Basic Res Cardiol 95: 152 – 162 (2000)

ORIGINAL CONTRIBUTION

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Cesium chloride induced ventricular arrhythmias in dogs: three-dimensional activation patterns and their relation to the cesium dose applied

Received: 6 August 1999
Returned for 1. revision: 8 October 1999
1. Revision received: 27 October 1999
Returned for 2. revision: 24 November 1999
2. Revision received: 9 December 1999
Accepted: 9 December 1999

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Abstract *Introduction:* Cesium chloride has widely been used in experimental models to produce various ventricular arrhythmias. The study was designed to evaluate whether type and mechanism of these arrhythmias are dose-dependent.

Methods: In 7 dogs with acute AV-block, 60 pins containing 4 bipolar electrodes each were inserted into both ventricles to provide 240 endo-, epi- and midmyocardial recording sites. A computerized mapping system was used to determine three-dimensional activation patterns of ventricular arrhythmias induced by three injections of 1mmol/kg cesium chloride at 20 minute intervals.

Results: Out of all arrhythmias induced, 25 ventricular extrasystoles, 31 monomorphic and 47 polymorphic ventricular tachycardias were mapped. Nonsustained ventricular tachycardias were readily inducible by a single bolus of cesium chloride, whereas sustained episodes required repetitive injections (1.45 ± 0.61 vs. 2.61 ± 0.57 doses, $p < 0.05$). Polymorphic tachycardias were observed more commonly than monomorphic tachycardias (87 vs. 31). Initiation and maintenance of cesium induced arrhythmias were exclusively based on focal mechanisms originating from the subendocardium, irrespective of morphology and dosage. All monomorphic arrhythmias were caused by repetitive firing of single immobile foci located in either the right or the left ventricle. Bi- and multifocal mechanisms, however, were found to underlie the polymorphic episodes.

Conclusions: Although there is a dose-dependence as to the sustenance of mono- or polymorphic tachycardias, this does not reflect on the three-dimensional activation pattern of cesium induced arrhythmias, which are due to mono- or multifocal activation originating from the subendocardium.

Key words Experimental electrophysiology – ventricular tachycardia – three-dimensional mapping – cesium chloride – dose-dependency

Introduction

Cesium chloride has been shown to induce QT prolongation, early afterdepolarizations and bradycardia-dependent multiform ventricular tachycardia in canine hearts (3), thus serving as an experimental model of the long QT syndrome (16, 3, 10). A recent mapping study suggested that cesium chloride induced ventricular arrhythmias are exclusively due to focal activity (17). In other experimental long QT models applying I_{Kr}-blockers or sea anemone toxins, induced arrhythmias have been demonstrated to involve focal as well as reentrant mechanisms (7, 9). A canine study using three consecutive bolus administrations of cesium chloride revealed that polymorphic VT occurred after two boli, whereas monomorphic VT required three. These dose-dependent effects on surface ECG morphology of VT might, apart from suggested differ-

ences in the mechanism of induction of arrhythmias (EADs, DADs, abnormal automaticity), reflect dose-dependent differences in activation patterns during maintenance of VT. To specifically address this question, a three-dimensional mapping technique was applied in dogs with acute AV-block to determine the activation patterns of cesium induced ventricular arrhythmias in relation to the dose applied.

Methods

Surgical preparation

All procedures were approved by the animal research ethics committee. Seven small beagle dogs weighing 10–13 kg were anesthetized with pentobarbital (0.5 mg/kg); anesthesia was maintained with periodic repeat boli of pentobarbital as required. An i.v. cannula in the forelimb was used for administration of fluids and drugs. The dogs were intubated and ventilated with a mixture of nitrous oxide and oxygen. Buprenorphin 0.3 mg i.v. was administered before starting any procedures. Complete AV-block was induced by transvenous radiofrequency catheter ablation of the compact AV node (Cerablate plus™ 735 catheter, HAT 200™ RF generator; Sulzer Osypka GmbH, Grenzach-Wyhlen, Germany). If the dog had no adequate junctional rhythm (> 40 beats/min) following the ablation, pacing was performed through a transvenous electrode catheter in the right ventricular apex, which turned out to be necessary in two dogs. Electrocardiographic leads I, II, III, aVR, aVL and aVF were continuously monitored with a physiological recorder (VR12™; Electronics for Medicine, Pleasantville, NY); at least two leads per experiment were digitized on an optical disk (EP Lab, Quinton electrophysiology, Markham, Ontario, Canada). The heart was then exposed through a midsternotomy and suspended in a pericardial cradle. Body temperature was maintained at ≈ 37 °C by using a heating lamp.

Recording techniques

Endo-, epi-, and midmyocardial electrograms were recorded through 60 plunge needle electrodes (12 mm in length). The needles contained 4 bipolar electrode pairs arranged along their length, each pair separated by 2.5 mm (interbipole space = 0.5 mm). The needles were inserted in the right and left ventricle in five transverse sections from the base to the apex. The first two sections around the AV groove contained 16 needles, sections in between and at the apex contained 4–14 needles, depending on the size of the heart. Two 5 F quadripolar electrode catheters were inserted into the femoral vein and artery, respectively, and positioned against the interventricular septum to record septal activation (Fig. 1). This electrode array resulted in a maximum interelectrode distance of about 1.0 cm in the right and left ventricular free walls and of about 1.5 cm at the endocardial aspects of each side of the interventricular septum. Bipolar electrograms were simultaneously processed through a 256 channel multiplexer. Signals were amplified and filtered from 20 to 500 Hz and recorded on a video tape for off-line digitization at a sampling rate of 1000 Hz and analysis on a custom-designed computer system. Due to the use of video tapes, the continuous recording time was 240 minutes.

