Regional differences in the dynamics of refractoriness in intact and hypertrophied \textit{in situ} canine hearts

Abstract Objectives Functional re-entry is thought to represent the predominant mechanism underlying ventricular arrhythmias. Functional conduction block may be caused by regional dispersion of refractoriness (ERP). Dispersion of ERP may not be evident at baseline, but may occur with sudden changes in heart rate, as ventricular arrhythmias are commonly induced by short-long-short cycles. Methods We examined the dynamics of local ERPs at two left ventricular (LV) sites in dogs with either no structural heart disease or biventricular hypertrophy (BVH). ERPs were determined at each of four bipoles of two adjacent needle electrodes in the LV apex and the lateral wall. The stimulation protocol included two different basic cycle lengths, one or two longer cycles after a train of 6 or 5 shorter cycles, and one shorter cycle after a train of 6 longer cycles. Results In normal dogs, a significant apico-lateral ERP gradient was only evident with the longer basic cycle length. One shorter cycle was sufficient to dissolve that gradient. One longer cycle was enough to create a regional ERP gradient. Dynamic regional gradients occurred because the apex responded more markedly and more readily to abrupt changes in cycle length. BVH led to an increase in ERP at both LV sites and to an aggravation of regional ERP gradients. Conclusions Dynamic ERP behavior seems to depend on topography and underlying pathology. Abrupt changes in heart rate might induce dynamic refractory gradients between various regions of the normal heart, but also between adjacent regions inhomogeneously affected by hypertrophy.

Key words Arrhythmia (mechanisms) – hypertrophy – repolarization – ventricular arrhythmias

Introduction

Ventricular arrhythmias, commonly due to re-entry, are typically induced by triggering extra-beats or short-long-short cycles. Functional conduction block as a prerequisite for re-entry may be caused by local refractory gradients. For local refractory gradients to occur, several factors might be of relevance: 1) baseline “steady state” refractoriness of adjacent myocardial regions at the intrinsic heart rate; 2) the difference in “steady state” refractoriness with faster or slower heart rates, reflecting the extent of rate-dependent changes; and 3) the difference in “steady state” and “instantaneous” refractoriness with abrupt changes in heart rate, reflecting the speed at which rate-dependent changes occur. Based on this concept, refractory gradients could be primarily evident at the intrinsic heart rate, could only prevail at faster or slower heart rates, or could only be detected transiently following abrupt changes in heart rate. With respect to static repolarization parameters, there is some regional disparity even in normal hearts [4], possibly exaggerated.
by pathological conditions like myocardial hypertrophy [13, 17]. The information on regional disparity of dynamic repolarization parameters, that is, on the speed of rate adaptation and on the extent to which refractoriness shortens with fast heart rates, is limited. Thus, in the present study, the response of local refractory periods at various left ventricular sites to different pacing rates and to abrupt changes in pacing rate was determined in normal and hypertrophied in situ canine hearts.

Material and methods

All animal experiments conformed to the “Position of the American Heart Association on Research Animal Use” adopted in November, 1984. Studies were performed in 10 foxhounds of either sex, weighing between 15 and 31 kg. Of those, 5 dogs had normal hearts, and 5 dogs had biventricular hypertrophy (BVH).

Model preparation

Surgery for induction of BVH was performed 6 ± 1 weeks prior to the final study, adopting the chronic AV-block model described by Vos et al. [21]. Complete AV block was achieved by transvenous radiofrequency catheter ablation of the compact AV node (Cerablate easy 735 catheter, bipolar, 4 mm tip and HAT 200 RF generator, Sulzer Osypka GmbH, Grenzach-Wyhlen, Germany) [18]. Postoperative care included analgesia with Buprenorphin. BVH in this model develops over several weeks due to chronic volume overload associated with bradycardia.

Study protocol

For the final ERP measurements, anesthesia was initiated with pentobarbital (0.5 mg/kg i.v.) and maintained by continuous ventilation with halothane (initial vapor concentration 1.0%). Buprenorphin 0.3 mg i.v. was administered before starting any procedure. Injections were repeated every 4 hours. ECG leads I, II, aVF and aortic blood pressure were continuously monitored on a physiological recorder (VR 12, Electronics for Medicine). To allow for refractory measurements at relatively slow heart rates, the AV node was ablated in normal dogs as well (Cerablate easy 735 catheter, bipolar, 4 mm tip and HAT 200 RF generator, Sulzer Osypka GmbH, Grenzach-Wyhlen, Germany). In all animals, the heart was then exposed by a midsternal thoracotomy and suspended in a pericardial cradle. A total of four custom-designed needle-electrodes were inserted into the left ventricle (LV), two into the apex and two into the lateral wall. The inter-needle distance was approximately 30 mm. The needles were 12 mm long and 1 mm in diameter. Each needle contained four bipolar electrodes with an inter-electrode distance of 3 mm. Thus, bipolar electrodes were located at 1, 4, 7 and 10 mm depth in the myocardium. The chest was then covered, and a heating lamp and heated i.v. saline were used to maintain body temperature at 38 °C. Body temperature was continuously monitored with a probe placed next to the descending aorta. Once stable conditions were reached, local ERPs were measured at all 16 bipole of the 4 needles using the extra-stimulus technique. A Biotronik stimulator (UHS 20 universal heart stimulator, Biotronik GmbH, Berlin, Germany) was used to deliver constant current rectangular impulses with pulse widths of 2 ms at twice diastolic threshold. Electrode sites with stimulation thresholds above 4 V were excluded to avoid far field stimulation. Premature beats (S2) were introduced after a basic drive of 8 beats (S1). S1S2 coupling intervals were reduced in steps of 5 ms. The largest S1S2 coupling interval not resulting in a propagated response was defined as local ERP.

ERP500 was measured after 8 consecutive beats (S1) at 500 ms BCL and ERP800 after 8 stimuli (S1) at 800 ms BCL. ERP500-800 was determined after 7 beats (S1) at 500 ms and 1 beat (S2) at 800 ms (short-long cycle). ERP500-800-800 consisted of a basic ventricular drive of 6 beats (S1) at 500 ms and 2 beats (S2, S3) at 800 ms (short-long-long cycle). Finally, ERP800-500 was measured after 7 beats (S1) at 800 ms followed by 1 extra-stimulus (S2) at a 500 ms coupling interval (long-short cycle).

Statistics

Data are expressed as mean ± SD. Statistical analyses were performed with The Primer of Biostatistics (version 4.02 for Windows). The statistical test applied was student’s t-test for unpaired samples. A p value < 0.05 was considered significant. To determine the homogeneity of ERP adaptation, proportional changes in ERP were calculated separately for apex and lateral wall. To describe the kinetics of ERP adaptation, the difference between ERPs with S1 stimulation (ERP500, ERP800) and ERPs with S2- or S3-stimulation (ERP500-800, ERP500-800-800, ERP800-500) was determined and given as a percentage of the difference between ERP800 and ERP500. ERPs with S1 stimulation were defined as “steady state” ERPs, ERPs with S2 or S3 stimulation as “instantaneous” ERPs.

Results

Pacing thresholds were similar for normal dogs and dogs with BVH (1.2 ± 0.2 V vs. 1.1 ± 0.2 V, respectively; p > 0.05) without any regional differences. For both groups, ERP measurements (steady state and instanta-