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PRECLINICAL STUDY

High-Septal Pacing Reduces Ventricular Electrical Remodeling and Proarrhythmia in Chronic Atrioventricular Block Dogs

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Objectives This study was designed to analyze the relevance of ventricular activation patterns for ventricular electrical remodeling after atrioventricular (AV) block in dogs.

Background Bradycardia is thought to be the main contributor to ventricular electrical remodeling after complete AV block. However, an altered ventricular activation pattern or AV dyssynchrony may also contribute.

Methods For 4 weeks, AV block dogs were either paced from the high-ventricular septum near the His bundle at lowest captured rate (n = 9, high-septal pacing [HSP]) or kept at idioventricular rate without controlled activation (n = 14, chronic AV block [CAVB]). Multiple electrocardiographic and electrophysiological parameters were measured under anesthesia at 0 and 4 weeks. Proarrhythmia was tested at 4 weeks by I_{Kr} block (25 μg/kg dofetilide intravenous).

Results At 0 weeks, the 2 groups were comparable, whereas after 4 weeks of similar bradycardia, QT duration at unpaced conditions had increased from 300 ± 5 to 395 ± 18 ms in CAVB (+32 ± 6%) and from 307 ± 8 ms to 357 ± 11 ms in HSP (+17 ± 4%; $p < 0.05$). Frequency dependency of repolarization was less steep in HSP compared to CAVB dogs after 4 weeks remodeling. Beat-to-beat variability of repolarization, a proarrhythmic parameter, increased only in CAVB from 0 to 4 weeks. Torsades de pointes arrhythmias were induced at 4 weeks in 44% HSP versus 78% CAVB dogs ($p = 0.17$). Cumulative duration of arrhythmias per inducible dog was 87 ± 36 s in CAVB and 30 ± 21 s in HSP ($p < 0.05$).

Conclusions High-septal pacing reduces the magnitude of ventricular electrical remodeling and proarrhythmia in AV block dogs, suggesting a larger role for altered ventricular activation pattern in the generation of ventricular electrical remodeling than previously assumed. (J Am Coll Cardiol 2007;50:906–13) © 2007 by the American College of Cardiology Foundation

One of the stimuli to induce ventricular remodeling is complete atrioventricular block (AVB) (1–16). In the dog, this induces a temporarily depressed cardiac output (1), biventricular hypertrophy (12,15), and adaptations in electrical characteristics including altered intracellular calcium fluxes (17) and decreased repolarizing currents (3,13). This compensatory ventricular remodeling restores cardiac output to near-normal levels but renders the heart susceptible to drug-induced torsades de pointes (TdP) arrhythmias (5,15,16) and sudden cardiac death (7,11). In the AVB rabbit, similar adaptations occur, although this species has more difficulties overcoming the initial drop in heart rate (9).

At least 3 factors can be identified that contribute to the cardiac adaptations secondary to AVB: bradycardia, altered ventricular activation pattern, and atrioventricular (AV) dyssynchrony. Using a pacing lead placed in the right ventricular (RV) apex of rabbit hearts with AVB, Suto et al. (6) showed that bradycardia by itself was responsible for most, if not all, of the ventricular electrical remodeling. It has been shown, both in clinical and experimental studies, that the choice of the ventricular pacing site has consequences for ventricular function (18,19), but little is known about its effects on electrical characteristics. Recent interest in

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direct His-bundle pacing (20,21) and para-Hisian pacing (22,23) facilitates experimental maintenance of a normal ventricular activation pattern after AVB.

In the present study, we investigated whether ventricular activation contributes to the development and the magnitude of electrical remodeling and ventricular proarrhythmia. For this purpose, we compared dogs with equal bradycardia but different ventricular activation patterns.

Methods

Experiments were conducted in accordance with the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609/EU). The Committee for Experiments on Animals of Utrecht University approved the experiments.

Adult purpose-bred mongrel dogs (Marshall, North Rose, New York) of either gender were used, 12 with high-septal pacing (HSP) and 19 with chronic AV block (CAVB). We excluded 3 dogs from the HSP protocol because of pacing failure, leaving 9 animals in this group for serial and comparative testing. Initially, 14 CAVB dogs were compared for frequency dependency (n = 9) and arrhythmia susceptibility (n = 9). Later, 5 CAVB dogs were added to exclude influence of acutely changing the pacing site.

Experimental setup. General anesthesia was induced with sodium pentobarbital (20 mg/kg intravenous) and maintained by halothane (0.5 to 1% in O_2/N_2O [1:2]). A standard 6-lead electrocardiogram (ECG) and 2 simultaneous endocardial left and right ventricular (LV and RV, respectively) monophasic action potentials (MAP) were recorded throughout the experiments (24). Atrioventricular block was induced in all dogs with radiofrequency ablation of the proximal His bundle (4).

