Abnormal conduction and repolarization in late-activated myocardium of dyssynchronously contracting hearts

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Abstract

Background: Cardiac dyssynchrony due to intraventricular conduction delay produces heterogeneous regional wall stress and worsens arrhythmia susceptibility in failing hearts. We examined whether chronic dyssynchrony per se induces regionally heterogeneous electrophysiological remodeling.

Methods and results: Adult dogs (n=9) underwent left bundle branch radiofrequency ablation (QRS duration increased from 50±7 to 104±7 ms); 6 untreated dogs served as controls. A subset of ablated (n=3) and control (n=4) dogs underwent tagged MR imaging to confirm ablation-induced left ventricular (LV) dyssynchrony. Four weeks later, hearts were excised and early (anterior)- and late (lateral)-activated myocardial segments were isolated. Conduction velocity (CV), action potential duration (APD), and refractory period (RP) of paced, arterially perfused myocardial wedges were studied by extracellular and optical mapping, and arrhythmia susceptibility was assessed by programmed stimulation. Regional stress-response kinase, calcium cycling, and gap junction protein expression were assayed by Western blotting, and the subcellular distribution of connexin43 was analyzed by immunofluorescence microscopy. CV, APD, and RP were significantly reduced in the late-activated, lateral wall of dyssynchronous hearts compared to the anterior wall. Normal differences in CV (endocardial > epicardial) were reversed in the dyssynchronous lateral LV. While the total expression of connexin43 was unaltered in dyssynchronous models, its subcellular location was redistributed in late-activated myocardium from intercalated discs to lateral myocyte membranes. Arrhythmias were rare in tissue from normal and dyssynchronous models. Total expression of calcium-cycling proteins (sarcoplasmic reticulum Ca²⁺-ATPase and phospholamban) and the stress-response kinase phospho-ERK did not vary regionally in either model.

Conclusions: Dyssynchrony even in the absence of LV dysfunction induces regionally specific changes in conduction and repolarization. These changes support a novel mechanism linking mechanical dyssynchrony to persistent electrophysiological remodeling and heterogeneity.

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Keywords: Action potential duration; Conduction velocity; Arrhythmia; Ventricular dyssynchrony

1. Introduction

Intraventricular conduction delay with concomitant left ventricular (LV) dyssynchrony is common in patients with heart disease and/or ventricular pacing, and independently predicts sudden death in patients with heart failure (HF) [1–3]. Dyssynchrony generates heterogeneous stress and strain in the LV, with the greatest load applied to late-activated (typically lateral wall) myocardium [4]. Chronic dyssynchrony induces regional alterations in blood flow, hypertrophy, and protein expression [5–7], and eventually compromises LV systolic function [8]. We hypothesized that LV dyssynchrony may also induce intraventricular electrophysiological remodeling, potentially contributing to arrhythmia susceptibility.

The effect of load on electrophysiology (mechano-electrical feedback) has long been appreciated as a potential...
mechanism for arrhythmogenesis [9–11]. Changes in global or regional loading generate effects specific to both the type and timing of mechanical stimulation. For example, steady-state increases in preload (i.e. volume applied over seconds to minutes) typically reduce action potential duration (APD) [12–14]. In contrast, pulsed increases (typically applied over ≤50 ms) may shorten or prolong APD depending on the timing of load application in systole [15]. Unlike chronically dyssynchronous hearts, however, these data reflect abrupt loading changes. Sustained increases in load (over days to weeks) due to heart block and bradycardia result in heterogeneous APD prolongation between the right ventricle (RV) and LV, with interventricular dispersion of repolarization and increased arrhythmia susceptibility [16–18]. However, these models introduce complicating features such as hypertrophy and bradycardia. Sustained ventricular pacing also alters regional loading, and induces both APD prolongation [19–21] and changes in myocyte protein expression [22]. This phenomenon (cardiac memory) is principally observed at the site of pacing [22,23], however, and may reflect altered local electrical activation rather than intra-chamber mechanical dyssynchrony [24].

