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REVIEW

Early-Excitation Segment Atrophy (EESA) Syndrome: Linking Electrical Dyssynchrony to Regional Myocardial Atrophy

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ABSTRACT

Identifying the underlying cause of cardiac dysfunction is essential for determining the appropriate treatment and prognosis. The current management paradigm for heart failure (HF) and cardiomyopathies predominantly emphasizes structural and ischemic etiologies, often overlooking the substantial role of electrical dyssynchrony in cardiac dysfunction and remodeling. This work introduces a novel conceptual framework that integrates existing evidence illustrating how electrical dyssynchrony induces mechanical dyssynchrony, culminating in regional cardiac impairment and structural remodeling. The myocardial area that activated early lacks proper afterload, impairing its ability to perform work effectively. Consequently, disuse atrophy gradually manifests in the early activation area over time. We propose the concept of early-excitation segment atrophy (EESA) syndrome to address the HF caused by asynchronous conduction. For the left ventricle, whichever part contracts first will become disused and may contribute to or exacerbate HF. The conduction abnormalities known to induce EESA include left bundle branch block (LBBB), right ventricular pacing (RVP), bilateral bundle branch block (BBBB), Wolff–Parkinson–White (WPW) syndrome, and premature ventricular contractions (PVCs). Appropriate diagnosis and treatment will lead to improved left ventricular ejection fraction and reduced mortality. By integrating EESA into clinical practice, we aim to improve the recognition and management of dyssynchrony-induced cardiomyopathies, ultimately enhancing patient outcomes. This review presents an update of the mechanisms, prevalence, incidence, and risk factors, as well as their diagnosis and management, while highlighting current gaps of knowledge.

1 | Introduction

The management of heart failure (HF) is primarily focused on identifying the underlying cause of cardiac dysfunction, as the specific pathology plays a crucial role in determining the subsequent treatment and predicting the prognosis. While the etiology of HF has always been attributed to coronary artery disease, valvular heart disease, cardiomyopathy, hypertension, or sustained tachyarrhythmias [1, 2]. However, current frameworks fail to address how electrical dyssynchrony drives regional dysfunction. Specifically, the impact of asynchronous conduction on cardiac mechanics and long-term remodeling has not been fully integrated into the clinical approach to HF management. Conditions such as left bundle branch block (LBBB), right ventricular pacing (RVP), and premature ventricular contractions (PVCs) can induce mechanical dyssynchrony, leading to regional cardiac dysfunction and remodeling [3, 4]. These conditions are often reversible with appropriate

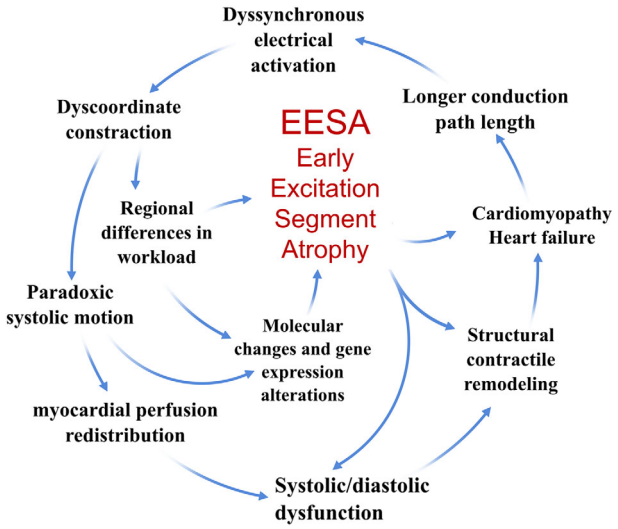

FIGURE 1 | Schematic representation of maladaptive processes following the onset of dyssynchronous activation. Various acute consequences of dyssynchronous electrical activation led to uncoordinated cardiac contraction. The myocardial region that is activated early lacks proper afterload, impairing its ability to perform work effectively. Consequently, disuse atrophy gradually manifests in the early activation area of the myocardium over time. Regional differences in molecular changes and gene expressions are also involved in this process. In the long term, the clinical manifestations are evidenced by a lower LVEF, lower strains, and ventricular dilation. Moreover, the conduction disturbance and the cardiac remodeling in patients with cardiomyopathy interact to produce a vicious cycle. [Color figure can be viewed at wileyonlinelibrary.com]

interventions, yet they are frequently not recognized as potential causes of HF.