In HSP dogs, the chest was opened through the fourth or fifth intercostal space after AVB. A screw-in His bundle pacing lead (Bakken Research Center, Medtronic, Maastricht, the Netherlands) was inserted through a right-sided purse-string atriotomy into the high interventricular septum, slightly distal to the ablation site and near the His bundle (25). Lead position was accepted when pacing yielded a QRS complex with an axis equal to that of sinus rhythm (Fig. 1). An atrial lead was placed in the auricle of the right atrium. Both leads were connected to a DDDR pacemaker (Vitatron, Arnhem, the Netherlands). Pacemaker function was checked 3 times per week during the experimental period. Following the experiment to create AVB (t = −2 weeks), the high-septal region was paced on atrial activation (VDD mode) for 2 weeks to ensure recovery from open-chest surgery. Thereafter (t = 0 weeks), baseline electrophysiological parameters were determined during VDD mode, idioventricular rhythm (IVR), and at fixed steady-state ventricular cycle lengths (600, 667, 750, 857, and 1,000 ms). The following day, the pacemaker was programmed to the lowest captured ventricular fixed rate (VVI mode, mean 51 ± 5 beats/min in conscious state), and controlled ventricular activation was maintained for 4 weeks.

Abbreviations and Acronyms

AT = activation time
(C)AVB = (chronic) atrioventricular block
ECG = electrocardiogram
HSP = high-septal pacing
IVR = idioventricular rhythm
LV = left ventricle/ventricular
MAP(D) = monophasic action potential (duration)
ΔMAPD = interventricular dispersion of monophasic action potential duration
RV = right ventricle/ventricular
STV = short-term beat-to-beat variability of left ventricular monophasic action potential duration
TdP = torsades de pointes

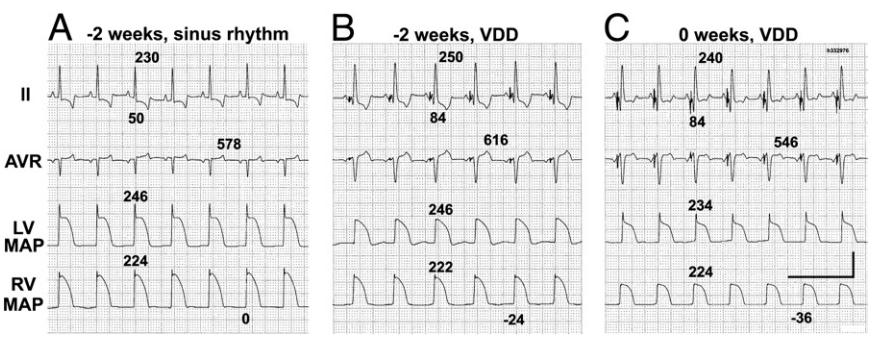

Figure 1 Electrophysiological Recordings of the Change From Sinus Rhythm to High-Septal Pacing

Electrophysiological recordings obtained from a single anesthetized dog in sinus rhythm (t = −2 weeks) **(A)**, in atrially triggered high-septal pacing (VDD) directly after atrioventricular (AV)-nodal ablation (t = −2 weeks) **(B)**, and in continued VDD pacing, 2 weeks after pacemaker implantation (t = 0 weeks) **(C)**. In each panel, electrocardiographic (ECG) leads II and AVR and left (LV) and right ventricular (RV) monophasic action potential (LV and RV monophasic action potential [MAP], respectively) recordings are shown. From **top to bottom** are indicated: RT, QRS, RR, duration of LV and RV MAP, and activation time (all ms). Horizontal and vertical calibrations represent 1 s (paper speed 25 mm/s) and 1 mV for ECG recordings and 20 mV for monophasic action potential (MAP) signals. Altering origin of ventricular activation from AV nodal to high septal preserves QRS axis but increases QRS duration and alters activation time to negative values. In contrast, VDD pacing does not alter ventricular repolarization parameters.

In the CAVB group, baseline measurements were acquired immediately following AVB (t = 0 weeks) in the spontaneous idioventricular rhythm and during fixed steady-state ventricular cycle lengths (600, 700, 800, 900, and 1,000 ms). Thereafter, these dogs remained without controlled activation (awake IVR, mean 58 ± 7 beats/min, p = 0.48 vs. awake VVI pacing rate in HSP group using unpaired Student *t* test). High-septal pacing and CAVB dogs were re-evaluated under anesthesia at 4 weeks.

