The Effects on Atrial Electrophysiology and Structure of Surgically Induced Right Atrial Enlargement in Dogs

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SUMMARY We evaluated the relationships between susceptibility to arrhythmias caused by right atrial (RA) enlargement and alterations in transmembrane potentials and ultrastructure. RA enlargement was produced in eight dogs (TI) by exciting the septal cusp of the tricuspid valve through a right atriotomy and constricting the pulmonary artery. This procedure resulted in RA dilation and hypertrophy. Four sham-operated dogs (S) also were studied. Neither TI nor S dogs developed spontaneous atrial arrhythmias. Atrial overdrive (OD) and premature stimulation (PS) were used to initiate and terminate arrhythmias. At 2 weeks and for 20 to 30 weeks after surgical preparation, TI dogs were more susceptible to arrhythmias than S dogs. The duration of arrhythmias exceeded 10 minutes more often in TI dogs than in S dogs. Sixty-one percent of all arrhythmias in the TI dogs had rates of 320-450 impulses/min, and electrogram and ECG characteristics of atrial flutter (type II rhythm), whereas no S dogs developed rhythms with these slower rates. The type II rhythms were persistent, 30% lasting longer than 30 minutes, while 22% lasted more than 60 minutes. Transmembrane potentials recorded in vitro from the RA free wall of TI dogs, and responses to norepinephrine and acetylcholine were not different from control. Histological and ultrastructural studies on TI atria showed hypertrophy of fibers and some increase in connective tissue between cells. These results suggest that altered susceptibility to long-lasting arrhythmias need not be associated with significant abnormalities of cellular electrophysiology.

ARRHYTHMIAS can occur in otherwise normal hearts, as under the influence of excessive concentrations of catecholamines, but, in general, arrhythmias are associated with some abnormality of cardiac structure or function or both. In recent years there has been a strong emphasis on the causal relationship between abnormalities in cellular electrical activity and the occurrence of specific disturbances of rhythm (Cranefield et al., 1973; Bigger, 1980). In most instances, however, the relative importance of changes in structure and changes in cellular electrophysiology are difficult to evaluate in relation to disturbances of rhythm. For example, several studies on small pieces of tissues removed from human hearts with congenital and acquired heart disease (Singer et al., 1973; Hordof et al., 1976; Mary-Rabine et al., 1979) have suggested that a hemodynamic abnormality sufficient to cause right atrial enlargement also caused abnormalities in the transmembrane potentials of right atrial cells and that this latter change predisposed to arrhythmias. These studies did not permit an evaluation of the relative importance of the alterations in structure and cellular electrophysiology, but did suggest a correlation between the presence of right atrial enlargement, atrial disease, and both the degree of abnormality of transmembrane potentials and the incidence of clinical arrhythmias.

We have attempted to evaluate the several components of this problem by surgically producing chronic right atrial enlargement in dogs and evaluating associated changes in susceptibility to arrhythmias, abnormalities of atrial transmembrane potentials, and changes in right atrial structure and ultrastructure. We have found that chronic right atrial enlargement causes consistent changes in susceptibility to arrhythmias in the absence of significant changes in transmembrane potentials or atrial morphology.

Methods

Surgical Procedures

We used mongrel dogs weighing 20-30 kg and free of heart disease. Eight were subjected to the surgical procedure for producing atrial enlargement, and comprise the group with experimentally induced tricuspid insufficiency (TI). Four additional animals were subjected to sham operations (S).

Each dog was anesthetized with sodium pentobarbital (30 mg/kg, iv) and ventilated by positive pressure. The chest was opened through a right thoracotomy and the right atrium opened during inflow occlusion. The septal cusp of the tricuspid valve was visualized and excised. The atriotomy was closed with 5-0 surgical silk. Umbilical tape was placed around the main pulmonary artery and...
tightened gradually until the mean right atrial pressure increased to 5–8 mm Hg or until severe right atrial distension was visible. The right atrial mean pressure was monitored through a PE 240 catheter inserted through theazygous vein.

Acrylic plaques containing five silver electrodes were sutured to the left atrial appendage and to the right atrial free wall, cephaled to the atriotomy, and used later to record bipolar electrograms or to stimulate the atria. Two circular Ag-AgCl electrodes (Beckman) were sutured subcutaneously, one on the dorsal and the other on the ventral aspect of the thorax, to record the electrocardiogram. All leads and the right atrial catheter were brought through a subcutaneous tunnel to the dorsal midline region and exteriorized. The pericardium was closed loosely and the chest was closed in layers. The dogs were treated with 1 g Bactocil im and 0.33 g Kantrax im on alternate days for 6 days postoperatively.

Since either the suturing of plaque electrodes to the atria or the atriotomy might alter the likelihood of an arrhythmia, we also did sham operations. In two dogs we only opened the chest and the pericardium and attached the atrial and subcutaneous electrodes (S-thoracotomy). Two other dogs were subjected to the same procedure and, in addition, an atriotomy was performed in the right atrial free wall (S-atriotomy).

