Triggered activity due to delayed afterdepolarizations in sites of focal origin of ischemic ventricular tachycardia

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Xing, Dezhi, and James B. Martins. Triggered activity due to delayed afterdepolarizations in sites of focal origin of ischemic ventricular tachycardia. Am J Physiol Heart Circ Physiol 287: H2078–H2084, 2004.—This study for the first time systematically evaluated the site of origin of focal ventricular tachycardia (VT) induced 1–3 h after acute coronary artery ligation in dogs. We determined whether delayed afterdepolarizations (DADs) and triggered activity (TA) are more often recorded from ischemic endocardium excised from focal sites of VT origin. A total of 145 α-chloralose-anesthetized dogs were studied: in 54 dogs without inducible VT, normal or ischemic endocardium was investigated in vitro; in 91 dogs, inducible VT was studied by three-dimensional activation mapping, with in vitro study of 51 endocardial foci compared with 40 endocardial ischemic sites not of VT origin. Incidence of DADs (71% vs. 33%, P < 0.05) and TA (32% vs. 11%, P < 0.05) was greater in ischemic than in normal Purkinje tissues. Purkinje sites of origin of focal VT demonstrated the greatest frequency of DADs (92%, P < 0.05) and TA (75%, P < 0.05), with repetitive TA predominating. Similar results were obtained in endocardial sites of origin. Action potentials were mildly depolarized and prolonged in the focal sites of origin. These abnormalities were stable up to 2.5 h of recording. This study demonstrated that DADs and TA may underlie a majority of focal VTs in ischemic endocardium and Purkinje tissue.

Sudden cardiac death is a major public health problem. Ventricular tachycardia (VT) and fibrillation (VF) are responsible for most cases of sudden cardiac death (22). The understanding of mechanisms of VT and VF in early myocardial ischemia and infarction is hampered in humans by rapidly changing substrate over the first hours, which are rarely observed in the hospital. Animal models have been studied instead (31). Although reentry has been thought to underlie early VT (25, 36) and VF, some studies have implicated focal mechanisms (1, 2, 10, 21, 25) in endocardial and Purkinje tissue (1, 2, 10). In vitro models of acute ischemia (3, 20, 27, 32) involving Purkinje tissue have suggested that triggered activity (TA) due to delayed afterdepolarizations (DADs) may explain these focal VTs. Abnormalities that may contribute to the occurrence of these mechanisms in acute ischemia include increased free fatty acids, oxygen free radicals, acidosis, and catecholamines (22). We studied our model of inducible VT (2) after acute coronary artery occlusion employing three-dimensional activation mapping to investigate the hypothesis that TA due to DADs may be found more frequently in endocardial and Purkinje tissues that were excised from sites of origin (SOOs) of focal VT.

METHODS

Animal preparation. A total of 145 dogs of either gender, weighing 8–20 kg, were studied. The protocol was approved by the University of Iowa Animal Use and Care Committee and adhered to the standards of the American Physiological Society. Anesthesia was initiated with ketamine (5 mg/kg im) and thiopental sodium (300 mg iv) and continued with α-chloralose given as a bolus (200 mg/kg iv) and then constant infusion (1). The trachea was intubated, and ventilation was maintained with a respirator (Harvard). The heart was exposed through a median sternotomy to facilitate electrode placement for mapping. A heating lamp was directed to the heart to maintain temperature at 37°C.

Electrophysiological methods. The sinus node was clamped, and the atrial appendage was paced with a stimulator with constant-current outputs at twice diastolic threshold with pulses of 2 ms. Pacing rate was 200 beats/min to control heart rates. Ventricular pacing of one pole of a multipolar needle in the normal zone employed an anode (7 cm² stainless steel) in the abdominal muscle.

Recording of electrograms. Surface ECG leads were recorded continuously. To record transmural signals, twenty-three 16-pole plunge-needle electrodes (J. Kassell, Fayetteville, NC) were inserted into the myocardium in the risk zone of the left anterior descending coronary artery as previously reported (1, 2, 36). The interneedle distance was 8–15 mm depending on the size of the heart and coronary artery anatomy.

