Biventricular hypertrophy in dogs with chronic AV block: effects of cyclosporin A on morphology and electrophysiology

Kirsten D. Schreiner,* Kamilla Kelemen,* Joerg Zehelein, Ruediger Becker, Julia C. Senges, Alexander Bauer, Frederik Voss, Patrizia Kraft, Hugo A. Katus, and Wolfgang Schoels

Department of Cardiology, University of Heidelberg, 69115 Heidelberg, Germany

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THE ACQUIRED LONG QT syndrome may be caused by various drugs that prolong repolarization (5). The occurrence of drug-induced QT prolongation and of polymorphic ventricular tachycardia (PVT) is facilitated by left ventricular (LV) hypertrophy. In the canine chronic atrioventricular (AV) block (CAVB) model, bradycardia-related volume overload leads to biventricular hypertrophy and electrical remodeling (21, 24). Accordingly, dogs with CAVB, but not with acute AV block (AAVB), show enhanced susceptibility to PVT after exposure to type III agents (24). Although pharmacological regression of hypertrophy has been suggested to be associated with reversal of electrical remodeling (13), it is unclear whether this is really the case. Calcineurin, a Ca\textsuperscript{2+}- and calmodulin-dependent phosphatase, seems to play a pivotal role in the development of hypertrophy (11, 20). Thus calcineurin inhibitors, such as cyclosporin A (CsA), should affect hypertrophy. CsA has been shown to block hypertrophy in transgenic mice, cultured cardiomyocytes (11), and several rodent models (7, 9, 18, 20). However, failure to prevent hypertrophy in rats (3, 8, 12, 25) and increased mortality with CsA have also been reported (9), suggesting that some forms of hypertrophy may be mediated by calcineurin-independent signaling pathways (19). For regression of hypertrophy, the role of calcineurin inhibition is also undetermined (7, 15, 18). Furthermore, all available data relate to in vitro models or to small animal in vivo models. Large-animal in vivo models have not been studied.

In the present study, the CAVB model was used to address the following questions: Is CsA relevant in the prevention and/or regression of biventricular hypertrophy in dogs? Because morphological remodeling in the CAVB model is accompanied by electrical remodeling, how are potential effects of CsA on morphology related to electrophysiology? Finally, if changes in morphology and/or electrophysiology occur, is inducibility of PVT affected? Respective information should help determine whether hypertrophy represents an epiphenomenon, the cause of electrophysiological changes, or the anatomic substrate for PVT.

METHODS

All animal experiments conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, Revised 1996).

Model preparation. In 45 foxhounds weighing 29.5 ± 1.5 kg, general anesthesia was induced with pentobarbital sodium (0.5 mg/kg) and maintained by halothane (±10%). Complete AV block was achieved by radio-frequency ablation of the AV node (17). Dogs were studied acutely (AAVB) or allowed to recover for 6 or 12 wk (CAVB). This related to dogs with or without CsA treatment. CsA (Sandimmune, Novartis) was administered orally at 10–20 mg·kg\textsuperscript{-1}·day\textsuperscript{-1} in an effort to achieve plasma levels of 400–800 µmol/l. To exclude direct CsA effects on electrophysiology and to allow for an analysis of CsA effects on prevention and regression of hypertrophy, the following control (CTL) and treatment groups were formed: 1) AAVB, no treatment (CTL-AAVB, n = 6), 2) AAVB, permanent CsA treatment, starting 6 wk before AV node ablation (CsA-AAVB, n = 3), 3) CAVB for 6 wk, no treatment (CTL-CAVB-6W, n = 11), 4) CAVB for 6 wk, permanent CsA treatment, starting

* K. D. Schreiner and K. Kelemen contributed equally to this study.

Address for reprint requests and other correspondence: K. Kelemen, Dept. of Cardiology, Univ. of Heidelberg, Bergheimerstr. 58, 69115 Heidelberg, Germany (E-mail: kamilla_kelemen@med.uni-heidelberg.de).

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on the day of AV node ablation (CsA-CAVB-6W, n = 7), 5 CAVB for 12 wk, no treatment (CTL-CAVB-12W, n = 12), and 6 CAVB for 12 wk, permanent CsA treatment from week 7 to 12 (CsA-CAVB-12W, n = 6).

Echocardiographic analysis. Transthoracic echocardiographic analyses were performed before AV node ablation and every 2 wk thereafter with the dogs in the conscious state. A 2.5-MHz imaging transducer (Toshiba Sonolayer SSH-260 A) was used to determine LV end-diastolic diameter and thickness of the septum and posterior wall.

