

Pathophysiological mechanisms underlying ventricular dyssynchrony

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Left ventricular dyssynchrony due to conduction system disease creates cardiac inefficiency even in normal hearts. Dyssynchrony in the failing heart results in the development of a discrete heart failure phenotype as it induces chamber heterogeneity at the cellular and molecular levels that leads to impaired excitation-contraction coupling, increased arrhythmia susceptibility, and decreased myocyte survival among other pathologic changes. Recent research has demonstrated that these biomolecular changes are amazingly reversed with cardiac resynchronization therapy, providing insight into how to target the therapy.

Keywords Cardiac resynchronization therapy • Heart failure • Dyssynchrony • Pathophysiology

The concept of ventricular dyssynchrony

It is estimated that ~5.7 million Americans will be diagnosed with congestive heart failure in 2009,¹ half of them with systolic dysfunction. Early reports aimed at understanding the natural history of this condition pointed to the importance of the QRS width as an independent marker for death. More specifically, individuals with wider QRS widths and/or left bundle branch block (LBBB) patterns² fared worse when compared with their counterparts.³ In fact, patients with QRS widths >120 ms had a 15% increase in mortality when compared with patients with QRS widths <120 ms independent of age, ejection fraction, severity, or aetiology of heart failure. Several hypotheses have been generated to explain this reason, the most convincing of which centres on the concept of ventricular dyssynchrony or previously known as myocardial non-uniformity of ventricular activation.

Normal cardiac function and prevalence of dyssynchrony

In order to understand the pathophysiological mechanisms governing dyssynchrony in diseased states such as heart failure, it is helpful to recognize that structurally normal hearts also exhibit some degree of non-uniformity in contraction due to its complex spatial and geometric architecture. Very early work utilizing myocardial fibre dissection and histological analyses demonstrated

that ventricular fibre orientation is governed primarily by its transmural location within the myocardial wall.^{4,5} Fibres within the epicardial and endocardial regions are oriented along the longitudinal axis of the heart, whereas fibres within the midwall region are oriented circumferentially. This arrangement allows for a complex contractile movement with systolic activation that involves both circumferential motion and longitudinal shortening from apex to base. Although these findings were isolated in a small sampling region of the heart, more recent work utilizing diffusion tensor magnetic resonance imaging (MRI) has given us a global appreciation of the heart architecture and has corroborated these earlier findings as well as provided additional insights. Through these latter efforts, Helm *et al.*⁶ demonstrated that myocardial fibre orientation is complex and comprised of two primary orientations (circumferential and longitudinal) that transition smoothly from one direction to another (Figure 1). Given the heterogeneous and complex fibre architecture, it is not surprising that myocardial regions must be electrically activated temporally for efficient pump function. More specifically, electrical activation through the His–Purkinje system results in a ventricular electrical wavefront that starts in the endocardium and apex and ends in the epicardium and base with resultant regional disparities in electrical activation by as much as 80–100 ms from start to finish. The result is a temporal mechanical activation of fibres especially between the endocardial and the epicardial layers as well as the apex and base regions. It is this intricate association between electrical activation and myocardial fibre architecture that allows for efficient pump function.

