REVIEW ARTICLE

Syncope and Rhythm Disturbances as Common Clinical Manifestations in Amyloidosis

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Abstract

Amyloidosis results from deposition of insoluble fibrillar protein compounds in various organs, including the heart. Cardiac involvement occurs in both atria and ventricles, leading to restrictive cardiomyopathy, heart failure (HF), and arrhythmias.

Five amyloid proteins affect cardiac tissue: light and heavy chain forms of immunoglobulin, transthyretin (TTR), apolipoprotein 1, and amyloid A. Approximately 95% of cardiac involvement stems from light chain of immunoglobulin and TTR deposition in heart. Chamber stiffness and rhythm disturbances occur in cardiac amyloidosis (CA), encompassing from HF to atrial and ventricular arrhythmias (VA), and both can compromise each other. It is known that conduction system disorders and VA increase sudden death risk, as amyloid infiltration, inflammation, and fibrosis alter myocardial electrophysiology.

Beyond the heart, autonomous nerve systems suffer amyloid deposition, contributing to syncope manifestation and increasing the risk of death and poor prognosis. In this context, our review sheds light on the importance of recognizing syncope and rhythm disturbances as crucial markers in the early identification and management of CA, potentially offering avenues for prompt intervention and improved patient outcomes.

Keywords

Introduction

Cardiac amyloidosis (CA) diagnosis has risen due to the recent therapeutic options that emerged recently, altering the disease's natural history. Current data show an incidence of 18 per 100,000 person-years.[1] Advanced imaging allows non-invasive diagnosis and early treatment initiation. Traditionally, CA silently progresses with amyloid fibrils deposits altering heart architecture, causing diastolic impairment followed by systolic compromise and clinical signs of worsening heart failure (HF) and proper functioning of other organs related to the heart, such as kidney and liver.[2]

Over 20 amyloid proteins exist, 5 of which can deposit in cardiac tissue, namely, immunoglobulin light chain proteins, immunoglobulin heavy chain proteins, transthyretin (TTR), apolipoprotein 1, and amyloid A. Nonetheless 95% of amyloid cardiac involvement is due to TTR amyloidosis (ATTR) and immunoglobulin light chain amyloidosis (AL).[3]

When evaluating patients with HF with preserved ejection fraction (HFpEF), the following red flags warrant consideration of CA:[2,4,5] unexplained hypertrophy; abnormal electrocardiogram (ECG) findings, such as low voltage of QRS at frontal leads and absence of R wave progression in septal precordial leads; peripheral sensitive and motor neuropathy; carpal tunnel syndrome; complaints related to lumbar spinal cord stenosis; tendinopathies leading to rupture; and family history.
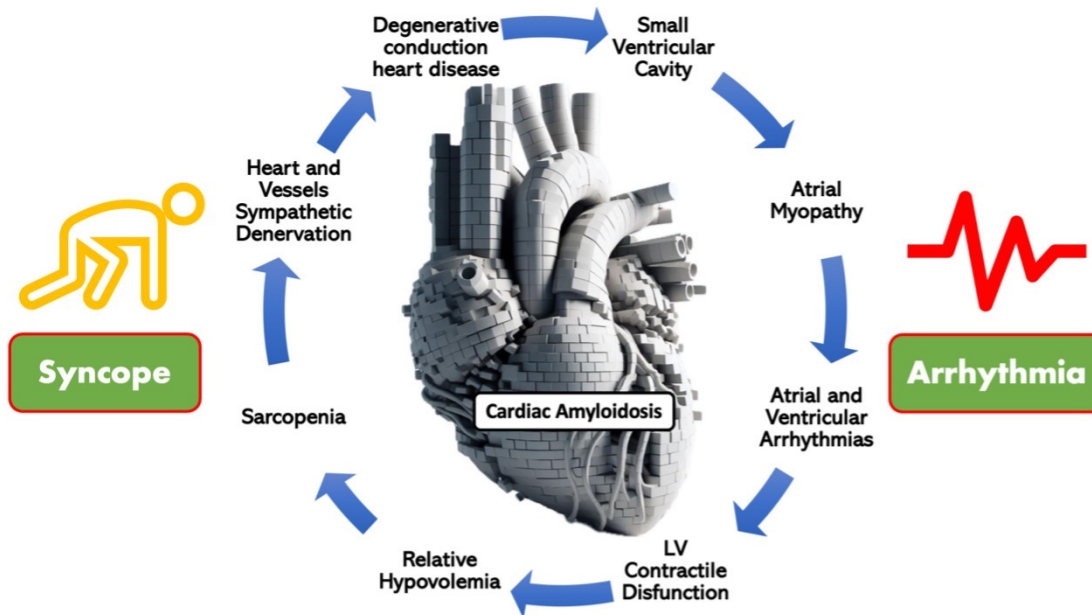
Syncope and arrythmias, which are common in CA, serve as early diagnostic red flags.[6,7]

Central Illustration: Syncope and Rhythm Disturbances as Common Clinical Manifestations in Amyloidosis

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The interaction between multifactorial causes of syncope in CA. LV: left ventricle. Figure generated with assistance of Microsoft Bing.