To address this, we propose the concept of the early-excitation segment atrophy (EESA) syndrome, which focuses on specific arrhythmias that may induce mechanical dyssynchrony and subsequent cardiac remodeling. The normal functioning of the His-Purkinje system is essential for cardiac synchronization. When electrical activation is asynchronous, the earliest-depolarized segment contracts against a markedly reduced afterload while the rest of the myocardium remains electrically—and therefore mechanically—quiescent. This temporal mismatch, termed mechanical dyssynchrony, deprives the early-activated region of its physiological workload, inducing a progressive disuse atrophy that manifests as regional thinning, weakening, and maladaptive remodeling. Regional differences in molecular changes and gene expressions are also involved in this process [4] (Figure 1).

Critically, EESA should not be viewed merely as a synonym for "dyssynchrony-induced" or "arrhythmia-induced cardiomyopathy," but rather as a focused mechanistic perspective within this broader category—one that emphasizes regional myocardial unloading and disuse atrophy as central drivers of remodeling. While terms such as abnormal conduction–induced cardiomyopathy describe clinical associations, EESA highlights a distinct biological pathway rooted in altered biomechanical loading due to asynchronous depolarization. What is novel about EESA is its emphasis on early-segment deconditioning, analogous to skeletal muscle disuse atrophy, which provides a rationale for early intervention before irreversible structural changes occur. This distinction has direct implications for ablation or resynchronization strategies aimed at "re-loading" the atrophied segment.

EESA encompasses a range of conduction abnormalities, including LBBB, RVP, bilateral bundle branch block (BBBB), Wolff–Parkinson–White (WPW) syndrome, and PVCs. These conditions share a unified pathophysiological mechanism: asynchronous electrical excitation, mechanical dyssynchrony, regional myocardial atrophy, and long-term cardiac remodeling. The EESA paradigm underscores the imperative to identify—and promptly correct—the culprit dyssynchrony. It highlights the need for targeted interventions such as cardiac resynchronization therapy (CRT) or catheter ablation. Embedding this paradigm into clinical practice will facilitate early diagnosis, guide targeted therapy, and ultimately reduce the morbidity and mortality of affected patients. In this paper, we aim to review the pathophysiology of these conduction abnormalities, specifically their role in inducing ventricular mechanical dyssynchrony. Additionally, we will also discuss the prevalence, predictors, and prognosis associated with EESA.

Recognizing EESA in clinical practice requires integration of medical history (whether conduction abnormalities preceded systolic dysfunction), electrocardiographic (prolonged QRS duration, typical LBBB morphology, paced rhythm with RV apex stimulation, pre-excitation patterns in WPW, or high PVC burden, especially with LBBB-like morphology), imaging (regional LV thinning and characteristic strain patterns showing reduced work in early-activated segments and increased work in late-activated regions), and hemodynamic findings (improvement in LV ejection fraction (LVEF) following correction of the conduction abnormality). These features help to distinguish primary structural cardiomyopathy with secondary conduction disease from conduction-driven cardiomyopathy via EESA.

2 | LBBB

The relationship between LBBB and HF was first proposed by the Framingham study [5]. During an 18-year follow-up period, 28% of the case subjects who were initially free from HF developed HF after the onset of LBBB. LBBB is considered to be a manifestation of underlying cardiomyopathy, and subsequent observational studies have confirmed its independent association with an increased risk of HF hospitalization and mortality [6–8]. Although LBBB is rare in the general population (less than 1%) [9], it has garnered great interest among cardiologists due to registries reporting rates as high as 20%–30% among patients with HF [10–13]. Furthermore, there has been recent attention on iatrogenic LBBB occurring after aortic valve interventions, with reported rates ranging from 4% to 30% with a balloon-expandable valve and 18%–65% with a self-expanding valve [14, 15].

Earlier studies have suggested that LBBB is a reversible cause of cardiomyopathy and HF. In a prospective study involving 29 patients with dilated cardiomyopathy and LBBB, complete reversal of left ventricular (LV) dysfunction was observed in a small but noteworthy subset (17%) of the patients after CRT, leading to the emergence of the concept of LBBB-induced cardiomyopathy [16]. Vaillant et al. [17] reported that HF may

develop after an average of 11.6 years of LBBB, with LBBB-induced cardiomyopathy identified in 1.6% of 375 patients receiving CRT. The specific syndrome was characterized by isolated LBBB and a history of progressive LV dysfunction, successfully treated by CRT.

We also reported a case series [18] showing that patients with LBBB-induced cardiomyopathy had a positive response to CRT. Furthermore, characteristic patterns of LV contractility and deformation could be identified using CMR tissue tracking. Atrophy of the LV septum and preservation of the lateral wall in patients with LBBB may serve as indicators for reversible cardiomyopathy and a favorable response to CRT.

