CARDIAC RESYNCHRONIZATION THERAPY in Heart Failure

William T. Abraham
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PREFACE

Cardiac Resynchronization Therapy for All HF Patients?

When the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study[1] reported benefits of cardiac resynchronization therapy, there was hesitation to adopt this new technology. The extent of the benefits was not entirely clear—the study showed improvements in 6-minute walk distance, New York Heart Association (NYHA) functional class ranking, and quality of life. These observations, however, provided impetus for the COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure)[2] and CARE HF (Cardiac Resynchronization—Heart Failure) trials,[3] which confirmed not only improvements in functional capacity but also survival benefits for cardiac resynchronization therapy with defibrillation and for cardiac resynchronization therapy alone. Based on these findings, the 2005 American College of Cardiology and American Heart Association guideline statement[4] recommended cardiac resynchronization therapy for chronic NYHA Class III and ambulatory Class IV heart failure patients with a reduced ejection fraction and ventricular dyssynchrony as a Class I indication with a level of evidence "A." Despite these unequivocal recommendations, there has been reluctance by some to use cardiac resynchronization therapy with a penetration of around 40% in the indicated heart failure population.[5] Thus, approximately 60% of eligible patients are currently denied or otherwise not receiving this evidence-based, guideline-recommended, life-sustaining therapy. The medical community simply must do better than this.

More recent data from the REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction)[6] and MADIT-CRT[7,8] trials demonstrate that the benefits of cardiac resynchronization therapy extend to NYHA Class I and Class II heart failure patients with ventricular dyssynchrony. Taken together, these trials should expand the clinical indication for cardiac resynchronization therapy to patients with asymptomatic or mildly symptomatic heart failure. The 2-year REVERSE study showed that cardiac resynchronization therapy significantly reduces the risk for heart failure hospitalization and improves ventricular structure and function in NYHA Class I and Class II patients. The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-CRT) trial evaluated the benefits of cardiac resynchronization therapy in mild to moderate heart failure (NYHA Class I and II) when compared to defibrillator alone. The Data Monitoring and Safety Board stopped the study, which enrolled 1,820 patients, because the use of cardiac resynchronization therapy with a defibrillator resulted in a statistically significant 29% reduction in the risk of death from any cause or heart failure hospitalizations, when compared to a defibrillator alone. Thus, the future looks bright for cardiac resynchronization therapy as a standard treatment across all NYHA classes of heart failure, in patients with ventricular dyssynchrony.

Heart failure hospitalizations continue to have both clinical and economic impact (billions of dollars) in the management of heart failure. As new data continues to emerge, regarding the benefits of cardiac resynchronization therapy in reducing length of stay, avoiding re-hospitalizations, and saving lives, it is inevitable that cardiac resynchronization therapy will be appropriately used in most if not all heart failure patients. Keeping this in mind, we have put together a panel of experts who have provided a comprehensive and cutting-edge overview of cardiac resynchronization therapy. This book should be useful to the practicing family care physician, internist, cardiologist, and other healthcare professionals, who will continue to manage an increasing number of patients eligible for and subsequently treated with cardiac resynchronization therapy.

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We dedicate this book to our heart failure patients, who have taught us first-hand about the benefits and limitations of cardiac resynchronization therapy, and to all the physician investigators, research coordinators, and patients who participated in clinical trials of cardiac resynchronization therapy, helping to establish it as a standard of care and saving countless lives.

In addition, we would like to acknowledge authors of the individual chapters for their dedication to the production of this book. And finally, we would also like to acknowledge our families for their love and support of our professional activities, including the editing of this book.

CONTENTS

CHAPTER

1

Pathophysiology of Ventricular Dyssynchrony and Mechanisms of Cardiac Resynchronization Therapy

Robert H. Helm • David D. Spragg • Khalid Chakir • David A. Kass

HEART FAILURE AND RESYNCHRONIZATION THERAPY

Heart failure (HF) is a systemic disease, which typically begins with an initial cardiac insult resulting in acute ventricular dysfunction. To maintain pump function and systemic perfusion, a series of neurohormonal and adrenergic adaptations occur. Chronically, these changes lead to remodeling and maladaptation at the molecular and cellular levels resulting in sustained pump dysfunction.[1, 2] Neurohumoral stimulation occurs at both the systemic and local myocardial levels, and myocardial responses can be induced by hormone-receptor interactions, or mechanical stress.[3] Catecholamines acutely recruit myocardial reserve; however sustained stimulation results in abnormal calcium handling and worsened myocyte survival.[4] Intersitial fibrosis, vascular insufficiency, activation of fibroblasts and matrix remodeling protein (metalloproteinase), and other factors contribute to chronic maladaptive remodeling.[1] The result is impaired basal and reserve heart function manifested by blunted responses to neurohumoral stimulation (i.e., sympathetic stimulation), loading, and increases in heart rate. Many factors contribute to this behavior, including down-regulation of G-coupled receptor pathways, abnormal calcium cycling,[5,6] activation of multiple stress response signaling pathways,[7,8] energetics,[9] and sarcomere changes. Impaired Ca^{2+} cycling into and out of the sarcoplasmic reticulum blunts myocardial force generation and delays relaxation. Activation of stress kinases, phosphatases, and associated transcription factors alters contractile function, calcium handling, growth remodeling, and cell survival. Cardiac bio-energetics is rendered inefficient with depressed fatty acid utilization. Lastly, myofilament proteins are altered in the failure state, including the type of myosin, and post-translational modifications of regulatory and structural proteins such as titin.[1,10] These and other pathologic alterations all contribute to the HF phenotype.[1]

On top of this disease *landscape*, about one-third of patients develop electrical conduction delays resulting in marked discoordinate contraction.[11–12] Dyssynchrony reduces chamber function and efficiency in a normal heart, and its superimposition in HF worsens an already compromised state. Furthermore, dyssynchrony effects may not be simply additive; they may trigger more complex pathophysiology and a unique form of heart failure. Understanding how and what is achieved by CRT is increasingly important, as it has become standard therapy for groups of heart failure patients. In this chapter, we update current understanding of the mechanical, cellular, and molecular changes induced by dyssynchrony in the failing heart and how CRT affects them.