Study protocol

Cesium chloride was dissolved in normal saline and administered intravenously as a bolus of 1 mmol/kg over thirty seconds. During and after cesium administration, the surface ECG and all intracardiac electrograms were recorded continuously and simultaneously for subsequent reconstruction of the three-dimensional activation pattern. If the dog had to be paced following AV node ablation, the demand pacing rate was set to 30 per minute to unmask the underlying ventricular escape rhythm and to facilitate the occurrence of bradycardia-dependent arrhythmias. All measurements were repeated after a second and third injection of 1 mmol/kg cesium chloride given at 20 min intervals. On completion of the experiment, ventricular fibrillation was induced by rapid pacing. The heart was then excised with the needle electrodes left in place. Following fixation in formalin for at least 24 hours, the heart

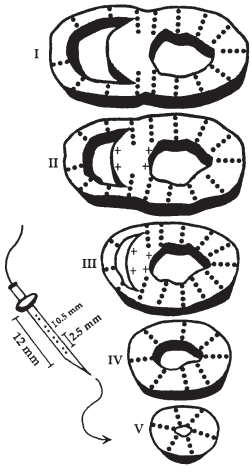

Fig. 1 Location of intramural electrode recording sites. An anterior-posterior projection of the heart is displayed in five sections (levels *I-V*) representing sequential slices from the AV ring at the top to the apex at the bottom. Dots represent bipolar electrode pairs along individual needles. Crosses in level *II* and *III* represent endocardial septal recording sites.

was cut transversely into slices approximately 8–10 mm thick. The insertion sites and directions of all pins were noted in relation to each other and to anatomical landmarks. The outline of each slice together with respective electrode positions was traced carefully on cross-sectional views of the heart, which were designated as levels I, II, III, IV and V from base to apex, and later enlarged for three-dimensional map construction (Fig. 1).

Data analysis

Details of the multiplexer recording system and the methods for constructing isochronal activation maps have been previously reported (25, 26). For off-line data analysis, electrograms were displayed and a time window of interest was chosen for processing. The moment of local activation for each individual electrogram was pre-selected by the computer. All computer selections were reviewed manually and revised if necessary. Activation times were calculated in relation to a time reference defined by the operator. In electrograms showing a sharp intrinsic deflection, the maximum first derivative was taken as the moment of activation, whereas in slow multiphasic electrograms, the peak of the major deflection was chosen. Based on local activation times at each electrode location, isochronal maps were constructed manually at 10 ms intervals to demonstrate the spread of activation. For interpolation of isochrones, it was required that the difference in activation time between adjacent electrode sites was less than 40 ms, and that the overall activation pattern would not allow for any other apparent possibility to activate respective electrode sites within the given activation times.

Definitions and interpretation

The region in which local activation was the earliest among all recognizable electrograms in each beat was defined as an *earliest activation site. Ventricular activation time* was defined as total duration of myocardial activity from the first to the last recorded activation in each individual beat. The activation pattern was considered to be *focal* when the site of initiation of a premature beat was remote from the site of termination of the preceding beat with no intervening depolarizations despite multiple intermediate recording sites (22). Obviously, a focal activation pattern might be caused by abnormal automaticity, triggered activity or protected micro-reentry and does, therefore, not imply an electrophysiological mechanism. *Ventricular tachycardia* was said to be present if there were more than three sequential premature complexes (PVCs) at a rate > 100/min. It was considered to be *sustained* if it persisted for more than 30 seconds without interruption. Ventricular tachycardia was referred to as being *monomorphic* if there were ectopic QRS complexes with uniform morphology, and as being *polymorphic* if there was more than one morphology of ectopic beats with a stable baseline between discrete forms.

Statistical analysis

Data are expressed as mean values ± standard deviation. Basic comparative statistics were performed using either a protected t-test or analysis of variance followed by a Student-Newman-Keuls test. A p-value < 0.05 was considered statistically significant.

Results

Incidence of arrhythmias

Administration of cesium chloride invariably produced significant arrhythmias, ranging from single PVCs to sustained monomorphic and polymorphic ventricular tachycardias. There was no apparent difference as to the spectrum of arrhythmias in dogs with a junctional or a ventricular escape rhythm.

More than 1000 single PVCs were observed, and 25 (i.e., 3–4 per dog) were randomly chosen for analysis. Polymorphic ventricular tachycardias, whether sustained or non-sustained, were observed in all dogs on at least one dose regimen. Monomorphic ventricular tachycardias were less common. Respective episodes turned out to be only non-sustained in 2 and both, sustained and non-sustained, in another 4 of the 7 dogs (Table 1). With 408 ± 88 ms for all monomorphic and 422 ± 96 ms for all polymorphic episodes, the mean cycle length of induced tachycardias was relatively long. There was, however, considerable variation from dog to dog and from episode to episode. Thus, some episodes would rather qualify

Table 1 Characteristics of all induced arrhythmias

	MVTns	MVTs	PVTns	PVTs
number of VT	20	11	70	17
number of beats	7 ± 5	–	8 ± 4	–
number of dogs	6	4	7	7
VT-CL (ms)	400 ± 96	424 ± 63	426 ± 88	400 ± 57
range (ms)	300 – 600	390 – 520	180 – 600	300 – 500
AT (ms)	78 ± 8	79 ± 5	75 ± 12	74 ± 15