Experimental protocol and arrhythmia induction. After confirmation of physiological blood gases and adequate anesthesia, the anterior descending artery was ligated 1 cm from the left atrial appendage and just distal to the first diagonal branch. This site spares the septum, so our mapping array covers and surrounds the risk zone (1). Ischemia was defined as a ≥45% decrease in bipolar electrogram voltage (1, 2, 26, 36); all data in vivo or in vitro are reported as “ischemia” when this definition in vivo was met. We waited 60 min because infarct size in the open-chest dog is then ~75% of the risk zone (2). We paced the endocardium at the base, apical septum, and lateral free wall in the normal zone to induce VT with up to four extrastimuli (2) (Fig. 2). The effective refractory period (ERP), defined as the longest S1-S2 that fails to capture the ventricle, defines the S1-S2 (where S1 is drive pacing and S2 is the 1st extrastimulus) of the induction protocol, and subsequent extrastimuli have progressively shorter coupling owing to peaking back of ERP by the prior extrastimuli.

Arrhythmia mapping. The three epicardial bipole electrodes on each recording electrode were mapped (BARD Electrophysiology) utilizing a personal computer-based system (Compaq Deskpro 286) with software that takes 64 channels of data at 12-bit resolution with a sampling frequency of 1 kHz per channel filtering over 30–300 Hz. An additional customized computer (267-MHz Pentium II Gateway

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2000) software system allowed us to resolve the Purkinje signals from the inner bipoles on each endocardial multipolar electrode by sampling at 3 kHz per channel filtering at 3–1,300 Hz (1). The bipoles between Purkinje tissue and epicardium were spaced to record the intervening midwall to account for transmural conduction.

Mapping analysis was done offline. The computer selected activation times by using the first, maximum rate of voltage development. Electrograms are included in maps when uniformly and reproducibly registered with each drive stimulus; there was no exclusion based arbitrarily on a low cutoff voltage of electrograms. Electrotmetric potentials were considered transiently present when a >75% reduction of voltage occurred in an electrogram, with extrastimuli or VT complexes produced by short coupling intervals; such electrotmetric suggests local, functional block of activation. Isochrones were calculated and drawn by hand. VT mechanisms were standard and defined as described elsewhere (1, 2, 36), including focal VT occurring when the electrogram recording the earliest SOO was surrounded on six sides by other electrodes within 1–2 cm that recorded progressive and gradually later activity with no late (>50% cycle) electrical activity on adjacent sites.

Mapping was done twice: The first maps were quickly constructed to determine tissues at the presumptive SOO of induced VT for selection of tissues for the in vitro study. The second map was constructed formally at a later time (the latter are reported) to confirm whether the tissues studied in vitro were taken from SOO. In this report, we consider VT mechanisms as endocardial focal or Purkinje with an SOO excised for in vitro study vs. ischemic sites far from the SOO of VT.

Intracellular recording techniques. After mapping, the heart was excised and placed in Tyrode solution, with the electrode recording the focal SOO of VT left in situ. Other normal and ischemic tissues were taken from sites where Purkinje spikes were recorded. Tissue (free-running 5-mm-long Purkinje strands or 5 × 5 × 2 mm endocardial sections) was excised from the area of the mapping electrode and placed endocardial-surface-up in a 3-ml tissue bath (Warner Instrument) that was superfused with 37 °C solution at 9 ml/min. Fibers were stimulated with a bipolar electrode at twice diastolic threshold. Action potential (AP) was measured during pacing at 1.5–5 Hz. The most superficial cells were impaled with 3 M KCl-filled glass capillary microelectrodes with tip resistances of 3–41 MΩ. Micro-electrodes were connected to a high-input-impedance preamplifier (Axoclamp-2A, Axon Instruments, Foster City, CA). The bath was grounded with an Ag-AgCl pellet. Potentials were recorded and stored on a computer with the use of software (Axon Instruments) with data filtered at 1 kHz and sampled at 2 kHz. Zero offsets are recorded to correct for drift. Purkinje cells were identified by spontaneous phase 4 depolarization at cycle lengths >1 s. Depolarization after phase 3 of paced APs was defined as DAD. TA was defined as spontaneous reproducible APs occurring at the peak of a DAD and linked to previous stimulated DADs by cycle lengths <1 s.

