Programmed Electrical Stimulation and Drugs Identify Two Subgroups of Ventricular Tachycardias Occurring 16–24 Hours After Occlusion of the Left Anterior Descending Artery

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Background. Spontaneous sustained ventricular tachycardia (VT) occurring 16–24 hours after left anterior descending (LAD) coronary artery occlusion in the canine heart is most likely based on abnormal automaticity. In vitro, it has been demonstrated that the rate of the arrhythmia and the effect of overdrive pacing depends on the maximal diastolic potential (MDP). The MDP is also of importance in understanding the effect of antiarrhythmic drugs. To study 1) the possible presence of different responses to overdrive pacing and 2) the relation between the response to overdrive pacing and the effect of different antiarrhythmic drugs in the intact heart, we investigated the effect of 1) (prolonged) pacing and 2) lidocaine (3 mg/kg), verapamil (0.4–1.0 mg/kg), or flunarizine (2 mg/kg) during VT.

Methods and Results. In 21 conscious dogs with chronic atrioventricular block, 60 sustained VTs were observed 1 day after LAD occlusion. During VT, pacing with interstimulus intervals of 400, 300, and 200 msec for 15, 60, and 120 seconds was done on 40 VTs. Based on their response to pacing, VTs were divided into a pacing-suppressible (PS group) and a pacing-nonsuppressible group (PNS group). The mean cycle length in the PS group was significantly longer (410 ± 50 msec) than in the PNS group (360 ± 35 msec, p < 0.01). Suppression was directly related to the rate and duration of pacing. Spontaneous recurrence of VTs was observed after 26 ± 45 seconds. Lidocaine and verapamil increased cycle length of the suppressible VTs and terminated them, whereas flunarizine had no effect. Except for verapamil, which increased cycle length of the VTs, no effects were seen in the PNS group.

Conclusions. In conscious dogs showing sustained VTs 16–24 hours after LAD occlusion, 1) the slower VTs can be suppressed by pacing, verapamil, and lidocaine but not by flunarizine, and 2) the faster VTs are not affected by pacing, lidocaine, and flunarizine, and are only slowed by verapamil. These findings are compatible with in vitro findings of abnormal automaticity, with the slower VTs originating from a higher MDP than the faster VTs. (Circulation 1992;85:747–755)

Since 1950,1 the conscious dog model of spontaneous ventricular tachycardia (VT) occurring 16–24 hours after occlusion of the left ante-

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Abnormal automaticity is defined as spontaneous impulse generation originating from a reduced maximal diastolic potential (MDP), normally showing a high diastolic membrane potent-

tial of -80 to -90 mV. The rate of these arrhythmias in vitro and their response to overdrive stimulation is dependent on the amount of reduction of the MDP.

After LAD occlusion, sustained VTs with varying QRS configuration have been observed in the intact heart. These different configurations likely represent different foci originating in Purkinje fibers localized at the subendocardial border of the infarcted area. The purpose of our investigation was to study 1) the response of these VTs to overdrive pacing, and 2) to compare the relationship between this response and the effect of three antiarrhythmic drugs: lidocaine, verapamil, and flunarizine. It was hypothesized that the VTs that were suppressible by pacing originated from a higher MDP, involving a channel in which current is mainly carried by sodium. Lidocaine should suppress these VTs according to its effect against automatic depressed fast responses. Because verapamil reduces phase 4 depolarization over a wide range of MDPs, this drug might also be effective against these VTs. On the other hand, VTs not responding to pacing were thought to originate from a lower MDP, with mainly the involvement of a Ca2+-dependent channel (slow responses). Verapamil was expected to be effective against those VTs, whereas lidocaine should have no effect. To investigate a possible role of triggered activity as the underlying mechanism, we also administered flunarizine, a drug that specifically abolished ouabain-induced VTs in vivo and suppressed DADs in vitro.

