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Effects of biventricular pacing and scar size in a computational model of the failing heart with left bundle branch block

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Abstract

Objectives—To study the impact of biventricular pacing (BiV) and scar size on left ventricular (LV) regional and global function using a detailed finite element model of three-dimensional electromechanics in the failing canine heart.

Background—Cardiac resynchronization therapy (CRT) clinical trials have demonstrated that up to 30% of patients may be classified as non-responders. The presence of a scar appears to contribute to those that do not respond to CRT. A recent study in patients with myocardial scar showed that LV dyssynchrony was the sole independent predictor of reverse remodeling, and not scar location or size.

Methods—Two activation sequences were simulated: left bundle branch block (LBBB) and acute simultaneous BiV (with leads in the left and right ventricle) in hearts with chronic scars of various sizes. The dependence of regional function (mean fiber ejection strain, variance of fiber isovolumic strain and fraction of tissue stretched during ejection) and global function (left ventricular dp/dt_{max} , ejection fraction, stroke work) on scar size and pacing protocol was tested.

Results—Global function and regional function averaged over the whole LV during LBBB and BiV decreased as a function of scar size. In the non-scarred regions, however, regional function was largely independent of scar size for a fixed pacing site.

Conclusions—The model results suggest that uniformity of mechanical contraction in non-scarred regions in the failing heart during biventricular pacing is independent of scar size for a fixed pacing site.

Keywords

CRT; scar; dog; computational; synchronicity

1 Introduction

Cardiac resynchronization therapy (CRT) is an increasingly popular strategy for improving pump function in heart failure patients with left bundle branch block (LBBB). CRT trials have

demonstrated improved quality of life in most patients (6), but that they also have shown that approximately 30% of patients do not respond to CRT (1,⁵). Patients who have suffered from prior myocardial infarcts appear to be the most likely to respond poorly or not at all (2,^{3,10,40}). The mechanisms by which the presence of a scar contributes to CRT non-responsiveness are unclear. A recent clinical investigation (15), however, showed that LV dyssynchrony was the only independent predictor of reverse remodeling – defined by a decrease in LV end-systolic volume exceeding 10% after 3 months – and not scar size.

Multi-scale computational models are useful for understanding the normal and diseased heart, by examining the effects of controlled numerical perturbations that might not be possible experimentally (21,³⁰). Anatomically detailed computational models of cardiac electromechanics have been able to predict the effects of ventricular pacing on the mechanics and hemodynamics of non-failing and failing hearts by only changing the activation pattern, while keeping all other input parameters (e.g. material properties, geometry) constant (19,^{20,35,36}).

Here, we investigated how regional and global ventricular function depends on scar size during LBBB and acute simultaneous biventricular pacing. We hypothesized that the uniformity of LV contraction is independent of scar size for a fixed pacing site.

2 Methods

2.1 Cardiovascular models of non-failing and failing hearts

Details on the computational model of non-failing and failing hearts have been published before (22,²³). Briefly, the analysis was conducted using three-dimensional finite element models of canine ventricular electromechanics, with Purkinje fiber network and realistic myofiber architecture. The geometries represented normal-sized and dilated dog ventricles. The same myofiber architecture was included in both geometries, since the myofiber distribution in normal and dilated hearts is not significantly different (13).

The ventricles were coupled to a systemic and pulmonary circulation, each consisting of two lumped windkessel compartments in series, one compartment for arterial and capillary blood and one for venous blood (24). The atria were represented by time-varying elastance models, relating atrial pressures to atrial volumes, and were activated 120 ms before the ventricles.

The effect of the pericardium was modeled by a pericardial pressure that acted on the ventricular epicardium, and was added to the atrial cavity pressures. Pericardial pressure was exponentially dependent on the total volume encompassed by the pericardium, hence included ventricular and atrial wall volumes, ventricular and atrial cavity volumes, and pericardial fluid volume. The difference in the pericardial pressure-volume relation between normal and dilated hearts was also included in the analysis (11).