It has been suggested that LBBB induces myocardial remodeling, which includes asymmetric hypertrophy, fiber disarray, and altered perfusion distribution. These changes contribute to LV dilatation and dysfunction, particularly manifesting as atrophy of the LV septum and hypertrophy of the LV lateral wall [19–22] (Figure 2).

In patients with LBBB, the early-activated septum contracts while the LV lateral wall is stretched (Figure 2B). This early septal peak shortening, which occurs within the first 70% of the ejection phase under minimal afterload, displaces blood opposingly and creates a high preload for the LV lateral wall. However, this does not lead to a significant increase in LV pressure, indicating the myocardial work of septal shortening is negligible or negative. When the lateral wall is activated, it contracts vigorously under high preload (in accordance with the Starling mechanism), displacing blood back toward the septum, which is then over-stretched toward the right ventricle. This process causes the septum to absorb energy from the work performed by the LV lateral wall. The increased preload in the LV lateral wall (due to early over-stretching) induces relative hypertrophy (Figure 2B). However, in patients with LBBB, the LV lateral wall peak shortening may occur after aortic valve closure, significantly impairing cardiac pump function during systole [18, 25].

LBBB also results in a redistribution of myocardial shortening and blood flow from the septum to the LV lateral wall [26, 27]. The under-perfusion of the septum is likely a functional adaptation to the reduced workload and decreased local oxygen demand in the early activated myocardial region [23, 28]. The abnormal septal motion, which increases intramyocardial pressure and shortens the diastolic period of coronary perfusion, may also impair septal perfusion. As a result, patients with LBBB appear to experience functional myocardial ischemia, which likely contributes to septal hypokinesia in addition to interstitial fibrosis. Over the long term, LBBB leads to cardiac remodeling and asymmetric LV dilatation [29] (Figure 2C).

Cardiac magnetic resonance (CMR) tissue tracking can be a valuable tool in identifying the unique abnormal movement of the septal wall and preserved systolic function of the LV lateral wall in patients with "LBBB-induced cardiomyopathy." In a CMR study of 63 patients with HF and LBBB, the temporal relation between HF and LBBB was determined in 14 patients. CMR imaging revealed a distinctive strain pattern and LV morphology in patients with "LBBB-induced cardiomyopathy." These individuals exhibited paradoxical movement of the septal wall during systole and retained systolic function (measured by lateral wall thickening rate and peak strain) and morphology (assessed by the diastolic lateral wall/septal wall thickness ratio) of the LV lateral wall [30] (Figure 2D).

The area of the LV pressure-strain loop can serve as an indicator of regional myocardial work and metabolic demand. Patients with LBBB demonstrate a marked decrease in the LV pressure-strain loop area in the septum (Figure 2E) [23].

Animal studies have shown that cardiac mechanical unloading (tenotomy) can lead to rapid and significant degeneration of cardiomyocytes following disuse [24]. Intriguingly, extensive loss of contractile elements in the unloaded tissue results in large areas of organelle-free cytoplasm, with the remaining myofibrils predominantly located near the cell periphery (Figure 2F). However, upon reloading after 1 week of unloading, the myofibrils refill the cytoplasm and regain a uniform orientation [31]. We postulate that the same pathophysiology applies to LBBB, where septal unloading could lead to long-term septal disuse atrophy. However, the degeneration of cardiomyocyte morphology and function may be reversible with reloading after cardiac resynchronization.

Furthermore, several other imaging modalities have also been suggested for recognizing characteristic LV contraction patterns in patients with LBBB. For instance, a 2D LV longitudinal strain study using echocardiography speckle-tracking highlighted a typical LBBB strain pattern that demonstrates early contraction in the septal wall and over-stretching of the LV lateral wall, followed by late contraction; this pattern is highly predictive of response to CRT [32]. Likewise, a U-shaped LV contraction pattern, along with a line of conduction block between the septum and lateral wall, has been identified using CMR cine imaging in patients with LBBB. This pattern is associated with a favorable response to CRT. The block line corresponds to the anterior part of the septum, which may serve as an indicator of dyssynchrony-induced atrophy [33].

Notably, in patients with LBBB, dyssynchrony-induced regional differences in gene expression, molecular changes, and key protein alterations are also pronounced [34–38]. The genes exhibiting significant heterogeneity between the early-activated septal and late-activated LV lateral wall are involved in key processes such as metabolic pathways, extracellular matrix remodeling, and myocardial stress responses [35, 36]. Dyssynchrony-induced expression changes can be homogenized by CRT to levels in normal hearts, as demonstrated by a reduction in regional heterogeneity of gene expression and significant reverse remodeling of transcripts with metabolic and cell signaling functions beyond mechano-energetics [37, 38].