MVTns/s nonsustained/sustained monomorphic ventricular tachycardia
PVTns/s nonsustained/sustained polymorphic ventricular tachycardia
VT-CL cycle length of ventricular tachycardia
range minimal and maximal value of cycle length
AT activation time

Table 2 Dose-dependency of induced arrhythmias

	MVTns			MVTs			PVTns			PVTs		
	d	VT	CL	d	VT	CL	d	VT	CL	d	VT	CL
bolus 1	3	8	348 ± 68	0	–	–	7	41	421 ± 94	0	–	–
bolus 2	3	11	433 ± 152	1	3	440 ± 34	3	19	429 ± 49	7	7*	450 ± 104#
bolus 3	1	1	(450)	3	8	418 ± 50	3	10	446 ± 120	6	10*	365 ± 24**
mean dose	1.65 ± 0.59			2.73 ± 0.47†			1.56 ± 0.73			2.53 ± 0.63‡		

* $p < 0.05$ vs. PVTs bolus1, respectively ** $p < 0.01$ vs. PVTns bolus 3
† $p < 0.05$ vs. MVTns, ‡ $p < 0.05$ vs. PVTns
# $p < 0.05$ vs. PVTs bolus 3
d number of affected dogs, *VT* number of ventricular tachycardia
CL cycle length of ventricular tachycardia
MVTns/s nonsustained/sustained monomorphic ventricular tachycardia
PVTns/s nonsustained/sustained polymorphic ventricular tachycardia
mean dose mean dosage required for induction of a specific arrhythmia

as idioventricular rhythms than as ventricular tachycardias, whereas others easily exceeded 300 beats per minute. At least two consecutive beats were analyzed for each of the 31 monomorphic ventricular tachycardias, and 3–10 beats for 47 of the 87 polymorphic tachycardias seen overall. Thus, 320 beats of arrhythmic events were looked at in detail. Since 81 ± 6 % of the 256 bipolar electrograms recorded in each dog were of sufficient quality to ensure a reliable determination of local activation times, this required analysis of more than 66000 individual electrograms.

Most sustained ventricular tachycardias were self-limited (n = 21, 75 %) and some were terminated by overdrive pacing (n = 5, 18 %). In case of degeneration into ventricular fibrillation, the experiments were stopped (n = 2, 7 %).

Dose-dependency of arrhythmias

All dogs had polymorphic PVCs after each dose. The number of PVCs per 20 minute interval was similar for the 1st, 2nd and 3rd dose of cesium chloride (48 ± 9, 51 ± 7 and 45 ± 6 PVCs, p = n.s., respectively). In contrast, the incidence of *non-sustained* ventricular tachycardias, irrespective of their morphology, tended to be inversely related to the cesium dose (p = n.s.). This was not only true for the number of dogs affected, but also for the total number of tachycardias observed. There was also a tendency for an increase in tachycardia cycle length with an increase in the cesium dose (p = n.s.). *Sustained* tachycardias, on the other hand, did not occur with the first bolus injection. The majority of *sustained monomorphic* tachycardias only developed after the third cesium dose, although one dog already demonstrated 3 episodes with the second bolus (p = n.s.). All 7 dogs exhibited *sustained polymorphic* tachycardias following the second injection of cesium chloride, and all but one with the third dose as well. The second and third bolus induced significantly more ventricular tachycardias than the first bolus ($p < 0.05$). Contrary to *non-sustained polymorphic* tachycardias, the cycle length of *sustained polymorphic* tachycardias decreased significantly with increasing cesium doses ($p < 0.05$, Table 2). Overall, the mean cesium dose inducing *sustained* ventricular tachycardias was significantly higher than that required for the induction of *non-sustained* tachycardias (2.61 ± 0.57 vs. 1.45 ± 0.61 mmol/kg, $p < 0.05$).

Three-dimensional activation maps

Single ventricular ectopic beats (PVC). There was no evidence for any dose-related differences in the activation patterns of the 25 PVCs analyzed. Thus, the following descriptions apply to all of them. The initiating focus was always found endocardially, 15 originating from the right and 10 from the left ventricle. All PVCs demonstrated a focal activation pattern with no evidence of reentry, as there was an interval of "electrical silence" between the latest activation of the preceding beat and the earliest activation of the PVC which on average lasted for 215 ± 28 ms. Still, protected micro-reentry could not be totally excluded. Activation times of PVCs were significantly longer than those of junctional beats (82 ± 11ms vs. 40 ± 10, $p < 0.05$). The increase in activation time was mainly due to the time needed for the impulse to traverse radially around the ventricle from the site of origin to the opposite side of the heart. Activation spread more rapidly throughout the endocardial layers