In the dilated hearts, passive mechanical properties of the non-scarred tissue were the same as in the non-failing heart. One dilated heart model was free of scar and the others had anterior scars of size 7, 14, 21, and 30% (percentage of LV wall volume, Fig. 1). The passive properties of the scars were based on a 22-week-old scar as determined by Walker et al (38), being about 15 times stiffer and less anisotropic as compared to healthy tissue. The active properties of the failing non-scarred tissue were scaled from human data (32), in which the peak force was 27% lower than in healthy tissue, and relaxation was 17% longer. Actively developed stress in scarred tissue was zero. Summarizing, there were four main differences between non-failing and failing heart properties. Compared with non-failing hearts, in failing hearts: geometry was dilated (Fig. 2); maximum activation time was larger (Fig. 2); peak fiber stress was reduced; and relaxation was prolonged.

2.2 Activation sequences

Activation sequences of LBBB and biventricular pacing (BiV) were simulated by solving a model of cardiac action potential propagation with modified FitzHugh-Nagumo kinetics (33, 35) in the ventricular geometries (Fig. 2). For BiV, leads were placed at the right ventricular apex and base of the left ventricular lateral free wall. For validation purposes, three additional simulations were performed in a normal-sized heart with non-failing material properties: with a synchronous activation pattern, representing a heart paced at the right atrium (RAp), and activation patterns of LBBB and BiV. The depolarization times served as input to the mechanics model, in which myofiber tension development was initiated with an 8 ms delay after local electrical activation.

2.3 Simulations and data analysis

Steady-state values were obtained for every simulation. Steady state was defined as the state in which the LV and RV stroke volume difference, normalized to LV stroke volume, was less than 1%. Hemodynamic data and deformed ventricular geometries were computed every 4 ms. Left ventricular $dP/dt_{\max}$, ejection fraction (EF), LV end-diastolic pressure (LVEDP), and stroke work (SW) were calculated for each cardiac cycle.

The standard deviation of electrical activation times in the LV non-scarred tissue was computed to quantify electrical dyssynchrony. Ejection strain was defined as strain in the direction of the myofiber at the end of ejection with the reference state at the beginning of ejection. Fiber isovolumic strain was defined as strain in the direction of the myofiber at the end of the isovolumic contraction phase with the reference state at the beginning of that phase (= end-diastole). To quantify regional mechanics, the spatial mean fiber ejection strain (MFES), variance of fiber ejection strain and the variance of fiber isovolumic strain were obtained in steady state for the whole LV (including infarcts) and for the LV non-scarred myocardium. For the calculation of MFES, mean fiber ejection strain was multiplied by -1. This definition yields a MFES that is positive for shortening. The fraction of tissue stretched during ejection (FTS) and the location of this tissue were also assessed (i.e. the fraction of tissue with a negative MFES), to quantify the amount of myocardium not contributing to ejection. These parameters were calculated separately for the whole LV, and for the non-scarred tissue, as a function of scar size. The CURE (Circumferential Uniformity Ratio Estimate) index of mechanical non-uniformity of contraction used by other workers (14) was computed for midwall fiber ejection strain in the LV; 0 is a completely asynchronous contraction, and 1 is completely synchronous.

2.4 Numerical Solutions

The multi-scale model was solved with the Continuity 6.3 package (<http://www.continuity.ucsd.edu>). All simulations were solved on a 105 node Dell™ Rocks Linux cluster with 3.2 GHz 64 bit Xeon® processors and 2 GB of RAM. Typically, calculations required 40 minutes per cardiac cycle and 120 MB RAM on 12 processors running in parallel.