Given that LBBB-induced dyssynchrony may be the primary driver of LV dysfunction in many patients with LBBB, guideline-directed medical therapy (GDMT) alone may prove to be an incomplete and ineffective therapy. In selected patients with LBBB and HF, CRT may merit earlier consideration within the treatment pathway, but this strategy still requires confirmation in prospective studies. Moving forward, prospective research should aim to identify the relative contribution of primary

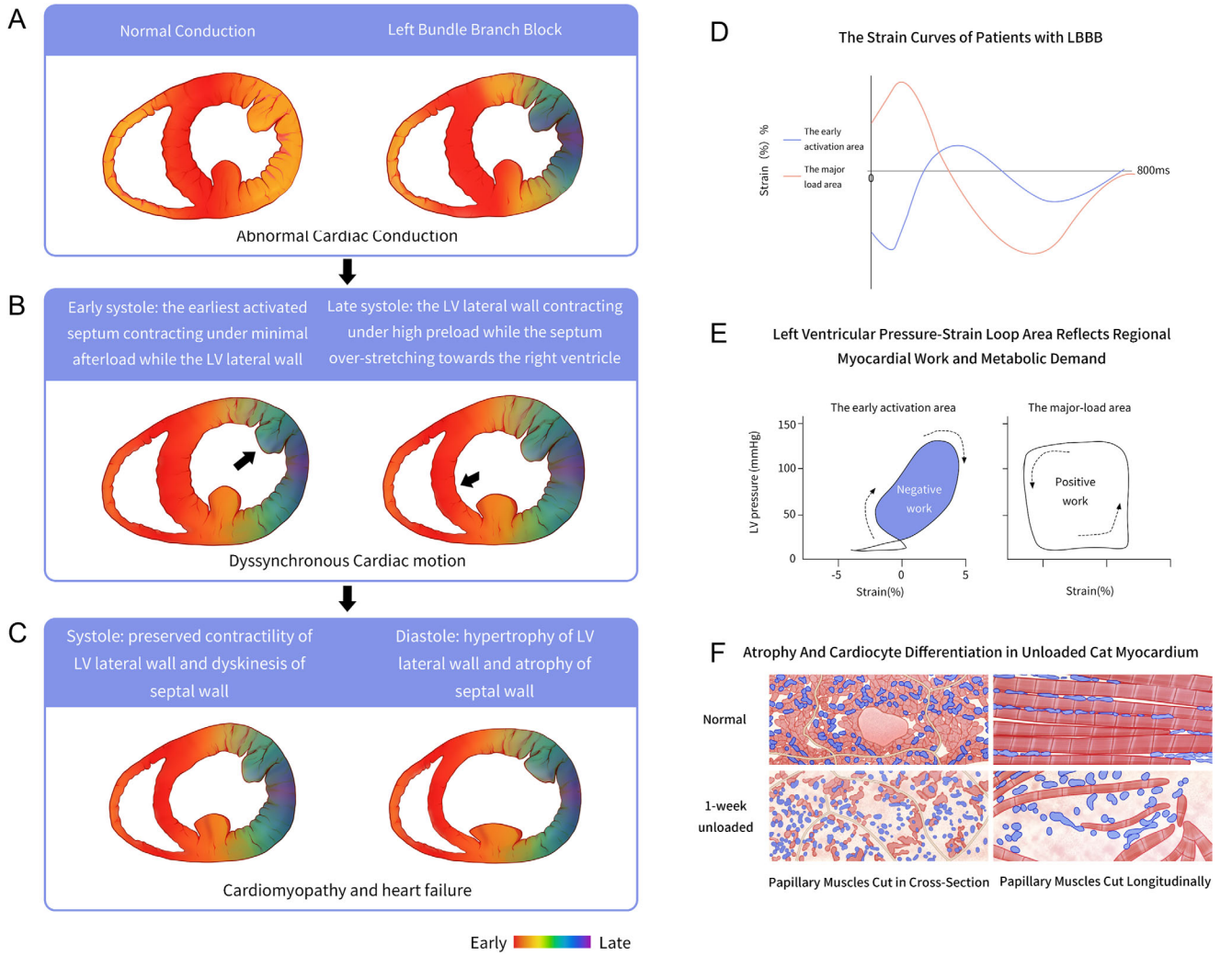

FIGURE 2 | Mechanisms of left bundle branch block–induced cardiomyopathy. (A) Asynchronous electrical activation in patients with LBBB; (B) septal flash motion and mechanical dyssynchrony in patients with LBBB, identified by early septal outward contraction, followed by late posterolateral contraction, causing septal rebound stretch; (C) long-term cardiac remodeling manifesting as atrophy of the LV septum and hypertrophy of the LV lateral wall in patients with LBBB; (D) instantaneous strain curves of patients with LBBB showed a specific contractile pattern with an initial presystolic septal contraction (negative strain) followed by stretching and dyskinesis (positive strain) of the septum during the entire systole; (E) LV pressure–strain loop area reflects regional myocardial work of LV septum and lateral wall (modified from K. Russell et al. [23]); (F) cardiac mechanical unloading can lead to atrophy and degeneration of cardiomyocytes following disuse under electron micrographs (modified from E. W. Thompson et al. [24]). [Color figure can be viewed at wileyonlinelibrary.com]

cardiomyopathy and electro-mechanical dyssynchrony to HF pathogenesis in patients with LBBB in order to select suitable candidates for CRT and predict prognosis.

Evidence base supporting LBBB-induced EESA: multiple prospective cohorts and CRT trials; high-quality meta-analyses support reversibility—the strongest level of evidence within the EESA spectrum.

3 | RVP

Asynchronous electrical activation, induced by RVP, shares the same underlying substrate for mechanical dyssynchrony and remodeling as LBBB. The presence of dyssynchrony after long-term RVP is associated with reduced LV systolic function, and LV functional capacity may recover after cessation of RVP [39–41]. The prevalence of RVP-induced cardiomyopathy is uncertain, but the incidence is estimated to be between 12% and 20% after 1 to 15 years, depending on the definition and follow-up [42, 43].

Several risk factors have been identified that contribute to the development of RVP-induced cardiomyopathy. The most consistent factors include high percentage and duration of RVP, as well as a wide QRS during RVP. A study that evaluated the percentage of RVP (20% to 39%, 40% to 59%, 60% to 79%, and > 80%) found that each level was associated with a progressively higher incidence of RVP-induced cardiomyopathy: 13%, 16.7%, 26.1%, and 19.8%, respectively [42]. Although 40% RVP is considered the threshold for developing RVP-induced cardiomyopathy, other studies suggest that even lower levels of RVP, such as 20%, can trigger the condition [42]. The duration of RVP required