Statistics. Values are means ± SE. Two-way ANOVA and Student’s t-test were employed for appropriate data. Pearson’s χ² test analyzed frequencies of observations in groups. P < 0.05 was accepted as statistically significant.

RESULTS

Dogs with no inducible VT (n = 51) underwent extrastimuli through S5, and ERP was 153 ± 4 ms. Dogs with VT but with excised tissues not taken from SOO (n = 43) were inducible with S2 up to S5, and ERP was 150 ± 3 ms; in 28 of these dogs, induction of VT was sustained or nonsustained; in 15 dogs, VT accelerated to VF. Dogs with SOO (Fig. 1) excised and studied in vitro (n = 51) were also induced with S2–S5, and ERP was 156 ± 3 ms: in 35 of these animals, VT was inducible; in 13 dogs, VT accelerated to VF. All 94 dogs were resuscitated, usually with burst pacing, so that mapping could be performed to choose the SOO. Seventeen dogs with inducible VT were given pharmacological intervention in vivo, which mainly consisted of adrenergic agonists and blockers.

The VTs described here were not present spontaneously as previously reported after 24 h of ischemia (4, 6, 16, 19, 21). Figures 2 and 3 show a typical induced focal Purkinje VT: the complexes at the onset were slightly variable but then became monomorphic VT with cycle length of 1.25 ms. Electrograms in Fig. 2 show activation of all sites surrounding the focus occurring within 57 ms (less than half the cycle length). The first two VT complexes originate from the Purkinje focus adjacent to the pacing site. The third VT complex originates at an adjacent Purkinje site. The origin of the fourth complex is distant from this electrogram grouping. In Fig. 3, the origin in the Purkinje site rapidly activates the remaining layer, with slower activation of the outer layers. Endocardial and Purkinje foci of VT were distributed throughout the ischemic zone (Fig. 1).

Figure 4 shows intracellular microelectrode measurements from the endocardial preparation removed from the focal
Fig. 2. Surface ECG leads II and V5R show the last 2 drive and 2 premature stimulated (+) complexes followed by 4 complexes of VT. Intracardiac electrograms from Purkinje (P), endocardium (E), and overlying (O) or surrounding, in various directions such as east (E), north (N), northwest (NW), southwest (SW), or south (S), focus (F) of VT. Second drive complex shows Purkinje potentials marked by downward arrows in P-F, P-SW, and P-S. Premature stimulation delays muscle from Purkinje at P-F but produces insufficient conduction delay to suggest reentry. Vertical lines mark onset of the surface QRS of VT complexes 1 through 3. Upward arrows mark earliest Purkinje potentials during complexes of VT, with subsequent activation of all surrounding areas, which show conduction delay less than half the cycle length of the VT. Downward arrows indicate conduction difference between Purkinje and lead II.

Purkinje SOO (Figs. 2 and 3), which demonstrates single, repetitive, and sustained TA at cycle length of 700 ms due to DADs. Figure 5 shows intracellular recordings from another Purkinje VT showing DADs and TA recorded from a cell with phase 4 depolarization.

Table 1 summarizes experiments in this study with and without inducible VT mapped in three dimensions. Purkinje and endocardial focal mechanisms predominate because visible epicardial collaterals were not ligated (36). The large number of ischemic sites that were not at the SOO of focal VT were excised from dogs with epicardial reentry or remote SOO. Offline mapping confirmed the first mapping for selection of tissues from the SOO of VT to be 56% (51 of 91 foci). Those sites not confirmed to be SOOs were added to ischemic sites from dogs without inducible VT. Incidence of DADs was greater in these ischemic sites than in normal sites. In vitro SOO of VT demonstrated similar high occurrence of DADs, but TA were observed more frequently, especially in repetitive form. To mimic in vivo conditions, TA was facilitated by isoproterenol superfusion, but in one-fourth of ischemic tissues, especially Purkinje, TA occurred without this drug. No early afterdepolarizations were observed. Spontaneous activity at cycle lengths of 500–700 ms was recorded from zero to two depolarized tissues in all ischemic categories as previously reported in older ischemic preparations (4, 8, 16, 19); it resolved spontaneously as superfusion persisted, and subsequently DADs and TA were observed in each tissue.