Stimulating and Recording Techniques for the Conscious Dog

We tested the effects of atrial stimulation in each of the 8 TI dogs and compared it to its effects in the 4 S dogs. On the 14th postoperative day, and at intervals thereafter, each dog was studied while conscious and standing in a sling. The ECG and right and left atrial electrograms were recorded on a DR-16 Electronics for Medicine recorder. One pair of atrial electrodes was connected to a digital programmable constant current stimulator (designed by Dr. Laurence Eisenberg of the Rockefeller University). The atria were stimulated with two different protocols. In one, the atria were driven at constant basic cycle lengths of 350, 300, and 200 msec with rectangular pulses of 2 msec duration and approximately 4 times diastolic threshold. After every 10th basic drive stimulus (S1), a premature test stimulus (S2) of same duration and strength was given at S1–S2 intervals that decreased in steps of 10 msec. The S1–S2 interval was decreased until S2 was ineffective in eliciting an atrial response, or until an arrhythmia was induced. A successful trial was one in which at least one S2 induced an arrhythmia. If an arrhythmia occurred, its rate, rhythm, and duration were studied. In the second overdrive (OD) protocol, the atria were paced at several basic cycle lengths between 250 and 90 msec for 30 seconds and the rate, rhythm, and duration of any induced arrhythmias studied. A successful OD trial was one in which at least one cycle length (S1–S1) induced an arrhythmia. As described in the Results, a rapid sustained atrial arrhythmia was induced regularly in TI dogs by single atrial premature stimuli or overdrive. We tested the ability of FS and OD to terminate the induced arrhythmia. All values are expressed as mean ± SD. Statistical differences between means were determined using an unpaired Student’s t-test for populations with and without equal variances.

In Vitro Transmembrane Potentials of Atrial Fibers

Five TI dogs, the four S dogs, and five control dogs were used for these studies. The dissection and isolation of the right and left atria, and the techniques used to monitor and record the transmembrane potentials of these fibers, have been described previously (Wit et al., 1973). Specifically, a section of atrial free wall and appendage (2 × 2 cm) was carefully dissected from each atrium. The right atrial preparation did not include the sinus node area, or any posterior free or septal wall. Transmembrane potentials were recorded from superficial fibers at endocardial sites separated by 5–8 mm over the entire surface of the right and left atrial preparations at a driven cycle length of 800 msec. At each site, resting membrane potential (RMP), action potential amplitude (APA), Vm, and the duration of the action potential at 50% (APD50) and 100% (APD100) repolarization were measured. Mean values for each parameter of potentials recorded from right atria of TI dogs were compared to mean values for the same parameter for left atrial fibers of the same group. In addition, data were compared to data collected from studies on S and control dogs. Statistical difference between mean values was evaluated by an unpaired Student’s t-test (Snedecor and Cochran, 1967). All results are presented as mean ± SD; P < 0.05 was taken as the level of significance.

To study the effects of norepinephrine (NE) HCl on transmembrane potentials, we added aliquots from a 1-norepinephrine HCl (Sigma) solution to normal Tyrode’s solution to achieve a final concentration of 5 × 10^{-6} M. Na-ethylene-diaminetetraacetic acid (EDTA) (5 × 10^{-5} M) also was added (Mary-Rabine et al., 1978). Effects of acetylcholine chloride (Ach) 1.4 × 10^{-6} M also were evaluated. Several fibers from each of several preparations were studied by a modified fast flow perfusion system (Gadsby and Cranefield, 1977). All effects of NE and Ach were determined for single impalements for several cells in each S and C preparation, and in five of the six TI dog preparations. Significance of a drug’s effect was evaluated using a paired Student’s t-test.

Pathology

Determination of Atrial Volume

In three TI dogs and in three control dogs matched for body weight, we measured right atrial
volume. The hearts were fixed in situ with glutaraldehyde. We used a modification of the procedure of Ross et al. (1967). Under light pentobarbital anesthesia (25 mg/kg, iv), the right atrial, right ventricular, and pulmonary wedge pressures were measured by inserting a #7 balloon-tipped catheter through the right jugular vein into the right heart. Intrathoracic pressure also was monitored continuously through the right jugular vein into the right heart. Pulmonary artery wedge pressure was considered to reflect left atrial pressure (Jonsson and Sanai, 1969). From the means of these measurements we determined the mean transmural pressure for each atrium and, therefore, the pressure at which the atria should be fixed in situ. The methods of fixation and of maintaining the desired transmural pressures during fixation have been described previously (Ross et al., 1967). After complete fixation, the heart was filled with silastic (Dow Corning, Inc.) and a cast was made of each atrial chamber. The volume of each cast was determined to be the weight of the water displaced by the cast. The mean ratio of the right to the left atrial volumes of TI dogs was compared to the mean volume ratio for the control dogs. Significance was evaluated by using a rank-sum test (Dixon and Massey, 1969).