Syncope

Definition

Syncope is defined as the transient loss of conscience due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery. It comes with loss of postural tone, leading to falls and sometimes traumas, accompanied by amnesia about the event.[8] The symptoms presented immediately before syncope are called prodromes. They represent the beginning of all processes of fainting, when the arterial pressure and consequently cerebral perfusion, begins to drop.
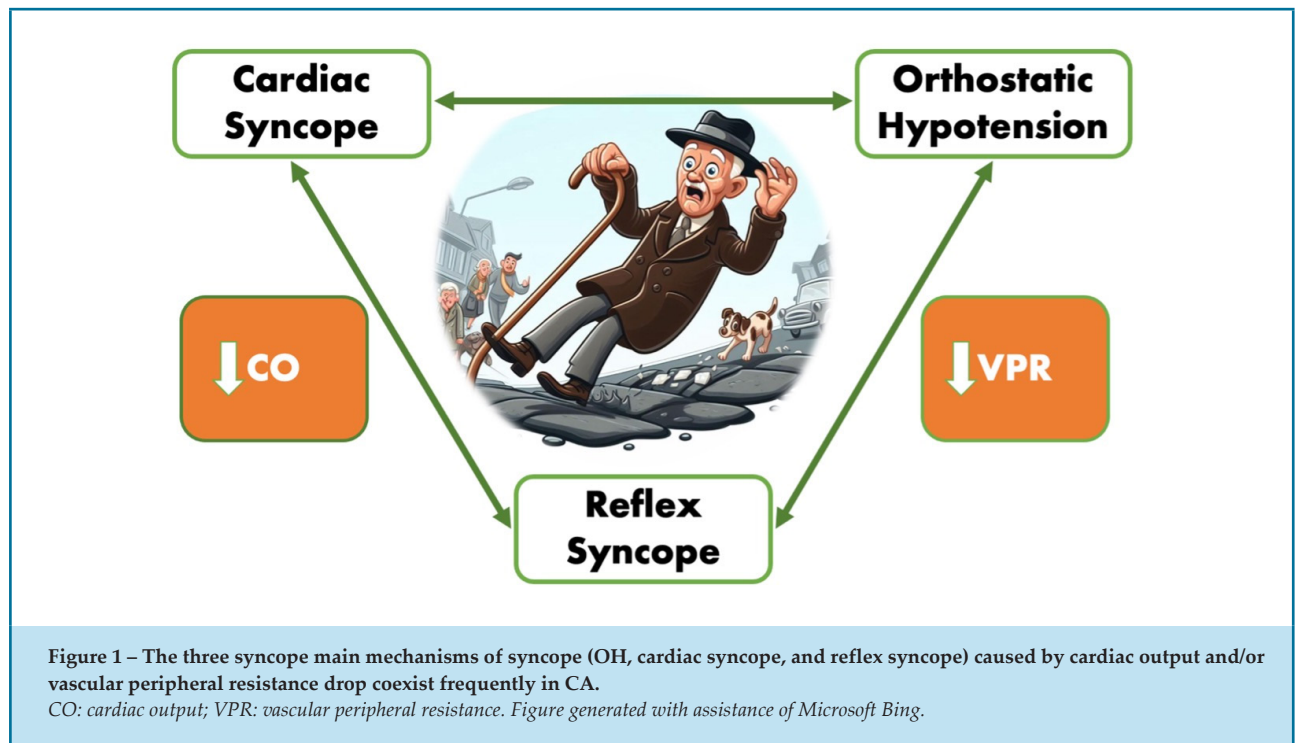
Pathophysiology

The pathophysiological mechanism of syncope is explained by global cerebral hypoperfusion; thus, for the occurrence of syncope, arterial pressure should drop abruptly or progressively for some reason. There are three main mechanisms that can result in syncope, namely, reflex, orthostatic hypotension (OH), and cardiac syncope. All these mechanisms are related to impairment of two hemodynamic parameters: vascular peripheral resistance and/or cardiac output[9] (Figure 1).

The duration of prodromes is correlated to the nature of the event; the shorter the prodrome, the greater the chance of a sudden drop of arterial pressure, such as paroxysmal arrythmias, severe dysautonomia, abrupt loss of blood, traumatic cardiac tamponade, massive pulmonary embolism, etc. Therefore, the length of the prodromes (10 seconds) is a clue to the main causal component (fast versus slow installation). When prodromes last less than 10 seconds they are considered suspect for arrythmias as a first good hypothesis. Despite this, severe dysautonomia or gradual drops in blood pressure (BP) in a standing position not recognized by the patient can also lead to short prodromes.[10] As all these issues can occur together in patients with amyloidosis, it is highly difficult to point out only one cause for syncope without investigating all the possible components involved in syncope in this disease (Central Illustration).

Reflex mechanism

Reflex syncope, also known as vasovagal syncope, is the most common cause of syncope in all ages. The mechanism is related to sympathetic withdrawal and vagal overstimulation secondary to a specific trigger, which

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Figure 1 – The three syncope main mechanisms of syncope (OH, cardiac syncope, and reflex syncope) caused by cardiac output and/or vascular peripheral resistance drop coexist frequently in CA.
CO: cardiac output; VPR: vascular peripheral resistance. Figure generated with assistance of Microsoft Bing.

leads to sudden drop of heart rate (HR) and/or arterial pressure. The most common trigger is orthostatic stress that involves a lowering in venous return to the heart, which frequently occurs in hot places and when people persist a lot of time standing up. It can be potentiated by hypovolemia or hypotensive drugs and venous pooling in the lower limbs (due to the presence of varicose veins or sarcopenia). In this specific situation the lower blood volume that reaches the heart provokes stimulation of mechanoreceptors in the ventricular wall through vigorous contraction of an "empty" heart, which can trigger vagal response. There are other triggers such as emotional (fear, pain, phobia) and situational ones (micturition, gastrointestinal stimulation like swallowing and defecation, cough, sneezing, post-exercise, and less common ones like laughing and brass instrument playing). Prodromes are compatible with autonomic activation (pallor, sweating and/or nausea).

This syncope mechanism can also be present in patients affected by amyloidosis, since patients are frequently on diuretics and have hypertrophied left ventricle with a small cavity.

OH

Syncope provoked by OH is common in amyloidosis and seems to be multifactorial. The definition of OH is a drop of more than 20 mmHg in systolic arterial pressure (SAP) or more than 10 mmHg in diastolic arterial pressure (DAP) when a patient adopts an orthostatic position, compared with supine arterial pressure measures. When the patient has supine hypertension (> 150/90 mmHg), the drop should be more than 30 mmHg in SAP and 15 mmHg in DAP. If the patient cannot adopt orthostatic position, the diagnosis of OH is made if there is a drop of more than 15 mmHg in SAP or 7 mmHg in DAP in the sitting position[11] (Table 1).

Classically, OH can result from exacerbated venous pooling and may be triggered by prolonged bed rest, deconditioning, post-exercise, and after carbohydrate-rich meals. Other significant causes include polypharmacy, volume depletion, primary autonomic failure (found in pure autonomic failure), multiple system atrophy, Parkinson's disease, and dementia with Lewy bodies. Also, there are secondary autonomic failure causes, due, for instance, to diabetes, amyloidosis, spinal cord injuries, autoimmune autonomic neuropathy, paraneoplastic autonomic neuropathy, and kidney failure. The typical OH prodromes include dizziness, light-headedness, fatigue, weakness, visual and hearing disturbances, low back pain, neck and shoulder pain (coat-hanger pain), or precordial pain.