Accordingly, the present study tested the hypothesis that sustained mechanical dyssynchrony due to chronic left bundle branch block (cLBBB) generates regional LV electrophysiological remodeling. cLBBB and control dogs were studied to assess local conduction and repolarization properties, and regional/transmural expression of calcium-cycling, gap junction, and stress response kinase proteins. We show marked reductions in CV, APD, and tissue refractoriness localized to the late-activated, lateral LV of cLBBB dogs. While previously reported protein expression changes seen in dyssynchronous failing hearts [7] were not present with cLBBB alone, we observed abnormal subcellular connexin43 (Cx43) distribution. Together, the data show that dyssynchrony generates trans-chamber disparities in CV, APD, and refractoriness, suggesting a novel mechanism that could link intraventricular conduction delay to increased arrhythmia susceptibility.

2. Methods

2.1. Preparation

Adult mongrel dogs (n=9) underwent left bundle branch radiofrequency ablation, as described previously [25]. Briefly, dogs were anesthetized (10–15 mg/kg thiopental, 1–2% isoflurane) and intubated. Baseline recording of LV pressure and dP/dtmax were obtained with a Milar catheter advanced from the femoral artery retrogradely to the LV. A 4 mm-tipped radiofrequency ablation catheter was similarly passed into the LV, and a pacing/sensing catheter was introduced through the femoral vein and placed at the RV apex. Electrograms documenting RV and LV activation were recorded at the RV and LV apices (Fig. 1A, left panel). Left
bundle branch potentials (Fig. 1A, center panel) were identified at the basal interventricular septum and ablated. LBBB was documented 45 min post-ablation, both by surface electrocardiogram and repeat intracardiac electrograms recorded at the RV and LV apices (Fig. 1A, right panel). Normal controls (n = 6) were also studied. Two and four weeks post-ablation, cLBBB dogs underwent surface electrocardiography to confirm persistence of LBBB. Four weeks post-ablation, dogs were sacrificed and the hearts excised. LV pressure and dP/dt\text{max} were measured as before, immediately prior to sacrifice. Full-thickness myocardial segments for electrophysiological measurements in arterially perfused wedges, Western blotting, and microscopy were isolated from the anterior and lateral LV walls. All protocols followed USDA guidelines, and were approved by the Animal Care and Use Committee of the Johns Hopkins Medical Institutions (which conform to NIH guidelines).

2.2. MR imaging

Selection of anterior and lateral LV myocardial segments as early-activated/low-strain and late-activated/high-strain tissue, respectively, was guided both by tagged MR imaging of cLBBB, non-failing dogs, and by previous imaging analyses by our lab [25,26] and others [4,27,28]. Briefly, a subset of cLBBB (n = 3; imaged 1 week post-ablation) and normal control (n = 4) dogs were anesthetized and intubated. Tagged cine MR images were obtained (GE Signa 1.5 T) during RA pacing and used to derive 3D finite strains. Regional mechanical activation time was measured from a fiducial marker (pacing stimulus) to the peak circumferential shortening and was averaged over 2–4 cross-sectional slices in the mid-ventricle region. Delay in mechanical activation of the lateral versus the anterior regions was expressed as an absolute time difference. Peak circumferential strain (contraction) within a region was averaged over 2–4 cross-sectional slices of the mid-ventricle region and expressed as a percent shortening. Strain analysis was performed using HARP (Diagnosoft Inc, Palo Alto, CA) and Matlab (MathWorks, Natick, MA) [29].