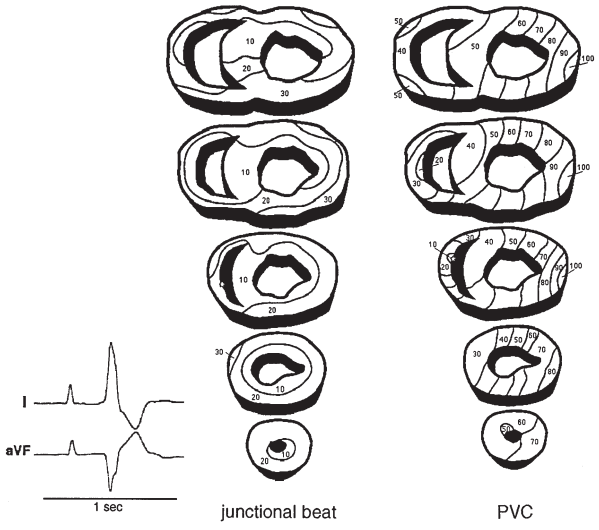

Fig. 2. Activation map of a junctional beat on the left and a PVC on the right side. The site of earliest activation during each beat is indicated by the white star. Each isochronal line includes electrode sites activated within the same 10 ms interval. Activation times are calculated relative to the earliest detected activation. Earliest activation of the junctional beat occurred in the right ventricular endocardium (level *III*); latest activation was found on the right ventricular epicardium at the AV groove (AT 28 ms). A 220 ms interval of electrical silence preceded the earliest activation of the PVC, again located in the right ventricular endocardium at level *III*. From this point the activation wavefront spread centrifugally along both axes of the heart (AT 96 ms).

of the myocardium, and spread from there to the epicardium. A representative example of an isolated PVC is shown in Fig. 2.

Non-sustained tachycardias – monomorphic and polymorphic. Irrespective of their morphology, and irrespective of the cesium dose applied, all non-sustained tachycardias exhibited a focal activation pattern with no apparent conduction delay or block; the focus was always located in the endocardium. Complete ventricular activation times for monomorphic and polymorphic non-sustained tachycardias were similar (Table 1). In monomorphic tachycardias, a single, constant focus would reproduce a more or less identical activation pattern from beat to beat. Polymorphic tachycardias, on the other hand, were bi- or multifocal in nature. The number of foci involved and the transition from one site of earliest activation to another suggested the differentiation of three different activation patterns: 1) Seemingly random, multifocal activation, where the site of earliest activation was different from beat to beat (67 %, type 1); 2) competitive bifocal activation, where two foci firing at variable rates would alternate in dominating the activation pattern (27 %, type 2); and 3) transitional, bi- to multifocal activation, where one site of earliest activation after initiating several monomorphic beats was gradually replaced by another one (6 %, type 3). For both, monomorphic and polymorphic tachycardias, the site of earliest activation was always found endocardially, with a slight preference for the right ventricle (59 vs. 41 %). Again, the location of the site of earliest activation was unrelated to the cesium dose applied.

A typical example of a relatively slow (480 ms) non-sustained monomorphic ventricular tachycardia observed in dog #3 after the second bolus of cesium is shown in Fig. 3. There was AV dissociation and the surface ECG displayed relatively narrow QRS complexes that were clearly different from the junctional beats. The earliest activation of each beat was located at exactly the same electrode pair at the inferior apical endocardium. Although the 10 ms isochrone extended transmurally, the activation sequence within isochrone 10 could be clearly delineated, due to an endoepicardial difference in activation time of 9 ms.

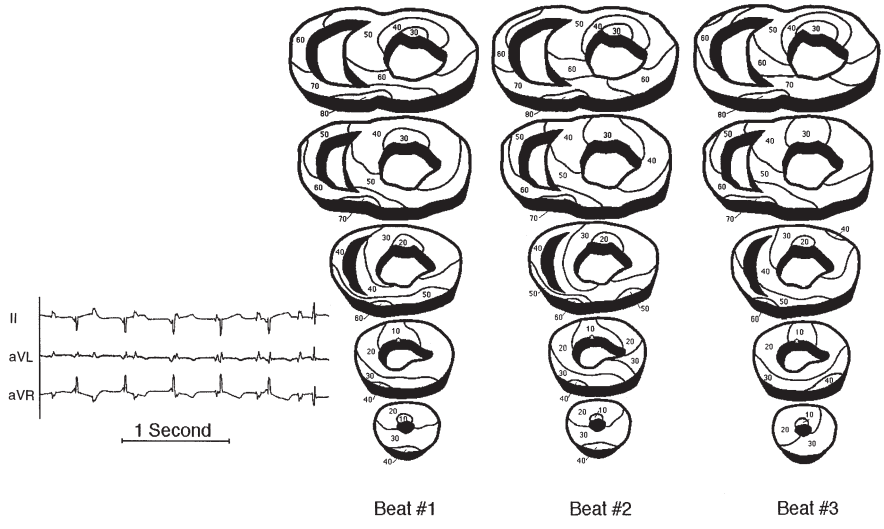

Fig. 3 Electrocardiographic leads *II*, aVL and aVR and three-dimensional activation maps of a slow, nonsustained run of a monomorphic ventricular tachycardia originating from an endocardial focus at the inferior part of the left ventricle at level *IV*. The three maps correspond to the first three beats seen in the ECG. The site of earliest activation and the overall activation pattern was identical for all beats. Activation spread centrifugally from the site of earliest activation (inferior endocardium, level *IV*) to the opposite site of the heart (anterior epicardium, level *I*).