OH is subdivided based on the time of occurrence, as follows: a) Initial OH takes place within 15

Table 1	
OH with supine normal AP	Drop > 20 mmHg in SAP or > 10 mmHg in DAP in standing position
OH with supine AP > 150/90 mmHg	Drop > 30 mmHg in SAP or > 15 mmHg in DAP in standing position
OH when patient cannot stand up	Drop > 15 mmHg in SAP or > 7 mmHg in DAP in the sitting position

seconds of orthostasis, with a drop of 40 mmHg in SAP or 20 mmHg in DAP. It appears to result from a transient mismatch between cardiac output and total peripheral resistance; b) Classical OH occurs between 15 seconds and 3 minutes of orthostatism due to impaired increase in total peripheral resistance and HR in autonomic failure, leading to blood pooling, or it can be secondary to severe volume depletion; and c) Delayed OH occurs after 3 minutes of orthostatism, where the progressive fall in venous return and low cardiac output seems to be the best explanation, almost always caused by autonomic neuropathies and classified as neurogenic OH (nOH).[9,11,12] Changes in HR on standing help determine if OH is neurogenic. In patients with nOH, reduced sympathetic innervation leads to a much smaller HR increase than expected for the BP fall magnitude. Thus, a blunted HR increase during hypotension indicates a neurogenic cause. A ΔHR/ΔSBP ratio < 0.5 bpm/mmHg upon standing or head-up tilt is diagnostic for nOH, while a ratio ≥ 0.5 suggests a non-neurogenic cause.[13] A tilt table test could be necessary to diagnose nOH since the BP fall can occur several minutes after orthostasis, mainly in early disease (Figure 2). Other non-invasive autonomic tests like HR variability, Valsalva test, respiratory test, or quotient 30:15 with orthostasis may be valuable in evaluating dysautonomia.[14]

Cardiac Syncope

Cardiac syncope results from heart malfunction, either due to pump deficit or rhythm disorders. Prodromes are often short or non-existent, sometimes preceded by palpitations. Patients with cardiac syncope face increased risks of death from any cause, non-fatal myocardial infarction, coronary heart disease death, and fatal or non-fatal stroke compared to controls. Various prognostic markers and risk calculators, including OESIL Score, San Francisco Score, EGYS Score, and Rose Score, help stratify sudden death risk in syncope patients.[15-18]

The two initial exams for cardiac syncope are ECG and echocardiogram. They are crucial for risk stratification.

Red flags for cardiac syncope and similarly for CA include abnormal ECG and/or echocardiogram.

In amyloidosis, multiple mechanisms are possible (Figure 1), and not infrequently, more than one of them contributes to manifestation of syncope. However cardiac syncope should always be looked for.

Syncope in Amyloidosis

CA initially manifests as HFpEF with reduced left ventricular end-diastolic volume and impaired diastolic functioning resulting in diminished stroke volume and cardiac output. Dilatation of both atria develops due to raised left ventricular filling pressures. The interstitial amyloid deposition leads to restrictive cardiomyopathy. Consequently, arrhythmias are common in CA, with atrial fibrillation (AF) being the most common, although complex ventricular arrhythmias (VA) are also observed. Atrioventricular (AV) conduction system disease and sinus disease have also been described.[6,19-24] All these rhythm disturbances can cause syncope as they can contribute to an additional decrease in cardiac output.[2]

Common symptom constellations of AL include HFpEF, nephrotic range proteinuria, organomegaly due to amyloid deposition (hepatomegaly, macroglossia, enlarged salivary glands, etc.), peripheral and autonomous neuropathy, and constitutional symptoms (weight loss, fatigue).[25] In AL, infiltration of cardiac structures, which is a consequence of plasma cell dyscrasia, can damage the tissues in two ways: first, amyloid deposits in the extracellular space of the myocardium and coronary blood vessels, which results in cardiomyocyte necrosis and interstitial fibrosis; second, it is thought that oxidative stress due to circulating light chain toxicity is directly myotoxic, which is unique to AL and may be responsible for the rapid progression to cardiomyopathy in patients with AL.[26] In addition to diastolic dysfunction, caused by cellular and interstitial damage, AL can also manifest with rhythm disturbance due to amyloid deposits in the conduction system (with sinoatrial and/or AV fibrosis).[2,7,21] Faraj et al. reported a
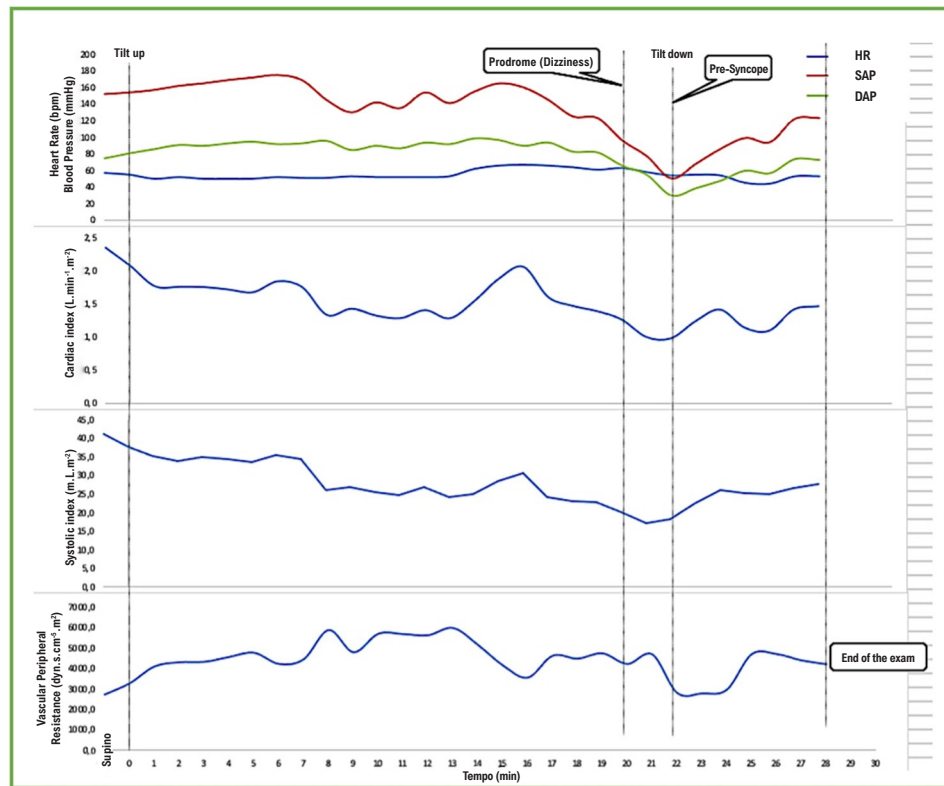
Figure 2 – Example of delayed OH (nOH) in tilt table test.

case of accelerated junctional rhythm as initial arrhythmic presentation of AL, followed by complete heart block (CHB) and syncope,[27] which highlights the possible occurrence of substitution rhythms.