Recording techniques. To allow for bipolar recording and stimulation at 240 intramural sites at depths of 1, 4, 7, and 10 mm, 60 plunge needles (12 mm long) containing 4 bipolar electrodes each (interpolated distance 0.5 mm, interelectrode distance 2.5 mm) were used. Electrodes were connected to a 256-channel computerized multiplexer mapping system developed at the University of Limburg (Limburg, The Netherlands) (1). Thus, apart from measuring local refractory periods with the extrastimulus technique, reconstruction of tridimensional activation maps from local activation times was also possible (17).

Study protocol. Electrophysiological studies were performed 2 h, 42 ± 2 days, or 84 ± 1 days after AV node ablation. The dogs were reanesthetized, and the heart was exposed through an extended midsternal approach. After pericardectomy, all 60 needles were inserted into both ventricles in 5 transverse sections from base to apex (Fig. 1), as described elsewhere (17). The chest cavity was closed, and body temperature was adjusted to 38°C with a heating lamp. For 20 min, surface ECG leads I, II, and III and all intracardiac electrograms were continuously recorded to capture any spontaneously occurring arrhythmia. To determine local effective refractory periods (ERPs), 24 ± 10 electrode sites within the right ventricle (RV) and 32 ± 12 electrode sites within the LV were randomly selected for stimulation. At each site, stimulation thresholds and ERPs were measured at a basic cycle length of 800 ms. After eight basic stimuli (S1) at twice diastolic threshold amplitude, an extrastimulus (S2) was introduced, decreasing the S1-S2 coupling interval in steps of 10 ms. ERP was defined as the maximum S1-S2 interval that failed to evoke a propagated ventricular response. Dispersion of ERP was defined as the difference between the longest and the shortest ERP found at any site. All measurements were repeated after intravenous administration of 0.34 µmol/kg almokalant.

Torsade de pointes (TdP) was defined as a PVT consisting of at least five beats, twisting around the baseline, having a rate of ≥200 beats/min. If no TdP occurred with the first dose of almokalant within 20 min, a second dose was given. Drug effects were observed for 20 min thereafter.

Morphological measurements. After the experiment, the heart was excised. To determine ventricular weight, the ventricles were removed from the atria and the RV was separated from the LV; the septum was taken as part of the LV. The thickness of the anterior LV wall, the RV wall, and the septum 1 cm below the AV ring was determined for each heart (Fig. 2). Measurements were adjusted for body weight (heart weight/body weight).

Statistical analysis. Values are means ± SD. Data were assessed with commercially available statistical software (SPSS, version 10.0). Basic comparative statistics were performed using the Mann-Whitney U-test. A confidence level of 95% was considered statistically significant.

RESULTS

Of the 36 dogs with CAVB, 11 (31%) died suddenly 23 ± 5 days after AV node ablation: 10 of 23 (43%) untreated (CTL) dogs and 1 of 13 (8%) CsA-treated dogs. All deaths in untreated dogs were classified as sudden; postmortem analysis demonstrated severe hypertrophy in 4 of 10 cases. The CsA-treated dog died from an intestinal infection.

Electrophysiological studies were performed in 9 dogs with AAVB (6 CTL and 3 CsA), 12 dogs with CAVB for 6 wk (6 CTL and 6 CsA), and 13 dogs with CAVB for 12 wk (7 CTL and 6 CsA).

With respect to morphological parameters (wall thickness and heart weight), there was no significant difference between CTL-CAVB-6W and CTL-CAVB-12W dogs or between CTL-AAVB and CsA-AAVB dogs.

Effects of CsA on development of ventricular hypertrophy. CAVB led to biventricular hypertrophy, indicated by a significant difference in heart weight-body weight index (HBWI) between CTL-CAVB and CTL-CAVB-6W dogs. CsA treatment did not totally prevent, but considerably attenuated, hypertrophy (Fig. 3). Accordingly, HBWI was significantly higher in CsA-CAVB-6W than in AAVB dogs but significantly lower than in CTL-CAVB-6W dogs. CsA treatment resulted in a 26.6% decrease in HBWI. The CsA effect was similarly reflected by total heart weight, LV weight, and RV weight.
Compared with AAVB, CAVB led to a significant increase in wall thickness. Again, CsA treatment significantly reduced the increase in the thickness of the septal wall as well as the LV and RV walls. As a result, wall thickness was not significantly different between CTL-AAVB and CsA-CAVB-6W dogs. Data are summarized in Table 1. Given the operator dependence and the difficulties in obtaining echocardiographic data from conscious dogs, respective values must be interpreted with caution. Still, with respect to the time course of hypertrophy development, it appeared that LV end-diastolic diameter increased most 2–4 wk after AV node ablation, whereas the increase in wall thickness was most prominent 1–2 wk after AV node ablation (Table 2). CTL-CAVB-6W dogs had significantly thicker septal and posterior LV walls and larger end-diastolic LV diameters than CTL-AAVB dogs. In CsA-CAVB-6W dogs, the thickness of the septal and posterior LV wall was comparable to that in CTL-AAVB dogs. However, end-diastolic LV diameters were increased as in CTL-CAVB-6W dogs (Table 3). CAVB and/or CsA treatment did not seem to affect cardiac function.