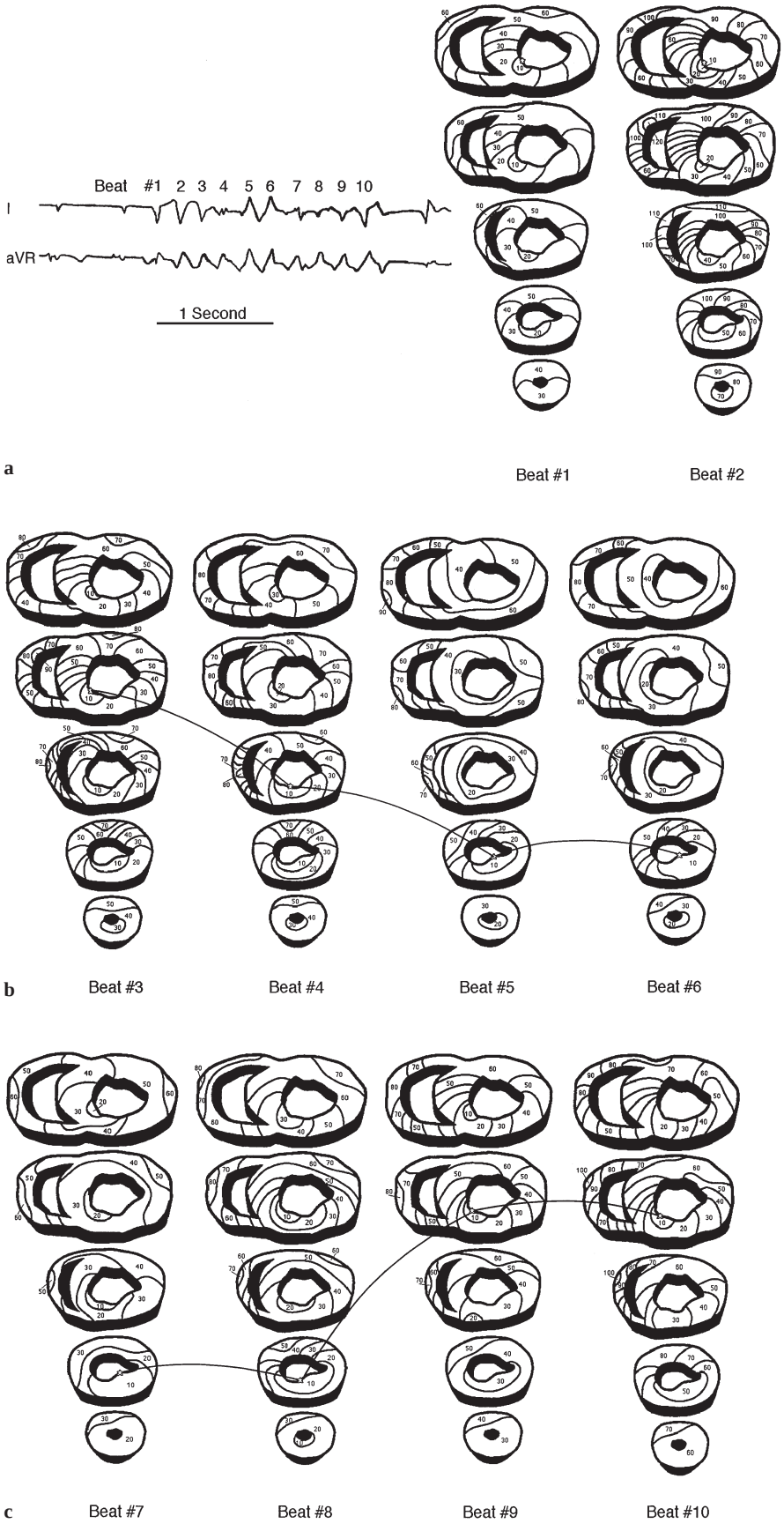

Fig. 4 Surface ECG and activation maps of a 10 beat run of a nonsustained polymorphic 'Torsade de pointes'-like ventricular tachycardia with seemingly random, multifocal activation. Beat 1 and 2 started at an endocardial site near the mitral ring at level *I* (AT 60 ms vs. 120 ms). With beats 3, 4, and 5, the site of earliest activation moved gradually to an endocardial site in the anterolateral left ventricular apex. For beats 6 and 7, the site of earliest activation remained at the apical location. Similar to beat 7, beat number 8 showed early activation at an antero-apical site, but also at a second site located closer to the AV ring, compatible with a fusion pattern. In beat 9 and 10, this more basal area became the only site of earliest activation. Consistent with the activation maps, the first 3 beats showed negative deflections on the ECG, then a positive morphology with beats 5 and 6 and again a subsequent move of the activation site produced a progressive change in QRS polarity towards a mainly negative deflection.

Figure 4 shows a representative example of a fast (Type 1) polymorphic ventricular tachycardia (CL 200 ms) induced by the first dose of cesium chloride in dog # 5. Some features of this ten beat run suggest a resemblance to "Torsade de pointes" tachycardias seen clinically: The underlying basic rhythm was relatively slow, the first beat of the tachycardia originated from the T-wave of the preceding normal beat and there was a shift in QRS axis and amplitude. Compared to all further intervals within the tachycardia, the coupling interval between the preceding normal beat and the first beat of the tachycardia was relatively long. The first beat started 322 ms after termination of the junctional beat at an endocardial site near the mitral ring, moving gradually to the anterolateral left ventricular apex over several beats and then back. The changing axis found on the surface ECG reflected the changing positions of the site of earliest activation in the map.

As with other beats, the 10 ms isochrone of beat 7 extended transmurally. Thus, the activation map seemed to suggest a large area rather than a site of earliest activation. However, looking at local electrograms and activation times within the 10 ms isochrone, as detailed in Fig. 5, the sequence of activation and the site of origin could be clearly appreciated.