to develop RVP-induced cardiomyopathy varies from months to years. One study showed that the median time to develop the condition was 4.7 years. In this study, baseline LBBB, a QRS duration > 155 ms, and an RVP > 86% were independent predictors [43]. Furthermore, the combination of these three predictors was associated with a 15-fold risk of developing RVP-induced cardiomyopathy.

During RVP, the electrical wavefront propagates through the myocardial cell instead of through the His-Purkinje conduction system. As a result, the electrical wavefront propagates more slowly, inducing heterogeneity in the electrical activation of the myocardium. This is characterized by a single breakthrough at the interventricular septum and the latest activation at the LV lateral wall [44, 45].

Similar to changes in electrical activation, long-term RVP also alters the mechanical contraction pattern of the LV. Animal studies have shown that the early activated regions near the pacing site exhibit rapid early systolic shortening, resulting in over-stretching of the late-activated regions. As a result, the late-activated regions exhibit an increase in systolic shortening, imposing over-stretching on the early-activated regions, thereby causing premature relaxation. This abnormal contraction pattern may lead to the redistribution of myocardial strain and work, subsequently resulting in less effective contraction of the LV [46].

Structural changes and LV remodeling also occur with long-term RVP [47, 48], which include redistribution of cardiac mass, cardiac metabolism, myocardial perfusion, hemodynamics, and mechanical function. Animal studies have shown that 3 months of epicardial LV pacing at physiologic heart rates decreased the thickness of the early-activated anterior wall by 1/5, without significantly changing the LV cavity area and septal thickness. The redistribution may vary with impulse conduction pathways and disease but is typically characterized by thinning of the myocardium activated early versus late [49]. Furthermore, cellular and intracellular alterations, including mitochondrial variations and degenerative fibrosis, may also occur after long-term RVP [50].

RVP-CM is reversible or partially reversible if RVP can be avoided or eliminated. This can be achieved by enabling algorithms to minimize RVP. If RVP is unavoidable, LBBB-like QRS morphology with LV dyssynchrony will persist, and treatment is similar to LBBB-CM. CRT with either BiV or CSP, including His-bundle pacing or left bundle branch area pacing (LBBAP), alone or LBBAP-optimized CRT, is the indicated procedure to improve LV function in RVP-CM and LBBB-CM. A recent study included 69 patients with RVP-CM using CRT upgrade; the results demonstrated that 71% of patients had an improvement of > 10% LVEF (mean 15% points), with most improvement taking place after 12 months [51]. It has also been shown that the detrimental effects of RVP on cardiac metabolism, remodeling, hemodynamics, and mechanical function can be prevented or partially reversed by CRT [52].