The cycle length of TA induced in vitro (420–840 ms) was longer than that of VT in vivo (100–200 ms). Given the limitations of mapping spatially (resolution of 1 cm²) as well as the DADs and TA observed in many of the ischemic tissues not at the SOO of focal VT, other cells within the immediate region of a focus may also serve as alternate foci that, with the others in adjacent areas, produced faster VT rates with similar morphological appearance on the ECG and map (Fig. 2, compare VT complexes 2 and 3). Alternatively, the effects of time, isolation, superfusion, and details of pacing and adrenergic protocols could have reduced the rate of TA.

APs from Purkinje and endocardial tissues (Table 2) were depolarized in ischemic sites but not to the extent reported in other models (4, 8, 15, 19). Prolonged AP duration in Purkinje and endocardial SOOs has been reported in tissues studied after 2 h of coronary occlusion followed by 22 h of reperfusion (12). The time of recording after coronary occlusion (3.5 ± 0.3 h) in the SOO group was not different from that in the ischemic, but the non-SOO, group (3.6 ± 0.5 h).

Table 3 shows data after 1–3.5 h (mean 2 h) of recording in vitro; APs from ischemic zones continued to be depolarized but tended to shorten. At this later time, DADs and TA were as commonly induced or more frequently induced than at initial implanation. This was especially true of SOOs of VT. These results suggest the persistent effect of the previous ischemia in this tissue.

DAD voltages are influenced by isoproterenol in ischemic Purkinje tissues in two ways. Isoproterenol increased DAD amplitude in the same cells (P < 0.05, n = 6) at all pacing cycle lengths; i.e., at cycle length of 500 ms, DAD increased from 2.6 ± 1.3 to 4.8 ± 2.7 mV, and at 285 ms, DAD increased from 3.5 ± 1.3 to 5.4 ± 2.0 mV. However, the drug also altered the cycle length dependency. Without isoproterenol, the amplitude of DAD plateaued at a cycle length of 285 ms. With isoproterenol, DAD amplitude increased further; i.e., at 200 ms, DAD amplitude was 6.9 ± 2.2 mV, as previously shown in other tissues (34). TA was not more likely with faster pacing, and no relation was observed between pacing cycle length and coupling interval of the TA: the correlation coefficient was 0.38. In individual experiments with TA at more than two pacing cycle lengths, no correlations were observed. These data are consistent with previous studies of TA produced by any intervention, except digitalis toxicity.
DISCUSSION

This study for the first time systematically evaluated the SOO of focal VT induced after 1–3 h of acute myocardial ischemia. Focal VT frequently originates in endocardial and Purkinje tissue underlying the ischemic zone (1, 2). Our results showed that the tissue at the SOO of focal Purkinje VT more commonly demonstrated DADs and TA in vitro with and without isoproterenol superfusion. The AP characteristics observed in ischemic sites and SOOs were consistent with mild depolarization and AP duration prolongation. These changes persisted for hours of superfusion.

Our model is unique among in vivo studies utilizing three-dimensional computer-assisted activation mapping (1, 2) because we attempted to record Purkinje signals at each multipolar needle. In vivo studies of spontaneous VT have been reported in many animal models focusing on the acute ischemic period defined as the first 2–4 h (33). Acute ischemia may produce VT and VF, which are thought to be reentry in the first 2–10 min (11, 25) and reentry or automaticity or TA thereafter. Detailed three-dimensional mapping studies in humans (25) and animals (11, 25, 35) also suggest the possibility of focal mechanisms, which may be TA because of the absence of adjacent conduction delay implicating reentry. Occasional Purkinje potentials have been recorded before the onset of premature ventricular contractions (10) in the first hours after coronary artery occlusion, although three-dimensional mapping techniques in the cat demonstrated that premature ventricular contractions and VT originated from 24% (25) to 100% (35) of focal endocardial sites. Even when macroreentry was recorded, focal VT was observed to maintain VT or transition to VF (25). None of these laboratories studied endocardial tissues from SOOs in vitro.