**Histology and Ultrastructure**

A small piece of tissue (1 cm x 1 cm) was taken for electron microscopic study from the isolated right and left atria of all TI and S hearts. In addition, atrial tissue was taken from hearts of four control dogs for comparison. The methods of preparation of the tissue blocks for both electron microscopy and histology have been previously described in detail (Fenoglio et al., 1976). The fine structure of atrial cells was studied at 1000 to 5000 x. To compare the size of atrial cells from control, S and TI dogs, at least one thick section (1 μm) from each of two blocks from each site sampled on one dog was stained with toluidine blue (1%) and examined with a light microscope with a calibrated eyepiece. Cell size was measured under low magnification (525X) as the diameter at the level of the nucleus. Cells for which diameter was measured were those which in transverse or longitudinal section had a centrally located nucleus.

**Results**

**Effect of Tricuspid Insufficiency and Partial Pulmonary Artery Occlusion on Right Atrial Pressure, Volume, Size, and Structure**

The mean body weight of the S dogs determined after recovery from surgery (25 ± 4 kg, n = 4) did not differ significantly from that of the TI dogs (26.6 ± 4 kg, n = 8).

**Right Atrial Pressure**

Pressure was measured just before the anesthetized dog was killed. Mean RA pressure of the TI dogs (4.57 ± 2 mm Hg, n = 7) was slightly higher than in two of the S dogs (3.8 and 4.8 mm Hg) and was also slightly higher than in a group of control dogs (2.94 ± 0.9 mm Hg, n = 5) studied under the same conditions. These values were not significantly different (P > 0.05). Nevertheless, the RA pressure tracing in all TI dogs were characteristic of tricuspid insufficiency. Mean right ventricular pressure in TI dogs (mean systolic = 43 ± 1.2 mm Hg, n = 7) was slightly higher than in open-chest, chloralose-anesthetized dogs (RV systolic pressure = 20 mm; range 16-42 mm Hg) as reported by Boyd and Williams (1967).

**Pathology**

Except for a thin layer of fibrous material that had replaced the pericardium, the hearts of the four S dogs showed no abnormalities. Each of the hearts from the eight TI dogs showed the absence of some portion of the septal cusp of the tricuspid valve and some degree of pulmonary artery occlusion. The right atria appeared mildly to moderately enlarged and the endocardial surface of its free wall was heavily trabeculated when compared to hearts of control or S dogs. The right ventricle was greatly hypertrophied and the right ventricular cavity was enlarged so that the apex of the right ventricle reached the apex of the heart. The interior walls of the right ventricle were coarsely trabeculated and trabeculae carnae were more prominent than in the S hearts. The left atrium and left ventricle of all TI hearts were normal in size and appearance as was the mitral valve.

**Right Atrial Volume**

Right atrial volume was measured for three TI dogs and three control dogs closely matched in body weight (see Table 1). The three TI dogs (TI #12, 14, 16) were typical of the TI group in terms of arrhythmias and other data. The mean ratio of the volume of the right atrium to the volume of the left atrium in TI dogs (3.58 ± 0.94, n = 3) was higher than in controls (1.99 ± 0.63, n = 3). The TI dog ratios were significantly different (P = 0.05) than the control ratios.

**Histology and Ultrastructural studies**

Histological and ultrastructural studies were done on four control, four S, and six TI dogs. The

**Table 1**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Body wt (kg)</th>
<th>RA Vol (ml H₂O)</th>
<th>LA Vol (ml H₂O)</th>
<th>Ratio (RA/LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁</td>
<td>26</td>
<td>35.846</td>
<td>13.330</td>
<td>2.695</td>
</tr>
<tr>
<td>C₂</td>
<td>23</td>
<td>21.7944</td>
<td>14.7589</td>
<td>1.475</td>
</tr>
<tr>
<td>C₃</td>
<td>24</td>
<td>33.3291</td>
<td>18.23</td>
<td>1.828</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>24 ± 1.5</td>
<td>15.4 ± 2.5</td>
<td>1.99 ± 0.63</td>
<td></td>
</tr>
<tr>
<td>TI#12</td>
<td>23</td>
<td>47.7767</td>
<td>13.7942</td>
<td>3.463</td>
</tr>
<tr>
<td>TI#14</td>
<td>24</td>
<td>37.2597</td>
<td>13.8123</td>
<td>2.699</td>
</tr>
<tr>
<td>TI#16</td>
<td>23</td>
<td>41.509</td>
<td>9.08</td>
<td>4.571</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23 ± 6</td>
<td>12.2 ± 2.7</td>
<td>3.36 ± 0.94</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1