During anesthetized experiments, pacing was performed in HSP by programming the pacemaker and in CAVB dogs with an external pacemaker pacing from the tip of the apically placed RV MAP catheter. To ensure comparability of repolarization duration measured at these 2 sites, 5 additional CAVB dogs were paced sequentially from the high septum and from the RV apex at 4 weeks. Each cycle length was maintained for >2 min.

Susceptibility to TdP arrhythmias was assessed at 4 weeks by pharmacological I_{Kr} block (dofetilide, 25 μg/kg intravenously over 5 min). Assessment of TdP susceptibility was performed in HSP dogs while pacing at 1,000 ms, whereas CAVB dogs were tested at IVR. After 10 min, the HSP dogs were left in IVR to determine the influence of activation on proarrhythmia. A TdP was defined as a polymorphic ventricular tachycardia of more than 5 beats with typical twisting around the isoelectric line. If normal rhythm was not restored after 15 s of TdP, the dog was electrically defibrillated. Proarrhythmic remodeling was evaluated only at 4 weeks, as previous studies have shown absence of TdP upon dofetilide challenge during sinus rhythm and acutely after AVB (26).

At 4 weeks, LV pressure was recorded in HSP dogs at IVR and 1,000 ms, using a pressure catheter (Sentron, Roden, the Netherlands) placed in the LV cavity (4). At sacrifice, all hearts were weighed, and gross indications of congestive heart failure were evaluated (ascites and pleural effusion).

Analyses. Using custom software, RR, QT, RT, and QRS intervals were measured in lead II. Because the pacing artifact and an altered Q-wave morphology in the ECG during HSP (Fig. 1) sometimes hampered precise determination of the QRS-complex onset, RT was added as a more accurate alternative to the (approximated) QT interval. In paced conditions, QRS onset was estimated from the initial deflection from the isoelectric line following the pacing artifact. The RT interval was measured from the peak of the R-wave until the end of the T-wave. In unpaced CAVB dogs, RT-QT regression analysis yielded a statistically significant correlation: QT = 0.9RT + 81 (R^2 = 0.78; $p < 0.05$).

Left and right ventricular MAP durations (MAPD) were measured at 100% repolarization. Interventricular dispersion of repolarization duration (ΔMAPD) was calculated as the absolute difference between LV and RV MAPD. Ventricular activation time (AT) was defined as the difference in timing of the MAP signal upstroke, with a positive value indicating earlier LV activation. Heart rate-corrected QT (QTc), RT (RTc), and MAPD (MAPDc) were calculated using Van de Water's formula (27). Beat-to-beat variability of repolarization duration was quantified as short-term variability (STV), describing the mean orthogonal distance to the line-of-identity on the Poincaré plot ($STV = \Sigma|D_{n+1}-D_n|/[30\times\sqrt{2}]$, where D represents LV MAPD), as described earlier (8). The maximal positive derivative of the LV pressure ($+dP/dt_{max}$) during systole was determined.

A dog was considered inducible if it showed ≥3 TdP. Incidence and duration of TdP were quantified over the first 10 min after start of infusion of the drug. The number of defibrillations was registered.

Statistical analyses. All data are presented as mean ± SEM. The following tests were used when appropriate: unpaired and paired Student *t* test, Fisher exact test, Mann-Whitney *U* test, and 1-way or 2-way ANOVA followed by a Bonferroni test (statistical packages: SigmaStat version 2, Systat Software Inc.; Primer of Biostatistics, Version 1, McGraw-Hill, Inc., New York, New York). A p value <0.05 was considered statistically significant.

Results

From sinus rhythm to HSP. All electrophysiological parameters were comparable between all dogs in sinus rhythm (data not shown). QRS duration increased when acutely changing ventricular activation from AV nodal to high septal (Table 1, Fig. 1) but did not change further during the course of the experimental (VDD) protocol. Pacing specifically lengthened the initial part of the QRS (Fig. 1), thereby increasing QT (Table 1), whereas RT, LV, and RV MAPD (Table 1, Fig. 1) did not change. Also, when correcting for individual differences in sinus rate, this QRS involvement remained reflected in QTc, but not in RTc and MAPDc. Normal QRS axis (Fig. 1) was achieved with

Table 1 Baseline Electrophysiological Measurements in the HSP Group Obtained at –2 and 0 Weeks Relative to Onset of Bradycardia

	−2 Weeks, Sinus Rhythm	−2 Weeks, VDD	0 Weeks, VDD
RR	603 ± 33	570 ± 46	547 ± 35
QT	265 ± 7	303 ± 11*	276 ± 6
QTc	300 ± 5	340 ± 9*	316 ± 7
RT	237 ± 8	244 ± 11	224 ± 7
RTc	272 ± 6	282 ± 2	263 ± 6
QRS	54 ± 2	82 ± 7*	84 ± 4*
LV MAPD	236 ± 8	233 ± 10	214 ± 5
LV MAPDc	271 ± 6	271 ± 7	253 ± 4
RV MAPD	213 ± 9	213 ± 8	204 ± 4
RV MAPDc	251 ± 6	254 ± 4	244 ± 4
AT	−3 ± 5	−21 ± 6*	−23 ± 8*

*p < 0.05 versus sinus rhythm; 1-way analysis of variance followed by Bonferroni *t* test. All values are in ms.