Sustained tachycardias – monomorphic and polymorphic. Although sustained tachycardias were only inducible with the second and third bolus injection of cesium chloride, the activation patterns observed were not different from those seen in non-sustained tachycardias. There was also no apparent difference between sustained tachycardias elicited by the second or third cesium dose, respectively. Both, monomorphic and polymorphic sustained ventricular tachycardias were exclusively based on focal activation, the foci being located in the endocardium of the left or, more commonly, in the right ventricle (36 vs. 64 %). As with non-sustained tachycardias, monomorphic sustained tachycardias were due to monofocal activation. Sustained polymorphic tachycardias revealed a bi- or multifocal activation pattern classifying for one of the three types described above. Rather than type 1, type 2 (n = 7; 41 %) was most common in sustained polymorphic tachycardia, whereas type 3 was again a rare observation. Similar to the non-sustained tachycardia in figure 3, activation maps of type 1 sustained polymorphic tachycardias (n = 6; 35 %) demonstrated multiple foci in a sense that one focus would move from beat to beat whereas type 2 tachycardias revealed competing endocardial foci, with no intermediate sites

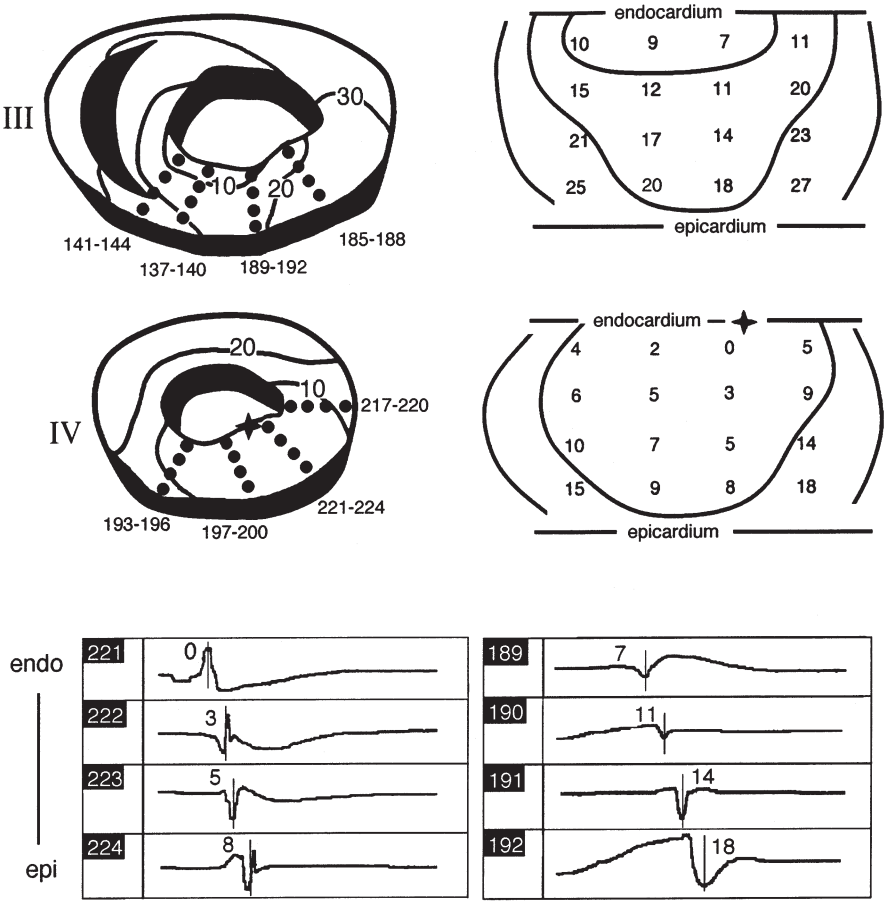

Fig. 5 Location of individual electrodes (black dots, top left panel), local activation times within the 10 and 20 ms isochrone (top right panel) and local electrograms recorded along two needles in levels *III* and *IV* during beat number 7 of the non-sustained tachycardia shown in Fig. 4. Earliest activation (black star) was recorded endocardially at electrode site 221.

between the separate origins. Sometimes focal sites appeared to discharge at different cycle lengths; however, these rates would vary in a repeating pattern. The site with the shorter cycle length would initiate 2 to 3 beats at the shorter cycle length, but then slow, such that the next beat expected at that cycle length would not appear. Instead, a beat from the other site discharging at the slower cycle length would take over. The slower site would then provide the rhythm for several beats until the faster site would again transiently override it. However, the slower site also did not run at a constant interval, as the period of interruption of the slower rhythm by the faster rhythm was not a multiple of the slower rhythm's cycle length. This indicates that there was some interaction between the two automatic sites, as it seemed that they would both inhibit and perhaps trigger each other's activity. Characteristic of type 3 tachycardias (n = 4; 24 %) were gradually changing QRS morphologies due to a wandering position of the site of earliest activation, with no significant change in the firing rate of the focus. This would seem to indicate a moving focal site, as there was little evidence of two competing sites, and there was no significant shift in heart rate to indicate either overdrive suppression of one site by a faster site, or a slower escape rhythm that emerged after gradual slowing of a previously dominant site.

Discussion

This study demonstrates that ventricular arrhythmias induced by bolus injections of cesium chloride in dogs with acute AV block exclusively exhibit focal activation patterns, with the site of earliest activation being located in the left or, more commonly, right ventricular endocardium. Although there is a dose-dependence as to the sustenance of induced mono- or polymorphic tachycardias, this does not reflect on the general spread of activation. Thus, irrespective of the dose applied, macroreentry does not seem to play a major role as a mechanism of cesium induced arrhythmias. This is not only true for the initiation, but also for the maintenance of induced tachycardias.