The finite element anatomic model of the canine heart was discretized into 48 tricubic Hermite elements, with 1968 degrees of freedom. The nonlinear finite element model was solved with a modified Newton-Raphson iteration scheme. Each time step was 4 ms. Integration was performed with 3x3x3 Gaussian quadrature points. Convergence was reached when both the sum of incremental displacements and the sum of the residuals were lower than 10^{-3} . The Jacobian was calculated and factorized in the first iteration of a new time step and when the solution was diverging. The system of linear equations was solved with SuperLU (27), a direct solver optimized for sparse matrices. The circulatory model was integrated in time with the Radau5 solver (12).

3 Results

3.1 Global function

Global function for the non-failing and failing hearts (RAp, LBBB, and BiV) were similar to previously published experimental results (table 1).

Compared with the non-failing synchronously stimulated heart, LV dP/dt_{max} , EF, and SW in the non-failing heart were reduced by 12, 3, and 8%, respectively with LBBB (table 1). Compared with the latter, these global parameters were reduced by 56, 48, and 14% in the failing heart without scar and the presence of scars further reduced these global parameters (Fig. 3). End-diastolic pressure increased by 8%. Compared with LBBB, biventricular pacing increased LV dP/dt_{max} , EF, and SW by 9, 3, and 8%, respectively in the non-failing heart.

3.2 Regional function

In the failing hearts, the standard deviation of electrical activation times in LV non-scarred regions during LBBB ranged from 24 to 27 ms (for a 0% and 30% scar respectively) and from 13 to 14 ms during BiV. Regional function in the failing hearts during CRT was always better than those during LBBB, for all scar sizes. In the failing hearts, most wall regions that shortened early during isovolumic contraction were stretched during ejection (Fig. 4B, see also the movie in the online supplement of fiber strains during the cardiac cycle for the LBBB and CRT hearts with different scar sizes). In the non-failing hearts this did not seem to occur: early activated fibers shortened further during ejection (Fig. 4A). Fibers located in the scars were always stretched during the isovolumic contraction phase, and most of them were also further stretched or remained akinetic during the ejection phase. Fiber shortening during ejection in the anterior wall – proximal to scar – decreased as a function of scar size (Fig. 4B). Conversely, fiber shortening during ejection in the posterior wall – distal from scar – increased as a function of scar size (Fig. 4B).

MFES in both the LBBB and BiV simulations, spatially averaged over the whole LV, decreased monotonously as a function of scar size (Fig. 5A). However, in the non-scarred tissue, MFES increased with increasing scar size. MFES was always larger during BiV (compared with LBBB with same scar size). Non-uniformity of ejection strain for the whole LV increased for increasing scar size during BiV, but reached a peak at about 14% scar size for LBBB (Fig. 5B). Non-uniformity of ejection strain in non-scarred regions was relatively independent of scar size. Fiber isovolumic strain was always more non-uniform during LBBB compared with BiV (Fig. 5C). In the whole LV for both LBBB and BiV, fiber isovolumic strain became more non-uniform with increasing scar size. However, in the non-scarred tissue, non-uniformity of fiber isovolumic strain remained about constant at a scar size above 14%.

In the non-failing synchronously stimulated heart, FTS was 0%. In the paced non-failing hearts, this fraction was generally also close to zero. In the failing hearts however, LV FTS was much larger: up to almost 25% during LBBB with a 21% scar (Fig. 5D). Most of the regions within the scars were stretched during ejection (Fig. 6), but even in the heart without a scar, 20% of LV tissue being stretched was observed with LBBB. BiV lowered the fraction of tissue stretched during ejection. Most of this stretching occurred near the pacing sites (Fig. 6). FTS in the non-scarred regions decreased with increasing scar size. The CURE index was higher during BiV compared to LBBB, with an optimal at a scar size of 14% (Fig. 5E).