AT = activation time; LV and RV MAPD = left and right ventricular monophasic action potential duration, respectively; MAPDc = heart rate-corrected monophasic action potential duration; RTc = heart rate-corrected RT; QTc = heart rate-corrected QT; VDD = atrially triggered high-septal pacing.

Table 2 Electrophysiological Parameters at Idioventricular Rhythm

	0 Weeks	4 Weeks
CAVB		
RR	1,190 ± 83	1,344 ± 73
QRS	88 ± 5	96 ± 4
QT	300 ± 5	395 ± 18*
RT	273 ± 5	363 ± 18*
LV MAPD	256 ± 8	356 ± 17*
RV MAPD	239 ± 7	304 ± 14*
ΔMAPD	17 ± 4	52 ± 9*
AT	13 ± 7	13 ± 6
STV	1.5 ± 0.9	2.7 ± 1.2*
HSP		
RR	1,146 ± 66	1,363 ± 79
QRS	76 ± 6	79 ± 3†
QT	307 ± 8	357 ± 11*†
RT	279 ± 7	320 ± 12*†
LV MAPD	266 ± 9	313 ± 10*†
RV MAPD	240 ± 9	276 ± 7*
ΔMAPD	26 ± 4	37 ± 8
AT	7 ± 11	−11 ± 11
STV	1.6 ± 0.7	2.0 ± 0.7

*$p < 0.05$ versus 0 weeks; †$p < 0.05$ versus CAVB; 2-way analysis of variance followed by Bonferroni *t* test. All values are in ms.

CAVB = chronic atrioventricular block; HSP = high-septal pacing; STV = short-term variability of repolarization; ΔMAPD = interventricular dispersion of repolarization duration; other abbreviations as in Table 1.

pacing for prolonged periods in all HSP dogs. The upstroke of the R-wave in lead II was narrow ($n_{dogs} = 4$) (Fig. 1), notched ($n_{dogs} = 3$), or showing a delta wave ($n_{dogs} = 2$). In sinus rhythm before AVB, LV and RV MAP depolarize approximately simultaneously (Fig. 1A, Table 1), whereas with HSP the RV activated earlier than the LV, as indicated by the more negative AT in Table 1.

HSP versus idioventricular rhythm. At 0 weeks, no differences were found in electrophysiological parameters between the 2 groups at spontaneous IVR (Table 2). After 4 weeks of ventricular remodeling in IVR, CAVB dogs showed significantly increased QT intervals, RT intervals, and LV and RV MAPD. Also, spatial and temporal dispersion of repolarization duration, represented by ΔMAPD and STV, respectively, was increased in the CAVB group. After 4 weeks of similar bradycardia in the HSP group, QT, RT, LV, and RV MAPD were lengthened, whereas ΔMAPD and STV remained unaltered (Table 2). At 4 weeks, HSP dogs had significantly shorter QRS durations, QT intervals, RT intervals, and LV MAPD than CAVB dogs (Table 2). Thus, compared to 0 weeks, relative increases in QT and LV MAPD were less pronounced in HSP (17 ± 4% and 19 ± 6%, respectively) than in CAVB dogs (32 ± 6% and 42 ± 7%, respectively, both $p < 0.05$ vs. HSP). Idioventricular rhythm in CAVB dogs at 4 weeks most frequently originated within the LV (11 of 14 dogs) (Fig. 2A).

Frequency-dependent behavior of RT interval was comparable at 0 weeks between CAVB and HSP dogs (Fig. 3). In this experiment, while pacing at 1,000 ms, repolarization duration (QT, RT, LV and RV MAPD) was not different between the 2 groups (Table 3), but QRS durations and ATs in HSP were smaller. Both groups showed a statistically significant increase in RT interval after 4 weeks at all paced cycle lengths, but at the longest pacing cycle length, RT was shorter in HSP dogs (Fig. 3, Table 3).