ATTR is a condition where TTR, a physiological protein synthesized by the liver, misfolds into insoluble β-pleated sheets and deposits as amyloids in the extracellular space of the myocardium. TTR is always present in serum, its physiological role being the transportation of retinol and thyroxine. The inherent propensity of TTR to fold and aggregate into insoluble amyloid fibers can be increased by a single-point mutation, as in hereditary TTR amyloidosis (h-ATTR). Wild-type TTR amyloidosis (wt-ATTR) is similar to h-ATTR, except that it is non-hereditary (sporadic), and the precursor protein is structurally normal TTR. It was also known as "senile systemic amyloidosis" and is still an underdiagnosed disease, accounting for a significant number (13%) of HFpEF cases.[28]

The h-ATTR phenotype varies based on the causative genetic mutation, tending to be either cardiac-predominant or neuropathy-predominant, determined by the amino acid substitution site on the TTR gene. For example, those with the Val30Met TTR mutation commonly have heart conduction issues requiring pacemaker (PM) implantation. Other variants like Val122Ile and Thr60Ala commonly affect the cardiovascular system, but less frequently primarily impact the conduction system. Importantly, those with wt-ATTR have a greater probability of rhythm disturbances (typically AF) than those with h-ATTR.

A valuable red flag for suspecting ATTR is a history of hypertension that resolves over time and intolerance of angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, or beta-blockers, which not infrequently leads to pre-syncope, syncope, and worsening fatigue on exertion.

The typical pattern of h-ATTR amyloid neuropathy is an ascending symmetrical length-dependent sensorimotor axonal polyneuropathy. Interestingly, patients with the Val122Ile mutation have more severe neurological symptoms and walking disability than those with wt-

ATTR. As in AL, h-ATTR is also associated with autonomic neuropathy, primarily presenting with gastrointestinal symptoms. The numerous diagnostic red flags, like bilateral carpal tunnel syndrome, tendon rupture, and lumbar spinal stenosis, are all associated with h-ATTR. In wt-ATTR, the heart is usually the most clinically affected organ. However, signs of HF may be preceded by lumbar spinal stenosis or bilateral carpal tunnel syndrome by 10 to 15 years.[29-31]

Literature data show that syncope is uncommon in ATTR (8%) and more frequent in AL (20%).[32] When it occurs during exertion, it represents the inability to increase cardiac output, which leads to high mortality. In addition, sensitivity to intravascular fluid depletion combined with autonomic neuropathy, depressed myocardial reserve, atrial dysfunction, and rigidity, and the presence of arrhythmias contribute to the occurrence of syncope. All these possibilities make syncope a multifactorial presentation in CA.[33]

nOH is a prominent and disabling manifestation of autonomic dysfunction in patients with h-ATTR, affecting an estimated 40% to 60% of patients and reducing their quality of life. As mentioned above, OH in patients with h-ATTR can be a consequence of HF due to amyloid cardiomyopathy or volume depletion due to diarrhea or drug effects. When none of these circumstances are apparent, OH is usually neurogenic, caused by impaired norepinephrine release from sympathetic postganglionic neurons due to neuronal amyloid fibril deposition. It is frequent, early, and severe in patients with the early-onset Val30Met mutation disease, but appears to be less severe in Val30Met cases with late-onset disease.[34,35] OH is also present in up to 100% of patients with the Ala97Ser mutation, with 71% of them having frequent syncope, particularly in the late stages of the disease. Conversely, OH appears to be infrequent in patients with TTR mutations with a high prevalence in Scandinavian countries (Ala45Ser, Tyr69His, Leu111Met variants) and in patients with the Val122Ile mutation, which is the most common TTR mutation in African Americans.[36-38] In a recent study involving > 3000 subjects enrolled in the multinational, longitudinal, observational Transthyretin Amyloidosis Outcomes Survey (THAOS), 58.7% had symptomatic OH. Moreover, the severity of the fall in BP when standing appeared to worsen at annual follow-ups, reflecting the progressive nature of autonomic failure. More pronounced orthostatic BP reductions were associated with increasing age, worse polyneuropathy disability stage, and diarrhea.

Autopsy studies in patients with h-ATTR and severe OH showed amyloid-related degeneration of the peripheral autonomic nervous system, namely, anterior, and posterior roots of the spinal cord, sympathetic ganglia, postganglionic sympathetic nerves, and the vagus nerve. Neuronal density in the intermediolateral column of the spinal cord was reduced, and there was degeneration of sympathetic postganglionic cholinergic fibers. Plasma levels of norepinephrine, the main sympathetic neurotransmitter, are severely reduced and fail to increase when standing in patients with h-ATTR.[39] Moreover, administration of norepinephrine elicits noteworthy increases in HR and BP, indicating sympathetic denervation oversensitivity.

The mechanisms of nOH in h-ATTR are similar to those of peripheral neurodegenerative synucleinopathies, like Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure, in which dysfunction of the sympathetic nerves is mediated by accumulation of another misfolded protein, α-synuclein, highlighting the high affinity that both misfolded TTR and α-synuclein have for the autonomic nervous system. Furthermore, studies with 123I-metaiodobenzyiguanidine (MIBG) cardiac neuroimaging showed reduced cardiac sympathetic innervation, which can be present before any abnormal echocardiographic sign.[40] Moreover, cardiac sympathetic denervation predicts worse prognosis.[13]

Treatment

The initial steps of syncope treatment in CA involve recognizing red flags for disease diagnosis, confirming the event as syncope, accessing the risk of death, excluding rhythm disturbances, and ensuring cautious prescription to avoid harm.