We previously showed that Purkinje potentials were recorded at the origin of 60% of VT complexes in the first 30 min after coronary artery occlusion (1). In the present study, we continued to study inducible VT in the dog after the first hour following coronary artery occlusion. This stable VT may be studied with interventions (2). Although the infarction process may be ongoing (5), we did not observe further increases in infarct size after the first hour of observation (2, 36). It is not clear whether this VT would occur spontaneously, although we occasionally saw a spontaneously occurring morphology of VT, which was induced later. We observed Purkinje signals ±50% of the time at the endocardial origin of induced focal VT. We observed epicardial reentry frequently in this model (±25% of inducible VTs), especially when we intentionally
ligated visible epicardial collaterals (36). Our mapping methods alone did not allow us to exclude microreentry; however, published examples suggest that our methods would allow reentry by showing a rotorlike activity. When we also used pacing methods such as entrainment, our focal VTs did not show any of the same characteristics. The present data also provide an additional argument for a nonreentrant mechanism.

Focal VT may be due to a point source of cells characterized by automaticity or TA; those exhibiting automaticity are suppressed by previous electrical activity. In previous studies, VT with automaticity or TA was slower and irregular, occurring later in the course of coronary occlusion (4, 6, 16, 19, 21); the VTs reported here were induced by prior stimulation that was faster, regular, and limited to endocardial focal sites. The
Table 1. DADs and TA recorded from Purkinje and endocardium

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>DADs, %</th>
<th>Total</th>
<th>Repetitive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purkinje</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>33</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Ischemic (not SOO)</td>
<td>32</td>
<td>71§</td>
<td>32§</td>
<td>12</td>
</tr>
<tr>
<td>SOO</td>
<td>28</td>
<td>92</td>
<td>75+</td>
<td>61+</td>
</tr>
<tr>
<td><strong>Endocardium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>14</td>
<td>22</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Ischemic (not SOO)</td>
<td>30</td>
<td>77§</td>
<td>44§</td>
<td>26</td>
</tr>
<tr>
<td>SOO</td>
<td>23</td>
<td>91</td>
<td>73+</td>
<td>52+</td>
</tr>
</tbody>
</table>

A total of 145 dogs were studied; n, number of tissues. DADs, delayed afterdepolarizations; TA, triggered activity; normal, nonischemic endocardial sites; ischemic, ischemic sites defined in vivo from dogs with or without VT; SOO, sites of origin of focal ventricular tachycardia. * P < 0.05 vs. normal sites; †P < 0.02 vs. noninducible or not SOO sites. Approximately 75% of data obtained with isoproterenol superfusion.

Table 2. Action potential characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MDP, mV</th>
<th>APA, mV</th>
<th>Overshoot, mV</th>
<th>APD90, ms</th>
<th>APD50, ms</th>
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<tbody>
<tr>
<td><strong>Purkinje</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>92±2</td>
<td>99±5</td>
<td>18±3</td>
<td>269±12</td>
<td>188±10</td>
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<tr>
<td>Ischemic (not SOO)</td>
<td>32</td>
<td>82±2*</td>
<td>97±4</td>
<td>20±5</td>
<td>256±10</td>
<td>155±9*</td>
</tr>
<tr>
<td>SOO</td>
<td>28</td>
<td>84±2*</td>
<td>96±4</td>
<td>16±2</td>
<td>284±7*</td>
<td>195±8*</td>
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<tr>
<td><strong>Endocardium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>14</td>
<td>83±3</td>
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<td>21±3</td>
<td>198±13</td>
<td>140±11</td>
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<tr>
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<td>95±3</td>
<td>19±3</td>
<td>225±8</td>
<td>155±7</td>
</tr>
<tr>
<td>SOO</td>
<td>23</td>
<td>77±3</td>
<td>90±3</td>
<td>15±2</td>
<td>256±10*</td>
<td>165±9</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of dogs. MDP, maximum diastolic potential; APA, action potential amplitude; APD90 and APD50, action potential duration at 50% and 90% repolarization. * P < 0.05 vs. normal.

