Remodeling by ventricular pacing in hypertrophying dog hearts

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Abstract

Objective: Asynchronous electrical activation of the left ventricle (LV), induced by ventricular pacing (VP), reduces mechanical load in early- and enhances it in late-activated regions. Consequently, chronic VP leads to asymmetric hypertrophy. We investigated whether such locally induced myocardial hypertrophy also occurs in the presence of pressure overload hypertrophy (POH).

Methods: POH was induced by aortic banding in puppies. At age 9 months, seven dogs were paced at the right ventricular (RV) apex at physiological heart rate for 6 months (POH-pace group), while four POH dogs served as POH-control group. Changes in volume of the LV cavity and the total LV wall and of five LV wall sectors were measured by means of 2D-echocardiography and X-ray marker detection.

Results: During the last 6 months of the protocol the volume of the five LV wall sectors increased in the POH-control group, ranging from 27\% to 30\% (mean S.D.). In POH-pace animals sector wall volume in the four sectors at intermediate to long distance from the pacing site increased to a similar extent (ranging from 31\% to 35\%), but wall volume in the early-activated apical septum increased significantly less (17\%). In these hearts myocyte diameter was significantly smaller in the apical septum than in the lateral LV wall. The regional difference in wall volume changes (19\%) was significantly smaller in the POH-pace group than in chronically paced, non-hypertrophic, canine hearts in a previous study from our laboratory (43\%).

Conclusions: In hypertrophying hearts chronic pacing at the RV apex suppresses the development of hypertrophy in the early-activated apical septum but does not cause additional hypertrophy in late-activated regions, as is the case in non-hypertrophic hearts. The latter suggests that the local growth response is reduced in hypertrophying hearts.

Keywords: Hypertrophy; Remodeling; Ventricular function

1. Introduction

In normal canine hearts asynchronous electrical activation, as induced by ventricular pacing, causes regional differences in workload within the left ventricular (LV) wall [1–4]. Total mechanical work and oxygen consumption were found to be decreased by \(-30\%\) in early-activated regions and to be increased by \(-30\%\) in late-activated areas. These conditions ultimately lead to asymmetric hypertrophy, especially due to increased wall mass in late-activated regions [5]. This observation indicates that local myocardial load is an important determinant of local myocardial growth.

It is as yet unknown whether ventricular pacing can also induce regional changes in myocardial mass in globally hypertrophied hearts. It may quite well be that the factors responsible for the induction of global LV hypertrophy, in such disorders as pressure overload, may dominate those

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involved in local myocardial growth. After all, it has been shown that the growth response to mechanical stimulation is reduced in hypertrophic hearts [6].

More detailed information about interference between growth stimuli of different etiologies, if any, is relevant for several reasons. Many patients, who receive a pacemaker, have pre-existing cardiac hypertrophy, but it is unknown how ventricular pacing in combination with preexisting hypertrophy affects the structure and function of these hearts. Better insight into this situation is important, because structural alterations due to chronic ventricular pacing are supposed to contribute to improved cardiac function in hypertrophic obstructive cardiomyopathy (HOCM) [7,8].

In the present study we investigated whether, like in normal hearts, local growth stimuli, as induced by ventricular pacing, are able to induce remodeling in hypertrophying hearts. To this end, the effects of ventricular pacing on LV geometry and LV function in dogs with developing pressure overload hypertrophy (POH) as induced by aortic banding were studied. Global and regional LV geometry was assessed by 2D-echocardiography and LV function in dogs with developing pressure overload hypertrophy (POH) as induced by aortic banding were studied. Global and regional LV geometry was assessed by 2D-echocardiography and X-ray marker analysis, before and at various intervals during 6 months of right ventricular (RV) apex pacing. Global LV function was characterized by LV pressure and aortic flow measurements. Post mortem, myocyte diameter and collagen fraction were determined in the LV free wall and septum. Non-paced POH dogs were used as controls.

2. Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation (WOD) and The European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Animal Experimental Committee of Maastricht University.

2.1. Induction of pressure overload

A total of 11 mongrel puppies, 2 months of age and weighing 7.0±0.8 kg, underwent aortic banding according to Nakano et al. [9]. In brief, the dogs were premedicated with a mixture of acepromazine 0.2 mg/kg, atropine 0.1 mg/kg i.m. and oxycodon 2 mg/kg i.m. Anesthesia was induced with Thiopental, 15 mg/kg i.v., and maintained by ventilation with halothane (0.75–1.5%) in a 1:2 mixture of O₂ and N₂O. The thorax was opened and a slightly constricting 5-mm-wide Mersilene ligature was placed around the ascending aorta. The peak systolic LV–aortic pressure gradient, measured in four animals, ranged from 5 to 10 mmHg. After induction of pressure overload, body weight and LV wall volume (by 2D-echocardiography, see below) were determined monthly.