Drugs that reduce intravascular volume (diuretics), induce vasodilatation (sildenafil, nitrates, vasodilators), block the pressure drop through a physiological compensation mechanism (beta-blockers), or block norepinephrine release/activity at the neurovascular junction (α-blockers, centrally acting α2-agonists, tricyclic antidepressants) worsen nOH and symptoms. Anemia also can worsen nOH and should be investigated and treated with erythropoietin (25 to 50 units/kg, subcutaneous, 3 times a week) and iron supplements. It is fundamental to make sure that there is no blood loss as a cause of hypovolemia.[13] Additionally, anemia is a high-risk feature in syncope patients at initial emergency department evaluation, suggesting gastrointestinal bleeding.[8]

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Commonly prescribed HF drugs have been proven to be unhelpful in CA. Angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers decrease mortality in most patients with HF. However, in patients with amyloidosis-induced HF, these drugs are detrimental. Angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers promote hypotension due to the added effect of autonomic dysfunction and can only be tolerated in low doses in patients with predominant cardiac phenotype. Similarly, beta-blockers have been shown to provoke bradycardia in these patients. Calcium channel blockers are ineffective due to the strong binding of the drug to amyloid fibrils, leading to worsening HF, hypotension, and syncope. Strong binding to amyloid fibrils can also occur with the use of digoxin, leading to digitalis toxicity, which includes yellow-tinted vision, cholinergic agonism, and arrhythmias.[2]

When OH is the cause of syncope, patients must be aware of the diuretic effects of alcohol and avoid sugary beverages (e.g., bottled juices and soda) because of the hypotensive effects of high-glycemic index carbohydrate ingestion. Fluid intake should be 2 to 2.5 L/day. Patients should be encouraged to increase salt intake by adding 1 to 2 teaspoons to a healthy diet. In patients with nOH, drinking 0.5 L of water produces a marked increase in BP, and this can be used as a rescue measure since the pressor effect is quick (peaks in around 30 minutes), although short-lived.[13]

On the other hand, cardiomyopathy and HF are present in many patients, complicating the management of nOH, as treatment of HF typically involves reducing the cardiac preload with diuretics, causing intravascular volume depletion, which worsens nOH. Similarly, diarrhea, a manifestation of gastrointestinal involvement in h-ATTR, causes volume depletion and aggravates nOH. The challenge is to avoid both hypovolemia and hypervolemia in patients with mixed phenotypes of cardiomyopathy and neuropathy.

Daytime hypertensive episodes are of lesser importance, while sleep-time hypertension should be treated if BP consistently exceeds 160/90 mmHg in uncomplicated cases (symptomatic OH without concomitant target-organ damage), preferably below 140/90 mmHg in patients with a history of cerebrocardiovascular disease, diabetes, or renal failure. A reverse dipping pattern with OH is particularly detrimental, indicating more than a doubled risk of incident cardiovascular disease. Thus, reducing nighttime BP and restoring normal sleep-time dipping are crucial, preferably with short-acting drugs like losartan, captopril, or hydralazine, which are easily monitored with repeated 24-hour ambulatory BP monitoring and patient diaries.[8] In severe cases, discontinuing antihypertensive treatment may be the only solution if the patient remains symptomatic despite treatment modification. Other educational methods include avoiding immobilization, prolonged recumbence, and physical deconditioning; gradually rising from supine and sitting positions, especially in the morning, after meals, and after urination/defecation; adapting to small and frequent meals; learning physical counterpressure maneuvers (e.g., leg crossing, muscle tensing, squatting) in the standing position and at the onset of prodromal symptoms; and sleeping with a head elevation of 10 to 30 degrees.[12] It is also critical to treat sarcopenia and do strength exercises for the legs and abdomen (Figure 3).

Even with proper non-pharmacologic methods, many patients still need pharmacologic treatment for symptomatic nOH. Two common strategies are expanding intravascular volume with fludrocortisone and increasing peripheral vascular resistance with midodrine or droxidopa. Selection depends on each patient's features, needs, peripheral sympathetic denervation, and heart disease degree.[13]

In reflex syncope, besides avoiding triggers, treating hypovolemia, stopping polypharmacy, and increasing salt and water intake, pharmacologic treatment may be necessary. The same drugs, midodrine and droxidopa (for low BP phenotype), are used if non-pharmacological approaches fail. PM implantation is recommended for dominant cardioinhibition, especially in older patients with CA. In the same group with short or non-existent prodromes, loop recorder implantation is advised due to the likely occurrence of arrhythmias.[8]

Cardiac syncope in CA, when caused by rhythm disturbance, will need a specific approach for each finding as will be addressed next.

Pharmacologic treatment of ATTR begins with drugs that avoid amyloid deposition, acting as TTR stabilizers (diflunisal and tafamidis) and RNA interference agents (patisiran and inotersen) in both hereditary and wild type.[41-45] There are 2 drugs approved and tested in large randomized trials for cardiac TTR phenotype: tafamidis and patisiran.[42,45]

The AL type is preferentially treated with stem cell transplants, chemotherapy, and proteasome inhibitors. The goal of treatment for AL is to reduce the production