Panel A—The arrangement of atrial cells in the right atrial wall of a TI dog. These fibers are located in the second, third, and fourth subendocardial cell layers. Myofibrils (MF) fill these cells and are oriented in the same direction within each cell. Individual cells are not aligned with each other and connective tissue seems to separate cells. f = fibroblasts; c = dense collagen bundles. The black bar corresponds to 5 μm. Panel B—A hypertrophied cell from the right atrium of a TI dog showing the presence of a large sarcolemmal invagination and numerous t-tubules. N = nucleus; g = glycogen particles; sag = atrial specific granules; large white arrows are pointing to a sarcolemmal invagination and t-tubule. The black bar corresponds to 2 μm.
structure and ultrastructure of the RA free wall of S dogs was identical to that in controls, and like that described for cat atrial myocardium by McNutt and Fawcett (1969). The gross and fine structure of the left atrial wall in TI dogs did not differ from that of control or S dogs. Right atrial structure of TI dogs differed from that of control and S dogs. Bundles of fibers were not packed as tightly as in control and S dogs, and interstitial connective tissue was more prominent (Fig. 1). In two TI dogs, this latter change was quite prominent. In each of these dogs, the right atrium had been exposed to the hemodynamic alteration for more than 200 days. The loose interstitial connective tissue was comprised of increased numbers of fibroblasts, and large amounts of collagen, elastin, and ground substance. Histological evidence of inflammation was not seen in the TI atria, especially around the atriotomy and near the site of the cusp excision.

Individual cells in the RA of the TI dogs were cylindrical in shape and varied in size; many were larger than atrial cells of control or S dogs. The diameters of control RA cells ranged from 6 to 14 μm (mean = 9.2 ± 1 μm, n = 126). Seventy-seven percent of the cells had diameters of 10 μm or less while only 23% had diameters >10 μm. There was no significant difference between the mean values for control and S-RA cells (range 6 to 16 μm; mean = 10.5 ± 1 μm, n = 156). In contrast, the mean diameter of cells from TI dog atria (16.4 ± 5 μm; range 8 to 28 μm, n = 184) was significantly greater (P < 0.001) than the mean for control or S dog group. In TI dog specimens, 92% of the cells had diameters >10 μm.

In the TI dogs, the sarcolemma of atrial cells of normal and increased size was similar to that of control cells. Generally, in the large diameter cells, tubular invaginations of the sarcolemma or t-tubules were seen extending deep into the interior of the cells. In the hypertrophied cells, Golgi complexes were more prominent than in control or S dogs, mitochondria were clumped, and increased amounts of glycogen and sarcoplasmic reticulum were present. Nuclei were centrally located and more lobulated than control nuclei.

The sarcomeres of normal and hypertrophied atrial cells in TI dogs were identical to those of control and S dogs. In the hypertrophied cells, the sarcomeres still were arranged in rows along the entire length of the cell and filled the cytoplasm but now, instead of 4–6 sarcomeres in register across the diameter of the cell as in controls, 6–10 sarcomeres were seen.

**Spontaneous Arrhythmias**

The average period of study for the four S dogs was 93 days (29, 38, 127, and 168 days). An ECG was recorded during each trial on these dogs. The average number of trials per dog was 7.5 (range 5–14). The average study period for the TI dogs was 98 days (range 34–310 days). The average number of trials per dog was 12 (range 6–19). In each dog, after the first 14 postoperative days, a trial occurred at least once every 10 days. No spontaneous arrhythmias were observed in any of the TI or S dogs.

**The Effects of Electrical Stimulation on Atrial Rate and Rhythm: Susceptibility to Arrhythmias**

We compared susceptibility to arrhythmias among groups. We determined the percentage of stimulation trials that initiated an atrial arrhythmia of any type. The group with the greatest percentage of successful trials was considered more susceptible. We also determined the range of overdrive cycle lengths and S-S coupling intervals that induced arrhythmias; the wider the range in a group the more susceptible was a group to arrhythmias. Finally, we determined the duration of each arrhythmia induced. The group of dogs with the longer lasting arrhythmias was considered to be more susceptible.

There were an average of 7.5 overdrive trials per dog (range 5–14) in the four S dogs, and 10 per dog (range 5–19) in the TI dogs. In all trials, an atrial tachyarrhythmia was initiated by atrial overdrive. Susceptibility to the initiation of an arrhythmia by overdrive was not greater in the TI dogs. For each dog, there was a specific range of cycle lengths that initiated an arrhythmia. The mean of the longest cycle length for each S dog (n = 4, mean (S1-S1) = 100 ± 16 msec) was significantly shorter than the mean value for the TI dogs (n = 8, mean (S1-S1) = 139 ± 11 msec) (P < 0.01). In addition, the mean shortest cycle length that induced an arrhythmia in the S group (n = 4, mean (S1-S1) = 77 ± 13 msec) was significantly shorter than for the TI group (n = 8, mean (S1-S1) = 96 ± 10 msec) (P < 0.02). Thus the range of effective cycle lengths was greater for the TI dogs than the S dogs.

There were on the average 7.5 atrial premature trials per dog in the S group and 6.7 in the TI group. The mean percent of trials that induced an arrhythmia in the S dogs (mean = 30.5 ± 24%) was significantly less than in the TI dogs (100%) (P < 0.05). In one S dog, no atrial arrhythmia was induced by premature stimulation.