Mechanics of Dyssynchrony

His-Purkinje disease and intra myocardial conduction delay in the failing heart result in regionally delayed electrical excitation,[13] yielding early- and late-activated regions that contract out of phase with each other to generate dyssynchrony. Both left-bundle branch block (LBBB) and right ventricular (RV) pacing delay lateral wall stiffening and are the most common causes of left ventricular (LV) dyssynchrony. With both, septal activation occurs first, but as the lateral wall remains quiescent, forces from septal contraction do not raise LV pressure but are largely converted into prestretch of the lateral wall. This slows the rise of pressure (dP/dt) and increases lateral wall stress. When the free wall does contract, it generates systolic forces late, which are partly dissipated by restretching the already relaxing septal region, lowering net cardiac output. Delayed papillary muscle activation can contribute to mitral regurgitation, further reducing forward ejection. This common pattern of mechanical dyssynchrony is shown in Figure 1.1A. Tagged magnetic resonance imaging (MRI) was used to assess regional strain in a canine with mechanical dyssynchrony induced by radiofrequency ablation of the left bundle.[14] Strain is plotted as a function of LV region. In early systole (dashed line), the septum contracts (negative strain), whereas the lateral wall stretches (positive strain). In late systole (solid line), this pattern is reversed; as the lateral wall contracts, the septum stretches. Regional disparities in cardiac stiffening can be appreciated by portraying dyssynchrony as two time-varying elastance curves representing the early- and late-activated regions (Fig. 1.1B). The vertical distance between curves reflects disparities in wall stiffening that generate discoordinate motion. This is most marked in early

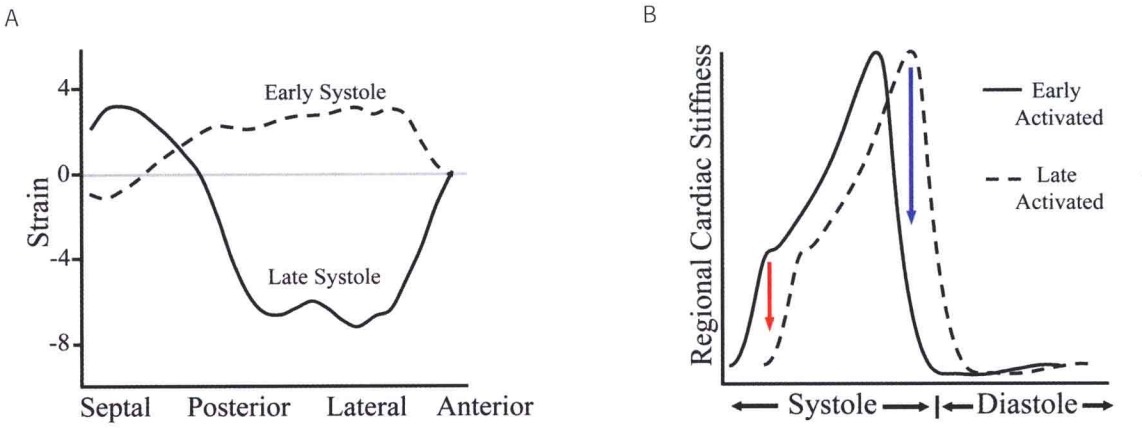

FIG. 1.1. A: Circumferential strain (relative shortening) at different regions across a short-axis section of the mid-LV in a dyssynchronous heart. Data for early (dashed) and late (solid) systole are shown, and reveal septal and lateral regions out of phase with each other. B: Model of dyssynchrony based on a time-delay of ventricular activation (stiffening). Plots of early-(solid) and late-(dashed) activated myocardial regions. Vertical distance between the curves indicates transfer of forces from one region to the other, and the arrows highlight two times—early contraction and late systole where this disparity is greatest and where discoordinate motion most manifests. (A, adapted from Byrne MJ, Helm, RH, Daya, S, et al. Diminished left ventricular dyssynchrony and impact of resynchronization in failing hearts with right versus left bundle branch block. *J Am Coll Cardiol.* 2007;50:1484–1490.)

systole (isovolumic contraction, lowering dP/dt_{max}), and late systole as one territory enters relaxation ahead of the other. The latter is when echoDoppler measures of dyssynchrony are typically observed.[15,16] The evolution and resolution of dyssynchrony highlight a critical time course and provide insight into how delayed contraction affects cardiac function throughout the cardiac cycle.

In contrast to LBBB and RV-paced associated dyssynchrony, right-bundle branch block (RBBB) results in delayed right-sided activation relative to LV free wall. The impact of RBBB on chamber synchrony and function is significantly less than with LBBB[14] largely due to the lack of symmetric heart geometry. Unlike the LV free wall, the septum is loaded not just by regional LV forces but also those from the RV. The size of the delay-activated region and its location are key factors that determine the net impact on global LV function and mechanical synchrony.