Evidence base supporting RVP-induced EESA: mid-size prospective studies and large device registries; reversibility documented after CRT upgrade—moderate-to-strong evidence.

4 | BBBB

In the 1940s, Unger and Richman identified an electrocardiographic (ECG) phenomenon called BBBB. This condition is characterized by the manifestation of LBBB in the limb leads, with absent S waves in leads I and aVL, coupled with right bundle-branch block (RBBB) in the precordial leads [53, 54]. On pathologic examination, there was evidence of infarction and fibrosis in the septal areas of both bundle branches.

Generally, LAFB is associated with advanced heart disease and significant LV dysfunction [55]. In the Cardiovascular Health Study (CHS), over a median follow-up period of 15.7 years, participants who exhibited left anterior fascicular block (LAFB) without overt cardiovascular disease were found to have an increased risk for atrial fibrillation (hazard ratio [HR], 1.89 [95% CI, 1.11–3.24], $p = 0.02$; incidence rate, 3.4 vs. 1.8), HF (HR, 2.43 [95% CI, 1.44–4.12], $p = 0.001$; incidence rate, 3.5 vs. 1.6), and death (HR, 1.57 [95% CI, 1.08–2.26], $p = 0.02$; incidence rate, 6.2 vs. 4.5) [56]. Study data on the relation between LPFB and HF is scarce, as left posterior fascicular block (LPFB) is an extremely rare finding both in the general population and in specific patient groups. However, patients with RBBB and LPFB may also have an increased risk of HF due to abnormal activation sequence; similarly, the same syndrome may also occur in non-specific intraventricular conduction block.

The left anterior fascicle is typically responsible for activating the anterosuperior portion of the LV. In patients with LAFB, the posteroinferior segments activated by the left posterior fascicle contract first, followed by a late contraction of the opposing segments in the anterosuperior area. A study assessing LV electrical delay (Q-LV) with a 12-lead ECG found that patients with MBBB had a long Q-LV interval, with values almost similar to those from the LBBB group [57]. Three-dimensional electroanatomic mapping data in patients with MBBB revealed not only was the RV activation abnormally delayed, but the LV activation was also delayed to a similar extent as in patients with typical LBBB [58]. Echocardiographic speckle tracking further indicated that patients with MBBB exhibited contractile abnormalities, indicating a significant delay between the inferior and anterior LV walls, similar to the abnormalities between septal and lateral LV walls in patients with LBBB [59].

Previous studies on CRT candidates with RBBB recognized a subgroup of patients who had significant LV mechanical dyssynchrony, identified by speckle tracking radial strain, and this subgroup exhibited clinical and echocardiographic benefits from CRT similar to those with LBBB [60]. Consistently, a prospective study involving 651 CRT recipients also found that LV dyssynchrony was an independent predictor of all-cause mortality or HF hospitalization among patients with RBBB after CRT implantation during long-term follow-up [61]. It can be reasonably postulated that the MBBB ECG pattern could identify a subset of patients with RBBB who are likely to respond positively to CRT. Further studies are required to determine the prognostic impact of BBBB in patients with HF and to evaluate the clinical efficacy of CRT in this specific population [62, 63].

Evidence base supporting BBBB-induced EESA: predominantly retrospective ECG-imaging series; data on CRT response emerging—low-to-moderate evidence, needing prospective validation

5 | PVCs

PVCs can also lead to LV dyssynchrony and remodeling [64]. In patients referred for PVC ablation, the prevalence of PVC-cardiomyopathy has been reported to range from 7% to 26% [3, 65, 66]. A large multicenter retrospective study of 1185 subjects with frequent PVCs (mean PVC burden 20% ± 13%) referred for PVC ablation showed that 21% of the cohort had an associated cardiomyopathy (LVEF < 50%) and a prevalence of PVC-cardiomyopathy of 13% (defined by an improvement of LVEF by more than 10% points after PVC suppression) [67]. Another study, a secondary analysis of a prospective randomized placebo-controlled trial of ventricular ectopy in patients with LV systolic dysfunction (LVEF < 40%), HF, and greater than 10 PVCs per hour (median PVC count 2800/day), reported a prevalence of PVC-cardiomyopathy (defined as PVC suppression > 80% and LVEF improvement > 10%) of 29% in patients treated with amiodarone compared to 1.8% in placebo [68].