2.2. Implantation procedure

At the age of 9±1 months, when body weight leveled off, the dogs were operated again and, initially, anesthetized as described above. At least 1 h before determination of the hemodynamic parameters anesthesia was switched to intravenous Midazolam (0.15 mg/kg per h) and Sufentanyl-forte (3 μg/kg per h), and the dogs were ventilated with room air. The thorax was opened for implantation of gold beads in the LV wall (see ‘X-ray marker implantation’). Pacing leads were inserted transvenously into the right atrium (Medtronic capsule sp 4523) and into the RV apex (Medtronic 4057M unipolar screw-in). In seven dogs (POH-pace, weighing 24.3±3.7 kg) a pacemaker (Medtronic Synergist H7027, H7071, Elite II or Thera DR 7941) was implanted. In four dogs (POH-control, weighing 24.1±0.7 kg) only leads were implanted. For short-term pacing in this group the leads were temporarily connected to an external pacemaker. The ECG was derived from limb leads. A dual tip micromanometer catheter (Sentron) was introduced into the left femoral artery to measure LV cavity and ascending aortic pressure (distal to the stenosis). Cardiac output was measured in triplicate by thermodilution (Baxter cardiac output computer) during stopped ventilation. Hemodynamic measurements were made under baseline conditions and 15 min after initiation of ventricular pacing.

2.3. X-ray marker implantation

Radiopaque gold beads (diameter 1.5 mm) were implanted in the ventricular wall to measure changes in regional myocardial wall volume. Quadruplets of markers (two subendocardially and two subepicardially) were implanted at three different LV sites: (A) apical septum, (B) LV basal anterior wall; and (C) LV posterior wall (Fig. 1, upper panel). At each site the four markers formed the corners of a quadrangle with a circumferential distance of ~1.5 cm and a transmural distance of ~8 mm. Care was taken that the markers were placed in a short axis plane. For dimensional calibration a golden ring, internal diameter 1 cm, was secured to the tip of the LV apex.

2.4. Protocol

At age 9±1 months, in the POH-pace group ventricular pacing was started (t=0, Fig. 2) and was continued for 6 months (t=6 months). The heart was stimulated at its own sinus rhythm by AV sequential pacing (VDD-mode, upper rate 175 beats/min). The AV stimulation interval was 25 ms to ensure complete ventricular capture. Proper pacemaker function was checked regularly. The POH-control animals remained in sinus rhythm for 6 months (Fig. 2).

X-ray and 2D-echocardiographic images of the LV were made at 0, 0.5, 1, 2, 4 and 6 months after onset of pacing in the POH-pace group and at the same time intervals in
the POH-control group. To this purpose, the dogs were slightly sedated with a mixture of acepromazine (0.2 mg/kg) and oxycodon (1.2 mg/kg). Parasternal short axis cross-sectional echo images were taken so that the tip of the papillary muscles and the ‘LV ant.’ group of implanted markers were visible (Fig. 1, lower panel). Subsequently X-ray images were made with a Siemens Cardioskop U, equipped with a CCD camera (756×485 pixels, C4505, Hamamatsu Photonics) for video imaging. Short axis projections were made by directing the camera so that the apical ring was positioned in the center of the three groups of X-ray markers. Subsequently, a long axis projection was made by rotation of the camera axis by 90°. For each animal the same camera positions were used throughout the study.

X-ray and echocardiographic images were stored on super-VHS tape for off-line analysis. The tracing of lead II from the ECG was inscribed in the image using an analog video mixer.

2.5. Terminal procedure

After 6 months of pacing (POH-pace) or sinus rhythm (POH-control) final hemodynamic measurements were made, using the same anesthesia and catheter insertion as during implantation. Hemodynamic parameters were measured in the POH-pace group while the pacemaker was still functioning and 15 min after the pacemaker had been switched off and in the POH-control group before and after 15 min of temporary pacing (Fig. 2).

The heart was arrested in diastole, the left and right ventricles were separated and weighed and samples for histological analysis were taken (from the apical septum and from the LV free wall at the basal level) and analyzed for myocyte thickness and collagen fraction as described before [5].