Table 3. Ischemic Purkinje action potential characteristics

<table>
<thead>
<tr>
<th></th>
<th>MDP, mV</th>
<th>APA, mV</th>
<th>Overshoot, mV</th>
<th>APD90, ms</th>
<th>APD50, ms</th>
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</thead>
<tbody>
<tr>
<td>Initial</td>
<td>86±3</td>
<td>97±5</td>
<td>17±3</td>
<td>258±6</td>
<td>179±5</td>
</tr>
<tr>
<td>1–3.5</td>
<td>84±4</td>
<td>95±5</td>
<td>16±3</td>
<td>233±4</td>
<td>167±3</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 13.

depolarization and AP shortening (5, 17) early, similar to the timing of the present studies. They clearly show mildly depolarized Purkinje tissues with TA more frequently observed at the SOO of induced VT documented by mapping, which implies causality.

TA due to DADs occurs in tissues with Na⁺ or Ca²⁺ overload, such as that produced by digitalis intoxication or high external Ca²⁺ (32), although Purkinje fibers may be particularly susceptible (15, 30). In coronary sinus, mitral valve, and some atrial preparations, catecholamines may also produce TA (32). Ischemia serves as a typical model as well, because the acute process produces intracellular Ca²⁺ (18) as well as Na⁺ (14) overload. The addition of catecholamines may also facilitate TA but is not required.

APs (Table 2) giving rise to TA show mild depolarization, as shown in previous studies (5, 17). The overshoot is preserved, in contrast to previous ischemic studies, suggesting that Na⁺ current depression is not severe. Therefore, the Na⁺ gradient may be adequate as a charge carrier for TA. Taken together, these findings suggest that the SOO of Purkinje VT may be less ischemic, perhaps better nourished by cavity blood (33). Thus our model of TA due to DADs is dissimilar to other models of this mechanism occurring at depolarized levels of −76 to −84 mV. Otherwise, DADs observed in ischemic tissues are single, unless TA is present (Figs. 4 and 5) (4, 32). The voltage of DADs increased with pacing cycle length to a plateau at 285 ms, unless isoproterenol was superfused (32). However, cycle length of pacing did not predict the presence or coupling interval of single TA or cycle length of repetitive TA. In general, induced TA in vitro was self-terminating, with slowing before cessation, probably resulting from activation of the Na⁺-K⁺ pump causing recovery of the membrane potential (32).

Limitations. It is possible that the very commonly recorded TA in ischemic tissues is not different from that recorded in the SOO of VT. We cannot totally exclude this possibility. However, the almost double frequency of TA, which was more frequently sustained in Purkinje tissue from the SOO of VT, makes a reasonable causal argument. The very common frequency of TA in all ischemic tissues suggests that multiple cells in the vicinity of that one cell from which we recorded were also triggered and, therefore, could produce faster VT in vivo than the TA recorded in vitro. Further pharmacological proof of a causal relation in VT due to TA and DADs should be sought; i.e., a Ca²⁺ entry blocker might block inducible focal VT in vivo and TA in vitro. Treatment with such agents in this model could lead to trials of patients in the coronary care unit (9, 29). Case reports have suggested the benefit of Ca²⁺ antagonists (22, 37) in patients with normal systolic function.

Conclusions. Acute myocardial ischemia promotes DADs in endocardium and Purkinje tissue. TA due to DADs occurs frequently in acutely ischemic tissues, especially at the sites of
focal origin of VT. These results support the hypothesis that DADs and TA may underlie a majority of focal VTs in ischemic endocardium and Purkinje tissue.

GRANTS

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REFERENCES