Dyssynchrony, Relaxation, and Loading

Cardiac dyssynchrony can delay ventricular relaxation. In an acute pacing study in dogs, Aoyagi et al.[17] demonstrated a significant correlation between left ventricular dyssynchrony (measured in early diastole) induced with ventricular pacing and prolongation in relaxation (increase in Tau, time constant of relaxation, Fig. 1.2A). Increased LV afterload can also induce relaxation delay and dyssynchrony. With acute aortic constriction in an otherwise normal canine, Yano et al.[18] showed an acute increase in Tau and onset of regionally delayed contraction (Fig 1.2B and Fig. 1.2C). Nearly 15 years later, attention is principally focused on cardiac dyssynchrony due to conduction delay (typically LBB pattern) but certainly abnormal loading associated with heart failure can contribute to chamber dyssynchrony. Wang et al.[19] further substantiated these data by showing that vasodilators and diuretics could improve dyssynchrony (measured during the diastolic period) and relaxation in HF patients (Fig. 1.2D). These data are particularly important because dyssynchrony due to abnormal loading is far less likely to be amenable to electrical resynchronization.[20]

Effect of Dyssynchrony on Pump Function and Efficiency

One critical consequence of LV dyssynchrony is reduced pump function, which can be demonstrated by pressure-volume loops.[21] Figure 1.3A shows example relations, and with dysynchrony induced by RV pacing, the end-systolic pressure-volume relationship (ESPVR) shifts rightward, indicating a fall in net function. Both stroke volume (loop width) and stroke work (loop area) also decline without a fall in end-diastolic volume. Furthermore, end-systolic wall stress is increased as the end-systolic volume rises. Rate of pressure development (dP/dt_{max}) declines by ~20%, stroke work by 10–15%, and relaxation (Tau) prolongs by ~10–15%.[22–23]

A second critical consequence of dyssynchrony is that LV efficiency is reduced. Work performed by one region of the heart is wasted by means of stretching the contralateral wall (intracavity energy sink). In a canine model of dyssynchrony induced with RV pacing, Prinzen et al.[24] assessed regional myocardial strain and work using tagged MRI. At baseline (right atrial pacing) regional work was fairly homogeneous; whereas with RV pacing a marked disparity in local work including a 125% increase in the lateral wall and a reciprocal

