The Importance of the DEIC/GEMIC/SBC 2021 Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis to Clinical Practice

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The latest edition of *Arquivos Brasileiros de Cardiologia* has brought us the publication of the Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis by the DEIC/GEMIC/SBC. This document was the result of the collaborative efforts of many experts in the area, exponents of cardiology in Brazil, but it also included other specialists, such as neurologists, hematologists and nuclear physicians.

The need to bring together this group of collaborators reflects a fundamental aspect of amyloidosis, namely, a complex and multifaceted disease that affects multiple organs and requires the assistance of several specialties for comprehensive management. This was, in fact, a positive aspect of the document: its scope and multidisciplinary character.

It is here appropriate to state the reasons that led the DEIC/GEMIC/SBC to produce this document, fulfilling the mission of producing documents that contribute to updating science and medical education, offering the signposts that are necessary to guide the practice of cardiology based on scientific evidence. The sense of urgency for this action was the clear perception of the recent and profound reformulation of concepts regarding cardiac amyloidosis (CA), including evidence that it is a more prevalent disease than previously imagined, the significant advance in imaging methods that has made non-invasive diagnosis possible, and the emergence of new specific treatments that can change the natural history of the disease (Figure 1).

Cardiac amyloidosis is a frequent cause of heart failure with preserved ejection fraction

The main cardiological phenotype of CA is that of an infiltrative restrictive cardiomyopathy, whose more general aspects of symptoms, increased thickness of the ventricular walls, and concentric remodeling of the left ventricle, overlap with those of heart failure with preserved ejection fraction (HFpEF), produced by risk factors such as high blood pressure, obesity, diabetes, and aging. Thus, CA should be considered as a differential diagnosis in patients who exhibit HFpEF.¹

Keywords

Amyloidosis; Cardiomyopathy; Diagnostic Methods; Treatment.

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Manuscript received September 09, 2021, revised manuscript September 24, 2021, accepted September 24, 2021.

DOI: <https://doi.org/10.36660/abchf.20210021>

It is worth remembering that, among the different amyloidogenic proteins that can be deposited in the myocardium and cause CA, the wild type transthyretin form (ATTR-CAwt), which is closely linked to aging, is the most frequently reported in several series of specialized medical literature. This has been repeated both in large reference centers and in real world registers.² Accordingly, a recent article has shown a very significant increase in CA as a cause of hospitalizations due to heart failure in several regions of the United States, between 2000 and 2012, exceeding the rate of 65 cases per 100,000 people/year, indicating that CA is not a rare disease according to the current criteria of the World Health Organization (Figure 2).³

It is important to remember that there are no similar statistics in our country to confirm the higher prevalence of CA in the Brazilian population. This is a gap that we hope will be filled in the near future.

Non-invasive diagnosis using bone tracer scintigraphy

Of all the advances in the clinical scenario of CA, the one with the greatest impact has been the development of the bases for non-invasive diagnosis of ATTR-CA, dispensing the use of endomyocardial biopsy. In the celebrated study published by Perugini et al. in 2005, it was well demonstrated that patients with ATTR-CA exhibited intense and anomalous myocardial accumulation of some bisphosphonate agents used for bone scintigraphy. In this seminal study, only patients with ATTR-CA exhibited ^{99m}Tc-DPD (3,3-diphosphono-1,2-propanedicarboxylic acid) uptake equivalent or superior to costal arch uptake (grades 2 or 3), while none of the patients with AL linked to light chains (AL form) showed the same behavior.⁴

It was subsequently identified that a certain percentage (20% to 30%) of patients with AL-CA could also exhibit expressive uptake of bone markers, making it essential to rule out the presence of immunoglobulin light chains for diagnostic confirmation of ATTR-CA in patients with positive cardiac scintigraphy using bone markers. In the fundamental study by Gillmore et al., this set of results (cardiac scintigraphy with grade 2 or 3 bone marker uptake + light chain exclusion) had 100% specificity and predictive value, thus defining the non-invasive criteria for diagnosis of ATTR-CA, which have gone on to become a standard of conduct worldwide.⁵

These fundamental aspects have guided the choices made by the panel of experts who created the flowchart for the diagnosis of CA in our Position Statement, which is reproduced in Figure 3. This alone is the most important item of the entire document, and we hope that it will be able to guide the diagnostic flow of CA in routine cardiology practice.

Cardiac amyloidosis New concepts about an old disease

Simões MV et. Posicionamento sobre o Diagnóstico e Tratamento da Amiloiose Cardíaca – DEIC/GEMIC/SBC, Arq Bras Cardiol 2021; online ahead print DOI: 10.3660/abc.20210718

Figure 1 – Illustration outlining the aspects involved in the profound reformulation of concepts regarding cardiac amyloidosis that have expanded in recent years. HFpEF: heart failure with preserved ejection fraction.

Increase of HF hospitalizations associated to Cardiac amyloidosis in US

Gilstrap LG et al. Circ Heart Fail 2019;12:e005407

Figure 2 – Heat map showing the increased prevalence of cardiac amyloidosis as a cause associated with hospitalizations due to heart failure in the United States, between 2000 and 2012. Reproduced from (Gilstrap et al., 2019).

New specific treatments

There is no doubt that any efforts made to improve our ability to diagnose a given condition are only fully valid and compensated when we are able link this finding to the use of specific treatments capable of alleviating symptoms and prolonging our patients' lives. The emergence of new therapies specific to CA has been the fundamental spring that has fueled research and initiatives to raise the level of care for more accurate and earlier diagnosis of CA.

The transthyretin tetramer stabilizer tafamidis was the first drug for specific treatment of ATTR-CA to be tested in a multicenter, randomized, blinded study, the ATTRACT

study.⁶ The main results of ATTRACT have shown that the use of tafamidis was associated with a significant reduction in all-cause mortality by 30% (HR = 0.70, 95% CI: 0.51 to 0.96) and a reduction in hospitalizations/year of around 32% (HR = 0.68%; 95% CI: 0.56 to 0.81). In this manner, tafamidis is the first specific treatment for ATTR-CA capable of changing the natural history of the disease, and it has received approval from the Brazilian Health Regulatory Agency for the treatment of ATTR-CA in Brazil.

Other very promising molecules are currently being developed and tested in phase 3 multicenter trials, including

Figure 3 – Flowchart for diagnosis of CA

strategies for silencing the gene expression of TTR production through “small interference RNA” (patisiran) and “anti-sense” oligonucleotide (eplontersen) platforms.

It is important to remember that we have recently witnessed the incorporation of significant advances in the treatment of AL-CA, using monoclonal antibodies and autologous bone marrow transplantation, which are associated with a surprising positive impact on mortality due to AL-CA, provided that patients are referred during earlier stages of disease evolution, which highlights the need for more accurate and quicker diagnosis of this disease.⁷

Final comments

As reviewed here, there is strong evidence to suggest that CA is a relatively prevalent but broadly underdiagnosed condition. The emergence of new therapies capable of changing the natural history of this serious disease has brought about the need for earlier and safer diagnosis. The publication of the DEIC/GEMIC/SBC 2021 Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis takes on fundamental importance at this moment by contributing to the incorporation of these new concepts in clinical practice and providing signposts based on the most recent scientific evidence.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Simões MV, Fernandes F.

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 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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