Methodological considerations

Although the insertion of multiple plunge electrodes represents a vigorous intervention, earlier studies could exclude major hemodynamic compromise or changes in the epicardial activation pattern as a result thereof (23). The fixation of reentrant circuits to the inhomogeneities created by the plunge electrodes might be another problem. As this was never detected in our experiments, it is unlikely to have interfered with data collection. The resolution in this model still allowed for 0.5 to 1.0 cm gaps between individual needles. Moreover, the interventricular septum was only mapped endocardially and potentially with even larger gaps between individual electrode catheters. However, as few of the arrhythmias showed initiation from the septum, and as no macroreentry was seen in other parts of the ventricles that were fully recorded, it is unlikely that any such mechanism occurred.

Controversy exists as to the determination of local activation times. While some authors chose the maximum amplitude (peak criterion) of the bipolar electrogram to define local activation (17, 22, 23), others (1, 5, 7, 8, 25, 26) relied on a maximum slope function in electrograms showing a sharp intrinsic deflection combined with the peak criterion only in slow multiphasic potentials. Investigators (15, 19, 20) who compared different electrode configurations concluded that both criteria were highly correlated with the local activation of the unipolar electrogram (intrinsic deflection). In our study the primary criterion used to determine local activation was the maximum slope function (~90 %) whereas the peak criterion was only used if no sharp deflection could be clearly defined (~10 %). Furthermore, as activation maps reflect the sequence of activation at multiple recording sites relative to each other, the criterion to determine local activation times seems to be of minor relevance, as long as all electrograms are evaluated identically.

Although monomorphic ventricular tachycardia, polymorphic ventricular tachycardia and ventricular fibrillation may as well occur in patients with the acquired long QT syndrome (13), our data must be interpreted with caution when relating to human arrhythmias. Nayebpour et al. already indicated the limitations of cesium chloride injections in dogs as a model of the long QT syndrome (18). Thus, the results and interpretation of our data should only be applied to the cesium chloride model of arrhythmias.

In experimental models (27, 11), the anesthetic agent pentobarbital has been shown to block potassium channels and thus affect the incidence of arrhythmias induced by repolarization prolonging agents. In this respect, the use of pentobarbital may also have affected the overall incidence of arrhythmias in our study. However, the focus was on the actual activation pattern, the site of earliest activation and the incidence of arrhythmias relative to the cesium dose applied, parameters which are very unlikely to be affected by pentobarbital.

Comparison with previous studies

Several reports in the literature indicate that the type and mechanism of ventricular arrhythmias induced by cesium chloride differs with the dose applied. Nayebpour et al. (18) observed sustained monomorphic and polymorphic ventricu-

lar tachycardias only after the second and third bolus of cesium (1 mmol/kg), but non-sustained tachycardias in 2 of 6 dogs after the first injection. Overdrive pacing most commonly caused acceleration for several beats, but could also lead to overdrive suppression or, rarely, to conversion to sinus rhythm. The authors concluded that the relatively moderate arrhythmogenicity of single cesium boli was based on mechanisms analogous to the long QT syndrome, whereas the more severe and sustained arrhythmias observed after repeated bolus administration might be due to other mechanisms, e.g., delayed afterdepolarizations or abnormal automaticity at low resting membrane potentials.

In Japanese white rabbits, Takahashi et al. (31) similarly found only isolated or coupled PVCs after a single cesium injection (1 mmol/kg), but non-sustained polymorphic ventricular tachycardias with the second, and sustained monomorphic tachycardias with the third dose (administration interval 20 min). Based on the response of these arrhythmias to vagal stimulation, they suggested that polymorphic tachycardias were triggered by early afterdepolarizations, but that monomorphic ventricular tachycardias were of different origin.

Recently, Murakawa and colleagues published three-dimensional activation patterns of cesium induced ventricular arrhythmias (17) (dosage 1 mM/kg). They found all monomorphic and polymorphic ventricular tachycardias to be based on focal activation, the foci being located endocardially or midmyocardially. However, the number of polymorphic tachycardias analyzed was very small (n = 8), and it was not specified how the number of cesium boli correlated with duration and morphology of induced arrhythmias. Complementing these findings, we demonstrated a positive correlation between the number of cesium boli and the sustenance of induced arrhythmias, whereas the spread of activation remained unaffected. In analogy to the study by Murakawa et al. (17), cesium induced arrhythmias were found to be exclusively based on focal mechanisms; while subendocardial as well as midmyocardial foci were encountered in the latter study, the foci detected in our study were exclusively located in the subendocardium. Obviously, any mismatch between wall thickness and needle length holds the potential for erroneously favoring subendocardial or midmyocardial sites, respectively. Our needle electrodes were 12 mm in length, whereas Murakawa et al. used needles that were 10, 13, and 20 mm long. According to previous studies in dogs with comparable body weight, left ventricular wall thickness averaged 7.1 ± 1.2 mm (14) and 9.2 ± 0.8 mm (5), respectively. Consistent with these data, the needles used in our study always reached or penetrated the endocardium, as confirmed by postmortem examination. Only with needles too short, one might misinterpret midmyocardial foci as being subendocardial. With needles too long, endocardial foci could be erroneously identified as midmyocardial. As we only identified endocardial foci, this was obviously not the case in our study, but might explain the occurrence of midmyocardial foci in the study by Murakawa et al. (17).