2.6. Electrophysiologic and hemodynamic measurements

Hemodynamic and ECG signals were digitized with 12 bits at 200 Hz. Data were analyzed off-line. Using software developed in our laboratory the duration of the QRS complex of the ECG was calculated. The time constant of monoexponential LV pressure decline (τ) was calculated using $P(t) = P(0) \exp(-t/\tau)$, where $P(t)$ is LV pressure at time $t$ and $P(0)$ is LV pressure at the moment of minimum LVdP/dt.

2.7. Analysis of echo images

Two-dimensional echocardiography was used to determine regional LV wall thickness and sector wall volume of a basal septal sector and a lateral LV wall sector (Fig. 1, lower panel). From digitized end-diastolic echo images wall thickness and volume were estimated as described in detail previously [5]. The wall sector area of the lateral LV
wall and of the basal septum was defined as depicted in Fig. 1. Wall thickness of a sector was calculated as the difference between the epicardial and endocardial radius. Sector wall volume was calculated as the wall sector area multiplied by the mean LV radius [5]. Cavity and wall volume of the entire LV were calculated from 2D-echo short- and long-axis dimensions using cylinder-ellipsoid model calculations [5]. For calculation of the LV mass to body mass ratio the regression equation of the relation between post mortem LV weight (\(W_{\text{LV,pm}}\)) and echocardiographically determined LV wall volume just before termination (\(V_{\text{LV,wall,echo}}\)) was determined. This relation could be described by the equation: \(W_{\text{LV,pm}} = -7.4 + 1.27 \times V_{\text{LV,wall,echo}}^3; r=0.93\). From this relation LV wall volume, determined at each time interval, was converted to LV wall mass.

2.8. Analysis of X-ray images

The X-ray measurements were used to estimate regional myocardial growth. In an off-line procedure for both mutually perpendicular viewing positions end-diastolic video images were selected and digitized, using a video frame grabber (8 bits gray-scale, 768×578 pixels, DT3155, Data Translation, Marlboro, MA). The ECG was used to synchronize the pairs of images relative to the cardiac cycle. The images were considered to form a stereo pair and were used to reconstruct the 3-D position of a marker [10]. The digitized images were analyzed using NIH Image software (V1.52). The image coordinates of the 12 markers were determined manually using the cross-hair tool. Using this method the root mean square error in marker position estimation is ~0.3 mm.

Sector wall area (\(A_{\text{sector,Xray}}\)) was calculated in each of the three locations with markers. To that purpose a plane was fitted to the 3-D marker positions. The projections of the marker positions to the plane were obtained and the area of the resulting quadrangle was calculated. Sector wall volume (\(V_{\text{sector,Xray}}\)) was estimated by

\[
V_{\text{sector,Xray}} = D_{a-b} \cdot A_{\text{sector,Xray}}
\]

where \(D_{a-b}\) = the distance between the centers of gravity of the markers located at the RV apex and at the LV base. \(D_{a-b}\) was used as an estimate of dimensional changes in the direction perpendicular to the short axis plane.

2.9. Statistical analysis

Total and local LV wall volume was expressed relative to the state at the start of pacing in the POH-pace group and the corresponding time interval in the POH-control group (\(t=0\)). The time course of global and local LV geometrical parameters was evaluated by analysis of variance (ANOVA) for repeated measurements. Intra-individual changes in hemodynamics were evaluated using the Wilcoxon signed rank test and inter-individual changes using the Mann–Whitney \(U\)-test. If significant differences were found, significant points were isolated using Bonferroni–Dunn correction. Data are presented as mean±S.D. \(P<0.05\) was considered significant.

3. Results

In all dogs in the POH-pace group cardiac pacing was possible throughout the study period. None of the dogs in this study showed signs of cardiac failure.

3.1. Changes in global cardiac geometry

Fig. 3 illustrates that body weight, LV wall mass, LV cavity volume and the LV wall mass/body weight ratio increased during the experimental period, and to a similar extent in both groups. In both groups these parameters increased significantly during the months before \(t=0\) (see Fig. 2 for protocol) and during the first 2 months thereafter. The parameters stabilized towards the end of the experimental period.