Figure 3 – Treatment of nOH treatment in CA
CA: cardiac amyloidosis; HF: heart failure.
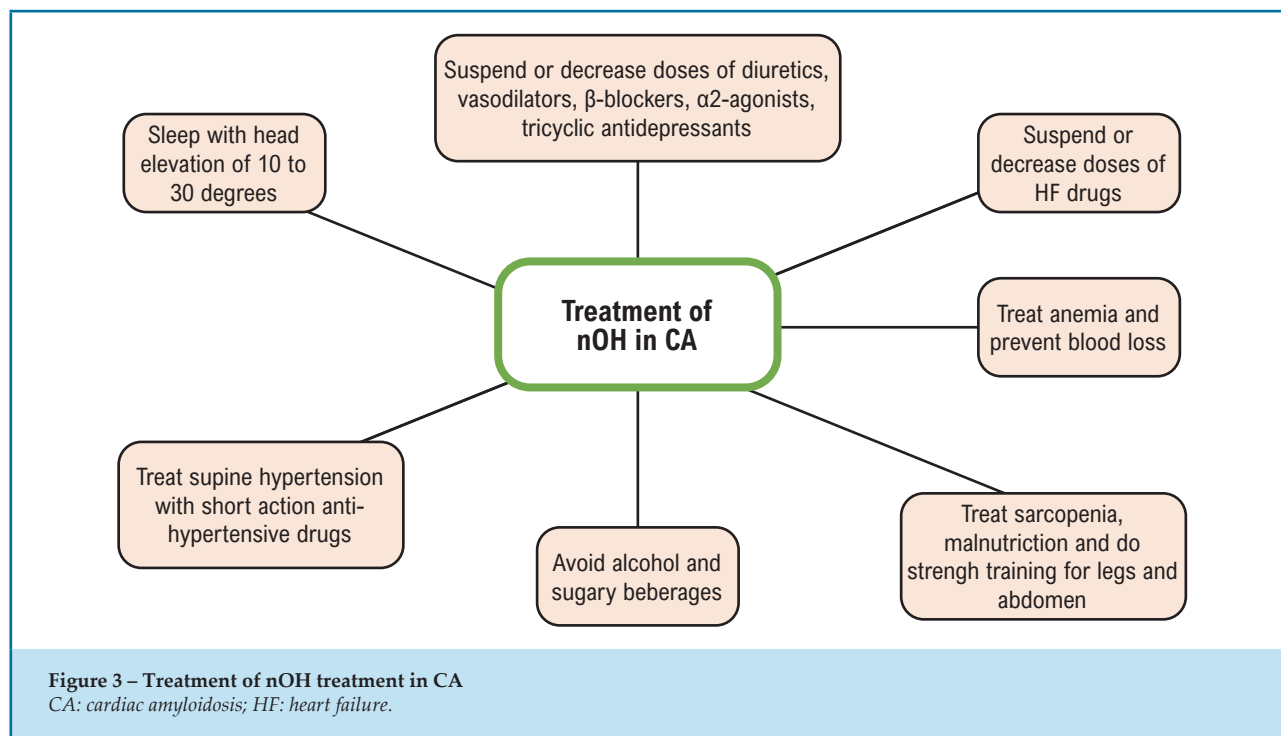
of light chains, remove light chain amyloid deposits, and inhibit amyloid fibril formation. The current standard of care for patients with AL is chemotherapy using cyclophosphamide, bortezomib, and dexamethasone (CyBorD). In the ANDROMEDA study (phase 3), daratumumab, (DARA-SC), a drug used in the treatment of multiple myeloma, was studied in conjunction with CyBorD. It demonstrated robust hematologic and organ responses. In patients with cardiac involvement of amyloidosis, the median time to respond was 114 days.[46]

Rhythm disturbance in amyloidosis

Rhythm disturbances are common in CA and are sometimes the initial clinical manifestation of this disease. Furthermore, rhythm disorders contribute to both the worsening of HFpEF symptoms and the decrease in cardiac output, which may contribute to the occurrence of syncope.

Pathophysiological mechanisms of cardiac arrhythmias in CA

The mechanism involved in the genesis of cardiac arrhythmias in amyloidosis is not unique, but multifactorial. The pathophysiology of CA with deposition of fibrillar proteins in the extracellular myocardial environment leads to increased filling pressures of cardiac cavities,

which culminate in electromechanical remodeling as a final pathway[7] (Figure 5). Amyloid deposits in the perivascular site, especially in the AL form, lead to microvascular dysfunction, and these inflammatory microregional changes can act as an arrhythmogenic substrate or even determine direct aggression with an increase in intracellular reactive oxygen species.[26,47] The characteristic of infiltrative cardiomyopathy, associated with secondary inflammatory damage or even the occupation of the extracellular space by polarized proteins, can directly damage the conduction system, leading to the emergence of conduction disorders such as intraventricular conduction delay, AV node conduction disorders, or even sinus dysfunction.[27]

Heart conduction system diseases

Cardiac involvement in amyloidosis can lead to conduction disturbances, with ECG manifestations. These manifestations range from changes in QRS duration to intraventricular bundle branch blocks, fascicular blocks, or even AV blocks. At the atrial level, we can find sinus node dysfunction. However, the main form of conduction system involvement is His-Purkinje system dysfunction, manifested by prolongation of the HV interval in invasive electrophysiological study.[24] These findings demonstrate a predilection for amyloid infiltration in the basal portion

of the septum, leading to impairment of the His-Purkinje system.[48] Spontaneous episodes of sinus dysfunction mediated by autonomic changes have been described.[49]

The incidence of AV block is higher in the ATTR subtype, probably due to the longer survival of these patients, which culminates in the progression of nodal dysfunction.[7]

In small cohorts of patients with the AL type with advanced heart disease, routine loop recorder implantation showed that all deaths were preceded by bradycardia (most of them by CHB).[6,50]

Eoin et al. found a high prevalence of high-grade AV block requiring definitive PM implantation in a cohort of 369 patients with ATTR. About 9.5% had a diagnosis of ATTR at the time of definitive PM indication, and at 28-month follow-up, 10% of patients with h-ATTR and 12% of patients with wt-ATTR had high-grade AV block. The most evident conduction abnormalities on baseline ECG were increased QRS duration (51% of wt-ATTR patients and 48% of h-ATTR patients), followed by first-degree AV block (39% of wt-ATTR patients and 43 % of patients with h-ATTR), but only increased QRS duration was associated with the development of subsequent high-grade AV block in this study.[51]

Another noteworthy finding in CA is the possibility of HV interval prolongation with narrow QRS duration (< 120 ms) (Figure 4) due to diffuse infiltration involving both left and right branches, leading to a balanced delay in intraventricular conduction.[24]

Atrial arrhythmias

The infiltrative deposit leading to restrictive cardiomyopathy also leads to increased intracavitary filling pressures and evolution to the emergence of atrial electrical and mechanical remodeling. In this context, the manifestation of atrial arrhythmias is not infrequent. AF represents the most frequent arrhythmia in CA.[52]

Patients with the wt-ATTR form have a higher incidence of atrial arrhythmias, mainly AF, with a higher prevalence.[7] Previous data show an incidence of approximately 62% of AF in the ATTR type.[53]