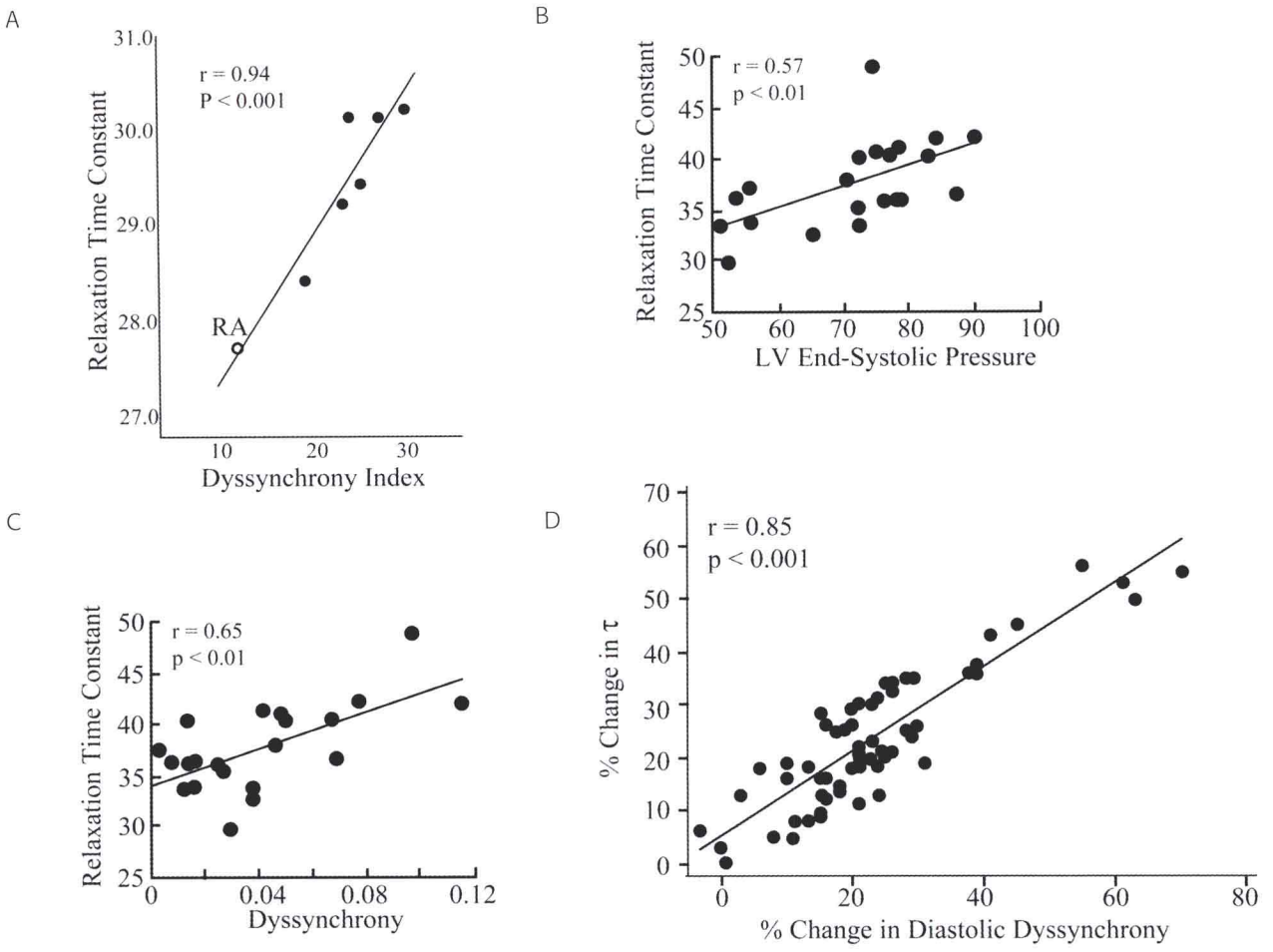

FIG. 1.2. A: Effect of mechanical dyssynchrony induced with ventricular pacing (closed-circles) on relaxation in a normal canine as compared with baseline synchronous contraction (right atrial pacing, open circle). Ventricular pacing was performed from various LV and RV sites. B and C: Cardiac dyssynchrony and delay in chamber relaxation induced by increasing afterload (systolic end-systolic pressure) by aortic occlusion. D: Percent change in relaxation and diastolic dyssynchrony after improving cardiac loading with pharmacologic therapy. (A, Adapted from Aoyagi T, Iizuka M, Takahashi T, et al. Wall motion asynchrony prolongs time constant of left ventricular relaxation. *Am J Physiol*. 1989;257:H883–H890. B and C, adapted from Yano M, Kohno M, Konishi M, et al. Influence of left ventricular regional nonuniformity on afterload-dependent relaxation in intact dogs. *Am J Physiol*. 1994;267:H148–H154. D, adapted from Wang J, Kurrelmeyer KM, Torre-Amione G, et al. Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy. *J Am Coll Cardiol*. 2007;49:88–96.)

decrease in the early-activated septum was observed. Local stress-strain plots illustrate these findings (Fig. 1.3B). Early shortening under low external load and late-systolic stretching under higher load creates a "figure-8" shaped stress-strain plot. The workload (loop area) for this territory is consequently low. In contrast, in the late-activated lateral wall, which functions at higher initial stretch and contracts against higher stress, the workload is much greater. These regional differences in work correlate with regional blood flow and metabolic demands.[25-27] Total myocardial oxygen consumption (MVO_2) is unaltered despite a striking decline in LV stroke work correlating with a marked decline in LV efficiency (work / MVO_2 consumption).[28, 29, 30]

Gross Pathologic Changes Associated with LV Dyssynchrony

Chronic dyssynchrony leads to maladaptive ventricular remodeling. Vernooy et al.[26] assessed structural and functional changes 16 weeks after ablating the left-bundle branch in dogs to create cardiac dyssynchrony. A decline in LV EF (–25%) paralleled an increase in chamber diameter by +23%. As previously discussed, RV pacing also generates LV dyssynchrony, and Thambo et al.[31] studied the long-term effects of RV pacing at physiologic heart rates in 23 patients with congenital heart block undergoing pacer implantation. Combined thinning of the early-activated septum and thickening in

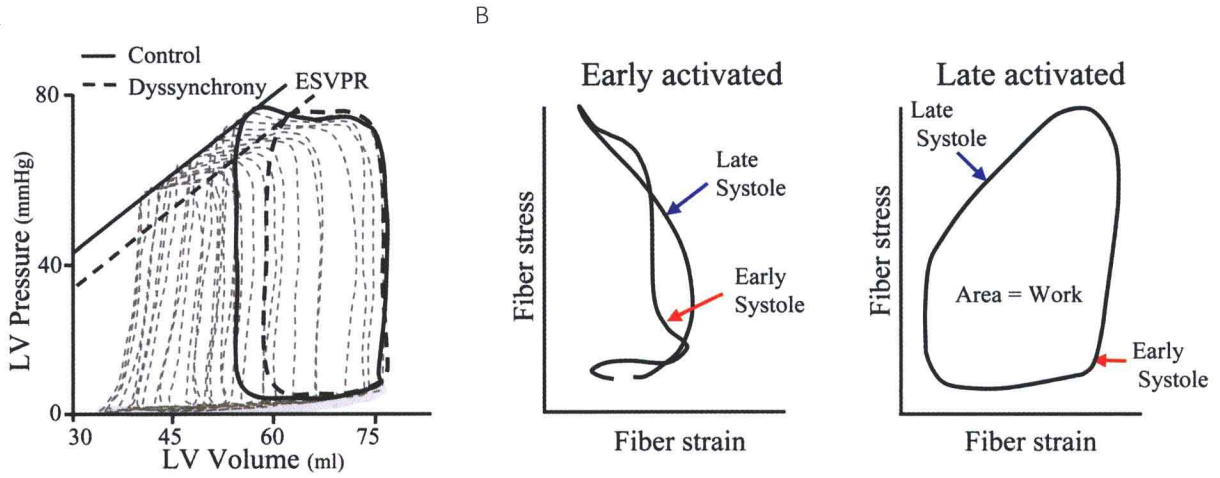

FIG. 1.3. **A:** Pressure-volume loops showing effect of dyssynchrony on end-systolic pressure-volume relation (ESPVR) and resting cardiac cycle (loop). The ESPVR shifts rightward, end-systolic volume increases, and stroke volume and work declines. **B:** Stress-strain loops from early- versus late-activated regions in a dyssynchronous heart. Whereas these loops would normally appear the same, with dyssynchrony the early-activated region first contracts at low load and is then stretched generating a figure-8 shaped loop with little area (reduced work). The late contracting lateral wall operates at higher preload and stress, requiring greater work. (A, adapted from Park, RC, Little WC, O'Rourke RA. Effect of alteration of left ventricular activation sequence on the left ventricular end-systolic pressure volume relation in closed-chest dogs. *Circ Res.* 1985;57:706–717.)