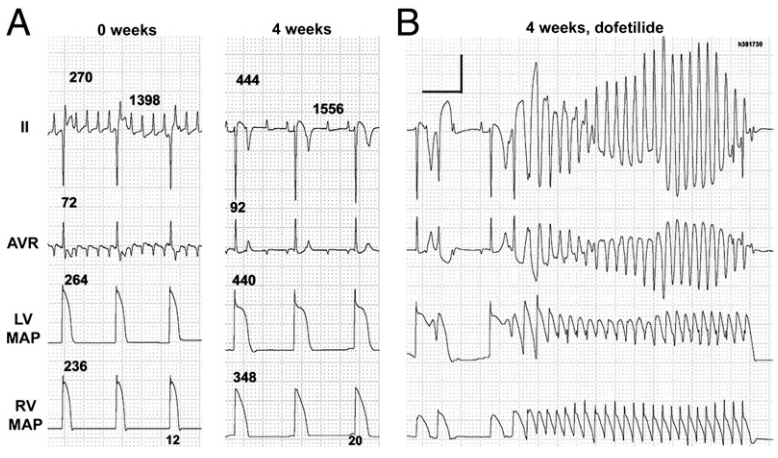

Figure 2 Electrophysiological Recordings of Electrical Remodeling and Proarrhythmia in the CAVB Dog

Representative electrophysiological recordings obtained from an anesthetized chronic AV block (CAVB) dog before and after 4 weeks of electrical remodeling. **(A)** idioventricular rhythm at 0 and 4 weeks. **(B)** Torsades de pointes (TdP) arrhythmia after proarrhythmic challenge with dofetilide at 4 weeks. In all tracings, ECG leads II and AVR and left and right ventricular monophasic action potential (LV and RV MAP, respectively) recordings are shown. From **top to bottom**, RT, RR, QRS, duration of LV and RV MAP, and activation time (all ms) are indicated. Horizontal and vertical calibrations represent 1 s (paper speed 10 mm/s) and 1 mV for ECG recordings and 20 mV for MAP signals. Four weeks of AV block caused prolongation of RT and LV and RV MAP durations (**A, right side**). Dofetilide reproducibly induced TdP in this **(B)** and 6 other CAVB dogs. Abbreviations as in Figure 1.

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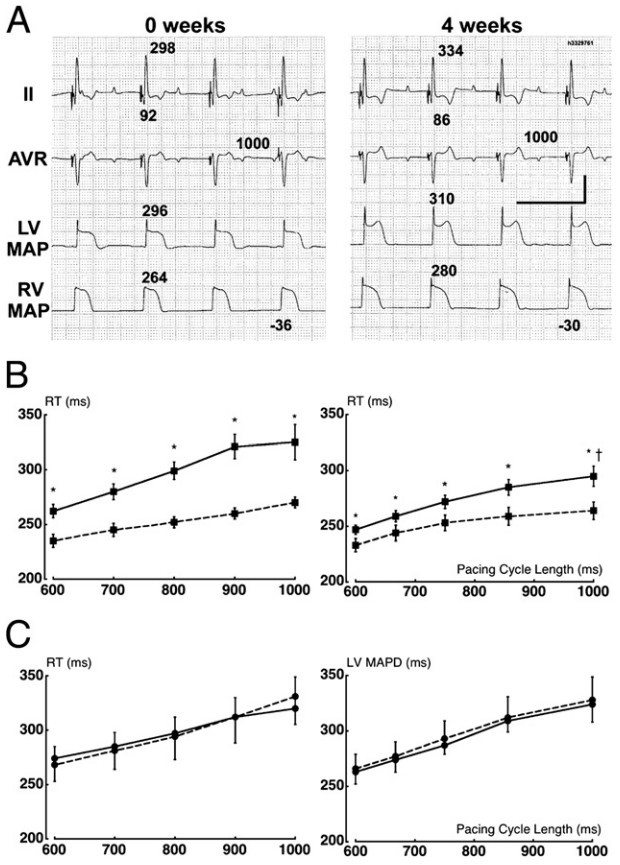

Figure 3 **Differences in Electrical Remodeling and Frequency Dependence Between HSP and CAVB Dogs**