Methods

Preparation of Study Dogs

A total of 30 mongrel dogs of either sex with body weight between 20 and 31 kg (mean, 26 ± 4 kg) were used. The animals underwent two operations at least 3 weeks apart: The first one aimed to induce atrioventricular (AV) block, and the second one to occlude the LAD. During both operations, the dogs were anesthetized with premedication (droperidol 5 mg i.m. and fentanyl 0.1 mg i.m.) and sodium pentobarbital (20 mg/kg i.v.). Anesthesia was maintained with a mixture of oxygen, nitrous oxide, and halothane. During the first (right-sided) thoracotomy, formalin (37%) was injected into the region of the bundle of His to induce AV block. At the same time, one electrode was sutured on the basal part of the right ventricle and another one on the apex of the left ventricle. These electrodes (Bakken Research Center, Medtronic, Maastricht, The Netherlands) were exteriorized through the skin of the dorsal surface of the neck. During the second (left-sided) thoracotomy, the two-stage Harris protocol was applied. In 15 animals, we attempted to induce a small infarction by ligating the second diagonal branch of the LAD (group A), whereas in the other 15 dogs, the original protocol of ligating the LAD 1 cm under the left atrium was applied (group B). Proper postoperative care was taken according to the statement of the American Physiological Society. Of these 30 animals, five dogs died within the first 18 hours. These dogs all belonged to the latter group. No deaths occurred in the first group, but four dogs had to be excluded because of absence of sustained arrhythmias. Therefore, the study was performed in 21 conscious dogs.

Experiments

With the animals lying on the floor, six external electrocardiographic (I, II, III, aVR, aVL, and aVF) and one epicardial lead were simultaneously registered on an ink-jet recorder (Siemens Elema, The Hague, The Netherlands) and stored on tape. PACING was performed with a programmable stimulator with a synchronizing circuit. Unipolar stimuli were given with a stimulus strength of twice diastolic threshold. Using a computerized QRS complex detecting system, values of RR intervals were continuously displayed on a monitor screen, allowing instantaneous evaluation of the ventricular cycle length.

When VT was present, all animals were studied twice: once at 16–18 hours and again at 22–24 hours after LAD occlusion. The spontaneous VT was recorded during a period of 20 minutes and the different QRS configurations were observed. In the case of a different VT dominantly present in the second session, the pacing protocol was performed on this VT, and the same drug as in the first session was administered.

In the case of the same VT dominantly present in the second session, we repeated the pacing protocol and administered a second drug only when lidocaine was given in the first session. Concerning the latter VTs, we did not observe any difference in rate or in response to pacing at these two episodes.

Overdrive Pacing

Stimulation was started when a particular VT configuration had been present for at least 1 minute. Stimulation during 15, 60, and 120 seconds was performed using interstimulus intervals of 400, 300, and 200 msec. We started with short-lasting pacing trains, but randomly varied the interstimulus intervals. Stimulation was preferably done on the right ventricle.

The QRS configuration(s), QRS width, and mean of 10 RR intervals before (VTCLpre) and after pacing (VTCLpost) were assessed by three independent observers. Also, the QRS configuration and the interval from the last paced beat to the first spontaneous QRS complex were determined (coupling interval). Suppression of VT by pacing was defined as a ventricular standstill or a ventricular rhythm with a different morphology having a cycle length longer than 800 msec for at least 5 seconds within 10 seconds after pacing. In the case that VT could be suppressed at least twice, the pacing protocol was ended and the longest interval of the idioventricular escape rhythm, the time to spontaneous recurrence of VT, and VTCL were measured. The VTs were divided
into a pacing-suppressible (PS) group and a pacing-nonsuppressible (PNS) group.

Drugs

At least 5 minutes after termination of the pacing protocol, a drug was administered during VT. The following dose regimens were used: flunarizine, 2 mg/kg/2 min; lidocaine, 3 mg/kg/2 min; and verapamil, 0.4–1.0 mg/kg/3 min (mean, 0.8±0.3 mg/kg). The pacing protocol was not repeated and the effect of the drug was registered during 30 minutes. Flunarizine was given during 13 VTs in 10 dogs, lidocaine during 11 VTs in nine dogs, and verapamil during nine VTs in eight dogs.