late-activated posterior wall resulted in a 30% increase in the ratio of posterior to septal wall thickness. In addition, LV chamber diameter increased by 20%.

Dyssynchrony induces regional changes in underlying cardiac fiber architecture. In a canine model of dysynchronous heart failure (LBB ablation followed by 3 weeks of atrial tachypacing), Helm et al.[32] used high-resolution MRI and computational anatomical registering to show that, while the primary fiber orientation (epicardium downward, endocardium upward, and mid-myocardial circumferential) was not significantly altered, the transmural fiber gradient was markedly increased in the septal region owing largely to wall thinning. In addition, they found that the orientation of laminar sheets (planes of muscle fibers that constitute the myocardium) were oriented more vertically in the early-activated septum but not changed in the lateral wall. Such regional alterations in fiber architecture could affect the local biophysical/mechanical properties of tissue and impact propagation of electrical excitation.

Biochemical Consequences of Dyssynchrony

The combined effect of dyssynchrony and heart failure alters expression and activity of various proteins beyond that observed with heart failure alone. In the first study to test for such effects, Spragg et al.[33] contrasted regional molecular changes in failing canine hearts with and without dyssynchrony (eg, right ventricular versus right atrial tachypacing). Sarcoplasmic reticulum (SR) Ca^{2+}-ATPase, which actively transfers Ca^{2+} from the cytosol into the SR, and phospholamban, a coregulator of the latter protein, were down-regulated (~20-30%) in the lateral endocardium versus other territories. The extracellular response kinase (ERK1/2), a mitogen-activated kinase that is associated with stress stimulation pathways modulating cell survival and differentiation, was highly activated in the lateral endocardium versus other regions. Connexin 43 (Cx43), a gap-junction protein that allows for rapid cell-to-cell depolarization, was marked downregulated. Importantly, these molecular changes in the lateral endocardium were not observed in failing myocardium without dyssynchrony. Recently Chakir et al. [34] showed differential activation of stress response proteins, such as tumor necrosis factor-alpha, Ca^{2+}-calmodulin-dependent kinase II, and p38 MAP kinase. Interestingly, these changes were only observed when dyssynchrony was combined with heart failure and not with dyssynchrony alone[35]—indicating that dyssynchrony interacts specifically with underlying heart failure substrate to trigger molecular alterations. Finally, Bilchick et al.[36] similarly observed regional expression of genes involved with growth and hypertrophy, stress signaling, and matrix remodeling in normal mice after only 7 to 10 days of RV (dyssynchrony) pacing. Regional molecular polarization in the dyssynchronous failing heart may contribute to heterogeneous electromechanical coupling and enhanced arrhythmia susceptibility.

Dyssynchrony Alters Regional Electrical Heterogeneity and Arrhythmia Susceptibility

Heart failure and QRS prolongation[11–37] are powerful and independent predictors of mortality due to ventricular arrhythmias in heart failure patients. Two prerequisites for reentrant arrhythmia are 1) unidirectional conduction block and 2) either sufficiently long circuit path-length or regionally delayed conduction allowing for adequate time to regain ex-

citability in the blocked limb. Selective prolongation of APD within mid-myocardial cells due to remodeling of delayed rectifier K current and possibly Ca^{2+} currents have been implicated in causes for QT-interval prolongation, transmural heterogeneity of repolarization, and susceptibility to conduction block (the first prerequisite for arrhythmia induction) observed in dyssynchronous HF.[38, 39] In addition, dyssynchrony alone (without HF) alters regional myocardial conduction and has been implicated in arrhythmia susceptibility, fulfilling the second prerequisite for reentry. Myocardial conduction is anisotropic with more rapid cell-to-cell conduction occurring along the myocardial fiber direction owing to gap junction protein coupling at intercalated discs. Spragg et al.[35] compared regional myocardial conduction in canine hearts with chronic mechanical dyssynchrony (LBB ablation) without superimposed heart failure to normal control dogs. Normal dogs with synchronous contraction had faster endocardial versus epicardial conduction in both anterior and lateral territories (Fig. 1.4A). However, in hearts with a chronic LBBB, the transmural pattern of conduction