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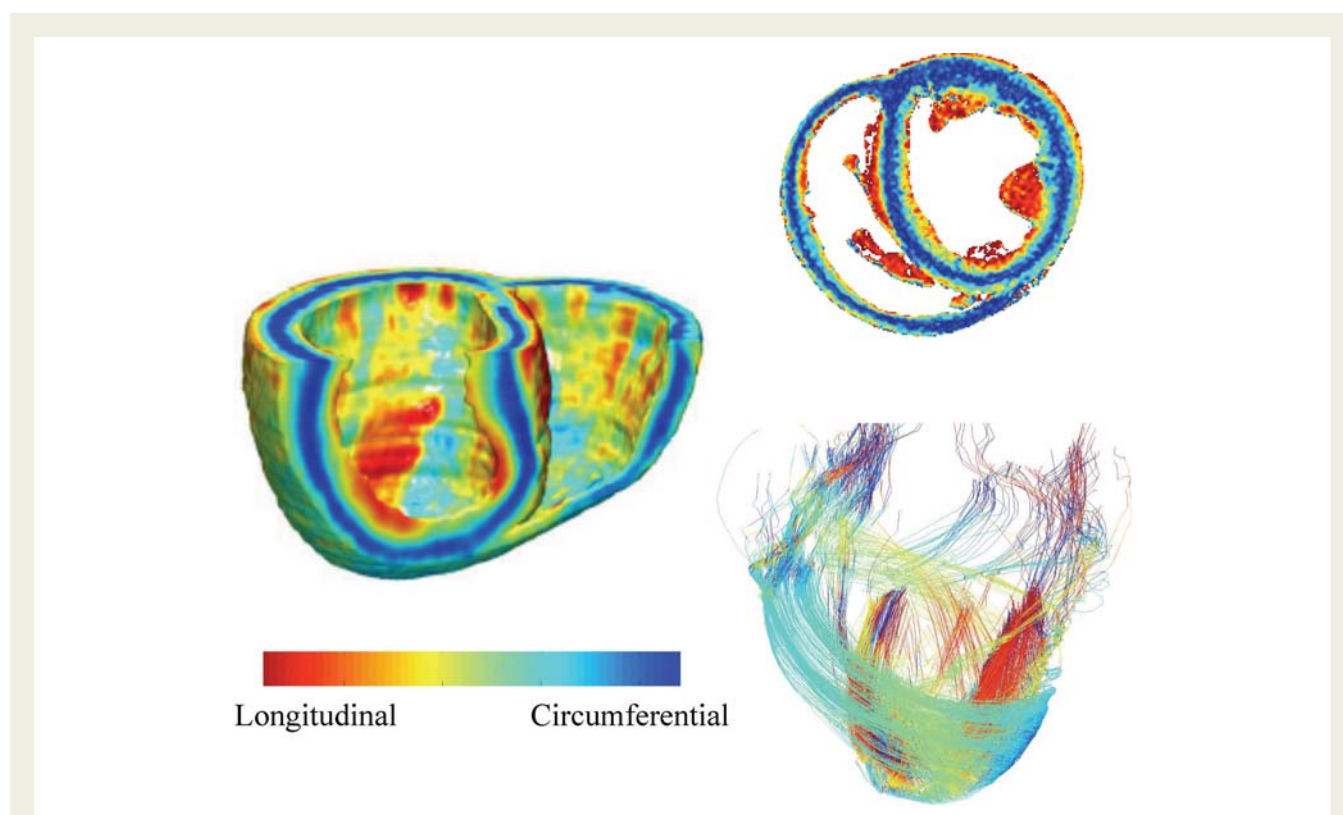


Figure 1 Diffusion tensor magnetic resonance imaging-based estimates of fibre inclination angle in a canine heart. Data were reconstructed and rendered in 3D model and 2D cross-section. Colour coding indicates orientation of primary fibre architecture. Tracing of fibres from apex shows contiguous fibre trajectory. From Helm *et al.*⁶ Reprinted with permission of Wiley-Blackwell. Copyright © 2009 The New York Academy of Sciences.

Abnormal cardiac function and the prevalence of dyssynchrony

Given the nexus between temporal electrical activation and mechanical function, it is not surprising that intra-ventricular (mechanical) dyssynchrony would be the result of an abnormal electrical activation pattern, so-called electrical dyssynchrony. In heart failure patients, conduction defects due to LBBB or slow intra-myocardial conduction are common and result in regionally delayed electrical activation. Abnormal temporal electrical activation of the complex myocardial fibre architecture reduces pump efficiency and cardiac performance. Although conduction defects are common, this is not always the case and patients with heart failure may have left ventricular (LV) dyssynchrony in the absence of regionally delayed electrical activation. Patients with systolic heart failure and a narrow QRS complex exhibit mechanical dyssynchrony with a prevalence between 30 and 50%.^{7–9} Similarly, 30–40% of patients with non-systolic heart failure have also been shown to have evidence of dyssynchrony.¹⁰ Despite some variability in the metrics used to define ventricular dyssynchrony, this phenomenon is very common and has been seen in many other entities including hypertrophic cardiomyopathy,¹¹ LV hypertrophy,¹² and pulmonary arterial hypertension resulting in right ventricular (RV) strain.¹³ The explanation for this may rest on an appreciation that not all dyssynchrony is the same and can result from one of two mechanisms.¹⁴ First, LV

dyssynchrony may be the result of temporal delay in electrical activation of one region vs. another. The classic example is LBBB where electrical activation occurs first in the septum and then propagates slowly via intra-myocardial conduction to the lateral wall. Improving the activation phase difference with biventricular pacing, one can achieve more synchronous mechanical contraction and enhance ventricular performance. A second mechanism of dyssynchrony occurs in the setting of normal temporal electrical activation. Relaxation delay and dyssynchrony can be induced by abnormal loading of the heart. In normal dogs, Yano *et al.*¹⁵ acutely clamped the aorta to increase afterload and showed that regional shortening became dyssynchronous and relaxation time constant was prolonged. These data were supported by Wang *et al.*¹⁰ who showed that vasodilators and diuretics could improve dyssynchrony and relaxation in heart failure patients. Simply put, abnormal myocardial loading, which is characteristic in heart failure patients, can in itself contribute to dyssynchrony and this type of dyssynchrony may not be amenable to electrical resynchronization.