Both atrial tachycardia and AF emergence can cause clinical decompensation due to rhythm irregularity and the lack of adequate atrial contractility, compromising ventricular filling. Patients with CA typically exhibit significant atrial remodeling at diagnosis. Even in cases without AF, anticoagulation may be necessary, irrespective of the CHA2DS2-VASc score. Despite advances in
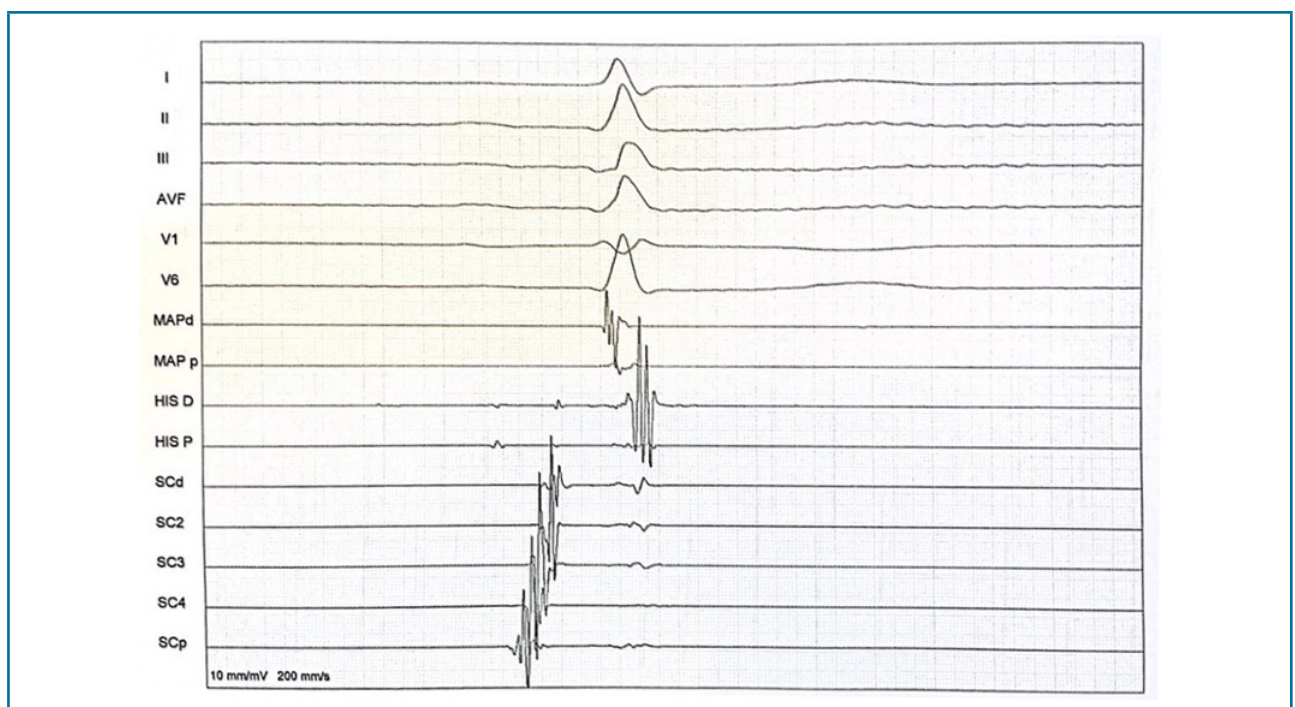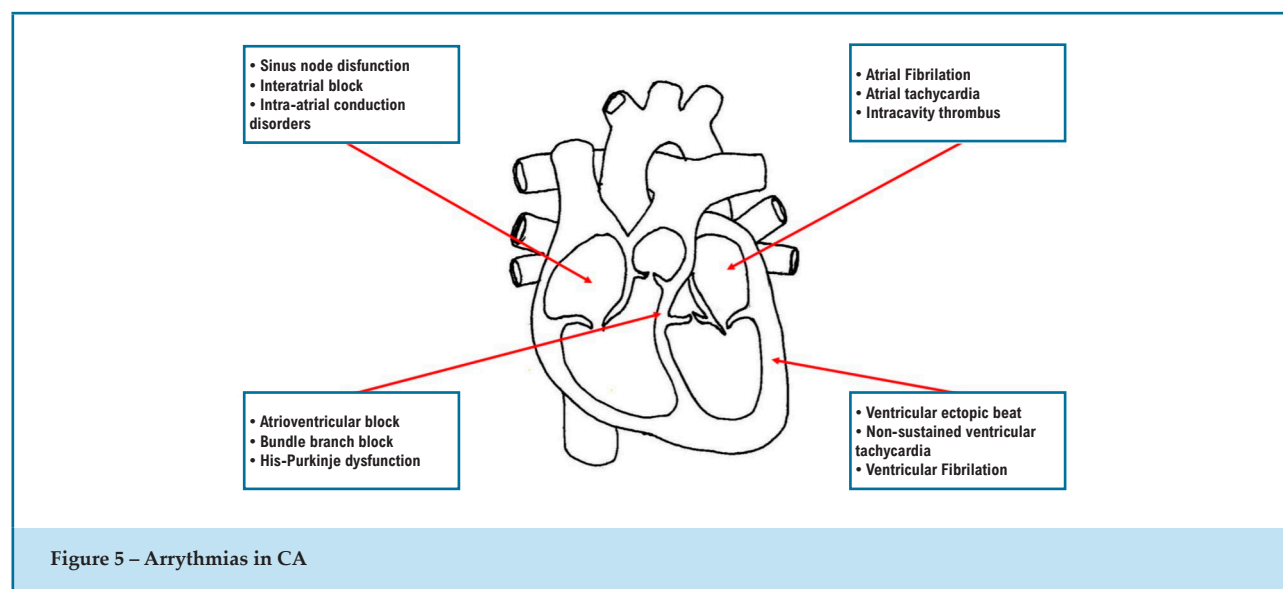

Figure 4 – His bundle potential during ablation procedure in patients with amyloidosis, normal QRS duration, and His dysfunction. HV: 88 ms; AH: 83 ms.