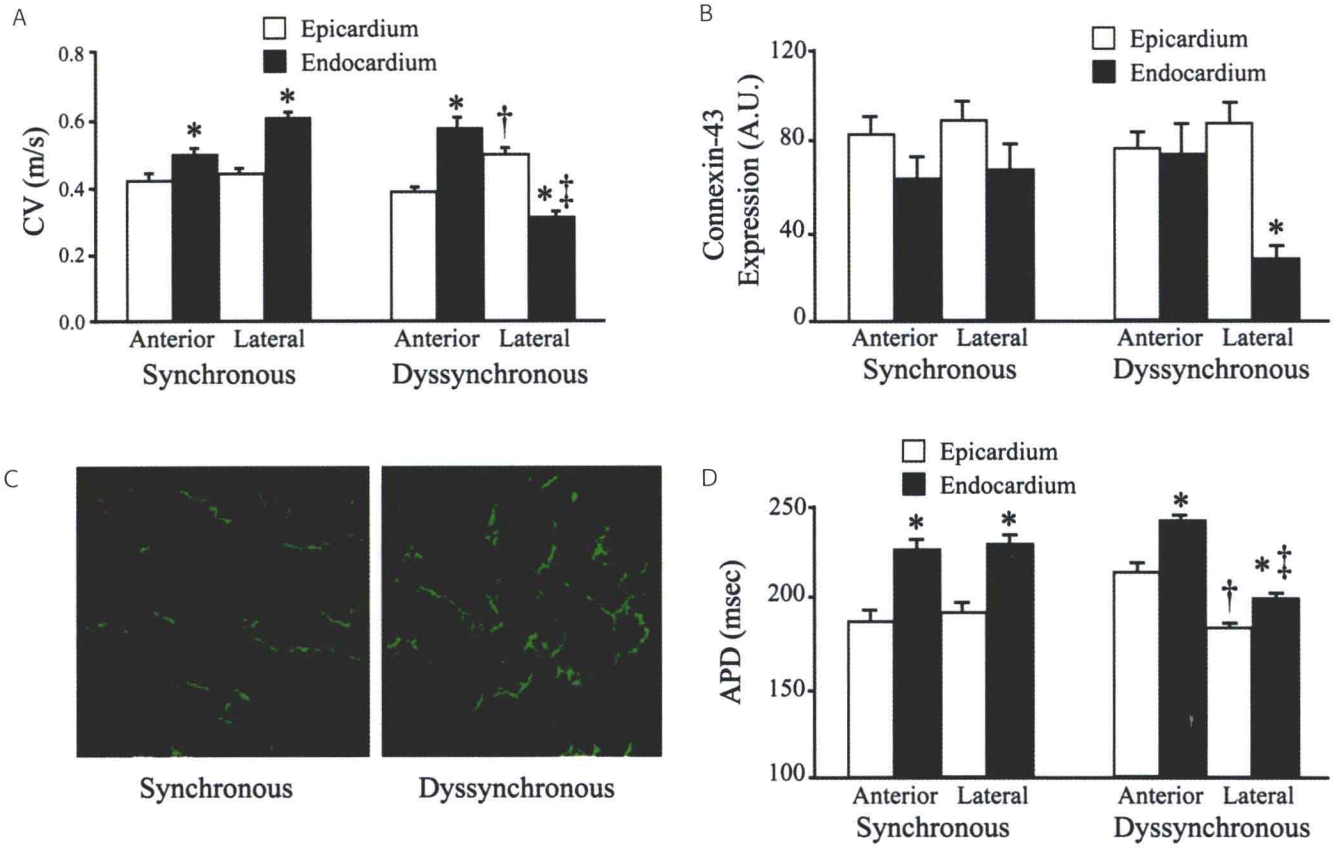

FIG. 1.4. **A**: Epicardial and endocardial conduction velocity in normal and dyssynchronous (LBBB) canine ventricular wedge preparations isolated from anterior and lateral regions. The normal pattern shows faster endocardial conduction throughout. However, with chronic dyssynchrony, there is reversal of this pattern in the lateral wall, but maintenance of the pattern in the earlier activated anterior wall. *p <0.001 versus corresponding epicardial value; † p = 0.001 versus all other epicardial values; ‡ *P* = 0.001 versus all other endocardial values. **B**: Expression of connexin-43 in synchronous controls is slightly reduced in endocardium overall, though these changes were not statistically significant. However, with chronic LBBB, expression fell markedly solely in the lateral epicardium, with a marked transmural gradient in this territory (**p* <0.001). **C**: Con-focal imaging of connexin-43 in myocytes from normal synchronous versus dyssynchronous hearts. Normal localization at the terminal intercalated discs was altered, as connexin-43 appeared more prevalent in the lateral margins of the cells (remodeling). **D**: Epicardial and endocardial action potential durations (APD) in normal synchronous and dyssynchronous (LBBB) canine ventricular wedge preparations isolated from anterior and lateral regions. The normal pattern shows prolonged APD in endocardium versus epicardium in both regions. However, with chronic dyssynchrony, there is a reduction in APD in both layers with maintenance of the endocardial to epicardial pattern. *p <0.05 versus corresponding epicardial value; †p<0.05 versus corresponding anterior epicardium; ‡*P* = 0.05 versus corresponding anterior endocardium. (Data from Spragg DD, Akar FG, Helm RH, et al. Abnormal conduction and repolarization in late-activated myocardium of dyssynchronously contracting hearts. *Cardiovasc Res.* 2005;67:77–86.)

speed was flipped in the lateral wall (epicardium faster than endocardium), but was unchanged from normal in the anterior wall. This was accompanied by both a reduction in the expression of the gap protein (Cx43) in lateral epicardium (Fig. 1.4B) and its redistribution away from intercalated discs to the lateral wall of the myocyte (Fig. 1.4C). Both lateral wall myocardial layers had similar Cx43 redistribution, so altered Cx43 trafficking was unlikely the only basis for reduced endocardial conduction velocity. Altered Cx43 phosphorylation and the formation of heterotypic and heteromeric gap junction channels (Cx43 + Cx45) with reduced conductance have been implicated in reduced velocity of propagation. Finally, Spragg et al. observed significant reductions in action potential duration and relative refractory period in the lateral compared to anterior wall, whereas both time periods were regionally similar in normal (synchronous) controls (Fig. 1.4D). The combination of shortened refractoriness and slowed conduction would seem a potential substrate for arrhythmia.[39]