![Fig. 3. Time course of body weight (panel A), global LV wall mass (panel B), LV cavity volume (panel C) and LV wall mass/body weight ratio (panel D) in the POH-pace (closed circles) and POH-control group (closed squares). Variables were normalized to their value at \(t=0\).](image-url)
3.2. Changes in regional cardiac geometry

In the POH-control group sector wall volume in the five sectors studied (Fig. 1) increased between $t=0$ and $t=6$ months. Increases in volume in individual wall sectors ranged from 27.0±9.2% in the apical septum to 29.8±5.8% in the lateral LV wall (no significant differences between the various sectors; Fig. 4A,C).

In the POH-pace group a similar increase in sector wall volume was found in the four sectors remote from the pacing site (LV anterior, LV lateral and LV posterior wall and basal septum). The increase ranged from 31.3±15.8% in the basal septum to 35.2±17.0% in the posterior LV wall (Fig. 4B,D). In the apical septum, however, sector wall volume increased by only 31.3±15.8% between $t=0$ and $t=6$ months (Fig. 4D). Using paired analysis this increase in apical septal wall volume was significantly smaller than the wall volume increases in the other regions of the same hearts. The degree of asymmetry of wall volume change (ratio of volume change of LV lateral wall and septum) was 19±21%.

3.3. Electrophysiology and hemodynamics

In both groups the QRS duration during sinus rhythm was significantly longer at $t=6$ than at $t=0$ (POH-pace: 19.2±14.0 ms, POH-control: 6.6±5.2 ms, NS between groups). In both groups acute (15 min) ventricular pacing more than doubled the QRS duration as compared with sinus rhythm ($P<0.05$, Table 1). At $t=6$ QRS duration during pacing was 24.0±17.8 ms (POH-pace group, $P<0.05$) and 12.2±16.2 ms (POH-control group, NS) longer than at $t=0$.

Switching from sinus rhythm to ventricular pacing reduced LV function in the POH-control and POH-pace groups to a similar extent (Table 1). Acute pacing reduced LV systolic pressure by ~3% (significant only in the POH-pace group) and stroke volume by ~28% and increased $\tau$ by ~9% (Table 1).

At $t=6$ the values of the hemodynamic variables were not significantly different between the POH-control and POH-pace group, during sinus rhythm or during ventricular pacing.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Implantation</th>
<th>Termination</th>
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<tbody>
<tr>
<td></td>
<td>SR</td>
<td>Pacing</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace</td>
<td>46.0±6.8</td>
<td>94.9±14.4*</td>
</tr>
<tr>
<td>Control</td>
<td>49.4±9.7</td>
<td>100.3±9.3*</td>
</tr>
<tr>
<td>PLVsys, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace</td>
<td>120.4±29.6</td>
<td>116.9±31.5*</td>
</tr>
<tr>
<td>Control</td>
<td>112.0±22.7</td>
<td>110.0±18.5</td>
</tr>
<tr>
<td>SV, ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace</td>
<td>29.7±13.1</td>
<td>23.9±9.2*</td>
</tr>
<tr>
<td>Control</td>
<td>36.8±17.4</td>
<td>20.7±0.7*</td>
</tr>
<tr>
<td>$\tau$, ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace</td>
<td>28.1±4.4</td>
<td>30.9±5.7*</td>
</tr>
<tr>
<td>Control</td>
<td>33.0±10.2</td>
<td>35.5±11.4*</td>
</tr>
</tbody>
</table>

*PLVsys, systolic LV pressure; SR, sinus rhythm; SV, stroke volume. Mean values±S.D. are presented. $P<0.05$ for the following comparisons: ventricular pacing compared with sinus rhythm the same day (*), sinus rhythm (†) and/or pacing ($) during implantation ($t=0$) compared with those during termination ($t=6$ months).
lar pacing. The changes in hemodynamics due to the switch from sinus rhythm to ventricular pacing were not significantly different from those observed during $t=0$.

The peak systolic LV–aortic pressure gradient was $25.0 \pm 23.5$ (POH-control) and $29.7 \pm 19.4$ mmHg (POH-pace) during $t=0$ and had increased to $41.4 \pm 16.2$ and $44.6 \pm 23.4$ mmHg, respectively, at the end of the experimental period.

3.4. Post mortem observations

The data from both groups of POH animals were compared with SHAM operated (non-paced, non-hypertrophic) dogs from a previous study [5] (Table 2).

Post mortem LV/body weight ratio was, respectively, 31 and 20% higher in POH-pace and POH-control animals than in SHAM animals ($P<0.05$). The RV/body weight ratio was not significantly different between the three groups (Table 2).