4 Discussion

The dependence of regional and global function on scar size during LBBB and BiV was tested, using a detailed computational model of canine ventricular electromechanics and hemodynamics. One of the main advantages of computational models for this purpose is the

tightly controlled conditions under which the models can be run. In the LBBB heart with a scar, two major sources of regional non-uniform contraction are present that affect global function: electrical dyssynchrony and the non-contractile scarred infarct. In this study we varied the input parameters of these two sources: the size of scars and electrical dyssynchrony (LBBB vs. BiV), while keeping all other input parameters constant. The most important findings from this study were: 1) non-uniformity of contraction in non-scarred tissue was largely independent of scar size; 2) fiber ejection strain in non-scarred myocardium improved with increasing scar size; 3) large regions of tissue were stretched during ejection in the failing hearts, and these regions were close to the pacing site or in the scar.

Simulated global function in the non-failing heart, paced at the RA and during LBBB, and in the failing heart during LBBB was in good quantitative agreement with previously performed experiments; BiV in the non-failing and failing heart was in good qualitative agreement, but the magnitudes of functional improvements were low with respect to LBBB. The quantitative discrepancy between experiment and simulation for the BiV simulations might be attributed to the comparison between the computational acute pacing study with chronic experimental pacing studies. In the latter case reverse remodeling might have taken place. In the failing heart, global function decreased with increasing scar size, where global function for BiV was better than LBBB for every scar. Except for MFES, relative improvements in regional function from LBBB to BiV were relatively greater than improvements in global function.

Simulated strain patterns were in good agreement with experimentally obtained strain patterns (i.e. fiber shortening and stretching during isovolumic contraction in early and late activated regions respectively), as measured by MRI tagging (39). The CURE index in the failing hearts without a scar was also in good agreement with dog experiments where values have been reported of 0.56 ± 0.08 and 0.87 ± 0.01 during LBBB and biventricular pacing, respectively (14). In the failing hearts with scars during BiV, the CURE index reached a maximum at a scar size of 14%, implying that above this scar size, mechanical dyssynchrony is increasing again. The other regional function parameters, averaged over the whole LV, were always decreasing with increasing scar size, but the regional function parameters for the non-scarred tissue were about constant for each scar size.

There were large differences between non-failing and failing hearts in the response to pacing: e.g. FTS was zero or close to zero for all activation patterns in the non-failing hearts, whereas values of up to 25% were seen in the failing heart. This stretching occurred in regions close to the pacing site and in scarred regions. Apparently, early-activated fibers in the normal hearts have enough potential to contract, possibly owing to the intact Frank-Starling mechanism when the aortic valve opens and late-activated fibers become active. One of the alterations in the failing heart, compared to the non-failing heart, is a reduced myofiber peak stress. Reducing peak stress lowers the overall active force-sarcomere length relation, thus reducing the slope of this relation, which is the basis of the Frank-Starling mechanism. As a result of the inhibited Frank-Starling mechanism in the failing hearts and the slower conduction, early activated fibers cannot generate enough active force when late-activated fibers become active, and thus are being stretched during ejection. However, when the scar becomes larger, the non-scarred tissue was able to contract against a larger fraction of passive tissue, resulting in a higher MFES and decreasing FTS in the non-scarred tissue.

4.1 Clinical relevance

Thirty percent of patients with heart failure receiving CRT appear to demonstrate little if any improvement. Those patients with prior myocardial infarcts represent about 50% of patients with a poor response (10). Recently it has been shown that patients with large akinetic regions were always classified as a non-responder (40) while echocardiographic studies that followed up on clinical trials have shown that significant reverse remodeling can occur in CRT

responders and is often used as an indicator of response. One clearly detrimental mechanical phenomenon is the presence of a non-uniform systolic contraction. These non-uniformities in regional function may result in altered reverse remodeling processes or complete lack thereof. Indeed, it has been shown that synchronicity of contraction is an accurate independent predictor of reverse remodeling (41). Jansen *et al.* (15) investigated the relation between location and extent of transmural scar, LV dyssynchrony, and reverse remodeling in CRT with tissue Doppler. In multivariate analysis, only LV dyssynchrony ($p=0.004$) independently predicted LV reverse remodeling, even in the presence of scar. The distance between the pacing site and scar might be an important determinant of mechanical synchronicity that can be obtained – and thus reverse remodeling in the long term. Shuros *et al.* (34) have demonstrated that pacing in the scar border zone attenuated adverse ventricular remodeling. Here we have shown that non-uniformity of LV fiber shortening in non-scarred tissue was independent of scar size for a fixed pacing site. It must be emphasized though that in this study we focused on acute biventricular pacing, and hence could not relate mechanical synchronicity to (reverse) remodeling. The development of computational models that include remodeling and growth algorithms in the whole heart (25) after chronic pacing would be a valuable tool in the clinic to predict long-term effects of CRT.