Effects of dyssynchrony on mechanical work

The His–Purkinje system allows for rapid electrical activation and synchronous inter- and intra-ventricular contraction. In heart

failure, conduction defects including LBBB are common and result in regionally delayed electrical activation. The right anterior septal region is activated rapidly via an intact right bundle, whereas the left basal posterolateral region is activated late as excitation propagates slowly via cell-to-cell, intra-myocardial conduction. Timing is critical for synchronous contraction and the net effect of regionally delayed electrical activation is discoordinate myocardial shortening and pump inefficiency.

Early systolic contraction of the 'early-activated' septum results in forces that are unopposed by the contralateral and quiescent lateral free wall. It is the conversion of these septal forces into pre-stretch of the inactive lateral wall that mitigates their effect on LV chamber pressure, delaying intra-cavitary pressure rise (dP/dt_{\max}). In late systole, the lateral wall is activated (via slow intra-myocardial conduction) with peak force generation typically occurring in early diastole after aortic valve closure. Late contraction and pressure development of 'late-activated' lateral wall is unopposed by the now relaxing septum and leads to end-systolic stretching of this region. In effect, the relaxing septum creates an energy sink (i.e. loss of energy) for the late-developing lateral forces and decreases overall ejection. Finally, late activation of the posterolateral papillary muscle also results in suboptimal mitral valve closure and mitral regurgitation, further decreasing cardiac output.

Myocardial strain analysis using various tissue tracking methods including tagged-MRI can be used to characterize mechanical dyssynchrony. Figure 2A shows regional myocardial strain in a heart with classic dyssynchrony due to LBBB.^{16,17} In early systole, the septum is contracting (negative stain), whereas the opposite region, the lateral wall, is passively stretched (positive strain). This biphasic pattern is reversed in late systole when the lateral wall contraction results in septal stretching. The impact of discoordinate contraction has been described using regional elastance curves¹⁸ (Figure 2B). Regional stiffness is plotted as a function of time. Differences in timing of activation between the early-activated septum and the late-activated lateral wall results in a rightward shift of the lateral wall curve relative to that of the septum. The vertical difference between the curves reflects the degree of volume shift from one wall to the other. This difference is great in early systole (red arrow) during isovolumic contraction explaining the reduction in dP/dt_{\max} and even greater in late systole/early diastole (blue arrow) reducing ejection and relaxation.

Left ventricular dyssynchrony reduces net cardiac output. Figure 2C is a plot of pressure–volume loops of baseline synchronous contraction (solid line) and of LV dyssynchrony (acutely induced by RV pacing—dotted line).¹⁹ Dyssynchrony results in a shift of end-systolic pressure–volume relationship (ESPVR) to the right, highlighting a load-independent compromise of LV function. In addition, stroke volume (loop width) is decreased, leading to increased LV end-systolic volume and, consequently, increased LV end-systolic wall stress.

Dyssynchrony not only decreases LV systolic function but also reduces myocardial efficiency. Work performed on one side of the heart is wasted by its stretching of the contralateral region. Using a canine model of ventricular dyssynchrony, Prinzen et al.²⁰ assessed regional myocardial work using tagged-MRI and found a significant increase in local work

performed by the lateral wall when compared with normal control (Figure 2D). In the early-activated septal region, the workload (loop area) is low owing to a figure-8-shaped stress–strain relationship. In early systole, the region contracts against low load, and in late systole, it is stretched at a higher load. This results in a low or near zero net work for this region. Workload is much greater in the late contracting lateral wall, which operates at a higher initial stretch and contracts against higher stress. Regionally displaced work correlates with regional differences in blood flow and further compromises myocardial energetics in the already impaired failing heart.^{21–23}

Although the most common conduction defect is LBBB, regionally delayed electrical activation may occur with right bundle branch block (RBBB). However, Byrne et al.¹⁶ showed that despite widening of QRS, RBBB is associated with less global LV dyssynchrony than LBBB. This disparity is largely due to the geometric asymmetry of the LV. Although the lateral free wall is principally dependent on LV loading conditions, the septum is loaded from both the RV and the LV. In RBBB, the early-activated lateral wall contracts against a quiescent septum; yet, RV loading may reduce significant pre-stretch and ventricular dyssynchrony. This may explain why the observed effect on pressure development (dP/dt_{\max}) is less than that with LBBB. The impact of cardiac resynchronization therapy (CRT) in RBBB is less and differences in the degree and pattern of mechanical dyssynchrony may be the reason.