In the POH-control group no significant difference in myocyte diameter could be detected between apical septum and lateral LV wall (Table 2), but in all hearts of the POH-pace group myocytes were thinner in the apical septum than in the lateral LV wall ($P<0.05$). Myocytes from the lateral LV wall were significantly thicker in both POH groups than in the SHAM group. Within and between the three groups collagen fractions were not significantly different (Table 2).

4. Discussion

The findings in the present study demonstrate that chronic asynchronous electrical activation, induced by pacing at the RV apex, causes remodeling in hearts which develop hypertrophy due to pressure overload. This remodeling is characterized by suppression of hypertrophy selectively in the early-activated apical septum without additional hypertrophy in regions remote from the pacing site. These structural changes are qualitatively similar to those after chronic ventricular pacing in non-hypertrophic hearts [5]. However, the degree of asymmetry of wall volume changes is significantly smaller in the paced POH hearts than in the paced non-hypertrophic hearts (Table 3), which is mainly due to the absence of additional hypertrophy in late-activated regions in POH hearts (Table 3). These findings demonstrate that, unlike normal hearts, in hypertrophy hearts additional local mechanical loading does not result in additional hypertrophy, but that in hypertrophying hearts local unloading can inhibit local growth.

Table 2

<table>
<thead>
<tr>
<th>POH-control</th>
<th>POH-pace</th>
<th>SHAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV</td>
<td>Apical septum</td>
<td>LV</td>
</tr>
<tr>
<td>Myocyte diameter, $\mu$m</td>
<td>$25.1 \pm 2.4^*$</td>
<td>$22.9 \pm 2.8$</td>
</tr>
<tr>
<td>Collagen fraction, %</td>
<td>4.1 $\pm$ 0.9</td>
<td>3.7 $\pm$ 0.2</td>
</tr>
<tr>
<td>LV/BW, g/kg</td>
<td>5.85 $\pm$ 0.78$^*$</td>
<td></td>
</tr>
<tr>
<td>RV/BW, g/kg</td>
<td>2.04 $\pm$ 0.12</td>
<td></td>
</tr>
</tbody>
</table>

$^*$ BW, body weight. SHAM: data from five healthy adult mongrel dogs, who had been sham operated and stayed for 6 months in our animal facilities [5]. Mean values $\pm$ S.D. are presented.$^{\dagger}$ $P<0.05$ as compared to SHAM.$^{\ddagger}$ $P<0.05$ apical septum compared to LV lat. within groups.

Table 3

<table>
<thead>
<tr>
<th>Non-hypertrophic SHAM</th>
<th>Non-hypertrophic PACE</th>
<th>POH-control</th>
<th>POH-PACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-activated</td>
<td>Late-activated</td>
<td>Difference</td>
<td></td>
</tr>
<tr>
<td>3 $\pm$ 7</td>
<td>5 $\pm$ 8</td>
<td>0 $\pm$ 7$^+$</td>
<td></td>
</tr>
<tr>
<td>$-5 \pm 12$</td>
<td>39 $\pm 13^*$</td>
<td>43 $\pm 14^#$</td>
<td></td>
</tr>
<tr>
<td>39 $\pm 13$</td>
<td>42 $\pm 10$</td>
<td>3 $\pm 14^+$</td>
<td></td>
</tr>
<tr>
<td>21 $\pm 20$</td>
<td>40 $\pm 13^*$</td>
<td>19 $\pm 21^#$</td>
<td></td>
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</table>

$^*$ Data are expressed as percentage increase in local wall volume as compared to the reference time. Data from non-hypertrophic hearts were derived from a previous study, where adult animals remained in sinus rhythm (SHAM) or were paced at the LV free wall for 6 months [5]. Regional hypertrophy in the POH animals was calculated as the relative change in local wall volume between $t=0$ and $t=6$ months plus the relative change in LV/BW between $t=2$ months and $t=0$. The latter factor represents the first part of the development of hypertrophy, before the onset of the pacing protocol. Note that the early-activated region was the LV free wall in the non-hypertrophic dogs and the apical septum in the present study, whereas the late activated region was the septum in the previous study and the LV free wall in the present study.$^{\dagger}$ $P<0.05$ as compared with early-activated region.$^{\dagger}$ $P<0.05$ as compared with non-hypertrophic PACE.$^{\dagger\dagger}$ $P<0.05$ as compared with corresponding control group.
4.1. Suppression of hypertrophy in early-activated myocardium

The selective suppression of hypertrophy in the early-activated apical septum during the development of global LV hypertrophy can be explained by mechanical unloading of the apical septum during pacing from the RV apex. Early-activated regions shorten rapidly by ~10% during early systole but show only minor shortening later in systole, causing total mechanical work of these regions to be ~30% lower than during normal sinus rhythm [2–4]. The notion that regional reduction in loading may lead to atrophy or suppression of hypertrophy is supported by the finding that unloading of a papillary muscle results in atrophy of that muscle [11]. This atrophy was found in normal hearts and in hearts with RV pressure overload hypertrophy. The finding in the present study that in hypertrophying hearts the LV wall grows less near the site of pacing than more remote from this site corroborates the findings in non-hypertrophic canine hearts [5] and in patients with left bundle branch block [12].