2.3. Extracellular and optical mapping

Arterially perfused wedges (~1 × 1.3 × 3 cm) from cLBBB (n = 6) and control dogs (n = 6) were studied as described previously [30]. Briefly, myocardial wedges were dissected from anterior and lateral LV walls, and perfused through an overlying epicardial artery with Tyrode's solution (50–60 mm Hg perfusion pressure; 36 ± 1 °C). Mapping studies were performed in a custom-designed perfusion chamber equipped with both an extracellular mapping electrode array, and a window for optical mapping. Extracellular mapping was performed with a 24-pin unipolar electrode array (3 cm² surface area, spatial and temporal resolution of 3 mm and 0.5 ms, respectively) during steady-state pacing from the array corner (1.5 × diastolic threshold; basic cycle length (BCL) 1000 ms). Local activation time was determined as the difference in milliseconds between pacing artifact and onset of dV/dt\text{max} of the local electrogram (Fig. 1B). Isochrones (Fig. 2A,B) qualitatively depicting epicardial and endocardial activation were constructed directly from activation times measured at each electrode. Average CV was calculated as the slope of the relationship between distance versus local activation time for all electrograms; CV was calculated for each point in the electrode array, and the results averaged to provide CV for the LV segment assayed.

Optical action potential mapping (spatial and temporal resolution of 365 μm and 0.6 ms, respectively) was performed in wedges (n = 3 cLBBB, n = 6 controls) paced as above, and stained with the voltage-sensitive dye di-4-ANEPPS (15 μM) as described previously [31]. Local activation time at each pixel was determined as the maximal first derivative of the local electrogram (Fig. 1B). Isochrones (Fig. 2A,B) qualitatively depicting epicardial and endocardial activation were constructed directly from activation times measured at each electrode. Average CV was calculated as the slope of the relationship between distance versus local activation time for all electrograms; CV was calculated for each point in the electrode array, and the results averaged to provide CV for the LV segment assayed.

2.4. Action potential duration

Action potential recordings were performed during steady-state pacing at a BCL of 1000 ms. Using a well-validated, previously described technique [30,31], APD was measured as the difference between the maximum first derivative of the AP upstroke and the maximum second derivative of the AP during repolarization (Fig. 1B).

2.5. Programmed electrical stimulation (PES)

Myocardial wedges from normal (n = 6) and cLBBB (n = 6) dogs were paced with a 20-beat drive train (S1, 1000 ms), followed by a premature extrastimulus (S2) initially coupled at 500 ms. S1 and S2 were delivered from unipolar electrodes placed at the endocardial and epicardial surfaces, respectively. S1S2 coupling was decremented by 10 ms in sequential drive trains until arrhythmia induction or refractoriness was reached. Wedge refractory period (WRP) was defined as the shortest S1S2 coupling interval capturing the wedge.

2.6. Western blotting

Frozen myocardium from normal (n = 6) and cLBBB (n = 9) dogs was homogenized in lysis buffer and run through SDS-PAGE in standard fashion, and membranes probed for phospho-ERK, sarcoplasmic reticulum Ca²⁺-ATPase, phospholamban, or connexin43, as well as for calsequestrin (loading control), as described previously [7].
All antibodies used have been previously validated in canine tissue [7]. After probing with HRP-conjugated secondary antibodies, protein levels were detected by chemiluminescence and autoradiography, and quantified (NIH ImageJ software).

2.7. Microscopy

Sections of anterior and lateral myocardium from normal (n = 6) and cLBBB (n = 6) dogs were fixed (4% paraformaldehyde), blocked (10% BSA with 0.075% Saponin in PBS), then probed for Cx43 (monoclonal antibody, Chemicon) and the intercalated disc protein cadherin (polyclonal Ab, Zymed). Sections were secondarily stained with fluorescent antibodies and imaged with a Zeiss Axiovert microscope. Cx43 signal (green) expressed on lateral myocyte borders and in the absence of cadherin (red) was identified as lateralized Cx43. Cx43 signal was quantified using Meta-morph software, with both green-only (lateralized Cx43) and green-total (total Cx43) signal identified and assigned a total pixel area in an automated fashion. Lateralized Cx43 was then expressed as a percent of the total Cx43 signal for a given field of view. Multiple fields (≥16) were analyzed in each region of normal and cLBBB hearts in a blinded manner.