Effect of CsA on electrophysiological parameters. Regarding stimulation threshold and total ventricular activation time, there was no significant difference between any of the groups. CAVB without CsA treatment resulted in prolongation of refractory parameters. This was true for global mean ERPs as well as for LV and RV ERPs. Q-T interval was significantly lower in the CsA than in the CTL-CAVB-12W group but not significantly different between any of the groups. CAVB and/or CsA treatment did not seem to affect cardiac function.

Effect of CsA on regression of hypertrophy. Despite this, CsA treatment 7–12 wk after induction of AV block had a significant effect on regression of hypertrophy (Table 4). Although HBWI was significantly higher in CsA-CAVB-12W and CTL-CAVB-12W than in CTL-AAVB-dogs, HBWI was 20% less in CsA-CAVB-12W than in CTL-CAVB-12W dogs (Fig. 3). Global heart weight, LV weight, and RV weight were significantly lower in the CsA than in the CTL-CAVB-12W group but significantly higher than in the CTL-AAVB group. Echocardiographic data reflected a very modest effect of CsA treatment on wall thickness 7–12 wk after induction of AV block, although LV end-diastolic diameter appeared to be markedly reduced (Table 3).

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To discern whether CsA treatment exerts its effect on TdP inducibility primarily through trigger elimination or through substrate modification, the number of premature ventricular contractions (PVCs) occurring within the first 6 min after application of almokalant was compared for the various subgroups. Not revealing any significant difference, this comparison was limited by the relatively small number of dogs per group and by considerable interindividual variability in the incidence of PVCs (5.5 ± 3.9, 9.9 ± 2.9, 8.8 ± 3.7, 4.4 ± 3.0, 3.0 ± 1.8, 3.3 ± 1.6, and 6.4 ± 2.1 PVCs/min for AAVB, inducible CTVB-CAVB-6W, noninducible CTVB-CAVB-6W, inducible CTVB-CAVB-12W, noninducible CTVB-CAVB-12W, CsA-CAVB-6W, and CsA-CAVB-12W, respectively, \( P = \text{not significant} \)). Nevertheless, the findings are at least compatible with the hypothesis that the antiarrhythmic effects of CsA are based on substrate modification, rather than on trigger elimination.

**ECG and activation pattern of PVTs.** All seven PVTs occurred spontaneously after drug application. Four episodes were initiated by a short-long-short sequence. Nonsustained episodes (6 of 7) lasted for 6–60 beats. One six-beat run was too short for a meaningful analysis of ECG morphology. All other episodes revealed characteristic changes in the QRS axis and amplitude closely resembling TdP in patients. A representative electrocardiographic example is given in Fig. 4A, and respective three-dimensional activation patterns of selected beats are presented in Fig. 4, B–F.

All PVTs were initiated by focal activation, originating from a subendocardial site. In six of seven episodes, subsequent beats also appeared to be exclusively due to focal activity. Focal initiation with transition to reentrant activation was observed in one case.

**DISCUSSION**

To the best of our knowledge, this is the first report on the effects of calcineurin inhibition on volume overload-induced hypertrophy in large animals. In dogs with CAVB, CsA attenuates the development and promotes the regression of biventricular hypertrophy. Although calcineurin inhibition does not prevent ERP prolongation typically seen with CAVB, the susceptibility to almokalant-induced PVTs is dramatically reduced. The lack of PVT inducibility, despite ERP prolongation, suggests that ERP prolongation provides the trigger and hypertrophy provides the substrate for PVT.