4.2 Limitations

In the simulations, the depolarization wave was not affected by the scarred regions. In reality, the effects of scar on depolarization are more complex. It appears that electrical wavefronts can propagate through scar (16) or at least appear to do so, for scars might not be completely transmural. Properties of scar are non-uniform in that for example viable tissue might be present in scar. Also, ventricular conduction blocks are not necessarily solely due to scar. Functional conduction blocks are typically observed in nonischemic cardiomyopathy and distributed differently within the LV (4). Conduction block may also exaggerate delays at late activated sites, worsening dyssynchrony (16). These considerations emphasize the need for patient-specific modeling, in order to optimize CRT and predict CRT outcome. A more elaborate investigation on optimal regional function will be part of a future study in which a sensitivity analysis will be performed by varying the location of the pacing sites, and location and size of myocardial scars, taking into account the electrical properties of myocardial scar.

It is generally known that myofibers exhibit heterogeneous electrophysiological properties. It has also been shown that unloaded shortening of isolated cardiac single cells is heterogeneously distributed transmurally (9). Some of these heterogeneities may be related to differences in excitation-contraction (EC) coupling characteristics that have been observed in cells isolated from the canine left ventricle. Although EC-coupling was different in the scar regions (by absence of active force generation), these transmural heterogeneities were not taken into account in the present study. Recently, with a computational model of cardiac electromechanics, we have shown that the transient outward current (I_{to1}) and crossbridge cycling kinetics are primary mechanisms underlying transmural variation of myocyte contractile function (8). It has been hypothesized before that transmural heterogeneity of mechanical properties is important for a uniform contraction in the normal heart (9,18). These heterogeneities might play an important adverse mechanical role during ventricular pacing in which the sequence of activation is altered. Therefore, inclusion of transmural heterogeneities in our model most likely will augment the non-uniformity of contraction during ventricular pacing overall, but might still be relatively independent of scar size.

The arterial baroreflex was not included in the computational models presented. Hence, baroreceptor-mediated control of heart rate, myocardial contractility, and vasomotor tone was neglected. The absence of mediated myocardial contractility might explain the lower dP/dt_{max} from the computational failing hearts *versus* experimentally obtained values. The

contractile properties of the computational model were based on measured excised human trabeculae (32), which were lacking adrenergic stimulation. Inclusion of the baroreflex (29) in computational models of heart failure would be an interesting future study.

Also, mitral regurgitation, common in dilated cardiomyopathy (31), was not taken into account. Cardiac resynchronization therapy is not only beneficial for a more coordinated ventricular contraction pattern, it has also been shown to reduce mitral regurgitation in patients with heart failure (7, ¹⁷). In the models presented, the absence of mitral regurgitation under all circumstances might explain the relatively small increase in $dP/dt_{\max}$ and EF for BiV (versus LBBB). In experiments, augmentations of >20% have been reported for $dP/dt_{\max}$ and EF in the biventricular paced heart with LBBB (7, ^{14, 26}). Since CRT decreases mitral regurgitation and thus increases EF and $dP/dt_{\max}$ (7), incorporating a model of the mitral valve-papillary apparatus might show a similar increase in these global function parameters for the current models.