Myocyte length-to-width ratios were determined by wheat germ agglutinin (WGA) staining. Frozen sections were fixed and blocked as described above, probed with rhodamine-labeled WGA, and imaged as above. Cellular dimensions were measured in at least ten fields of view from each LV region examined. Fibrosis was determined by Masson’s trichrome staining of paraffin-embedded sections. Slides were examined and scored in a blinded, qualitative manner by a cardiac pathologist from the Johns Hopkins Hospital Department of Pathology.

2.8. Data analysis

Comparisons of CV, WRP, APD, Cx43 lateralization and protein expression between endocardial and epicardial surfaces of anterior and lateral ventricular segments was performed by 1- or 2-way ANOVA, with post hoc Tukey tests for multiple comparisons. Comparison of arrhythmia susceptibility was performed by Fisher’s exact test. All histograms represent mean values ± SEM.

3. Results

3.1. Hemodynamics and imaging of cLBBB

LBB ablation acutely increased QRS duration by 108%, significantly delaying LV activation relative to the RV apex (Table 1). All cLBBB dogs maintained prolonged QRS...
duration until sacrifice. Dyssynchronous hearts had normal peak rates of pressure rise (dP/dtmax) and systolic pressures (SBP; Table 1). Average LV end-diastolic pressure (LVEDP) in cLBBB dogs was in the normal range, though significantly higher than that seen in controls (Table 1).

Data from tagged MR imaging of normal and cLBBB dogs are shown in Table 2. Lateral LV activation was significantly delayed in cLBBB models, but not in controls. Regional circumferential shortening (i.e. strain) was significantly increased in the cLBBB lateral LV, relative both to the anterior LV in cLBBB dogs and to lateral LV in control animals. Strain in normal controls did not vary significantly between anterior and lateral regions.

### 3.2. Conduction velocity

As expected [33], endocardial CV was greater (by 20–30%, \( p<0.001 \); Fig. 2A,C) than epicardial CV in wedges from normal hearts (\( n=6 \)) mapped with the electrode array. In wedges from cLBBB dogs (\( n=6 \)), a similar pattern of CV was observed in anterior myocardium (Fig. 2B, upper panels), but was reversed in lateral, late-activated tissue (Fig. 2B, lower panels). Endocardial CV in the lateral wall was slow compared with the lateral endocardium in controls (31 ± 1 cm/s v. 60 ± 2 cm/s, \( p<0.001 \); Fig. 2C) and the anterior endocardium in normal and dyssynchronous hearts (\( p<0.001 \) for all comparisons; Fig. 2C). Dyssynchronous lateral epicardial CV, in contrast, was increased relative to lateral epicardial CV in normal dogs (50 ± 1 cm/s v. 44 ± 1 cm/s, \( p<0.001 \); Fig. 2C), and anterior epicardium in both groups (\( p<0.001 \) for all comparisons; Fig. 2C). The net effect of these changes was a 40% reduction in lateral endocardial CV relative to overlying epicardium in the dyssynchronous lateral LV (\( p<0.001 \); Fig. 2C).

CV measurements in dyssynchronous hearts by electrical recording (cm scale) were supported by optical action potential mapping (mm scale). Epicardial CV in the anterior and lateral dyssynchronous LV were similar (44 ± 2 and 45 ± 3 cm/s, respectively). CV in anterior endocardium was 55 ± 4 cm/s. In contrast, CV in lateral endocardium was significantly reduced relative to anterior endocardium, at 34 ± 3 cm/s (\( p<0.03 \); Fig. 3). Movies depicting regional