**Calcineurin inhibition and morphology.** Data on the effects of calcineurin inhibition on hypertrophy are inconsistent, and whether calcineurin plays a key role in the development of hypertrophy is the subject of an ongoing debate (19). In vitro and some in vivo studies in transgenic mice and in pressure-overloaded rodents have demonstrated that inhibition of cal-

### Table 3. Echocardiographic data in dogs with AAVB and CAVB, untreated or treated with CsA

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<th>Thickness, cm</th>
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<tr>
<td>Septal wall</td>
<td>1.01±0.09</td>
<td>1.27±0.11*</td>
<td>1.03±0.12†</td>
</tr>
<tr>
<td>LV</td>
<td>0.99±0.12</td>
<td>1.29±0.15*</td>
<td>1.09±0.08†</td>
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<tr>
<td>LVDD, mm</td>
<td>36.8±3.9</td>
<td>41.2±3.7*</td>
<td>41.3±4.2</td>
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Values are means ± SD. *\( P < 0.05 \) vs. CTL-AAVB; †\( P < 0.05 \) vs. CTL-CAVB-6W.

### Table 4. Morphological measurements in dogs with AAVB and 12 wk of CAVB, untreated or treated with CsA

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<tr>
<td>Septal wall</td>
<td>1.1±0</td>
<td>1.1±0</td>
<td>1.1±0</td>
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<tr>
<td>LV</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
<td>0.8±0.1</td>
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<tr>
<td>RV</td>
<td>1.1±0.1</td>
<td>1.2±0.3</td>
<td>1.9±0.3</td>
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Values are means ± SD. *\( P < 0.05 \) vs. CTL-AAVB, CTL-AAVB.

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than in the CTL-CAVB-12W group. As a result, the difference in mean ERPs between CsA-CAVB-12W and CTL-AAVB dogs no longer reached statistical significance. This was not true for the Q-T interval, which was significantly longer in the CsA-CAVB-12W than in the CTL-CAVB-12W group. Dispersion of ERP was similar in dogs with AAVB and CAVB and was not affected by CsA treatment (Table 5). Almokalant significantly prolonged ERP in all dogs, whether the AV block was acute or chronic and with or without CsA treatment. Mean ERPs with almokalant treatment in dogs with CAVB (treated or untreated) and with AAVB were no longer significantly different. A subanalysis for either ventricle yielded similar results. Almokalant led to a slight increase in the dispersion of ERP, similarly affecting all subgroups. Thus, even with almokalant treatment, there was no significant difference in the dispersion of ERP between dogs with AAVB and those with CAVB, with or without CsA treatment (Table 5).

**Inducibility and vulnerability.** CAVB without CsA treatment significantly increased the inducibility of TdP (0 of 9 AAVB dogs vs. 4 of 6 CAVB-6W dogs; \( P < 0.05 \)). None of the AAVB dogs (6 without and 3 with CsA treatment) developed TdP with almokalant treatment. In contrast, the first bolus of almokalant in four of six CTL-CAVB-6W dogs and in one of seven CTL-CAVB-12W dogs resulted in various arrhythmias within the first 6 min. In four dogs, seven episodes of TdP occurred, six of which were nonsustained. One episode deteriorated into ventricular fibrillation (VF). The remaining dog developed VF directly after drug application. The observation that only one of seven CTL-CAVB-12W dogs developed arrhythmias was quite surprising. However, this could have been due to the high mortality in the untreated CAVB group (10 of 23) during the waiting period, possibly resulting in a negative selection of surviving noninducible dogs. CsA seemed to completely prevent inducibility of TdP in CAVB dogs. None of the six CsA-CAVB-6W dogs and none of the six CsA-CAVB-12W dogs developed PVTs.
whether calcineurin prevents or at least attenuates hypertrophy (7–9, 11, 18, 20). Other studies, however, indicate that CsA and FK-506 are ineffective in preventing hypertrophy (8, 12, 25) and may even be deleterious (7–9, 25). With respect to regression of hypertrophy, there are also conflicting data (7, 15, 18). Some investigators demonstrated that CsA administration in hypertensive rats partially reverses hypertrophy and fibrosis in a dose-dependent manner (7, 18). In contrast, using the same animal model, Sakata et al. (15) found that FK-506 attenuated the initial stage of hypertrophy without affecting fibrosis but failed to prevent cardiac remodeling and to induce regression in the advanced stage of hypertrophy. Species differences, variations in the methodology and the models used, and the timing, dose, and route of CsA administration may account for these controversial results. It is well known that there are marked differences in physiology and drug metabolism between certain species (2). Recent data also suggest that the signal transduction pathway may vary depending on the duration and/or the type of intervention (i.e., volume or pressure overload) inducing hypertrophy. Thus calcineurin may only be of relevance for a certain phenotype of hypertrophy (10, 15, 19). Our results would then suggest that the calcineurin pathway is involved in the development of volume overload-induced hypertrophy in dogs. CAVB results in biventricular hypertrophy accompanied by electrical remodeling (23, 24). In our study, CsA attenuated the development of hypertrophy and partially reversed established hypertrophy without increasing mortality. HBWI was significantly lower in CsA-treated dogs with CAVB than in nontreated CAVB dogs but higher than in AAVB dogs. The fact that CsA did attenuate, but did not completely block, hypertrophy could have been a matter of dose and/or timing of administration. It could, however, also indicate that not only a single pathway is responsible for the overall hypertrophic response. Instead, an interaction with other signaling pathways, such as the MAPK pathways, seems to be likely.