The proportion of arrhythmias lasting more than 10 minutes was significantly greater in the TI dogs than in the S dogs. In the latter, most arrhythmias were of short duration (1 second to 10 minutes) (Table 2). Only 4% of the arrhythmias lasted for

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>1 sec to 10 min</th>
<th>&gt;10 to 30 min</th>
<th>&gt;30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated</td>
<td>84 (141)</td>
<td>4 (6)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>TI dogs</td>
<td>63 (254)*</td>
<td>11 (39)*</td>
<td>23 (82)*</td>
<td></td>
</tr>
</tbody>
</table>

N = total number of dogs in each group, X % = mean percentage of total number of arrhythmias induced in this duration interval, (n) = total number of episodes.

* P < 0.05 by Student’s t-test for unpaired values.
more than 10 minutes but less than 30 minutes, while even fewer lasted for more than 30 minutes. The percentage of short-lived arrhythmias (0 to 10 minutes) in the TI group was significantly less (P < 0.05) than in the S group. On the other hand, 82 episodes in the TI dogs were of long duration, lasting for more than 30 minutes. The percent of long-lasting arrhythmias (>30 min) was significantly greater (P < 0.05) in the TI than in the S group.

Therefore, not only were the TI dogs more susceptible to the initiation of atrial arrhythmias by electrical stimulation, but the atrial arrhythmias lasted longer in the TI group.

Characteristics of Electrically Induced Arrhythmias in S and TI Dogs

Rate

The rates of arrhythmias (six or more repetitive depolarizations) in S and TI dogs are illustrated in Figure 2. A total mean of 61% of all arrhythmias in TI group fell within the range of 321-450 impulses (imp/min). No arrhythmias in the S group had rates in this range. In TI dogs only occasional arrhythmias had rates similar to those in S group. Fifty-four percent of all arrhythmias in S-thoracotomy had rates from 521 to 600 imp/min, while an 76% of arrhythmias in S-atriotomy had rates in this interval. The total mean percent of all arrhythmias in this range in the TI dogs was 10%.

To a much lesser degree, stimulation initiated slower arrhythmias (200–300 imp/min) in the TI group (6%), in the S-thoracotomy (2%) and in S-atriotomy (1%). Occasionally, stimulation initiated arrhythmias with very rapid rates (>640 imp/min; TI = 7%, S-thoracotomy = 15%, and S-atriotomy = 18%).

Electrogram and ECG Characteristics—Classification

To aid description, we identified five types of arrhythmias in terms of rate and electrogram and ECG characteristics (Fig. 3). The type I arrhythmia was induced in both S and TI dogs. Its rate ranged from 200 to 300 imp/min. The interval between con-
Figure 3 Electrocardiogram and bipolar atrial electrogram recordings during the different types of arrhythmias induced by electrical stimulation in the conscious TI and S dogs. In each panel, the upper trace is the electrogram recorded from the left atrial appendage and the lower trace is the electrocardiogram recorded with the subcutaneous electrodes. Panel A shows the type I arrhythmia, Panel B is the type II, panel C is type III, panel D is type IV, and panel E is type V arrhythmia. See text for description of different arrhythmias. The time between the vertical black lines is 1 second.

Type IV arrhythmia also occurred in both S and TI dogs. The amplitude and configuration of the electrograms varied from beat to beat and the interval between complexes was not constant. The rate was difficult to determine but was usually

Table 3 Comparison of the Initiation of Type II Arrhythmia and Other Types of Atrial Arrhythmias by Overdrive (OD) or Atrial Premature (PS) Stimulation in the TI Dog

<table>
<thead>
<tr>
<th>Dog</th>
<th>Protocol</th>
<th>N</th>
<th>% Type II</th>
<th>% Other types</th>
<th>Type II vs other</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI#1</td>
<td>total</td>
<td>15</td>
<td>93</td>
<td>7</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>8</td>
<td>88</td>
<td>13</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>7</td>
<td>100</td>
<td>0</td>
<td>&gt;</td>
</tr>
<tr>
<td>TI#6</td>
<td>total</td>
<td>49</td>
<td>65</td>
<td>35</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>31</td>
<td>58</td>
<td>42</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>18</td>
<td>78</td>
<td>22</td>
<td>&gt;</td>
</tr>
<tr>
<td>TI#9</td>
<td>total</td>
<td>174</td>
<td>67</td>
<td>34</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>115</td>
<td>70</td>
<td>30</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>59</td>
<td>61</td>
<td>39</td>
<td>&gt;</td>
</tr>
<tr>
<td>TI#10</td>
<td>total</td>
<td>66</td>
<td>46</td>
<td>54</td>
<td>&lt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>26</td>
<td>62</td>
<td>38</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>39</td>
<td>36</td>
<td>64</td>
<td>&gt;</td>
</tr>
<tr>
<td>TI#11</td>
<td>total</td>
<td>61</td>
<td>51</td>
<td>49</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>25</td>
<td>28</td>
<td>72</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>36</td>
<td>67</td>
<td>33</td>
<td>&gt;</td>
</tr>
<tr>
<td>TI#12</td>
<td>total</td>
<td>24</td>
<td>67</td>
<td>33</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>20</td>
<td>60</td>
<td>40</td>
<td>&gt;</td>
</tr>
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<td></td>
<td>PS</td>
<td>4</td>
<td>100</td>
<td>0</td>
<td>&gt;</td>
</tr>
<tr>
<td>TI#14</td>
<td>total</td>
<td>125</td>
<td>31</td>
<td>69</td>
<td>&lt;</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>92</td>
<td>38</td>
<td>62</td>
<td>&gt;</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>33</td>
<td>12</td>
<td>88</td>
<td>&lt;</td>
</tr>
<tr>
<td>TI#16</td>
<td>total</td>
<td>73</td>
<td>77</td>
<td>23</td>
<td>&gt;</td>
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<tr>
<td></td>
<td>OD</td>
<td>64</td>
<td>78</td>
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<td>&gt;</td>
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<tr>
<td></td>
<td>PS</td>
<td>9</td>
<td>67</td>
<td>33</td>
<td>&gt;</td>
</tr>
</tbody>
</table>