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control (( n=6 ))</th>
<th>cLBBB (( n=6 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration (ms)</td>
<td>50 ± 7</td>
<td>104 ± 7</td>
<td>(&lt; 0.001)</td>
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<tr>
<td>LV delay (ms)</td>
<td>-7 ± 4</td>
<td>45 ± 7</td>
<td>(&lt; 0.001)</td>
</tr>
<tr>
<td>dP/dtmax (mm Hg/s)</td>
<td>2301 ± 890</td>
<td>2312 ± 585</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>141 ± 3</td>
<td>136 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.3 ± 3</td>
<td>11.4 ± 4</td>
<td>(&lt; 0.05)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
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<th></th>
<th>Control (( n=5 ))</th>
<th>cLBBB (( n=3 ))</th>
<th>( p )</th>
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</thead>
<tbody>
<tr>
<td>LV activation delay (ms)</td>
<td>14.9 ± 4.9</td>
<td>91.6 ± 4.8</td>
<td>(&lt; 0.001)</td>
</tr>
<tr>
<td>% Circumferential shortening (anterior LV)</td>
<td>8.27 ± 0.52</td>
<td>5.66 ± 0.83</td>
<td>NS</td>
</tr>
</tbody>
</table>
| % Circumferential shortening (lateral LV)| 10.16 ± 1.07†   | 17.47 ± 0.27‡†* | \( p=NS \) v. control anterior LV; \( p<0.003 \) v. cLBBB anterior LV; \( *p<0.04 \) v. control lateral LV
membrane depolarization in cLBBB hearts are provided in the on-line Data Supplement.

3.3. Regional APD and wedge refractory period

In control hearts, anticipated transmural differences in APD (endocardial > epicardial) were seen in both anterior and lateral territories (Fig. 4A) [34–36]. APD was similar within a given layer between anterior and lateral regions (Fig. 4A). In contrast, dyssynchronous hearts displayed significantly shorter APDs in the lateral wall than in the anterior wall (~16% reduction in both the lateral epicardial and endocardial layers, \( p < 0.05 \); Fig. 4A). Net average intraventricular gradients in APD between lateral and anterior walls were 32 ms (epicardial) and 43 ms (endocardial; Fig. 4A).

Consistent with the magnitude and direction of dyssynchrony-induced changes in APD, WRP in lateral wedges from cLBBB dogs (230 ± 10 ms) was significantly reduced (~20%; \( p < 0.05 \) for all comparisons) relative to WRP in corresponding anterior wedges from cLBBB models (285 ± 28 ms), and relative to anterior and lateral wedges from controls (276 ± 5 and 272 ± 8 ms, respectively). Differences in WRP between anterior and lateral wedges from controls, and anterior wedges from cLBBB dogs, were not significant.

3.4. Arrhythmia induction

Arrhythmias inducible by a single premature stimulus (S2) were rare in wedges from both control and cLBBB dogs. One of 16 wedges from controls versus 2 of 14 wedges from LBBB models (\( p = NS \)) undergoing PES developed polymorphic VT (>150 bpm, >2 s duration). All inducible wedges were from the lateral LV.

3.5. Microscopy studies

Cx43 principally localized to intercalated discs (identified by co-probing for cadherin) in controls, with minimal staining of the myocyte longitudinal surface (Fig. 5A). A similar pattern was observed in anterior tissue of dyssynchronous hearts (Fig. 5B). However, lateral LV segments from cLBBB hearts exhibited substantial Cx43 signal at the longitudinal membrane (Fig. 5C), with 17 ± 2% of total Cx43 signal lateralized (versus 8 ± 1% in anterior wedges from cLBBB hearts, and 4 ± 1% in control tissue, \( p < 0.001 \) for both comparisons; Fig. 5D). No differences in myocyte dimensions or extracellular fibrosis were evident in either region of cLBBB dogs compared to normal controls.

3.6. Regional protein expression: connexin43, calcium handling proteins, and phospho-ERK

PLB levels in normal lateral LV endocardium were reduced compared to levels in overlying epicardium (Fig. 6A,B). Furthermore, we found that Cx43 levels in controls were significantly reduced in lateral LV endocardium relative to overlying epicardium (21% reduction, \( p < 0.001 \); Fig. 6C).
There were no transmural variations in phospho-ERK levels (Fig. 6D).