Figure 5 – Arrythmias in CA

radiofrequency ablation, AF recurrence rates after ablation are high, reaching 83%, compared to 23% in AF patients without CA.[7]

Regarding the use of antiarrhythmic drugs, amiodarone represents the best option for rhythm control. Beta-blockers, calcium channel blockers, and digitalis, commonly prescribed for rate control, should be used with caution.[7,54]

VA

Advanced stages of HF are the main cause of death in patients with CA, and VA is part of this scenario. AL has a higher incidence of VA when compared to the ATTR type.[7]

Electrophysiological data from patients with CA show intraventricular conduction delay, smaller and fractional epicardial potentials, as well as longer and more dispersed repolarization.[55] These changes favor the development of VA.

The presence of ventricular ectopic beats, non-sustained ventricular tachycardia, and sustained ventricular tachycardia have been related to sudden cardiac death events.[56] A study with Holter monitoring found 72% of ventricular ectopic beats and 18% of non-sustained ventricular tachycardia in patients with AL-type amyloidosis.[57] Sustained ventricular tachycardia can be induced during an electrophysiological study or even documented in an implanted cardioverter-defibrillator (ICD). However, it is infrequent in CA when compared to other cardiomyopathies.[58]

Some authors suggest that the presence of non-sustained ventricular tachycardia in patients with CA should be considered a risk factor in decision-making for ICD implantation.[62]

Ventricular fibrillation can result from ventricular ectopic beats originating in the His-Purkinje system, particularly in patients with ischemic cardiomyopathy. On the other hand, the cause of ventricular fibrillation in patients with CA is not well understood.[48]

Sudden cardiac death and ICD Implantation in CA

Studies indicate that half of patients with CA experience sudden death. However, there is no consensus on ICD implantation, whether for primary or secondary prevention.[54] The main factors that corroborate this scenario are the poor prognosis of these patients, with low survival after diagnosis, and the high defibrillation thresholds of patients with CA. Besides that, previously published data show that the leading cause of sudden death in this population is related to electromechanical dissociation, culminating in pulseless electrical activity, and not due to shockable malignant VA.[59]

Most studies evaluating ICD in CA have a small number of participants. In a series that evaluated 19 patients who had implanted an ICD, 11% received appropriate device therapy.[60] Another study found 28% of appropriate device therapy in 1 year.[61]

Therefore, ICD implantation in CA is still controversial and should consider the stage of HF, 1-year survival, and the presence of non-cardiac factors that may influence short-term mortality.

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Definitive PM in CA

Conduction disorders are prominent in CA. Fibrillar protein infiltration in the basal septal region notably affects the His-Purkinje system, often necessitating permanent PM implantation. This requirement is common in CA patients with severe conduction system disorders, especially in patients with wt-ATTR.[38]

In a large cohort of patients with AL and ATTR-CA, 8.9% received a PM within 3 years after diagnosis.[62] The study population comprised 405 patients: 29.4% AL, 14.6% h-ATTR, and 56% wt-ATTR; 82.5% were male, median age 76 years. During a median follow-up of 33 months, 36 (8.9%) patients experienced the primary outcome: 10 AL, 2 h-ATTR, and 24 wt-ATTR (p = 0.08 at time-to-event analysis). At multivariable analysis, history of AF, PR interval, and QRS > 120 ms on baseline ECG were independently associated with PM implantation. The absence of these 3 factors had a negative predictive value of 92% with an area under the curve of 92% at 6 months.

Right ventricular (RV) cardiac pacing is a globally established technique for correcting bradyarrhythmias. However, it can lead to electrical dyssynchrony and, consequently, to mechanical dyssynchrony, with the possibility of worsening HF symptoms.[63] A study analyzed consecutive patients receiving permanent PM from 2000 to 2014 for CHB with left ventricular ejection fraction (LVEF) > 50%. Of the 823 study patients, 101 (12.3%) developed PM-induced cardiomyopathy (PICM) over the mean follow-up of 4.3 ± 3.9 years, and post-PM implantation LVEF was 33.7% ± 7.4% in patients with PICM versus 57.6% ± 6.1% in patients without PICM (p < 0.001). In multivariable analysis, lower pre-PM LVEF and RV pacing % both as a continuous and categorical variable (< 20% or ≥ 20% RV pacing) were independently associated with PICM. Thus, PICM is not uncommon in patients receiving PM implantation for CHB, even in patients with preserved LVEF, and it is strongly associated with RV pacing burden > 20%.[64]

Regarding the best mode of cardiac pacing, the literature is still scarce about the indication of cardiac resynchronization therapy (CRT) as preferential to single RV pacing in these patients, since the population of HF patients, where CRT is more effective, are those with left bundle branch block (LBBB) morphology, aiming to reduce symptoms and left ventricular size and increase LVEF. In contrast, patients with CA have a small left ventricular cavity, ECG with various manifestations of non-LBBB conduction disturbances, and often develop AF, which makes these patients less eligible for CRT.[6] On the other hand, some case reports have demonstrated clinical and echocardiographic improvement after CRT implantation in patients with advanced CA and HF. In a recent retrospective study with 78 patients with ATTR, CRT led to improvement in LVEF and functional class, reduction of mitral regurgitation, and stabilization of NT-ProBNP levels, compared to those with exclusive RV pacing > 40%.[65] Taking this into account, PM implantation in patients with CA can precipitate worsening of ventricular function with RV exclusive pacing > 20% to 40%, due to the high incidence of first-degree AV block and high-grade AV block in this population, and it is not always possible to avoid a high percentage of RV pacing.[51,66]

Nowadays, a growing publication of studies comparing CRT with physiologic stimulation has shown that mechanical and electrical resynchronization seems to be equally or even more effective with His or left bundle branch stimulation,[67] which may also be one of the options of choice in the near future.[63,68-76] While robust multicenter randomized studies to answer these questions have not been published yet, the decision regarding the type of stimulation of patients with CA should be made after a multidisciplinary discussion, weighing the severity of symptoms and the risks, combined with the expected benefit.

The application of multimodality imaging to identify areas of amyloid infiltration can optimize left ventricular pacing.

Conclusion

Syncope and rhythm disturbances are common findings in CA. It is important to keep in mind that such symptoms can appear at the beginning of the disease, as well as during its course, in both the ATTR and AL forms. Thus, syncope and arrhythmias must be incorporated as signs and symptoms that corroborate warning signs for the diagnosis of CA.

Author Contributions

Conception and design of the research: Nunes N, Marques E, Gismondi RA, Nascimento E; acquisition of dat and, writing of the manuscript: Nunes N, Nascimento E; analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Marques E, Gismondi RA.

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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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