A different long QT model using the I_{Kr} blocker anthopleurin A (7) supports the relevance of subendocardial focal activity for induction of polymorphic ventricular tachycardia, but differs from our results with respect to the fact that both reentrant and focal mechanisms were found to maintain respective tachycardias.

Focal versus reentrant activation

The results of this and of Murakawa's study (17) indicate that all individual and repetitive ventricular arrhythmias induced by cesium chloride in normal dogs are of a focal nature. The activation patterns are consistent with the non-reentrant mechanisms seen with three-dimensional mapping in animal studies of acute myocardial infarction and in human studies of ventricular tachycardia (21–24). Our experiments show a clear spatial and temporal difference between the latest activation of the preceding beat and the initiation of the index beat. No reentrant circuits were seen, and no evidence of the prerequisites for reentry such as conduction block or localized slow conduction were evident. There was electrical silence at all of the electrode pairs surrounding the initial site for at least 150 ms prior to the activation of any given beat. The electrode spacing in most areas where foci were found was close, being no more than 10 mm between electrode pairs around the site of earliest activation. Given the area of myocardium unrecorded and the time between local electrical activations recorded at adjacent sites, reentrant circuits mimicking focal activation would have had to be less than one centimeter in diameter. Conduction this slow was not seen in any mapped areas of the hearts. Furthermore, given the multiple sites of earliest activation, suspected circuits would have had to occur at many different sites in the heart, in each case exactly between the recording electrodes. Finally, the activation wavefront spread in a centrifugal fashion from the site of earliest activation, suggesting homogeneous refractory patterns, which are not easily compatible with a reentry circuit exiting at that site. Still, the possibility that a small, self-contained reentrant circuit could have produced at least some of the seemingly focal activation patterns cannot be totally excluded.

Surface ECG and activation patterns

The moving ECG patterns were related to moving foci, an observation that was also made in similar studies (17). These foci could gradually migrate from one point to another, competitively alternate between two sites, or randomly change from beat to beat. The interaction of respective sites did not appear to be simply one dominant site slowing and being over-

taken by a second escape rhythm, but these foci seemed to trigger each other's activity with one site speeding up to take over dominance coincident with slowing of the original site. Focal activation patterns are consistent with either triggered activity or abnormal automaticity. Triggered activity has been previously demonstrated in single cell experiments with action potential prolonging agents – due to either EADs or DADs. Such activity easily explains pause-dependent isolated ectopic beats, but cannot completely explain polymorphic ventricular tachycardias, as our traditional understanding of triggered activity requires a pause prior to the initiation of a subsequent beat. How any site can develop triggered activity during a run of polymorphic ventricular tachycardia originating from a separate site is difficult to understand using present concepts. Perhaps this is due to some form of local entrance block, or interactions in multicellular substrates that have not yet been explained by single cell experiments.

Polymorphic ECG patterns based on bi- or multifocal activation have also been described in previous studies. Bardy et al. (4) performed epicardial surface mapping of canine hearts during pacing from two separate endocardial sites. By gradually changing the rates of the two pacemakers such that the sites would alternate dominance, they could produce a twisting ECG morphology. This was similar to the epicardial activation maps recorded during induced polymorphic ventricular tachycardia from quinidine and hypokalemia. Inoue (12) showed a similar focal pattern with epicardial mapping in the same model, but in this case felt that the moving ECG pattern was due to moving foci.

Site of earliest activation

All focal sites seemed to originate from the endocardium or immediate subendocardial region. The spread of activation from the point of origin was universally faster in the subendocardial levels, consistent with spread throughout the faster conducting His-Purkinje system, whereas it was slower from the endocardial to the more epicardial levels, suggesting that the arrhythmias were caused by repetitive focal activity within the Purkinje fibers.

In response to QT prolonging agents and bradycardia, mid-myocardial M cells may produce EADs and triggered activity (29, 30). Most of the M cells are located in the deep subepicardial levels of the myocardium (28); however, they are also found in the deep subendocardial levels of the anterior wall, papillary muscles, trabeculae, and the interventricular septum. While some authors (17) suggest that both myocardial muscle fibers and Purkinje cells are a substrate for cesium-induced ventricular arrhythmias, no activations originating from the mid-myocardial or sub-epicardial levels of the ventricles were seen in our study. It is possible that some of the endocardial foci could have originated from sub-endocardial M cells. However, earliest activation occurred from all subendocardial areas of both ventricles, and predominantly from the right ventricle. Thus, endocardial Purkinje cells are a more likely source, since they are distributed throughout the endocardium; the preference to the right ventricle may be due to a longer action potential duration of Purkinje fibers in the right compared to the left ventricle although this regional difference has not yet been elucidated. Consistent with this interpretation, Antzelevitch and co-workers found that early afterdepolarizations are not readily inducible in M cells coupled to epicardium and endocardium, as in the arterially perfused wedge preparation or, accordingly, in the intact ventricle (2).

Conclusions

Although cesium chloride induces different types of arrhythmias at different doses, the underlying activation patterns are exclusively focal and of subendocardial origin. With I_{Kr}-blockers or sea anemone toxins, on the other hand, reentry seems to be involved in arrhythmias mimicking the electrocardiographic morphology of Torsade de pointes. Thus, various drugs may induce arrhythmias with similar ECG morphologies, but different electrophysiologic mechanisms.

Acknowledgment This study was supported by a grant from the Deutsche Forschungsgemeinschaft, Bonn, Germany within the Sonderforschungsbereich 320 „Herzfunktion und ihre Regulation“, University of Heidelberg, Germany.

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