ACUTE EFFECTS OF CARDIAC RESYNCHRONIZATION THERAPY

Mechanics and Energetics

The mechanical and hemodynamic effects of CRT occur rapidly—essentially within a beat. Figure 1.5A shows the abrupt hemodynamic effects (increase in dP/dt_{max} and aortic pulse pressure) of CRT in a patient with dilated cardiomyopathy (DCM). Pressure-volume analysis (Fig. 1.5B) shows a marked increase in stroke volume and decline in end-systolic stress, with little change in end-diastolic volume or pressure. Improved chamber contraction is accompanied by enhanced efficiency.[40] Figure 1.5C compares myocardial oxygen consumption per beat during dobutamine infusion versus CRT. While both similarly enhanced dP/dt_{max}, a fall in O_2 consumption was observed with CRT. The finding of negligible energetic cost despite improved systolic function from CRT has been supported by other studies,[41,42] and is a particularly unique feature of CRT among current HF therapies. Thus far, inotropic drugs that acutely enhance systolic function have been found to worsen mortality when employed chronically. This likely relates to the precise mechanism of action, and the success of CRT indicates that if done the right way, chronic systolic improvement with enhanced survival is possible. Finally, CRT improves functional reserve both acutely[43] and following chronic therapy.[44,45] Figure 1.5D shows an example of how the systolic disparity between dyssynchronous and resynchronized hearts is amplified at faster heart rates. The force-frequency relationship during acute LV-only or BiV pacing (compared to RV pacing - dyssynchrony baseline) increased more with both modes of CRT.

Contractile synchrony from CRT can be best documented using regional circumferential strain maps (Fig. 1.6A and Fig. 1.6B).[46] CRT reduces the out-of-phase reciprocal stretch and shortening in anteroseptal versus lateral walls. These data were also used to generate the first temporal plot of the evolution and resolution of dyssynchrony (Fig. 1.6C). A vector index that increases not only if regions of the heart are contracting out of phase, but particularly if they are geographically clustered (i.e., lateral wall),[46] was used to quantify dyssynchrony, and a color cine is available on line.[46] Dyssynchrony increases throughout systole peaking shortly after end-systole and then declining in diastole. CRT reduces both systolic and diastolic dyssynchrony.

CHRONIC EFFECTS OF CARDIAC RESYNCHRONIZATION THERAPY

Reverse Chamber Remodeling

Chronic CRT induces further changes in LV remodeling.[47–50] End-systolic and end-diastolic volumes decline in most studies by an average of 10% over a 6-month period. As first shown by Yu et al.[50] this reduction of heart volumes is not an acute effect of CRT. When pacing is temporarily suspended after chronic CRT, the observed reduction in chamber volumes persists in the short term (Fig. 1.7A). In contrast, suspension of pacing in this setting results in an abrupt fall in dP/dt_{max} (Fig. 1.7B). Reduction of end-systolic volume has been used as a surrogate for mortality in heart failure patients receiving CRT,[51] and marker of response,[15] whereas acute hemodynamic changes have not generally predicted long-term response to therapy.[52]

CRT Alters Gene Expression

CRT improves excitation-contraction coupling and calcium handling, both of which are impaired in heart failure, and consequently enhances cardiac reserve. As previously discussed, acute CRT improves cardiac reserve or force-frequency relationship (FFR), (Fig. 1.5D), owing to improved diastolic filling rather than gene modulation. In contrast, chronic CRT therapy upregulates gene expression of calcium handling proteins involved in excitation-contraction coupling. With endomyocardial biopsies from the left interventricular apical septum in heart failure patients, Mullens et al.[44] compared the gene expression of key calcium-handling proteins at the time of CRT implant to 4 months follow-up. Significant up regulation in the expression of the sarcoplasmic reticular ATPase (SERCA2α), phospholamban, and β1- adrenergic receptor were observed after chronic CRT, and the SERCA2α/PLB ratio was found to increase. The latter is associated with improving calcium uptake into the SR and FFR. There was also a trend toward increased sodium calcium exchange (NCX) gene expression, which has also been associated with an improved FFR.[53] The authors found that these chronic gene expression changes were accompanied by an increase in the FFR at the time of follow-up compared to pre-implant.