In a study conducted on swine models with paced ectopic beats, a substantially more severe cardiomyopathy, depressed LVEF, and disrupted cellular calcium metabolism were observed in paced PVCs compared to regular RV pacing. The result suggests that PVC-induced cardiomyopathy is mechanistically different from tachycardia-mediated cardiomyopathy [69]. The PVC-induced ventricular mechanical dyssynchrony and hemodynamic derangement can be attributed to two features associated with PVCs. Firstly, the propagation of the depolarization wave independently activates the local myocardium, separate from the conduction system, causing a slower and dyssynchronous motion of the remaining area [70]. Secondly, the abnormal coupling interval of PVCs may be followed by a compensatory pause, which leads to increased filling pressure from the extended diastolic period [71].

The severity of the PVC-induced cardiomyopathy exhibits an "origin effect," wherein the most severe cardiomyopathy develops in response to ectopic activity originating from the LV epicardial surface, which is associated with higher levels of LV dyssynchrony. Other predictors for developing PVC-induced cardiomyopathy include a higher PVC burden, increased PVC-QRS duration, and a longer history of PVCs [64, 69].

Catheter ablation is currently being evaluated as a potential first-line therapy for patients with PVC-induced cardiomyopathy. Recent publications have highlighted the superior effectiveness of catheter ablation over pharmacotherapy. Current data strongly suggest the majority of patients, after successful elimination of PVCs, have significantly improved or normalized their LV function [72].

Evidence base supporting PVC-induced EESA: multicenter ablation registries and animal data; no randomized PVC-suppression trials—moderate evidence, but causality largely inferred.

6 | WPW Syndrome

Cardiomyopathy associated with pre-excitation syndrome was first reported in case reports and has gained recognition since then. The incidence and prevalence of PE-CM are unknown. Although RVP and LBBB-induced cardiomyopathy are mostly seen in the adult and older population, WPW-induced cardiomyopathy is an entity that is most frequently reported in children and young adults [73].

The WPW syndrome causes premature activation of ventricular segments adjacent to the accessory pathway (AP). This early activation prompts a segmental contraction that is not synchronized with the remaining areas of the LV. Reduced workload imposed on the early-activated segments leads to local atrophy. The dyskinetic segments, working as a functional aneurysm, lead to remodeling and progressive ventricular dilation [74].

The extent of the pre-excited ventricular myocardium depends on the different location of AP. Studies have identified that right-sided free wall and septal APs were associated with abnormal motion and LV remodeling. However, left-sided APs are less likely to manifest pre-excitation since they are the farthest from the AV node, allowing most intrinsic conduction via the His-Purkinje system by the time AP depolarization occurs [75–78].

Dai et al. [78] analyzed a substantial number of cases with different AP locations. Utilizing speckle tracking echocardiography, they assessed LV wall motion and found that right-sided APs could impair ventricular wall motion and LV systolic function. This impairment led to a decrease in LVEF and an increase in LV end-diastolic diameter. Catheter ablation of the AP restored mechanical synchronization, reversed cardiac remodeling, and improved LV function in these patients. These findings suggest ventricular pre-excitation, causing LV dyssynchrony and abnormal interventricular septal motion, may be responsible for LV dysfunction and remodeling [76–78].

Evidence base supporting WPW-induced EESA: case series and pediatric cohorts; reversibility after ablation demonstrated—low evidence, limited to small observational studies.

7 | Conclusions

In summary, arrhythmias causing premature electrical activation of regional ventricular areas could induce mechanical dyssynchrony and long-term cardiac remodeling. We propose a unified concept, the "Early-Excitation Segment Atrophy syndrome (EESA)." This theory refers to the disuse atrophy in the early activation areas and exertional hypertrophy of the late activation areas of LV. The systolic loss of the early activation area and the increased workload in the late activation area are major stimuli for adverse remodeling; additionally, redistribution of blood flow, regional alteration of gene expression, regulation of metabolic transcripts, and expression of paracrine factors also contribute to long-term LV remodeling (Figure 3: Central illustration).