Calcineurin inhibition and mortality. Whether hypertrophy is salutary or detrimental is a matter of debate. In mice subjected to pressure overload, Meguro et al. (9) found a 7.2-fold higher mortality due to heart failure in the CsA-treated group, supposedly due to the lack of an adequate hypertrophic response. In the present study, none of the animals developed heart failure. One could speculate that an attenuated hypertrophic response might still suffice to compensate for the hemodynamic situation. Increased mortality associated with CsA treatment in pressure-overloaded rats in the study by Zhang et al. (25) was attributed to the general toxicity of systemic CsA. Consistent with the findings of other groups (4, 15, 18), we could not find increased mortality rates in CsA-treated animals. On the contrary, mortality was higher in untreated CAVB dogs dying prematurely from sudden death. The incidence of severe drug-related complications was very low (1 of 13 dogs), possibly because of the short-term drug application (≤6 wk). Furthermore, as with the beneficial effects of CsA, detrimental effects may also depend on drug metabolism. Thus controversial findings might again be explained by differences in the model, the species, and the drug dose.

Calcineurin inhibition and changes in electrophysiology. Hypertrophy is associated with prolonged repolarization parameters and a predisposition to ventricular arrhythmias (22–24). Thus regression of hypertrophy might resolve electrophysiological abnormalities and the susceptibility to ventricular arrhythmias. Rials et al. (13) provided convincing evidence, in vitro and in vivo, that angiotensin-converting enzyme inhibition induces regression of hypertrophy, normalizes action potential duration, and decreases VF inducibility in different hypertrophy models (13). In our study, CAVB also resulted in prolongation of mean ERPs. The fact that we could not demonstrate a significant increase in the dispersion of ERP is in contrast with other studies (13, 23) and probably points to a weakness of the methodology applied. ERP measurements with the extrastimulus technique do not allow us to perceive dynamic changes and are very time consuming. This could have accounted for different time windows for data acquisition, a factor of potential relevance with respect to the stability of the preparation, temperature, and drug levels. Furthermore,
because of a mismatch between needle length and wall thickness, longer endocardial ERPs may have been missed in some cases, thereby falsely suggesting a minor degree of dispersion. Although it would have been reassuring to reproduce previous findings on the dispersion of repolarization (13, 23), even with ERP measurements, this was certainly not the focus of the present study. Fundamental effects of CAVB, namely, biventricular hypertrophy, ERP prolongation, and PVT inducibility, could be confirmed. Thus assessment of the effects of CsA relied on these parameters. CsA did not seem to affect electrical remodeling. Despite a significant ERP prolongation, CsA-treated CAVB dogs were no longer susceptible to almokalant-induced PVTs but produced single PVCs as frequently as untreated dogs. This latter finding is compatible with the idea that the initial beat of a PVT is due to prolongation of repolarization and early afterdepolarizations (EADs). The lack of PVT inducibility in CsA-treated CAVB dogs with significantly reduced hypertrophy suggests that hypertrophy provides the substrate for continuation of the arrhythmia.

Recently, Schoenmakers et al. (16) demonstrated that CAVB dogs may develop dofetilide-induced TdP, even after 2 wk of complete AV block (CAVB2). The authors concluded that ventricular hypertrophy in the CAVB dog is not a prerequisite for electrical remodeling or drug-induced TdP. However, they also found that CAVB2 dogs exhibit longer Q-T intervals, LV monophasic action potential durations, RV monophasic action potentials, and ventricular ERPs than control AAVB dogs, indicating the presence of electrophysiological changes associated with the development of hypertrophy. Electrophysiological changes associated with hypertrophy could relate to local heterogeneities in conduction and/or refractoriness or to alterations of electrical coupling. It is quite conceivable that respective changes could precede morphological changes evident at a macroscopic level.