The model results suggest that uniformity of mechanical contraction in the failing heart during biventricular pacing is relatively independent of scar size for a fixed pacing site.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

BiV	biventricular pacing
CRT	cardiac resynchronization therapy
CURE	circumferential uniformity ratio estimate
$dP/dt_{\max}$	maximum rate of pressure change
EF	ejection fraction
FTS	wall volume fraction of tissue stretched during ejection
LBBB	left bundle branch block
LV	left ventricle/ventricular
LVEDP	left ventricular end-diastolic pressure
MFES	- mean fiber ejection strain
RAp	simulation representing normal sinus rhythm
RV	right ventricle/ventricular
SW	stroke work

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Figure 1. Posterior view of a cross-section of the ventricles, showing the size of scars as fraction of LV wall volume [%]. The scars did not extend into the septum for the 7 and 14% case. A volume fraction of 0.8 and 2% of the septum was affected for the 21 and 30% sized scars,

Figure 2.

Activation times for left bundle branch block (LBBB) and biventricular pacing (BiV). Numbers near the ventricles are maximum activation times, with stimulus at 0 ms (note that maximum activation time is very similar to QRS width). Also note the difference in geometries between the non-failing and failing hearts. Crosses indicate pacing sites.

Figure 3. LV global function quantified by dp/dt_{max} (A), ejection fraction (B), stroke work (C), and end-diastolic pressure LVEDP (D) as a function of scar size.

(A) Fiber strain in non-failing hearts

(B) Fiber strain in failing hearts

Figure 4.

A) Fiber strain in non-failing hearts at several circumferential locations in the LV midwall at the equator during right atrial pacing (RAp), left bundle branch block (LBBB) and biventricular pacing (BiV). B) Fiber strain in failing hearts at similar locations for different scar sizes during left bundle branch block and biventricular pacing. Cardiac phase transitions are indicated by circles, starting at end-diastole (which is also the state strain is referenced to). Numbers indicate depolarization time in that region. Regions proximal and distal to scar are indicated by black bars.

Figure 5.

LV regional function during LBBB and BiV quantified by A) mean ejection strain; B) variance of ejection strain; C) variance of isovolumic strain; D) LV fraction of tissue stretched during ejection and E) CURE index of mechanical dyssynchrony as a function of scar size. Regional function parameters A-D were averaged for the whole LV and for non-scarred regions.

Figure 6. Fiber ejection strain for left bundle branch block (LBBB) and biventricular pacing (BiV), showed in a longitudinal cross-section on the anterior half of the ventricles. Blue indicates shortening, red stretching, and white is ~0 strain. The percentages indicate scar size. See the online supplement for a dynamic view of stretching and contraction.

Table 1

Simulated and experimental LV global function.

	Experiment/ Simulation	Non-failing heart			Failing, No Scar	
		RAp (abs)	LBbB (abs)	BiV (%)	LBbB (abs)	BiV (%)
dP/dt _{max} [mmHg/s]	Liu et al (28)	1162±106.1	830.6±135.8			
	Verbeek et al (37)	1627±644	1345±413	18.9±6.4		
	Leclercq et al (26)				1048±242	32.8
	Helm et al (14)		1212.1±158.7	33.73±2.91	737.1±78.0	32.84±0.79
P _{max} [mmHg]	Simulation	1630	1440	8.6	628	10.1
	Liu et al (28)	94.5±4.7	87.01±18.2			
	Verbeek et al (37)	98.8±12.0	92.2±16.3			
	Leclercq et al (26)				86.6±7.7	12.5
EF [%]	Simulation	101	97.4	3.6	88.1	2.3
	Leclercq et al (26)				23±12.7	20.0
	Verbeek et al (37)	38	28			
SW [mmHg ml]	Simulation	43.8	42.3	2.8	22	2.7
	Verbeek et al (37)	3480±1062	1972±635	15.2±3.6		
	Simulation	1662	1523	7.8	1321	5.2

BiV(%) represents percentage change with respect to LBbB. abs = absolute value; dP/dtmax = maximum pressure increase; EF = ejection fraction; Pmax = maximum pressure; RAp = synchronous stimulation; SW = stroke work