By integrating the EESA paradigm into clinical practice, we aim to improve the recognition and management of

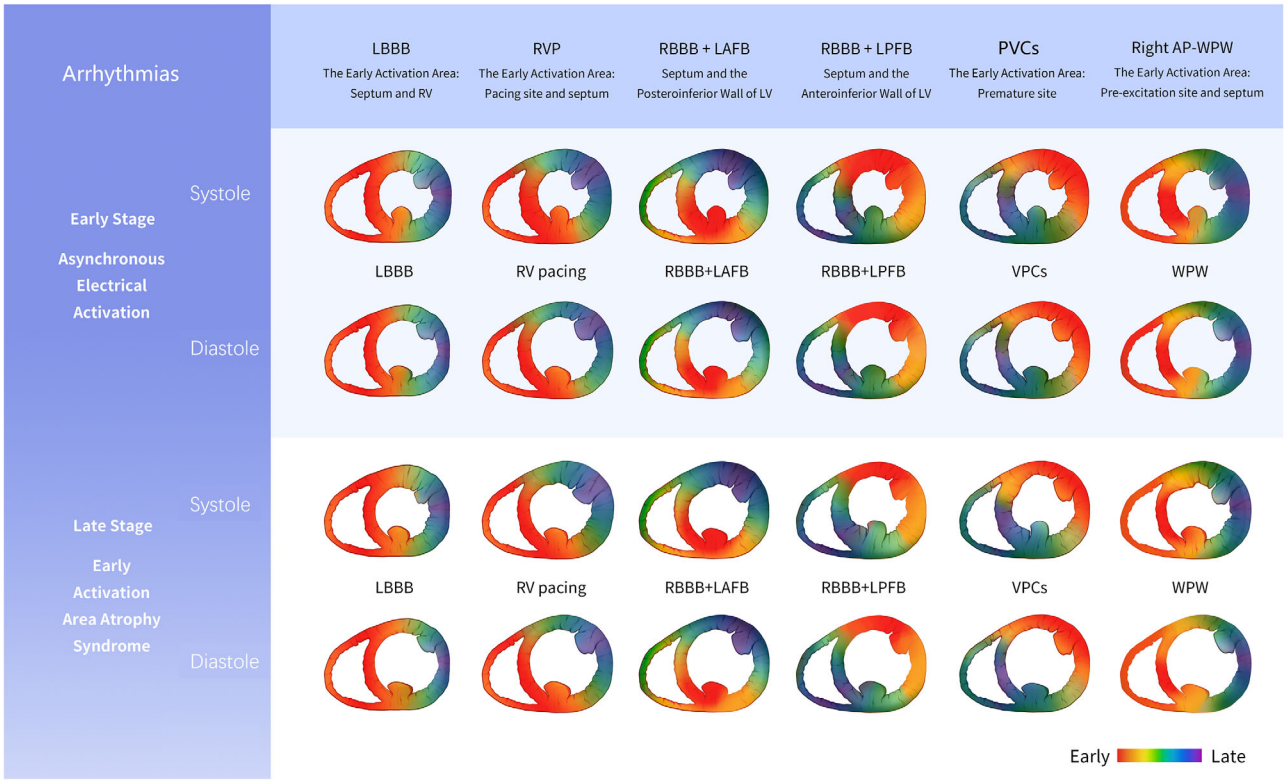

FIGURE 3 | Central illustration. Early-excitation segment atrophy syndrome (EESA): etiology, mechanisms, and progression. Arrhythmias that may induce EESA include left bundle branch block (LBBB), right ventricular pacing (RVP), right bundle branch block (RBBB) + left anterior fascicular block (LAFB), RBBB + left posterior fascicular block (LPFB), premature ventricular contractions (PVCs), and Wolff–Parkinson–White (WPW) syndrome. In the early stage, arrhythmias give rise to asynchronous electrical activation of regional ventricles without cardiac remodeling. In the late stage, the long-term dyssynchrony leads to disuse atrophy in the early activation areas and exertional hypertrophy of the late activation areas of the LV. [Color figure can be viewed at wileyonlinelibrary.com]

dyssynchrony-mediated cardiac remodeling. The core insight—that early-activated myocardium undergoes disuse atrophy due to mechanical unloading—provides a biologically plausible explanation for regional and global dysfunction in various conduction disorders. This framework encourages clinicians to view certain arrhythmias not only as electrophysiological disturbances but also as direct contributors to myocardial damage.

It is important to note that current data primarily focus on LV manifestations of EESA. However, similar principles may apply to the RV or biventricular systems—particularly in conditions like RVP or BBBB, where RV activation precedes LV activation, potentially inducing RV segment unloading. Whether such mechanisms contribute to RV dysfunction or pulmonary vascular consequences warrants future investigation.

The EESA offers a new paradigm for understanding and managing dyssynchrony-induced cardiomyopathies. By recognizing the reversible nature of these conditions and the importance of targeted interventions, clinicians can improve outcomes for patients with HF. Further research and validation are needed to fully integrate EESA into clinical practice, but the potential benefits for patients are significant. This new framework has the potential to transform the way we approach and treat cardiac dyssynchrony, ultimately leading to better patient outcomes and reduced morbidity and mortality.

Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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