N = total number of trials; OD = atrial overdrive stimulation trials; PS = atrial premature stimulation trials; > = the percent of type II arrhythmias initiated by the indicated protocol is greater than the percent of other types of arrhythmias initiated; < = the percent of type II arrhythmias initiated by the indicated protocol is less than the percent of other types of arrhythmias.
greater than 600 imp/min. The ECG showed no distinct P waves but only rapid irregular oscillations of the baseline. Ventricular rate was highly irregular (Fig. 3, panel D). Type V arrhythmia, induced in both groups, showed alternate periods of type III and IV (Fig. 3, panel E).

In summary, arrhythmias of types I, III, IV, and V were initiated in both S and TI dogs; type II arrhythmia was initiated only in the TI dogs.

**Duration**

Arrhythmias of types I, III, IV, and V generally were of short duration. The type I arrhythmia only rarely (3/45 = 7%) lasted for more than one minute and its maximum duration was 3 minutes. The type III arrhythmia occasionally was long lasting (>30 min) in both groups; however, this tendency was greater in the TI dog group (8% vs. 4% in S group).

**Figure 5** Initiation of the type II arrhythmia in a conscious TI dog by electrical stimulation of the left atrium. In each panel, the top trace is a bipolar left atrial electrogram, the middle trace is the ECG recorded from the subcutaneous electrodes, and the bottom trace is a time marker with the time between the two lines being 100 msec. Panel A illustrates the initiation of the arrhythmia with an atrial premature stimulus coupled to a basic drive cycle length of 350 msec at 100 msec (note the stimulus artifacts). Panel B illustrates the initiation of the type II rhythm with a period of overdrive stimulation at a cycle length of 100 msec. Upon termination of this rapid atrial drive, the type II rhythm is initiated.

**Figure 6** Atrial overdrive cycle lengths ($S_1 - S_2$) (panel A) and premature stimulus coupling intervals ($S_1 - S_2$) (panel B) at which type II rhythms were initiated in the TI dog group. In both panels, the mean percentage of trials in which a premature stimulus or atrial overdrive stimulation was successful in initiating atrial arrhythmias is on the ordinate. The total number of trials is the total number of trials that were successful in initiating any type of arrhythmia. The height of the unfilled columns indicates the percentage of successful trials in which a type II arrhythmia was induced. The height of the lined columns represents the percentage of successful trials in which arrhythmias other than type II were initiated. The number of dogs from which each mean is derived is indicated by the number above each column.

Type IV and type V arrhythmias in both S and TI dogs groups were not persistent. A majority of both types of arrhythmias in each group lasted for less than one minute.

The type II arrhythmia, a characteristic of TI dogs, was an arrhythmia that lasted for long periods of time (Fig. 4). A mean 30% of all the type II arrhythmias lasted longer than 30 minutes, while 22% lasted for more than 60 minutes. In fact, nine episodes in two of the TI dogs (TI #6 and #10) lasted for approximately 18 hours.

**Characteristics of the Type II Arrhythmias in TI Dogs**

Table 3 shows the incidence of type II in all TI dogs. In six TI dogs, overdrive (OD) or premature
stimulation (PS) caused type II in more than 50% of the trials; in the other TI dogs, type II occurred only in 46% of trials with OD and 31% with PS. An example of the induction of the type II arrhythmia by OD and PS is shown in Figure 5.

Induction of the type II arrhythmia in TI dogs at specific OD rates is shown in Figure 6A. Rapid rates \((S_1-S_2 = 90\text{ msec})\) and relatively slow rates \((S_1-S_2 = 140\text{ msec})\) rarely were successful in initiating any arrhythmia; moreover, rapid rates initiated other arrhythmias as frequently as the type II. Generally, slower OD initiated type II; in fact, the probability of eliciting type II was greatest if the drive rate was 461 imp/min or \((S_1-S_2 = 130\text{ msec})\). The coupling interval \((S_1-S_2)\) of the PS that most often elicited a type II arrhythmia varied among dogs; however, in all dogs \((S_1-S_2 = 120\text{ msec})\) more frequently initiated a type II rather than another type of arrhythmia (Fig. 6B).