Effects of dyssynchrony on molecular expression

Heart failure is characterized by a complex process of pathophysiological changes modulated by systemic and local neurohormonal stimulation resulting in maladaptation and remodelling at the molecular and cellular levels. Impaired sarcomeric Ca^{2+} handling and activation of various stress kinases, phosphatases, and associated transcription factors are among the myriad of biomolecular changes that result in reduced myocardial force generation, delayed myocardial relaxation, decreased cell survival, and maladaptive growth remodelling. When electrical conduction delay and mechanical dyssynchrony are superimposed on this heart failure milieu, the biomolecular effects are not just additive, but trigger more complex pathophysiology and a unique form of heart failure with increased arrhythmogenic susceptibility.

Recent studies have yielded great insight into the molecular phenotype of dyssynchronous heart failure. Specifically, dyssynchrony induces regional difference in protein expression and has important consequences at the global and cellular level. In a canine model of ventricular dyssynchrony, Spragg et al. demonstrated significant transmural and trans-chamber gradients of stress-response kinases, calcium handling, and gap junction proteins. In particular, they found a two-fold increase in phosphorylation of a mitogen-activated protein (MAP) kinase, *erk*, with concomitant down-regulated expression of sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA), phospholamban, and connexin-43 in the late-activated,

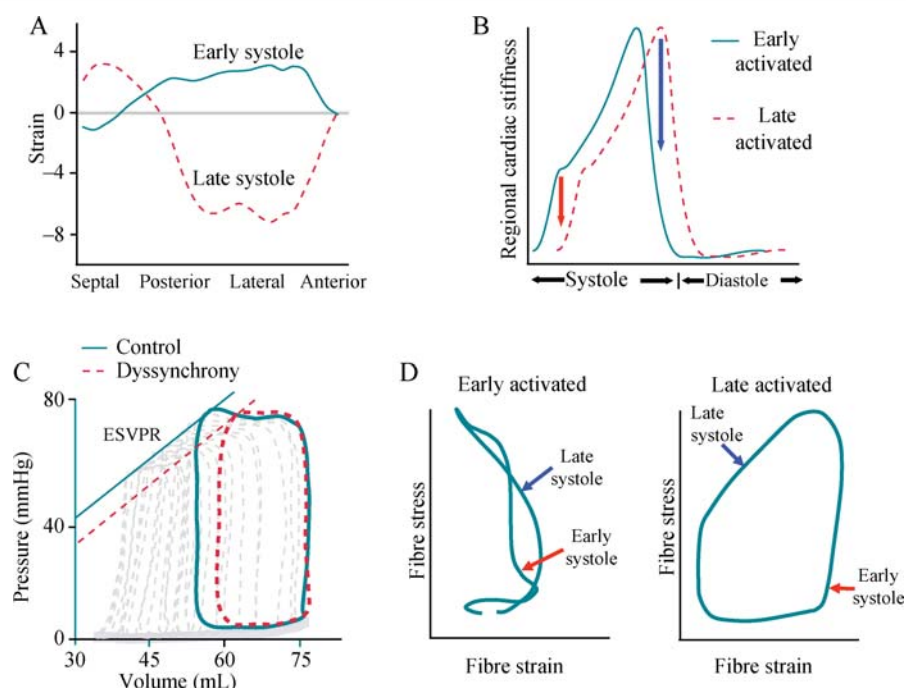


Figure 2 (A) Plot of instantaneous circumferential strain at different regions across a short-axis section of the mid-LV in a dyssynchronous heart during early (solid line) and late (dashed line) systole. At both phases, septal and lateral regions are clearly out of phase with each other. Adapted from Byrne *et al.*¹⁶ with permission. Copyright © 2007 American College of Cardiology Foundation. (B) Regional elastance (stiffening) plots of a dyssynchronous heart. Plots of early (solid) and late (dashed) activated myocardial regions are time-delayed. Vertical distance between the curves reflects transfer of forces from one region to the other. This difference is significant in early systole (red arrow) during isovolumic contraction reducing pressure development and this difference is even greater in late systole/early diastole (blue arrow) reducing ejection and relaxation. From Kass.¹⁸ Reprinted with permission. Copyright © 2005 Blackwell Publishing. (C) Pressure–volume loops showing effect of dyssynchrony on ESPVR. The ESPVR shifts rightward (dashed line), end-systolic volume increases, and stroke volume and work declines. From Park *et al.*¹⁹ Reprinted with permission from Wolters Kluwer Health. Copyright © 1985 American Heart Association. (D) Stress–strain loops from early- and late-activated regions in a dyssynchronous heart. The early-activated region initially contracts at low load and then is stretched under high load in late systole generating a figure-8-shaped loop with little area (reduced net work). The late contracting lateral wall operates at higher preload and stress, requiring greater work. In the normal synchronous heart, these loops would be similar for all regions. From Prinzen *et al.*²⁰ Reprinted with permission. Copyright © 1999 American College of Cardiology.