In **panel A**, recordings of ECG leads II and AVR, and left and right ventricular monophasic action potential (LV and RV MAP, respectively) are shown during high-septal pacing (HSP) with a cycle length of 1,000 ms at 0 weeks **(left side)** and 4 weeks **(right side)**. From **top to bottom**, RT, QRS, RR, duration of LV and RV MAP, and activation time (all ms) are indicated. Horizontal and vertical calibrations represent 1 s (paper speed 25 mm/s) and 1 mV for ECG recordings and 20 mV for monophasic action potential signals. Graphs in **panel B** show RT time in CAVB **(left side)** and HSP dogs **(right side)** during pacing at cycle lengths between 600 and 1,000 ms. Note that controlling activation with HSP reduces electrical remodeling after AVB. **Dashed lines** = 0 weeks; **solid lines** = 4 weeks. For differences in RT between 0 and 4 weeks at the same pacing cycle length within the CAVB and HSP groups, paired Student *t* tests were used. *$p < 0.05$ versus 0 weeks. For differences between CAVB and HSP at 600 and 1,000 ms pacing cycle length, 2-way analysis of variance followed by Bonferroni post-hoc test was used. †$p < 0.05$ versus CAVB. **Panel C** shows values of RT interval **(left side)** and LV MAPD **(right side)** in 5 CAVB dogs with consecutive RV apex pacing **(solid lines)** or HSP **(dashed lines)**. Paired Student *t* tests were used to analyze differences between RV pacing and HSP at the same pacing cycle length (all $p > 0.7$). Abbreviations as in Figures 1 and 2.

Ventricular electrical remodeling, including spatial and temporal dispersion of repolarization duration (ΔMAPD and STV), was also observed when CAVB dogs were paced at 1,000 ms at 4 weeks. In HSP, at that time point, only QT, RT, and LV MAPD were prolonged (Table 3). Similar to the situation at IVR, HSP dogs showed significantly shorter QT, RT, LV, and RV MAPD than CAVB dogs at 4 weeks (Table 3). Five dogs were consecutively paced at different cycle lengths from the 2 locations (HSP and RV apex). This provided similar ($p > 0.7$) RT intervals (Fig. 3C, left panel) and LV MAPD (Fig. 3C, right panel) for both pacing sites.

Proarrhythmia at 4 weeks. Dofetilide reproducibly induced TdP in 7 of 9 CAVB dogs (78%) (Figs. 2B and 4A) versus 4 of 9 HSP dogs (44%) ($p = 0.17$) (Fig. 4A). Although the average number of TdPs in susceptible dogs was not significantly different between groups ($p = 0.14$) (Fig. 4B), the cumulative duration of TdPs (Fig. 4C) or defibrillation frequency (Fig. 4D) was lower in HSP dogs (both $p < 0.05$).

Hypertrophy and contractility. Heart-to-body-weight ratio in the HSP group after 4 weeks AVB was comparable to that of the hypertrophied CAVB heart (12.0 ± 1.6 vs. 11.9 ± 1.9 g/kg, respectively, p = NS). Enhanced LV contractility seen in HSP dogs, $+dP/dt_{max}$ 2,877 ± 446 and 2,709 ± 465 mm Hg/s at IVR and 1,000 ms pacing cycle length, respectively, was comparable to earlier reports in CAVB dogs (1). No signs of cardiac failure were observed in either group at autopsy.

Discussion

In this study, maintaining a constant high-septal ventricular pacemaker site reduced ventricular electrical and proarrhythmic remodeling in HSP compared to a group of CAVB dogs that served as positive controls for cardiac proarrhythmic remodeling. Thus, altered origin of ventricular activation is contributing to bradycardia-induced electrical remodeling and proarrhythmia.

Table 3 **Electrophysiological Parameters at Paced Cycle Length of 1,000 ms**

	0 weeks	4 weeks
CAVB		
QRS	101 ± 3	102 ± 4
QT	319 ± 7	397 ± 15*
RT	270 ± 6	326 ± 16*
LV MAPD	267 ± 3	336 ± 16*
RV MAPD	257 ± 9	291 ± 10*
ΔMAPD	11 ± 9	45 ± 12*
AT	−67 ± 6	−57 ± 4
STV	1.5 ± 0.2	3.2 ± 0.7*
HSP		
QRS	80 ± 4†	80 ± 4†
QT	315 ± 12	353 ± 10*†
RT	264 ± 8	295 ± 9*†
LV MAPD	266 ± 10	302 ± 11*†
RV MAPD	242 ± 7	260 ± 5†
ΔMAPD	24 ± 6	42 ± 9
AT	−27 ± 8†	−25 ± 7†
STV	1.1 ± 0.2	2.1 ± 0.4

*$p < 0.05$ versus 0 weeks; †$p < 0.05$ versus CAVB; 2-way analysis of variance followed by Bonferroni *t* test. All values are in ms.
Abbreviations as in Table 2.