Other investigators have similarly shown altered gene expression in CRT patients. Iyengar et al. [54] obtained endomyocardial biopsies from the RV septum in patients with nonischemic cardiomyopathy undergoing CRT implantation and compared gene expression of various proteins after

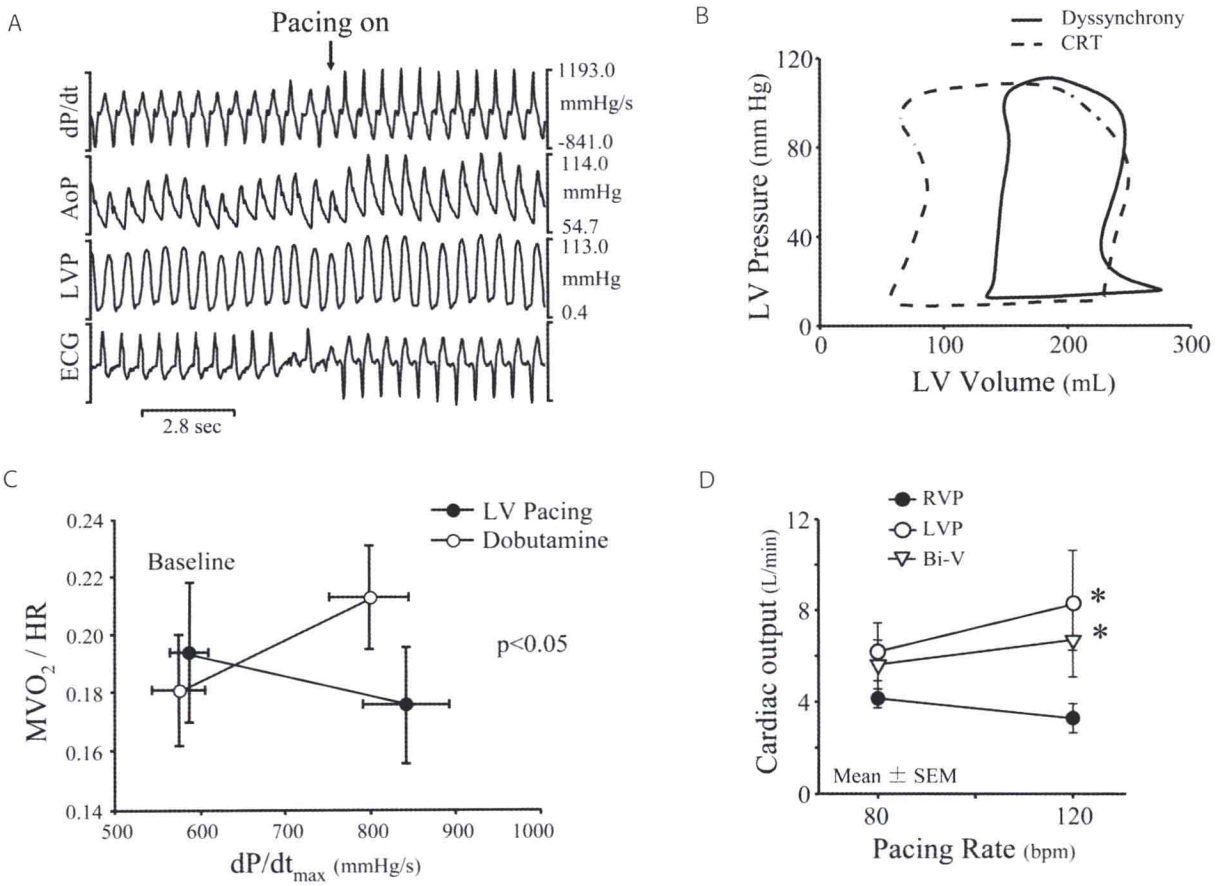

FIG. 1.5. **A**: Acute hemodynamic effects of CRT in a patient, assessed by peak rate of pressure rise (dP/dt_{max}), aortic pressure (AoP) pulse (indicating enhanced cardiac output), and LV pressure (LVP). Changes occur abruptly upon initiating CRT (note change in QRS morphology). **B**: Pressure-volume loops showing the acute effect of CRT (dashed line) compared with baseline dyssynchronous contraction (solid line). Resynchronization induces a left shift of the entire loop, with increased stroke volume and reduced end-diastolic filling pressures. **C**: CRT improves LV energetics. Data shows comparison to intravenous dobutamine. Both interventions raised dP/dt_{max} over baseline, but dobutamine increased myocardial oxygen consumption (MVO_2) whereas CRT reduced it. **D**: CRT enhances cardiac output with increasing heart rates. Data from patients with complete AV block undergoing RV, LV, or BiV pacing. Output was lowest with RV pacing (LBBB-type dyssynchrony) and was improved by LV-only and Bi V pacing at heart rate of 80 bpm. These disparities became enhanced at the faster pacing rate due to improved diastolic filling with CRT (*$p < 0.05$). (B, from Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardio myopathy and ventricular conduction delay. *Circulation*. 1999;99:1567–1573. C, from Nelson GS, Berger RD, Fetics BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. 2000;102:3053–3059. D, from Hay I, Melenovsky V, Fetics, BJ, et al. Short-term effects of right-left heart sequential cardiac resynchronization in patients with heart failure, chronic atrial fibrillation, and atrioventricular nodal block. *Circulation*. 2004;110:3404–3410.)

6 months of CRT. Resynchronization increased the expression of α–myosin heavy chain (MHC) with a trend toward decreasing β–MHC, an isoform switch that is the reversal of that observed in heart failure (fetal gene recapitulation pattern).[55] The authors also found a rise in phospholamban and trend toward increased SERCA2α expression. Recently, Vanderheyden et al.[45] reported similar changes in gene expression, and further showed this occurred only in clinical "responders" to the therapy and not "non responders." However, these data may be confounded by apparent baseline differences in the two groups, with nonresponders having expression levels at baseline often equal to those in the responder group after CRT.

To study the molecular and cellular remodeling effects of CRT in more detail, we have developed a canine model of dyssynchronous failure (DHF) and examined effects of CRT. All dogs are first atrially tachypaced in the presence of a LBBB to