Postmortem Examination

At least 1 week after the experiments, the animals were anesthetized and the hearts were excised. In 15 hearts (eight of group A and seven of group B), we determined size of the infarction. First, the exact site of the ligation was assessed, followed by visualization of the infarct by inspection of the left ventricle (LV). For this purpose, the latter was cut into 0.5-cm-thick transverse sections from apex to base, parallel to the AV groove. In some animals of group A, the slices were incubated in nitro blue tetrazolium (NBT). In most animals, the infarcted area was clearly visible, avoiding the necessity of NBT staining. Thereafter, total LV mass and the infarcted tissue mass (unstained area, in the case of NBT staining) were measured. Infarct size was expressed as the ratio of infarcted tissue to total LV mass.

Statistics

For statistical testing, we used analysis of variance (ANOVA) to determine significance between more than two groups, such as behavior of the first postpacing interval in relation to interstimulus intervals or duration of pacing. When the F value permitted, additional analysis using Bonferroni's t test was applied. Student's t test was used to compare data between two groups, and χ² testing was applied when the data were presented as percentages. Significance was considered present at a value of p≤0.05. All data were expressed as mean±SD.

Results

QRS Configuration of VT

Sustained VTs were observed in all 21 animals investigated between 16 and 18 hours and in 18 of 21 dogs investigated between 22 and 24 hours after LAD occlusion. A total of 60 different VTs were seen. The number of different VT configurations varied between one and seven (mean, 2.6±1.6) per dog. Usually, one QRS configuration was dominant during a time period of sufficient length to study the effect of the interventions. Competition between different foci was seen that resulted in continuous fusion and multiform VT; because of this phenomenon, an additional three experiments (two at 18 hours and one at 24 hours) were excluded. One dog died at 24 hours due to pacing-induced ventricular fibrillation. Therefore, the results of 40 different configurated VTs are presented.

Programmed Electrical Stimulation

Suppression. A total of 238 stimulation trains were applied to these 40 VTs. Pacing suppressed 25 VTs (PS group, 63%). An example is given in Figure 1 in which overdrive pacing resulted in 1) suppression of VT, 2) a short first postpacing interval, 3) a longest interval of 9,520 msec, and 4) recurrence of VT after 11 seconds. An example of a nonsuppressible VT is presented in Figure 2.

The VTCLpre of the PS group was significantly longer (410±50 msec) than in the PNS group (360±35 msec, p≤0.01). There was no difference in QRS width between the groups (82±15 versus 85±17 msec, respectively). Suppressible and nonsuppress-
TABLE 1. Suppression of Ventricular Tachycardias in Relation to Pacing Interstimulus Interval and Duration of Pacing

<table>
<thead>
<tr>
<th>Interstimulus interval (msec)</th>
<th>Duration of pacing</th>
<th>400</th>
<th>300</th>
<th>200</th>
</tr>
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<tr>
<td>0.19%</td>
<td></td>
<td>15</td>
<td>92</td>
<td>22</td>
</tr>
<tr>
<td>40/110=36%*</td>
<td>60</td>
<td>430</td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>46/109=42%*</td>
<td>120</td>
<td>435</td>
<td>67</td>
<td>54</td>
</tr>
</tbody>
</table>

*p≤0.001 compared with 400 msec.
†p≤0.05 compared with 15 seconds.

TABLE 2. Effects of Interstimulus Interval

<table>
<thead>
<tr>
<th>Interstimulus interval (msec)</th>
<th>PNS group</th>
<th>VTCLpre</th>
<th>VS-V</th>
<th>VTCLpost</th>
<th>PS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td></td>
<td>380±25</td>
<td>430±65</td>
<td>385±45</td>
<td>350±45*</td>
</tr>
<tr>
<td>300</td>
<td></td>
<td>415±50†</td>
<td>925±1,380</td>
<td>425±50</td>
<td>420±65‡</td>
</tr>
<tr>
<td>400</td>
<td></td>
<td>415±50†</td>
<td>725±940</td>
<td>420±65‡</td>
<td>2,980±2,495</td>
</tr>
</tbody>
</table>

PS, pacing-nonsuppressible; VTCLpre, cycle length tachycardia pre-pacing; VS-V, first postpacing interval; VTCLpost, cycle length tachycardia post-pacing; PS, pacing-suppressible; LI, longest interval after suppression.