Another study in the CAVB model found that hypertrophy is associated with an increase in the dispersion of activation recovery intervals and that PVTs are exclusively due to reentry (6). Because dispersion of refractoriness as a prerequisite for functional conduction block is the hallmark of reentry, both observations are compatible with the idea that hypertrophy by increasing dispersion facilitates reentry. Kozhevnikov et al. (6) analyzed 14 episodes of PVT, and their typical example shows a 9-beat run based on macroreentrant circuits. We did, indeed, also observe a six-beat PVT with focal initiation but transition to this type of macroreentrant activation, at least indicating that the methodology applied was able to trace respective activation patterns. However, the majority of episodes, which consisted of up to 60 beats and closely resembled TdP in patients, clearly exhibited a centrifugal spread of activation and were, thus, termed “focal.” This does not necessarily imply a certain mechanism with respect to the focus, which could as well be based on microreentry. However, such a focal activation pattern is clearly different from the more-or-less circular spread of activation observed in one of our experiments and by others (6). The prevalence of activation pattern during PVTs in the CAVB model and the basis of long-lasting, TdP-like runs need to be determined.

Furthermore, the fundamental question on the issue of focal versus reentrant activity during TdP is the relevance of hypertrophy. Our data and present knowledge only allow for speculation and for the creation of hypotheses that need to be confirmed. The concept of reentry as the basis of TdP does not explain the unique ECG morphology of the arrhythmia or clinical characteristics, such as spontaneous termination, mode of induction, or etiology (e.g., drug induced and congenital). It is also surprising that one rarely sees transition of TdP to a monomorphic tachycardia, which is usually based on reentry.

Our hypothesis would be different: The initial beat of a TdP is generally accepted to result from EADs and triggered activity. That, however, is a bradycardia-dependant process and could, therefore, not account for subsequent beats of the tachycardia. If, however, subtle changes in local electrophysiology (uncoupling, local conduction delay, and local dispersion of refractoriness) associated with hypertrophy would result in tachycardia-dependant entrance block to certain regions, these regions would experience long reactivation intervals and could, thus, develop bradycardia-dependant EADs during TdP. This would explain the need for a continuous shift in the site of earliest activation. This would also explain the ECG appearance, its similarity from patient to patient, and the tendency toward spontaneous termination. QT prolongation alone might not be sufficient to create TdP; otherwise this arrhythmia should be easily inducible in every patient or in multiple experimental settings. Instead, one would need QT prolongation to provoke EADs, as well as local electrophysiological changes (e.g., those associated with hypertrophy) to provide the basis for local entrance block.

Limitations of the study. Electrical and ventricular remodeling processes due to volume-overload hypertrophy start within 24 h after induction of AV block (21, 23, 24). Sufficient blood levels of CsA required ≥2–3 days of treatment. Thus pretreatment of the dogs with CsA might have resulted in a more pronounced effect on hypertrophy.

The development of hypertrophy could have been influenced by the blood pressure of the dogs, which was not measured in this study. Furthermore, cyclosporin-induced changes in blood pressure of the dogs, which was not measured in this study. Furthermore, cyclosporin-induced changes in blood pressure could have been influenced by the blood pressure of the dogs.
pressure could have contributed to the development and/or regression of hypertrophy.

The resolution with our electrode array allowed for 1.0- to 1.5-cm gaps between individual needles. Furthermore, a significant part of the interventricular septum was not covered. This might not have been sufficient to resolve small functional reentrant circuits. However, even with small circuits, the activation pattern at a distance from the circuit should remain somehow circular, except one would postulate a microreentrant circuit being surrounded by functional conduction block with only limited exit.

Apart from the limitations of multiple ERP measurements already discussed, the lack of septal sites might have also contributed to the inability to detect significant dispersion. However, functional conduction block as a prerequisite for reentry requires local refractory gradients. Thus the relevance of ERP differences between septal and other sites at a certain distance is at least questionable.

For refractory measurements, a train of eight basic beats preceded application of an extra beat. With that, steady-state conditions were probably not reached. However, the emphasis of our study was on the comparison of normal and hypertrophied hearts, and the given limitation applies to both.

Our data on the role of CsA treatment for the occurrence of PVCs are limited by the small number of observations. Thus these findings have to be interpreted with caution.

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