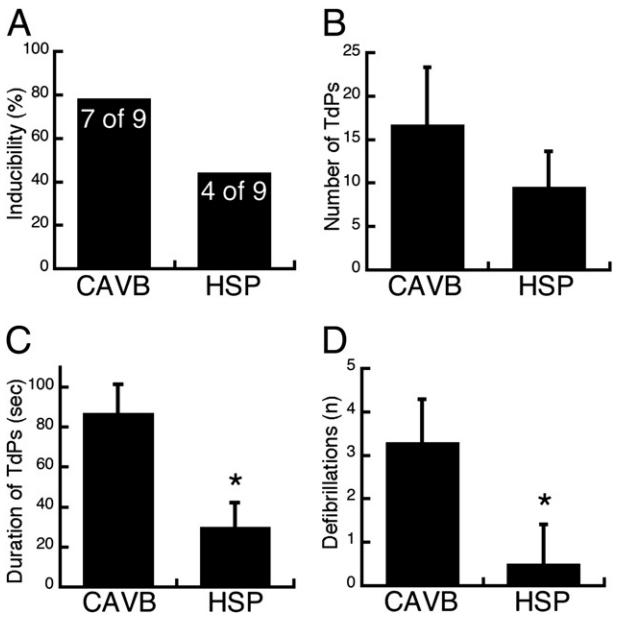

Figure 4 **Quantifications of Response to Proarrhythmic Challenge**

Arrhythmogenic outcome is depicted for CAVB and high-septal pacing (HSP) dogs. **(A)** Number of dogs with reproducible TdP relative to group size. Actual numbers indicated in **bars** (p = NS, Fisher exact test). **(B)** Mean number of TdP per inducible dog in each group. **(C)** Mean cumulative durations of TdP within inducible dogs. **(D)** Mean number of defibrillations necessary to terminate arrhythmias. Mann-Whitney *U* tests were used for statistical testing in **B, C,** and **D**. *$p < 0.05$ versus CAVB. Note that HSP dogs show less proarrhythmia than CAVB dogs. Abbreviations as in Figures 1 and 2.

Idioventricular rhythm, ventricular remodeling, and proarrhythmia. Creation of chronic, complete AVB activates an intrinsic ventricular pacemaker to maintain cardiac pump function. The origin of activation of the resulting IVR is not predictable, and the rate is much lower than when the ventricles would be activated from the atria (Tables 1 and 2). This lower rate creates volume overload that is thought to initiate numerous cardiac adaptation processes. In the dog, an increased adrenergic tone initially contributes to maintaining cardiac output (2,4,28). In time, electrical remodeling (4,15,29), biventricular hypertrophy (5,15,29), and contractile remodeling (1,2) develop while plasma levels of norepinephrine normalize (15,28). These remodeling processes compensate for the acutely depressed cardiac output (2). As a consequence, mortality attributable to incomplete hemodynamic recovery is low. However, ventricular remodeling predisposes the dogs to drug-induced TdP (78%) (Fig. 4A) and sudden cardiac death under drug-free circumstances (10%) (7,11).

In rabbits, it appears more difficult to compensate AVB hemodynamically, possibly due to a larger absolute drop in ventricular rate, resulting in high acute mortality (9). Ventricular backup pacing is necessary for their survival. Biventricular hypertrophy and electrical remodeling develop over time, predisposing the animal to cardiac arrhythmias and sudden death (10).

Constant activation, ventricular remodeling, and proarrhythmia. In AVB rabbits with a constant pacing site (RV apex), bradycardia, and AV dyssynchrony (6), QT interval increased from 206 ± 7 ms to 230 ± 6 ms (12% increase), whereas no change in QT was observed in rabbits paced at physiologic rates. This bradycardia seems to be the main factor determining ventricular electrical remodeling. The increase in QT interval, however, is much smaller than seen in CAVB or HSP dogs in the present study, possibly because of the short follow-up time of 8 days. The short follow-up may also be responsible for the absence of hypertrophy or heart failure at sacrifice (6,9,10). Three to 5 weeks after AVB, a high mortality rate was seen, which necessitated earlier sacrifice of the animals around 21 days, at which biventricular hypertrophy and chronic heart failure were clearly present (9,10).

Bradycardia and AV dyssynchrony characterized both the CAVB and HSP dogs. Although AV synchrony can potentially contribute to ventricular remodeling after AVB, this influence could not be tested in the present study, as AV dissociation was constantly present in both groups during the 4 weeks of bradycardia.

We investigated the role of ventricular activation pattern in the development of ventricular electrical and proarrhythmic remodeling and therefore chose to compare dogs with very extreme kinds of ventricular activation: controlled physiologic HSP versus uncontrolled IVR.

The drop in ventricular rate from sinus rhythm to bradycardia was around 50%, which was a comparable percentage as in the rabbit study (6). Only the HSP dogs had a constant and controlled origin of ventricular activation mimicking that of sinus rhythm. Both CAVB and HSP dogs showed electrical remodeling, but to different extents, thereby confirming that bradycardia by itself can lead to development of ventricular electrical remodeling.