*p≤0.01 compared with 300 msec.
†p≤0.05 compared with 400 msec.
‡p≤0.05 compared with VTCLpre.

Figure 2. Tracings show effect of overdrive pacing on a ventricular tachycardia (VT) in the pacing-nonsuppressible group. Overdrive pacing for 120 seconds, using 600 stimuli (n(Vs)) and an interstimulus interval (Vs-Vs) of 200 msec was performed from the left ventricle. VT has a cycle length of 340 msec (left panel). Pacing (s) did not result in suppression of the VT or in modification of VT cycle length. First postpacing interval had a length of 340 msec.

Data were expressed as a fraction of VTCLpre (p≤0.05) to correct for the difference in VTCL between the subgroups. Second, shortening of the interstimulus interval in the PS group resulted in blunting of overdrive suppression: An initial lengthening of the first postpacing interval seen when the interstimulus interval was decreased from 400 to 300 msec was followed by a subsequent shortening of the coupling interval on a further reduction of the pacing interval from 300 to 200 msec. These data, however, did not reach significance. The longest intervals after suppression showed no differences. After pacing, some subgroups showed a small increase in VTCL. This reached significance (p≤0.05) only in the 200-msec subgroup of the PS group. Lengthening the duration of pacing (Table 3) did not modify the first postpacing interval in the PNS group but significantly increased this variable in the PS group (p≤0.05). Again, most subgroups demonstrated a small increase in VTCLpost, whereas no difference in the longest intervals was measured.

Drugs

PS group. Lidocaine was administered to six VTs, verapamil to five, and flunarizine to eight (Table 4). Lidocaine increased VTCL from 445±55 to 485±80 msec (p≤0.05) and suppressed five of the six VTs. An example is given in Figure 4. Verapamil increased VTCL (p≤0.05) and suppressed all tachycardias (five of five). Flunarizine did not change VTCL and suppressed only 1 of 8 VTs. After suppression of VT by lidocaine, backup pacing was often needed to overcome the concomitant suppression of the idioventricular rhythm (Figure 4). This was not seen with verapamil.

PNS group. Lidocaine was given to five, verapamil to four, and flunarizine to five VTs (Table 4). Only verapamil increased the VTCL in this group (340±65 to 400±55 msec, p≤0.05), but it did not induce suppression (none of four). An example is given in
Figure 5. Neither lidocaine nor flunarizine modified VTCL or suppressed VTs in five cases.

Infarct Size

Mean infarct size was 9.1 ± 6.4% of the left ventricle. In group A, the size was 3.9 ± 2.2%, whereas the size of the infarcts in group B accounted for 15.1 ± 3.3% of the left ventricle. Cycle length of the VTs was longer in group A (415 ± 50 msec) than in group B (355 ± 45 msec, p = 0.001). Second, the ability to suppress VTs in group A was higher (73%) than in the larger infarcts (57%, p = 0.001). The number of VT configurations differed also (3.9 ± 2.3 in group B versus 2.6 ± 1.4 in group A), although it did not reach significance.

Discussion

Arrhythmias occurring 1 day after LAD occlusion (the Harris model) are widely used to test the efficacy of antiarrhythmic drugs.2–5 The mechanism underlying these VTs is probably abnormal automaticity.12–21 Triggered activity resulting from DADs as a cause for the perpetuation of these arrhythmias is less likely, as will be discussed later.