SERCA2a, PLB, Cx43, and p-ERK levels displayed no transmural disparities in hearts with cLBBB (Fig 6), with abrogation of the PLB and Cx43 expression gradients seen in controls (Fig. 6B,C), suggesting a relative increase in endocardial expression. These results stand in marked contrast to previously demonstrated transmural expression gradients in the lateral wall for each of these proteins in hearts with both chronic dyssynchrony and cardiac failure [7](cf. Fig. 6).

4. Discussion

4.1. Summary

In the current study we provide evidence that mechanical LV dyssynchrony in the setting of cLBBB induces regional ventricular electrophysiological remodeling. As expected, tagged MR imaging demonstrated late activation and increased tissue strain in the lateral LV wall of cLBBB dogs. In this same territory, endocardial CV, APD, and tissue refractoriness were all significantly reduced relative to values measured in the anteroseptal LV. In addition, cellular distribution of Cx43 was uniquely altered in the lateral LV, with redistribution of Cx43 protein to the lateral sarcolemmal surface. In contrast to previous studies of cLBBB-heart failure models [7], regional variations in total Cx43, calcium handling (SERCA2a and PLB), and MAP kinase proteins were not observed.

4.2. APD and mechanoelectrical feedback (MEF)

The effect of myocardial stretch on APD is variable, and depends in part on both the duration and the timing of the applied stretch. Pulsatile stretch (typically applied over 50 ms) can lead to APD shortening if applied during phase 2 of the action potential. Similar stretch pulses applied during phases 3–4 of the action potential, in contrast, prolong the APD [15]. These disparate effects may be due to cationic efflux or influx through stretch-activated channels, as driven by positive or negative cell membrane potentials (respectively).

In the current model, we found that cLBBB induces intraventricular disparities in APD between the lateral and anteroseptal LV. APD was shortest in the lateral LV, a region shown by tagged MR imaging to undergo early-systolic stretch (i.e. during phase 2 of the AP). Conversely, APD in the anterior LV (shown by MRI to undergo late-systolic stretch) was relatively increased. Both results are consistent with previous investigations of pulsed stretch applied at different phases of the cardiac AP. What is unexpected about our results is that they occurred in vitro, minutes after the tissue had been removed from its in situ, dyssynchronous setting.
Studies evaluating dynamics of stretch-activated channels (SAC) demonstrate a reduced-activity plateau phase (adaptation) after roughly 1 s of stretch application, with channel closure approximately 50 ms after stretch release [38]. Repeated application of stretch causes both attenuation of adaptation and increased background channel activity [38]. In contrast to studies of single-channel kinetics in isolated myocytes subjected to limited cycles of stretch, our studies were performed in tissue subjected to approximately 5 million stretch cycles applied over four weeks. Conceivably, sustained dyssynchrony induces marked and disparate changes in SAC background activity between the anterior and lateral LV, and these disparate changes underlie our observed differences in regional APD. Alternatively, we acknowledge that while our observed patterns of APD disparity between anterior and lateral myocardium correlate well with known patterns of SAC activation during different phases of the AP, regional disparities in APD may be due to other, as yet unknown mediators of MEF.

4.3. CV and Cx43

In the setting of cLBBB, CV was significantly and uniquely reduced over the lateral LV endocardial surface. The mechanism for this change remains unclear. Determinants of tissue CV include myocyte connectivity, sodium current density, cellular architecture, and tissue fibrosis. Additionally, conduction over the endocardial surface may vary with the extent to which the His–Purkinje system is recruited. cLBBB resulted in lateralization of Cx43 protein in the late-activated, lateral LV. This redistribution was not unique to the endocardial surface, however, suggesting that alterations in cell–cell coupling do not entirely account for the observed changes in local CV. Changes in myocyte length:width or in myocardial fibrosis were not seen. Previous studies have shown that Purkinje fiber electrophysiology is remodeled in tachycardia-induced cardiomyopathy, with alterations in both calcium- and potassium-channel kinetics [39]. The net effect of these changes was to increase the plateau phase of the action potential and reduce repolarization reserve. Conceivably, similar changes could occur in the lateral LV of cLBBB models, and contribute to observed changes in tissue CV.