The type II arrhythmia often terminated spontaneously. Usually this termination was abrupt with no preceding alteration in rate or electrogram morphology. Sometimes it was associated with either a prior decrease or increase in atrial cycle length. During 10 episodes of type II in four TI dogs, premature stimuli were not effective in terminating the arrhythmia. However, type II was terminated in 58% of 91 episodes by overdrive. In 44% of these episodes, after abrupt cessation of the drive, normal sinus rhythm was restored. In 14%, several rapid repetitive depolarizations preceded restoration of sinus rhythm.

The rate of type II arrhythmia during one episode varied only slightly. An example of the stability of the type II rate in three TI dogs is shown in Figure 7. The greater change in rate was from 450 imp/min to 390 imp/min, representing an 8% change in rate from control. Frequency histograms of cycle lengths for a 1-minute period of type II are unimodal or bimodal, with the greatest difference between the longest and shortest cycle length being 15 msec (Fig. 8). An analysis of the beat-to-beat changes in cycle lengths (Fig. 9) shows that the greatest beat-to-beat change in cycle length ranged from 0 to 1 msec in one episode (panel A) to 9.1 to 10 msec in another episode (panel B).

The type II arrhythmia was reproducibly initiated in a TI dog each day the dog was subjected to a stimulation protocol. In seven of eight TI dogs, a type II arrhythmia lasting for more than 20 minutes was initiated on at least 60% of the trial days. In
In Vitro Electrophysiological Properties of Fibers from the Atria of Control, Sham-Operated, and TI Dogs

Transmembrane Potential Characteristics

Values of RMP, APA, \( V_{\text{max}} \), APD_{100}, and APD_{50} were compared for 180 right atrial fibers of TI dogs and 132 and 192 fibers of S dogs and controls. No significant differences were found. Values for the left atrium also showed no significant differences among groups. Similar results were obtained when values of left atrial fibers were compared to those of right atrial fibers (Table 4).

Pharmacological Effects

In RA from TI, S and control dogs, Ach (1.4 \( \times \) \( 10^{-5} \) M) caused a significant increase in the RMP, APA, and \( V_{\text{max}} \) (Table 5), and significant decrease in APD_{100} and APD_{50}.

In control and S dogs, NE (5 \( \times \) \( 10^{-5} \) M) caused a slight but insignificant (\( P = 0.05 \)) increase in RMP, APA, and \( V_{\text{max}} \), and slight changes in APD_{100} and APD_{50} (Table 5). In TI atrial fibers, NE caused a significant increase in RMP and a concomitant change in APA and APD_{100}. However, these changes were not accompanied by significant changes in \( V_{\text{max}} \) or APD_{50}.

Nondriven Sustained Activity

During stimulation or during long periods of quiescence, none of the RA preparations from control, S, or TI dogs exhibited any type of nondriven sustained rhythmic activity during superfusion with normal Tyrode's solution, or during exposure to Ach. During exposure to NE and in the absence of electrical stimulation, one control, one S, and three TI dog right atrial preparations began to beat spontaneously. Rhythmic stimulation during exposure to NE caused sustained nondriven activity in one C and two S dogs, but in no TI RA preparations. Action potentials followed by delayed afterdepolarizations were recorded from right atrial cells (three in control, and three in S) just before the initiation of this type of activity.

Discussion

The principal findings in this study are that moderate chronic enlargement of the canine right atrium is associated with an altered susceptibility to atrial arrhythmia and, second, that this change does not appear to result from any abnormality in the transmembrane potentials of the fibers which constitute the right atrium. An unanticipated result was the emergence of an apparently unique atrial arrhythmia, resembling slow flutter, in the dogs with chronic right atrial enlargement.

It is important to try to evaluate the role of right atrial enlargement in causing the increased susceptibility to arrhythmias induced by overdrive and premature stimulation. We have presented evidence that the RA of the TI dogs were dilated and hypertrophied. The right atria of the TI dogs were larger relative to heart size than the right atria of control or sham dogs, and the ratio of right to left atrial volume in TI dogs differed significantly from that determined for control dogs.

Inspection of TI RA showed increased trabeculation, and microscopic examination showed that a
high proportion of cells had significantly increased diameters. The enlarged cells showed other ultrastructural evidence of hypertrophy (Pham et al., 1978; Maron and Ferraris, 1978). The only other obvious structural changes were moderate alterations in the arrangement of the muscle cells and a somewhat increased amount of connective tissue.

The next question to evaluate is whether or not the right atrial enlargement was the cause of the altered susceptibility to electrically induced arrhythmias. Pericarditis was present in both S and TI dogs and seems an unlikely cause of the difference in susceptibility between the groups. Pericarditis was present in both S and TI dogs and seems an unlikely cause of the difference in susceptibility between the groups. The presence of a healed right atriotomy might be expected to increase the likelihood of a reentrant rhythm by providing an inexcitable barrier around which the impulse could circulate. This was present both in the S-atriotomy and TI dogs and again does not seem to account for the unique characteristics of the latter. We conclude, therefore, that the susceptibility of the TI dogs to the type II arrhythmia resulted from the right atrial enlargement.