lateral free wall when compared with the left ventricular early-activated septum.²⁴ Such disparities were not seen in synchronous control hearts, despite comparable degrees of heart failure suggesting that dyssynchrony in itself induced such molecular polarization. These data were corroborated by Vanderheyden *et al.*²⁵ who showed that remodelling of Ca^{2+} handling proteins including SERCA2 and Na^{+} – Ca^{2+} exchanger was reversed by CRT in so-called ‘responder’ patients. The effects of altered regional expression of gap junction proteins have been implicated in increased arrhythmia susceptibility. Using myocardial wedge preparations from a dyssynchronous canine model, the same investigators found regional differences in conduction velocity and action potential duration (APD). A follow-up study demonstrated that LV dyssynchrony induces regional differences in K^{+} and Ca^{2+} currents, which increased APD in the lateral wall. Early after-depolarizations were increased in the dyssynchronous failing heart but reduced by CRT.²⁶ The electrophysiological remodelling caused by dyssynchrony may create a potential substrate for arrhythmia susceptibility.

Molecular changes associated with maladaptive growth remodelling in the dyssynchronous failing heart have also been recently identified. Amplification of stress kinase expression and activity including p38 MAP, calcium–calmodulin-dependent kinase II, and tumour necrosis factor- α have been observed in the high-stress, late-activated region in dyssynchronous hearts and these, in-turn, have important consequences on muscle function, survival, and fibrosis.²⁷ Furthermore, dyssynchrony appears to down-regulate global phosphorylated AKT expression, an important mediator of cell-survival signalling. Cardiac resynchronization therapy appears to homogenize local stress kinase amplification and decrease global apoptosis via enhanced cell-survival signalling.

More recently, Barth *et al.*²⁸ have shown a profound effect of mechanical dyssynchrony on the regional cardiac transcriptome. Specifically, they found a more pronounced down-regulation of transcripts for energy-deriving, KEGG pathways including oxidative phosphorylation, tricarboxylic acid cycle, and fatty acid and amino acid metabolism in the low-stress anterior wall when compared

with high-stress lateral wall. In addition, they observed that cell-signalling pathways and extracellular matrix components were up-regulated in the anterior wall, but predominantly down-regulated in the lateral wall suggesting qualitatively different transcriptomic responses to electromechanical stress. The transcriptomic heterogeneity induced by dyssynchrony is effectively reversed with CRT.

Much recent work has enhanced our understanding of the complex and unique pathophysiology that underlies dyssynchronous heart failure. Mechanical dyssynchrony leads to significant biomolecular heterogeneity, which has critical implications at the global and cellular level. Improving synchrony of contraction with CRT reverses maladaptive growth remodelling, increases cell-survival signalling, enhances Ca^{2+} handling, and boosts β -adrenergic responsiveness²⁹ among other effects.

Summary

Left ventricular dyssynchrony due to regionally delayed electrical activation is characterized by a unique heart failure phenotype. Acutely, dyssynchrony reduces pump function and energetic efficiency while chronically it induces regional and global molecular signalling that alters excitation–contraction coupling, energetics, arrhythmia susceptibility, and myocardial survival. Incredibly, simply restoring electrical synchrony with CRT not only improves global heart function and energetics, but also has a profound beneficial effect on the molecular and cellular phenotype. Understanding the unique pathophysiology underlying dyssynchronous heart failure and the effects of CRT may provide insight into how to better select suitable CRT candidates and to improve implementation of this therapy.

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