In vitro, it has been demonstrated that automatic arrhythmias differ in their response to overdrive pacing13,23 and drugs,13,24–27,34 depending on their MDP. In the case of a high MDP (≥ –70 mV), an Na⁺-dependent channel is likely to play an important role in depolarization. Therefore, either activation of the Na⁺,K⁺ ATPase by overdrive pacing23 or the use of drugs such as lidocaine, which blocks the depressed fast response and/or suppresses the depolarization, is highly effective in suppressing VTs arising from a high MDP.24–26 The effect of verapamil was more difficult to predict. It either might be effective against these VTs because of its suppressive effect on phase 4 depolarization over a wide range of MDPs or its dose-dependent blocking effect on the depressed fast response.27,28 Arrhythmias having a less negative MDP (≤ –60 mV) are faster and are more likely to arise through a Ca²⁺-dependent channel. Even prolonged overdrive pacing does not result in arrhythmia suppression, and only drugs with Ca²⁺-channel blocking properties are effective.13,23,26,27 They either suppress phase 4 depolarization at this MDP or block the slow response. Dangman and Hoffman23 also described an intermediate group (between –60 and –70 mV) that only responded to overdrive pacing with long duration and/or fast stimulation rates.

Table 3. Effect of Changes in Duration of Pacing

<table>
<thead>
<tr>
<th>Duration (seconds)</th>
<th>15</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNS group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTCLpre</td>
<td>365±40</td>
<td>365±35</td>
<td>355±45</td>
</tr>
<tr>
<td>Vs-V</td>
<td>385±85</td>
<td>405±80</td>
<td>365±75</td>
</tr>
<tr>
<td>VTCLpost</td>
<td>380±60</td>
<td>370±35</td>
<td>360±40</td>
</tr>
<tr>
<td>PS group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTCLpre</td>
<td>410±55</td>
<td>410±50</td>
<td>420±55</td>
</tr>
<tr>
<td>Vs-V</td>
<td>515±130</td>
<td>905±1,250*</td>
<td>1,160±1,755*</td>
</tr>
<tr>
<td>VTCLpost</td>
<td>420±60†</td>
<td>430±55†</td>
<td>420±50</td>
</tr>
<tr>
<td>LI</td>
<td>2,580±2,560</td>
<td>3,040±2,330</td>
<td>2,550±2,645</td>
</tr>
</tbody>
</table>

PNS, pacing-nonsuppressible; VTCLpre, cycle length tachycardia pre-pacing; Vs-V, first postpacing interval; VTCLpost, cycle length tachycardia postpacing; PS, pacing-suppressible; LI, longest interval after suppression.

* p ≤ 0.05 compared with 15 seconds.
† p ≤ 0.01 compared with VTCLpre.

Table 4. Effects of Lidocaine, Verapamil, and Flunarizine During Ventricular Tachycardia

<table>
<thead>
<tr>
<th></th>
<th>PS group</th>
<th>PNS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTCLpre</td>
<td>445±55</td>
<td>365±80</td>
</tr>
<tr>
<td>VTCLpost</td>
<td>485±80*</td>
<td>370±70</td>
</tr>
<tr>
<td>VT suppression</td>
<td>5/6</td>
<td>0/5</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTCLpre</td>
<td>405±40</td>
<td>340±65</td>
</tr>
<tr>
<td>VTCLpost</td>
<td>445±65*</td>
<td>400±55*</td>
</tr>
<tr>
<td>VT suppression</td>
<td>5/5</td>
<td>0/4</td>
</tr>
<tr>
<td>Flunarizine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTCLpre</td>
<td>445±45</td>
<td>395±30</td>
</tr>
<tr>
<td>VTCLpost</td>
<td>430±50</td>
<td>360±40</td>
</tr>
<tr>
<td>VT suppression</td>
<td>1/8</td>
<td>0/5</td>
</tr>
</tbody>
</table>

PS, pacing-suppressible; PNS, pacing-nonsuppressible; VTCLpre, cycle length tachycardia pre-pacing; VTCLpost, cycle length tachycardia postpacing; VT, ventricular tachycardia.

