Health System (SUS, acronym in Portuguese). At the Brazilian Society of Cardiology we had the creation of the Study Group on Myocardiopathies (GEMIC) in 2014. Incor (Figure 1E) has, for a long time, been developing research activities focused on the identification of molecular markers associated with the genesis of cardiovascular diseases and the development of new therapeutic approaches for cardiac regeneration. We also have the Projeto Renômica, which is a research program that studies causes of hereditary cardiovascular diseases in the Brazilian population, in which any institution in Brazil that provides care for SUS patients can participate, with genetic testing throughout the years of the study. In addition, 3-dimensional

printing has emerged to assist teaching and research, as well as surgical programming in differentiated cases. In this area, Professor Claudio Tinoco of Universidade Federal Fluminense (UFF) has been developing printed hearts of patients with cardiac amyloidosis at the UFF Healthscience laboratory, in partnership with Professor Marcus Simões of Universidade de São Paulo, Ribeirão Preto (Figure 1F).

And the future? Advances, as made clear by the previous exposition, have been slow, as in any study involving highly complex topics, and, unfortunately, greater interest has only emerged in the recent past. We are still in the prehistory of achieving specific treatments for each compartment of the myocardium, with all the etiological variations. We have a long way to go to advance our knowledge in the field of cardiomyopathies. Best of luck to all those who dedicate themselves to the arduous task of studying these diseases.

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