While dyssynchrony-induced Cx43 lateralization may not explain changes in regional CV, it remains an intriguing finding. Zhuang et al., have shown in cultured neonatal rat myocytes that pulsatile stretch causes marked Cx43 upregulation, without changes in subcellular distribution [40]. The current study suggests that chronic, pulsatile in vivo stretch in an adult heart has clearly distinct effects,
notable primarily for changes in Cx43 trafficking rather than in net expression. These disparities may be due to the degree or duration of stretch, species differences, or other unidentified factors in Cx43 signaling. Patel et al., demonstrated redistribution of Cx43 protein to the lateral sarcolemma in paced hearts [22], but only in early-activated tissue (i.e. near the pacing site). In contrast, we observed Cx43 lateralization specifically in late-activated, high-stress tissue, suggesting that a variety of mechanical and/or electrical stimuli can alter subcellular Cx43 trafficking.

4.4. Arrhythmia susceptibility

There is ample evidence from a wide variety of cardiac disease models, including long QT syndrome [30], HF [41], ischemia [33], and infarction [42], that increases in dispersion of CV, APD, or both result in increased susceptibility to reentrant (typically transmural) arrhythmias. Zones of unidirectional conduction block and variable tissue refractoriness provide an ideal substrate for reentry. In the current study, we found that the lateral LV endocardium was characterized by slow CV and reduced refractoriness, while adjacent anterior LV tissue had preserved CV and relatively increased refractoriness. However, we found no significant difference in arrhythmia inducibility (with single premature extrastimuli) between anterior and lateral wedges from cLBBB dogs. This may be due in part to the preparation itself. By necessity, anterior and lateral LV segments (the limbs of a putative reentrant circuit) were studied in isolation. While PES studies from our group of long QT [30] and HF [41] models induced arrhythmias using a similar protocol, reentrant circuits in these models were transmural, rather than transverse. Arrhythmia susceptibility, both in the myocardial wedge preparation and in humans, is likely a “multi-hit” phenomenon, with ischemia, fibrosis, LV dysfunction, and remodeling exerting cumulative deleterious effects [43]. LV dyssynchrony is likely another member of this growing list of insults.

4.5. Limitations

The arterially perfused wedge preparation does not allow for mapping of putative reentrant circuits between anterior and lateral segments. Rather, assessment of CV and APD was confined to local sites. Measurement of transmural CV was avoided, due to unpredictable patterns of fiber orientation and tissue resistivity that could confound comparisons between LV regions. Clearly, conclusions based on ex vivo, paced, perfused tissue should be cautiously applied to in vivo systems.

Second, optical mapping requires tissue immobilization. We physically stabilized our preparations, which may introduce mechanical artifact; however, all specimens were stabilized identically, permitting relative comparisons between regions.

Finally, WRP as measured provides a global assessment of refractoriness in the wedge, but was not measured using standard methods employed in clinical electrophysiology. WRP values were inferred from the PES protocol. Accordingly, the site of pacing for the drive train and the extrastimulus were delivered on different sides of the wedge (~2.2 cm apart). We therefore expect WRP to exceed local refractoriness by a value determined by conduction time between the two pacing sites (40–50 ms).

4.6. Conclusion

LV dyssynchrony in the absence of heart failure induces substantial regional electrophysiological remodeling, generating trans-chamber gradients in CV, APD, and refractoriness. These changes suggest a novel mechanism underlying electrophysiological heterogeneity in HF with LV dyssynchrony. In the presence of additional heart-failure derived abnormalities in excitation and contraction, this is likely to generate a potent arrhythmogenic substrate.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cardiores.2005.03.008. Movie 1 is Anterior Epicardium; Movie 2 is Anterior Endocardium; Movie 3 is Lateral Epicardium; Movie 4 is Lateral Endocardium.

References