* p ≤ 0.05 compared with VTCLpre.
In the intact heart, the following observations support that different MDPs are also present: 1) the inconsistent results of antiarrhythmic drugs,2-15 2) the described relation between the response of these arrhythmias to drugs and the rate of the VT,4,5,35 3) differences in the ability to suppress the VT by pacing,12-15,18,21,35 and 4) the observation that pacing-induced suppression was dependent on the rate of the arrhythmia.21,35 A limitation of the previous investigations is the difficulty in studying the behavior of the VTs (or specific QRS configurations during VT) because of interference of conducted sinus beats. Therefore, our experiments were performed in conscious dogs with chronic complete AV block.

Programmed Electrical Stimulation

Suppression. In 63% of VTs, it was possible to suppress the arrhythmia completely by overdrive pacing. Suppression was dependent on the rate of VT and the stimulation mode. The slower the VT and/or the faster and longer the stimulation train, the greater the chance that the VT was suppressed. These data are consistent with in vitro observations23 and previous findings in the intact heart.21,35

According to in vitro results, the suppressible VTs are likely to originate from high and/or intermediate MDP. VTs originating from high MDP are likely to be suppressed by short and/or slow pacing, whereas intermediate forms had to be paced longer and faster. The mechanism of suppression is explained by activation of Na⁺,K⁺-ATPase, which hyperpolarizes the cell membrane.23 Recurrence of VT, which was observed after all instances of VT suppression, is explained by the gradual spontaneous decrease of the MDP to prepacing values. The nonsuppressible VTs are likely to originate from a low MDP.

When the interstimulus intervals were expressed as a fraction of VT rate, no differences were found between the PS and PNS groups, indicating that pacing rate per se was not responsible for the difference seen between the two groups.

First postpacing interval and VT cycle length. In the PNS group, we noticed the following responses to pacing: 1) a shortening of the first postpacing interval on decreasing the interstimulus interval, and 2) no change in length of the first postpacing interval when the duration of pacing was increased. The reduction in first postpacing interval remained present after corrections were made for VTCLpre. This behavior has been described to be specific for VTs resulting from DADs.36-39

In the PS group, an increase in the first postpacing interval was expected when the interstimulus interval was reduced and/or the duration of pacing was increased.23 This behavior typical for overdrive suppression was only clearly present after changing the duration of pacing. Decreasing the interstimulus interval from 400 to 300 msec resulted in the expected lengthening of the first postpacing interval. However, this was followed by a decrease when the pacing interval was further shortened to 200 msec (blunting of overdrive suppression).
A possible explanation for both the decrease of the coupling interval in the PNS group and for the blunting observed in the PS group could be the induction of DAD-dependent beats by pacing. This mechanism has been demonstrated when pacing was performed on Purkinje fibers isolated from the infarcted canine heart.13,22,23 The following observations support this hypothesis: 1) in the PS group, a single QRS complex was often seen after pacing and was followed by a much longer interval (Figure 1), 2) faster pacing rates more frequently induced triggered beats with shorter coupling intervals (acceleration or blunting of overdrive suppression), and 3) on the contrary, increasing the duration of pacing more often resulted in an increase in overdrive suppression.

Apart from the direct relation between coupling interval and interstimulus interval, several authors have described a (temporary) acceleration of the rate of the VTs after pacing as being specific for DAD-dependent arrhythmias.36-39 Acceleration, however, was not seen in the experiments presented in this study, indicating that an arrhythmogenic mechanism other than triggered activity seems to be responsible for the perpetuation of these VTs 18–24 hours after LAD occlusion.

Drugs

The effect of verapamil and lidocaine on the two groups of VT are partially in agreement with our hypothesis. After suppression of the VTs by lidocaine, the idioventricular rhythm returned less frequently than after verapamil, indicating that the normal MDP (−90 mV) was also affected by lidocaine but not by verapamil. The fact that verapamil only slowed but did not suppress VTs of the PNS group is more difficult to explain.