In the TI dogs, but not the S dogs, both overdrive and premature stimulation quite reproducibly ini-
tiated a persistent arrhythmia, with rates between 320 and 450 impulses per minute, which we have called type II; a similar rhythm with rates higher than 450 impulses per minute could be induced in both TI and S animals.

Although we did not study the mechanism for this arrhythmia, some speculation may be permissible. Since the type II arrhythmia was induced by either overdrive or premature stimulation and could be terminated by overdrive, it is more likely caused by reentry (Allessie et al., 1973; Allessie et al., 1976; Allessie et al., 1977; Wit and Cranefield, 1978) or afterdepolarizations (Cranefield, 1975) rather than by other mechanisms. We do not think that the arrhythmia was caused by a reentrant path including the sinoatrial or atrioventricular nodes because intravenous doses of phenylephrine, sufficient to cause strong reflex vagal stimulation (Boyden and Hoffman, 1978) neither terminated the arrhythmia nor changed the cycle length; in addition, a bolus injection of methylcholine increases the rate of the type II rhythm by shortening the atrial cycle length (Boyden, unpublished observation). If it is caused by reentry, as may be the case for some types of atrial flutter (Lewis et al., 1920; Rosenblueth and Garcia Ramos, 1947; Kimura et al., 1954; Lanari et al., 1956; Hayden et al., 1967; Boineau et al., 1980), it probably is reasonable that its rate was slower than that of similar rhythms in S dogs and also that it tended to be persistent. In dogs, most episodes of experimentally induced flutter and fibrillation are of short duration (Lewis et al., 1920), whereas in the larger atria of cows and goats, atrial fibrillation may be quite persistent (Moore et al., 1962). Also, when the right atrium is acutely dilated in dogs with an interceval crush (Hayden et al., 1967) the rate of induced flutter decreases. Similarly, in humans, the rate of atrial flutter is lower in patients with markedly enlarged atria (Rytynd et al., 1958).

Our data for the transmembrane potentials of fibers from the right and left atria of TI, S and control dogs showed no differences among groups. However, we did not test the effects of overdrive and premature stimulation on the isolated tissue preparations. The TI dog atria might have shown abnormal responses. The atria of TI dogs showed no consistent evidence of abnormal mechanism for impulse initiation such as afterdepolarizations. Finally, since values for resting potential, action potential amplitude, and $V_{max}$ were comparable both for right and left atria of TI dogs and for atria from TI and S dogs, there is little reason to assume that some impairment of impulse generation due to an alteration in cellular electrical activity is crucially related to the altered susceptibility to arrhythmia.

For the in vitro cellular electrophysiological studies, the piece of atrium isolated for study was a large section (4 cm$^2$) containing mostly anterior, and some appendage, wall. This particular section was chosen since, as the atrium enlarges in situ, it is impeded by other structures on three sides, whereas most enlargement is by the expansion of the free wall (Arvidssen, 1958). Although no generalized abnormalities in transmembrane potentials were found in these atrial sections, the possibility remains that changes in potentials occurred in fibers in sections not studied. We feel this is unlikely, since these sections of atrium, the posterior wall and septum, should not have been exposed to any more stress from the pressure-volume overload than the section removed for study.

The final observation deserving of comment is the finding that the right atrial enlargement modified the susceptibility to arrhythmias without causing any demonstrable change in cellular electrical activity. This is an interesting finding in light of earlier data for human atrial tissue from diseased hearts (Singer et al., 1973; Hordof et al., 1976; Gelband et al., 1977; Mary-Rabine, et al., 1979) and the general impression that there is a correlation between the likelihood of clinically occurring atrial arrhythmias and abnormalities of cellular electrical activity.

It may be that the difference between the findings for this animal model and the human atrium can be explained on the basis of the length of time enlargement is present, the degree of enlargement, and the presence of spontaneous atrial arrhythmias. However, in studies on the left atria of dogs with mitral insufficiency (Boyden et al., 1980), we have obtained findings similar to those reported here. In these animals, there was severe left atrial enlargement that had occurred over years, and spontaneous arrhythmias, including chronic atrial fibrillation, were present. Nevertheless, the transmembrane potentials of single fibers in isolated preparations of left atrium showed no significant abnormalities. The data emphasize the need to consider more carefully possible relationships between changes in morphology and susceptibility to arrhythmias. In the TI dogs, morphological change also was minor; however, in the left atria of dogs with mitral insufficiency, the changes in the morphology of the atrial wall were more significant. It may well be that we have not completely evaluated the structural correlates of significance. For instance, our study cannot eliminate the possibility that in situ the velocity of the propagating wavefront is decreased due to the structural changes associated with the atrial enlargement. Perhaps the increased connective tissue and hypertrophy in TI RA alter the anisotropic properties of the atrial myocardium, reeding it more susceptible to block and reentrant excitation.

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