While hypertrophy was suppressed in the apical septum, this suppression was absent in the basal septum. This can, most likely, be explained by the larger distance from the basal septum to the pacing site, because mechanical load increases with increasing distance from the pacing site [4]. The echocardiographic technique to measure local wall mass in the basal septum has an accuracy of ±5% [5], sufficient to measure even smaller changes in hypertrophy than those occurring in the apical septum.

4.2. Lack of additional hypertrophy in late-activated myocardium

At least as interesting as the suppression of hypertrophy close to the pacing site is the lack of additional hypertrophy in regions remote from the pacing site. Such an increase in hypertrophy might have been expected because during pacing the workload is increased in late-activated regions due to the early systolic stretching (~10%) followed by pronounced shortening later during systole and a ~30% increase in total mechanical work [2–4]. This stimulus was sufficient to increase the degree of hypertrophy by ~40% in normal, non-hypertrophic hearts (Table 3). It is unlikely that the lack of additional hypertrophy in hypertrophying hearts is due to a maximum limit of hypertrophy. The increase in LV/body weight ratio of 30–40% in our POH model is moderate as compared to the increases of 50–200% observed in other experimental studies [13,14]. The absence of additional hypertrophy in the late-activated areas may be caused by a reduced growth response of hypertrophic myocardium to mechanical stimulation as has been shown in a study on isolated rat hearts [6].

In the present study the dogs were paced from the RV apex, whereas in our previous study on non-hypertrophic hearts the dogs were paced from the LV free wall [5]. It is unlikely that the less pronounced asymmetry of hypertrophy as observed in the present study is due to differences in the asynchrony of activation. Pacing from both sites more than doubled QRS duration. Moreover, MRI tagging studies showed that regional differences in fiber strain and fiber work are similar, though opposite, during RV apex and LV free wall pacing [4].

4.3. Possible relevance of the experimental findings

The present study indicates that asymmetric remodeling due to altered local myocardial loading may be less in hypertrophic hearts than in normal hearts. Also in patients with left bundle branch block (LBBB) the asymmetry in wall thickness was found to be substantially smaller (maximum 10% in the subgroup with most severe LBBB) than in chronically paced non-hypertrophic canine hearts (43%). The small degree off asymmetry in the LBBB patients could be explained by significant myocardial hypertrophy in these patients, potentially associated with the high prevalence of valvular disease [12].

RV apex pacing in patients with HOCM acutely improves the LV–aortic pressure gradient and this improvement increases over time [7,8]. It may quite well be that the long-term beneficial effect of ventricular pacing results from local suppression of hypertrophy in the early-activated septum. The present study demonstrates the principle of local suppression of hypertrophy by early-activation, but does not show suppression of hypertrophy in the basal septum. The latter would fully explain the long-term effects of pacing in HOCM patients. Because the present study demonstrates a significant suppression of hypertrophy only close to the pacing site (RV apex), hypertrophy in the thickest part of the septum (usually the basal septum) would be most suppressed by positioning the pacing lead closer to the basal septum. This may, however, be at the cost of the acute reduction in LV–aortic pressure gradient, which was shown to be absent when pacing high in the septum [15]. The data from the present study should be extrapolated with care to HOCM patients, because the genetically abnormal myocardium of HOCM patients may respond differently to growth stimuli than normal myocardium during pressure overload hypertrophy.

4.4. Experimental approach

We used AV sequential pacing with a short AV interval (30 ms) to ensure activation of the entire ventricle from the ectopic site. This setup enabled us to study cardiac function during sinus rhythm and ventricular pacing at implantation and termination. In patients short AV intervals may decrease cardiac output by ~20% [16,17]. In a separate series of experiments in AV-blocked dogs we did not find a significant difference in cardiac output between pacing at AV intervals of 100 and 25 ms (Peschar and