In an earlier study,15 we reported that flunarizine had no effect on VT occurring 18–24 hours after LAD ligation. However, in that study, we did not classify VTs based on their response to pacing. The results of this study show that flunarizine has no effect on either group. The inability of flunarizine to terminate these spontaneously occurring arrhythmias 18–24 hours after LAD occlusion makes the involvement of triggered activity resulting from DADs for the perpetuation of the VTs unlikely. The possible role of pacing-induced DADs for the behavior of the first postpacing interval has been discussed.

The presence of different QRS configurations during VT that could originate from different MDPs may explain the inconsistent effects of certain drugs in previous reports.2-15 This holds true especially for lidocaine. From our data, it can be concluded that first, lidocaine exerts a direct antiarrhythmic effect on these VTs and that its action is not due to overdrive suppression of the VT by acceleration of the sinus rhythm.5,7 Second, the data can explain why Bergey et al6 reported no suppressive effect of verapamil but only slowing of VTs (low MDP), whereas Karagueuzian et al35 reported termination of six of nine VTs that could not be suppressed by pacing for 30 seconds. As shown by our data, their duration of pacing does not identify all suppressible VTs. It is conceivable that the six VTs that were suppressed by verapamil represent those originating from an intermediate MDP, whereas the other three belong to VTs that occurred at a low MDP. Third, our findings might explain why a combination of lidocaine and verapamil as used by Karagueuzian et al35 did not result in abolition of all VTs.

The slowing in rate of VT by verapamil may, however, be sufficient to enable the sinus node to control cardiac rhythm. It is known that excessive catecholamine release 1 day after myocardial infarction may markedly increase the sinus rate.

The results presented in this article indicate that the Harris dog model incorporates at least two subgroups of arrhythmias that react differently to antiarrhythmic drugs.

Size of Infarction

We presented evidence that the size of the infarction is of importance for the rate, suppressibility, and number of VT configurations 1 day after LAD occlusion. We believe that infarct size only increases the likelihood that the MDP of the different Purkinje fibers will be more severely reduced by increasing the area and severity of the ischemic region. However, other factors, such as collaterals, must play an important role. The exact nature of the factors responsible for the reduction in MDP is unknown.

The data presented are compatible with the study of Dangman and Hoffman,23 which can be explained by the existence of different MDPs in the infarcted canine heart. In vitro, different MDPs ranging from −50 to −80 mV have been recorded from (Purkinje) fibers excised from infarcted tissue.16,23 We did not attempt to demonstrate a relation between the MDP of the infarcted tissues with its response to pacing and/or drugs for several reasons: 1) the difficulty in identifying specific sites in a region in which a specific VT developed, 2) the knowledge that excision and perfusion of Purkinje fibers lead to changes in MDP,16 and 3) the knowledge that in the intact heart, additional variables are present, such as autonomic tone, which are very difficult to mimic in the in vitro environment.

The possibility of intracellular registration of MDP by microelectrodes in the intact beating heart still presents a technical problem.

Conclusions

Slow automatic VT can be suppressed by pacing, verapamil, and lidocaine but not by flunarizine, whereas fast automatic VT can only be slowed by verapamil. This suggests that slow automatic VT originates from a higher MDP than faster VT.

Implications for Identification of Arrhythmogenic Mechanisms in Humans

The relevance of mechanisms as triggered activity and abnormal automaticity for arrhythmias in the
intact human heart is largely unknown because of the lack of diagnostic methods to properly identify these mechanisms. Therefore, there is need to perform more (animal) work to develop better tools. An example of such a tool is the introduction of flunarizine, which seems to be able to identify DAD-dependent arrhythmias in patients.\textsuperscript{40} Our results suggest that abnormal automaticity consists of at least two subgroups that originate from different MDPs. At present, only combinations of interventions (pacing and drugs) seem adequate to allow identification of (subgroups of) mechanisms of arrhythmias.

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Key Words: ventricular tachycardia • overdrive pacing • lidocaine • verapamil • flunarizine • conscious dogs
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