In addition to bradycardia, the influence of the ventricular activation pattern on the magnitude of electrical remodeling is considerable; the increase in QT in HSP is 17 ± 4% compared to 32 ± 6% in CAVB dogs, a difference of ~50% ($p < 0.05$) (Table 2). All measures of LV repolarization duration were significantly more prolonged in the CAVB dogs compared with the HSP dogs, both at IVR and constant pacing rates (Tables 2 and 3, Fig. 3). Furthermore, interventricular dispersion and short-term variability of repolarization duration were increased only in the CAVB dogs (Tables 2 and 3). Similar to CAVB dogs (15), HSP dogs showed enhanced LV contractility (1), absence of prominent heart failure, and biventricular hypertrophy.

The observed differences between HSP and CAVB dogs can reflect that preservation of activation facilitates recovery from the acute demand for larger stroke volume directly after AVB. The altered activation pattern in CAVB could create a larger hemodynamic deficit to overcome. As contractile remodeling reached comparable end points in the 2

groups, a comparable hemodynamic burden seems to be present in both groups after AVB. Nevertheless, factors initiating ventricular remodeling after bradycardia and volume overload may be expressed with lower intensity in HSP dogs, resulting in less prolongation of the action potential.

The sequence of ventricular activation is also important for proarrhythmia. Electrocardiographic analysis of CAVB dogs showed that the predominant focus of ventricular activation was located in the lower LV septum in 11 of 14 dogs. On the other hand, 93 ± 3% of all ventricular beats in HSP dogs were paced, thus originating in the high RV septal region. The LV origin of activation in CAVB dogs leads to a relatively larger increase in LV MAPD than RV MAPD, thereby increasing ΔMAPD (Tables 2 and 3). In HSP, the homogenous ventricular activation invokes equal increases in MAPD in the LV and RV and thus no change in ΔMAPD (Tables 2 and 3). The resulting dispersion in refractoriness is thus smaller in HSP than in CAVB dogs, suggesting a lower chance of sustained reentrant arrhythmias in HSP (Fig. 4).

Although the number of inducible dogs relative to group size after dofetilide was not significantly different, the proarrhythmic intensity was lower in HSP; the cumulative duration of arrhythmias was significantly longer in CAVB versus HSP dogs (Fig. 4). As a consequence, CAVB dogs had to be defibrillated more frequently. This reduced proarrhythmia in HSP dogs coincides with the reduced electrical remodeling compared with CAVB dogs.

Possible experimental and clinical implications. Although this study was not set up to determine an optimal site of pacing, the results show that the pattern of ventricular activation also determines electrical remodeling. In the past decades, the choice of the RV apex as the standard pacing site in patients with a pacemaker indication has been influenced by the relative simplicity of lead implantation and not by consequences for mechanical function or electrical remodeling. The RV apex is not the most optimal site for LV performance (18,30,31) and can lead to unfavorable structural and contractile remodeling (30–33), which is especially important in patients with heart failure. Alternatives such as LV or biventricular pacing, HSP (23,32), or even direct His-bundle pacing (20) have been advocated. The impact of ventricular pacing site on electrical remodeling and proarrhythmia has often been overlooked in clinical studies.

Our findings suggest that the pacing site, and thus the ventricular activation pattern, is of importance for ventricular electrical remodeling and proarrhythmia. Therefore, the choice of the pacing site in patients should be guided by the combination of mechanical, electrophysiological, and proarrhythmic consequences. Likewise, future research to gain insight into finding the optimal ventricular pacing site should take these consequences into account.

Study limitations. Pacing during experiments (Fig. 3) was applied from different sites in the 2 groups: CAVB dogs were paced from the RV MAP and HSP dogs from the HSP lead (Table 3). The comparability of these 2 pacing sites was validated in 5 CAVB dogs (Fig. 3C), where no acute effect of the different pacing sites on ventricular electrophysiological parameters was found, verifying that the observed long-term differences were due to electrical remodeling.

During dofetilide, HSP dogs were paced at a cycle length of 1,000 ms, which could reduce susceptibility to arrhythmias (8). However, switching to IVR 10 min after the start of administration of dofetilide did not change TdP incidence. Ventricular remodeling and proarrhythmia was assessed only at 1 time point (4 weeks), disregarding long-term temporal aspects of remodeling.

Conclusions

The ventricular activation pattern has a larger role in generation of ventricular electrical remodeling than previously assumed. Maintenance of a constant origin of ventricular activation by HSP in AV block dogs attenuates the magnitude of ventricular electrical remodeling and proarrhythmia.

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